Optimal Management of Portal Hypertension

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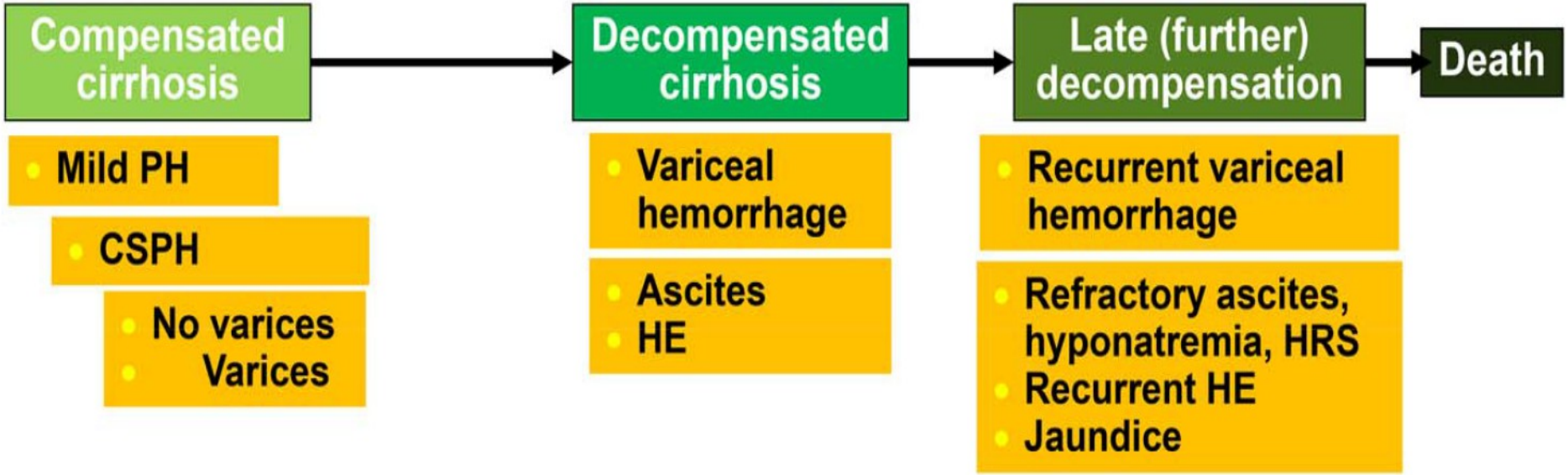
Disclosures

I have no disclosures related to this topic

Natural History of Cirrhosis

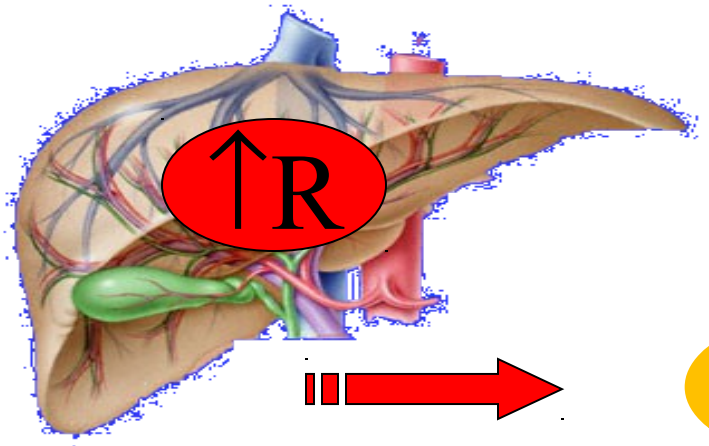


→ **Risk stratification and individualizing care for PH**

Garcia-Tsao G, Abraldes J, Berzigotti A and Bosch J, Hepatology 2017

PH: Pathophysiology

Hepatic



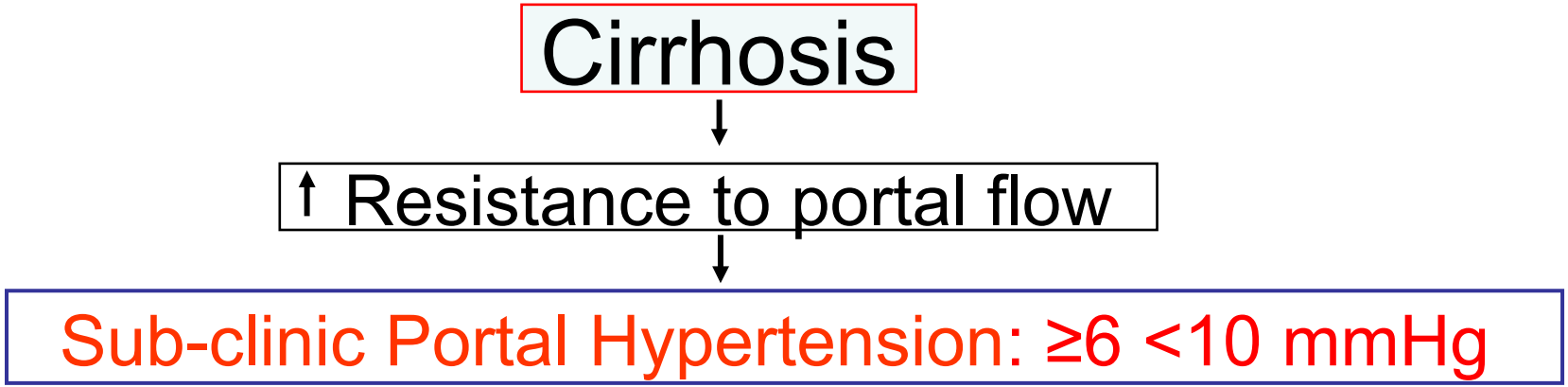
Collateral circulation

Extrahepatic

Splanchnic vasodilation

PH

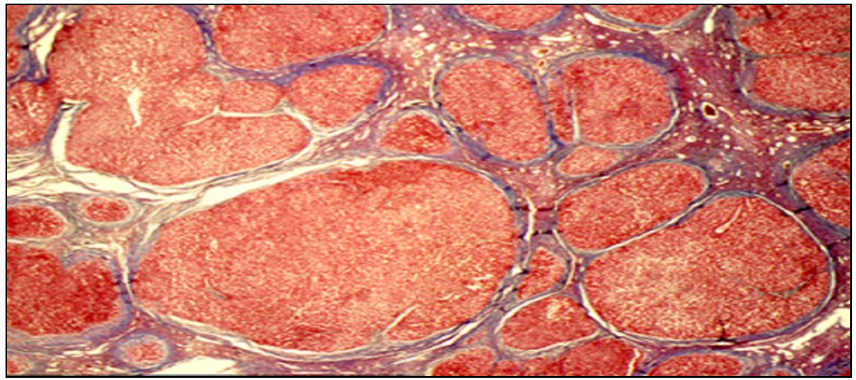
↑Q


Cirrhosis
↑ Resistance to portal flow
Sub-clinic Portal Hypertension: ≥6 <10 mmHg

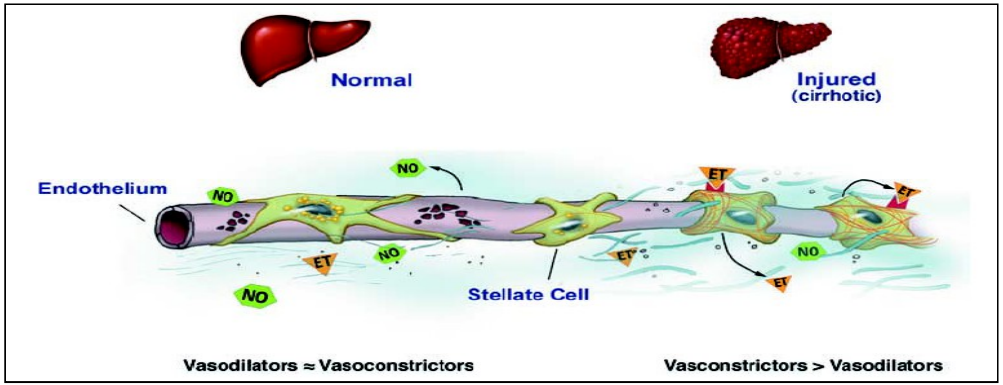
Cirrhosis

↑ Resistance to portal flow

Sub-clinic Portal Hypertension: ≥6 <10 mmHg



Structural component

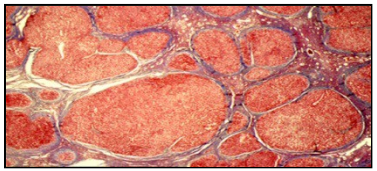


Functional component

Cirrhosis

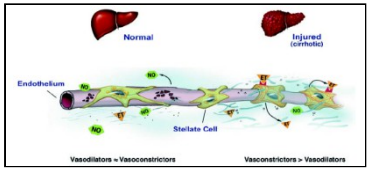
↑ Resistance to portal flow

Sub-clinic Portal Hypertension: ≥6 <10 mmHg



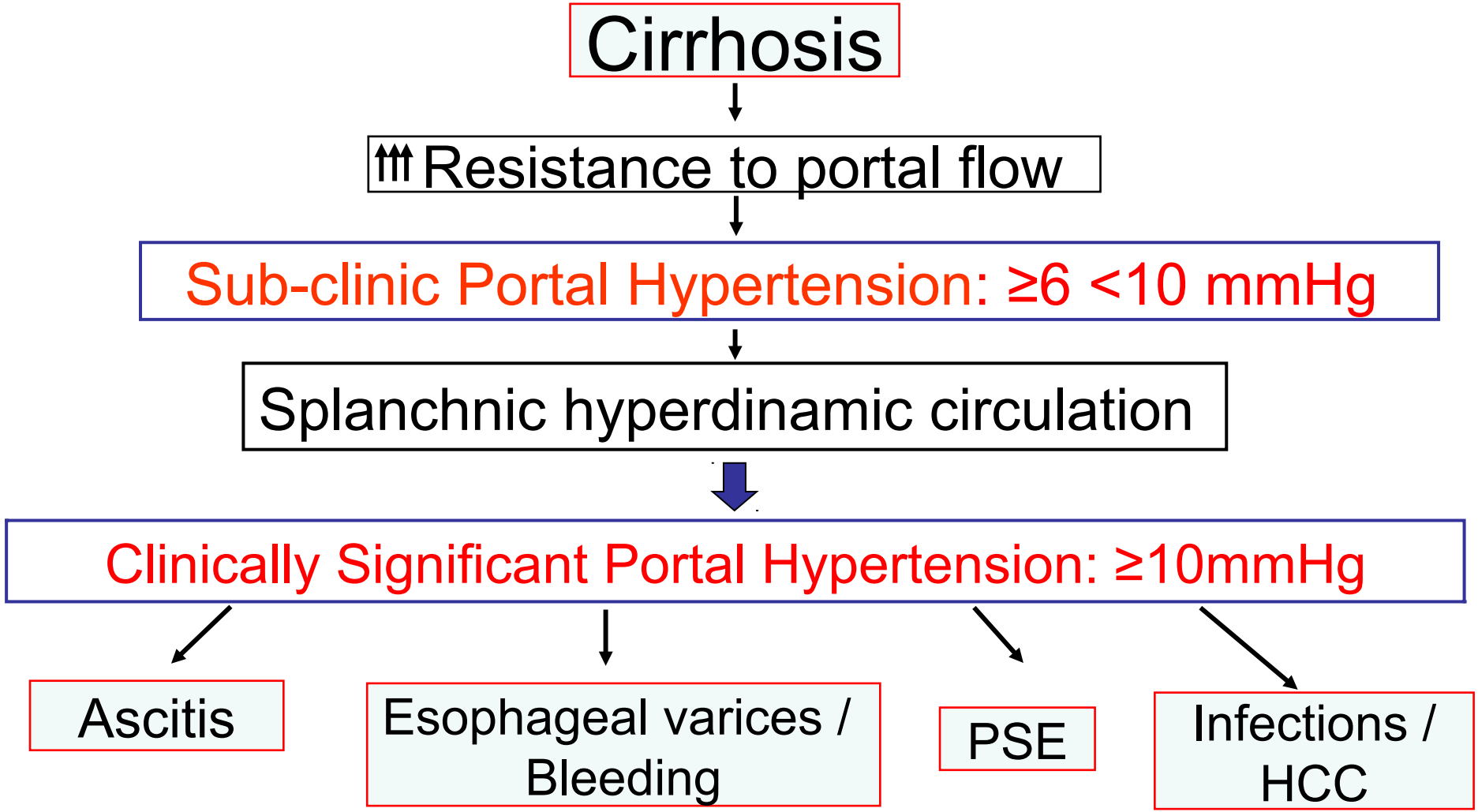
Structural component

Aim



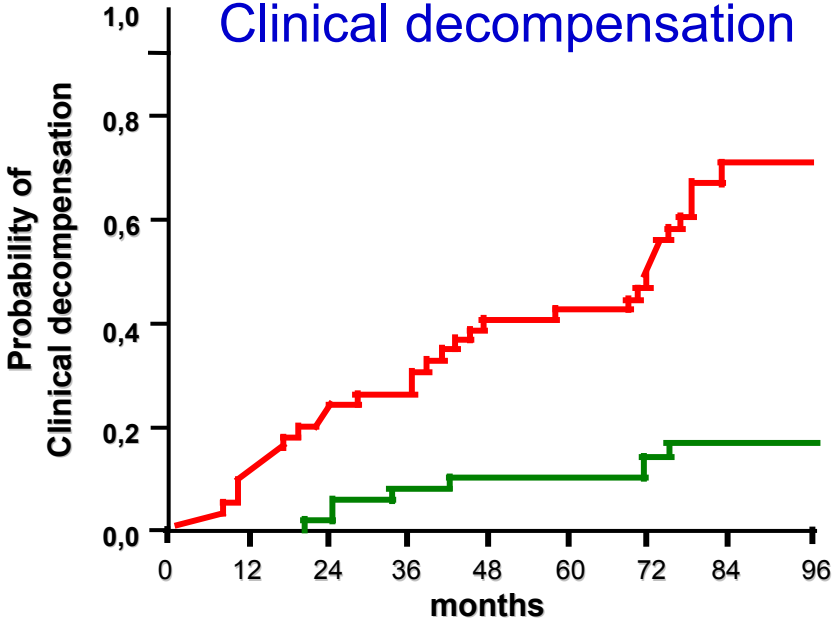
Functional component

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


Cirrhosis
↑↑↑ Resistance to portal flow
Sub-clinic Portal Hypertension: ≥6 <10 mmHg
Splanchnic hyperdinamic circulation
Clinically Significant Portal Hypertension: ≥10mmHg
Ascitis
Esophageal varices / Bleeding
PSE
Infections / HCC

Clinical decompensation: relationship with PH

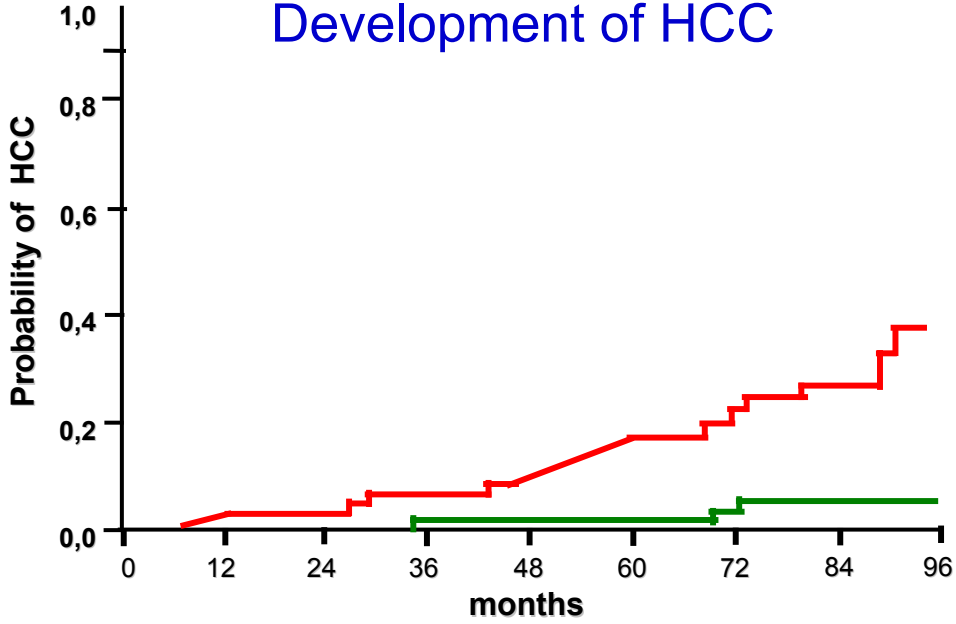
Clinical decompensation



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

Ripoll C et al.; Gastroenterology 2007

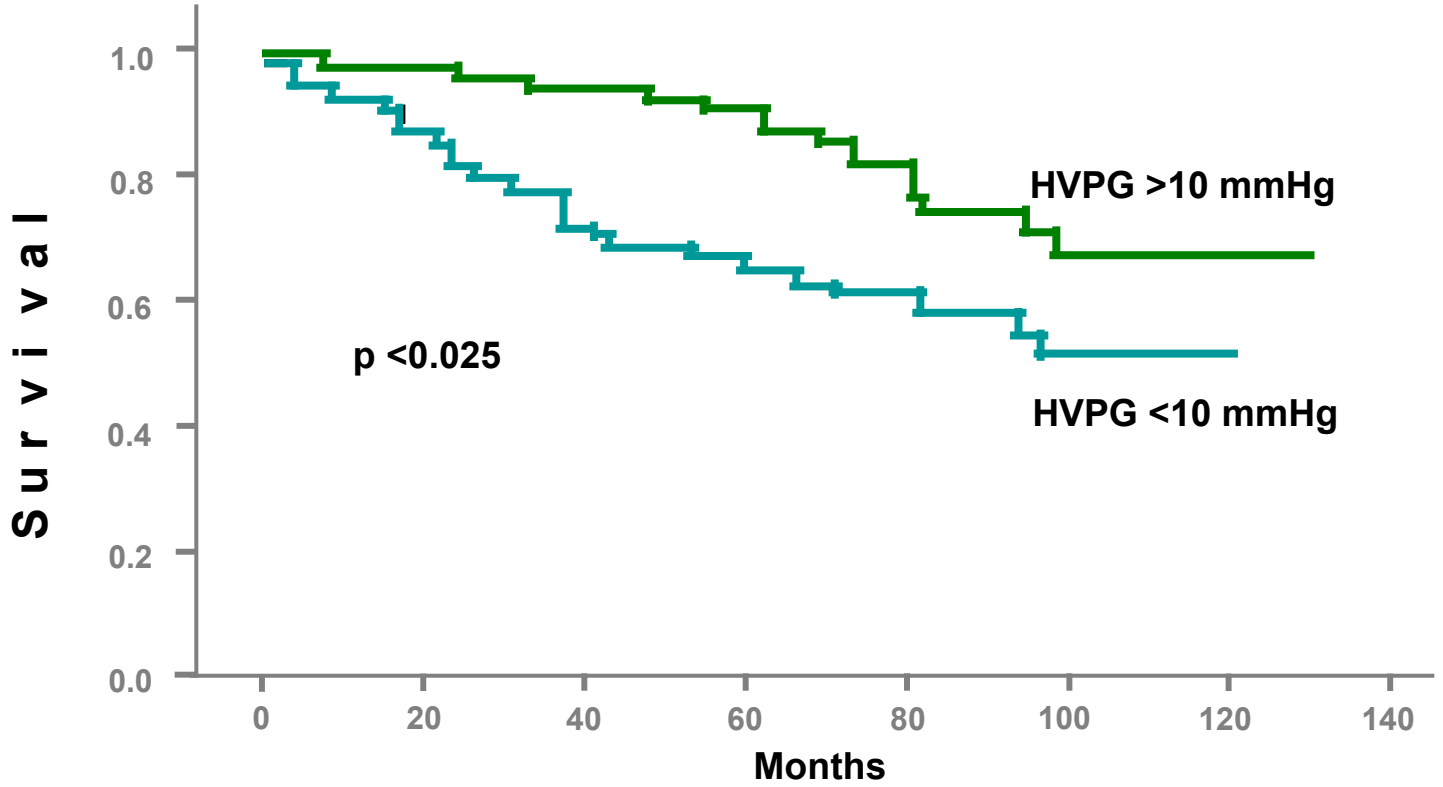
Development of HCC



HVPG <10 mmHg						
At risk	79	74	72	68	46	24
Events	0	0	0	1	1	3
HVPG ≥10 mmHg						
At risk	134	126	116	102	71	21
Events	0	3	5	8	12	16

Ripoll C et al.; J Hepatol 2009

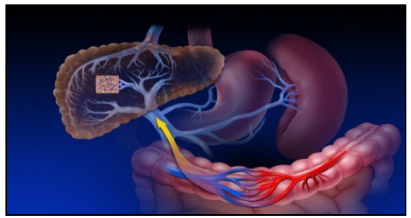
Compensated cirrhosis: HVPG and survival



Zipprich A et al.; Liver International 2012

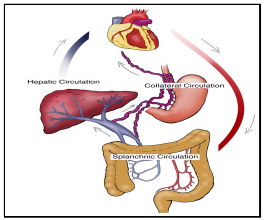
Splanchnic hyperdinamic circulation

Clinically Significant Portal Hypertension:
≥10mmHg



Splanchnic vasodilation

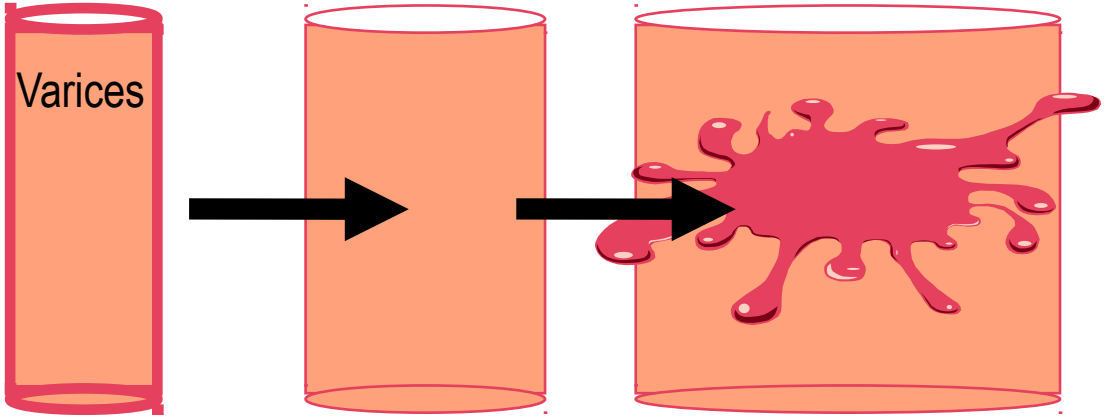
Aim



Collateral circulation

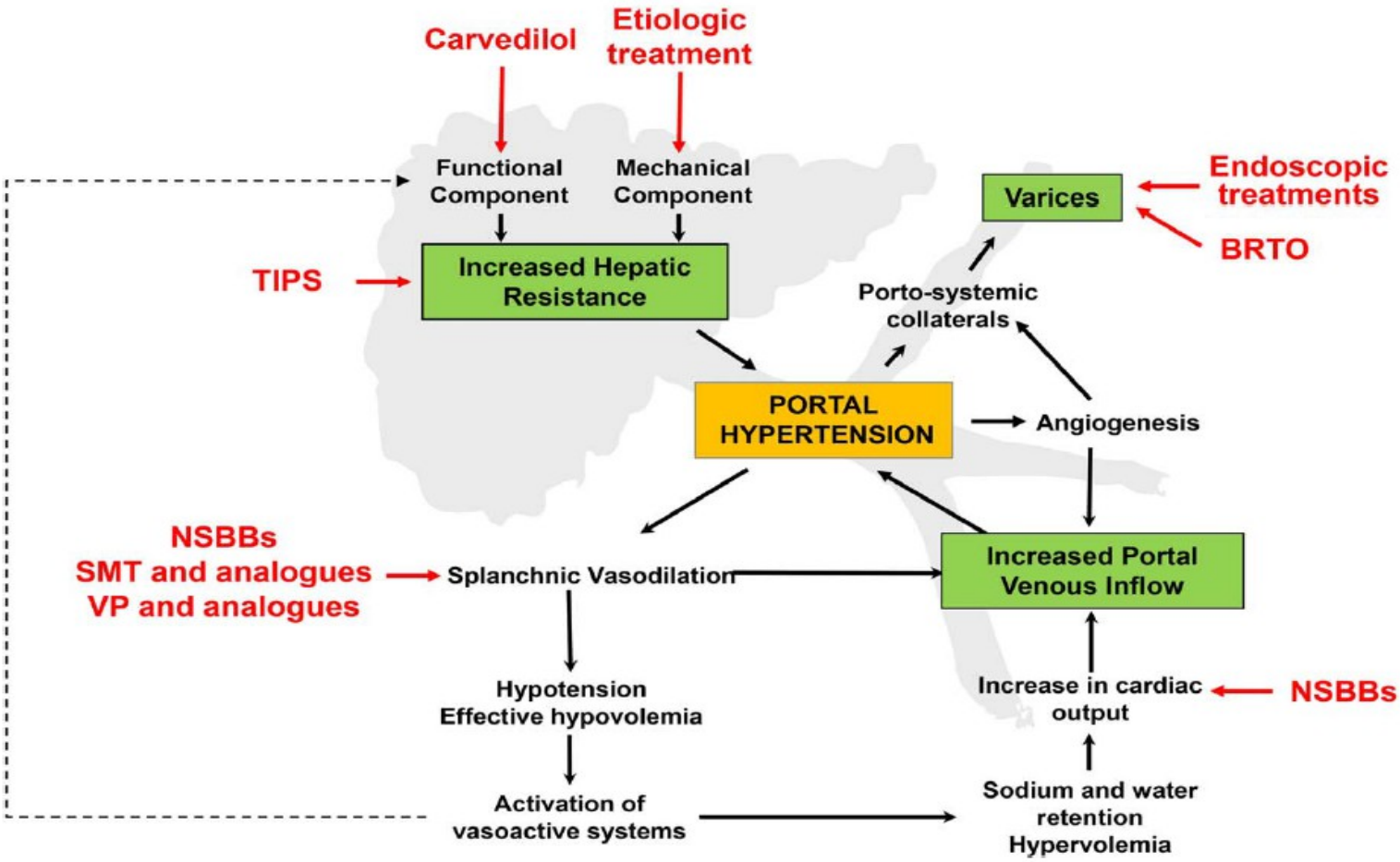
To prevent the development of complications

GEV are present in approximately 40% of patients with Compensated Cirrhosis and in up to 85% of patients with Decompensated Cirrhosis



First Variceal Bleeding	*Variceal Rebleeding*
Incidence: 19-40% at 2 years	Incidence: ± 60% at 1 year
Mortality: ± 10-25%	Mortality: 50%

Garcia-Tsao G, Abraldes J, Berzigotti A and Bosch J, Hepatology 2017



Garcia-Tsao G, Abraldes J, Berzigotti A and Bosch J, Hepatology 2017

Optimal Management of Portal Hypertension

- Pre-primary prophylaxis
- Prevention of the first bleeding episode
- Treatment of acute bleeding
- Prevention of recurrent bleeding
- Issues with β-blockers

Optimal Management of Portal Hypertension

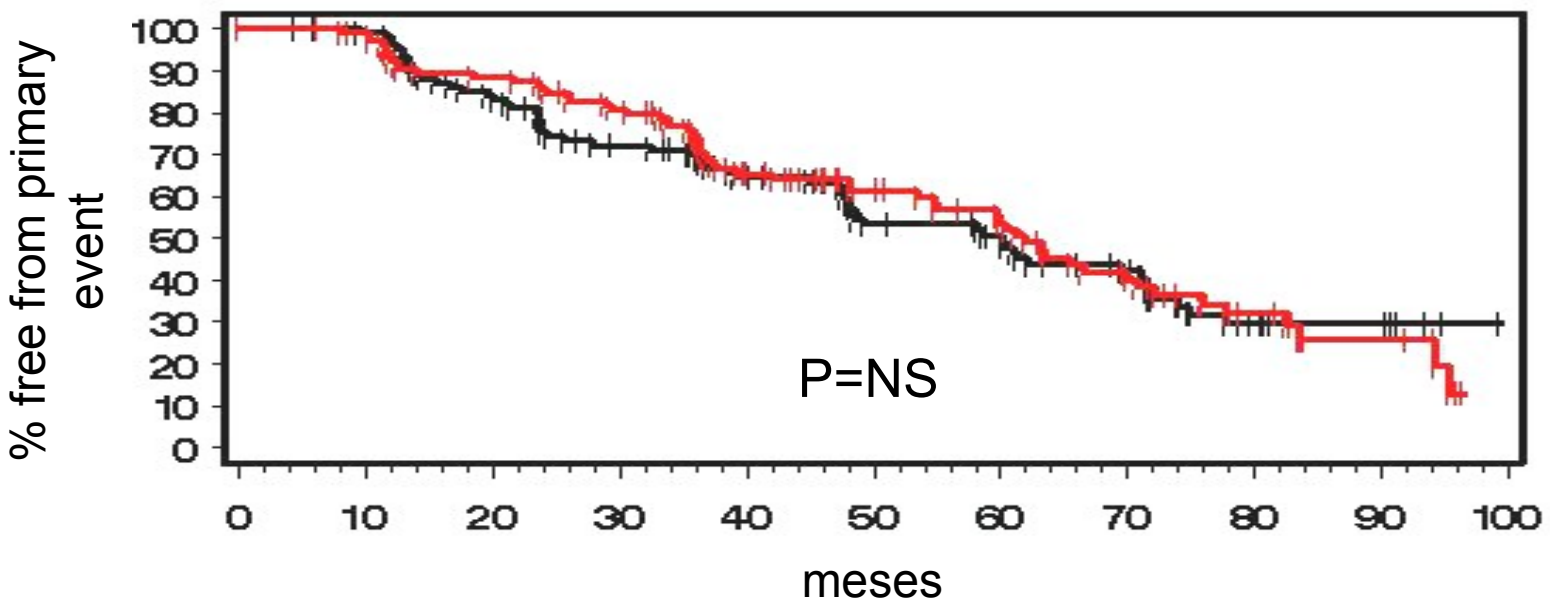
- **Pre-primary prophylaxis**
- Prevention of the first bleeding episode
- Treatment of acute bleeding
- Prevention of recurrent bleeding
- Issues with β-blockers

Pre-primary Prophylaxis: Baveno VI Recommendations

- All patients with cirrhosis should be screened for varices at diagnosis.
- Patients with an LS <20 kPa and platelet count >150,000/mm3 have a very low probability (<5%) of having high-risk varices, and EGD can be avoided.
- Underlying cause of liver disease should be treated when possible.
- There is **NO indication to use β-blockers to prevent the formation of varices.**

de Franchis R and Baveno VI Faculty. J Hepatol 2015

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%)

Groszmann R et al.; N Engl J Med 2005

New!

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 varices requiring treatment** or previous decompensation (n=210)

Acute HVPG response to iv Propranolol*:

acute responders ➔ **Propranolol vs placebo**

non-responders ➔ **Carvedilol vs placebo**

- Patients developing varices requiring treatment received **EBL**

0.15 mg/Kg IV; Acute Responders: HVPG ≥ 10% of baseline

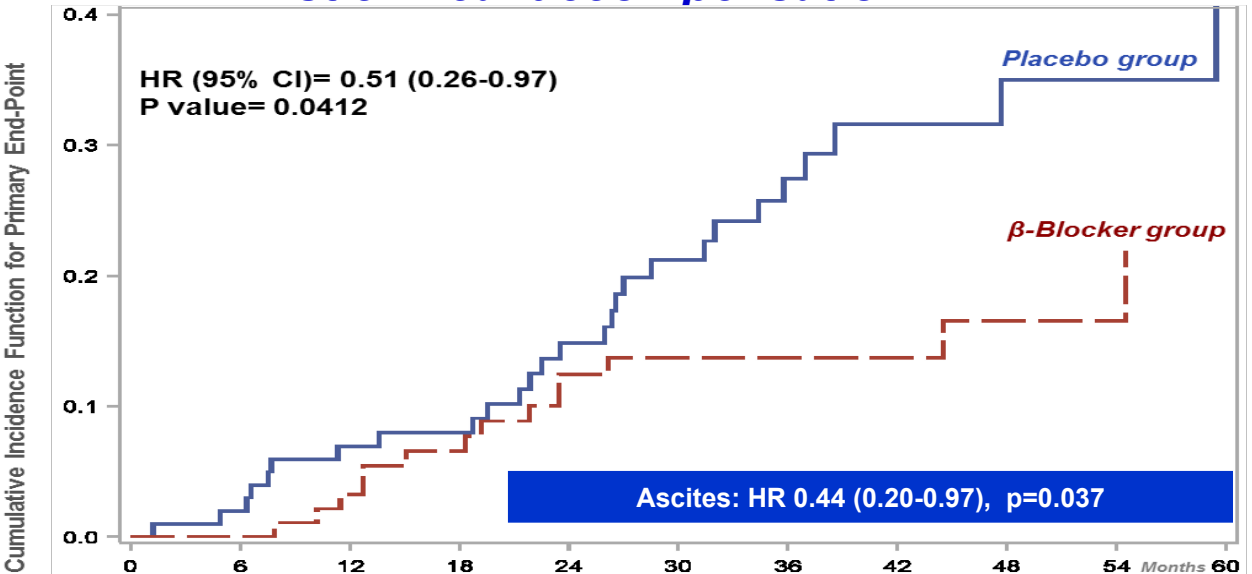
Villanueva et al. Lancet (in press)

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

New!

First clinical decompensation

A



Villanueva et al. Lancet (in press)

Optimal Management of Portal Hypertension

- Pre-primary prophylaxis
- **Prevention of the first bleeding episode**
- Treatment of acute bleeding
- Prevention of recurrent bleeding
- Issues with β-blockers
- Future treatments

Prevention of the First Bleeding Episode

- All patients at this stage have by definition CSPH because the lowest HVPG is 10-12 mmHg.
- **Primary prophylaxis of VH is indicated in patients at a high risk of bleeding:**
  a. medium/large varices
  b. small varices with red wale signs
  c. decompensated patients with small varices
- Reductions in HVPG >10% induced by use of NSBBs in the prevention of first hemorrhage are associated not only with a lower incidence of first VH, but also to a lower incidence of ascites and death.

de Franchis R and Baveno VI Faculty. J Hepatol 2015

Prevention of the First Bleeding Episode

- Either **NSBBs (propranolol, nadolol) or EBL can be used to prevent first VH** in patients with medium/large varices, and that choice of treatment should be based on local resources and expertise, patient preference and characteristics.
- In cases NSBBs have to be discontinued because of intolerance, the patient can be switched to carvedilol.
- Because EBL is a local therapy, surveillance endoscopies to detect variceal recurrence are necessary after variceal eradication.

de Franchis R and Baveno VI Faculty. J Hepatol 2015

Optimal Management of Portal Hypertension

- Pre-primary prophylaxis
- Prevention of the first bleeding episode
- **Treatment of acute bleeding**
- Prevention of recurrent bleeding
- Issues with β-blockers

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 in regards to coagulopathy
9. Prompt endoscopic therapy (EBL)
10. Ultrasound
11. Possibility of tamponade or endoscopic stents
12. Possibility of TIPS

Systematic review - 26 studies

Sclerotherapy still used in 19%

No endoscopic intervention-14%

Prophylactic antibiotics -53% !

Tapper E. CGH 2017

Early TIPS in 9 %

Thabut D, et al. J Hepatol 2017

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

Treatment of Acute Variceal Bleeding

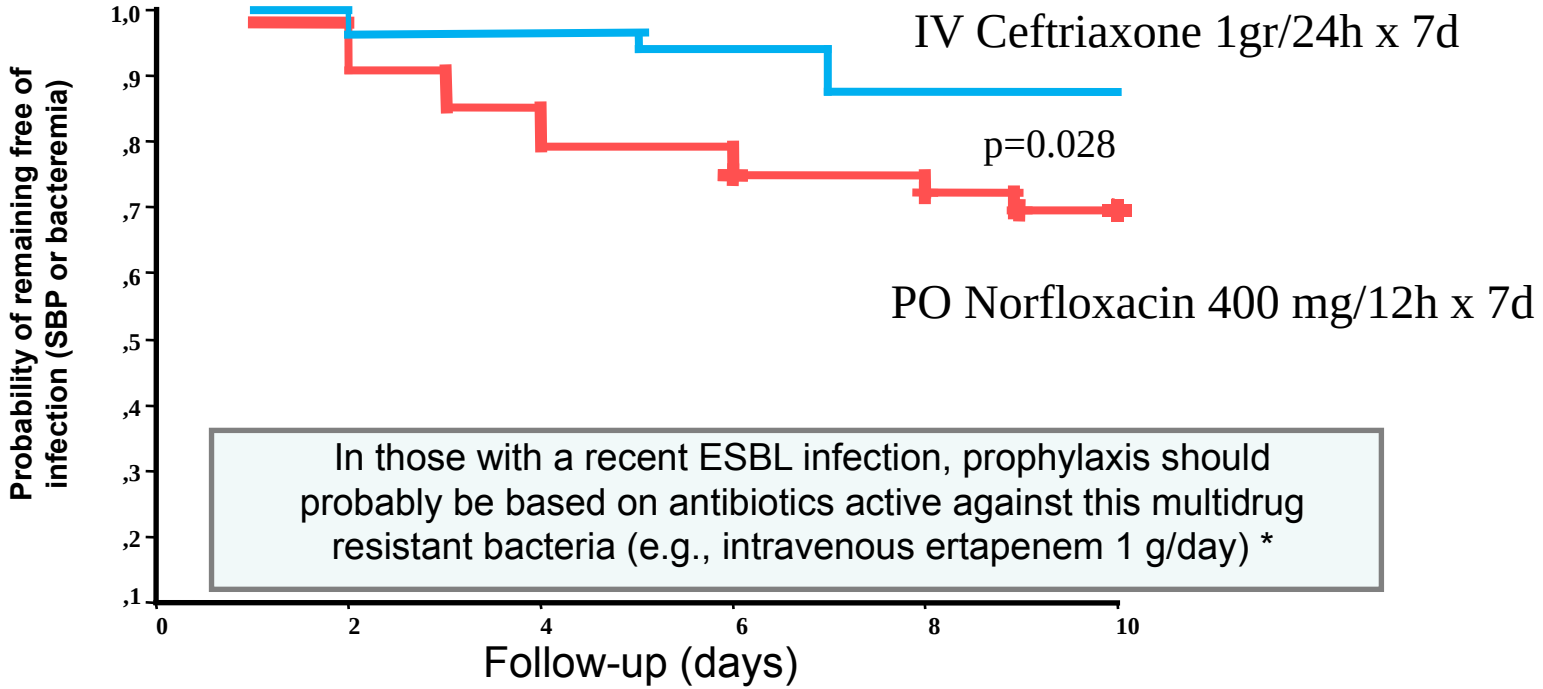
Stratify patients

5-year mortality is very different, depending on whether VH occurs as an isolated event (20%) or whether the patient presents with other complications of cirrhosis as ascites or encephalopathy (over 80%).

Garcia-Tsao G, Abraldes J, Berzigotti A and Bosch J, Hepatology 2017

Antibiotic prophylaxis in AVB & advanced cirrhosis

(malnutrition, Bili>3, Ascites, HE, massive bleed)



In those with a recent ESBL infection, prophylaxis should probably be based on antibiotics active against this multidrug resistant bacteria (e.g., intravenous ertapenem 1 g/day) *

Fernández J, Gastroenterology 2006
*Fernandez et al. Hepatology 2016; *J Hepatol 2018*

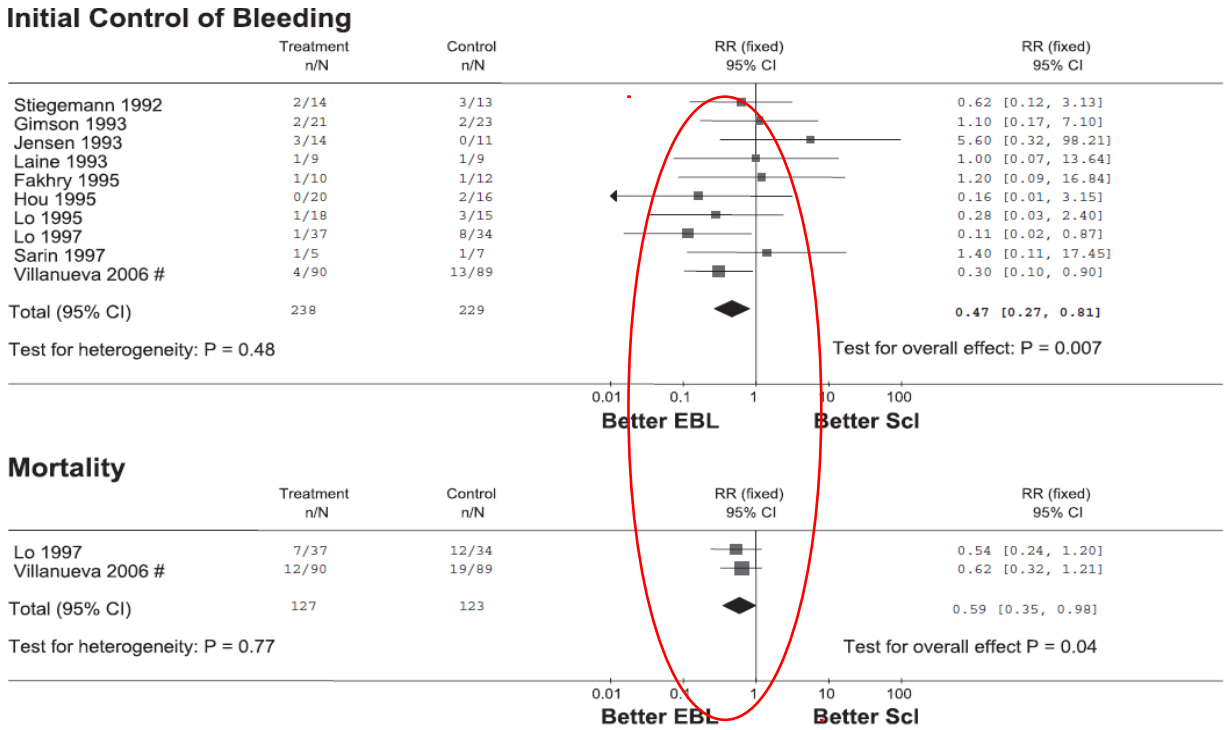
Prospective, multicenter, randomized, noninferiority trial Terlipressin, Somatostatin,and Octreotide in AVB

n= 780 patients (all with EBL)- randomized to 3 groups

Treatment Response	All Patients (n = 780)	Terlipressin Group (n = 261)	Somatostatin Group (n = 259)	Octreotide Group (n =2 60)	*P* Value
Control of index bleeding without rescue therapy, n (%)	690 (88.5)	234 (89.7)	227 (87.6)	229 (88.1)	0.752
Time interval from T0 to bleeding control, hours	9.8 ± 10.3	9.6 ± 10.7	10.1 ± 10.1	9.7 ± 10.2	0.839
Time interval from commencement of vasoactive drug to bleeding control, hours	8.0 ± 10.3	7.8 ± 10.6	8.2 ± 10.1	8.1 ± 10.3	0.899
Patients with rebleeding, n (%)*	29 (4.2)	8 (3.4)	11 (4.8)	10 (4.4)	0.739
Time interval from T0 to rebleeding, hours†	66.8 ± 23.6	70.0 ± 27.5	69.0 ± 19.6	61.9 ± 26.0	0.730
Time interval from bleeding control to rebleeding, hours†	62.1 ± 24.4	64.7 ± 26.4	64.2 ± 22.4	57.9 ± 26.8	0.801
Mortality, n (%)	67 (8.6)	21 (8.0)	23 (8.9)	23 (8.8)	0.929
Cause of mortality					0.920
Uncontrolled index bleeding, n (%)***	60 (89.6)	19 (90.5)	20 (87.0)	21 (91.3)	
Uncontrolled rebleeding, n (%)‡	2 (3.0)	1 (4.8)	1 (4.3)	0 (0)	
Liver failure, n (%)‡	3 (4.5)	1 (4.8)	1 (4.3)	1 (4.3)	
Infection, n (%)‡	2 (3.0)	0 (0)	1 (4.3)	1 (4.3)	
5-day treatment success, n (%)	659 (84.5)	225 (86.2)	216 (83.4)	218 (83.8)	0.636

Seo, et al Hepatology 2014;60:954-963

Endoscopic therapy AVB - Meta-analysis of ligation vs sclerotherapy

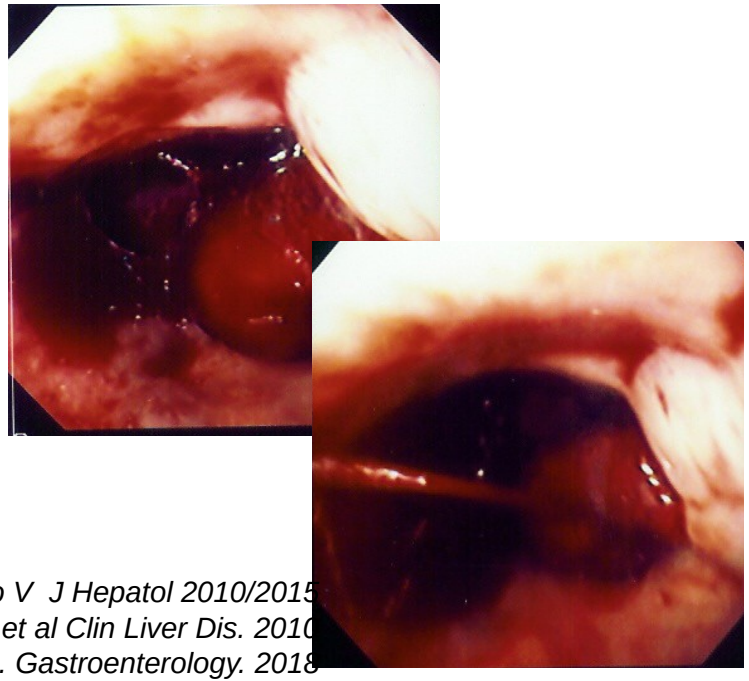


Abraldes et al. J Clin Gastroenterol 2007; 41: S312-317

Refractory bleeding

The time frame for AVB is 5 days

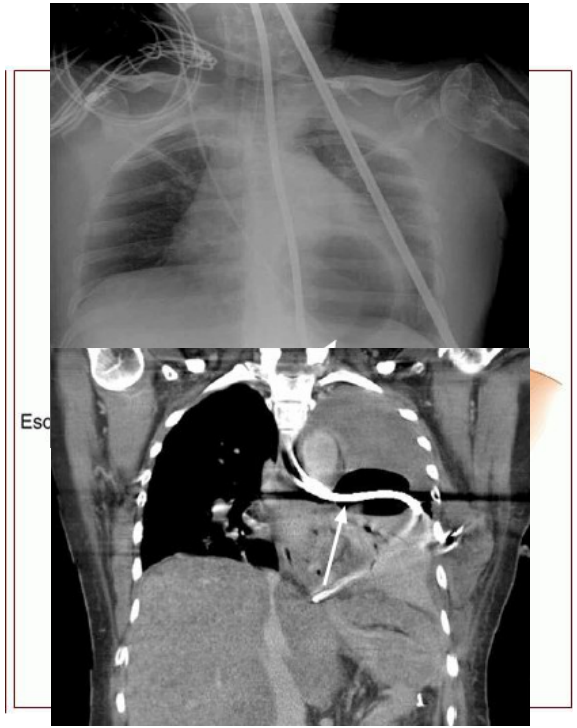
- In 10-15 % of cases, patients are not controlled with therapy.
- Left untreated mortality rates > 50%.
- Several approaches:
  - Repeat EGD
  - Tamponade (balloon or stent)
  - TIPS



Baveno V J Hepatol 2010/2015
D'Amico M , et al Clin Liver Dis. 2010
Ibrahim. Gastroenterology. 2018

Tamponade

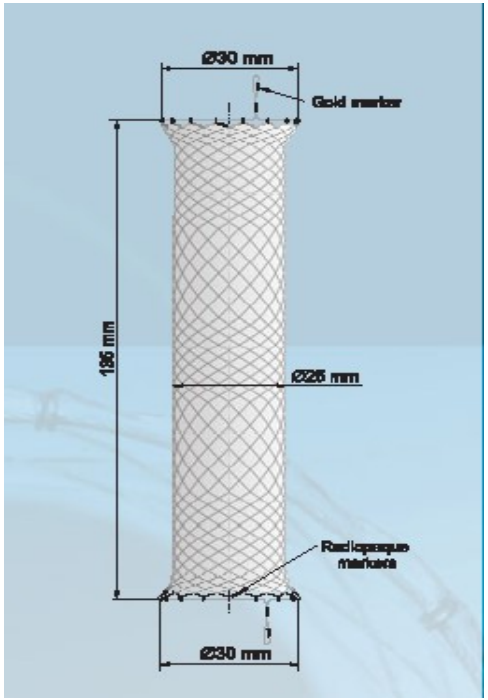
- Ballon tamponade
  - Inflate gastric balloon first
  - Esophageal balloon (if bleeding persists)
  - Intubation required
- Temporary ‘‘bridge’’ (for a maximum of 24 -48 h)
- Beware of complications!
  - Perforation ~ 5-10%
  - Aspiration neumonia ~25 -35%
  - Ulcers / necrosis ~ 10 -15%



Choi . Korean J Intern Med. 2018 Jul;33(4):696-704
Nadler, et al J Emerg Med 2017 Oct;35(10):1500-1502

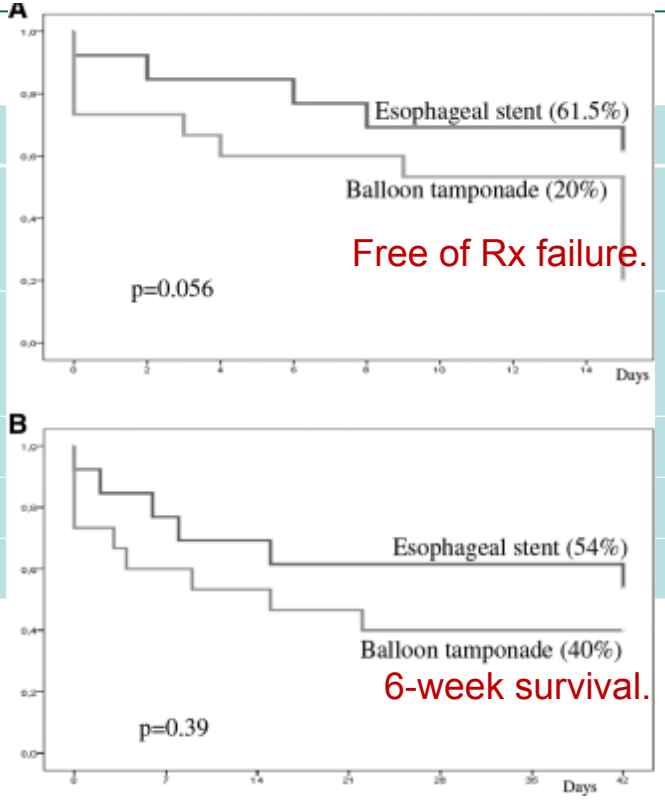
Fully covered expandable esophageal metallic stents

- Easily implanted
- With or without endoscopy
- Highly effective and safe
- Oral intake soon afterwards
- Remove after 7 days
- BRIDGE to TIPS or LT



Self Expandable Esophageal Stent vs Balloon Tamponade in Esophageal Variceal Bleeding Refractory to Medical and Endoscopic Treatment: A Multicenter RCT

	P value
Success of therapy	0.025
Control of bleeding	0.037
Transfusion	0.037
Adverse events	
TIPS	0.07



Escorsell et al, Hepatology 2016

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 ?

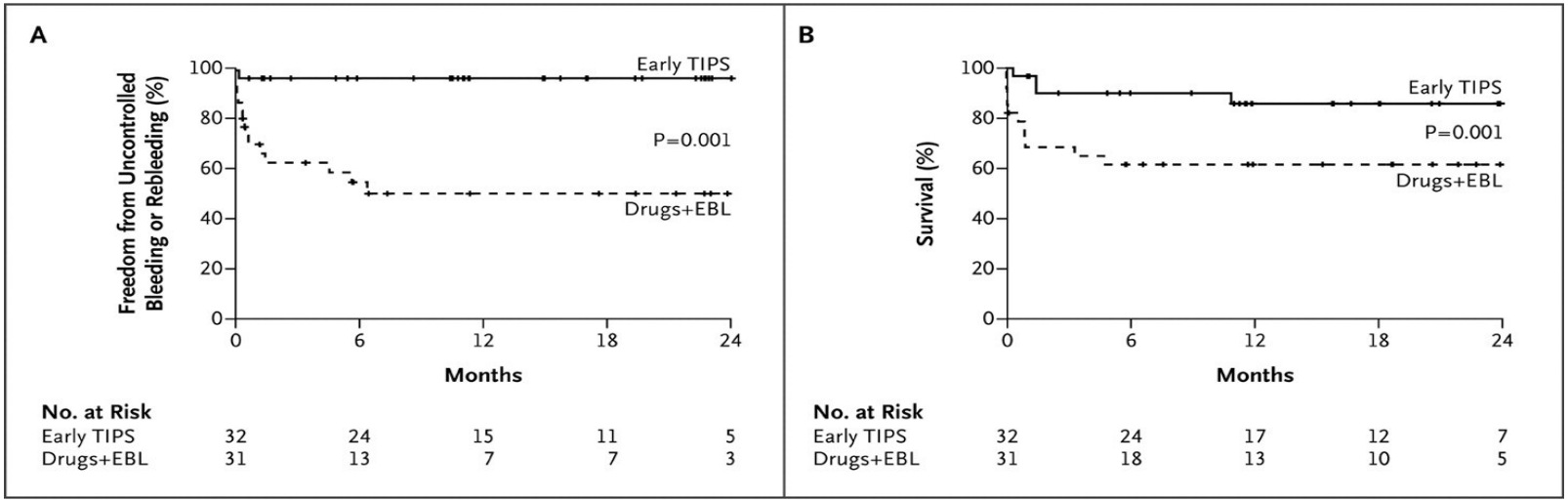
RudlerM et al, Transplant Int 2014
Bouzbib, AFEF 2018

Multicenter RCT of Early TIPS (1st 72 hrs) vs SMT in Patients with Acute Variceal Bleeding

(Child B with active bleeding and Child C ≤ 13)

Primary end-point

Survival



García-Pagán JC et al. N Engl J Med 2010;362:2370-2379.

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).

De Franchis, J Hepatol 2015

Criteria for high-risk patients should be refined…

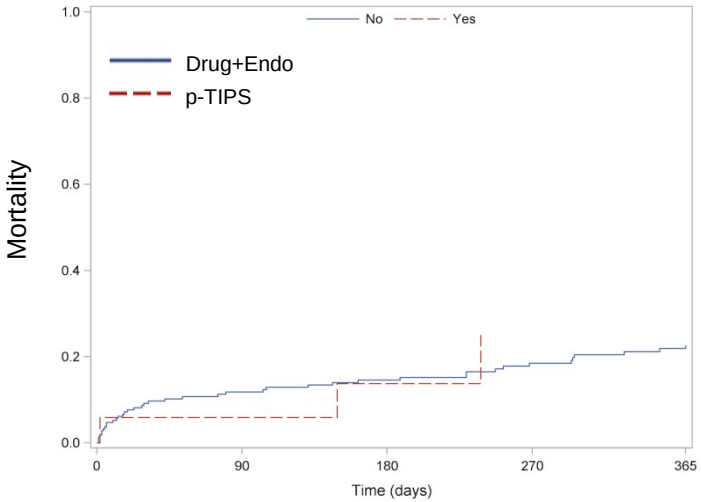
Preemptive-TIPS improves outcome in high-risk variceal bleeding

(Propensity score matched analysis)

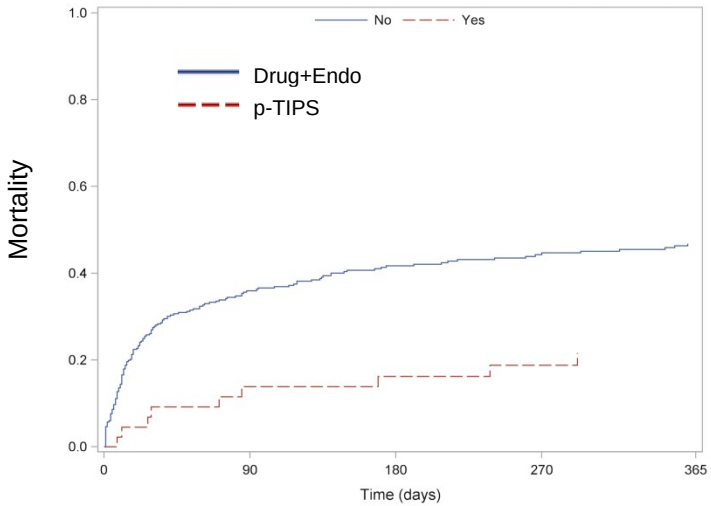
Multicenter, international study in 34 centers

66 Early TIPS vs 605 Drugs and EBL

Child-Pugh B + Active Bleeding



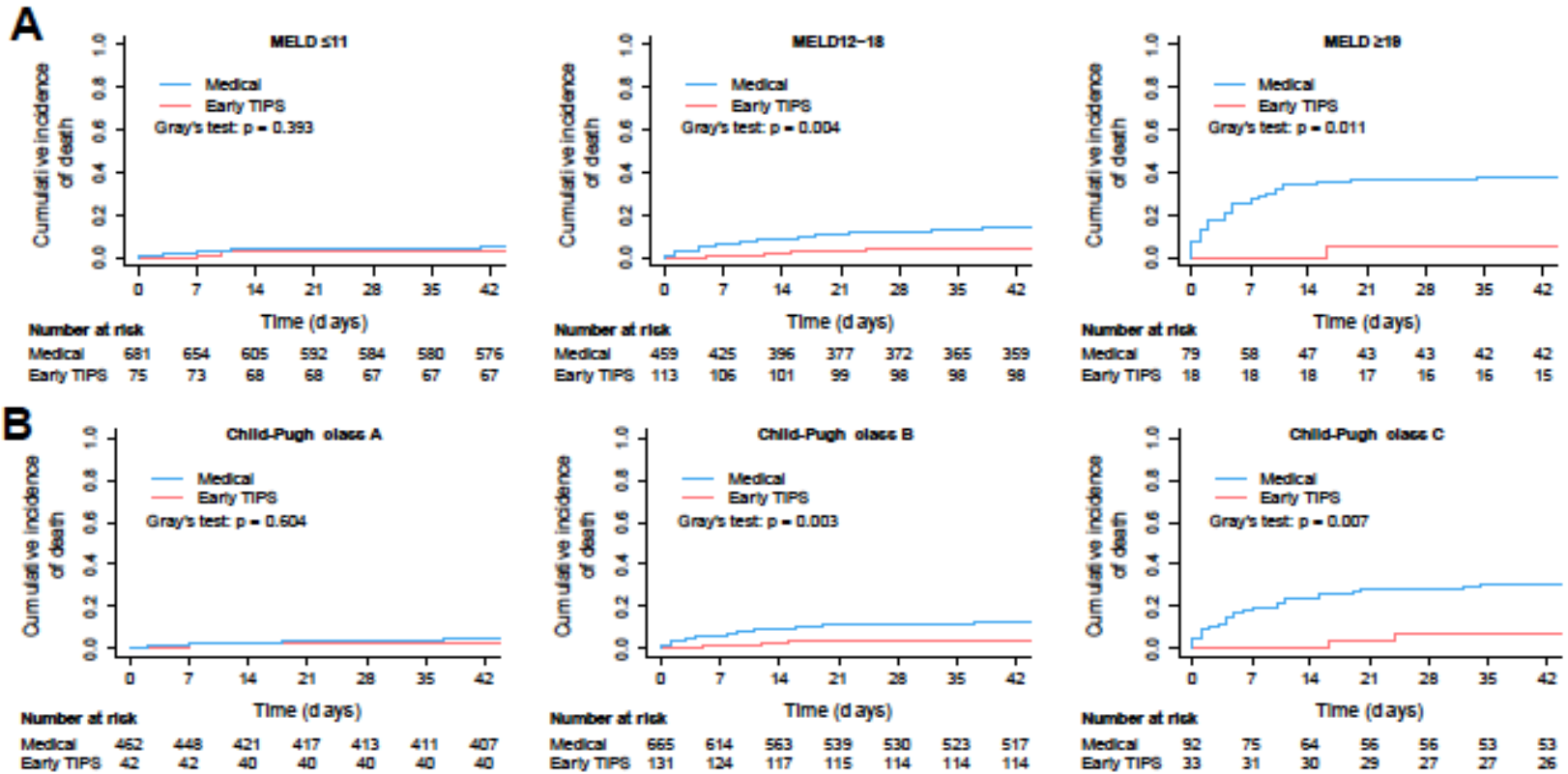
Child-Pugh C



Hernandez-Gea et al. Hepatology 2018

Identifying optimal candidates for early TIPS among patients with cirrhosis and acute variceal bleeding: a multicentre observational study

Early TIPS group, n=206 Medical group, n=1219



Lv Y, et al. Gut 2018

Optimal Management of Portal Hypertension

- Pre-primary prophylaxis
- Prevention of the first bleeding episode
- Treatment of acute bleeding
- **Prevention of recurrent bleeding**
- Issues with β-blockers

Prevention of Re-Bleeding

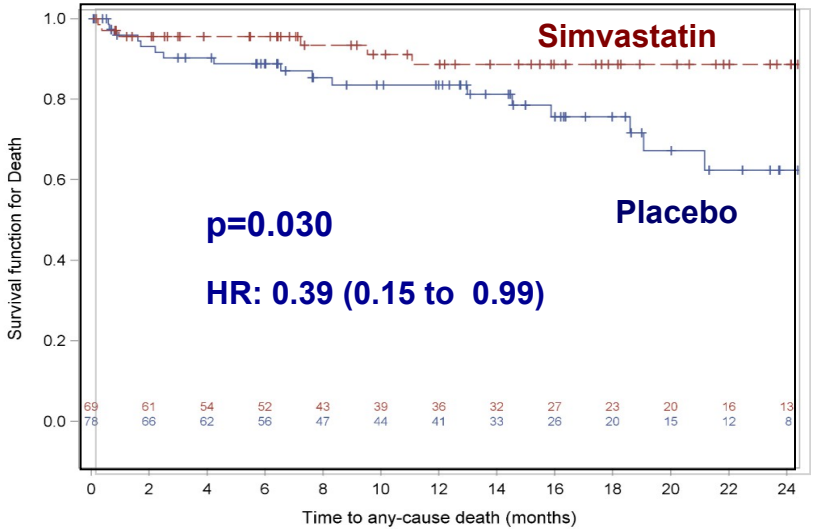
- First line therapy is the combination of NSBB **+** EBL.
  NSBB should be used as monotherapy in patients who are unable or unwilling to be treated with EBL.
- Covered TIPS is the treatment of choice in patients that fail first line therapy.
- Because carvedilol has not been compared to current standard of care (NSBB + EBL), its use cannot be recommended in the prevention of rebleeding.

de Franchis R and Baveno VI Faculty. J Hepatol 2015

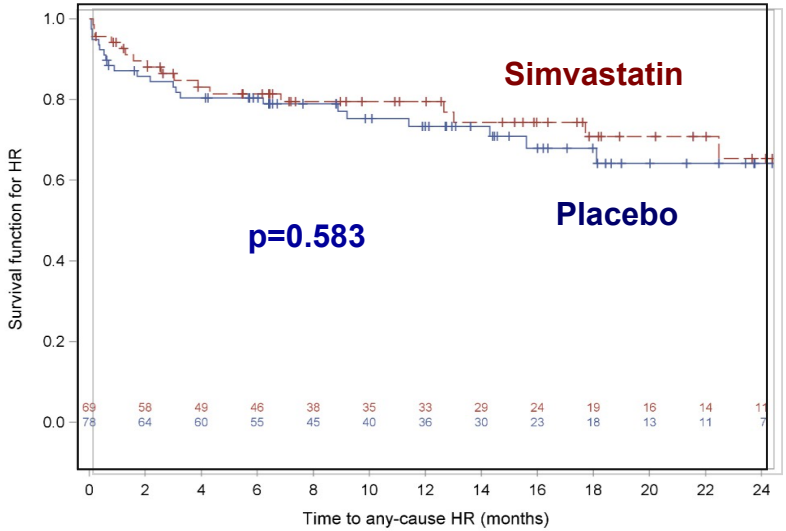
New !

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

Death*



Rebleeding



* less deaths due to bleeding and infections

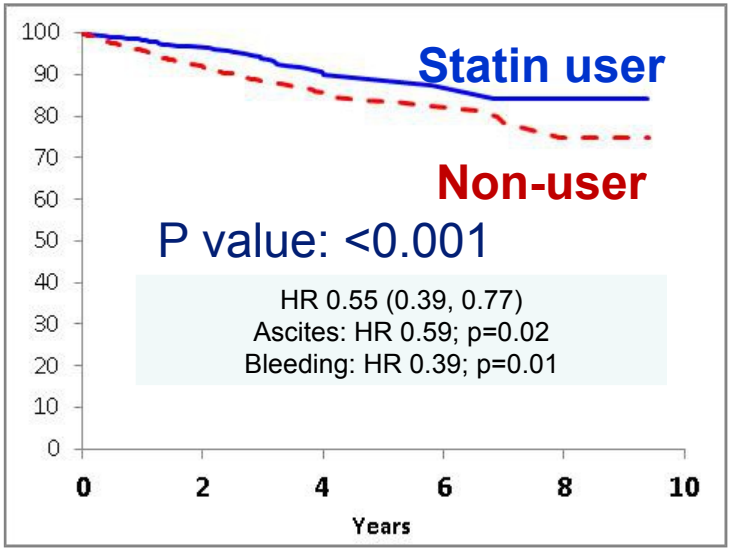
Abraldes et al. Gastroenterology 2016

Simvastatin prevents **ACLF** in cirrhotic rats (Tripathi et al, Gastroenterology 2018)
Simvastatin protects the liver from **LPS** induced injury (LaMura et al, Hepatology 2013)
Simvastatin protects the cirrhotic liver during **acute bleeding** (Meireles et al, Shock 2016)

New!

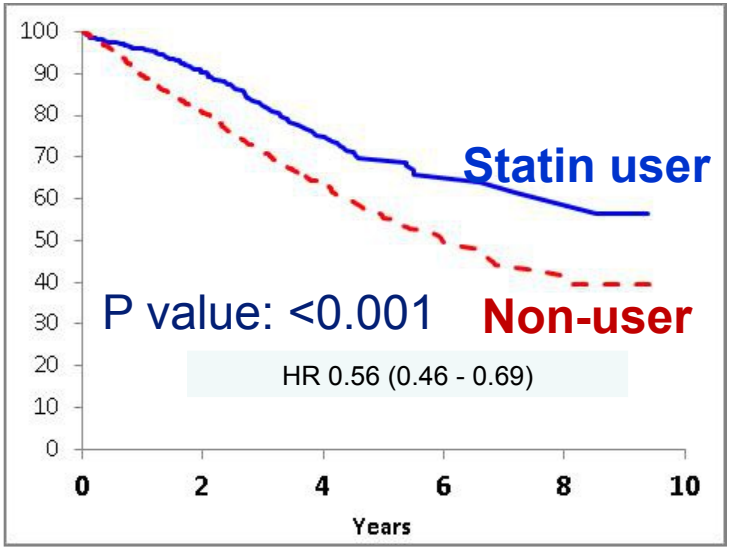
Statins are associated with a decreased risk of decompensation and death in compensated HCV cirrhosis*

Decompensation



No. at risk					
User	685	386	154	48	13
Nonuser	2062	924	333	92	22

Death



No. at risk					
User	685	399	165	53	17
Nonuser	2062	991	370	107	27

*Propensity score matched study

Mohanty et al. Gastroenterology 2016

Optimal Management of Portal Hypertension

- Pre-primary prophylaxis
- Prevention of the first bleeding episode
- Treatment of acute bleeding
- Prevention of recurrent bleeding
- **Issues with β-blockers**

Areas of controversy on the NSBB use

— Refractory ascites

— Decompensated cirrhosis

Areas of controversy on the NSBB use

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— Decompensated cirrhosis

Patients with Refractory Ascites treated with NSBB

No. Patients: 174

Statistics: Competing risk

Diuretic-intractable: 119 (68%)

Diuretic-resistant: 55 (32%)

NSBB → 89 (51%)

Sersté et al. J Hepatol 2012;57:274-80

Independent Predictors of Death in 174 Patients with Refractory Ascites

Variable	SHR*	95% CI	*P* value
NSBB therapy	2.04	1.31 to 3.18	0.0016
Child-Pugh Score	1.43	1.28 to 1.60	<0.0001
Serum sodium <125 mmol/L	2.11	1.34 to 3.34	0.001
Serum creatinine > 1.5 mg/dL	1.46	0.92 to 2.29	0.1
Frequency of paracentesis	1.42	1.25 to 1.61	<0.0001

SHR, subdistribution hazard ratio.

Sersté et al. J Hepatol 2012;57:274-80

Patients with Refractory Ascites treated with NSBB

- NSBBs' deleterious effects may be related to the development of paracentesis-induced circulatory dysfunction (PICD).
- Patients with RA receiving NSBB should be shifted to EBL.

Sersté et al. J Hepatol 2011;55 :794-9.

Areas of controversy on the NSBB use

— Refractory ascites

— Decompensated cirrhosis

8-Year Outcomes After a 1st Bleeding According to the Hemodynamic Response to Propranolol*

Outcome	Responders (N=28)	Nonresponders (N=45)
	Probability at 8-yr (%)	
No rebleeding	72	43**
No ascites recurrence	70	42**
No SBP	94	58**

Traditional definition.P<0.05.*

Abraldes et al. Hepatology 2003;37:902.

Non-selective betablocker therapy decreases intestinal permeability and serum levels of LBP and IL-6 in patients with cirrhosis

Journal of Hepatology **2013** vol. 58 | 911–921

Thomas Reiberger[1,*], Arnulf Ferlitsch[1], Berit A. Payer[1], Mattias Mandorfer[1], Birgit B. Heinisch[1], Hubert Hayden[1], Frank Lammert[2], Michael Trauner[1], Markus Peck-Radosavljevic[1], Harald Vogelsang[1], Vienna Hepatic Hemodynamic Lab

[1]*Div. of Gastroenterology & Hepatology, Dept. of Internal Medicine III, Medical University of Vienna, Austria;*
[2]*Dept. of Medicine II, Saarland University Medical Center, Homburg, Germany*

NSBBs can be used in decompensated patients who do not fulfill the criteria for refractory ascites

Take home messages

- Cirrhosis should be managed in two distinct clinical stages, compensated and decompensated, defined by the presence or absence of clinical complications (ascites, VH, and HE).

- The identification of patients with cirrhosis and clinically significant portal hypertension (CSPH) is mandatory. Non invasive tests will be of great help as diagnostic tool.

- In patients with cirrhosis and CSPH but without varices, the objective of treatment should no longer be to prevent varices, but to prevent clinical decompensation. New data concerning therapy related to this issue is being generated...

Take home messages

- In patients with compensated HCV cirrhosis, it has been shown that statins lower the incidence of decompensation (ascites and VH) and lower mortality. Therefore, they might become an additional tool in the management of these patients.

- After an episode of acute variceal bleeding, in patients at high risk of failure or rebleeding (CTP class C cirrhosis or CTP class B with active bleeding), an “early” (pre- emptive) TIPS may benefit selected patients.

- NSBB should not be used in patients with refractory ascites but they can benefit patients with ”non-refractory” ascites.

The Father of Non-Selective β–Blocker (NSBB) Therapy in Portal Hypertension

Didier Lebrec

The Father (big brother…) of this Speaker on the Optimal Therapy in Portal Hypertension

Richard Moreau

HOSPITAL ITALIANO
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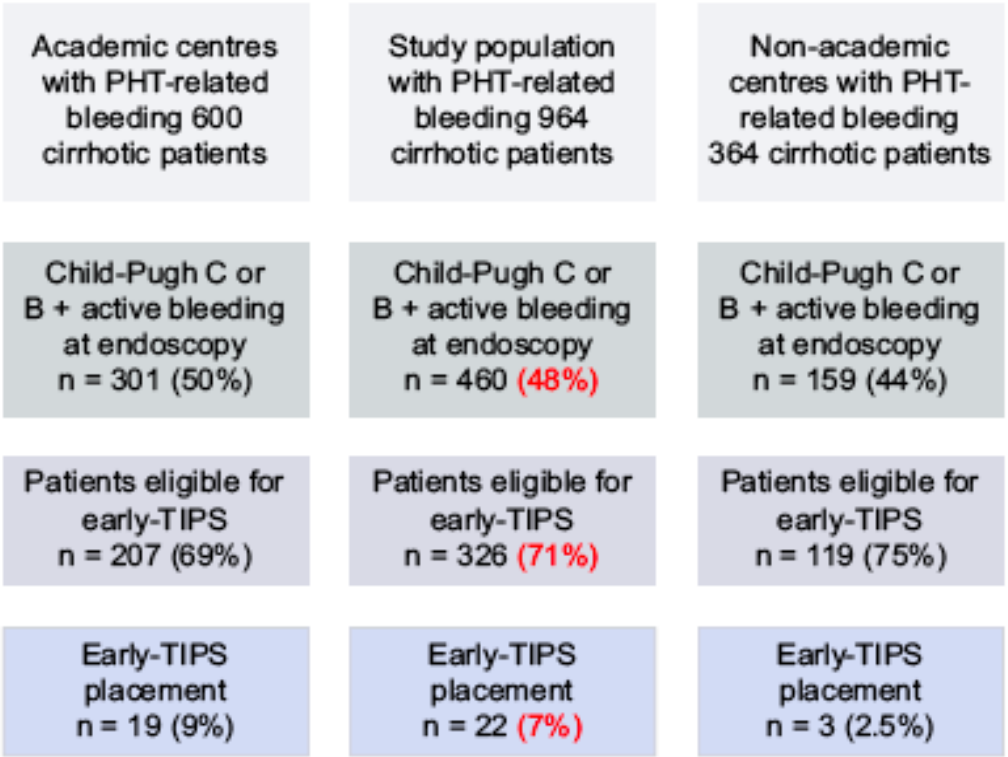
Sección Hepatología

- Sebastián Marciano
- Omar Galdame
- Juan Carlos Bandi
- Alejandra Villamil
- Paola Casciato
- Joaquín Solari
- Leila Haddad
- Ezequiel Mauro
- Carla Bermúdez
- Fabiola Moreno

Thank you !!!!

In practice: CHOC French observatory



Thabut D, et al. J Hepatol 2017