Portal Hypertension: 2020 Update

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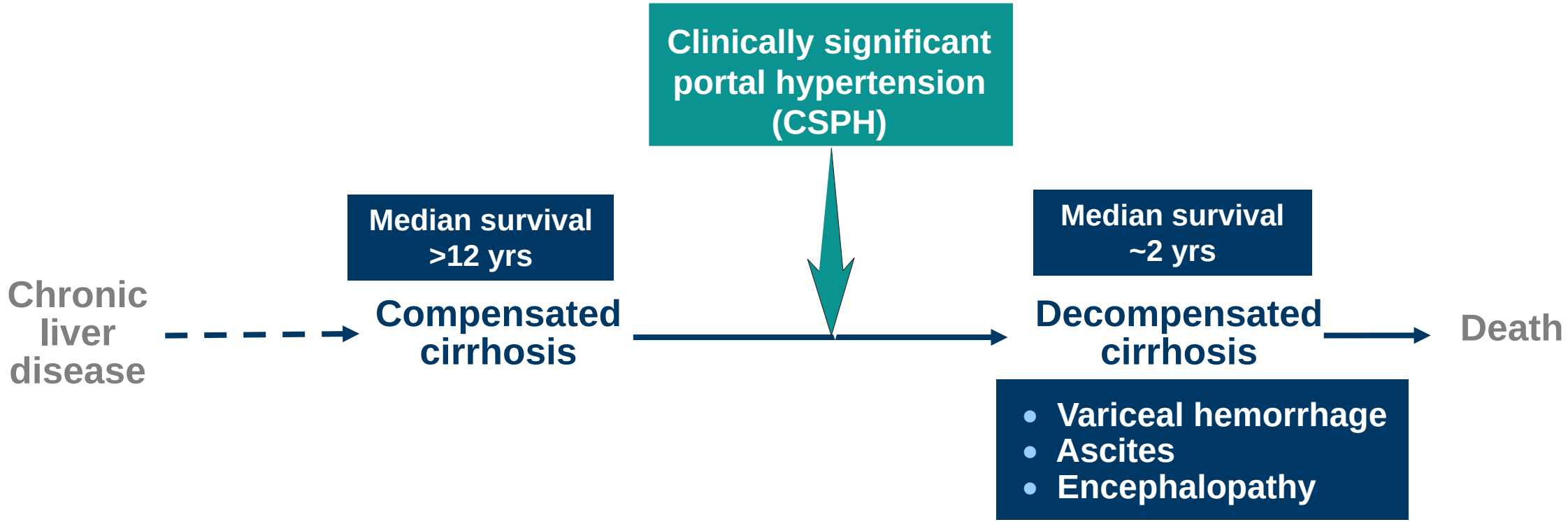
I have no disclosures to make relative to my presentation

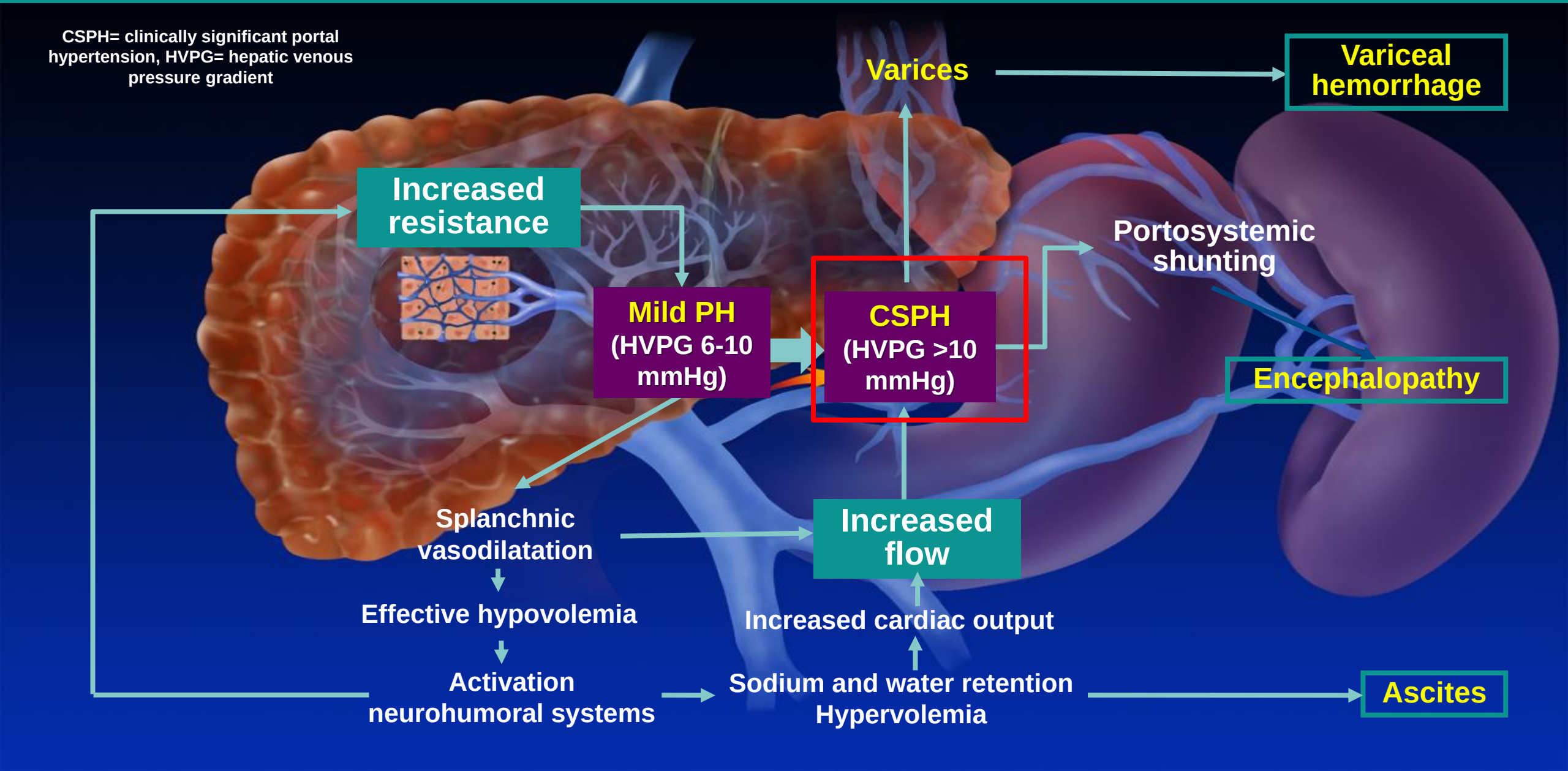
Cirrhosis has two main stages (compensated and decompensated) with CSPH being the main driver of decompensation



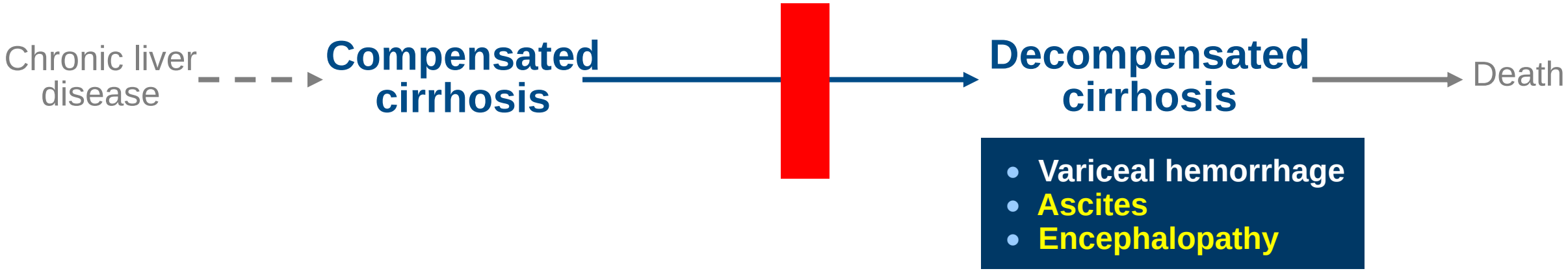
Defined as a hepatic venous pressure gradient (HVPG) ≥ 10 mmHg

Ripoll et al. Gastroenterology 2007; 133:481.

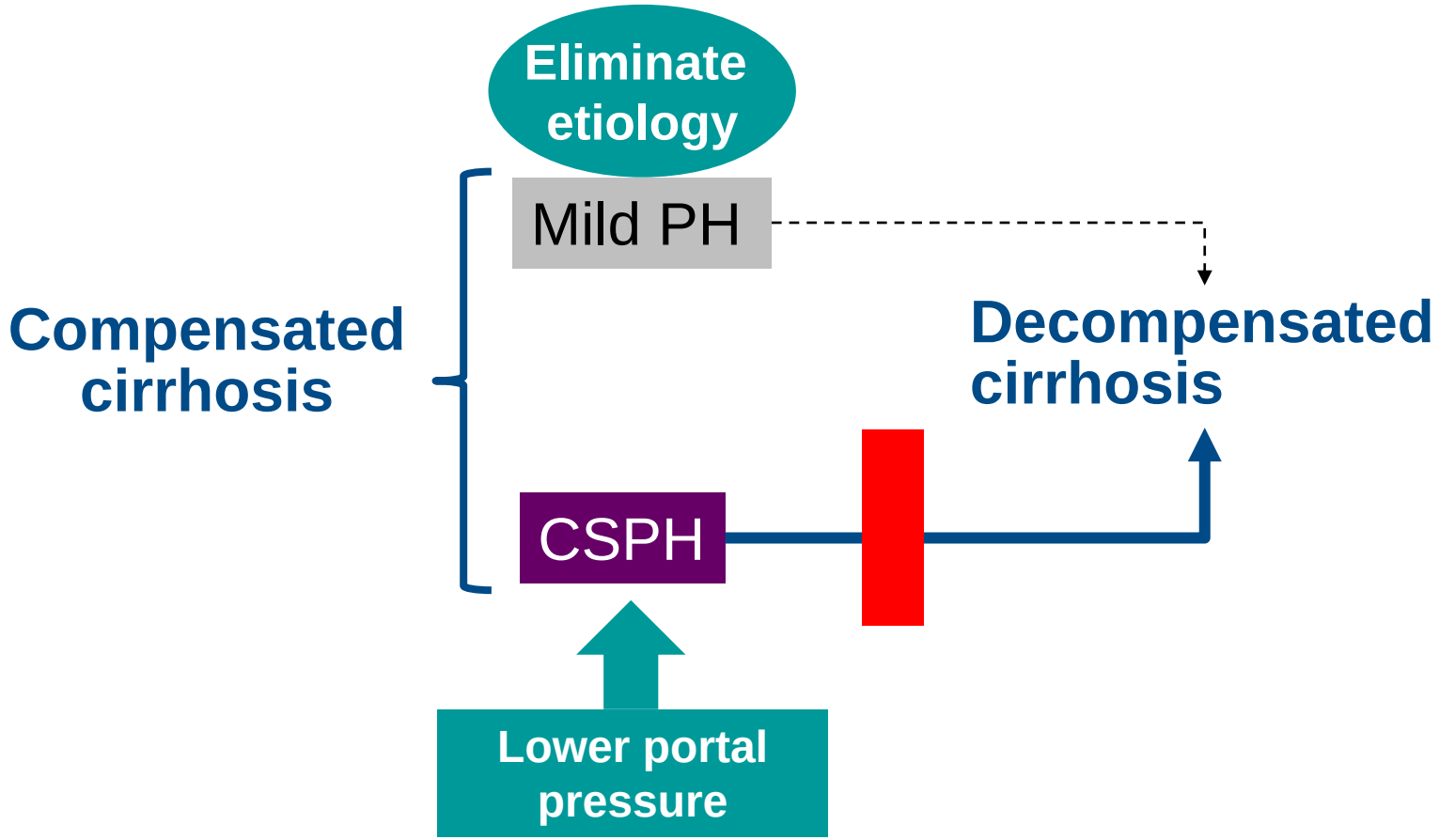
CSPH is the main driver of decompensation and results from increased intrahepatic resistance and increased portal venous inflow



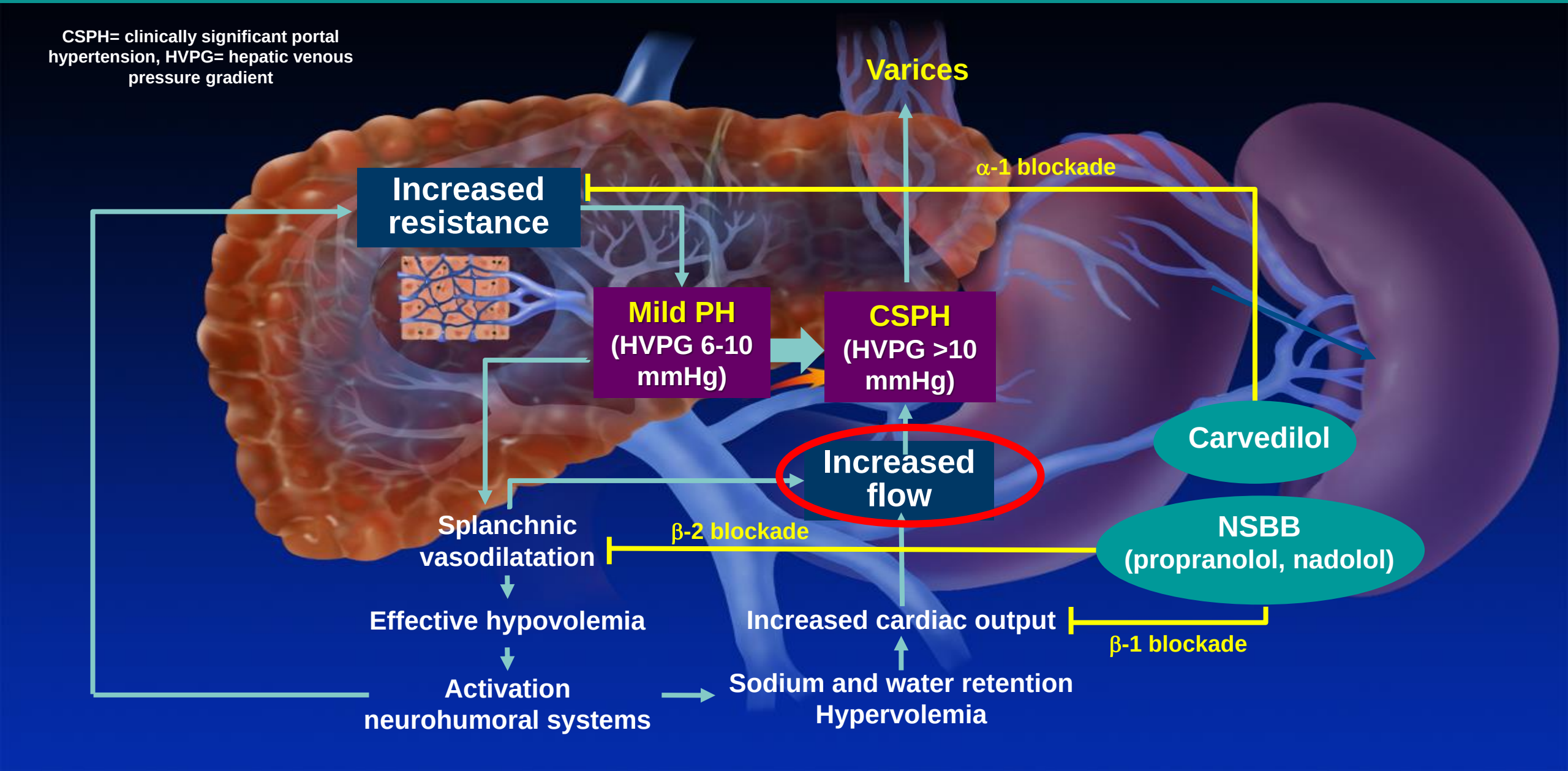
The main objective of treatment in compensated cirrhosis is to prevent decompensation



Among patients with compensated cirrhosis, the target population is constituted by those with CSPH

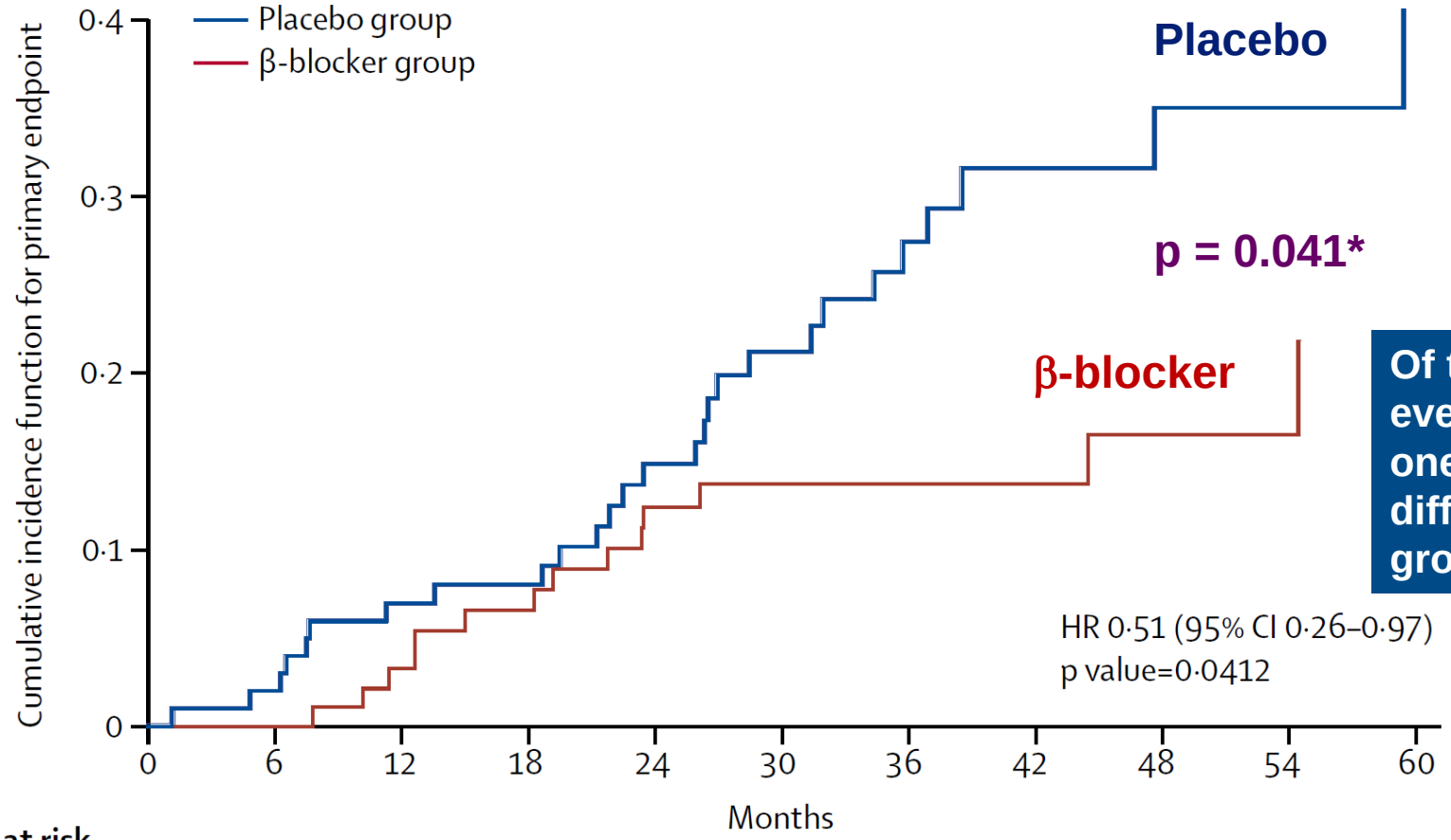


NSBB are the mainstay in the treatment of portal hypertension and act by decreasing portal venous inflow



In a RCT, β-blockers prevented decompensation and/or death in patients with compensated cirrhosis and CSPH (no or small varices)

Probability of developing any decompensating event / death



Of the 3 decompensating events, ascites was the only one that was significantly different between study groups (9% vs. 20%)

*competing risk analysis (non-liver related deaths were competing events)

Villanueva et al (PREDESCI trial). Lancet 2019 20;393:1597-1608

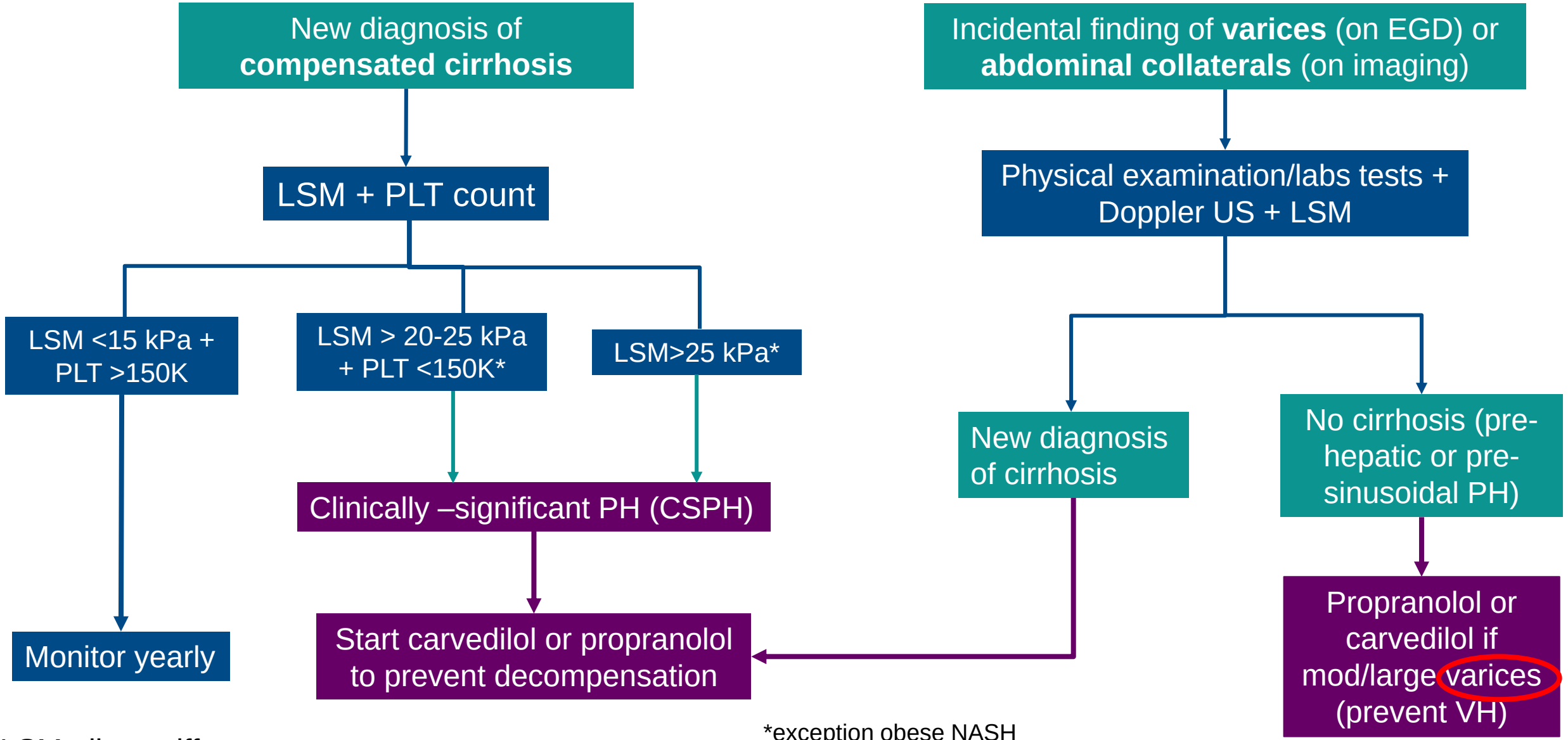
In post-hoc analysis, carvedilol seemed to outperform propranolol

	Propranolol	Carvedilol
Decompensation/death	**19%** (vs. 26% in placebo)	**9%** (vs. 27% in placebo)
Ascites (hazard ratio)	**0.50** [0.22-1.18]	**0.22** [0.02-1.94]
Death (hazard ratio)	**0.94** [0.31-2.78]	**0.44** [0.08-2.43]
% decrease in HVPG at 12 months	**10%**	**16%**
% decrease in HVPG at 24 months	**9%**	**15%**

- Propranolol dose 40-160 mg twice a day
- Carvedilol dose 6.25 to 25 mg once a day
- Dose titrated to maximal clinical tolerance, keeping heart rate above 55 beats/minute and systolic blood pressure > 90 mm Hg

Villanueva et al (PREDESCI trial). Lancet 2019 20;393:1597-1608

Diagnostic/management strategy in patients with new diagnosis of cirrhosis or portal hypertension

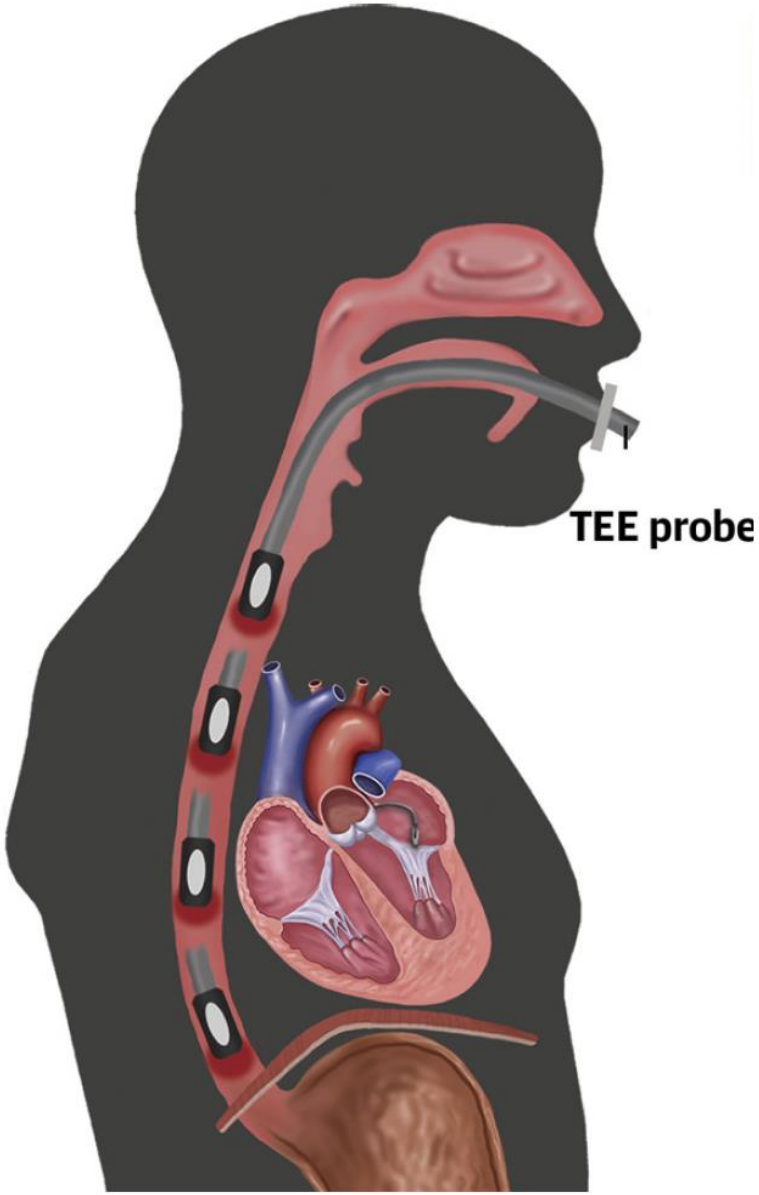


*exception obese NASH

LSM= liver stiffness

*Baveno VI. J Hepatol 2015;63:743; Abraldes et al. Hepatology. 2017;65:2131; *Pons et al. NASH-ANTICIPATE. Am J Gastro 2020 [Epub]*

Is the presence of esophageal varices a risk for bleeding during the performance of transesophageal echocardiography (TEE)?



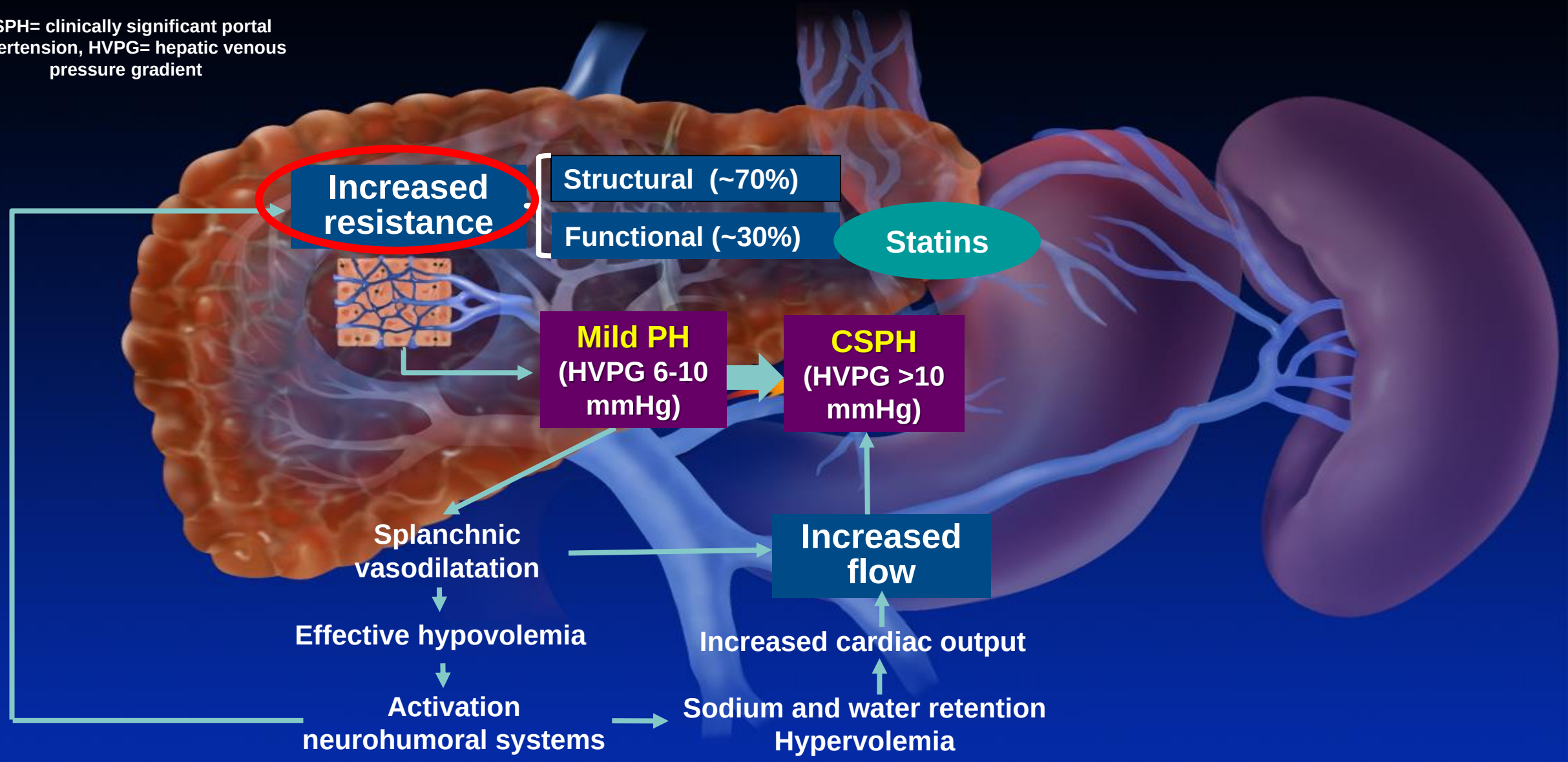
- 191 patients with cirrhosis underwent TEE
  - 79 (41%) had varices: 55 small, 24 were large
- **No patient experienced gastrointestinal bleeding within 48 hours of TEE**
- The likelihood of a 2 g/dL decline in hemoglobin or blood transfusion was not increased in patients with vs. those without esophageal varices (OR 1.49 [0.74-3.00])

- In patients with cirrhosis:
  - Performing endoscopy prior to TEE is not warranted
  - The presence of varices is not a contraindication to TEE

Sack et al. AASLD 2020

Statins decrease portal pressure by decreasing intrahepatic resistance

CSPH= clinically significant portal hypertension, HVPG= hepatic venous pressure gradient



Proof of concept study of simvastatin in patients with clinically- significant portal hypertension

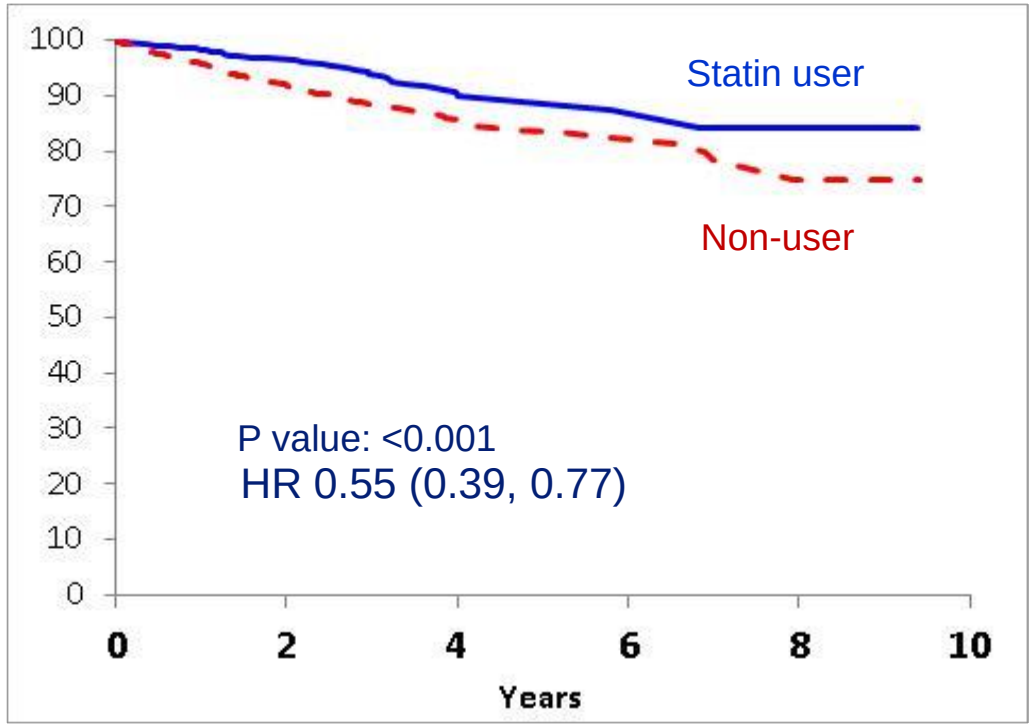
	Placebo (n=29)			Simvastatin (20 →40mg/day) (n=30)		
	Baseline	4 wks	p	Baseline	4 wks	p
HVPG (mmHg)	19.8 ± 3.8	19.4 ± 4.4	0.473	18.5±7.2	17.1 ± 4.6	0.003
HBF (L/min)	939 ± 458	830 ± 339	0.109	1124±548	1216 ± 676	0.440
ICG clearance	237 ± 148	222 ± 129	0.436	221±104	276 ± 182	.017
MAP (mmHg)	90 ± 9	86 ± 9	0.013	86 ± 15	86 ± 14	0.982

HBF= hepatic blood flow
ICG = indocyanine green
MAP= mean arterial pressure

Abraldes, Albillos et al. Gastroenterology 2009;136:1651-8.

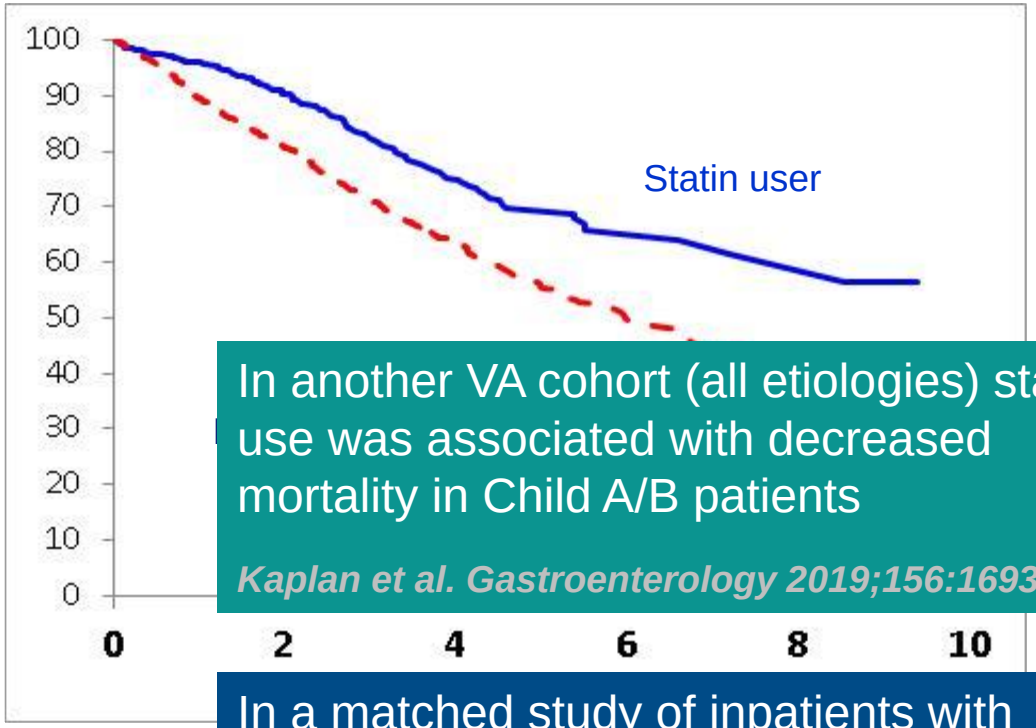
Statins are associated with a decreased risk of decompensation and death in HCV compensated cirrhosis*

Free of decompensation



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

Free of death



No. at risk		
User	685	
Nonusr	2062	

In another VA cohort (all etiologies) statin use was associated with decreased mortality in Child A/B patients

Kaplan et al. Gastroenterology 2019;156:1693-1706

In a matched study of inpatients with advanced cirrhosis (mean bilirubin >3 mg/dl), those on statins at admission (n=221) had poorer outcomes, including a greater in-hospital mortality (10% vs 5%)

Garcia-Tsao for NACSELD. AASLD 2020

Mohanty, Tate and Garcia-Tsao. Gastroenterology. 2016;151:374

Variceal hemorrhage is an episodic but deadly complication of cirrhosis

Management of variceal hemorrhage – Standard of Care (SOC)

- Cautious PRBC transfusion: start at 7 g/dL, maintain at 7-9 g/dL
- Short term (maximum 7 days) antibiotic prophylaxis (ceftriaxone 1 g/d)
- Safe IV vasoactive drug (octreotide, somatostatin, terlipressin)

↓

Endoscopy (within 12 hours): VH confirmed

↓

Perform endoscopic therapy (EVL)

↓

Continue IV vasoactive drug (2-5 days)

- **No bleed** → **D/C IV drug, start NSBB**
- **Rebleed** → **Rescue TIPS**

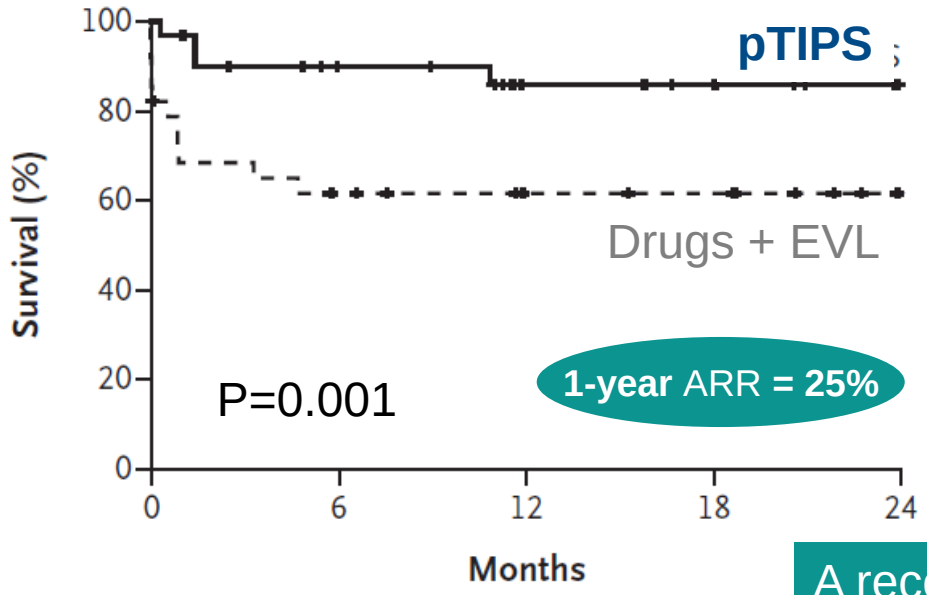
Child C patients are the most likely to fail

Abraldes, J Hepatol 2008
Amitrano, AJG 2012

In Child C (10-13 points) and in selected Child B with acute variceal hemorrhage, pre-emptive TIPS (pTIPS) placed within 72 hours of admission improves survival

50% 50%

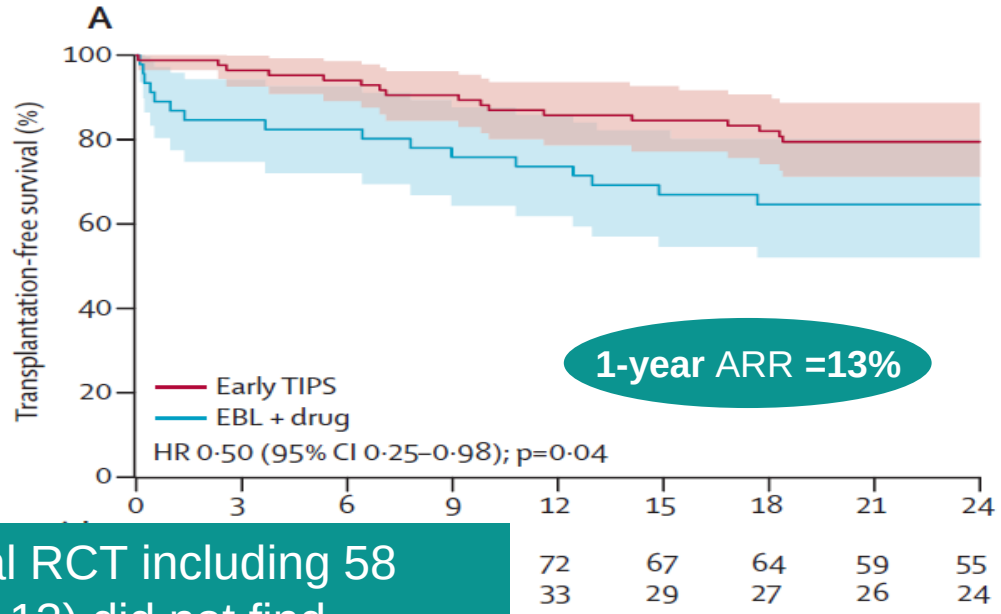
Child C 10-13 + Child B with active bleeding at endoscopy



1-year ARR **= 25%**

22% 21% 57%

Child C (10-13) + Child B with or without active bleeding at endoscopy



1-year ARR **=13%**

A recent additional RCT including 58 patients (B8, C10-13) did not find differences in survival and encountered problems regarding feasibility of pTIPS within the timeframe

Dunne et al. Aliment Pharmacol Ther. 2020;52:98–106

Mostly EtoH/HCV cirrhosis

BV cirrhosis

García-Pagán et al. N Engl J Med 2010; 24:2370-9.

erol Hepatol 2019:587-598

ARR = absolute risk reduction

Management of variceal hemorrhage

- Cautious PRBC transfusion: start at 7 g/dL, maintain at 7-9 g/dL
- Short term (maximum 7 days) antibiotic prophylaxis (ceftriaxone 1 g/d)
- Safe IV vasoactive drug (octreotide, somatostatin, terlipressin)

↓

Endoscopy (within 12 hours): VH confirmed

↓

Perform endoscopic therapy (EVL)

Not pTIPS candidate

- Child A
- Child B7
- Child C 14-15

↓

Continue IV vasoactive drug (2-5 days)

No bleed → **D/C IV drug, start NSBB**

Rebleed → **Rescue TIPS**

pTIPS candidate

↓

pTIPS (placed within 72 hours, i.e. "early")

- Child C (10-13 pts) *Nicoara-Farcau et al. Gastro 2020*
- Child B:
  - score >7 + active bleeding at endoscopy
    Nicoara-Farcau et al. Gastro 2020 [Epub]; Lv et al ILC 2020
  - modified CLIF-AD score >48
    Lv et al. ILC 2020

Patients excluded from pTIPS studies (TIPS ineligibility)

- Age >70–75 years
- Child-Pugh score >13 points
- Recurrent overt encephalopathy without precipitating factors
- Serum creatinine above 2.5-3 g/dl
- Sepsis/active infection
- Heart failure
- Pulmonary hypertension

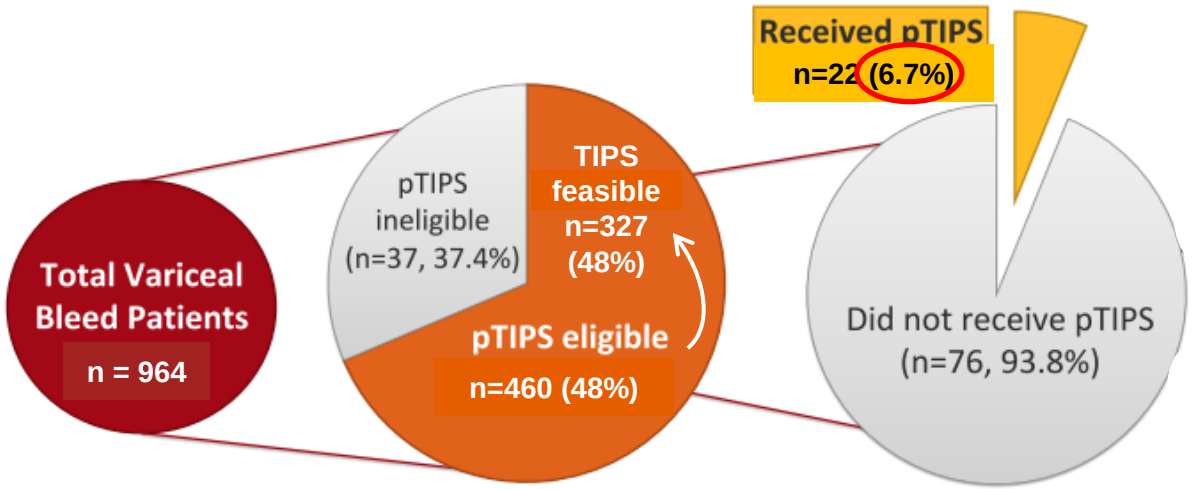
Cardiac echo

- HCC beyond Milan
- Complete PV thrombosis

Doppler US or cross-sectional imaging

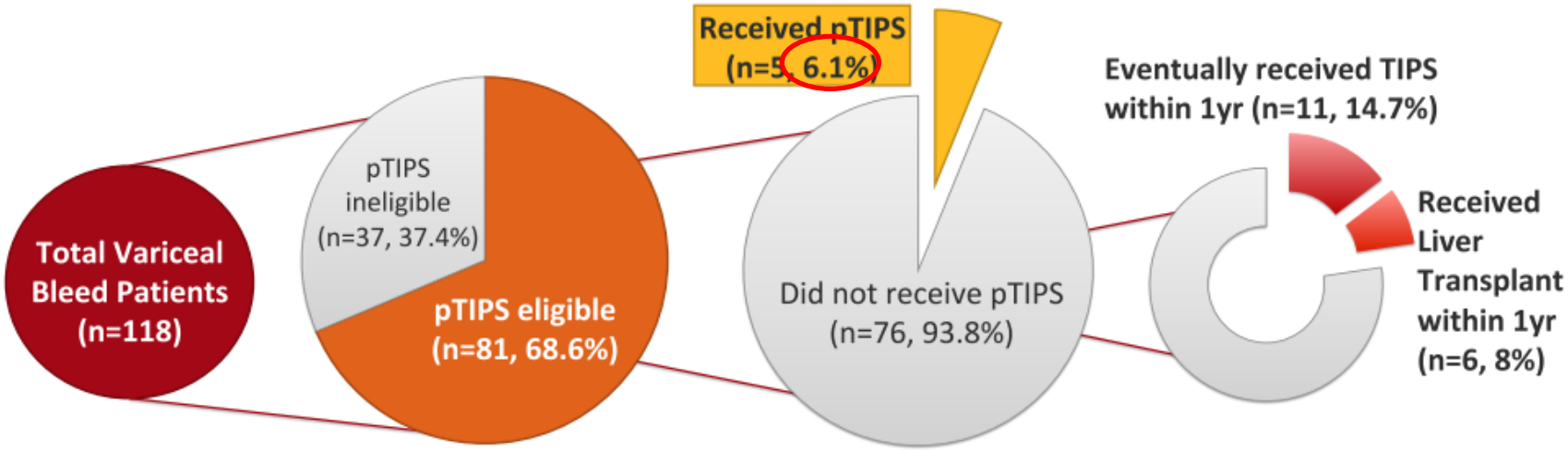
Less than 10% of patients who are candidates for pTIPS actually have the TIPS placed

Europe



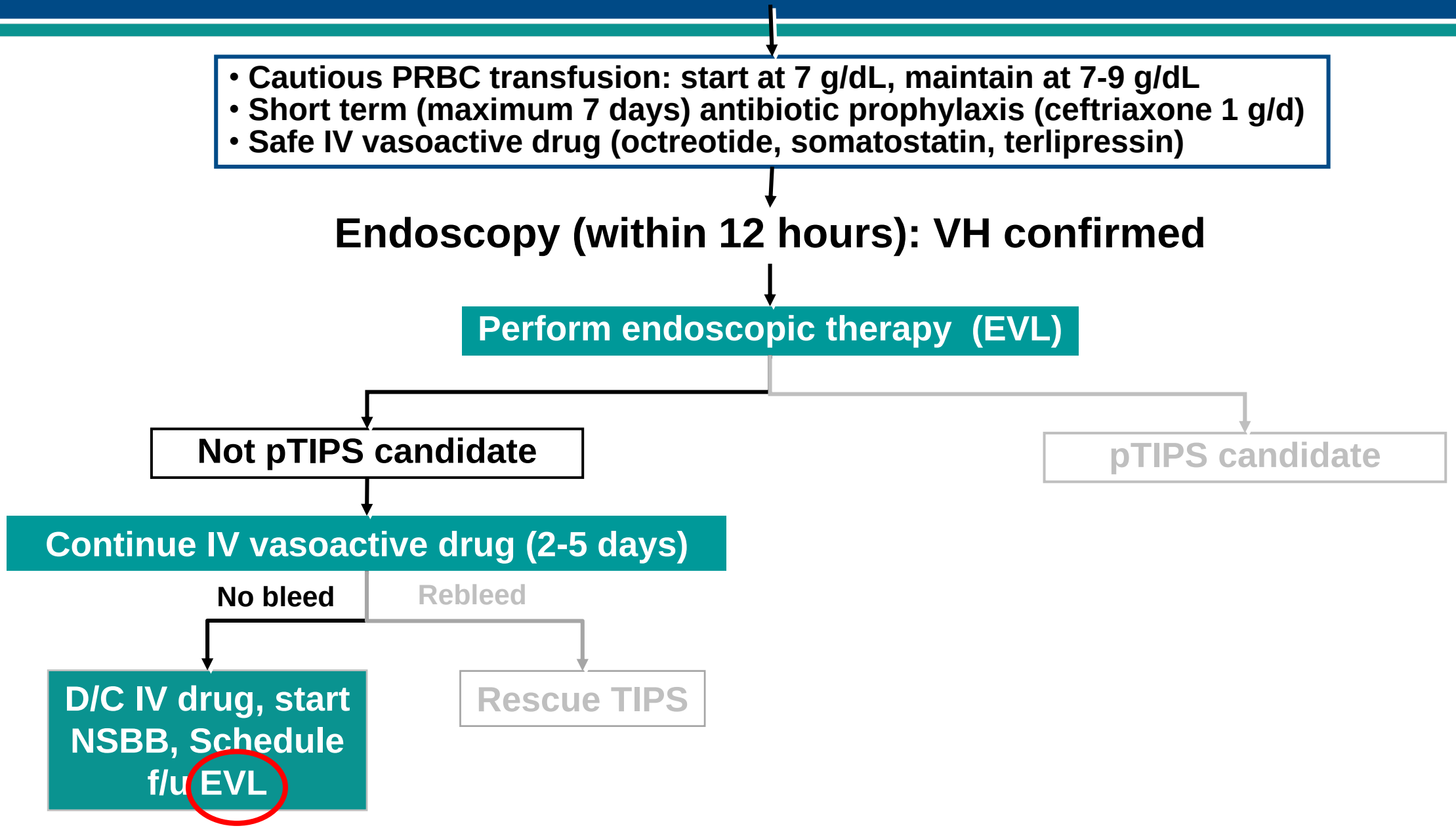
Thabut et al. J Hepatology 2017;68:73-81

U.S.A.



Wong, et al. AASLD 2020

Management of variceal hemorrhage – Standard of care (SOC)



Bleeding post endoscopic variceal ligation (EVL) is rare and is unrelated to baseline INR/platelet coung or to prior transfusion of blood products

- Multicentre retrospective analysis of consecutive EVL procedures in 536 patients (median MELD 11, Child A/B/C: 59%/33%/8%
- FFP and/or platelet transfusion administered at the discretion of the physician if **INR was >1.5** and/or **platelet count <50 x 10^9/L**

EVL procedures	**1,472**
Primary/secondary prophylaxis	51%/49%
Median number of ligations per patient (range)	2 (1−4)
Use of prophylactic transfusion protocol Procedures with high INR **and** low PT Procedures with high INR **or** low PLT	 12.5% 32.4%
Administration of FFP and/or platelets, patients (%)	**37 (7%)**
Incidence of post-EBL bleeding, n (%) **Number who met criteria for product transfusion**	**26* (1.8%)** **7 (27%)**

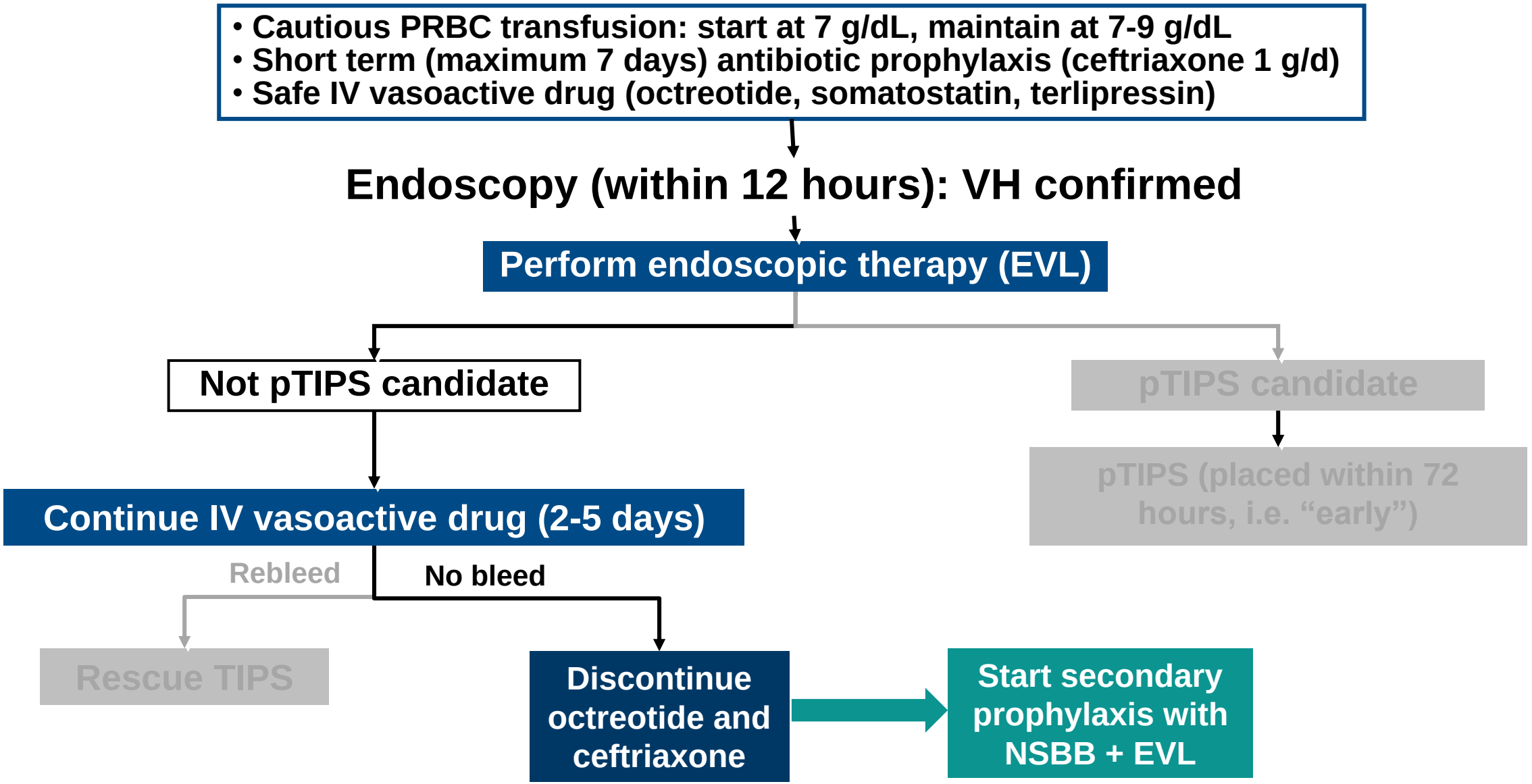
There was no association between INR/PLT and post-EBL bleeding
Bleeding associated with higher Child (p=0.03) and MELD (p=0.02)

Due to conflicting data in the literature, there is no data-driven specific INR or platelet cutoff in which procedural bleeding risk is reliably increased

AASLD 2020 Practice Guidance

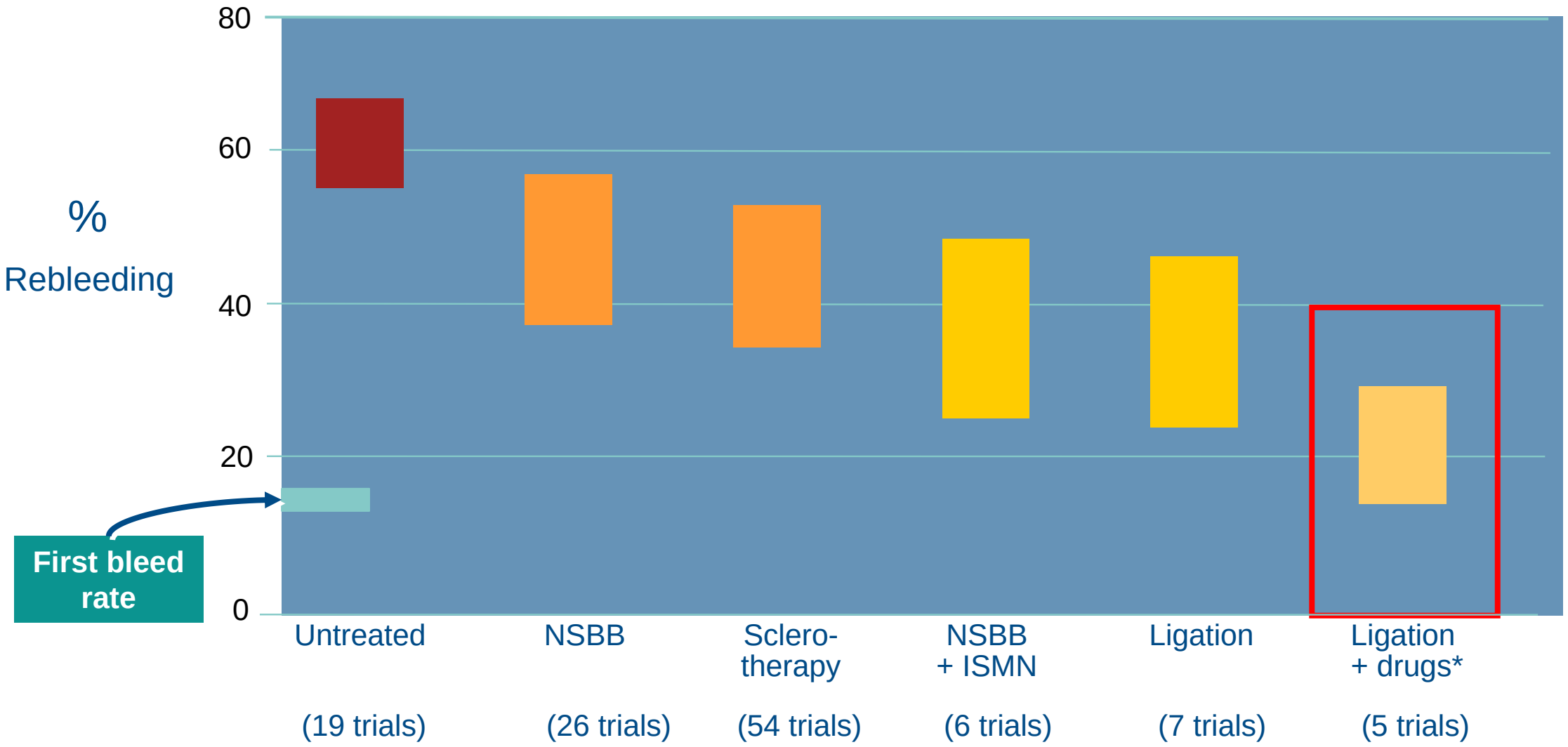
Blasi A, et al. EASL 2020

In patients who did not have TIPS placed during admission, secondary prophylaxis with NSBB and EVL is recommended to prevent rebleeding



AASLD guidance. Garcia-Tsao et al. Hepatology 2017;65:310-335

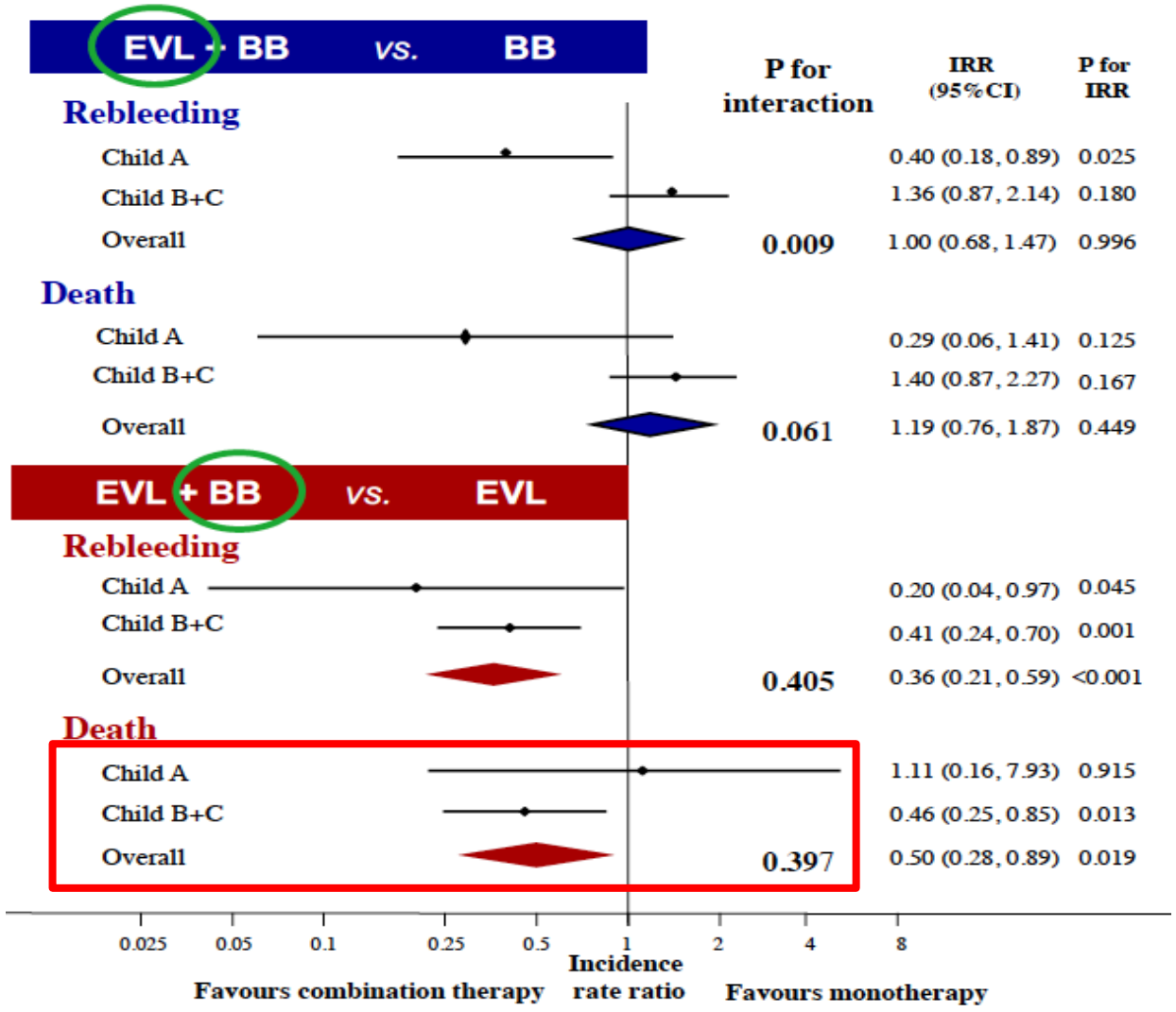
The combination of NSBB + ligation is first line therapy in the prevention of recurrent variceal hemorrhage



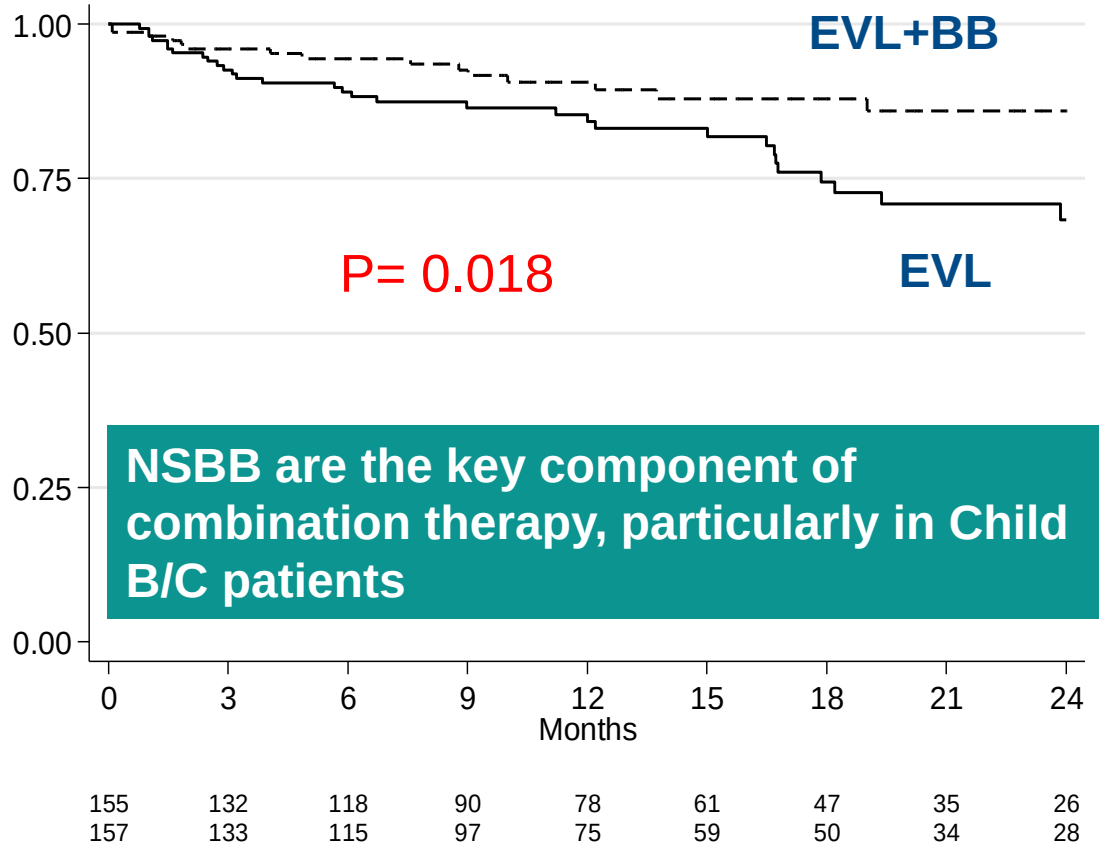
From Bosch and García-Pagán, Lancet 2003; 361:952

* non-selective β-blockers (NSBB) ± nitrates

In an individual meta-analysis, rebleeding and death were significantly lower in trials of BB+EVL vs. EVL



Child B/C patients

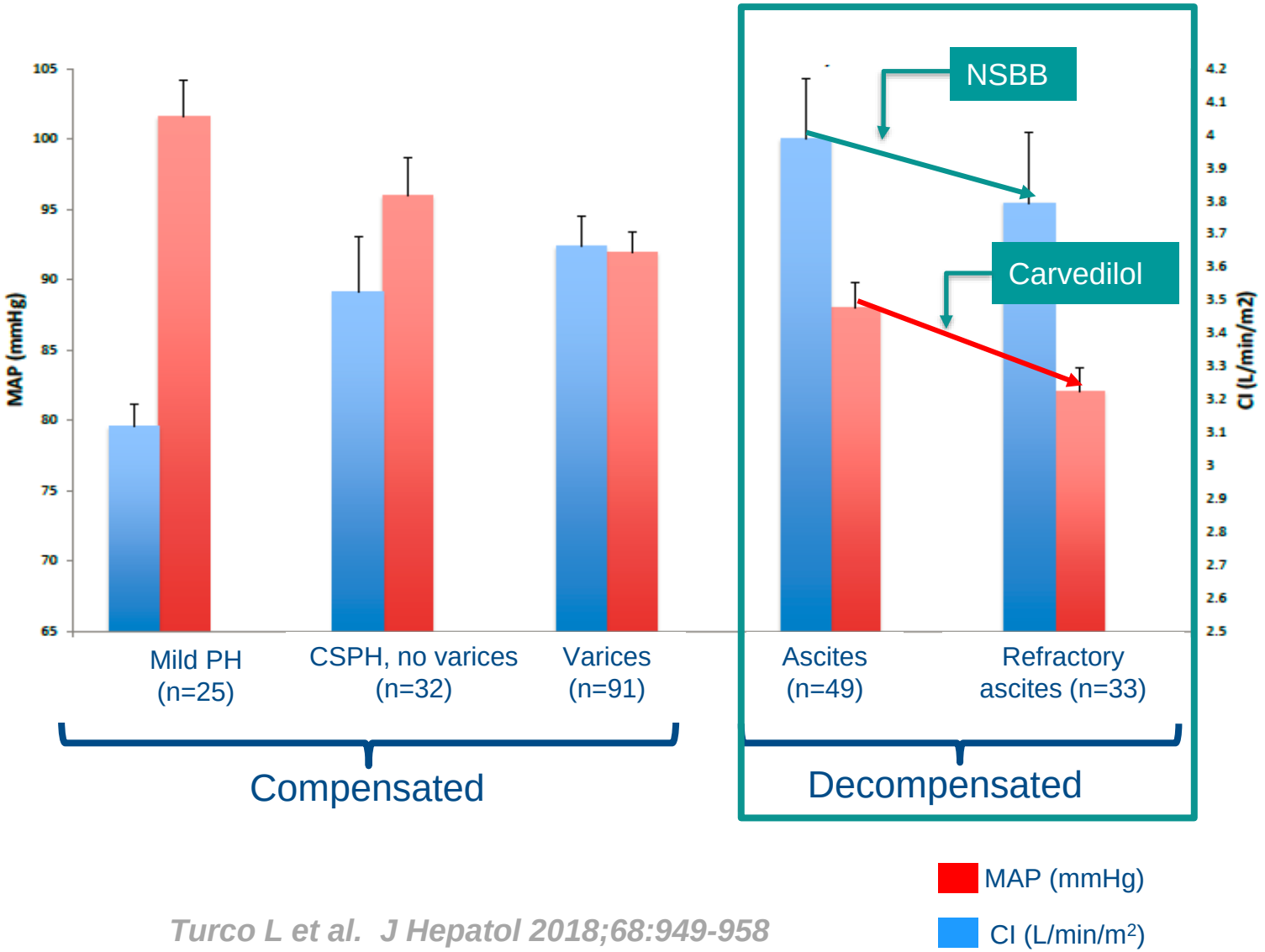


NSBB are the key component of combination therapy, particularly in Child B/C patients

Albillos et al. Hepatology; 2017: 66:1219-1231

Systemic hemodynamics are more altered in patients with refractory ascites, compared to those with treatment-responsive ascites

Two retrospective studies show that propranolol or carvedilol was associated with higher mortality in patients with ascites *(Serste et al. Hepatology 2010;52:1017)* and in those with SBP *(Mandorfer et al Gastroenterology 2014;146:1680)*

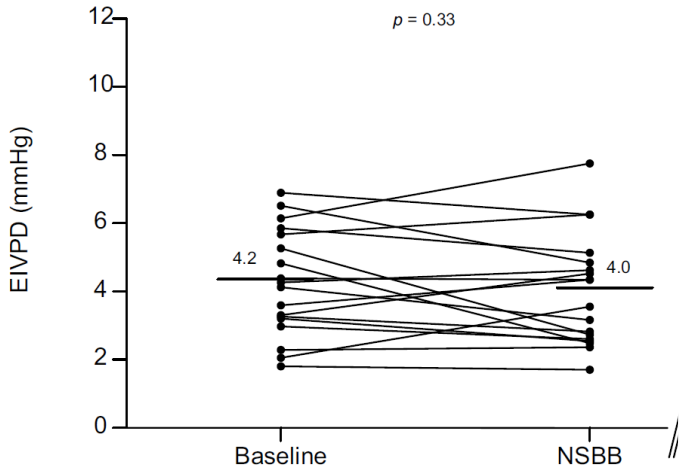


Turco L et al. J Hepatol 2018;68:949-958

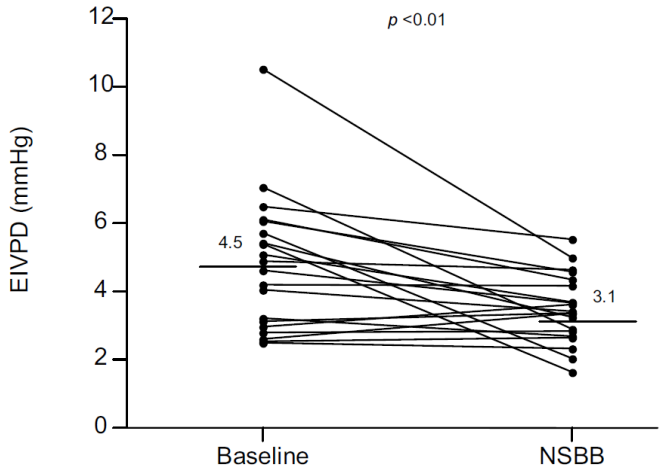
NSBBs are associated with decrease in systolic function and significant renal perfusion pressure only in patients with refractory ascites

Systolic function by ejection intraventricular pressure difference (mmHg)

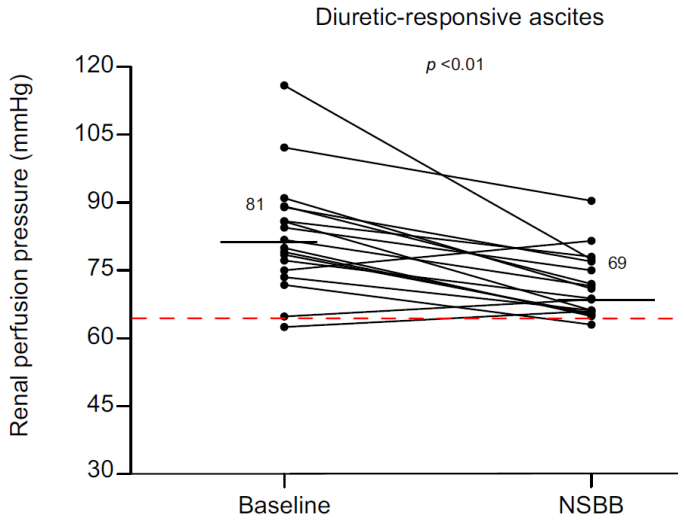
Diuretic-responsive ascites

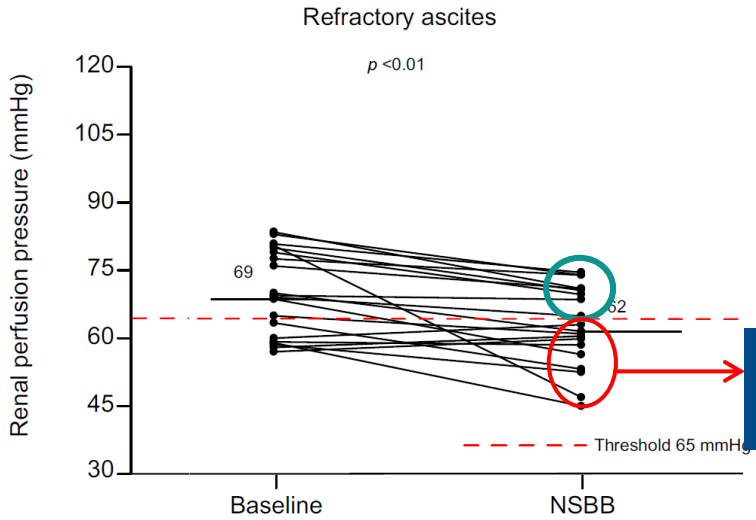


Refractory ascites



Renal perfusion pressure (mmHg)



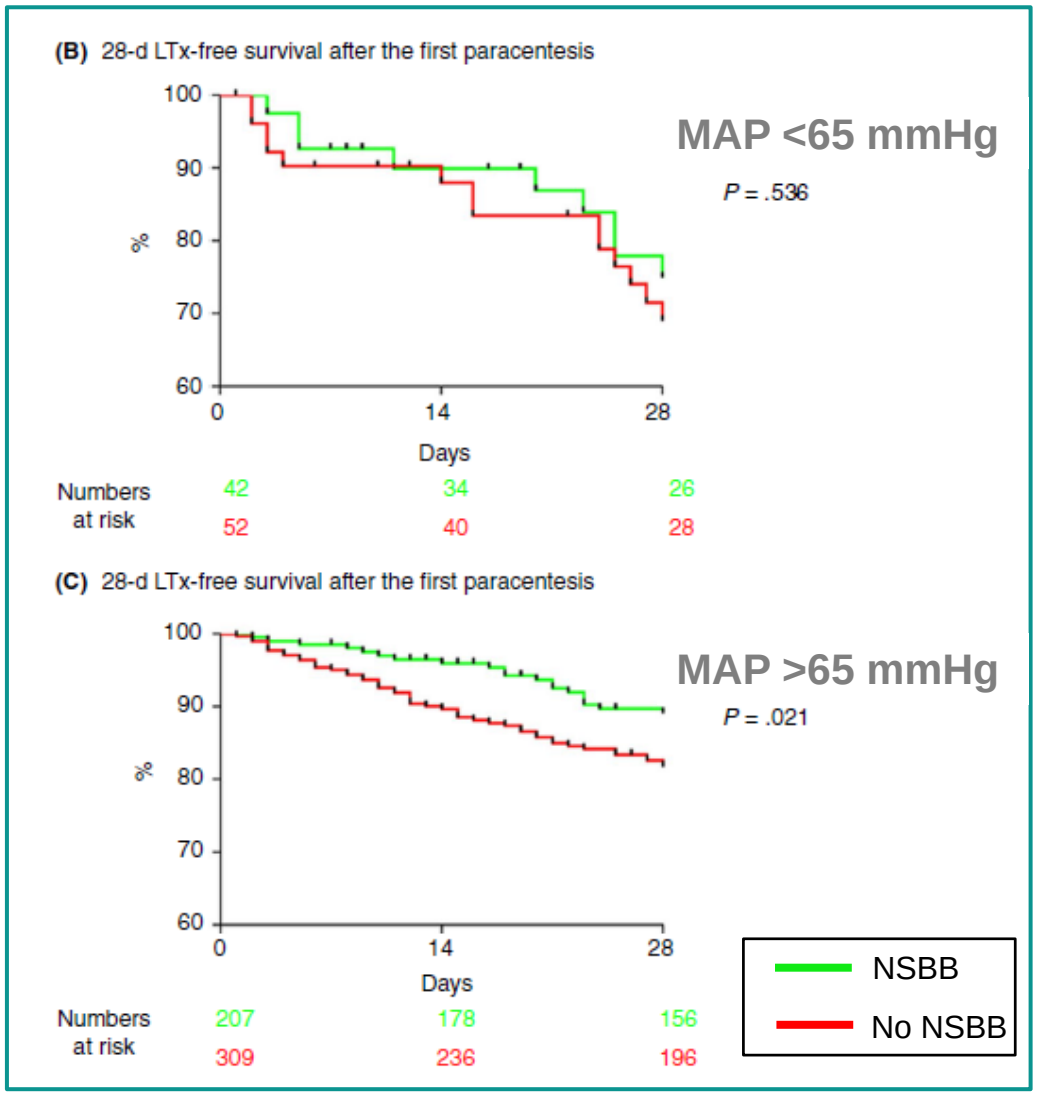


11 of the 20 (55%) pts, 4 of them with hepatorenal syndrome

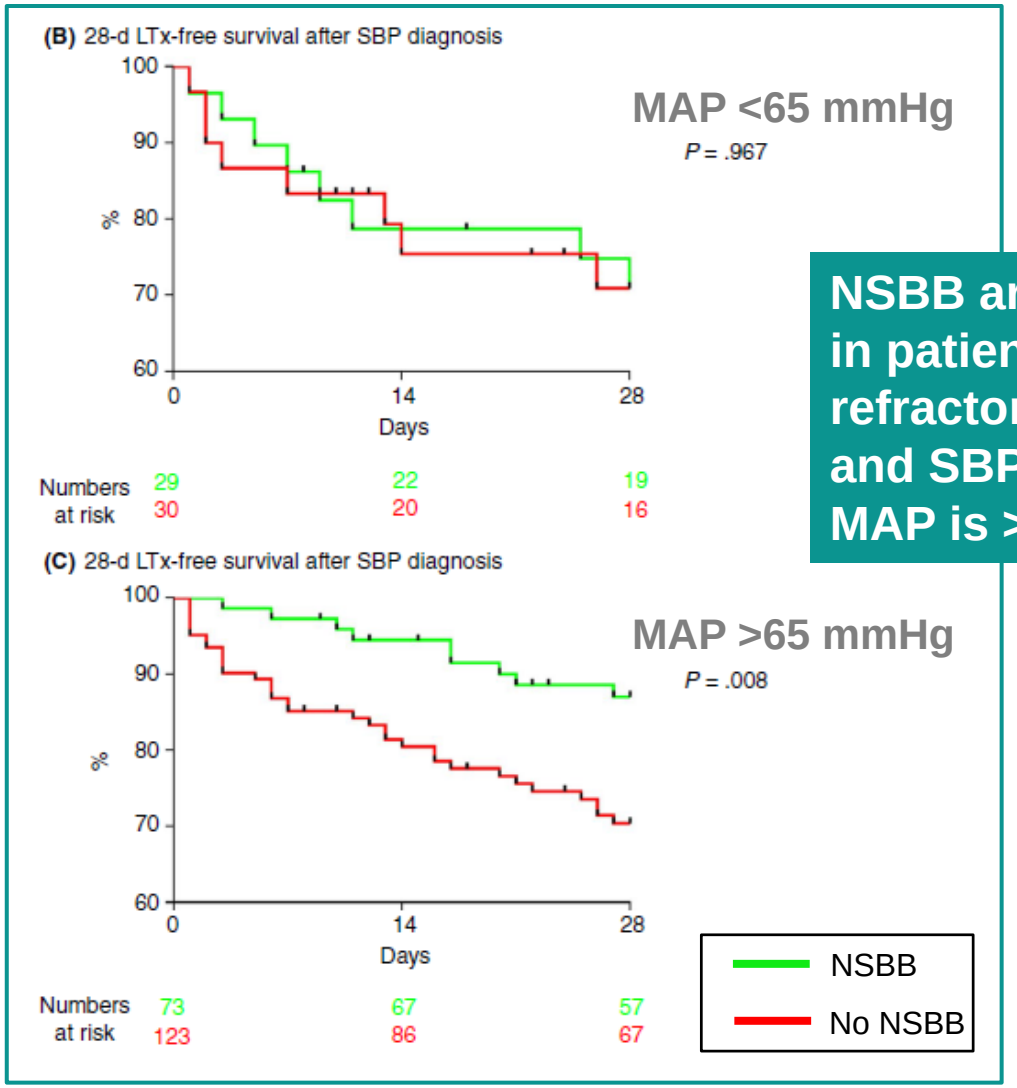
Tellez et al. J Hepatol 2020 [Epub]

Systemic arterial blood pressure determines the therapeutic window of non-selective beta-blockers (NSBB) in decompensated cirrhosis

Ascites requiring LVP



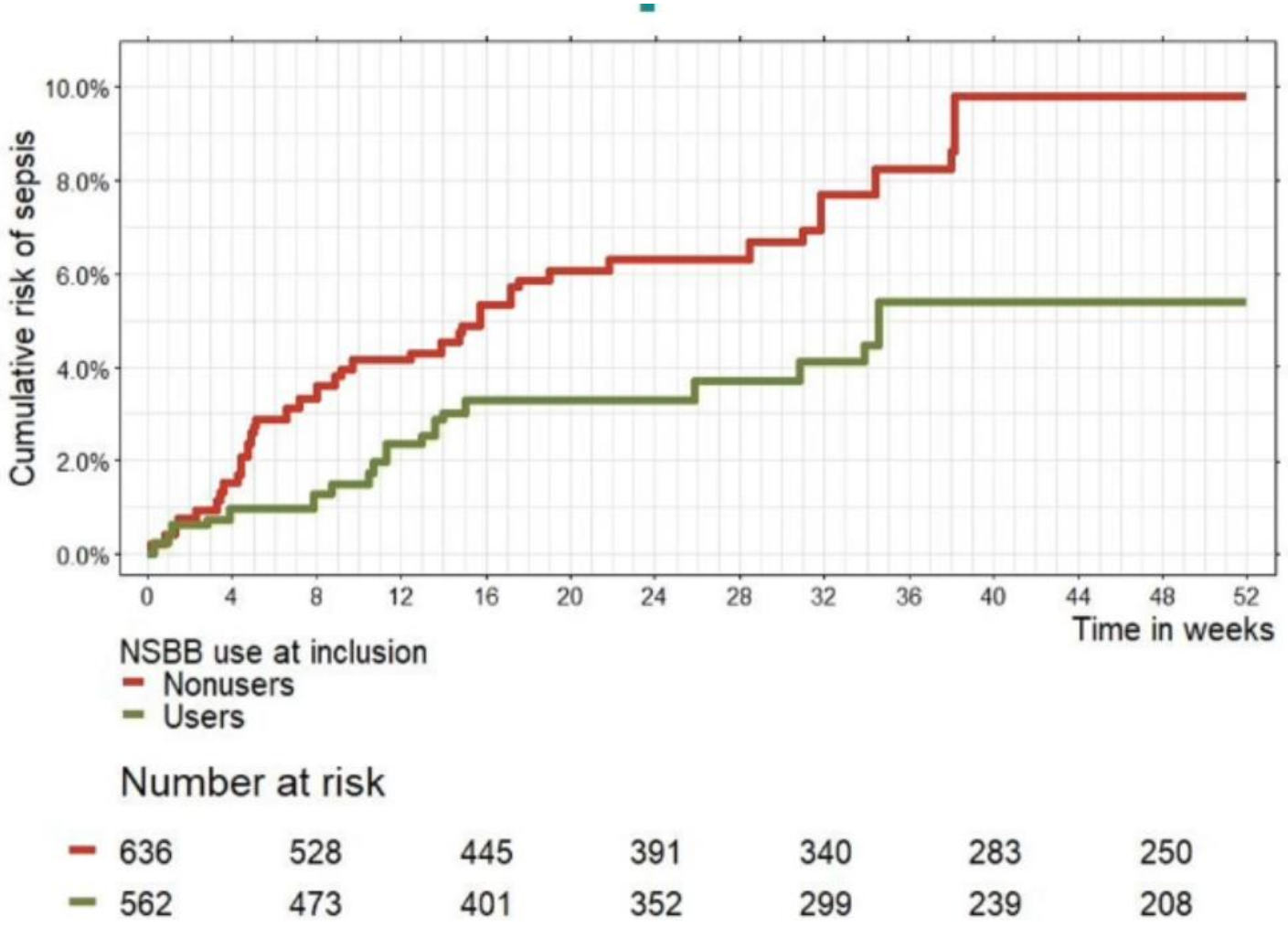
Ascites with SBP



NSBB are beneficial in patients with refractory ascites and SBP as long as MAP is >65 mmHg

Tergast et al. APT 2019;50:696–706

In a large cohort of patients with ascites (52% refractory) there was a lower risk of sepsis in NSBB users compared to non-users



9.8% (95% CI 5.9-13.5)

5.4% (95% CI 2.5-8.2)

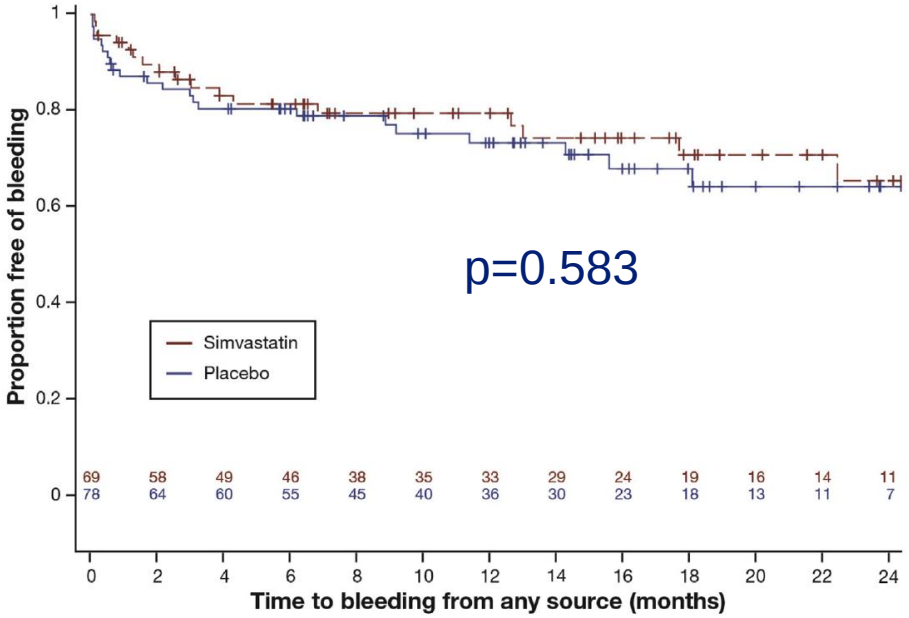
HR for sepsis (adjusted by refractory ascites and MELD):

0.5 (0.3-0.9)

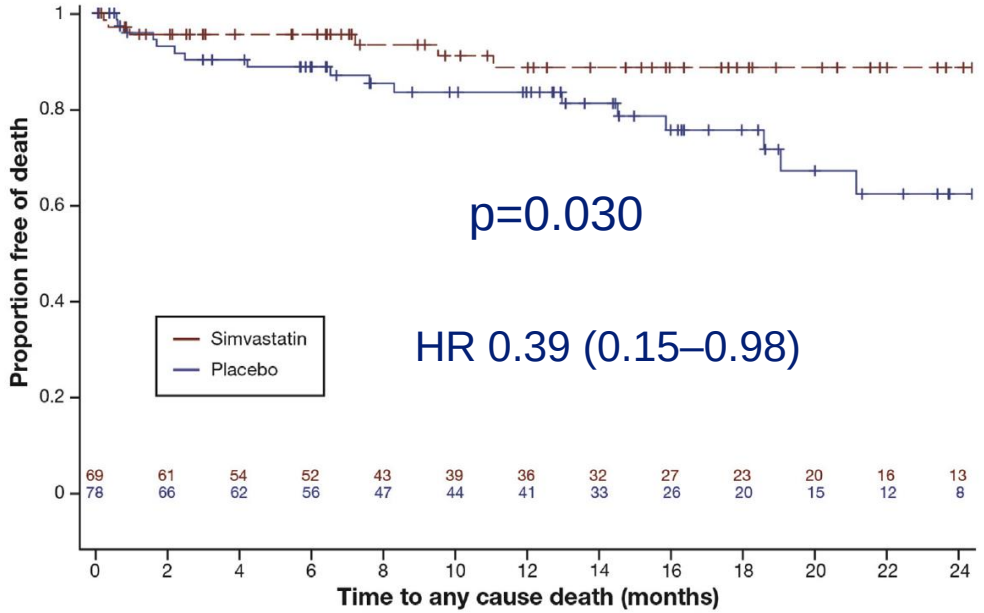
Jansen et al. AASLD 2020.

In patients who had bled from varices, the addition of simvastatin to NSBB + ligation reduced mortality but not rebleeding

Rebleeding



Mortality

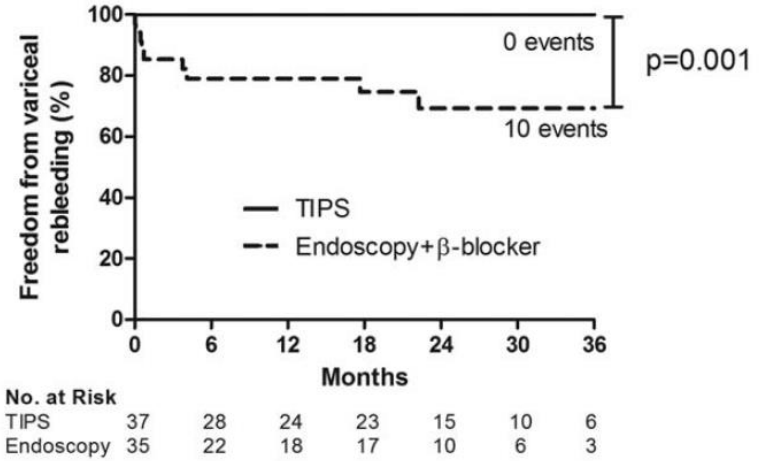


Symptomatic rhabdomyolysis occurred in two (3%) patients (bilirubin >5 mg/dL) in the simvastatin group

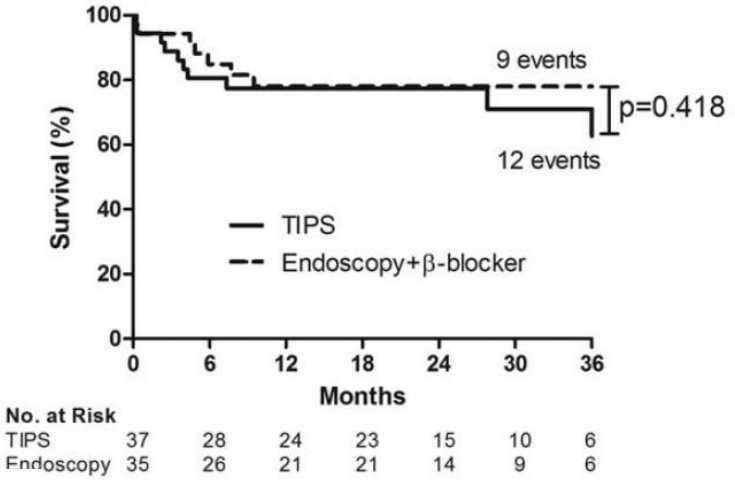
Abraldes, Villanueva et al. Gastroenterology 2016;150(5):1160-1170

Covered TIPS is more effective than NSBB+EVL in preventing recurrent variceal hemorrhage but with more encephalopathy

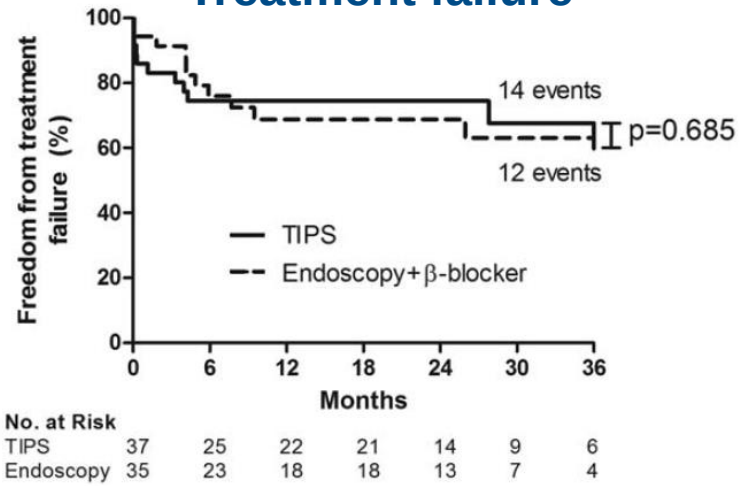
Rebleeding



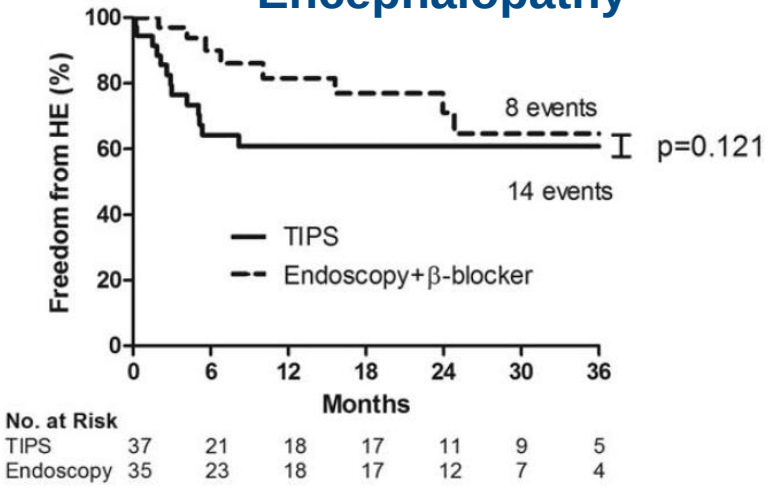
Survival



Treatment failure



Encephalopathy



TIPS is the recommended therapy in patients who experience recurrent hemorrhage despite combination therapy NSBB + EVL

Garcia-Tsao et al. AASLD guidance. Hepatology 2017

Think of TIPS sooner if:

- Patient has difficult-to-treat ascites
- Patient has PVT
- Patient had been compliant to NSBB

Holster et al. Hepatology 2016;63:581-589

New Concepts in Portal Hypertension

- In compensated cirrhosis, rather than screening for varices one should be screening for CSPH
- Portal-pressure reducing strategies (NSBB, ?statins) can prevent cirrhosis decompensation in those with CSPH
- In patients with acute variceal hemorrhage, think of pre-emptive TIPS candidacy at time of admission
- NSBB should not be avoided but should be used cautiously in patients with refractory ascites and discontinued if SBP is $\leq$ 90 mmHg or MAP < 65 mmHg
- In patients with NASH cirrhosis, some of these concepts will require re-evaluation