Portal Hypertension:

An update on prevention and management strategies

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The stage of cirrhosis matters

Compensated

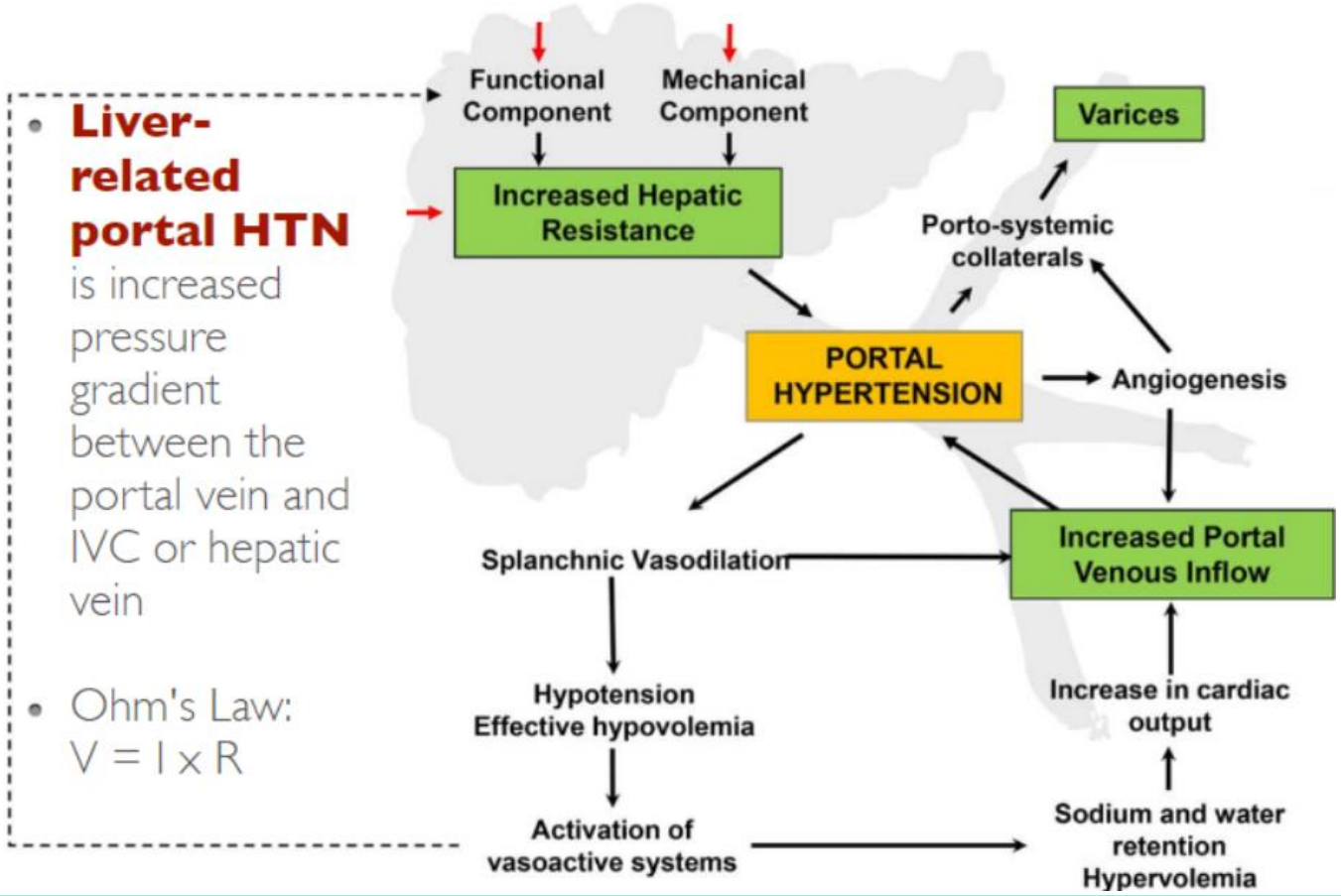
- Median survival > 12 years

Decompensated

- Median survival ~2 years, liver transplant referral

The ***progression*** from compensated to decompensated cirrhosis involves many steps

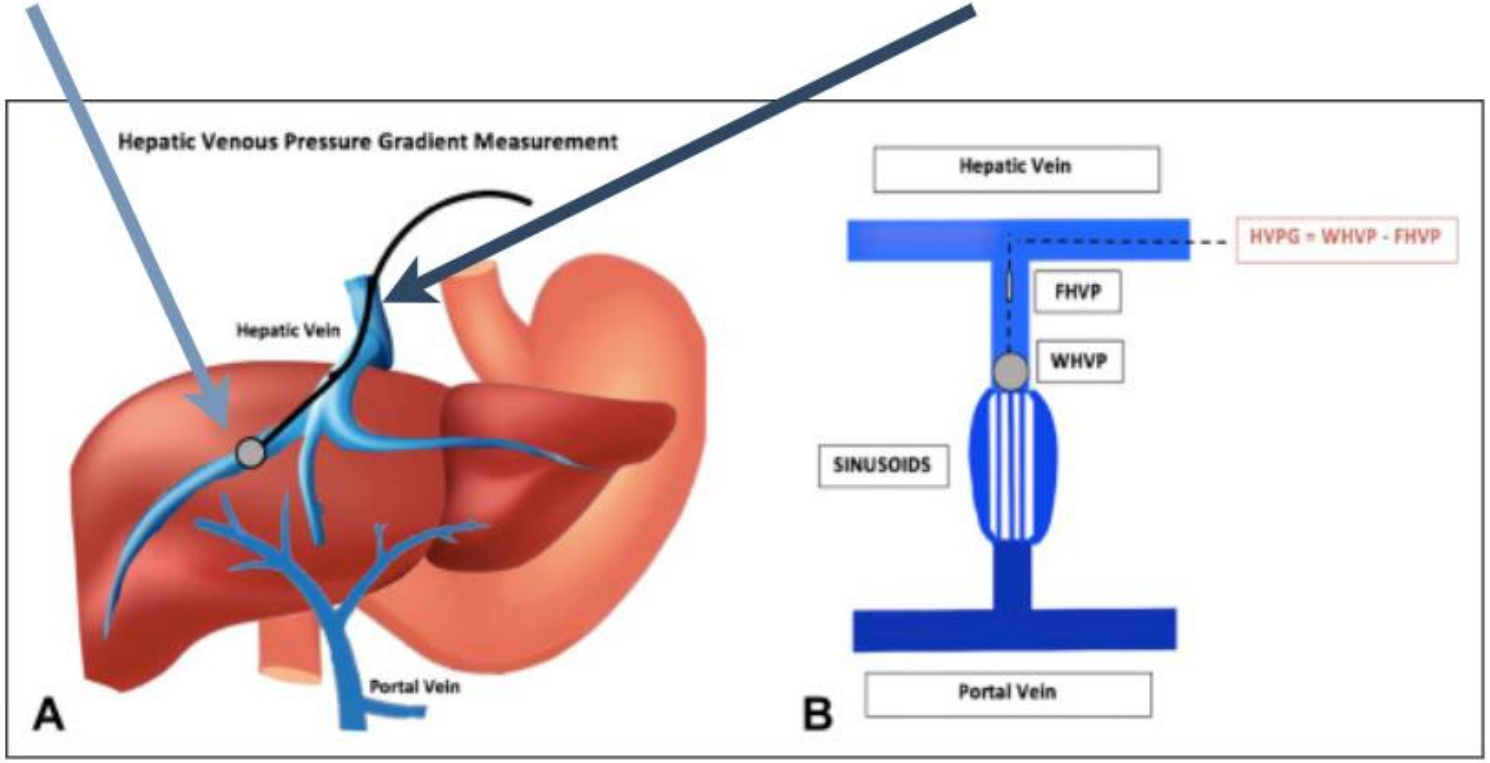
- **Liver-related portal HTN** is increased pressure gradient between the portal vein and IVC or hepatic vein
- Ohm's Law: V = I x R



How to we measure portal hypertension?

Hepatic Venous Portal Gradient (HVPG)

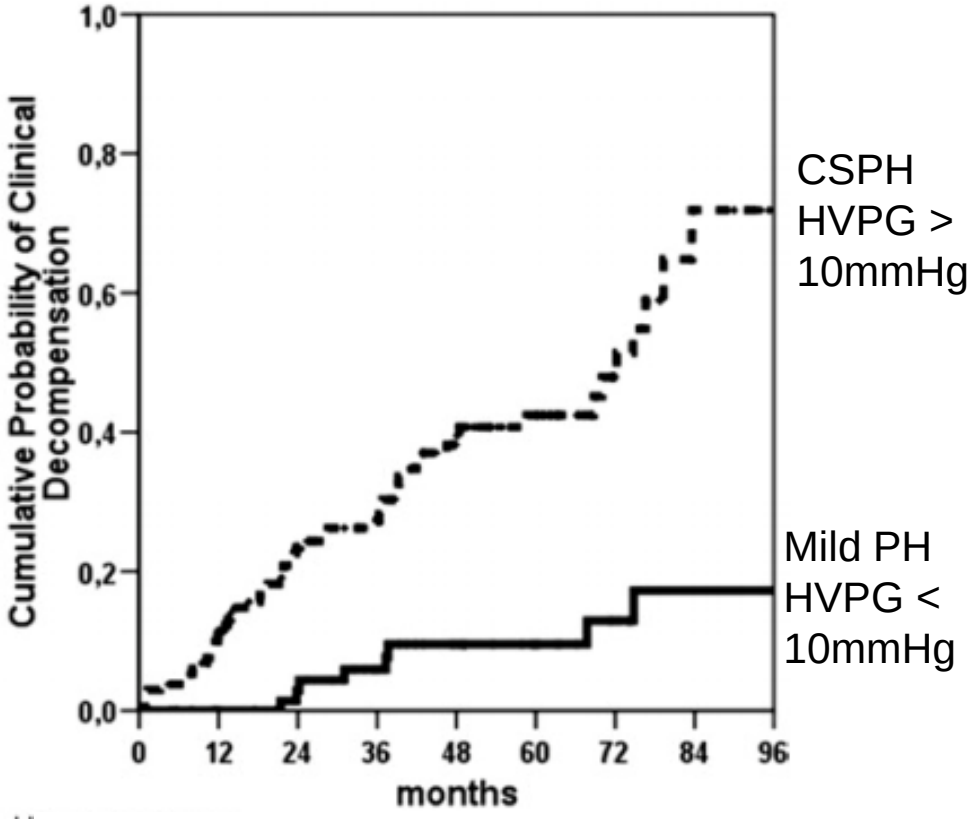
HVPG = (Wedge Hepatic Vein Pressure) - (Free Hepatic Vein Pressure)



HVPG > 10mmHg independently predicts first decompensation in cirrhosis

- 213 patients with compensated cirrhosis and portal HTN *without* varices
- Ascites was the most common decompensation (74%)

Patients with HVPG <10 mmHg have a 90% probability of not developing clinical decompensation (median 4-year f/u)



Ripoll et al. Gastroenterology. 2007 Aug;133(2):481-8.

Redefining the stages of advanced liver disease

Disease Stage	Compensated Cirrhosis		Decompensated Cirrhosis
HVPG	**Mild PH** < 10mmHg	**Clinically Significant PH** ≥ 10mm Hg	≥ 12mm Hg
Complications of portal HTN	None	Nonbleeding Varices	Variceal bleed Ascites Encephalopathy

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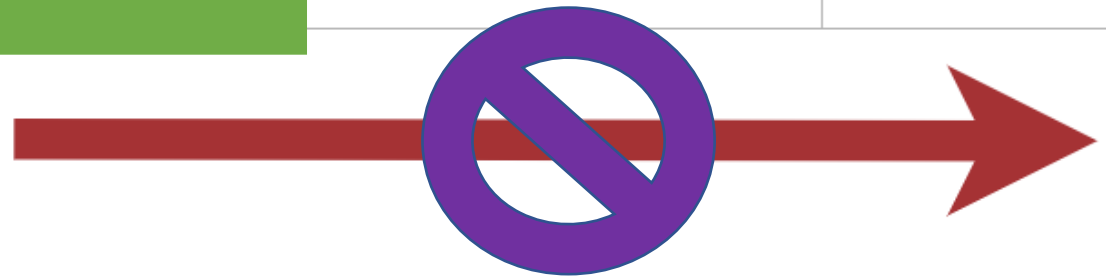


We know non-selective beta blockers (NSBB) can prevent variceal hemorrhage

Primary Prophylaxis

(Prevent first hemorrhage)

- Compensated
  - Large varices
    - NSBB (goal HR 55-60, SBP > 90) or endoscopic band ligation (EBL)
  - Small varices
    - NSBB or EBL only for high-risk stigmata (red wale sign)
- Decompensated
  - Small and large varices
    - NSBB or EBL

Secondary Prophylaxis

(Prevent recurrent hemorrhage)

- EBL and NSBB

Garcia-Tsao et al. Hepatology. 2017 Jan;65(1):310-335.

Non-selective beta blockers (NSBB)

Site of Action	Mechanism of Action	Drug Choices
β-1 blockade	Decreases cardiac output	Nadolol Propranolol Carvedilol
β-2 blockade	Splanchnic vasoconstriction	Nadolol Propranolol Carvedilol
α-1 blockade	Intrahepatic vasodilation	***Carvedilol*** ****more potent***

Banares et al. Hepatology. 1999 Jul;30(1):79-83.

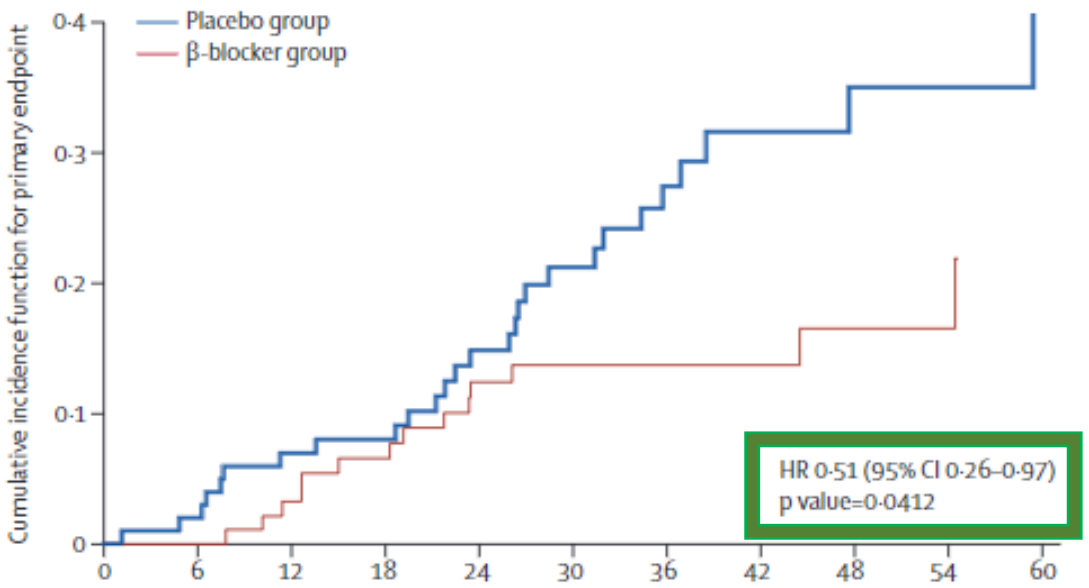
Lowering portal pressure ***improves many outcomes*** of patients with cirrhosis

- Meta-analysis of NSBB use in prophylaxis of variceal hemorrhage
- 15 studies, 968 patients treated with NSBB
- NSBB responders (50-60%) compared to non-responders (40-50%)
  - HVPG decrease of >20% from baseline or HVPG < 12mmHg

Outcome	Without Ascites	With Ascites
Clinical events (Hepatic decompensation)	OR, 0.35 95% CI, 0.22-0.56	OR, 0.27 95% CI, 0.16-0.43
Death or liver transplantation	OR, 0.50 95% CI, 0.32-0.78	OR, 0.47 95% CI, 0.29-0.75

Turco et al. Clin Gastroenterol Hepatol. 2020 Feb;18(2):313-327.e6.

β blockers could increase decompensation-free survival in patients mainly by ***reducing the incidence of ascites*** (PREDISCI Trial)



	Placebo group (n=101)	β-blockers group (n=100)	Risk (95% CI)*	p value†
Decompensation or death				
Overall‡	27 (27%)	16 (16%)	0·51 (0·26–0·97)	0·0412
Secondary outcomes				
Ascites	20 (20%)	9 (9%)	0·42 (0·19–0·92)	0·030
Gastrointestinal bleeding	3 (3%)	4 (4%)	1·52 (0·34–6·82)	0·61
Overt hepatic encephalopathy	5 (5%)	4 (4%)	0·92 (0·40–2·21)	0·98
Death from any cause	11 (11%)	8 (8%)	0·54 (0·20–1·48)	0·23
Varices	56 (56%)	58 (58%)	1·15 (0·65–2·02)	0·72
High-risk varices§	25 (25%)	16 (16%)	0·60 (0·30–1·21)	0·15
Spontaneous bacterial peritonitis	4 (4%)	2 (2%)	0·49 (0·10–2·70)	0·40
Other bacterial infections¶	19 (19%)	15 (15%)	0·81 (0·41–1·59)	0·54
Hepatorenal syndrome	1 (1%)	1 (1%)	0·99 (0·06–15·96)	0·96
Hepatocellular carcinoma	17 (17%)	13 (13%)	0·76 (0·37–1·54)	0·43

Percentages are crude incidences of events occurring at any time during the follow-up. *Values indicate the hazard ratio of an outcome in the β-blockers group as compared with the placebo group. †Comparison of cumulative incidences by competing-risk analysis (differences assessed by Gray's test). ‡The absolute reduction in the incidence of the primary outcome was of 11% (95% CI 0–22). §Among patients with high-risk varices, oesophageal variceal ligation to prevent bleeding was performed in 18 (72%) of 25 patients in the placebo group versus 11 (69%) of 16 in the non-selective β-blockers group. ¶Including spontaneous bacterial peritonitis, and other documented bacterial infections during follow-up.

Table 3: Long-term outcomes

Villanueva et al. Lancet. 2019 Apr 20;393(10181):1597-1608.

Paradigm Shift

Current Model  ***Future Model***

- Emphasis on *preventing variceal hemorrhage*
- Responding to the presence/absence of varices to determine the use of NSBB

- Emphasis on *preventing a first decompensating event*
  - Ascites
  - Variceal hemorrhage
- Responding to the presence of CSPH to determine use of NSBB

But do we need to measure HVPG on every cirrhotic? ***No!***

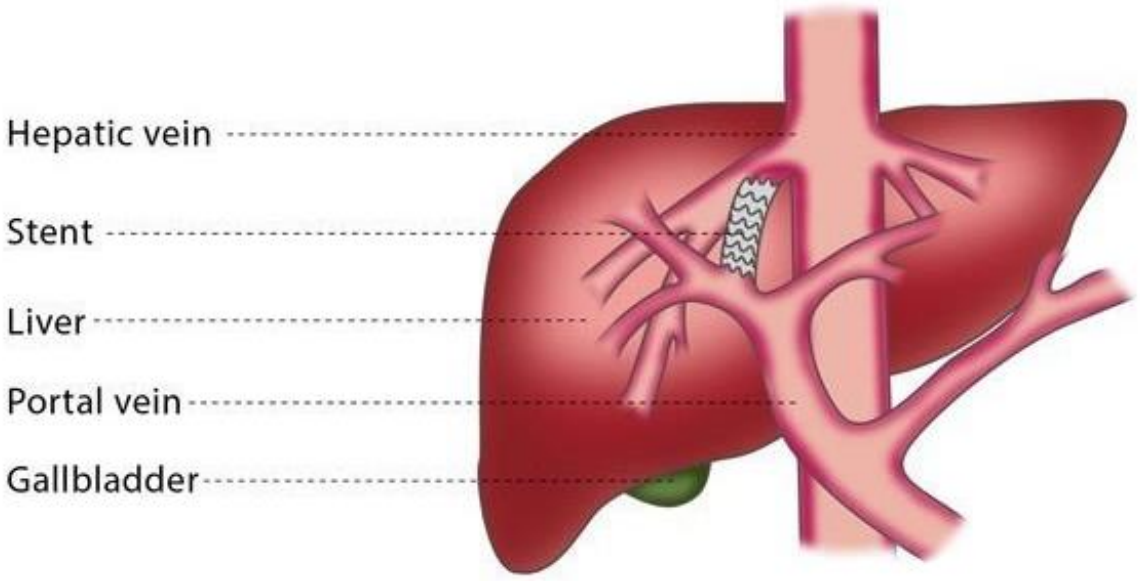
- Presence of varices on endoscopy
- Porto-systemic collaterals on cross-sectional imaging
- Liver stiffness measurements
  - Liver stiffness > 20kPa
    - Diagnostic accuracy of > 90%
  - LSPS calculation
    - Liver stiffness [kPa] x spleen size [cm]/platelet count [number/mm3] > 2.06
    - 90% specific in ruling in CSPH
    - PPV >90%

Castera et al. J Hepatol 2012;56: 696-703.
Augustin et al. J Hepatol 2014;60:561-569.
Berzigotti et al. Gastroenterology 2013;144:102-111.

Is there rescue therapy for portal hypertension after decompensation?

A side note about **T**ransjugular **I**ntrahepatic **P**ortosystemic **S**hunts (**TIPS**)

TIPS



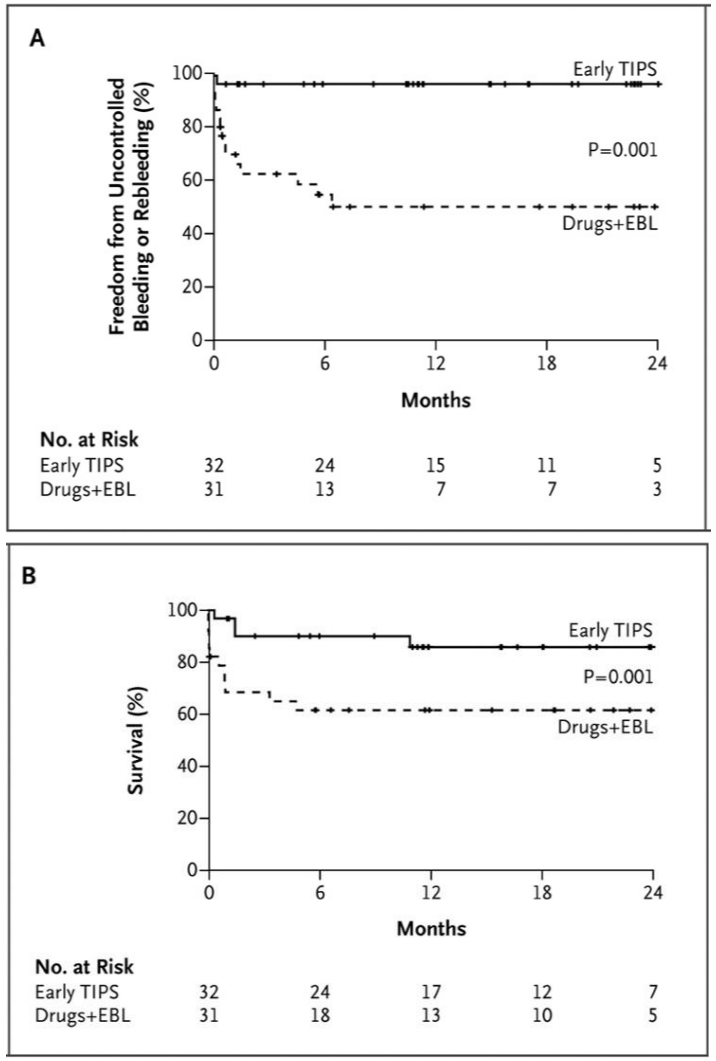
Indications:

- Variceal hemorrhage
  - Salvage (uncontrolled bleeding)
  - Rescue (rebleeding after EBL)
  - Pre-emptive (before EBL failure to prevent need for rescue TIPS)
- Refractory ascites
- Portal vein thrombosis

Pre-Emptive TIPS

- Patients with first variceal hemorrhage
  - Child–Pugh class C (10-13)
  - Child-Pugh class B (7-9) *with active bleeding* at endoscopy

- Patients were banded then received TIPS with in 72hrs



63 patients randomized 1:1

Garcia-Pagan et al. N Engl J Med. 2010 Jun 24;362(25):2370-9.

	Early TIPS group (n=84)	Control group (n=45)	ARD (95% CI)*	HR (95% CI)	p value
Death or liver transplantation	17 (20%)	16 (36%)	−16% (−31 to −0·04)	0·50 (0·25 to 0·98)	0·04
Liver transplantation	2 (2%)	1 (2%)	−1% (−10 to 5)	0·87 (0·08 to 9·57)	0·91
Death	15 (18%)	15 (33%)	−15% (−32 to −0·2)	0·47 (0·23 to 0·96)	0·04
Cause of death†	..	..	..	..	0·66‡
Liver failure	6 (40%)	3 (20%)	..	..	..
Gastrointestinal bleeding	2 (13%)	4 (27%)	..	..	..
Sepsis/pneumonia	3 (20%)	2 (13%)	..	..	..
Multiorgan failure	0 (0%)	2 (13%)	..	..	..
Hepatorenal syndrome	0 (0%)	1 (7%)	..	..	..
Hepatocellular carcinoma	1 (7%)	1 (7%)	..	..	..
Unrelated to liver disease	3 (20%)	2 (13%)	..	..	..
Failure to control bleeding or rebleeding	11 (13%)	17 (38%)	−25% (−40 to −9)	0·26 (0·12 to 0·55)	<0·0001
Failure to control bleeding (≤5 days)	1 (1%)	6 (13%)	−12% (−25 to −3)	0·08 (0·01 to 0·68)	0·02
Early rebleeding (>5 days to 6 weeks)	1 (1%)	3 (7%)	−6% (−17 to 1)	0·12 (0·02 to 1·51)	0·16
Late rebleeding (>6 weeks to 2 years)	9 (11%)	8 (18%)	−7% (−22 to 5)	0·50 (0·19 to 1·29)	0·15
Sources of bleeding§	..	..	..	..	0·31‡
Variceal bleeding	9 (82%)	13 (76%)	..	..	..
Portal hypertensive gastropathy	1 (9%)	1 (6%)	..	..	..
Peptic ulcer bleeding	1 (9%	1 (6%)	..	..	..
Post-endoscopic therapy	0 (0%)	2 (12%)	..	..	..
New or worsening ascites	14 (17%)	20 (44%)	−27% (−44 to −11)	0·28 (0·14 to 0·55)	<0·0001
Refractory ascites	0 (0%)	4 (9%)	−9% (−21 to −2)	NE	0·01
Overt hepatic encephalopathy	29 (35%)	16 (36%)	−1% (−18 to 15)	0·89 (0·48 to 1·64)	0·72
More than one episode	13 (15%)	5 (11%)	4% (−9 to 15)	1·30 (0·46 to 3·65)	0·43
Episodes per patient¶	2·4 (1·3)	1·7 (1·2)	0·7% (−1·0 to 1·5)	NE	0·27**
Severe hepatic encephalopathy (grade III/IV)	5 (6%)	4 (9%)	−3% (−15 to 6)	0·61 (0·16 to 2·28)	0·73
Spontaneous overt hepatic encephalopathy	9 (11%)	4 (9%)	2% (−11 to 12)	1·12 (0·34 to 3·62)	0·67
Precipitating overt hepatic encephalopathy††	20 (24%)	12 (27%)	−3% (−19 to 12)	0·78 (0·38 to 1·60)	0·67

	Univariate analysis		Multivariate analysis	
	HR (95% CI)	p value	HR (95% CI)	p value
Death or liver transplantation				
Treatment (early TIPS vs control)*	0·50 (0·25–0·98)	0·04	0·44 (0·22–0·88)	0·02
Child-Pugh score (per point increase)	1·32 (1·03–1·70)	0·03	..	..
MELD score (per point increase)*	1·11 (1·02–1·21)	0·02	1·13 (1·03–1·23)	0·01
Serum total bilirubin (per mg/dL increase)	1·25 (0·98–1·60)	0·07	..	..
Creatinine (per mg/dL increase)	1·76 (1·01–3·04)	0·05	..	..
Failure to control bleeding or rebleeding				
Treatment (early TIPS vs control)*	0·26 (0·12–0·55)	<0·0001	0·25 (0·12–0·54)	<0·0001
Previous bleeding (yes vs no)*	1·88 (0·90–3·95)	0·09	..	..
New or worsening ascites				
Treatment (early TIPS vs control)*	0·28 (0·14–0·55)	<0·0001	0·25 (0·13–0·50)	<0·0001
Age (per year increase)*	0·968 (0·939–0·997)	0·03	0·960 (0·929–0·992)	0·02
Overt hepatic encephalopathy				
Child-Pugh score (per point increase)	1·27 (1·01–1·59)	0·04	..	..
MELD score (≥19 vs <19)	1·98 (1·13–3·45)	0·02	..	..
Ascites (yes vs no)*	1·27 (0·96–1·68)	0·09	..	..
Serum total bilirubin (per mg/dL increase)*	1·34 (1·10–1·63)	0·003	1·30 (1·08–1·58)	0·01

Lv et al. Lancet Gastroenterol Hepatol. 2019 Aug;4(8):587-598.

We are not taking advantage of pre-emptive TIPS for variceal hemorrhage

- French study of real events
- ***35%*** *of the patients were eligible* for pre-emptive-TIPS
- Only ***6.8%*** *underwent pre-emptive-TIPS* placement
- Issues with TIPS availability
- *Probability of survival was better with pre-emptive TIPS* at one year (85.7±0.07% vs 58.9±0.03%, p=0.04)

Thabut et al. J Hepatol. 2017 Dec 14;68(1):73-81.

TIPS can improve transplant-free survival for refractory ascites

- 1-year survival in patients who develop ascites ~85%
  - ***Survival decreases to 32%*** with refractory ascites
  - Risk of spontaneous bacterial peritonitis and hepatorenal syndrome

- Make sure to...
  - Carefully select your patients (lower MELD, consider hepatic encephalopathy)
  - Use covered stents (this is standard now)
  - Reduce the pressures only as much as you need

Planas et al. Clin Gastroenterol Hepatol. 2006;4(11):1385–1394.
Bureau et al. Gastroenterology. 2017 Jan;152(1):157-163.

Summary

- Getting ahead of the problem
  - Treatment of CSPH ***before*** the patient decompensates
  - NSBBs is the mainstay of treatment

- Even after decompensation develops, ***we can still intervene***
  - Pre-emptive TIPS for variceal hemorrhage
  - TIPS for refractory ascites

Thank you!