Alcohol and portal hypertension

Portal Hypertension Session
Moderated by Prof J Bosch

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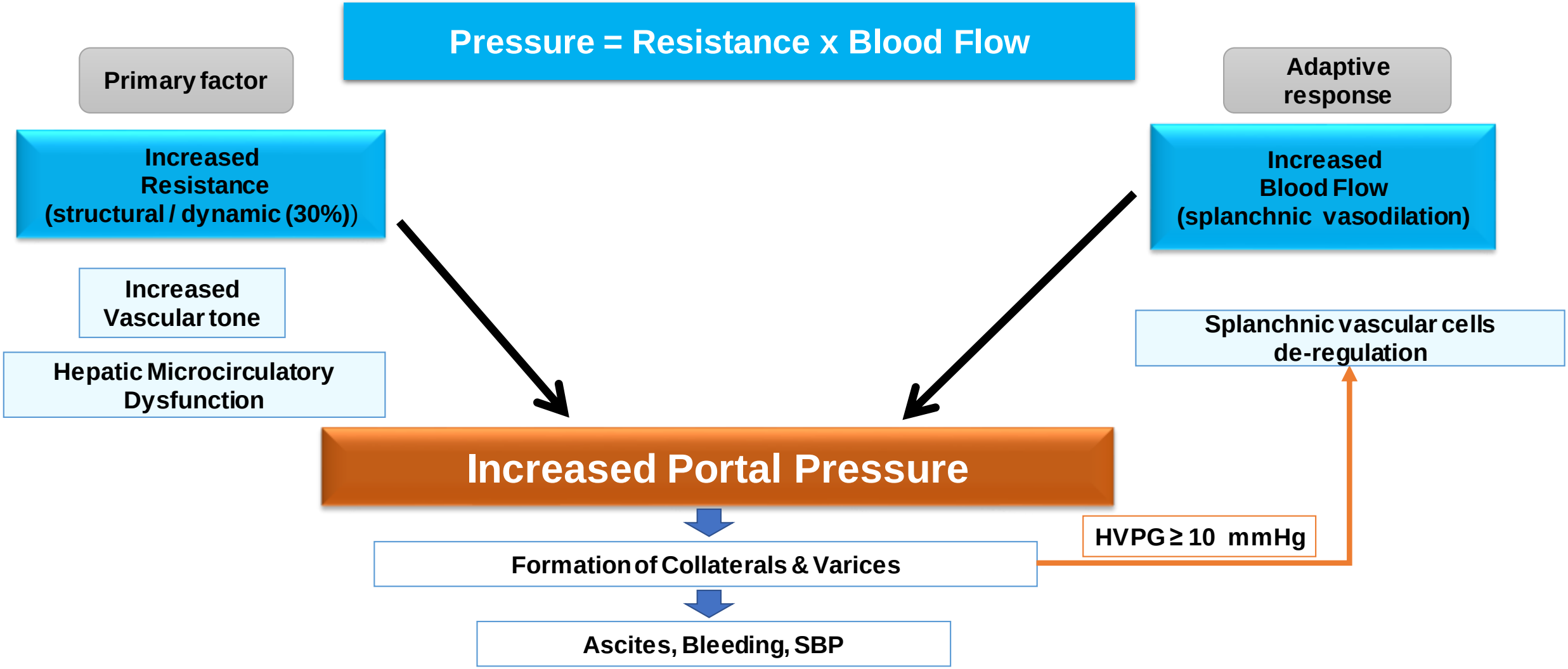
MECHANISMS

Mechanisms of portal hypertension (PH)

Time	Paradigm	Therapeutic applications	
Past (from Hippocrates to Child)	Congestion (↑ resistance, ↓ blood flow)	**Established** Surgical portal-systemic shunt	**Non-established**
Present 1980s	Hyperdynamic circulation	Splanchnic vasoconstrictors (vasopressin, somatostatin and its derivatives) Non-selective beta-blockers	
1985	Increased hepatic vascular tone	Vasodilating nitrates (combined with vasoconstrictors/beta-blockers)	
1998	Mechanism of sinusoidal endothelial dysfunction		NOS-gene transfer, antioxidants statins, BH_4
2000	Reversal of fibrosis/cirrhosis	Etiologic treatments	Antifibrotic drugs
2004	Angiogenesis		Antiangiogenic drugs Modulation of endogenous anti-angiogenic factors
2008	Intrahepatic vascular occlusion and parenchymal extinction lesions		Anticoagulation
2000-14	Bacterial translocation/inflammation/ altered microbioma as factors worsening PH		Antibiotics, probiotics

Bosch, Groszmann, Shah. J Hep 2015

Mechanisms of portal hypertension



Adapted from Bosch ILC- EASL 2017 & Gracia-Sancho, Laleman, Clin Liver Dis 2016

Pathobiology of the hepatic sinusoids

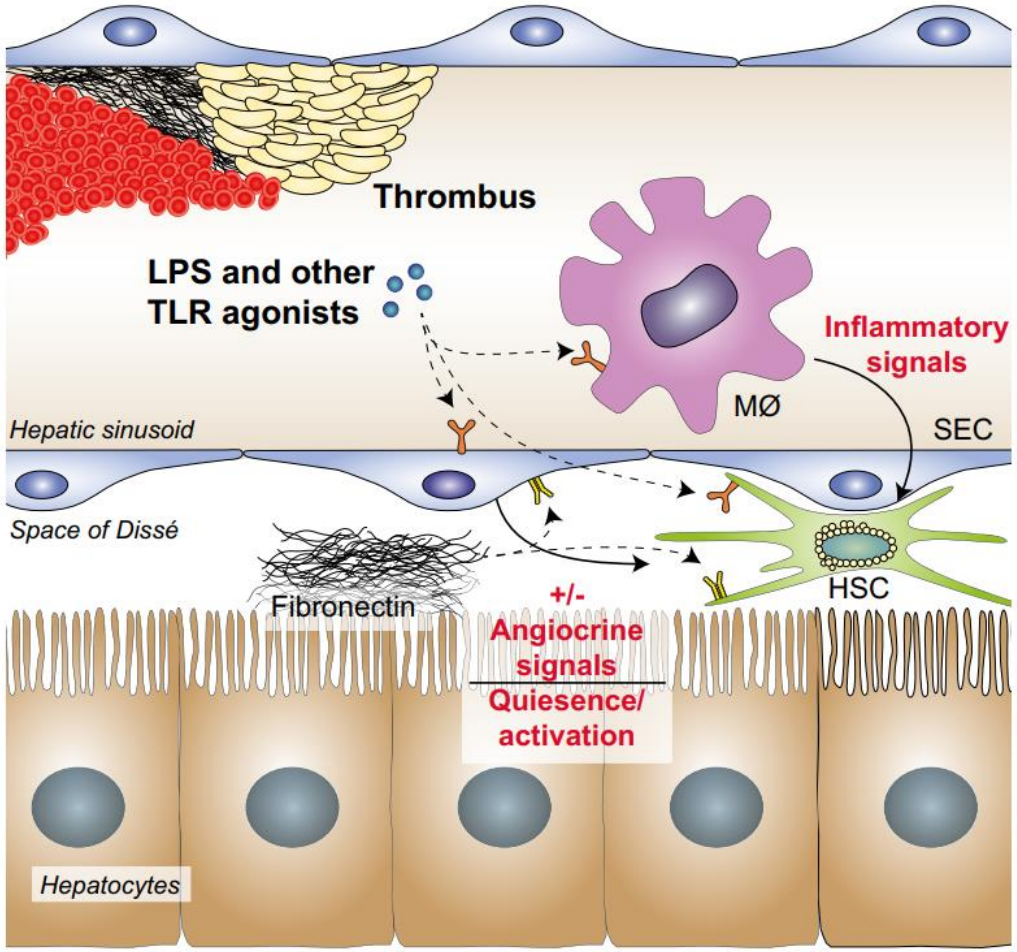
Diminished production of, NO, produced by endothelial NO synthase (eNOS)

Microthrombi within the sinusoids →increased intrahepatic resistance liver injury and fibrosis development

ET-1 and NO, regulate hepatic vascular tone in the presence of ethanol

Angiocrine signalling: angiogenic endothelial cells may stimulate HSC activation

Capillarization; early fibrosis. Early role in liver injury and fibrosis



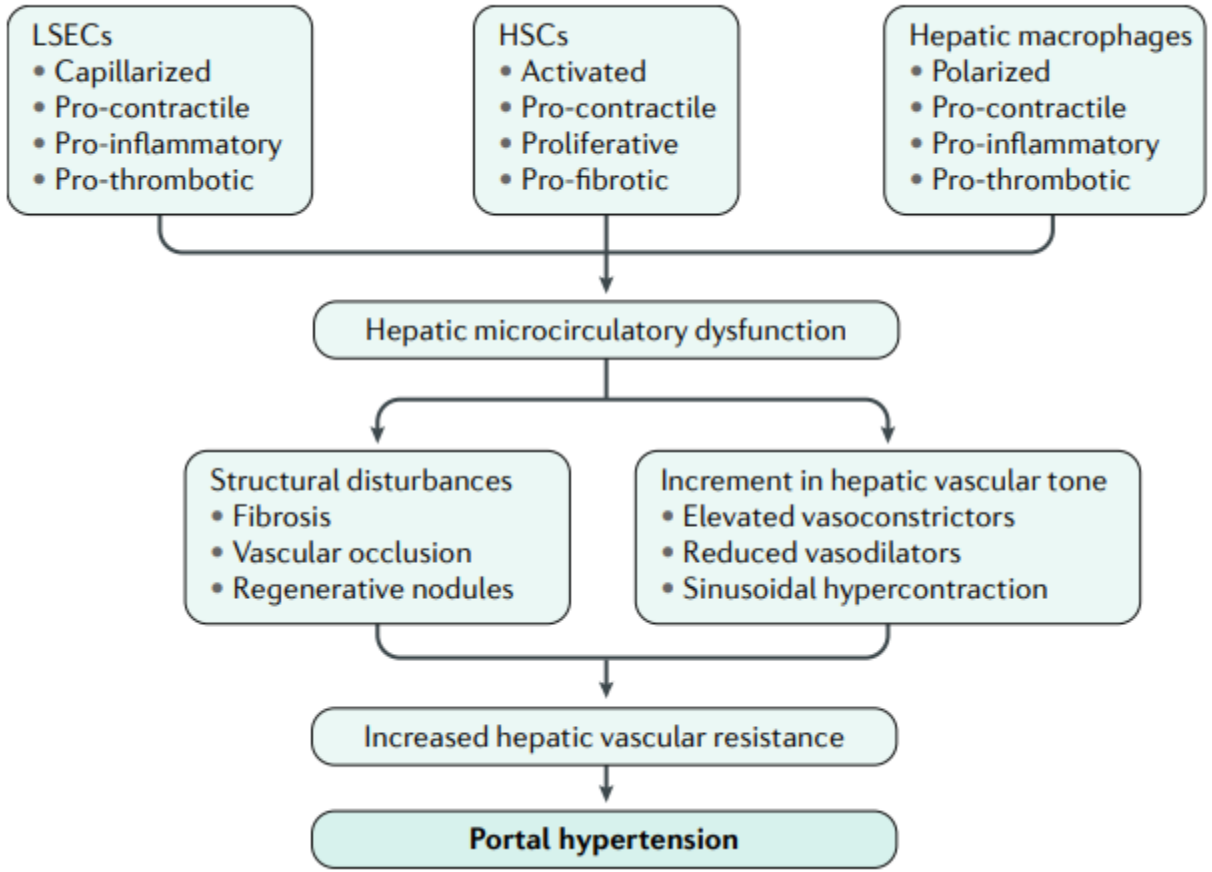
Toll-like receptor 4 (TLR4) → hepatic stellate cell activation, key for sinusoidal constriction and deposition of matrix protein

Ethanol & acetyladehyde→ MEOS produced free radicals of lipid aldehydes→ fibrotic extracellular matrix

Matrix proteins by HSC → increased intrahepatic resistance through the mechanical effects of the matrix and signalling actions

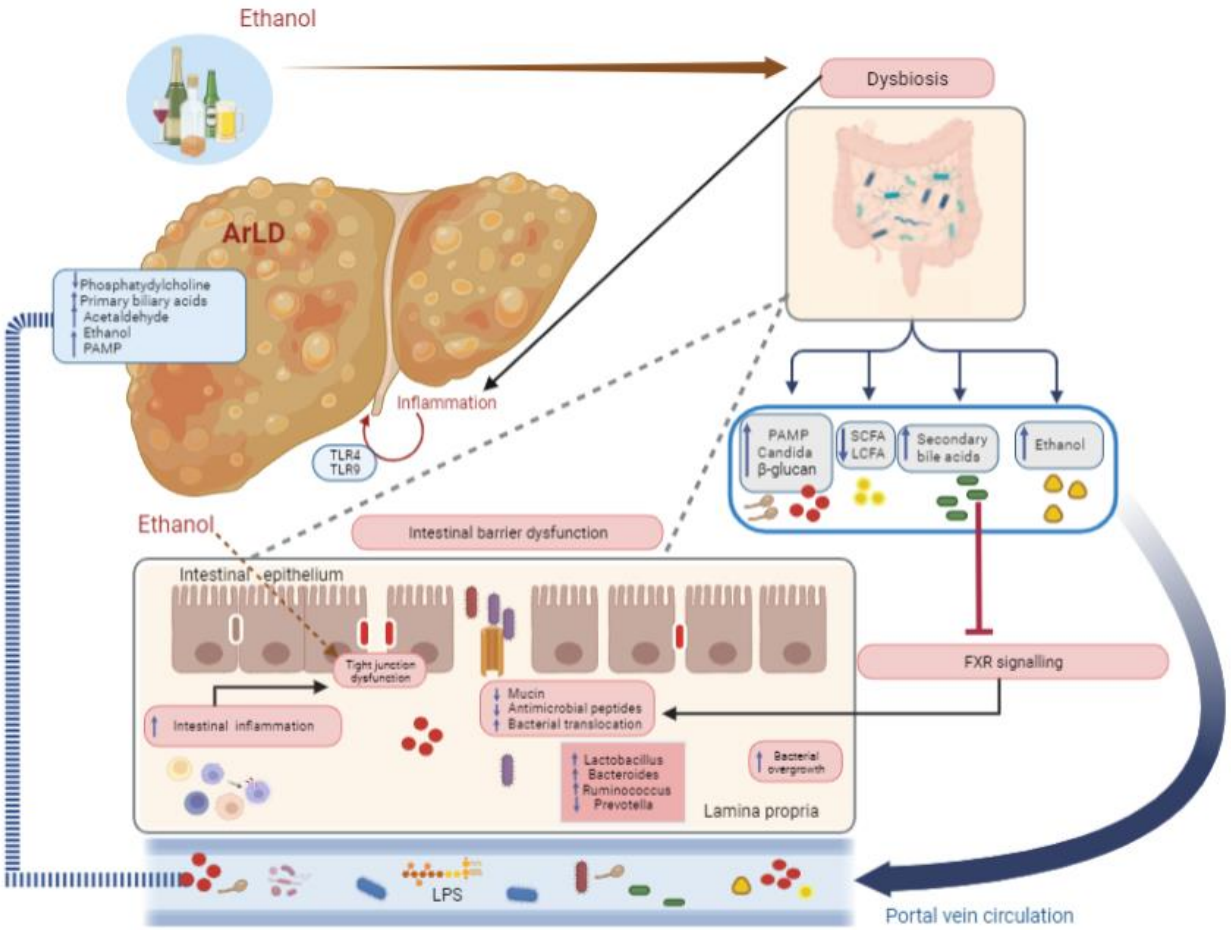
Bosch, Groszmann, Shah. J Hep 2015

Pathobiology of the hepatic sinusoids



Gracia-Sancho et al. Nat Rev Gastro & Hep 2019

Gut-liver axis in ALD & portal hypertension



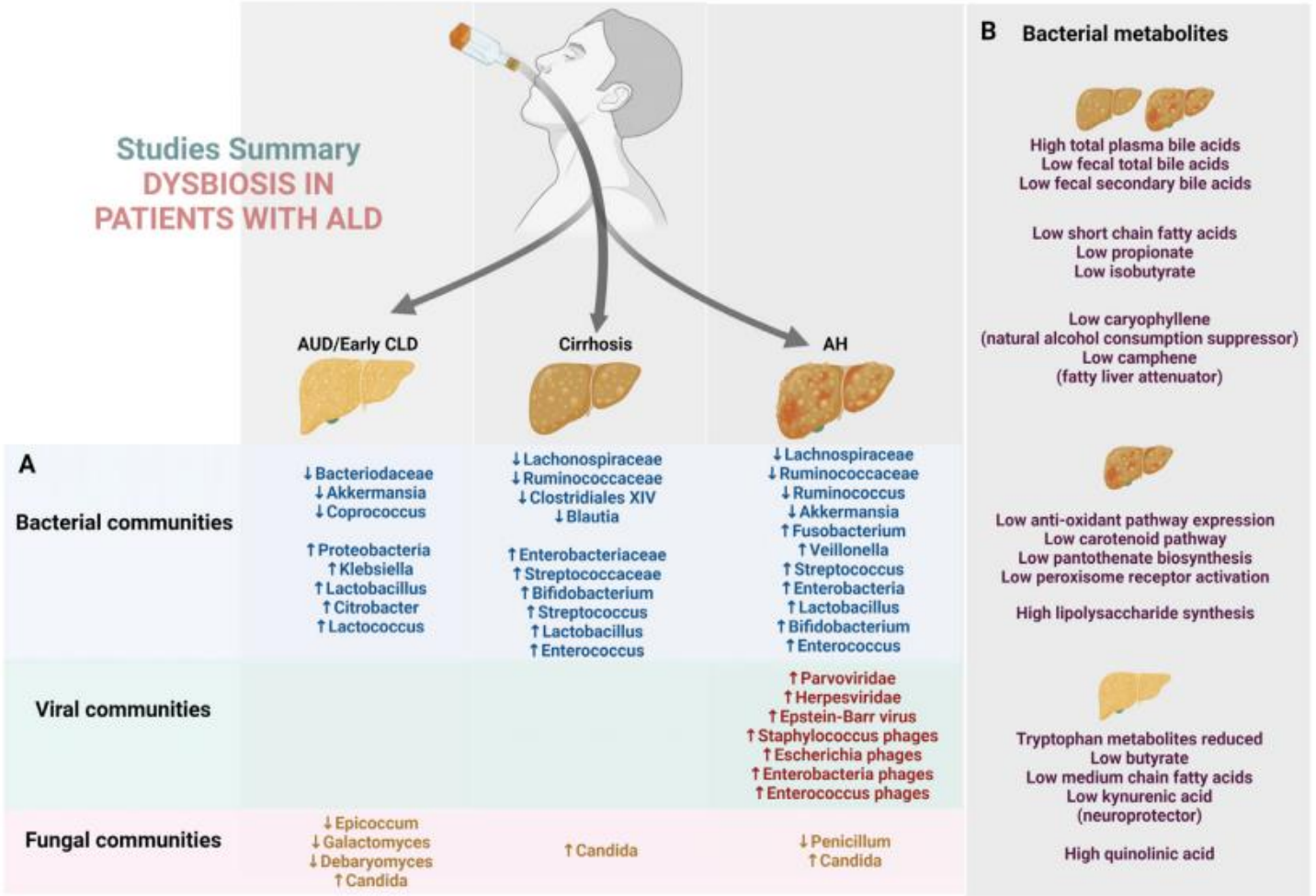
- Alcohol damages tight junction integrity in the distal epithelium →increased gut permeability → leads to increased levels of bacterial lipopolysaccharide in intestinal venous circulation→ portal vein

- Secreted bile acids modified by the intestinal microbiota → decreased FXR stimulation which may increase the contractility of HSCs → PH

- Specific microbial members may aggravate hepatic Inflammation→ hepatic resistance.

Verbeke et al. Hepatol 2014
Ubeda et al. J Hepatol 2016
Munoz et al. Hepatol 2019
Schierwagen et al. Gut 2019

Gut-liver axis in ALD & portal hypertension



Philips et al. J clin and exp hep 2022

HEMODYNAMICS

Specificities of PH hemodynamics in ALD

Table 1 Portal-hepatic hemodynamics in alcohol-related and viral cirrhosis

	Alcohol-related cirrhosis	Viral cirrhosis
Increase in intrahepatic resistance	Increase in sinusoidal and postsinusoidal resistance	
Portal pressure	Higher increase in sinusoidal pressure	Lower increase in sinusoidal pressure
Hepatic venous pressure gradient	Accurately reflects portal pressure	Less accurately reflects portal pressure
Portal perfusion of the liver per gram of tissue in end-stage liver disease	Higher reduction	Lower reduction
Reversal portal blood flow	More common	Rare
Patent paraumbilical vein	More common	Less common
Hyperdynamic circulation	More pronounced	Less pronounced

Bolognesi et al World J Gastroenterol 2014
Pomier-Layrargues et al. Hepatology 1985
Thalheimer et al. Dig Liver Dis 2005

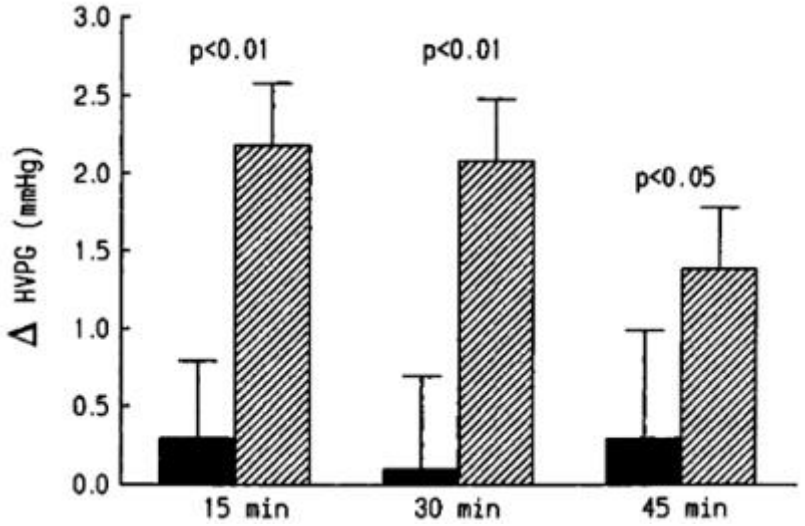
- Hepatocyte swelling, a characteristic of ALD observed after the acute administration of alcohol, role in acute increase in intrahepatic resistance?

Wondergem et al. Alcohol Clin Exp Res 1994

- Role of alcohol-related cardiomyopathy in the progression of hemodynamic changes → PH?

Ethanol increases HVPG through hepatic resistance

- 16 patients alcohol-related cirrhosis and PH
- At 15 minutes, ethanol increases PP and azygos flow (index of flow through PS shunts), worsening PH syndrome
- No increase in hepatic blood flow → possibly due to flow through PS collaterals
- Increase in HVPG without increase in blood flow → due to increase in hepatic resistance



Luca et al. Gastro 1997

HVPG in Alcohol-related hepatitis

- Early measurement of HVPG provides important prognostic information on the short-term outcome (in hospital mortality) of patients with severe AAH.
- Cut-off: HVPG 22 mmHg

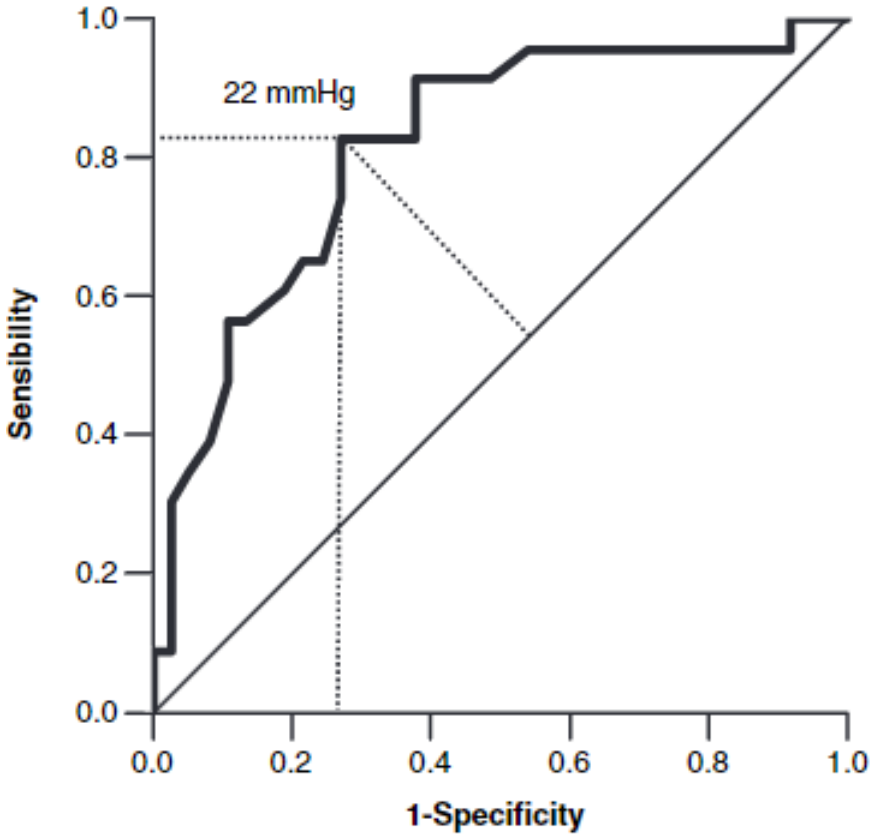
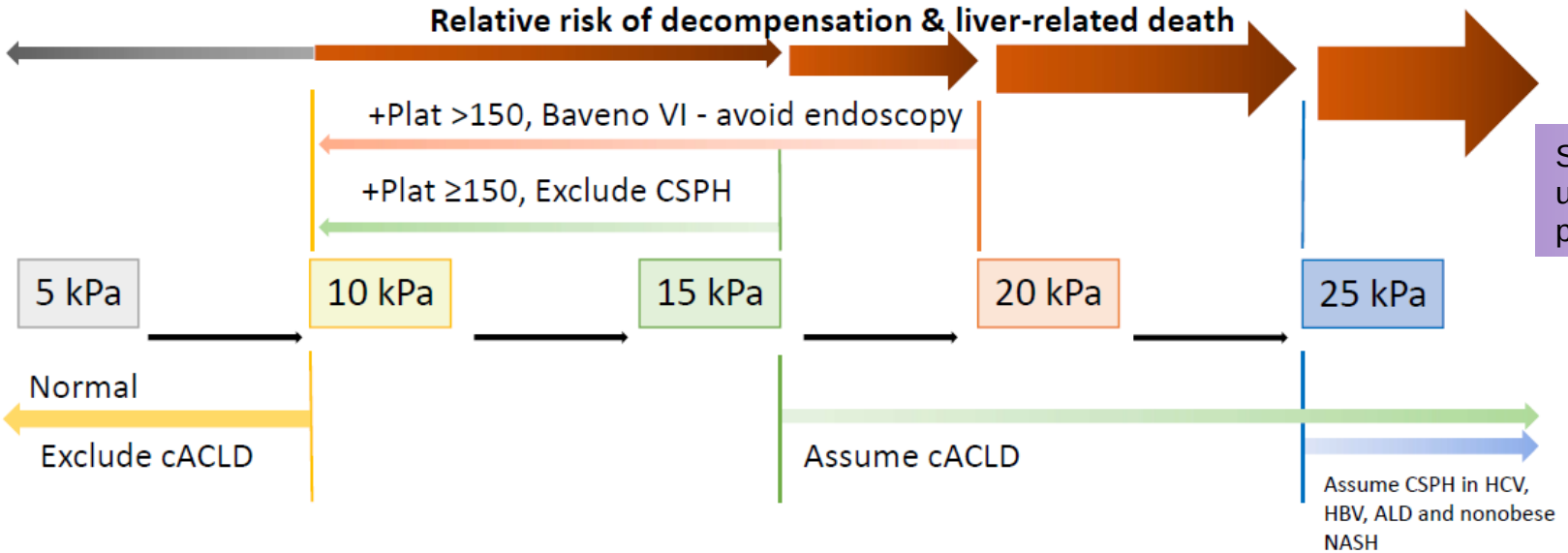


Figure 1. ROC curve analyzing the predictive value of HVPG in severe acute alcoholic hepatitis.

Rincon et al. APT 2007

STAGING & MANAGEMENT

Baveno VII shifts in paradigm



SSM ≤ 40 kPa by TE can be used to identify those at low probability of high-risk varices

3-year risk (≤1%) of decompensation and liver-related death

cACLD: repeat FS every 12 months

≥20% associated with LSM <20 kPa or any decrease to a LSM <10 kPa

Baveno VII Consensus; J Hepatol 2022

Elastography cut-offs for ArLD for CSPH

▶ **Table 2** Sensitivity and specificity for CSPH and SPH in each included study.

	cut-off value for CSPH	sensitivity	specificity	cut-off value for SPH	sensitivity	specificity
Kumar	21.8 kPa	0.88 (0.80–0.94)	0.50 (0.19–0.81)	29.1 kPa	0.81 (0.71–0.88)	0.58 (0.28–0.85)
Zykus	21.8 kPa	0.88 (0.62–0.98)	1.00 (0.29–1.00)	29.1 kPa	0.86 (0.57–0.98)	0.80 (0.28–0.99)
Schwabl	21.8 kPa	0.90 (0.68–0.99)	0.86 (0.57–0.98)	29.1 kPa	0.83 (0.59–0.96)	0.81 (0.54–0.96)
Kitson	21.8 kPa	0.88 (0.71–0.96)	0.86 (0.42–1.00)	29.1 kPa	0.89 (0.71–0.98)	0.67 (0.35–0.90)
Hong	21.8 kPa	0.82 (0.67–0.93)	0.74 (0.49–0.91)	29.1 kPa	0.81 (0.63–0.93)	0.81 (0.58–0.95)
Reiberger	19.0 kPa	0.89 (0.83–0.94)	0.73 (0.60–0.83)	23.0 kPa	0.91 (0.85–0.95)	0.77 (0.66–0.85)
Lemoine	21.8 kPa	0.98 (0.87–1.00)	0.50 (0.16–0.84)	29.1 kPa	0.93 (0.80–0.98)	0.63 (0.24–0.91)
Bureau	21.8 kPa	0.98 (0.88–1.00)	0.67 (0.30–0.93)	29.1 kPa	0.95 (0.84–0.99)	0.67 (0.28–0.85)
Cho	21.8 kPa	0.73 (0.63–0.81)	0.70 (0.61–0.79)	–		

▶ **Table 3** Summary of diagnostic characteristics for CSPH and SPH.

	cut-off value	sensitivity	specificity	LR+	LR-	DOR	AUROC	pre-test probability	post-test probability (test positive)	post-test probability (test negative)
CSPH	21.8 kPa	0.89 (95 % CI, 0.83–0.93)	0.71 (95 % CI, 0.64–0.78)	3.1 (95 %CI, 2.4–4.0)	0.15 (95 % CI, 0.10–0.24)	20 (95 %CI, 12–35)	0.77 (95 %CI, 0.73–0.81)	0.50 0.70 0.90	0.76 0.88 0.97	0.13 0.26 0.58
SPH	29.1 kPa	0.88 (95 % CI, 0.83–0.92)	0.74 (95 % CI, 0.67–0.81)	3.4 (95 %CI, 2.6–4.5)	0.16 (95 % CI, 0.11–0.23)	21 (95 %CI, 12–37)	0.80 (95 %CI, 0.76–0.83)	0.50	0.77	0.14
								0.70	0.89	0.27
								0.90	0.97	0.59

Song J et al. Ultraschall Med 2020

Alcohol abstinence and portal hypertension

- Improvement in Child Pugh Score
- Ascites was absent in 16 of the 21 abstainers and 1 of the 9 non-abstainers; (*P* . 0.01).
- Difference in the mean HVPG between abstainers and non-abstainers: (-15.9% ± 3.5% vs. 18.4% ± 5.7%, respectively)
- Survival was greater for abstainers than for non-abstainers (P <0.05) (better in Child A vs Child B/C patients)

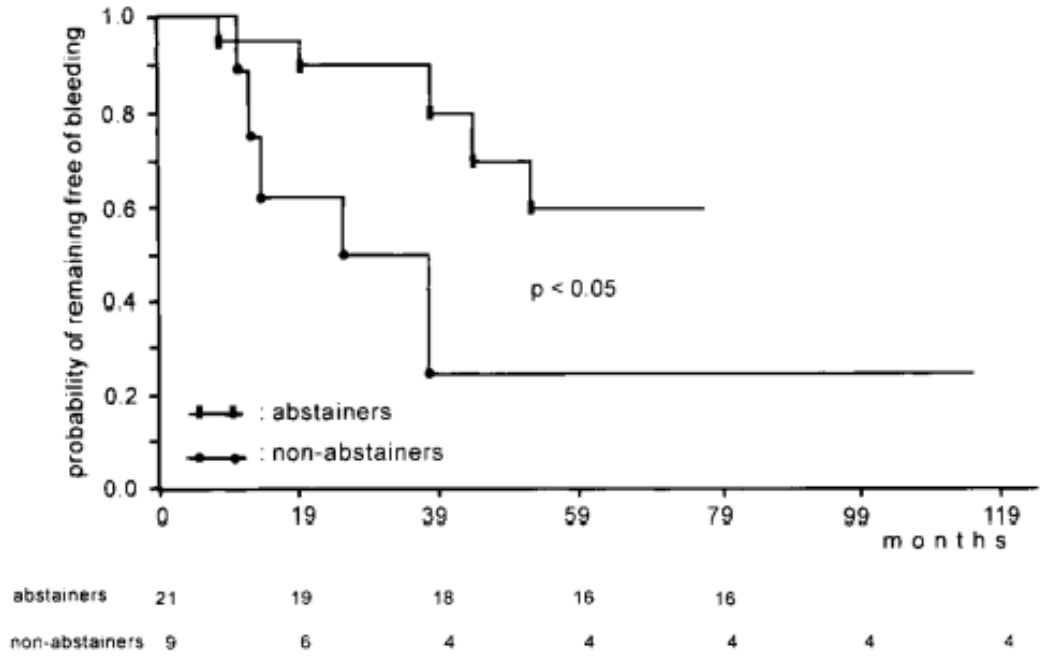
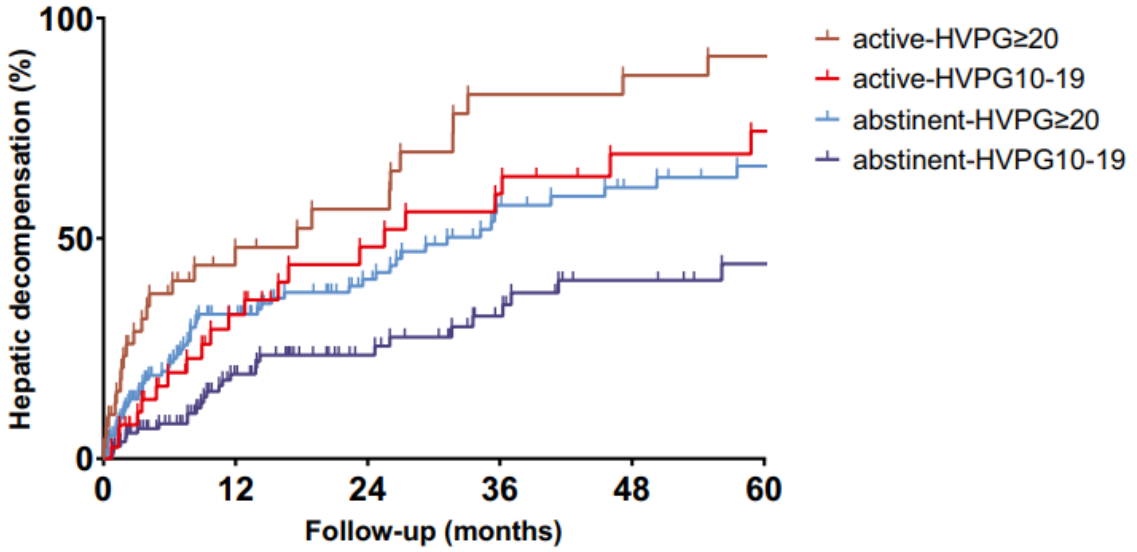


Figure 4. Probability of remaining free of bleeding according to alcohol intake status.

Vorobioff et al. Gastro 1996

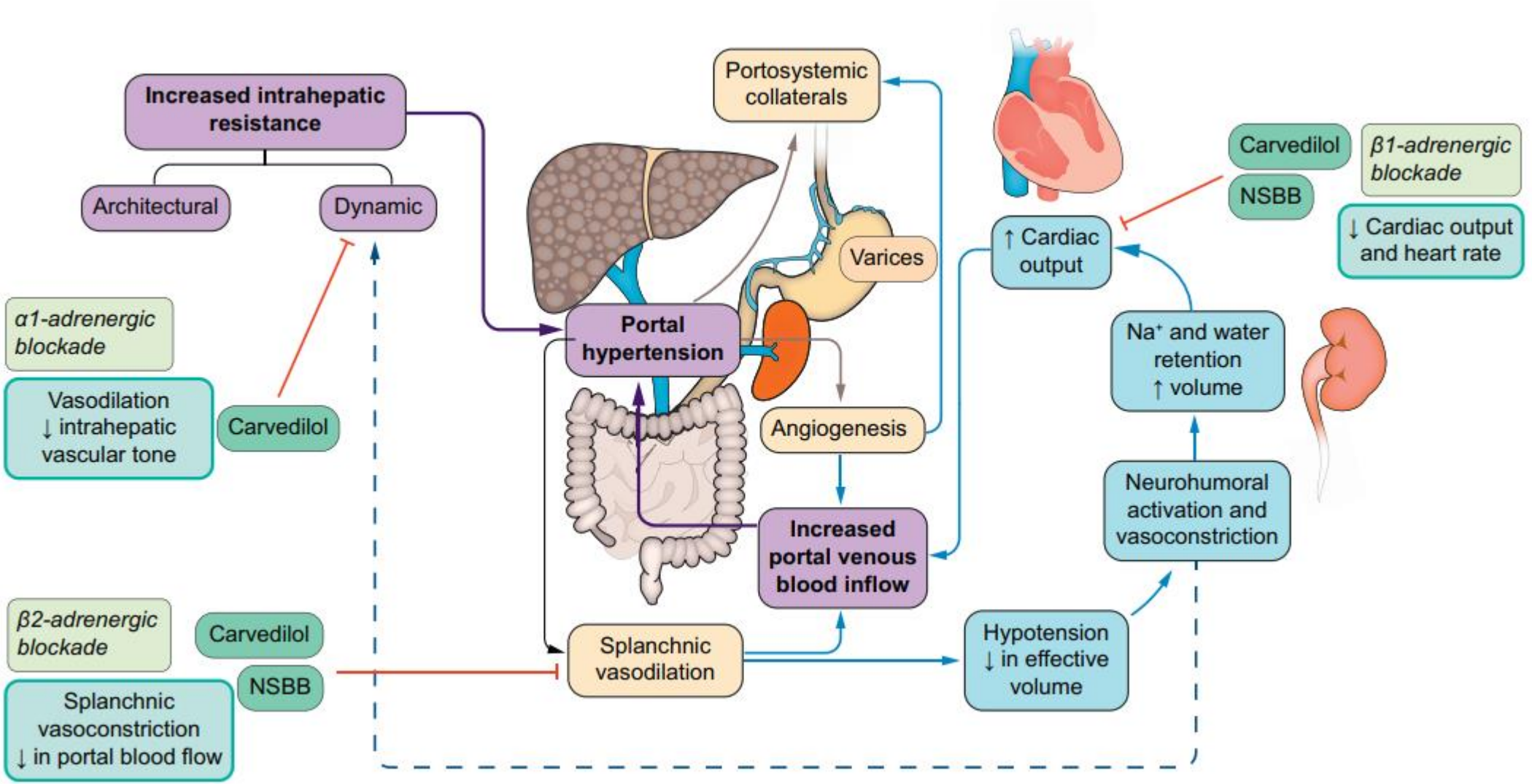
Abstinence decreases decompensation

- 75.3% patients with CSPH abstinent
- Abstinence reduced risk of decompensation (aHR, 0.391; P < .001), as well as liver-related (aHR, 0.428; P < .001) and all-cause (aHR, 0.453; P < .001) mortality
- Abstinence reduced cumulative incidence of decompensation in HVPG 10–19 mm Hg (P < .001) and HVPG ≥20 mm Hg (P = .002).
- 3-year decompensation probability was 32.4% vs 60.0% in HVPG 10–19 mm Hg and 57.5% vs 82.6% in HVPG ≥ 20 mm Hg for abstinent patients vs active drinkers, respectively



Hofer et al. Clin Gastro Hep 2022

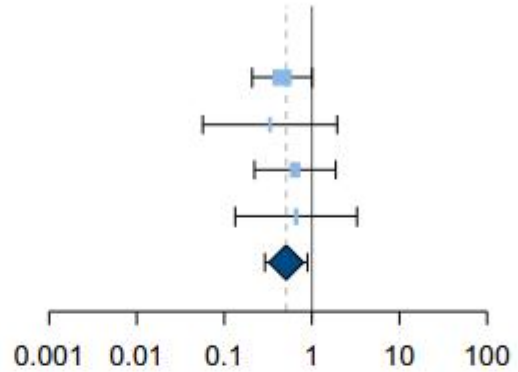
Beta-blockers: the cornerstone of PH therapy



Rodrigues et al. JHEP Rep 2019

Decompensation with liver transplant and death as competing events

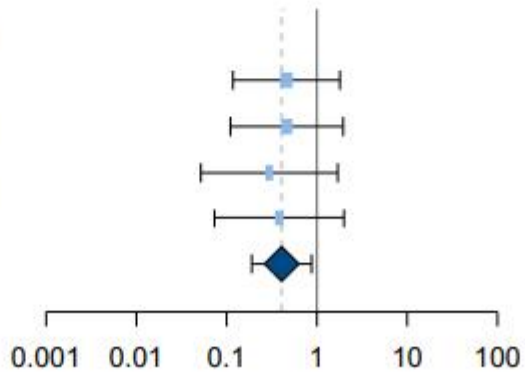
Study	Control	Carvedilol	SHR (95% CI)	Weight (%)
Tripathi 2009	16(1)/26 [53]	10(2)/36 [84]	0.444 (0.202-0.976)	51%
Shah 2014	5(4)/53 [54]	2(3)/48 [55]	0.344 (0.059-1.999)	10%
Bhardwaj 2017	9(5)/59 [73]	6(2)/64 [96]	0.630 (0.216-1.841)	27%
Villanueva 2019	4(3)/33 [90]	2(1)/33 [96]	0.745 (0.148-3.761)	12%
Pooled	34(13)/171 [270]	20(8)/181 [331]	0.506 (0.289-0.887)	100%



Random effects models. Group effect $p = 0.0173$
Descriptive statistics for control and carvedilol are events(competing-events)/n [person-years]
Heterogeneity: Q = 0.67 (df = 3, $p = 0.8802$), I^2: 0.0% [0.0%-31.5%]

Death with liver transplant as a competing event

Study	Control	Carvedilol	SHR (95% CI)	Weight (%)
Tripathi 2009	6(4)/26 [68]	4(0)/36 [99]	0.466 (0.120-1.812)	32%
Shah 2014	5(1)/53 [56]	3(0)/48 [55]	0.463 (0.109-1.962)	28%
Bhardwaj 2017	5(1)/59 [77]	2(0)/64 [101]	0.344 (0.057-2.073)	18%
Villanueva 2019	4(0)/33 [91]	2(1)/33 [98]	0.364 (0.072-1.856)	22%
Pooled	20(6)/171 [291]	11(1)/181 [353]	0.417 (0.194-0.896)	100%



Random effects models. Group effect $p = 0.0250$
Descriptive statistics for control and carvedilol are events(competing-events)/n [person-years]
Heterogeneity: Q = 0.12 (df =3, $p = 0.9898$), I^2: 0.0% [0.0%-0.0%]

Villanueva C et al. J Hepatol 2022

Start NSBB as soon as CSPH is diagnosed

- Treatment with non-selective beta-blockers (NSBBs) (propranolol, nadolol or carvedilol) should be considered for the prevention of decompensation in patients with CSPH (B.1).

- NITs can be used to identify patients with CSPH and high risk of decompensation, and to start NSBBs.

- Carvedilol is the preferred NSBB in compensated cirrhosis, since it is more effective in reducing HVPG (A.1), has a tendency towards greater benefit to prevent decompensation and towards better tolerance and has shown an improvement in survival compared to no active therapy in compensated patients with CSPH.

- Patients on NSBBs to prevent decompensation should not receive endoscopy, since this would have no impact on their clinical management (B.2).

Baveno VII Consensus; J Hepatol 2022

Baveno VII Criteria

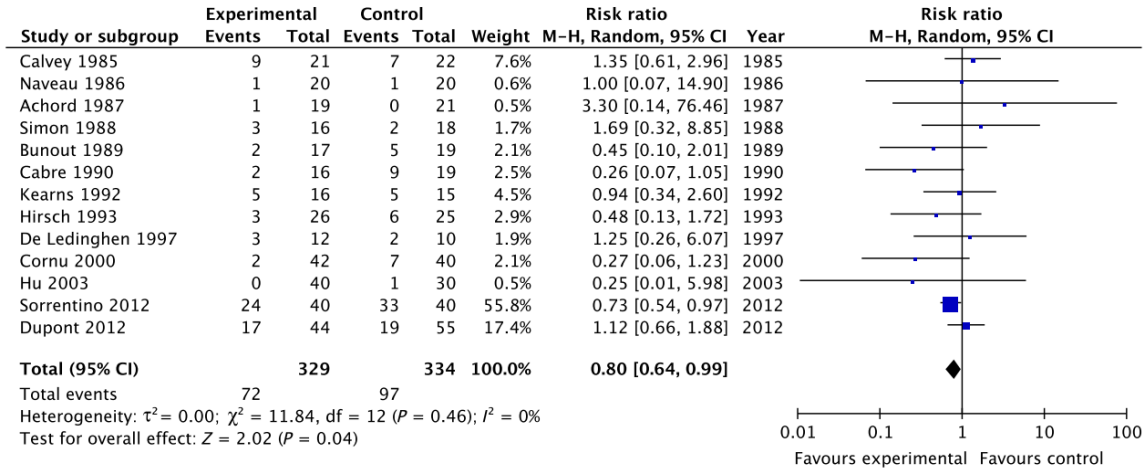
Post-treatment LSM & PLT	CSPH/ Varices/ Decompensation	Management
Consistent improvement: LSM < 12kPa & PLT > 150G/L	Exclude CSPH (sensitivity: 99.2%) No risk of hepatic decompensation	Discharge from PH surveillance if no co-factors ! Continue HCC surveillance !
LSM < 20kPa & PLT > 150G/L	Rule-out high-risk varices Low prevalence of CSPH Low risk of hepatic decompensation	No need for screening endoscopy
NSBB-therapy & LSM < 25kPa	Unknown	Repeat endoscopy & discontinue carvedilol (NSBB) if no varices
NSBB-therapy & LSM ≥ 25kPa	Rule-in CSPH (specificity: 93.6%)	Continue carvedilol (NSBB) treatment

Semmler et al. J Hepatol 2022

Nutrition in advanced ALD with PH: Cirrhosis

- Sarcopenia and malnutrition should be screened
- Optimal daily energy: 35 kcal/kg
- Optimal daily protein intake should not be lower than the recommended 1.2–1.5 g/kg. actual BW/d
- Oral supplements or enteral nutrition
- Administer micronutrients and vitamins if suspected or confirmed deficiency Thiamine (B1), pyridoxine (B6), folate (B9), cobalamin (B12), Zinc, Vitamin D

EASL CPGs Nutrition J Hep 2018



Study or subgroup	Experimental Events	Total	Control Events	Total	Weight	Risk ratio M-H, Random, 95% CI	Year
Calvey 1985	9	21	7	22	7.6%	1.35 [0.61, 2.96]	1985
Naveau 1986	1	20	1	20	0.6%	1.00 [0.07, 14.90]	1986
Achord 1987	1	19	0	21	0.5%	3.30 [0.14, 76.46]	1987
Simon 1988	3	16	2	18	1.7%	1.69 [0.32, 8.85]	1988
Bunout 1989	2	17	5	19	2.1%	0.45 [0.10, 2.01]	1989
Cabre 1990	2	16	9	19	2.5%	0.26 [0.07, 1.05]	1990
Kearns 1992	5	16	5	15	4.5%	0.94 [0.34, 2.60]	1992
Hirsch 1993	3	26	6	25	2.9%	0.48 [0.13, 1.72]	1993
De Ledinghen 1997	3	12	2	10	1.9%	1.25 [0.26, 6.07]	1997
Cornu 2000	2	42	7	40	2.1%	0.27 [0.06, 1.23]	2000
Hu 2003	0	40	1	30	0.5%	0.25 [0.01, 5.98]	2003
Sorrentino 2012	24	40	33	40	55.8%	0.73 [0.54, 0.97]	2012
Dupont 2012	17	44	19	55	17.4%	1.12 [0.66, 1.88]	2012
Total (95% CI)		**329**		**334**	**100.0%**	**0.80 [0.64, 0.99]**	
Total events	72		97				

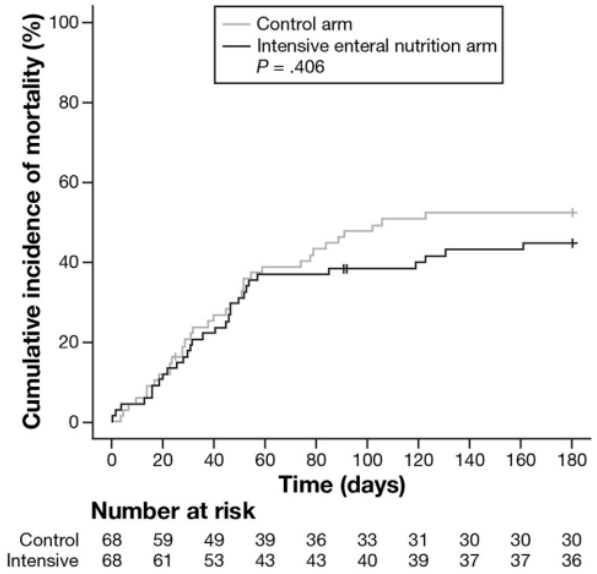
Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 11.84$, df = 12 ($P = 0.46$); $I^2 = 0\%$
Test for overall effect: $Z = 2.02$ ($P = 0.04$)

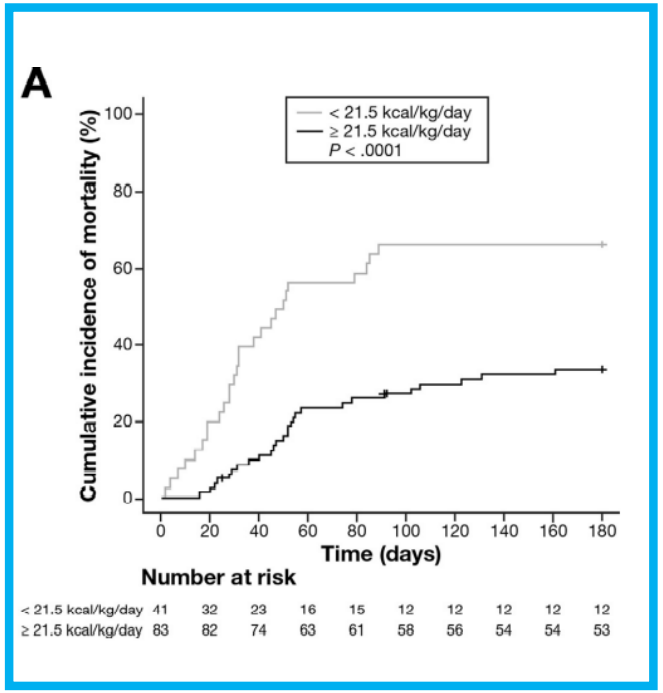
- Reduced mortality 0.80 (95% CI, 0.64 to 0.99).
- Prevented overt hepatic encephalopathy (0.73; 95% CI, 0.55 to 0.96)
- Prevented infection (0.66; 95% CI, 0.45 to 0.98, respectively)

Fialla et al. Liver Int 2015

Nutrition in advanced ALD with PH: Alcohol-related Hepatitis

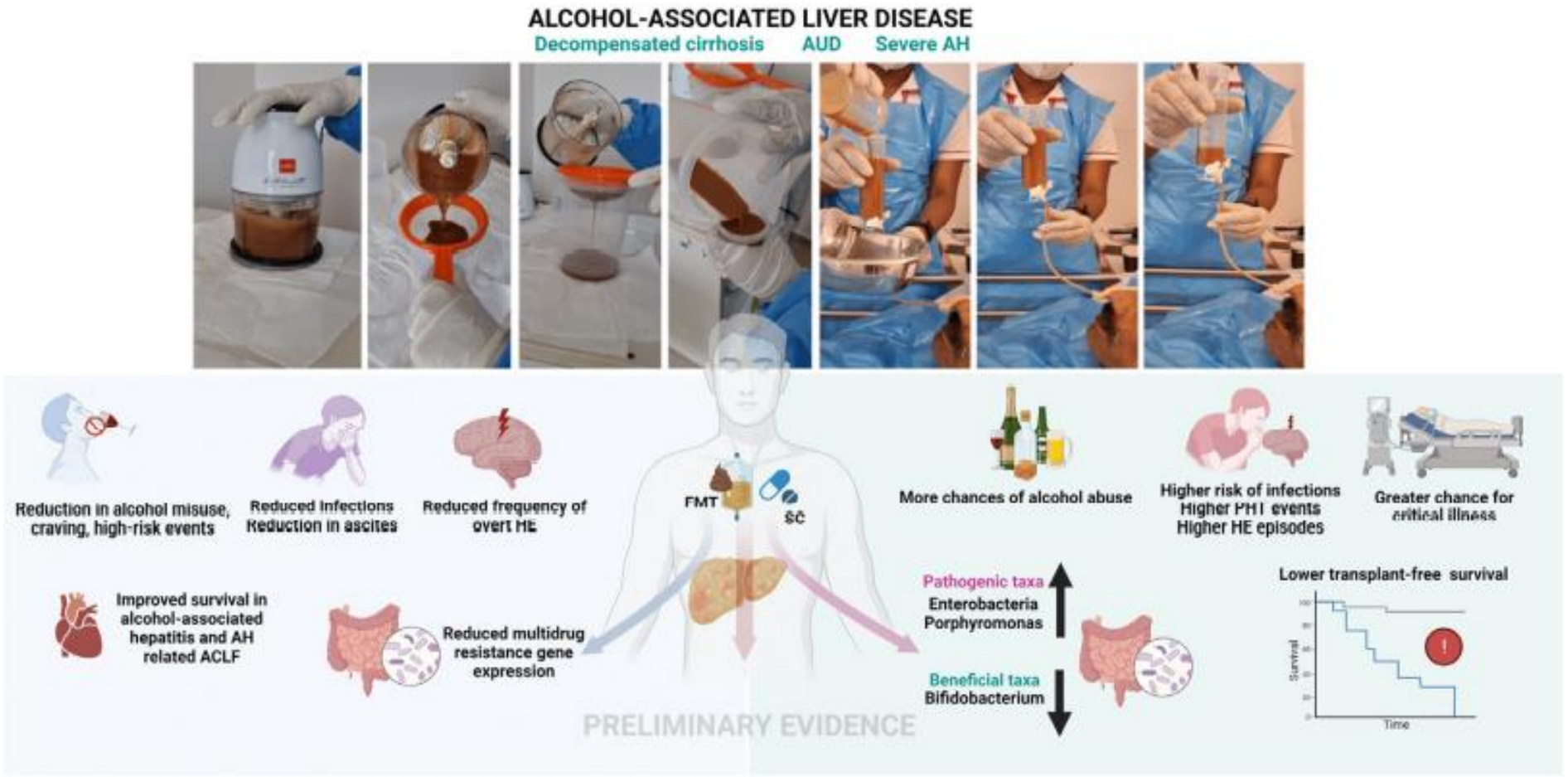
Enteral feeding tube was withdrawn prematurely from 48.5%





Moreno et al. Gastro 2016

Fecal microbiota transplantation & ALD with portal hypertension



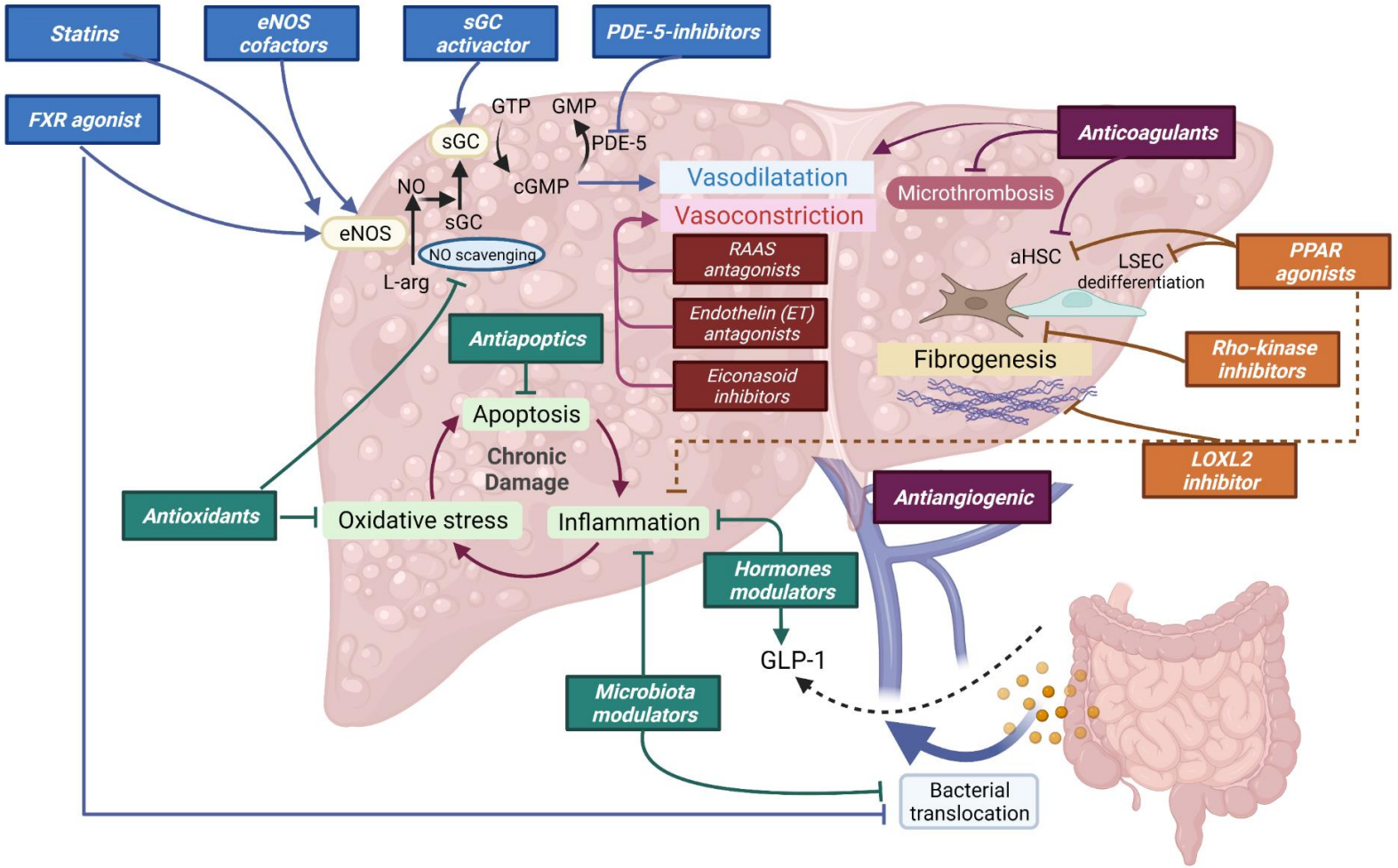
Philips et al. J CLIN AND EXP HEP 2022

AUD treatment in ALD

Drug	Approved Country	Mechanism of action	Dose	Available data on efficacy and safety in AUD patients with ALD	Main side effects
ACAMPROSATE	US and EU	Glutamate receptor modulation	1.3 g/day (weight < 60 kg) and 2 g/day (weight > 60 kg) in three daily administrations	Only one day administration study in Child A-B liver cirrhosis	Diarrhea
BACLOFEN	France	GABA-B agonist	10 mg t.i.d. in patients with liver disease	In Child A-C liver cirrhosis	Sedation with high doses, hypotonia
DISULFIRAM	US and EU	Inhibitor of aldehyde dehydrogenase	800-1200 mg/day for 3-4 days, then 400 mg/day until the 7th day, after 200 mg/day	NO	Hepatotoxicity (particularly in patients with liver disease), sleepiness, headache
NALMEFENE	EU	Selective opioid receptor ligand with antagonist activity at the μ and δ receptors and partial agonist activity at the κ receptor	18 mg per day "on demand"	NO	Insomnia, Headache, Nausea
NALTREXONE	US and EU	Opiate antagonist with the highest affinity for the μ receptor	50-100 mg/day	NO	Headache, sedation, nausea/vomiting
SODIUM OXIBATE (GHB)	Italy Austria Kazakhstan	GABA-B/ GHB receptor agonist	50 mg/kg divided into three or six daily administrations	Only one case report (see ref 99)	Dizziness, headache, nausea, vertigo

Arab et al. Clin Gast Hep 2023

Therapy targets for portal hypertension



Rodrigues et al. Expert Opin Investig Drugs 2022