Portal Hypertension Update

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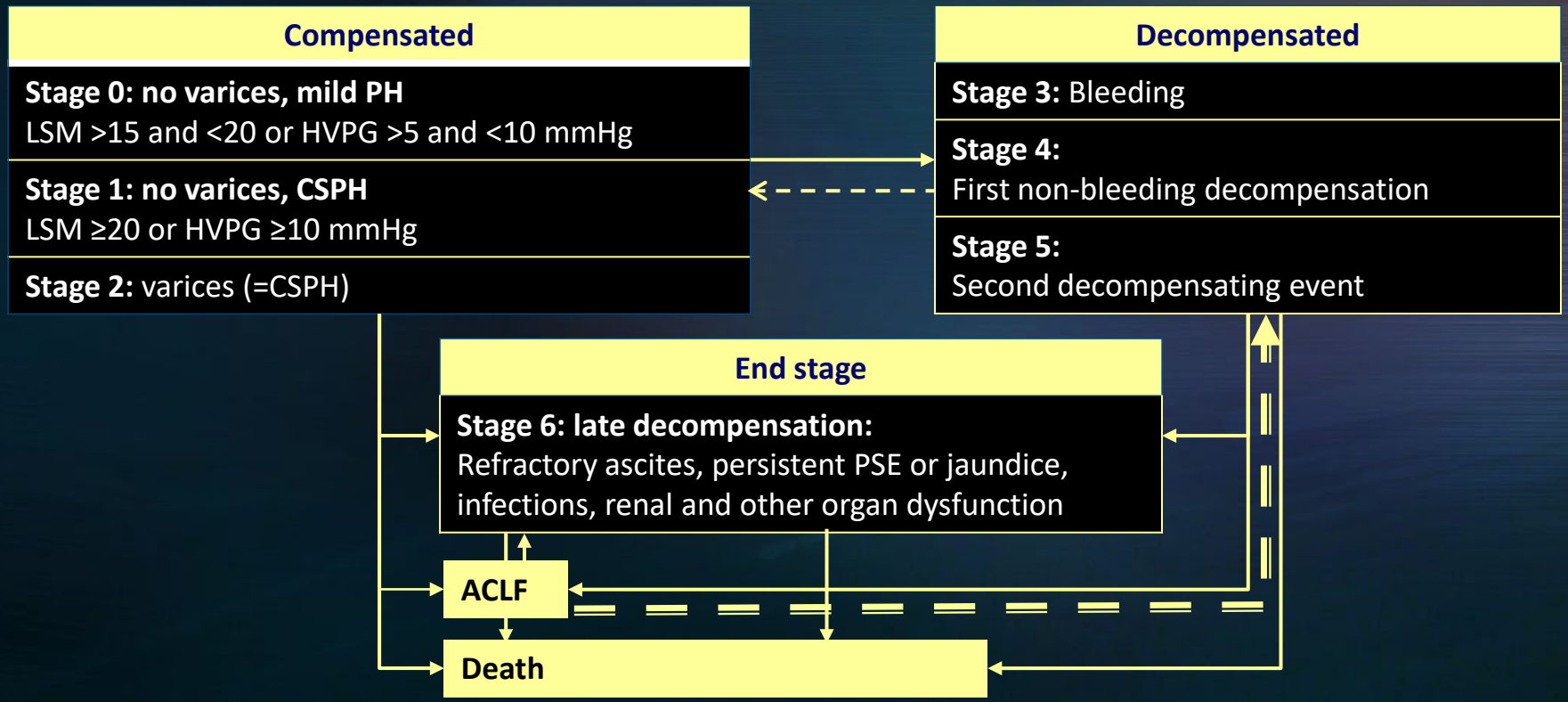
Portal Hypertension

Prediction and Prognosis

Multi-stage model for the clinical course of cirrhosis

- Transition from compensated cirrhosis to DC occurs at a rate of ~5–7% per year
- DC is a systemic disease, with multi-organ/system dysfunction



D'Amico G, et al. J Hepatol 2018;68:563–76;
EASL CPG decompensated cirrhosis. J Hepatol 2018;doi: 10.1016/j.jhep.2018.03.024

Multi-stage model for course of cirrhosis

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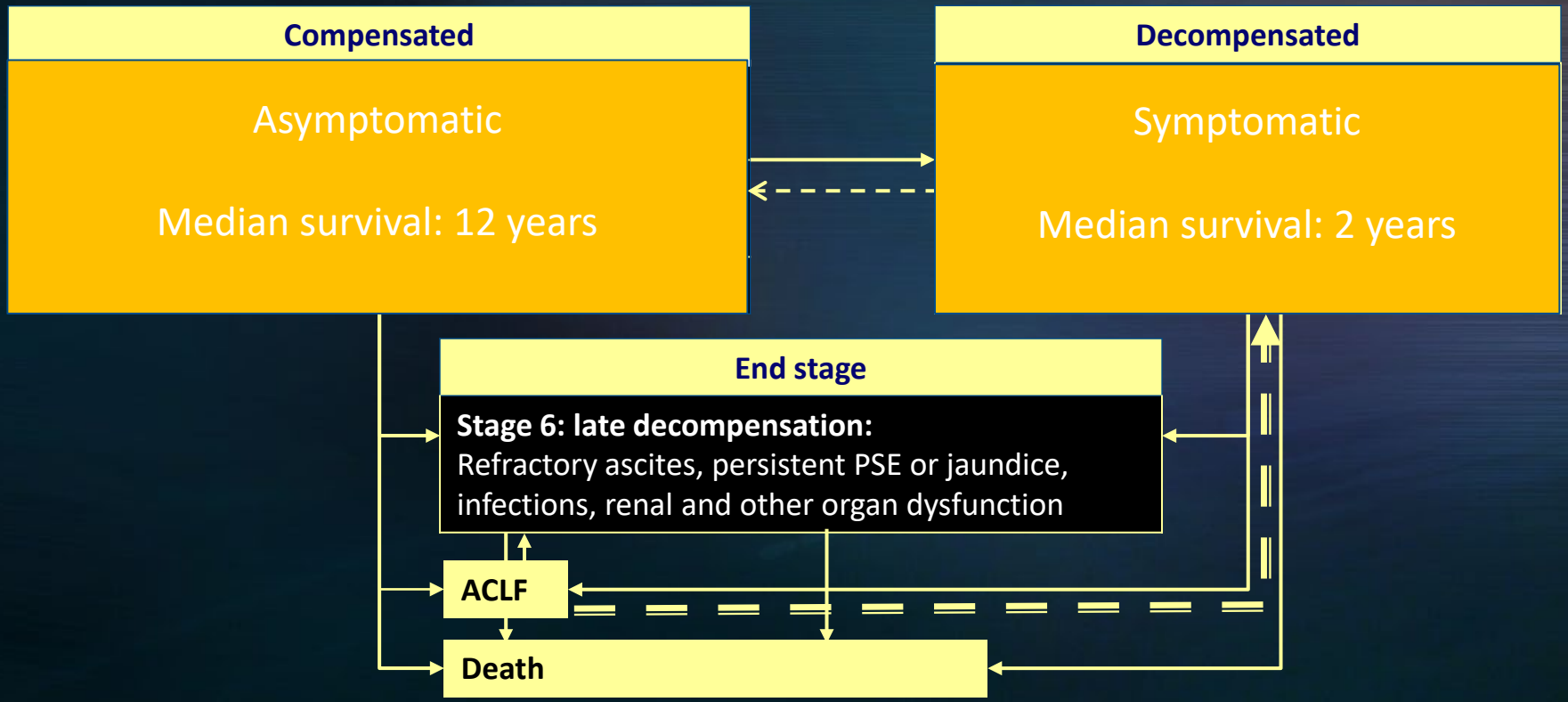


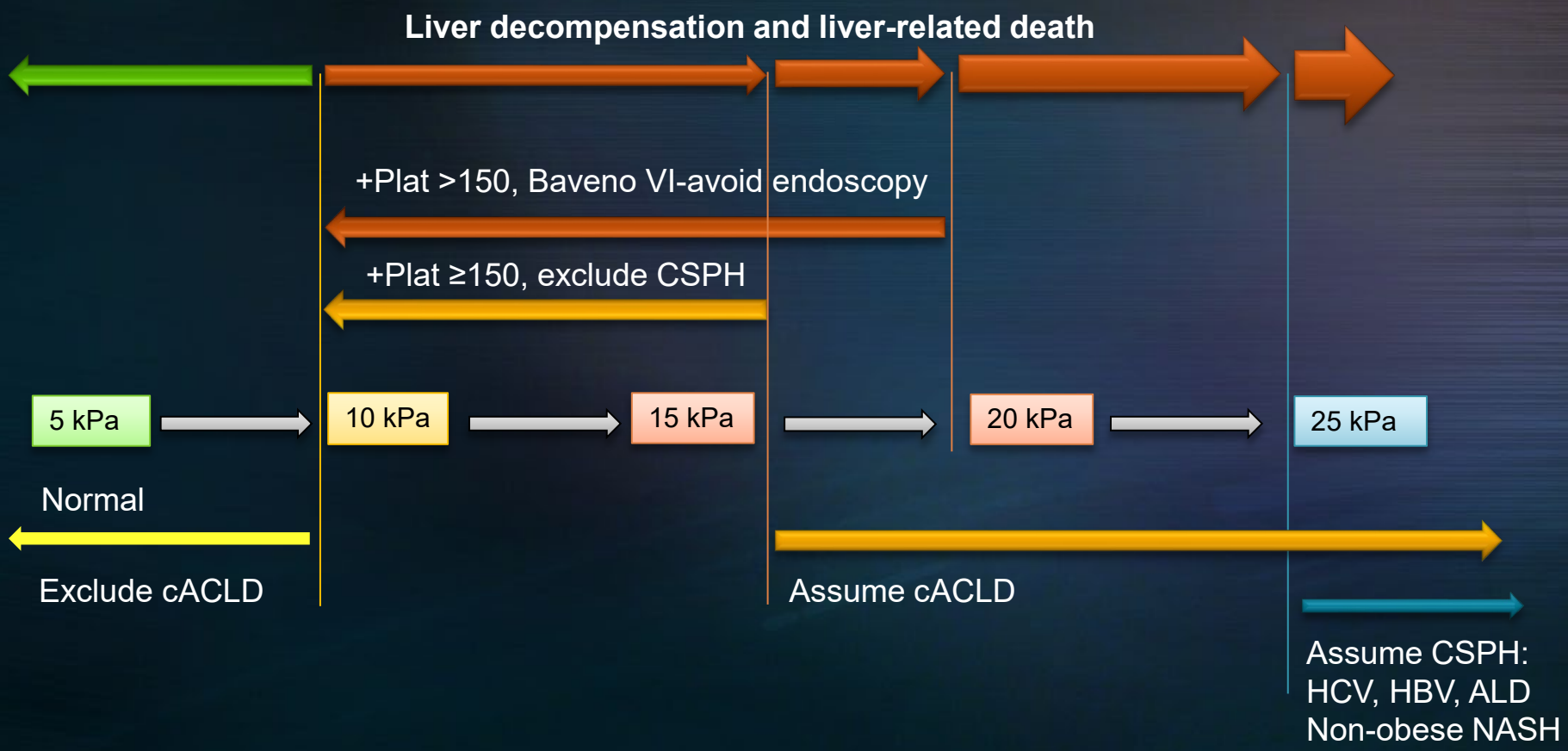
D'Amico G, et al. J Hepatol 2018;68:563–76;
EASL CPG decompensated cirrhosis. J Hepatol 2018;doi: 10.1016/j.jhep.2018.03.024

Baveno VII: Terminology

- Compensated Advanced Chronic Liver Disease (cACLD)
- Reflects continuum of advanced fibrosis and cirrhosis
- Liver stiffness measurement used to stratify risk of Clinically Significant Portal Hypertension (CSPH) ie HVPG $\gtrsim$ 10 mmHg

De Franchis 2022

Algorithm for Non-Invasive Determination of cACLD and CSPH



Baveno VII 2022

Diagnosis of CSPH in Cirrhosis

- In PBC presinusoidal component of Portal Hypertension may be underestimated by HVPG
- In NASH manifestations of CSPH even if HVPG < 10 mmHG
- Reduction in HVPG with beta-blockade reduces risk of variceal bleeding in cirrhosis due to alcohol or viral hepatitis

Baveno VII

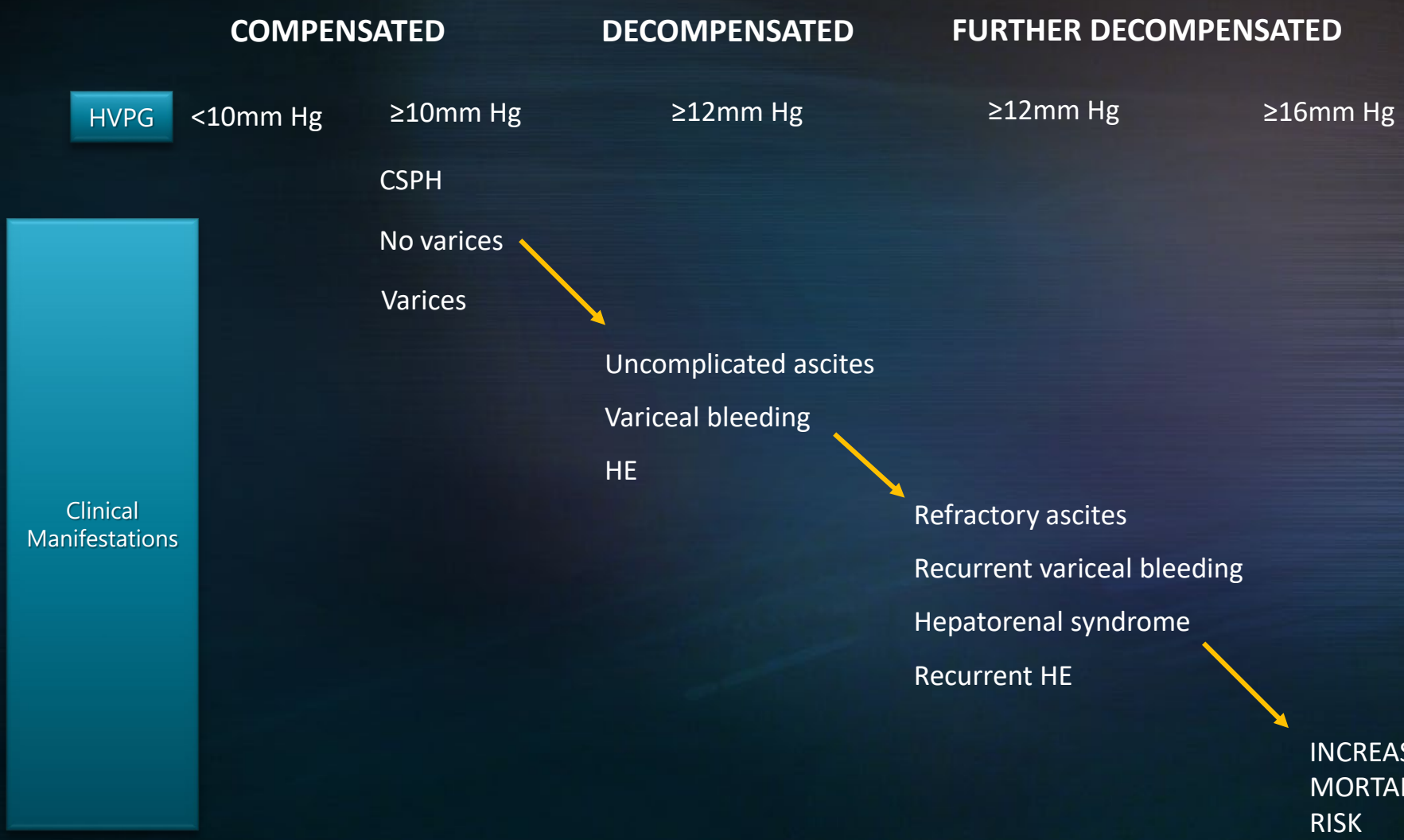
Portal Hypertension

Prediction and Prognosis

Management of Cirrhosis

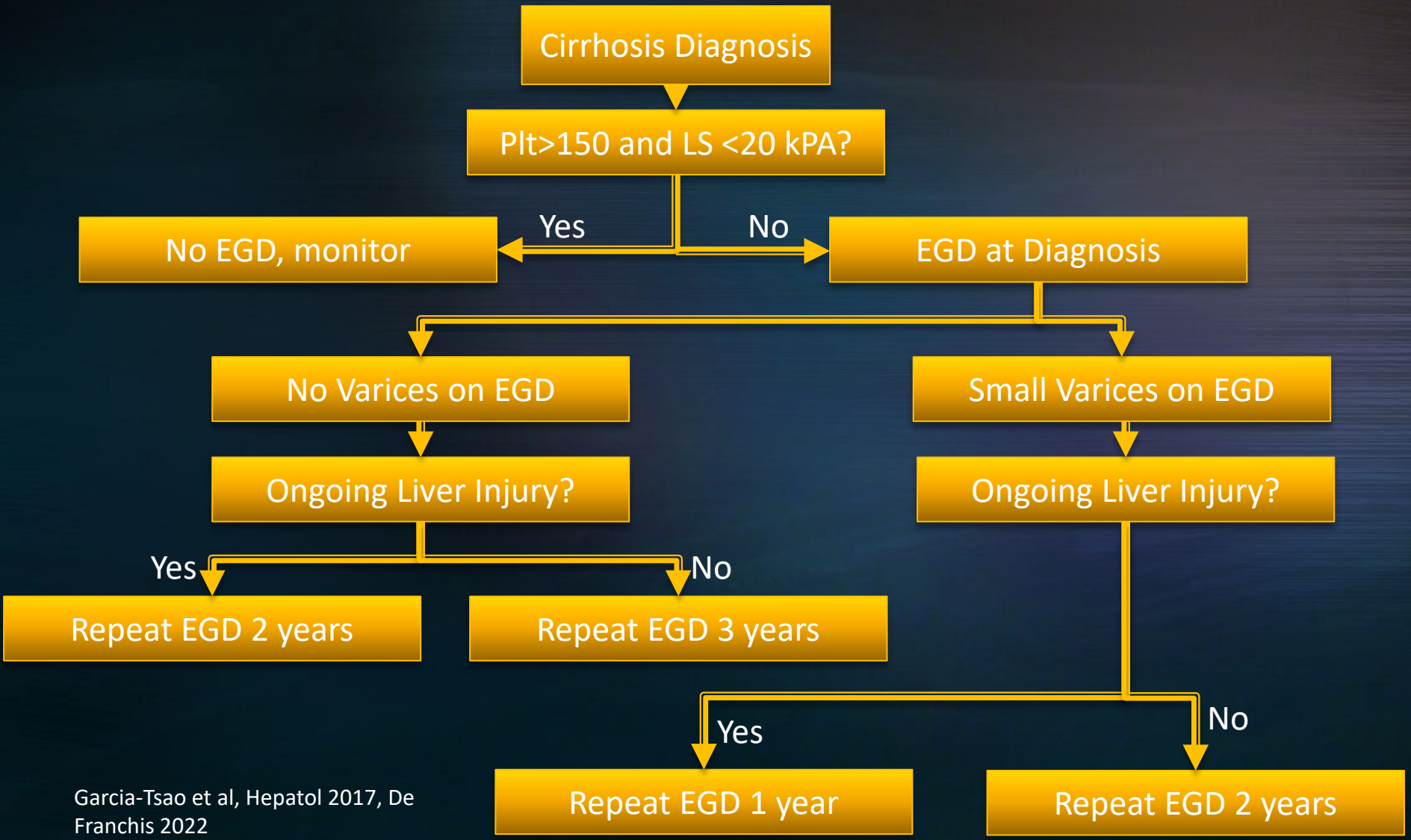
Varices

Natural History Of The Progression Of Portal Hypertension



Adebayo et al. Ascites and Hepatorenal Syndrome, *2019*

Variceal Screening and Surveillance



Garcia-Tsao et al, Hepatol 2017, De Franchis 2022

Management of large varices that have not bled

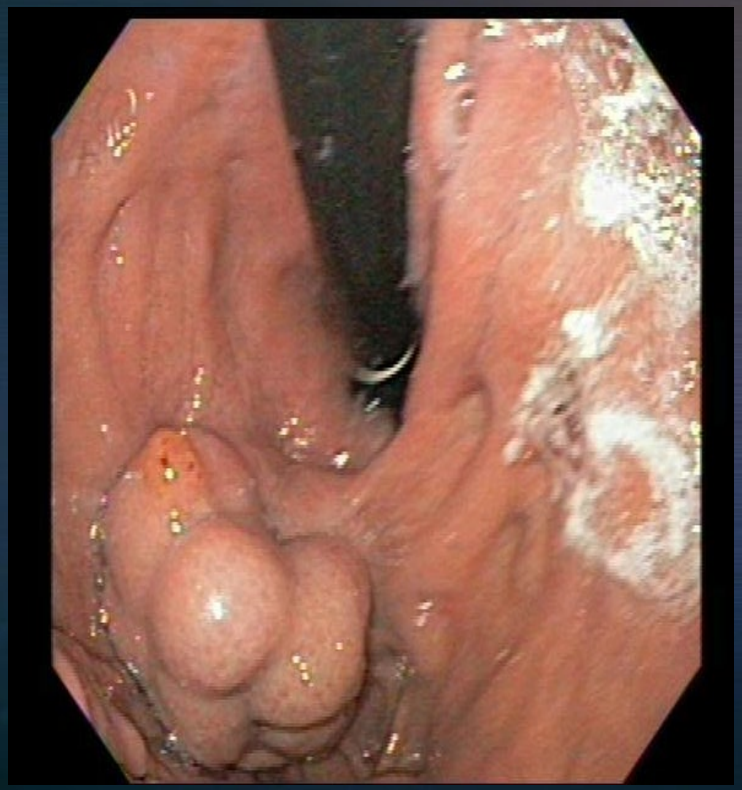
Therapy	Dose and recommended goals	Maintenance/Follow up
Propranolol	Start at 20-40 mg bid Titrate to HR 55-60/min Avoid systolic <90 mm Hg	Monitor HR No need for F/U EGD
Nadolol	Start at 20-40 mg daily Titrate to HR 55-60/min Avoid systolic <90 mm Hg	Monitor HR No need for F/U EGD
Carvedilol (Baveno VII)	Start at 6.25 mg daily Maximum dose 12.5 mg daily Titrate to HR 55-60/min Avoid systolic <90 mm Hg	Monitor HR No need for F/U EGD
Endoscopic banding	Variceal eradication	First EGD 3-6 months after eradication Subsequent EGD every 6-12 months

Portal Hypertension

Gastric Varices

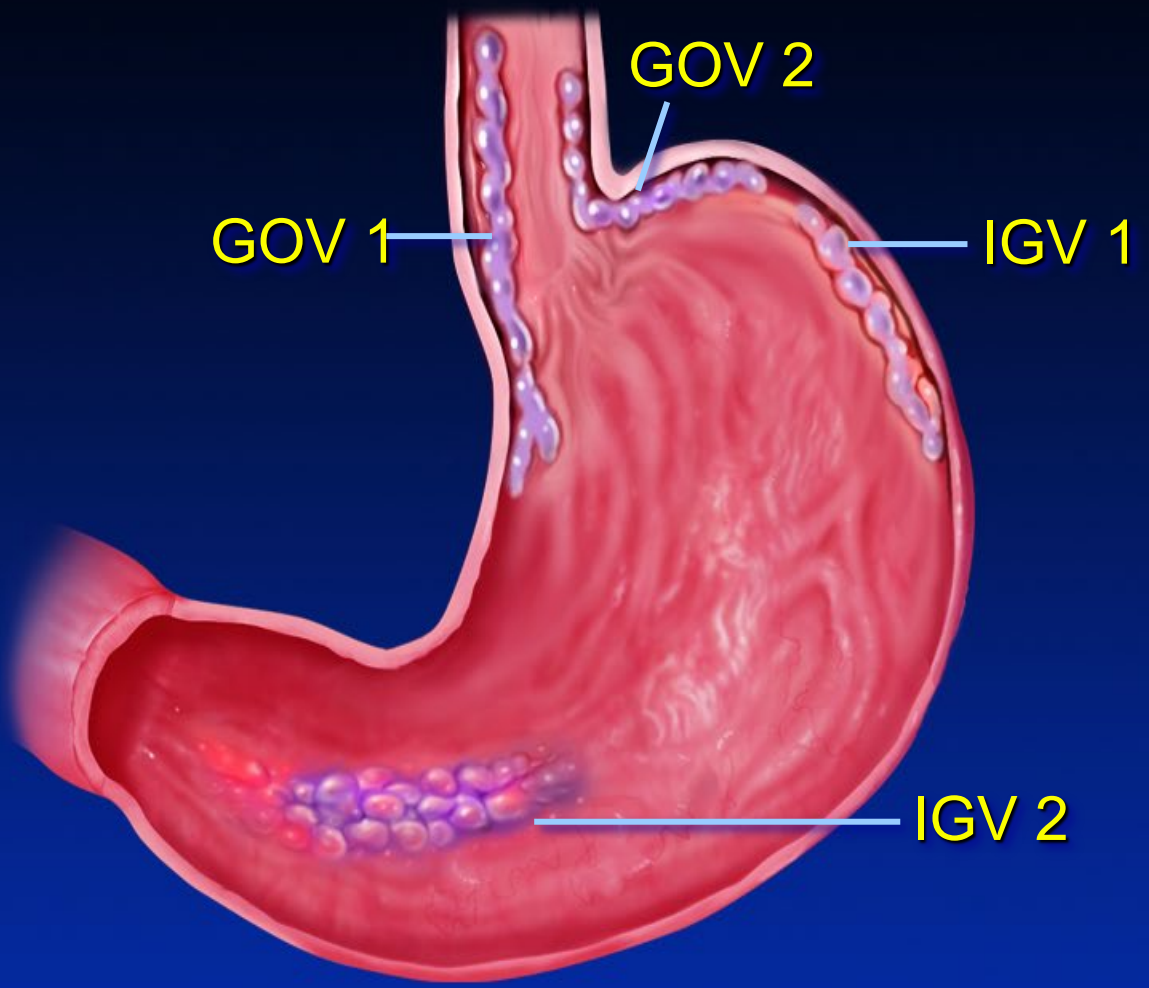
Gastric Varices

- Present in 5-30% of patients with cirrhosis
- Account for 10-15% of variceal bleeding episodes
- Risk factors: location, size, Child class, presence of red spots, HCC
- Bleed less but more severe
- Therapy can be challenging



Tripathi D, Aliment Pharmacol Ther. 2006
Irani S, J Clin Gastroenterol, 2011
Bazarbashi AN, Ryou M. Curr Opin Gastroenterol. 2019

Classification of Gastric Varices



Sarin et al, Am J Gastro 1989; 84:1244

Esophageal vs Gastric Varices

	Esophageal varices/GOV1	GOV2	IGV1/IGV2
Localization	Mucosa/lamina propria	Mucosa/lamina propria Submucosa	Submucosa
Size	Variable	Variable/mostly large	Large (>1 or 2cm)
Colateral pathway	Left and right gastric vein	Left and right gastric vein	Small veins Posterior gastric vein
Actively bleeding at endoscopy	Up to 20%	Uncommon	Very rare
HVPG	> 12 mmHg	> 12 mmHg	May occur at < 12 mmHg
Severity	Standard	Severe	Severe

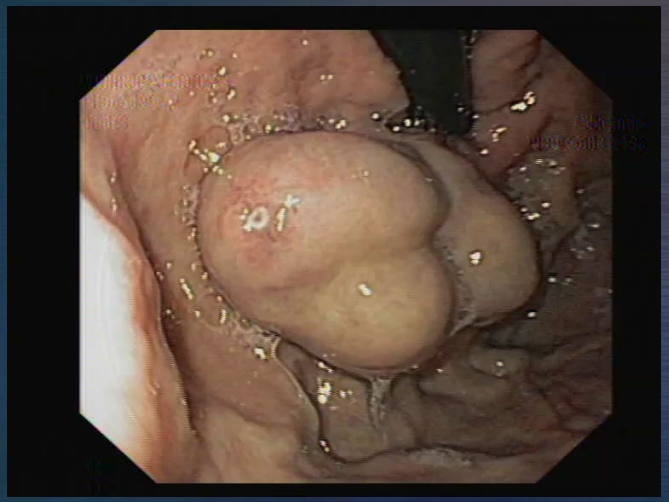
Principles of Therapy of Gastric Varices

Primary Prophylaxis	Acute Bleed	Secondary Prophylaxis
Uncontrolled studies	Same as EV	NSBB + glue
No clear role for endoscopy	Glue / Bands	TIPS
NSBB- preferred choice	BRTO	
No indication for TIPs or BRTO	Massive: linton + TIPS	

Treatment of acute GV bleeding

Endoscopy – first choice

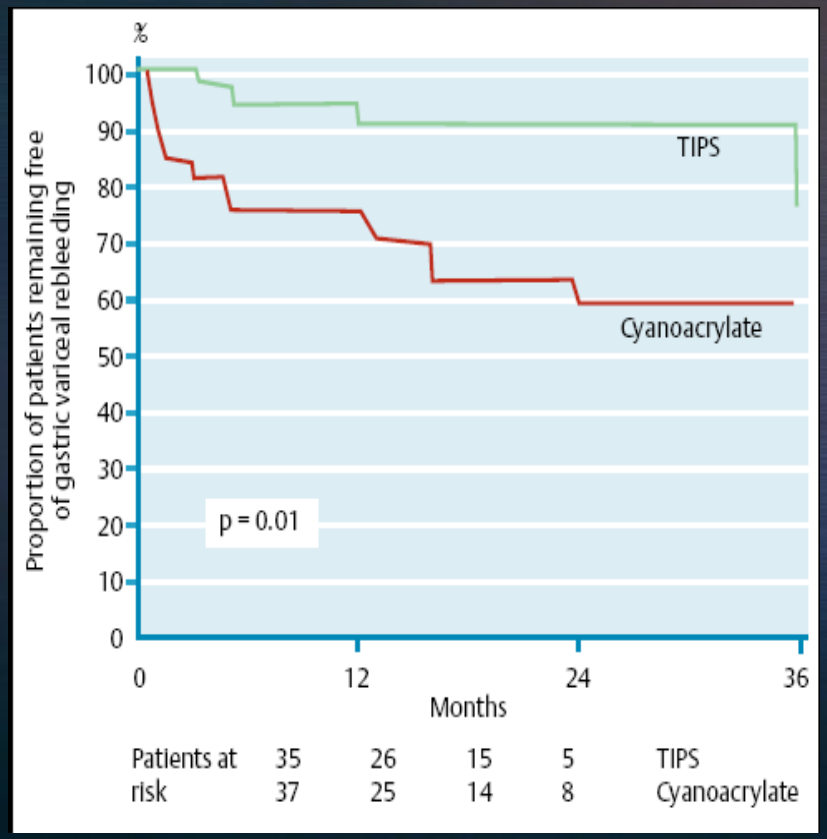
- Cyanoacrylate injection (free hand):
  - 90-98% control of bleeding
- Thrombin injection:
  - 92-100% control of bleeding
- EUS – Guided glue +/- coils
  - Promising, rates similar to endo-glue therapy
- BRTO & TIPS:
  - 95% control of bleeding



Rios-Castellanos. Cochrane Database Syst Rev. 2015 May 12;(5):CD010180.
Qiao A. Medicine (Baltimore). 2015 Oct;94(41):e1725.
Bhurwal A et al. Dig Dis Sci. 2021 Mar 17. doi: 10.1007/s10620-021-06915-5.
Lo GH et al Endoscopy. 2020 Jul;52(7):548-555.
Mohan BP et al . Endoscopy. 2020 Apr;52(4):259-267

TIPS vs Cyanoacrylate for rebleeding Prospective RCT- Taiwan (n=35 vs n=37)

- Rebleeding
  - Tips (11%) vs Glue (38%)
- Less transfusions (Tips)
- Complications
  - > HE (Tips)
- Similar survival
- TIPS better at preventing rebleeding
- Mostly GOV 1/2, only 3 patients with IGV.



Lo GH, et al Endoscopy 2007

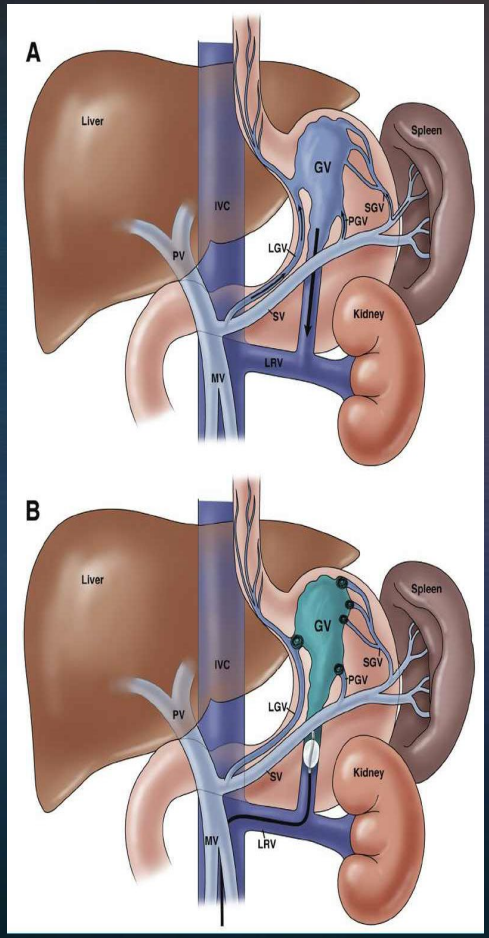
Balloon-occluded retrograde transvenous obliteration (BRTO)

Occlusion of blood flow with balloon catheter with instillation of a sclerosant proximal to the site of balloon occlusion.

Requires spontaneous shunt into which a balloon catheter is retrogradely introduced.

In the case of gastric varices, there frequently is a spontaneous gastrorenal shunt

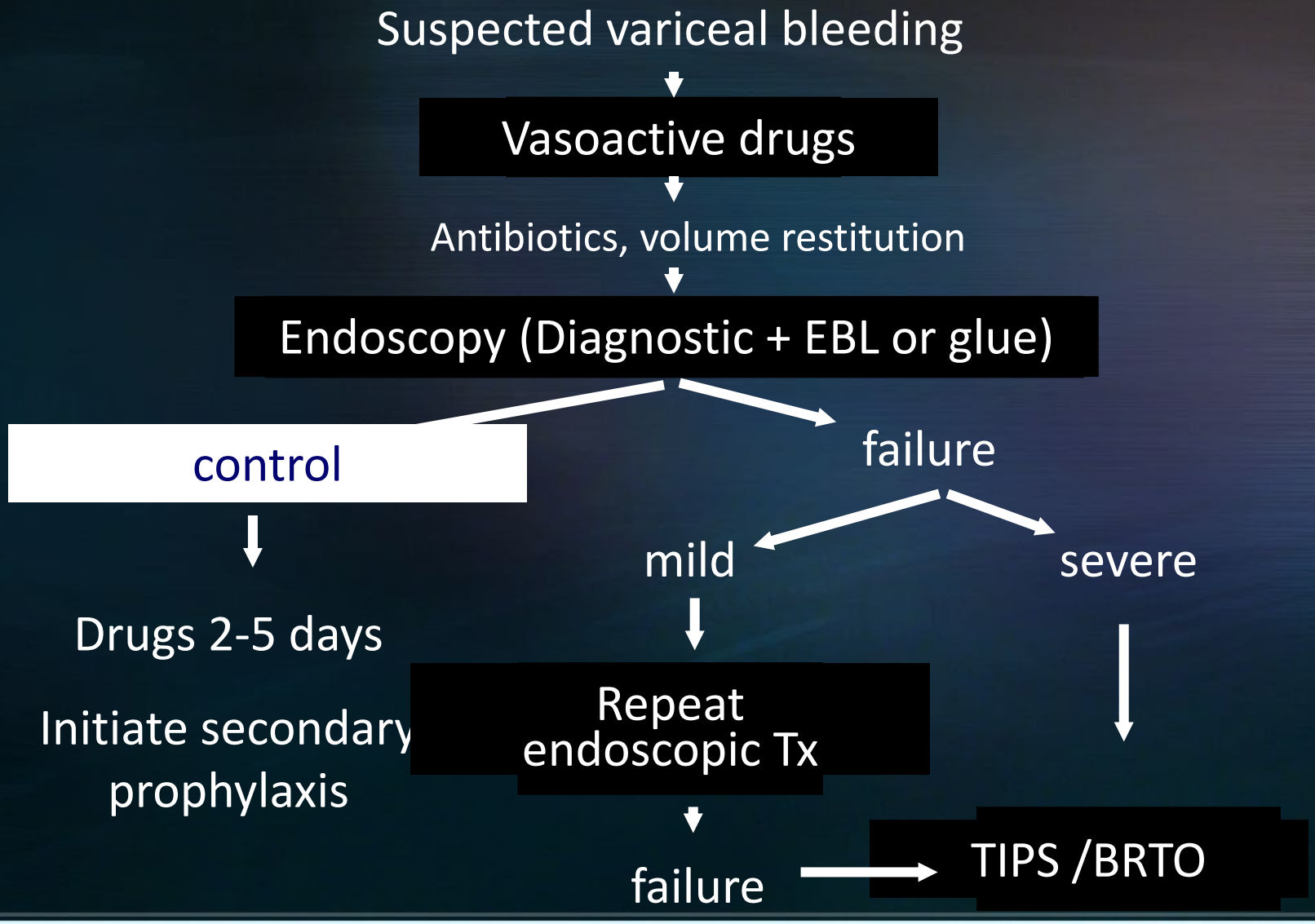
Hemostasis 90%, comparable to TIPS



Imai Y, J Gastroenterol Hepatol,2016

Treatment of Acute GV Bleeding

Baveno 2022, AASLD guidance 2017

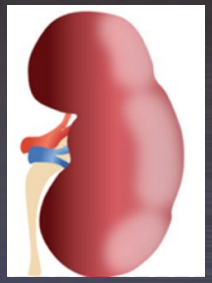


Portal Hypertension

Acute Kidney Injury

Hepatorenal syndrome

- Renal dysfunction
  - Occurs in 20-40% of patients with advanced cirrhosis
  - Associated with ↑ mortality
  - "Normal" serum creatinine can be falsely reassuring
    - Patients with cirrhosis and sarcopenia have lower muscle mass and so less creatine to convert to creatinine
- Hepatorenal syndrome
  - One of the causes of renal dysfunction in patients with liver disease
  - Diagnosis of exclusion
  - Poor prognosis



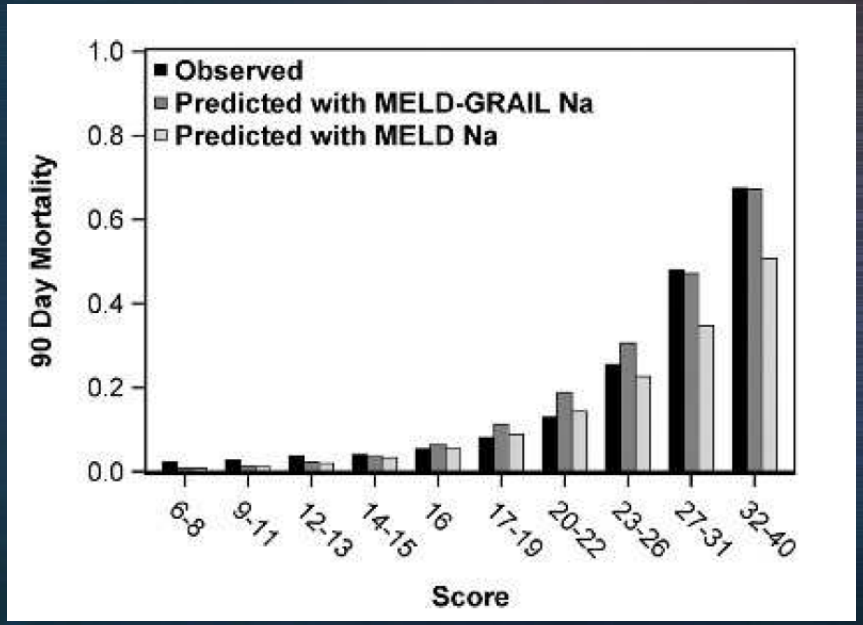
Adebayo D. *Clin Liver Dis* 2019

Limitations of Creatinine in Cirrhosis

- Creatinine can take days to reach a steady state after injury:
  - Up to 50% of kidney function can be lost before creatinine starts to rise
  - Reflects perfusion, not injury
- Creatinine is a poor estimate of kidney function in cirrhosis:
  - Impacted by diet, muscle mass, muscle metabolism, low liver production of creatinine, hydration status and medications
  - Bilirubin and other substances have a variable impact on creatinine measurement depending on assay and calibration

Creatinine as the Measure of Kidney Function in the MELD Score: Impact on LT Candidates

- Patients with low baseline creatinine are disadvantaged
  - Clearly impacts the increase wait list mortality among women
- Substitution of creatinine with eGFR improves performance of MELD score to predict wait list mortality
  - MELD-GRAIL-Na



Asrani SK, et al. Hepatology 2019

Acute kidney injury in cirrhosis

AKI:

- ↑ sCr ≥ 0.3 mg/dL within 48 hours
- ↑ sCr ≥ 50% from baseline with change presumed within prior 7 days

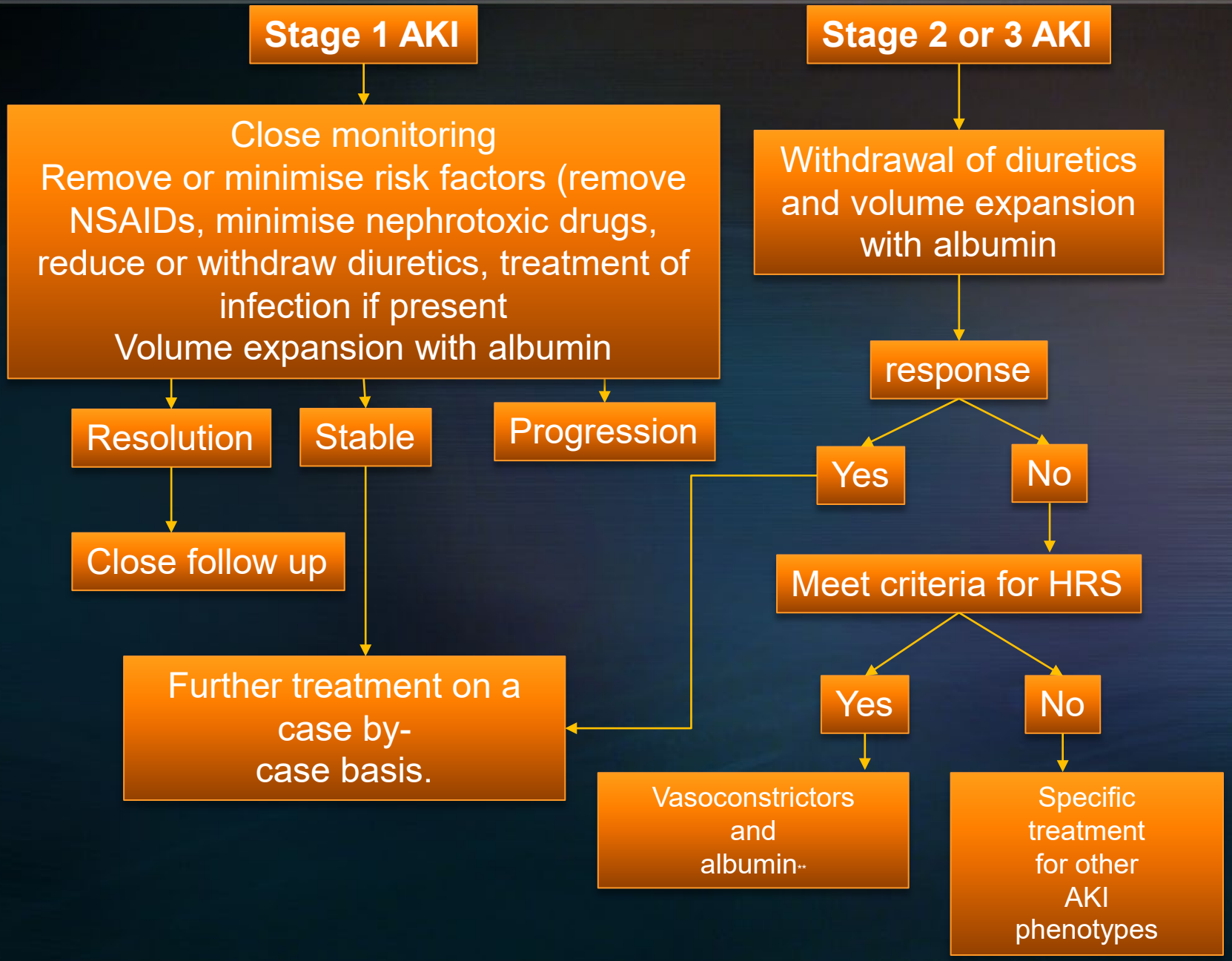
Stage 1
↑ sCr > 0.3 mg/dl OR ↑ sCr > 1.5 to 2-fold baseline
1a: sCr < 1.5 mg/dl at diagnosis
1b: sCr ≥ 1.5 mg/dl at diagnosis

Stage 2
↑ sCr > 2 to 3-fold baseline

Stage 3 (any of the following)
↑ sCr > 3-fold baseline
sCr > 4.0 mg.dL with acute ↑ ≥ 0.3
Renal replacement therapy initiation

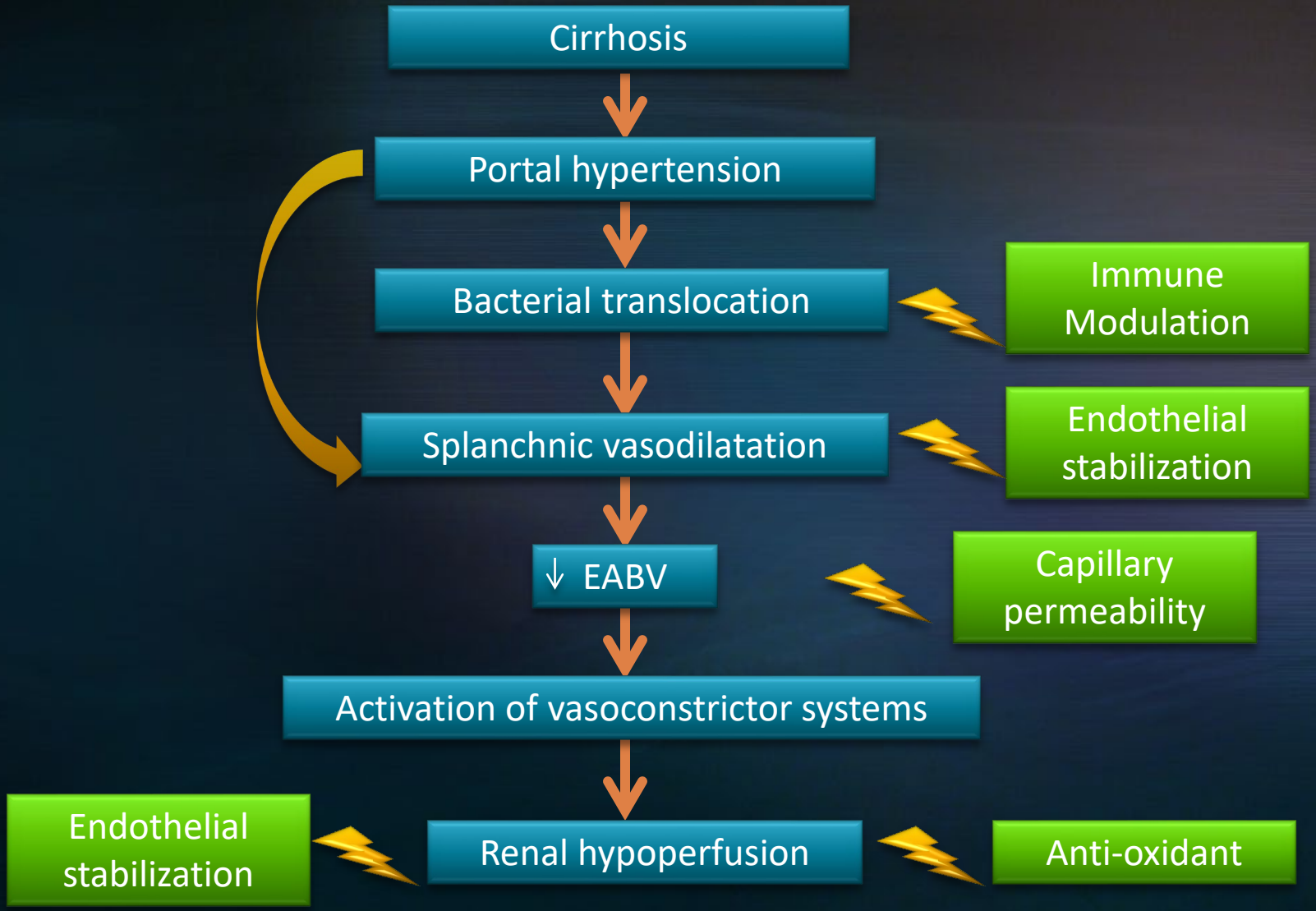
sCr: serum creatinine

Angeli P. *Gut* 2015; EASL. *J Hepatol* 2018



Amin et al. Seminars in Nephrology, *2019*

Albumin Can Help to Correct Pathophysiology



Caraceni Lancet 2018

When to reduce/stop β-blockers

Reduce

- Systolic BP < 90 mmHg
- Creatinine >1.5 mg/dl
- Serum sodium < 130 mmol/L

Stop

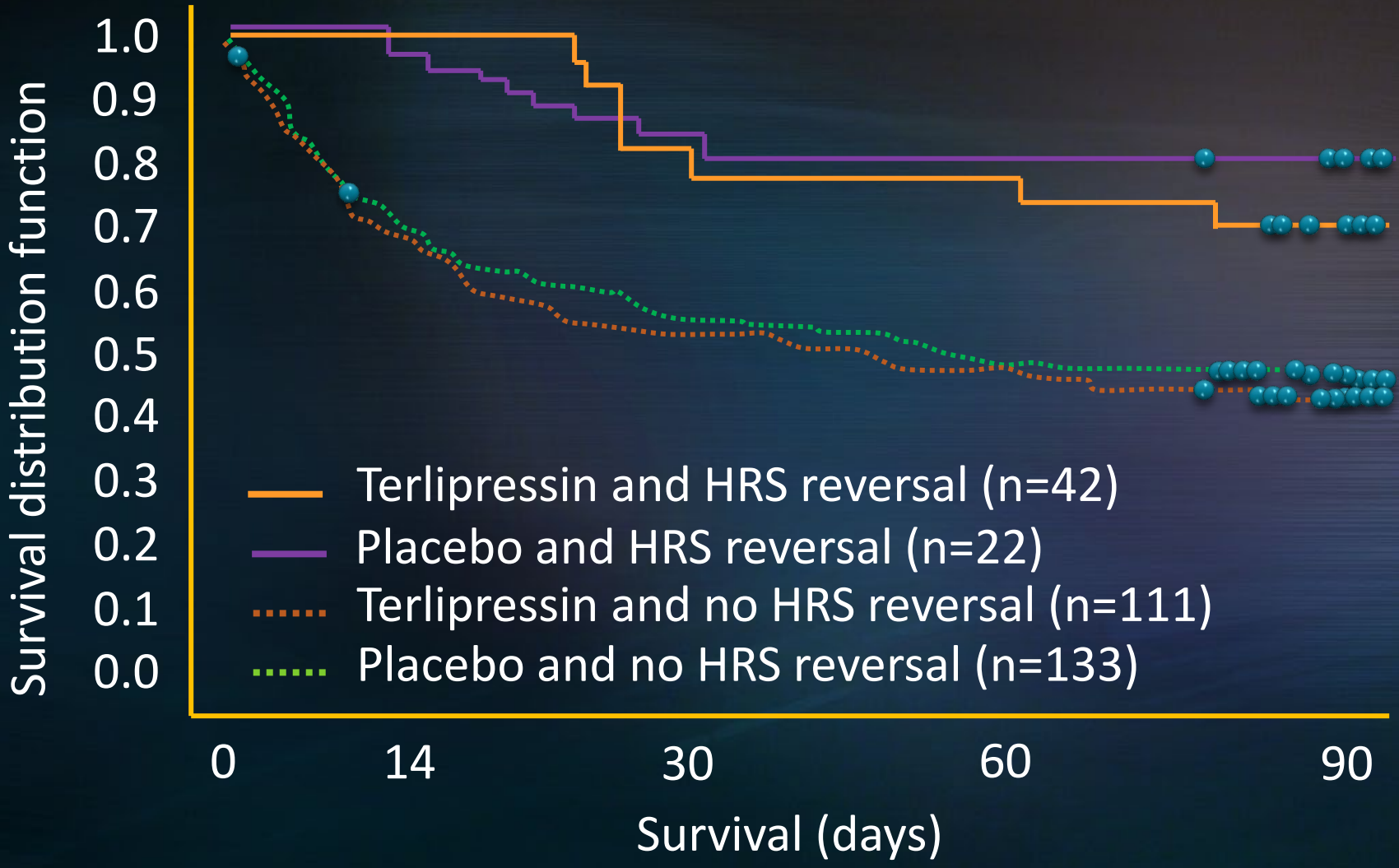
- Pressors started

Reiberger 2018

Renal Dysfunction in Liver Disease

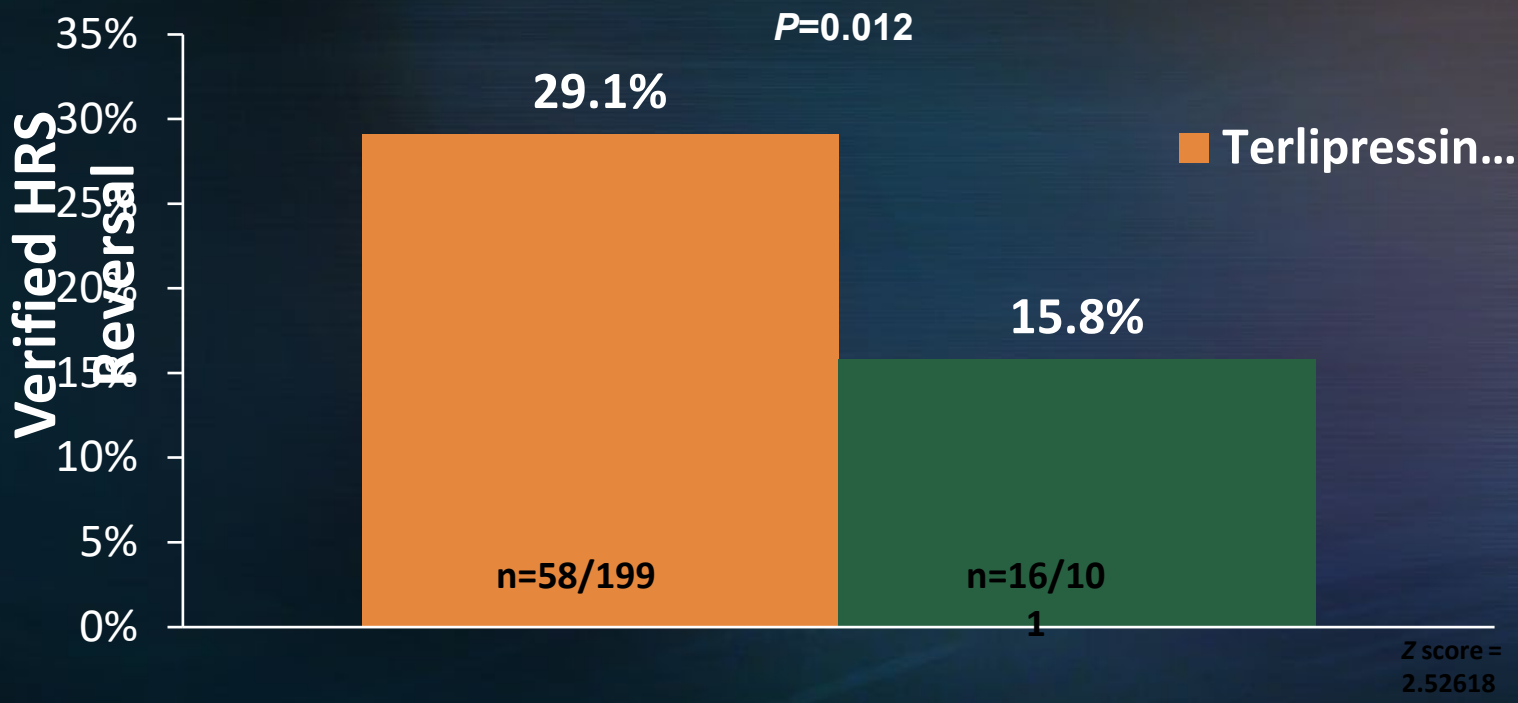
Role of Vasoconstrictors

Reversal of HRS1 Improves survival



Sanyal A. et al, Aliment Pharm & Therap 2017

The CONFIRM Study: Verified HRS Reversal

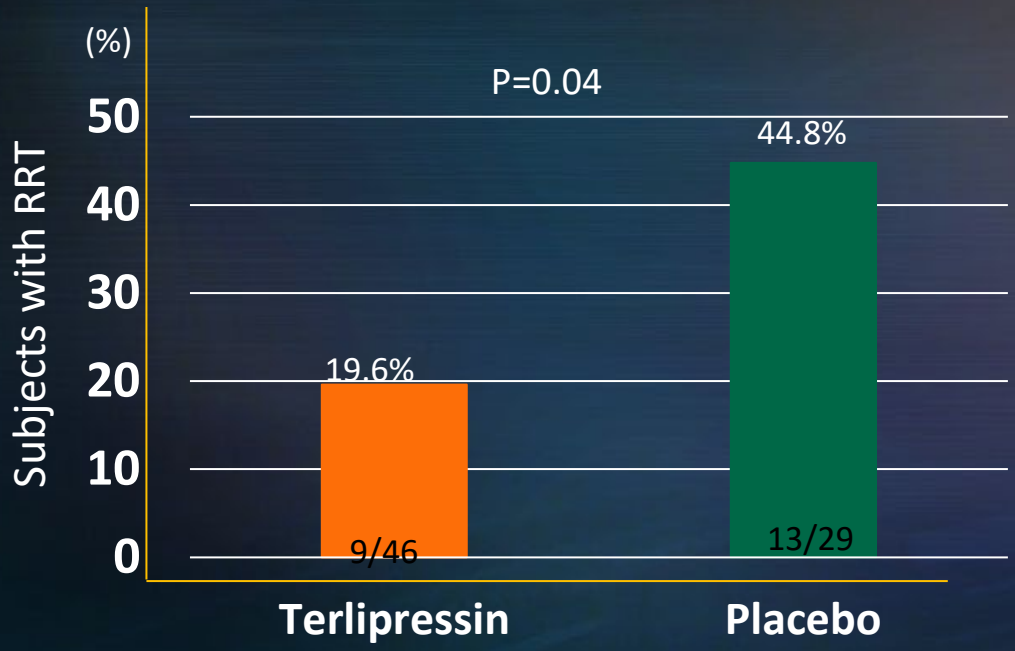


The CONFIRM Study: Secondary Endpoints and Efficacy Variables

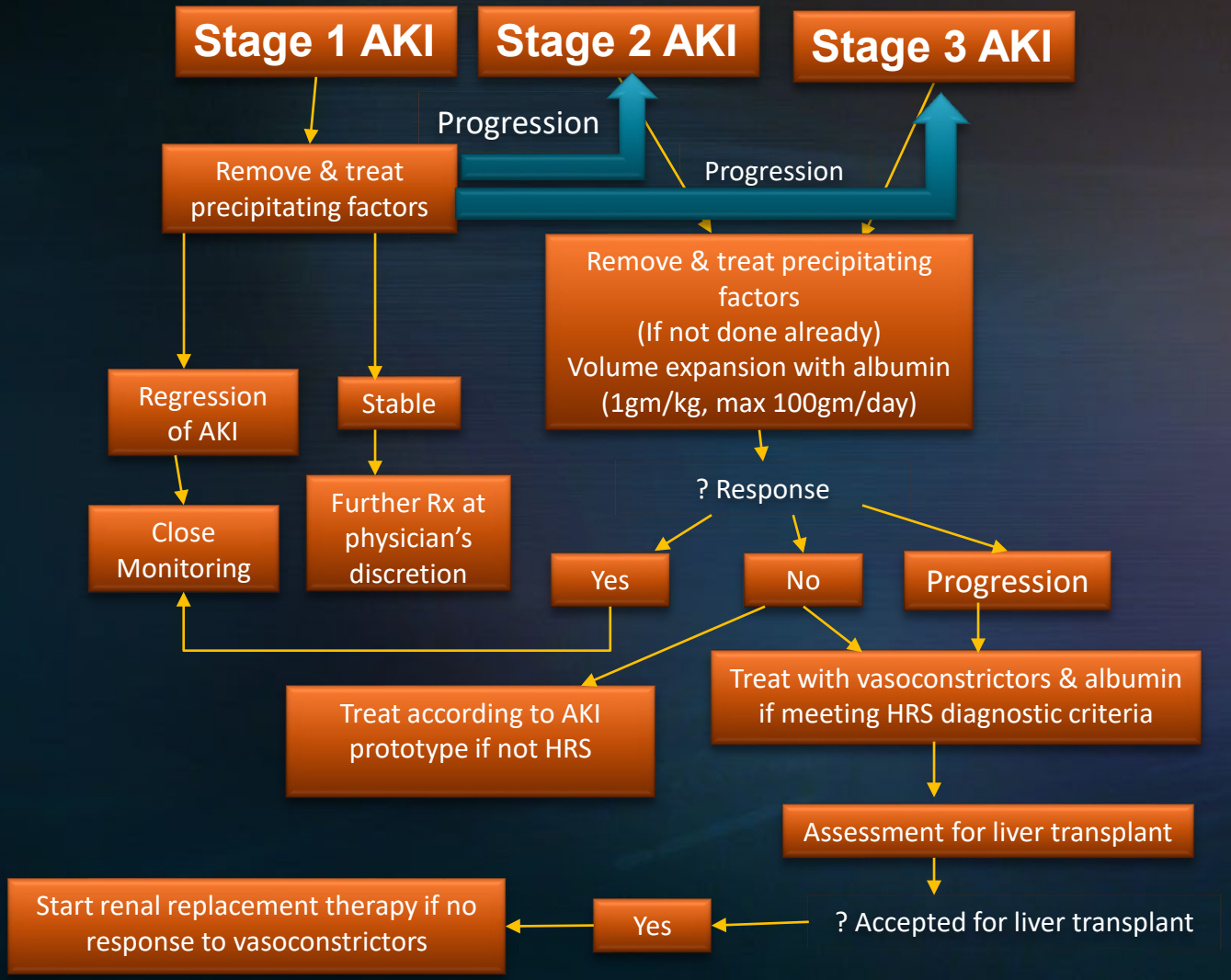
Outcome, n (%)	Terlipressin (n=199)	Placebo (n=101)	*P* Value
Durability of HRSR (no RRT to Day 30)	63 (31.7)	16 (15.8)	0.003
HRSR in the SIRS subgroup	28 (33.3)	3 (6.3)	<0.001
VHRSR with no recurrence of HRS by Day 30	48 (24.1)	16 (15.8)	0.092
Alive and transplant-free at Day 90	52 (26.1)	27 (26.7)	0.78

Wong NEJM 2021

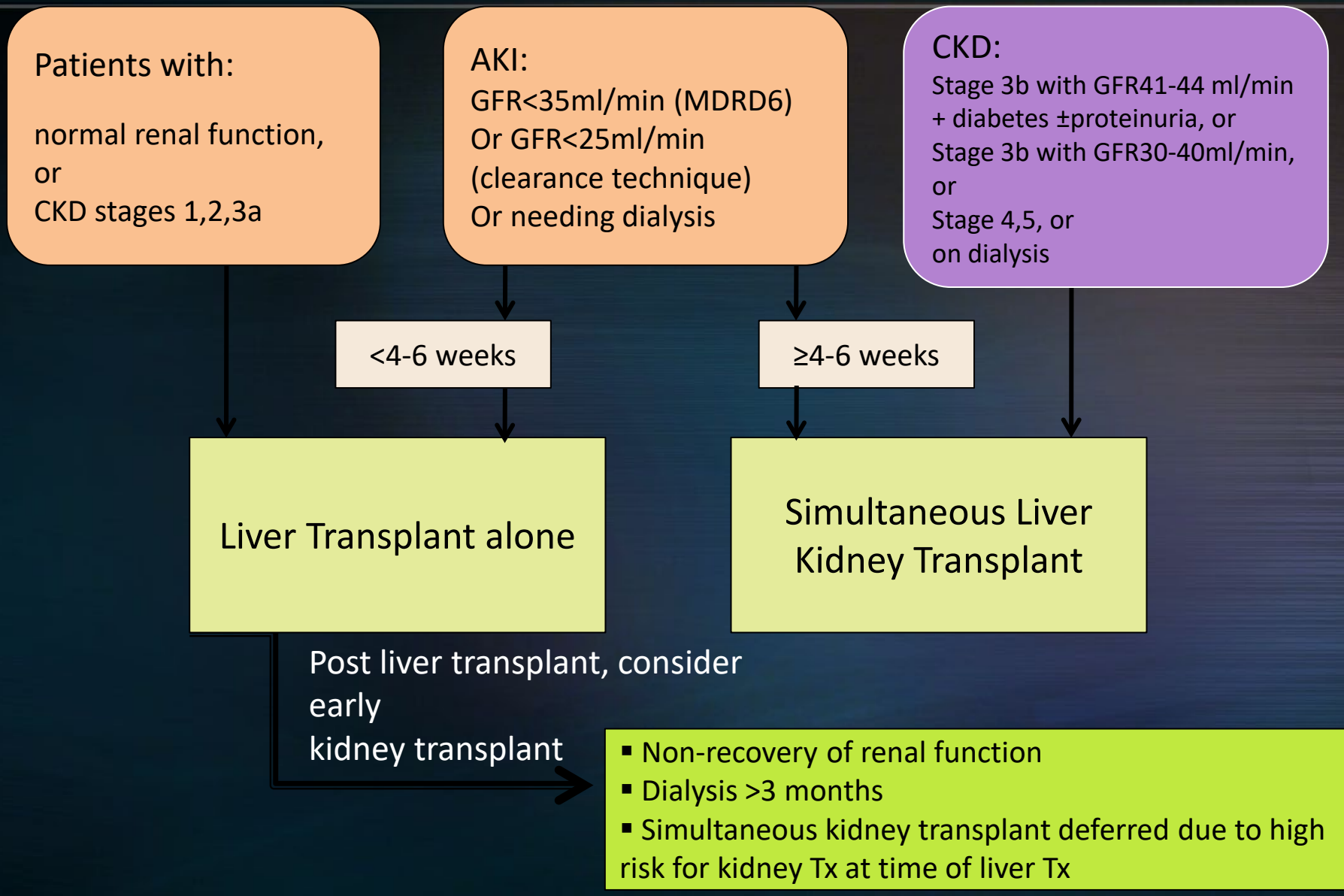
The CONFIRM Study: Percentage of Renal Replacement Therapy Post–Liver Transplant



Wong NEJM 2021



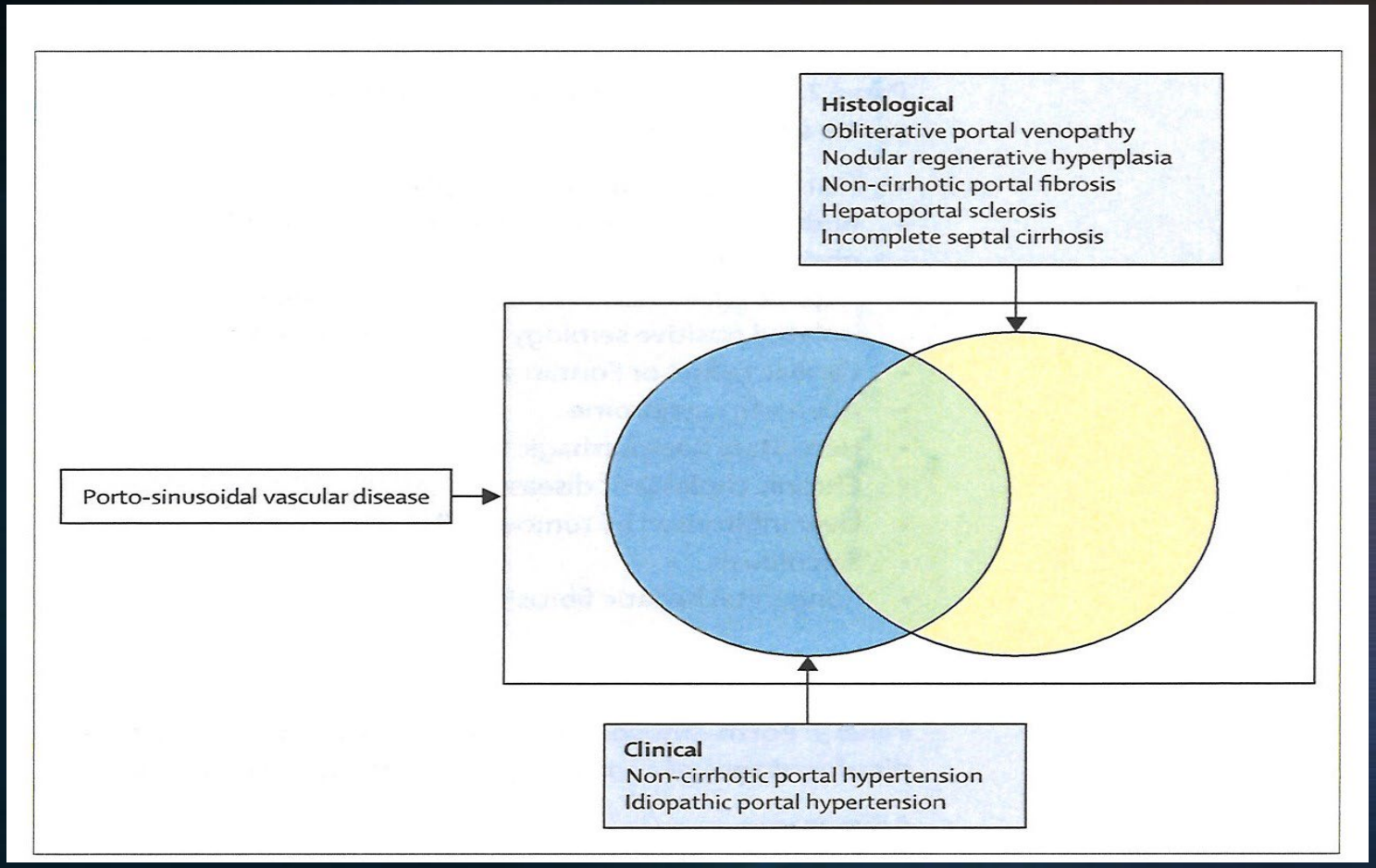
Wong F. et al. Clin Mol Hepatol, *2019*



Gines P. et al. Nature Rev Dis Primers, 2018

Portal Hypertension

Non-Cirrhotic Etiologies



Porto-sinusoidal Vascular Disease - De Gottardi 2019

Porto-Sinusoidal Vascular Disorder

- Broad Clinico-Pathological entity
- Portal hypertension in absence of typical features of cirrhosis (eg smooth liver without atrophy of segment IV)
- Liver Stiffness < 10 mmHg
- Associated Systemic Disorder (hematological, immunological etc)

De Franchis 2022

Porto-Sinusoidal Vascular Disease

	Feature of portal hypertension	**Histological lesions suggestive of porto-sinusoidal vascular disorder assessed by an expert pathologist**
Specific	• Gastric, oesophageal, or ectopic varices • Portal hypertensive bleeding • Portosystemic collaterals at imaging	• Obliterative portal venopathy (thickening of vessel wall, occlusion of the lumen, vanishing of portal veins) • Nodular regenerative hyperplasia Incomplete septal fibrosis (also called incomplete septal cirrhosis); • This latter feature can only be assessed on liver explants and not on liver biopsies

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Porto-Sinusoidal Vascular Disease

	Feature of portal hypertension	**Histological lesions suggestive of porto-sinusoidal vascular disorder assessed by an expert pathologist**
Not specific	• Ascites • Platelet count <150,000/mm3 • Spleen size >−13 cm in the largest axis	• Portal tract abnormalities (multiplication, dilatation of arteries, periportal vascular channels, aberrant vessels) • Architectural disturbance: irregular distribution of the portal tracts and central veins • Non-zonal sinusoidal dilatation • Mild perisinusoidal fibrosis

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PSVD: Management

- Endoscopy to screen for varices
- Confirm patency of portal vessels
- Treat systemic disorders (hematological, immunological etc) if present
- Screen for portal vein thrombosis with ultrasound every 6 months

De Franchis 2022

Portal Hypertension 2022

- Increasing role of elastography for prognosis and management
- Increasing options for gastric varies
- HRS reversal with vasoconstrictor therapy
- Non cirrhotic portal hypertension defined