Going Against the Flow: Management of Ascites and Spontaneous Bacterial Peritonitis

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DISCLOSURES

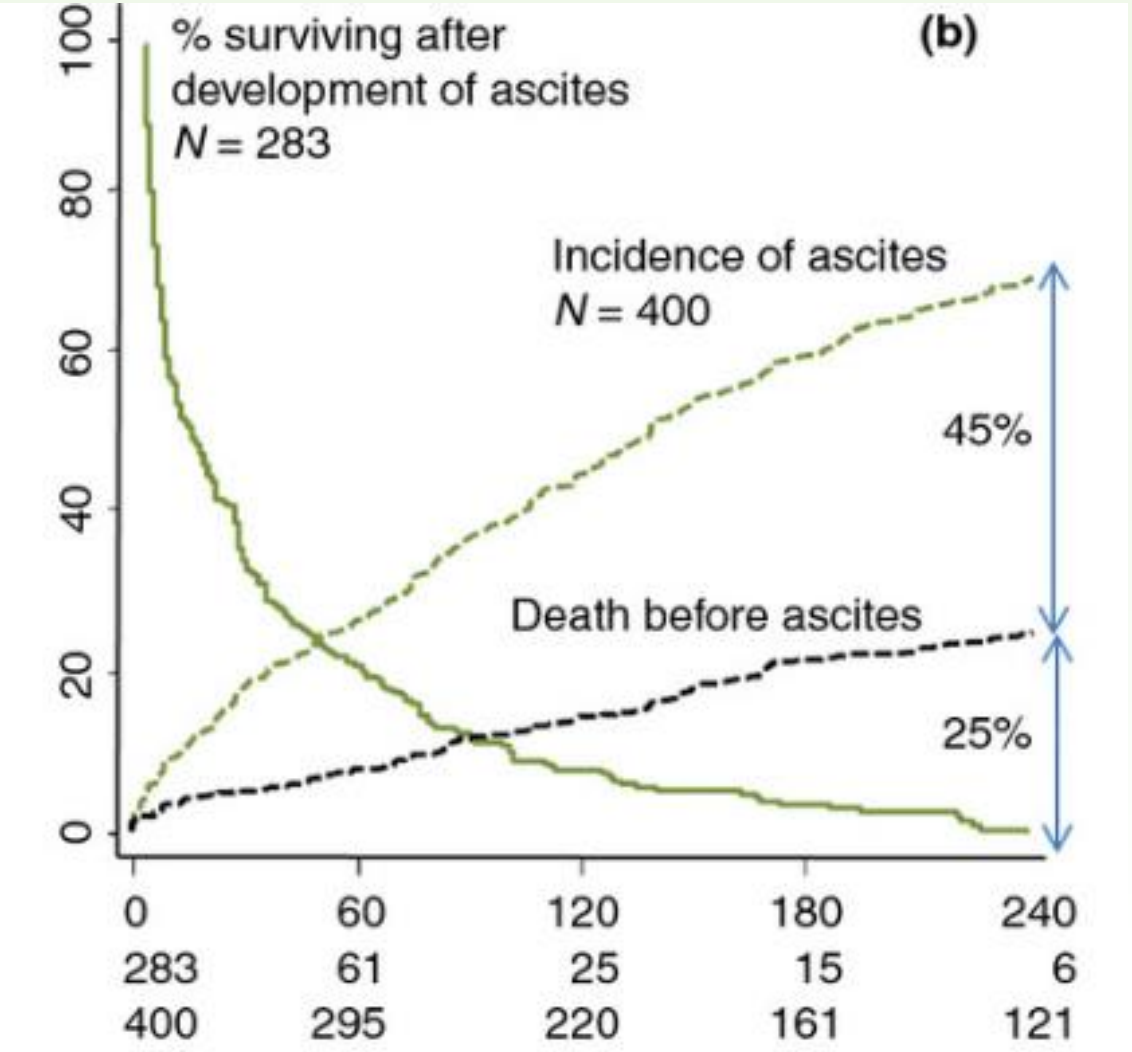
None

Outline

- Prevention of Ascites?
- Diagnosis/Initial Management
- Refractory Ascites
  - Large Volume Paracentesis (LVP)
  - Transjugular Intrahepatic Portosystemic Shunt (TIPS)
  - Liver Transplantation (LT)
  - Alfapump/Catheter
- Spontaneous Bacterial Peritonitis
  - Diagnosis/Management/Prevention

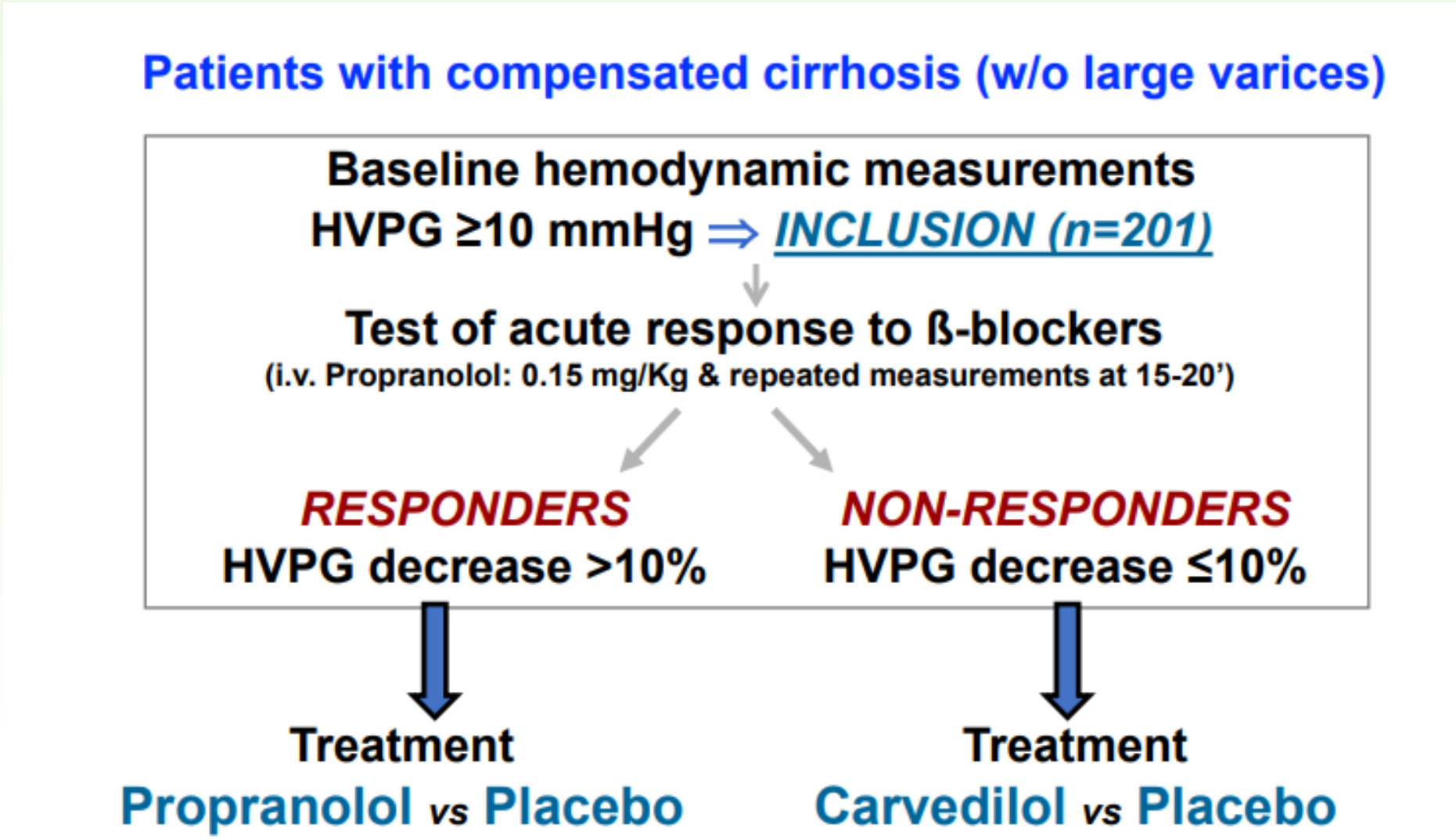
Natural History of Cirrhosis and Portal Hypertension

- Ascites is most frequent initial decompensation
  - **Ascites 33%**
  - Bleeding 10%
  - HCC 9%
  - PSE 5%
  - Jaundice 3%



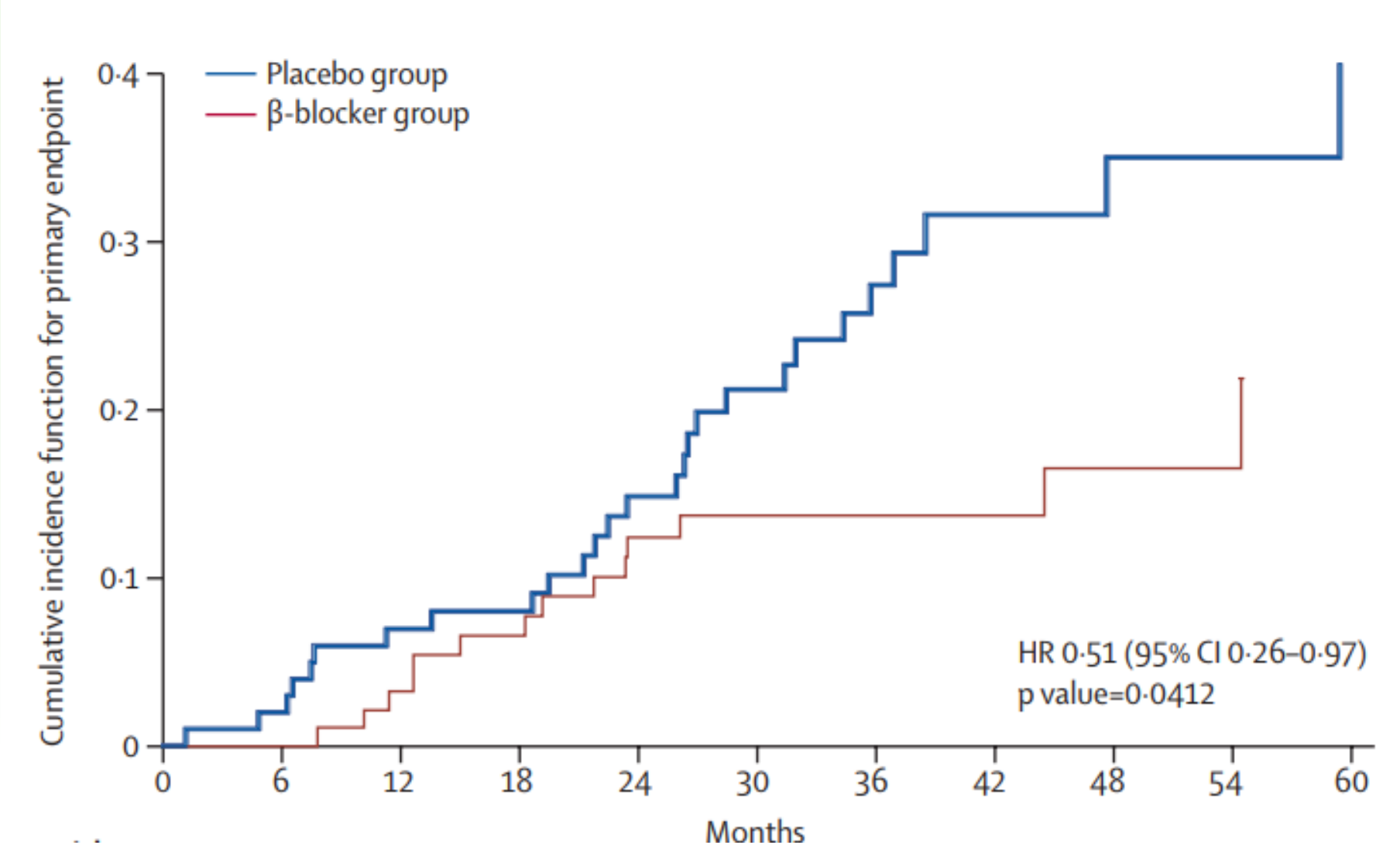
D'Amico. APT 2014

Prevention of Decompensation? – Role of Beta Blockers



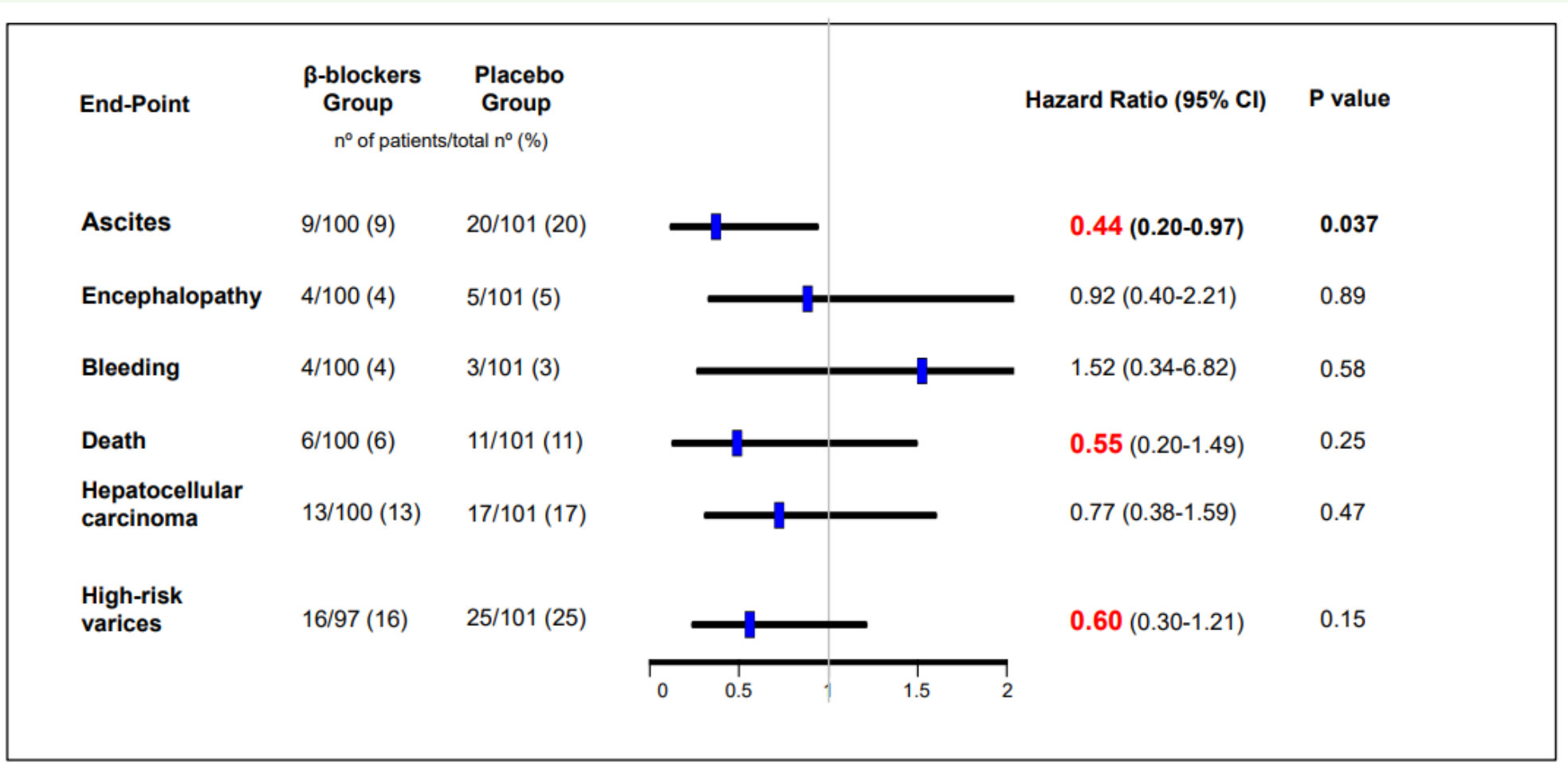
Villanueva et al. Lancet 2019

Beta Blockers for Prevention of Decompensation



Villanueva et al. Lancet 2019

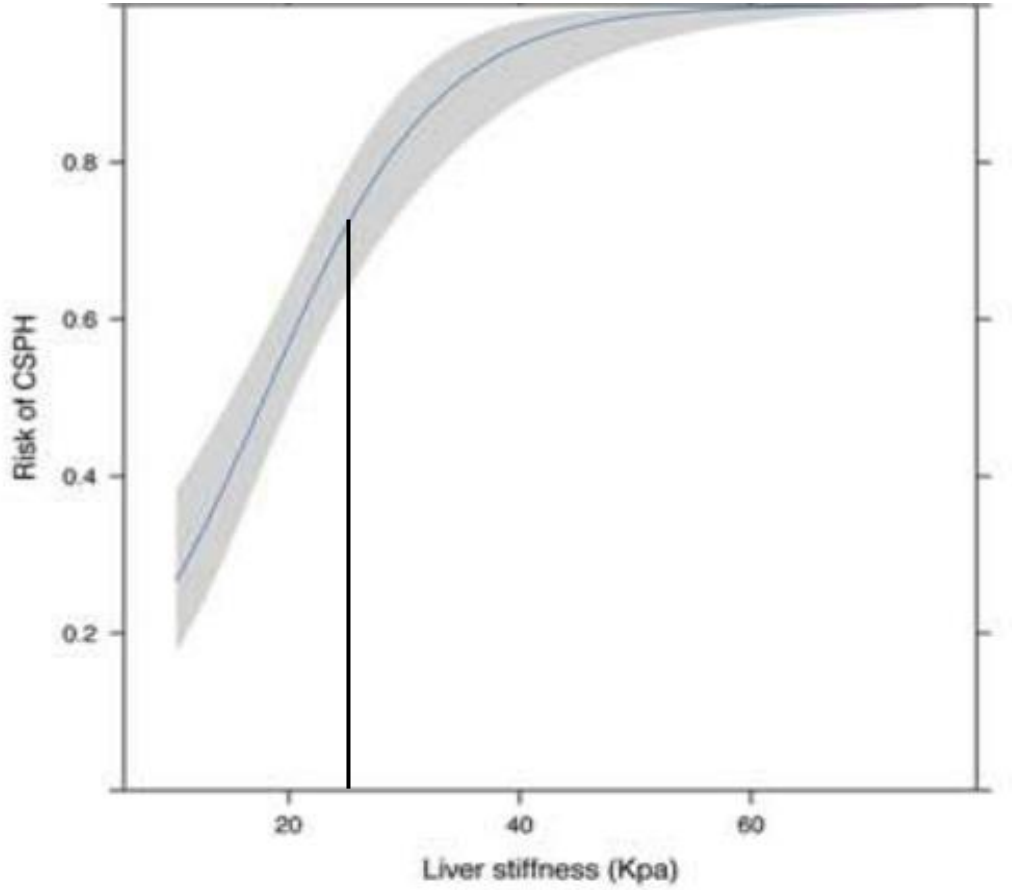
Can ascites be prevented?



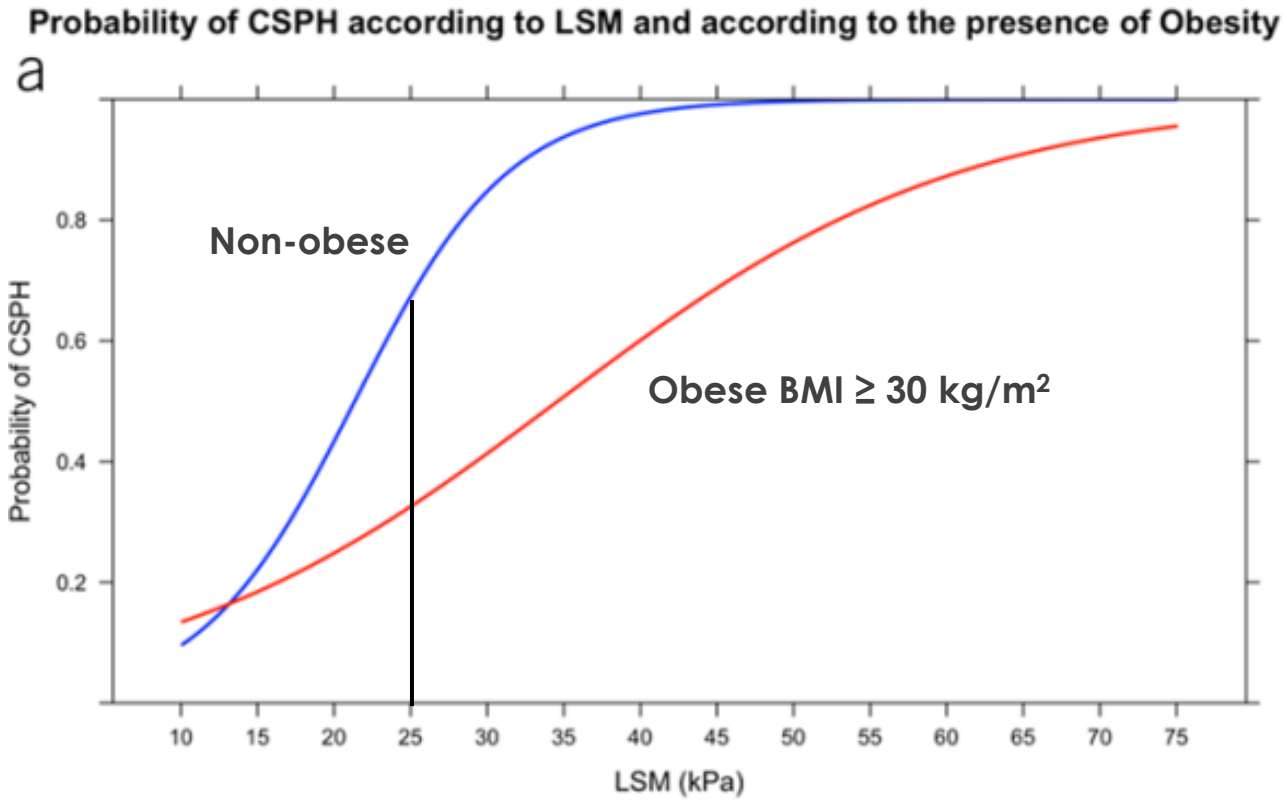
Long term treatment with NSBBs could increase decompensation free survival in patients with compensated cirrhosis and clinically significant portal hypertension (CSPH), mainly by reducing ascites incidence

Villanueva et al. Lancet 2019

Patient Selection for NSBB: Non-invasive measurement of CSPH



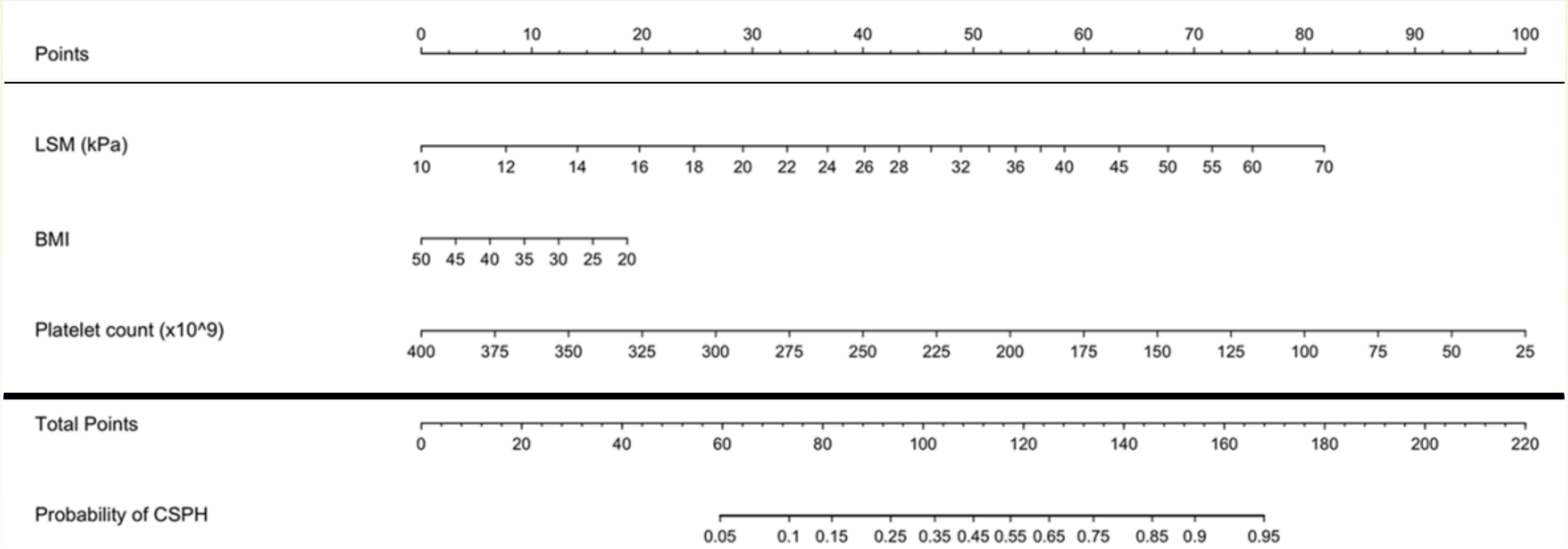
Hepatitis C and Alcohol



NASH

Albrades et al. Hepatology, 2016; Pons et al. AJG, 2021;

Non-invasive measurement of CSPH: ANTICIPATE NASH



Pons et al. AJG, 2021

Patient with suspected cirrhosis without decompensation

Treat etiology if possible (HCV/ alcohol)

Screen for HCC with Ultrasound Q 6 months

Non-invasive assessment of CSPH

In patients with virus, alcohol or non-obese NASH

LSM ≥ 25 kPA

LSM 20-25 kPA and platelet <150

LSM 15-20 kPA and platelet <110

In patients with NASH use ANTICIPATE NASH model

Suspected CSPH

NO

YES

Reassess annually

Carvedilol –goal 12.5mg/day (no need for EGD)

- **Baveno VII**
  - **Treatment with NSBBs (propranolol nadolol, or carvedilol) should be considered for prevention of decompensation in patients with CSPH**
  - **Carvedilol is the preferred NSBB since it is more effective at reducing the HVPG**

De Franchis et al, Journal of Hepatology 2022; AASLD Webinar 2020

Initial Diagnosis and Management

- History
- Physical
- Abdominal ultrasound with doppler
- Complete blood count
- Liver function tests (INR, bilirubin, albumin)
- Urine protein
- Diagnostic paracentesis
  - Serum ascites albumin gradient (≥1.1 g/dL)
  - Total protein (<2.5 g/L)
  - Cell count/differential

General Management

- Dietary Sodium Restriction- 2g/day (88 mmol/day)
  - Fluid restriction is **NOT** necessary unless hyponatremia (Na ≤ 125)
- Diuretics
  - Aldosterone antagonist
    - **Monotherapy can be adequate for initial ascites diagnosis**
    - 100mg/day recommended->max dose 400mg/day
    - Long half life-takes about 3 days to see full effect
  - Loop diuretics
    - Furosemide 40mg/day->max dose 160mg/day
    - Torsemide or bumetanide may improve naturesis in patients with suboptimal response to furosemide
- Daily weights to monitor weight loss
  - Without edema-0.5kg/day
  - With edema-1 kg/day
- Avoid nephrotoxins
  - NSAIDS, ACE inhibitors, ARBs

Biggens et al. Hepatology. 2021

Diuretic Side Effects

- AKI
- Hyponatremia
- Hypo/hyperkalemia
- Hepatic encephalopathy
- Gynecomastia
  - Spironolactone 100mg= Eplereone 50mg= 10mg amiloride
- Muscle cramps
  - Correct electrolytes
  - Baclofen 10mg/day

Biggens et al. Hepatology. 2021

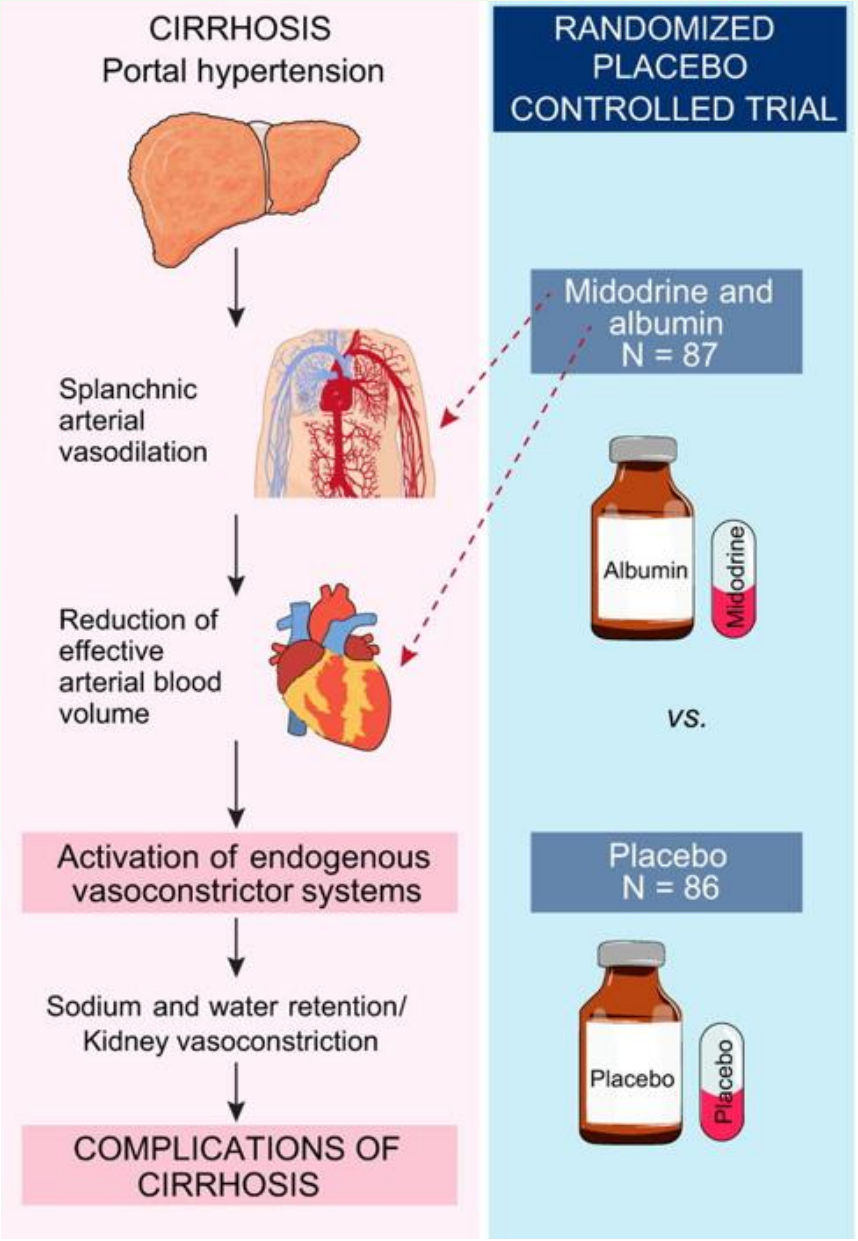
Albumin?

ANSWER Study

- 431 patients with diuretic-responsive ascites randomized to standard medical treatment or standard medical treatment plus 40 g albumin twice a week for 2 weeks then once a week for 18 months
- Improved overall survival in albumin group (38% reduction in mortality)

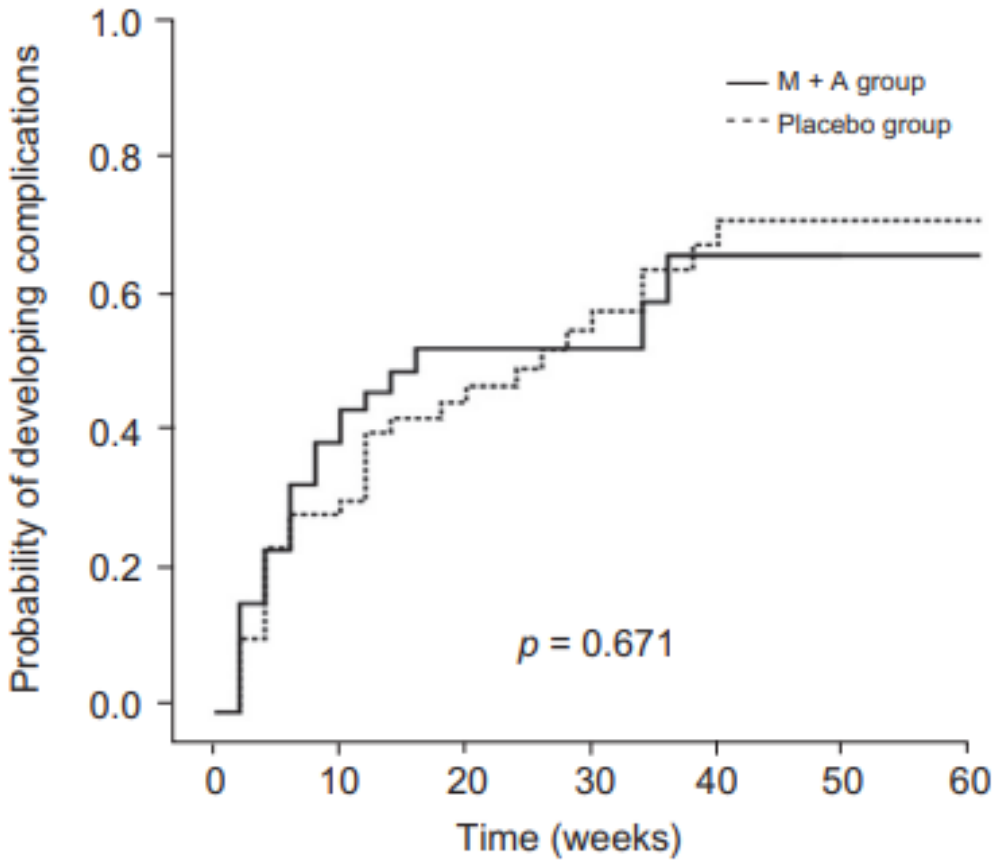
MACTH trial

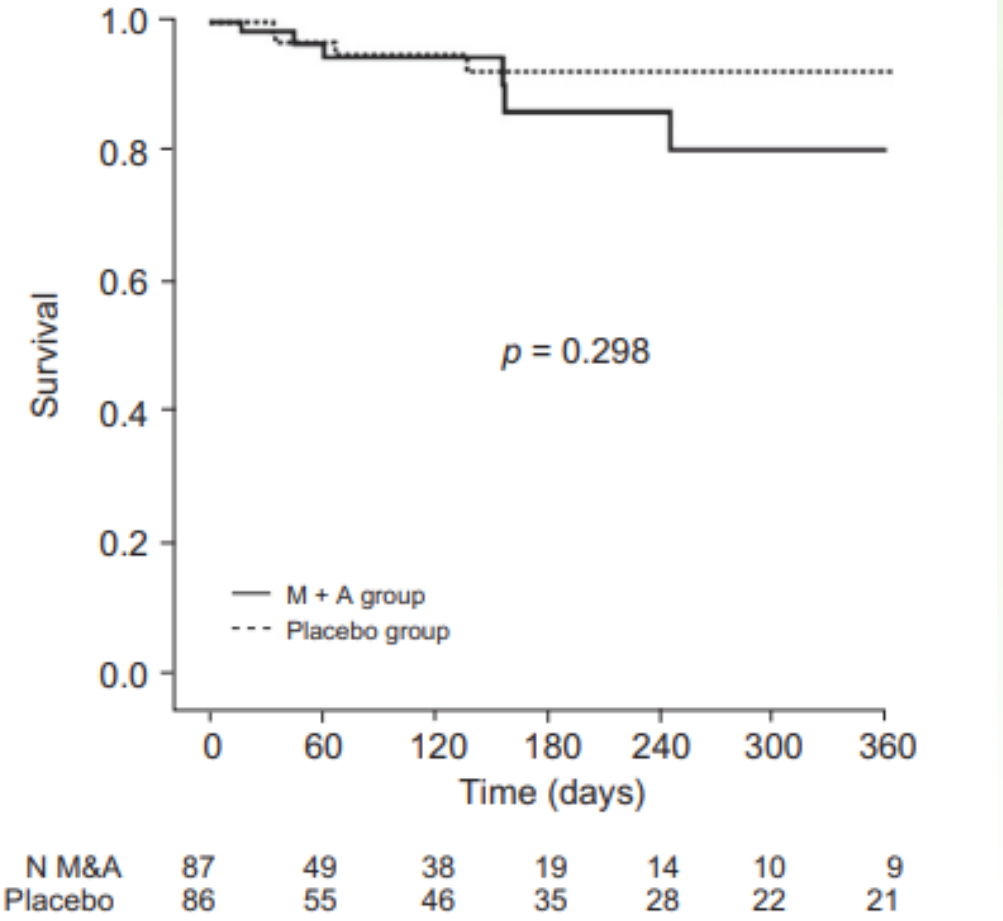
- Multicenter, randomized, double blind placebo-controlled trial including 196 patients with cirrhosis and ascites awaiting LT



Ceraceni et al. Lancet 2018; Sola, E. et al. Journal of Hepatology 2018

MACHT Study





Median dose of midodrine 23mg/day; albumin dose 40 grams Q 2 weeks

Sola, E. et al. Journal of Hepatology 2018.

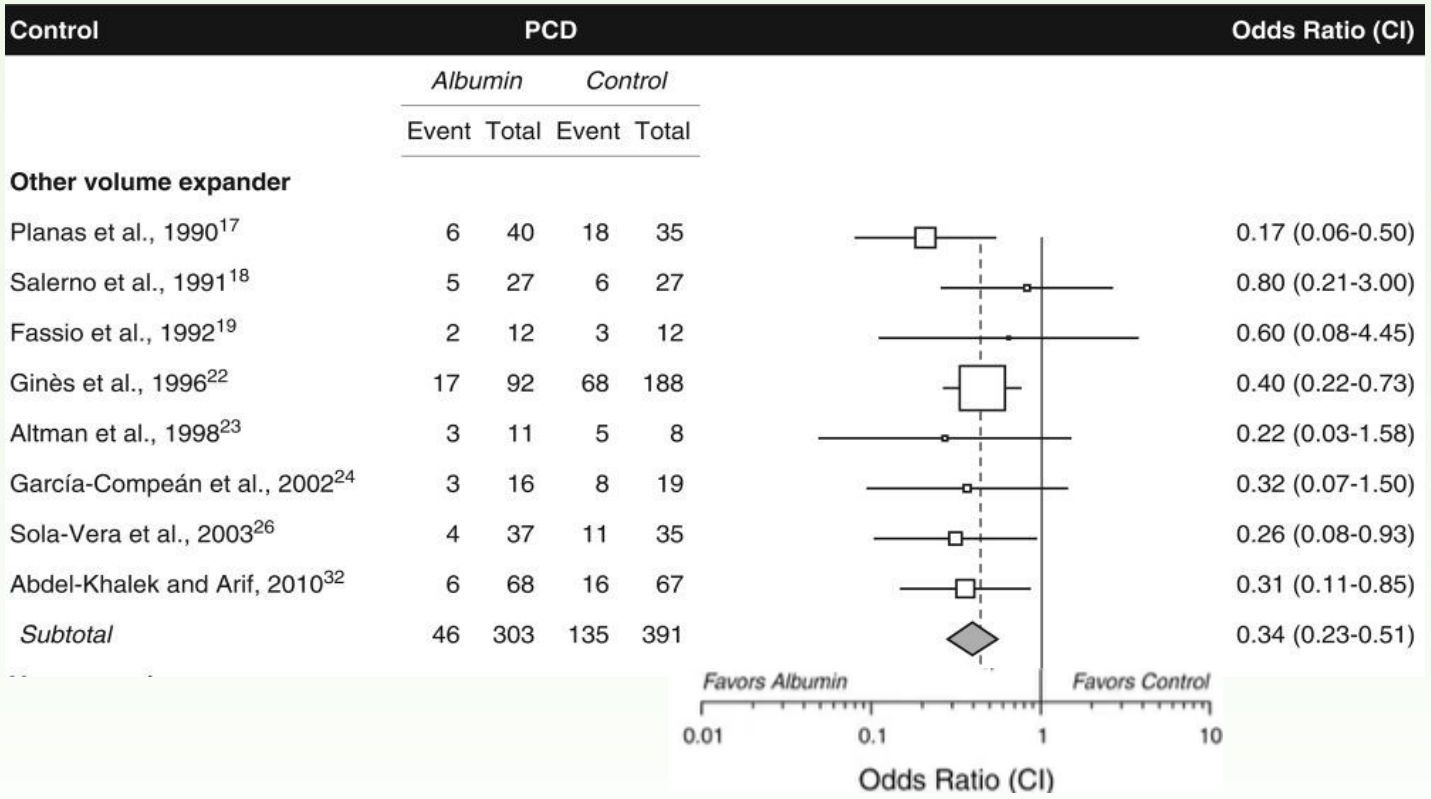
Refractory Ascites

- 5-10% of all patients with cirrhosis and ascites
- Poor survival-50% 6 months
- Ascites that cannot be mobilized or recurs after LVP despite dietary sodium restriction and diuretic therapy
- Diuretic Resistant
  - Weight loss ≤ 1.5 kg/week while on
    - 30mg amiloride or 400mg spironolactone PLUS 160mg furosemide for ≥ 1 week
    - Dietary Na restriction 88mmol/day
      - Spot urine Na/K ratio >1 suggests patient should be losing fluid weight and dietary noncompliance should be suspected
- Diuretic Intolerant
  - Patients with ascites who cannot have their diuretics doses increased because of development of complications

Adebayo et al. Am J Gastroenterol. 2019; AASLD Webinar 2020

LVP

- LVP is first line treatment for RA
- 6-8g 25% albumin should be administered per liter of ascites removed for LVP>5L
- The risk of post paracentesis circulatory dysfunction increases with >8 L fluid evacuation
- No threshold INR or platelet count

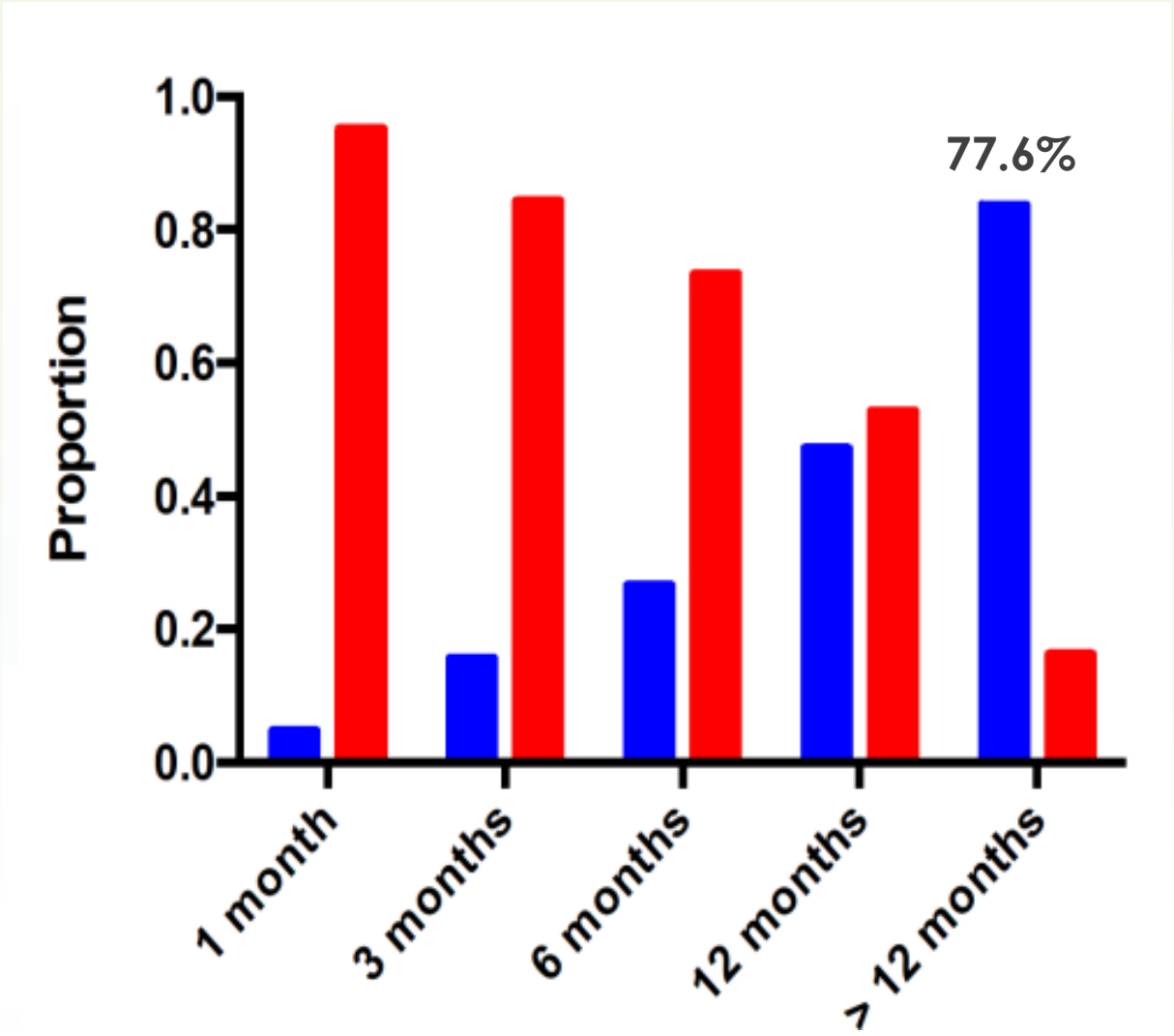


Bernardi et al. Hepatology. 2012. ; O'Leary et al. Gastroenterology 2019

TIPS or Taps?

- TIPS has been shown to be more beneficial in control of ascites in **well selected** patients with RA
- Reduction of portal pressure with TIPS allows gradual return of splanchnic volume to systemic circulation through TIPS, improving effective blood volume and in turn suppressing neurohormonal vasoconstrictor systems over 4-6 months
- Optimal outcomes depend on
  - careful patient selection
  - technically proficient placement
  - peri procedural care

Clinical Response Post TIPS



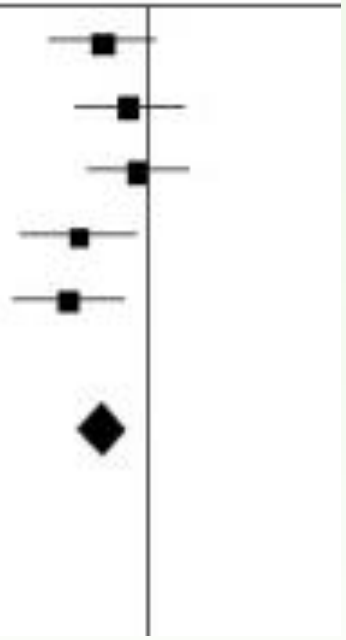
Tan et al. Journal of Gastroenterology and Hepatology 2015

Liver Transplantation Free Survival-TIPS vs LVP

Study or subgroup	log [HR]	SE	TIPS Para Total	Total	Weight	HR, 95%CI
Rössle, 2000	-0.52	0.32	29	31	20.7%	0.59 [0.32, 1.11]
Ginès, 2002	-0.21	0.32	35	35	20.7%	0.81 [0.43, 1.52]
Sanyal, 2003	-0.09	0.31	52	57	22.0%	0.91 [0.50, 1.68]
Salerno, 2004	-0.80	0.35	33	33	17.3%	0.45 [0.23, 0.89]
Narahara, 2011	-0.92	0.33	30	30	19.4%	0.40 [0.21, 0.76]
Total	Fixed		179	186	100.0%	0.61 [0.46, 0.82]

Heterogeneity: $\chi^2 = 4.92$, $df = 4$ ($P = 0.30$); $I^2 = 19\%$

Test for overall effect: $Z = 3.35$ ($P = 0.0008$)



Favors TIPS Favors Para

Bai et al. World Journal of Gastroenterology 2014

Indications for TIPS

Indications

- Requires >2 LVP/month
- Intolerant of repeated paracentesis
- Refractory ascites associated with hepatic hydrothorax

Patient selection

- Young (< 65 years)
- Normal cardiac, renal function
- No prior encephalopathy
- Child Pugh Score <12, MELD <18
- No sepsis (including dental sepsis)

Adebayo et al. Am J Gastroenterol. 2019

Contraindications to TIPS for RA

Absolute Contraindications

- Child Pugh ≥ 12 or MELD ≥ 18
- Congestive heart failure
- Severe pulmonary hypertension
- Unrelieved biliary obstruction
- Untreated infection or uncontrolled sepsis
- Multiple hepatic cysts

Relative

- Age >70 years
- Hepatoma
- PVT
- Noncompliance with sodium restriction

Adebayo et al. Am J Gastroenterol. 2019

Risk for post TIPS hepatic encephalopathy

Incidence is 25-45% with 13-36% being new or worsening episodes

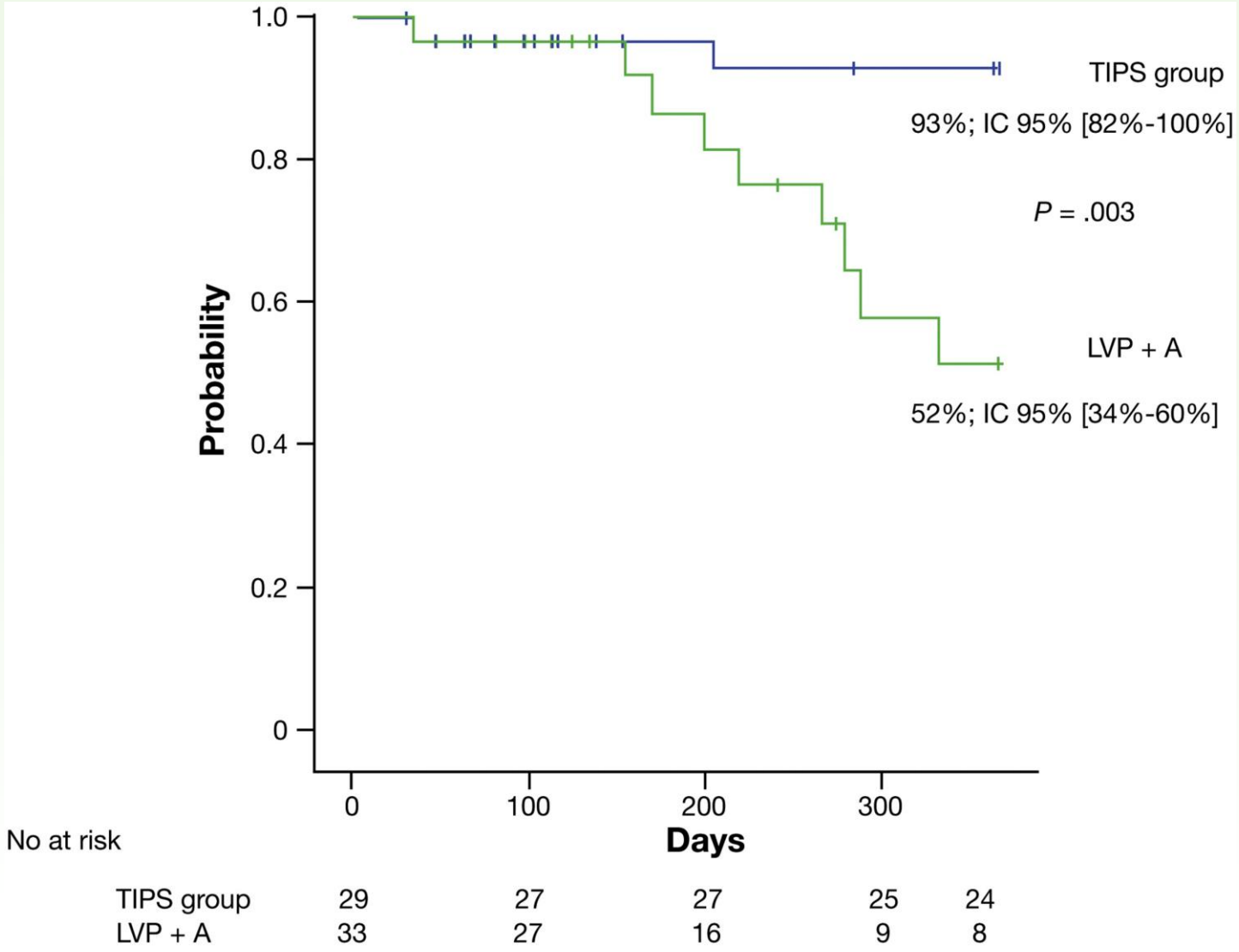
Risk factors

- Pre –TIPS encephalopathy
- Age > 65
- MELD >15
- CPS >12
- Low portosystemic gradient post TIPS < 5mmHg
- Large diameter stent >10mm

Adebayo et al. Am J Gastroenterol. 2019; Riggio et al. Clin Liver Disease 2012

Early TIPS for Ascites

- RCT to assess efficacy of covered TIPS stents on transplant free survival in patients with recurrent ascites
- Recurrent ascites : at least 2 LVP within a period of least 3 weeks



Bureau et al. Gastroenterology 2017

Liver Transplantation

- Definitive treatment for RA is LT
- Patients with RA and significant liver dysfunction that precludes TIPS should be considered for LT
- No MELD exception for RA
- MELD exception for hepatic hydrothorax
- Patients with RA and HRS-CKD have worse prognosis than those with RA alone-> Need timely referral for LT

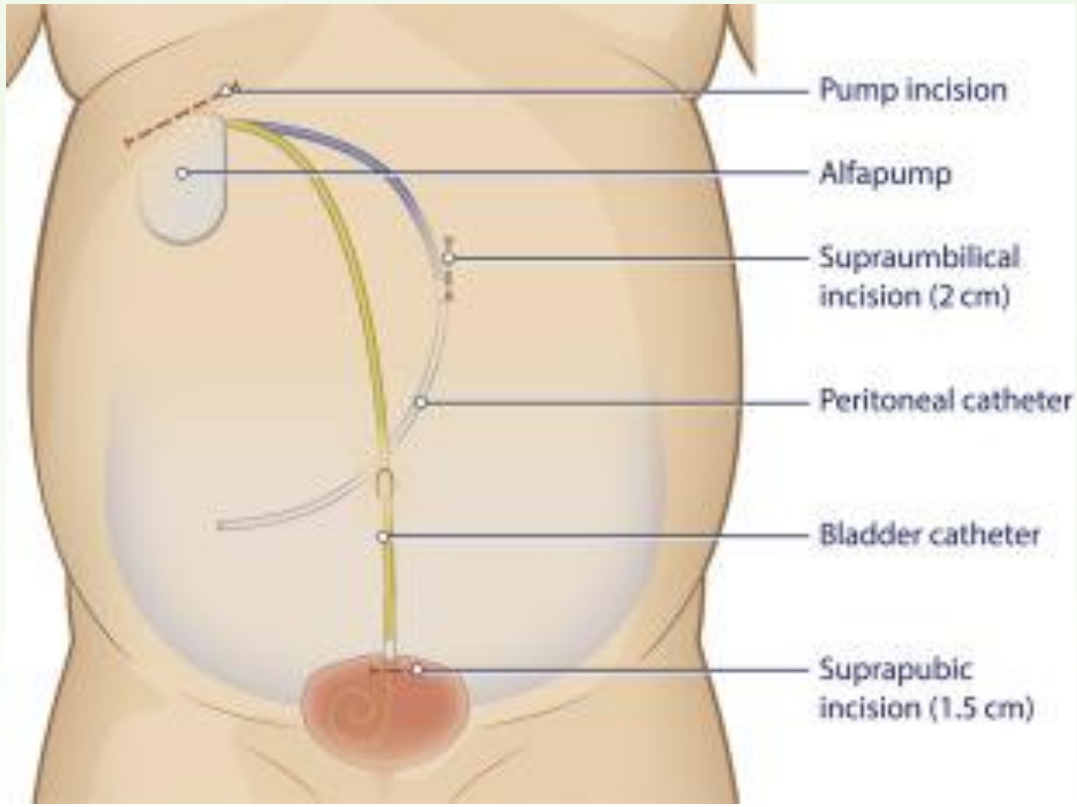
Alternatives?

Peritoneal catheter

- 13% infection rate

Automated Low-Flow Ascites (ALFA) Pump

- Implantable battery-powered pump that automatically and continuously moves ascites from peritoneal cavity into bladder
- Only used in clinical trial
- Reduces paracentesis requirement
- Cannot be used in advanced kidney disease
- Risk AKI



Bureau et al. Journal of Hepatology 2017; Macken et al. Liver Int 2019

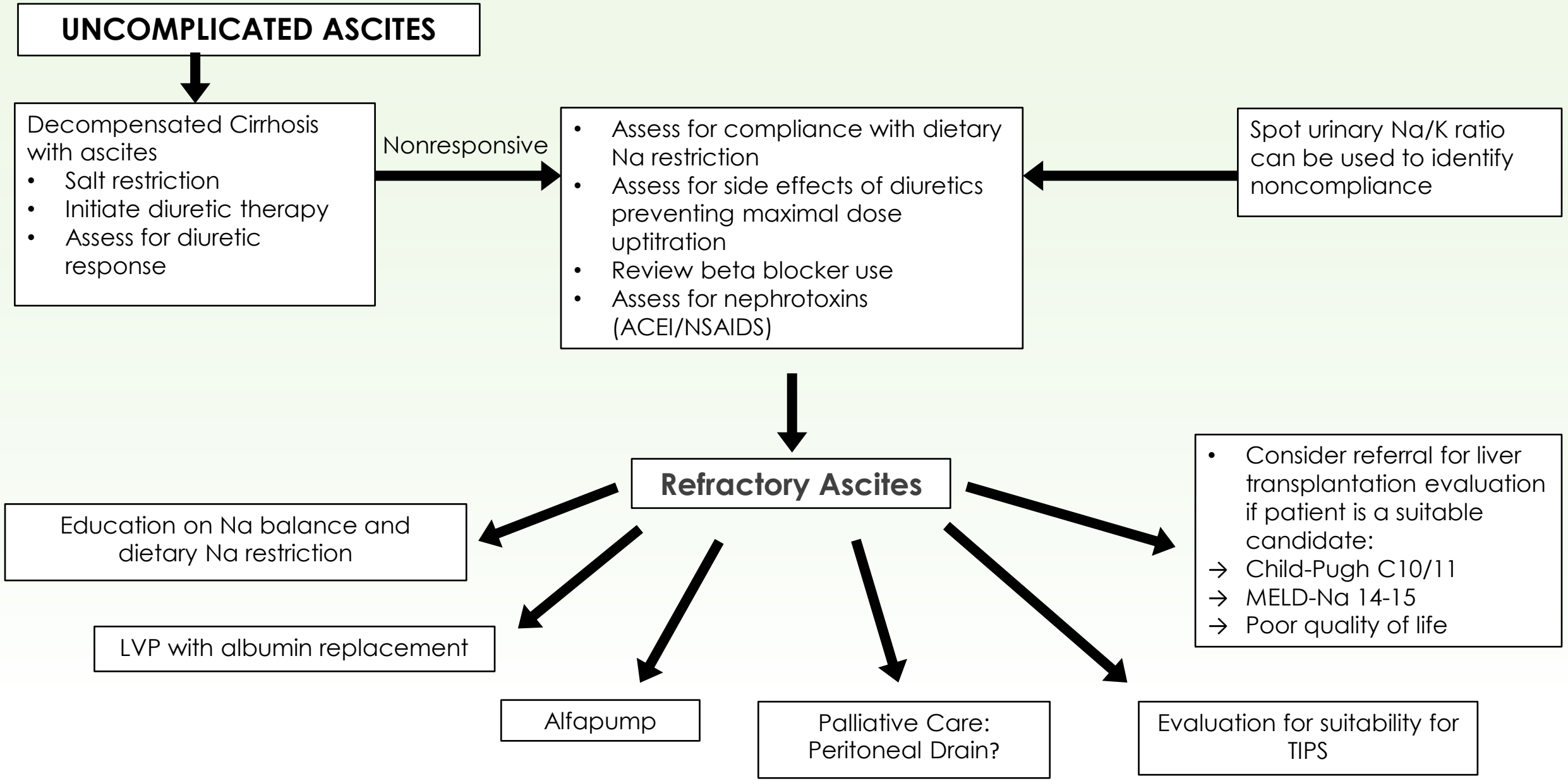
Beta Blockers?

Not necessarily contraindicated in patients with RA

- SBP< 90 mmHg
- Na < 130 mmol/L
- Cr >1.5 mg/dL

	N	Study Group	Baseline MELD No BB vs BB	Baseline MAP No BB vs BB	Follow-up (months)	Adjusted HR for mortality associated with BB
Serste et al	**151**	**Refractory Ascites**	**18.8 vs 18.9**	**123 vs 103**	**8**	**2.62 (1.62-4.19)**
Mandofer et al.	**182**	**SBP**	**20.0 vs 21.6**	**83 vs 77**	**9.6**	**1.64 (1.1-2.3)**
Leithead et al.	**322 (208 matched)**	**Ascites on transplant list**	**16 vs 17**	**89 vs 86**	**2.4**	**0.35 (0.14-0.86)**
Bossen et al.	**1188**	**Ascites in RCT of stavaptan/placebo**	**11 vs 12**	**85 vs 83**	**12**	**1.02 (0.74-1.40)**
Mookerjee et al.	**349**	**Acute on chronic liver failure**	**29 vs 27**	**79 vs 78**	**1 (28 d)**	**0.60 (0.36-0.98)**

JHEP VP: 63 2-16 Garcia-Tsao; Biggins et al. Hepatology 2021



Adapted from Adebayo et al. Clinics in Liver Disease. 2019

SBP

- Bacterial infections present in 1/3 patients with cirrhosis who are hospitalized (36% SBP)
- 50% infections were community acquired and present on admission
- Up to 1/3 patients are asymptomatic or present only with encephalopathy/AKI
- Fluid PMN > 250/mm^3=SBP
- **Patients with ascites due to cirrhosis emergently admitted to hospital should undergo diagnostic paracentesis to r/o SBP even in absence of signs/symptoms**

Biggens et al. Hepatology. 2021

SBP

- Empiric antibiotics should be started in patients with ascites/pleural fluid PMN count >250/mm^3
  - First line therapy is 3rd generation cephalosporin
  - Duration 5-7 days
- Response to empiric therapy should be assessed 2 days after antibiotics
  - Response= decrease in fluid PMN > 25%
- IV albumin should be administered on day 1 (1.5g/kg) and day 3 (1g/kg)
- NSBB should be held in patients with hypotension

Biggens et al. Hepatology. 2021

Prophylaxis

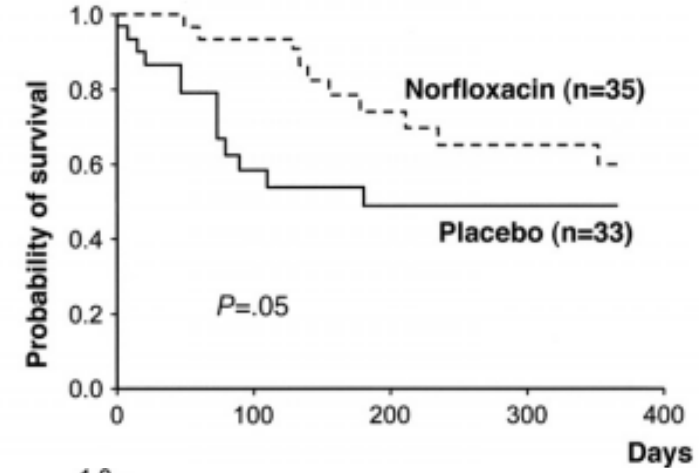
Should receive prophylaxis

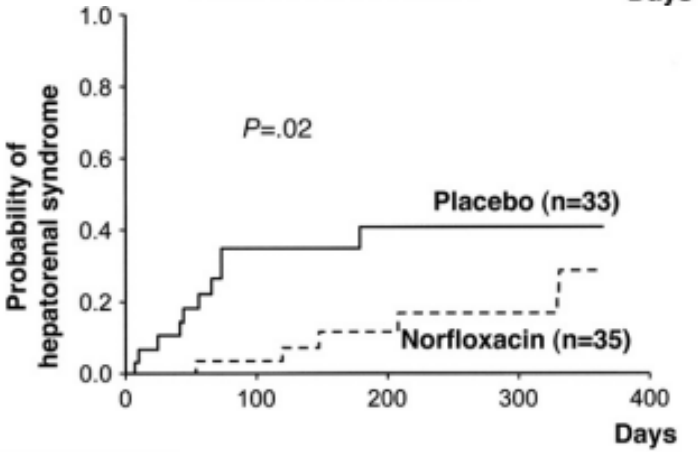
- Patients recovered from an episode of SBP (ciprofloxacin 500mg daily)
- Patients with cirrhosis and UGIB (IV ceftriaxone 1g daily for maximum 7 days)

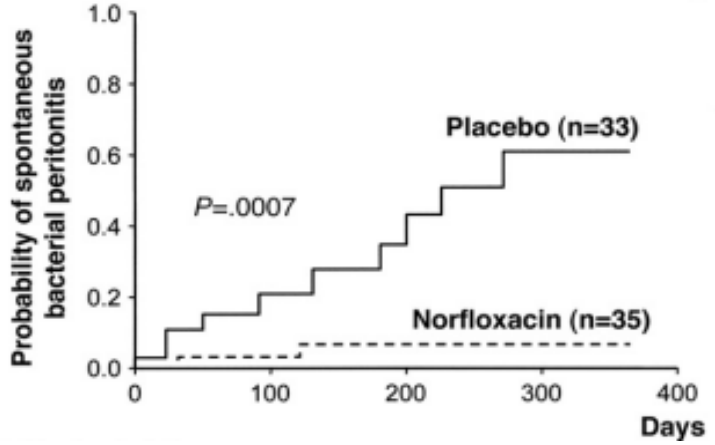
Can be considered

- Primary prophylaxis in patients with low protein ascites (< 1.5 g/L) and either
  - Renal dysfunction (Cr >1.2 mg/dL, BUN > 25 mg/dL, or Na <130 mEq/L) **OR** Liver Failure (CTPS >9 and bilirubin >3 mg/dL)

Alternatives: Norfloxacin, Sulfamethoxazole-Trimethoprim, Rifaximin







Biggins et al. Hepatology 2021. Fernandez et al. Gastroenterology 2007

Conclusions

- In patients with CSPH, NSBBs can decrease the risk of decompensation (mainly by decreasing the risk of ascites)
  - Avoid hypotension (SBP < 90 mmHg, MAP <65 mmHg)
- A diagnostic paracentesis should be performed in all patients with cirrhosis with ascites presenting emergently to the hospital
- Na restriction and diuretics are the mainstay of ascites management
  - Spironolactone monotherapy can be effective for initial management
- TIPS should be considered in carefully selected patients with RA
- In patients with RA who are not TIPS candidates, LT must be considered
- SBP prophylaxis is indicated for patients with a history of prior SBP and for patients with cirrhosis and upper GI bleeding

CME/MOC QUESTION

Which of the following scenarios is appropriate for antibiotic prophylaxis for SBP prophylaxis?

A. A patient with cirrhosis and newly diagnosed ascites with fluid total protein 2 g/dL

B. A patient with cirrhosis presenting with variceal hemorrhage

C. A patient with cirrhosis undergoing an upper GI endoscopy for variceal screening

D. A patient with cirrhosis and newly diagnosed ascites and fluid total protein 1.4 g/dL with normal renal function and sodium and bilirubin 2 mg/dL

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