Beta-blockers in cirrhosis: Cons

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Agenda

1) Are beta-blockers always indicated to prevent variceal hemorrhage in cirrhotic patients?

2) Can beta-blockers be safely used at all stages of cirrhosis?

3) Which subset of cirrhotic patients could benefit the most from beta-blocker therapy?

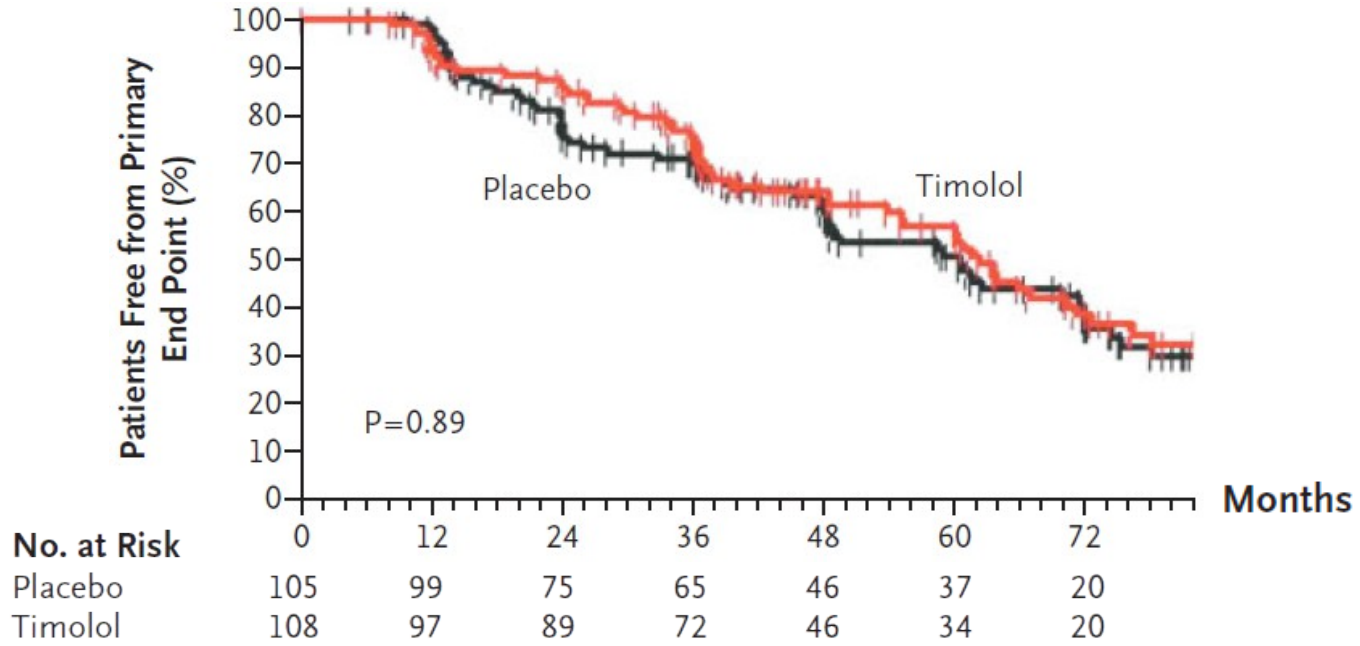
1) Are beta-blockers always indicated to prevent variceal hemorrhage in cirrhotic patients?

Beta-blocker therapy and prevention of gastroesophageal varices

- 213 cirrhotic patients with portal hypertension (HVPG ≥ 6 mmHg)

- Randomized to receive either placebo (n=105) or NSBB (timolol) [n=108]

  - Primary end point: development of gastroesophageal varices or variceal bleeding



- Adverse events were significantly higher in the timolol group (48% vs. 32%)

Groszmann et al. *NEJM* 2005

Adherence to beta-blocker therapy

- Despite well established guidelines and recommendations, as few as 6–22% of patients with known medium or large varices received primary prophylaxis with beta-blockers[1]

- Side effects led to treatment discontinuation in approximately 15% of patients in the various beta-blocker trials in patients with cirrhosis[2]

Cardiac	Non-cardiac
Symptomatic bradycardia	Fatigue
Exacerbation/precipitation of heart failure	Headaches, dizziness
High grade heart block	Erectile dysfunction
	Cold extremities, claudication
	Shortness of breath

[1]Mellinger et al. *Clin Gastroenterol Hepatol* 2013
[2]García-Tsao et al. *Am J Gastroenterol* 2009

Pathophysiology of portal hypertension in cirrhosis

↑ Intra-hepatic resistance to blood flow

↓

Portal hypertension

↓

Hyperproduction of nitric oxyde and other mediators

↓

Peripheral arterial vasodilatation

↓

↓Effective arterial blood volume

↓

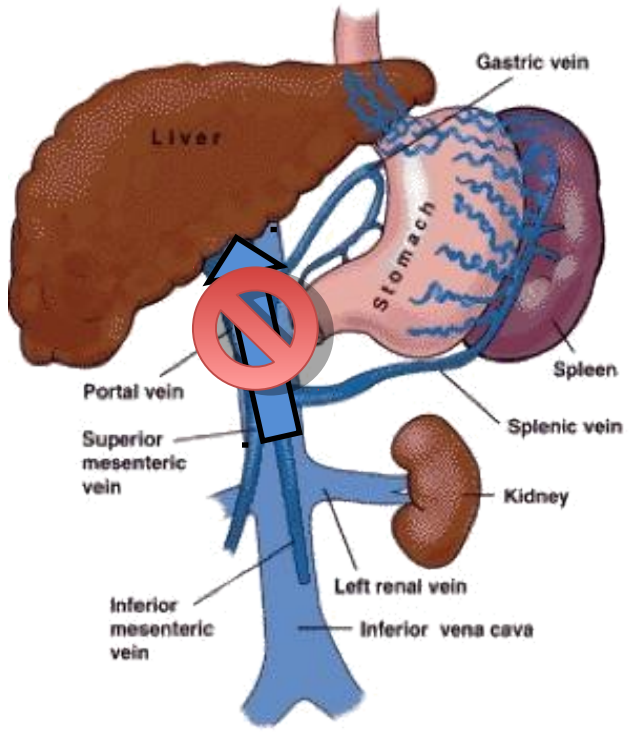
↑Sympathetic nervous system
Renin-angiotensin-aldosterone system

↓

↑ Cardiac output → Hyperdynamic circulation

Vasoconstriction of renal circulation → Hepatorenal syndrome

Water and salt-retaining mechanisms → Ascites



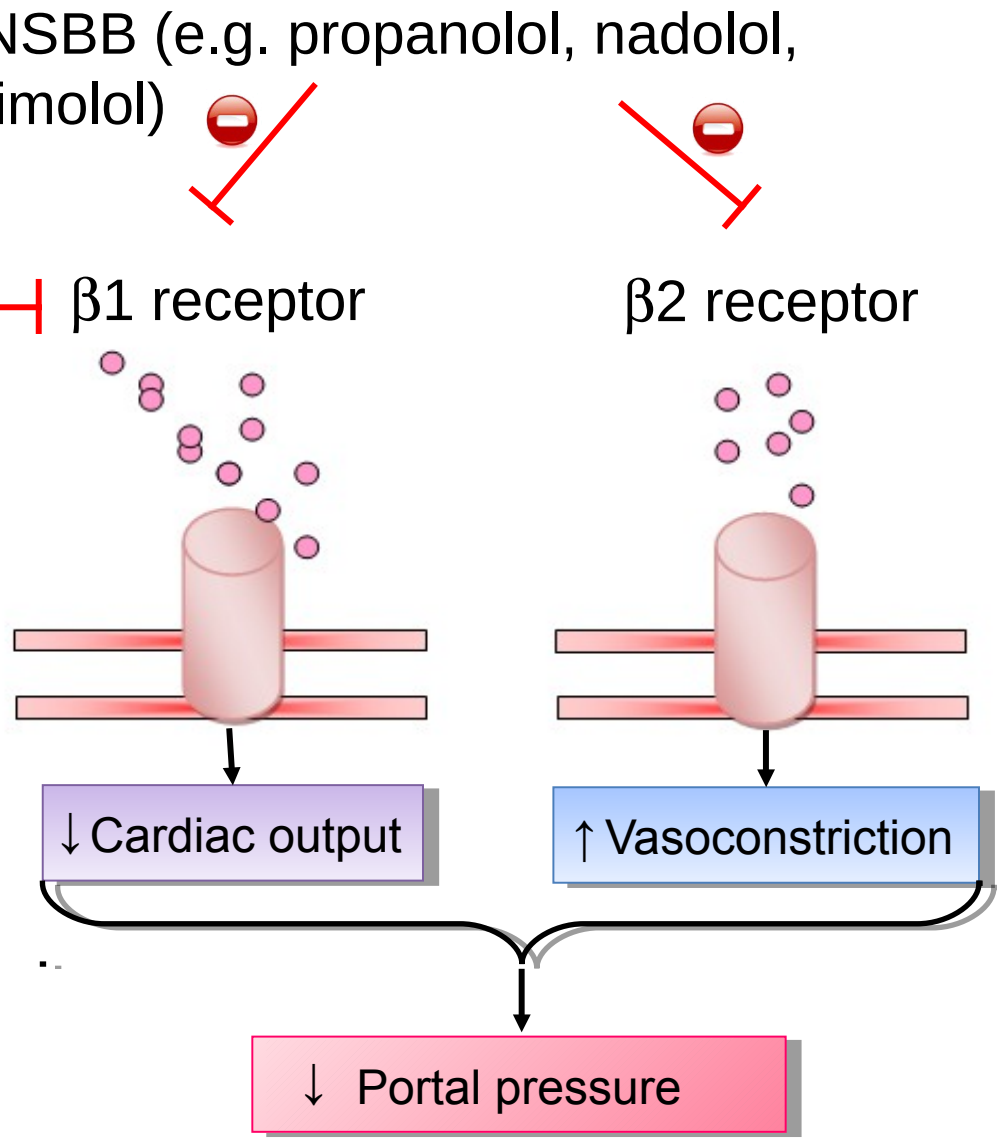
Schrier et al. *Hepatology*

Pharmacological effects of beta-blockers

β1-antagonists,
(e.g. atenolol, metoprolol)

Less effective and not recommended for the prophylaxis of variceal hemorrhage

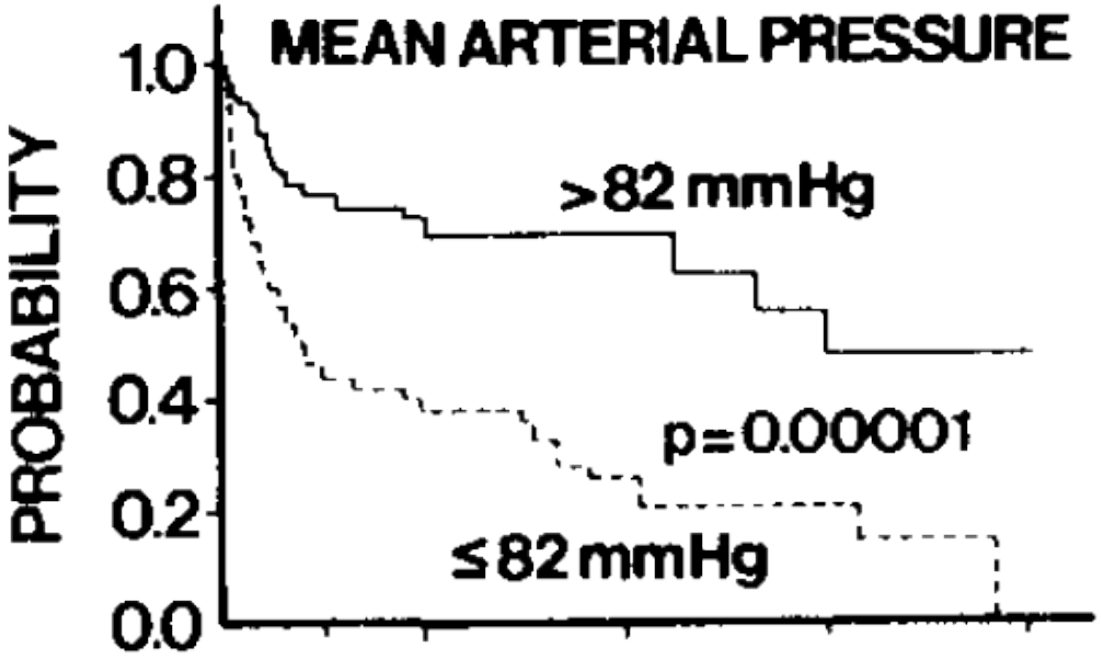
Hilon et al. *Hepatology* 1992
Westaby et al. *Gut* 1985



2) Can beta-blockers be safely used at all stages of cirrhosis?

Why could NSBB be harmful?

- Studies in patients **without** NSBB established an association between blood pressure and survival
- 139 patients with cirrhosis and ascites, mean follow-up of 12.8 months

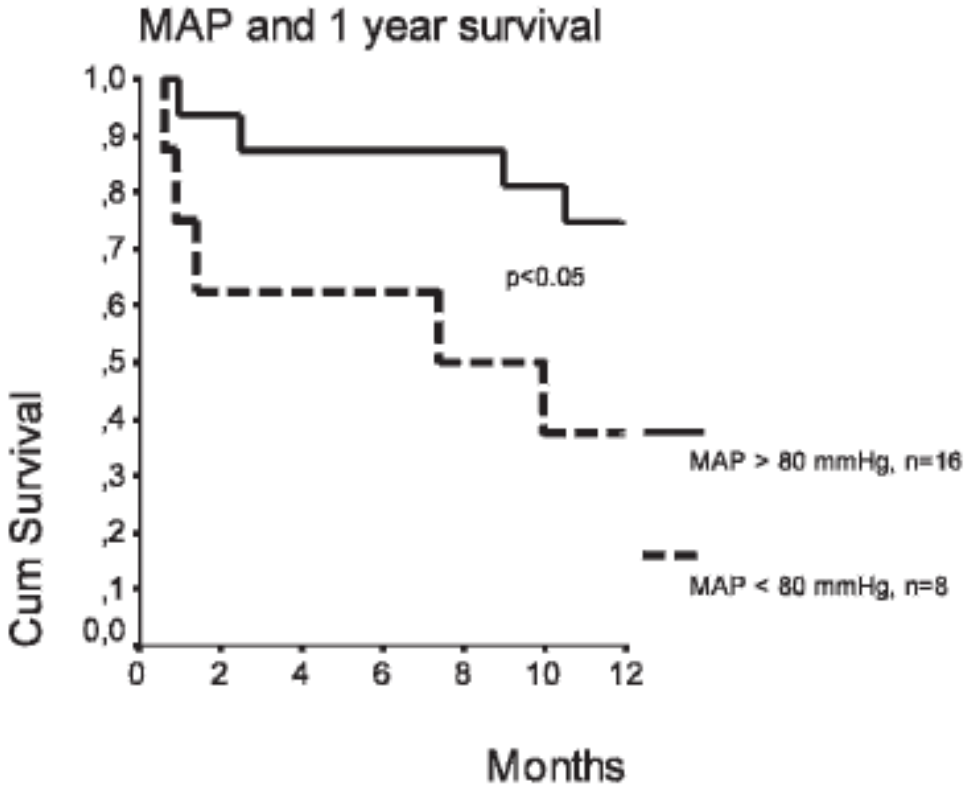


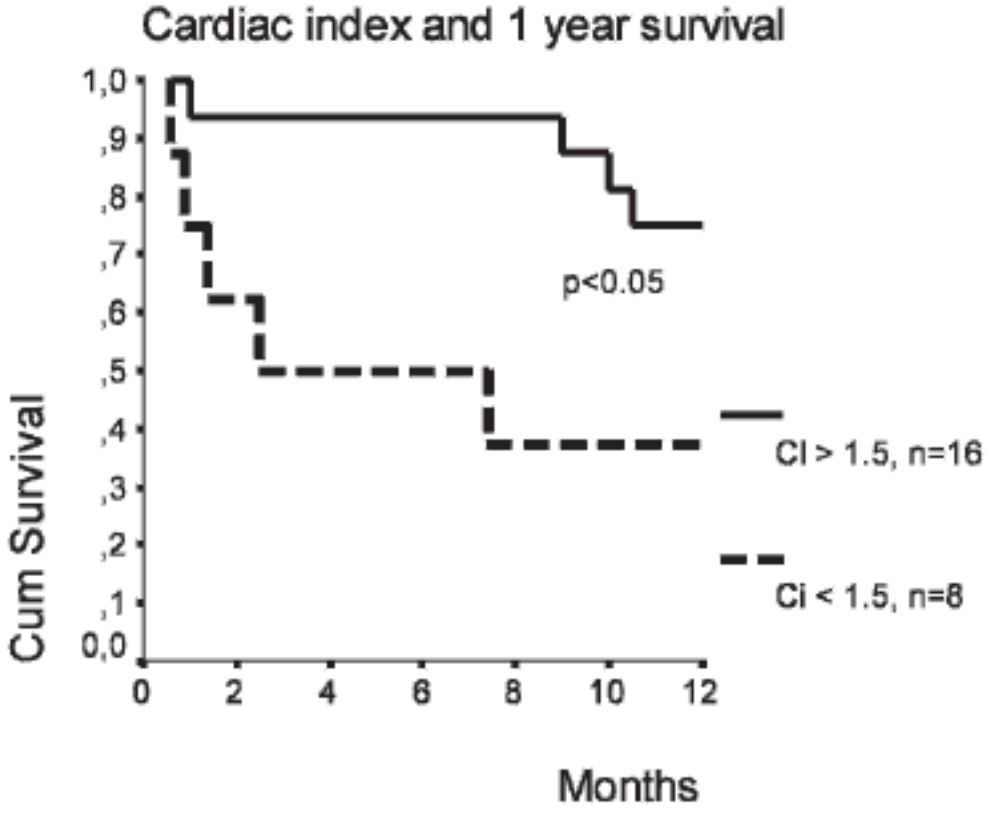
- **Hypothesis**: as cirrhosis progresses, the cardiovascular system loses its compensatory ability

Llach et al. *Gastroenterology* 1988

Low cardiac output and MAP are associated with a worse prognosis in cirrhotic patients

- 24 patients with cirrhosis and ascites without NSBB



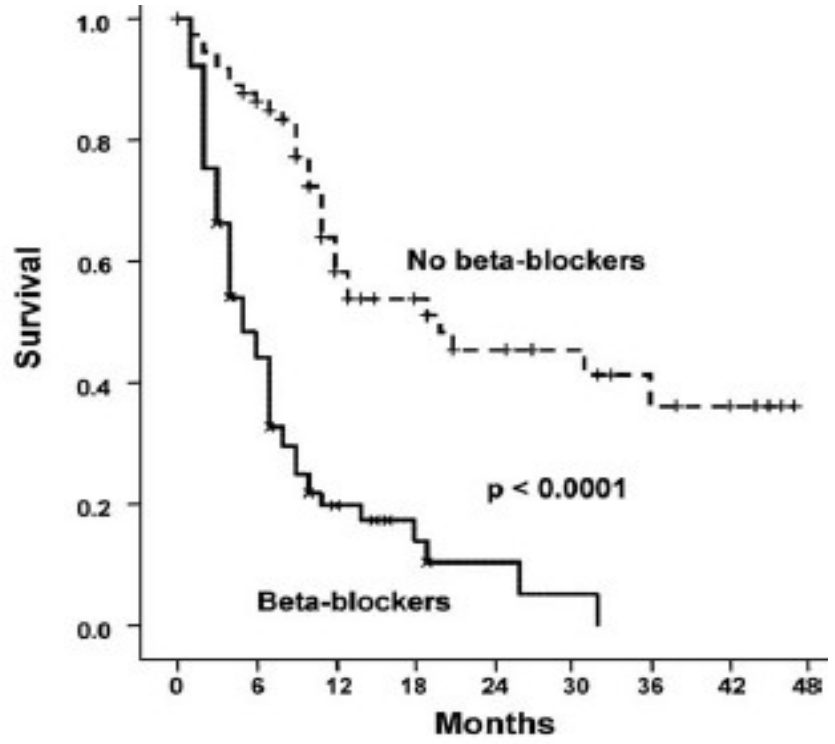


Beta-blockers may worsen hemodynamics resulting in subsequent mortality

Krag et al. *Gut* 2010

Deleterious effects of NSBB in cirrhotics with refractory ascites

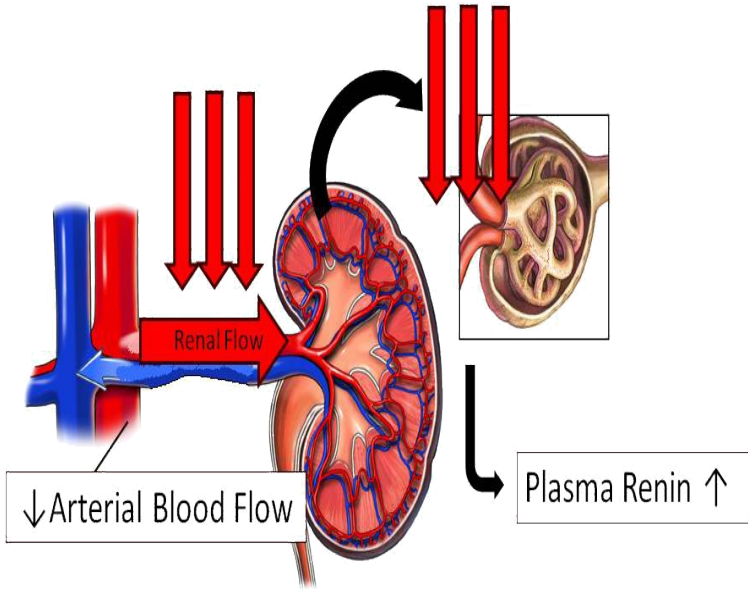
- One prospective non-randomized study included 151 cirrhotic patients with refractory ascites and frequent large-volume paracentesis with intravenous albumin administration
- Patients given NSBB were not significantly different from the others (MELD, Child-Pugh score)



Sersté et al. *Hepatology*

Pathophysiological hypothesis

- The characteristic of refractory ascites is repeated paracentesis



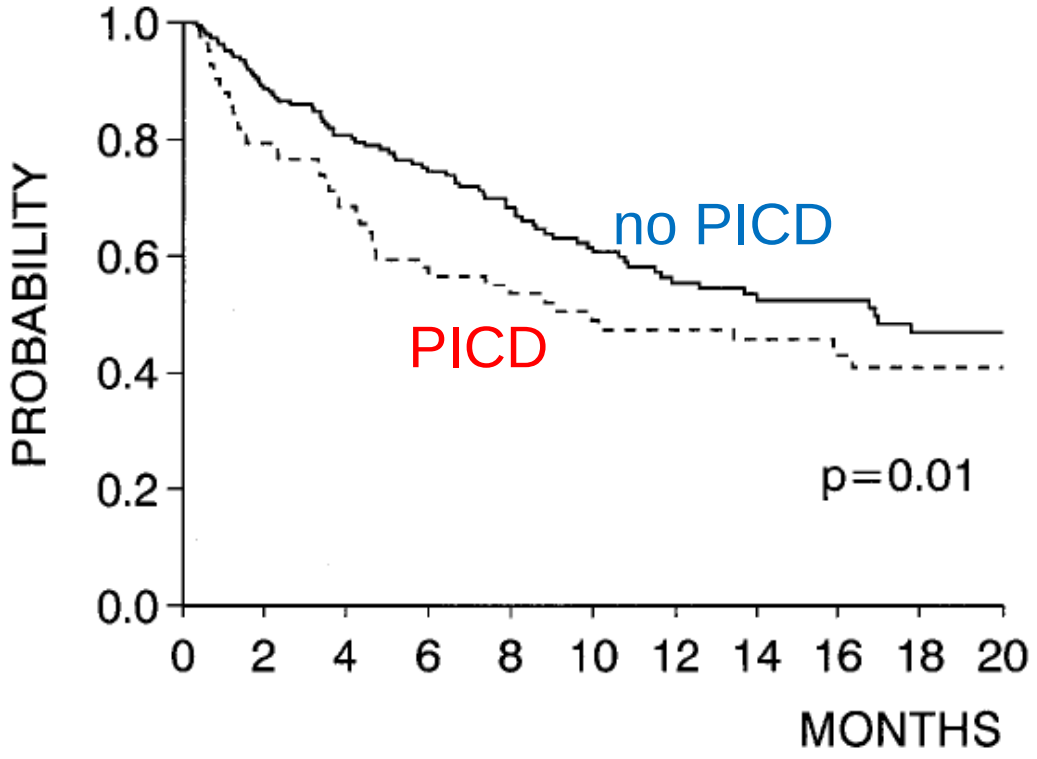
- Paracentesis further induces arteriolar vasodilation and results
  in additional decrease in effective arterial blood volume

- Paracentesis has been shown to trigger a paracentesis induced circulatory dysfunction syndrome (PICD) characterized by systemic vasodilation

- PICD is defined as an increase in plasma renin concentration of at least 50% one week after paracentesis

Paracentesis-induced circulatory dysfunction is associated with a decreased survival

- 289 patients with ascites treated by total paracentesis

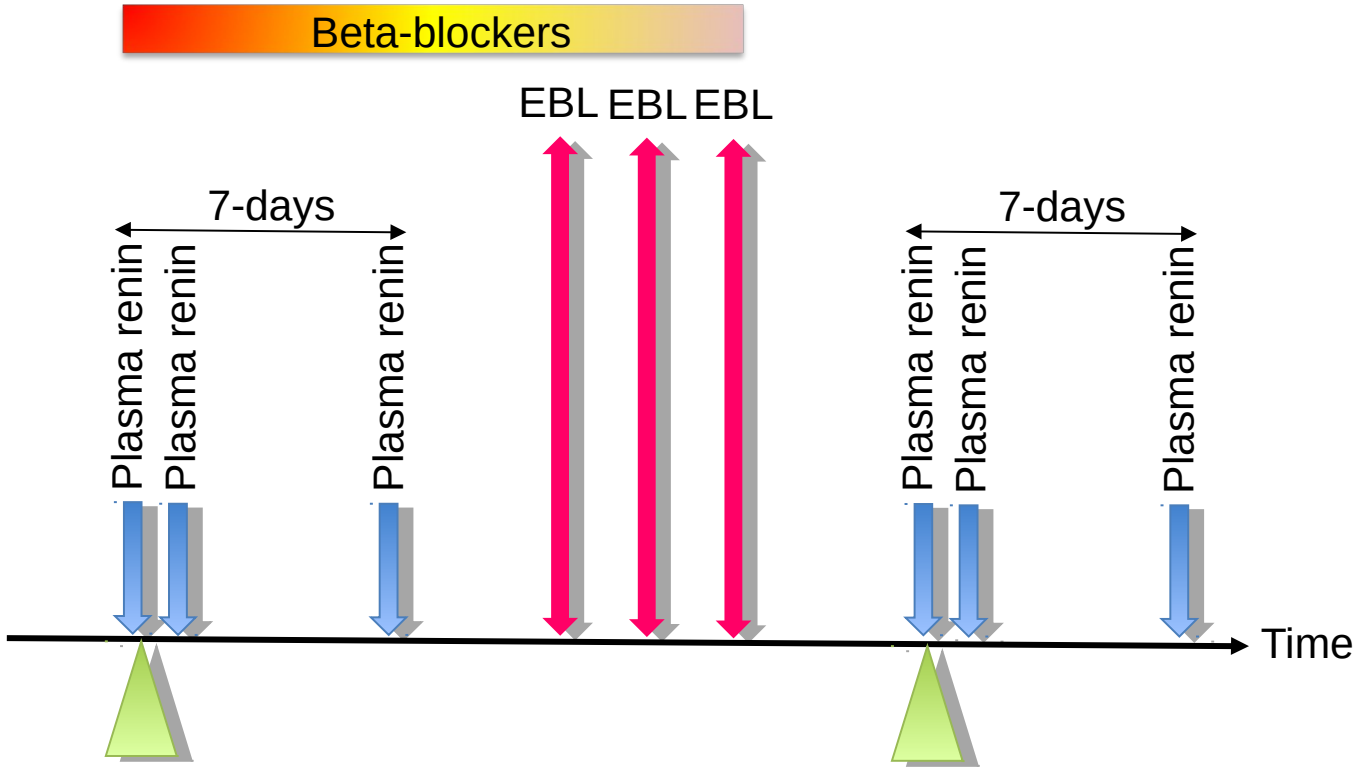


Ginès et al. *Gastroenterology* 1996

β-blockers could contribute to PICD by blocking the increase in cardiac output normally observed

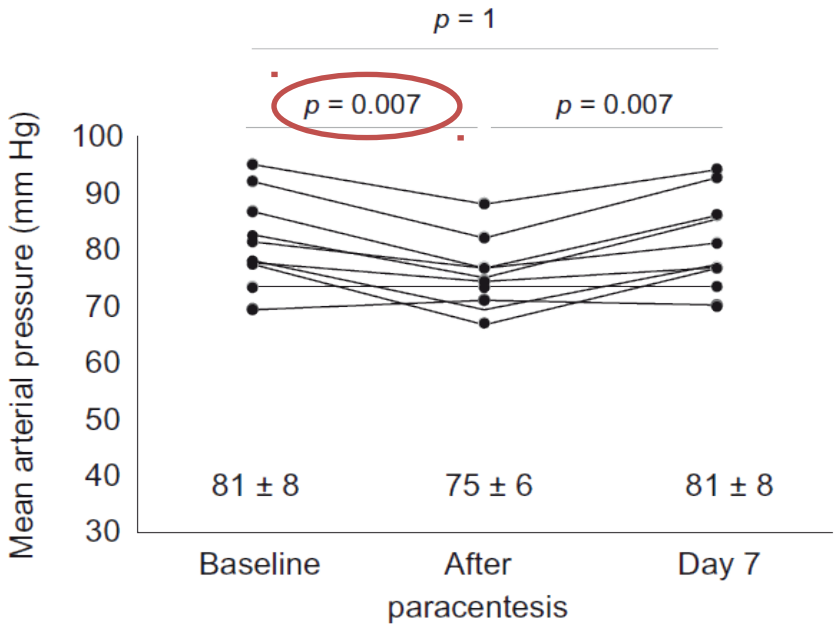
Beta-blocker therapy is associated with PICD

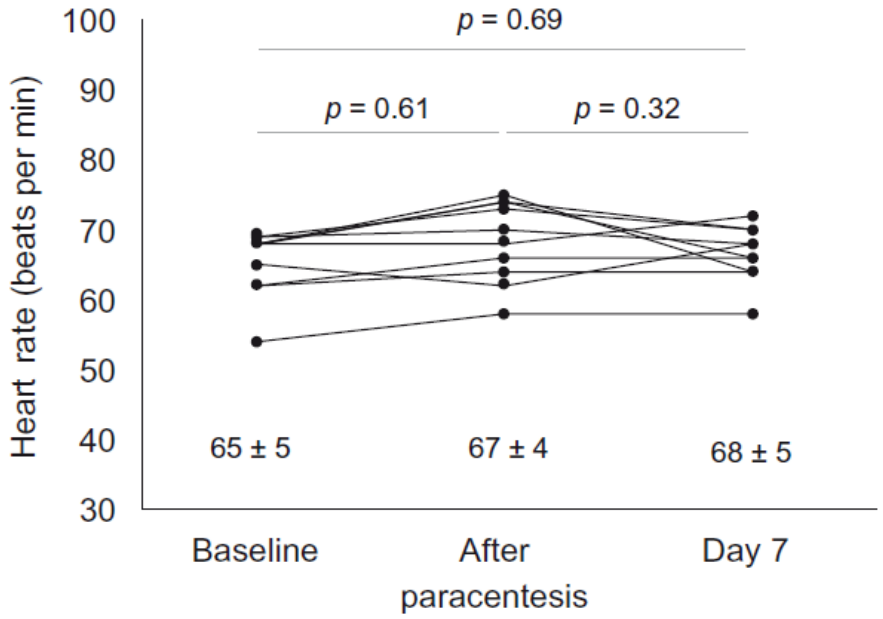
- 10 patients with cirrhosis and refractory ascites who had paracentesis at least twice in 1 month
  for 3 months
- Self-controlled cross-over design (i.e. each patient was his own control)

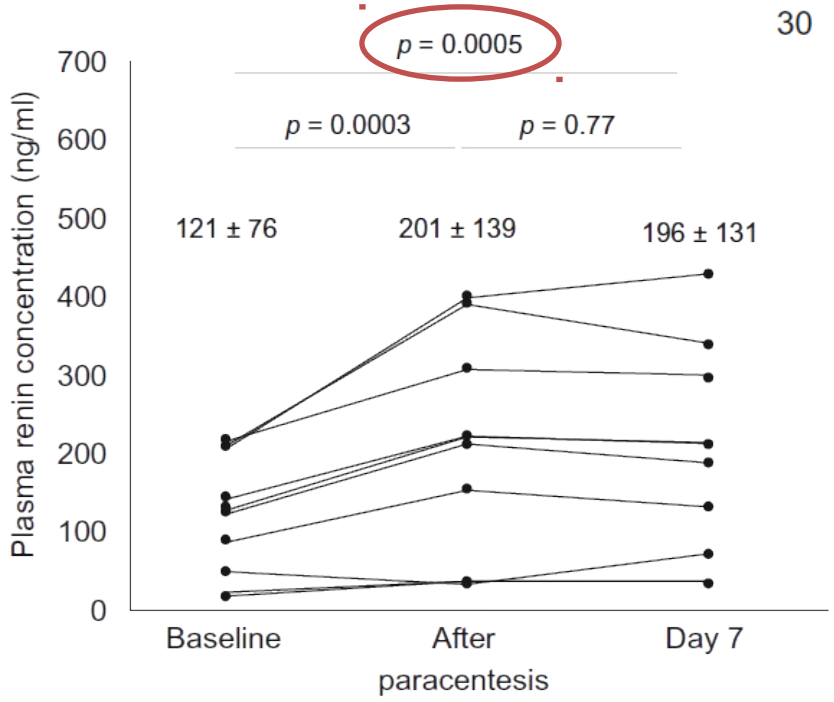


Sersté et al. *J Hepatol* 2011

Assessment of PICD in patients given beta-blockers

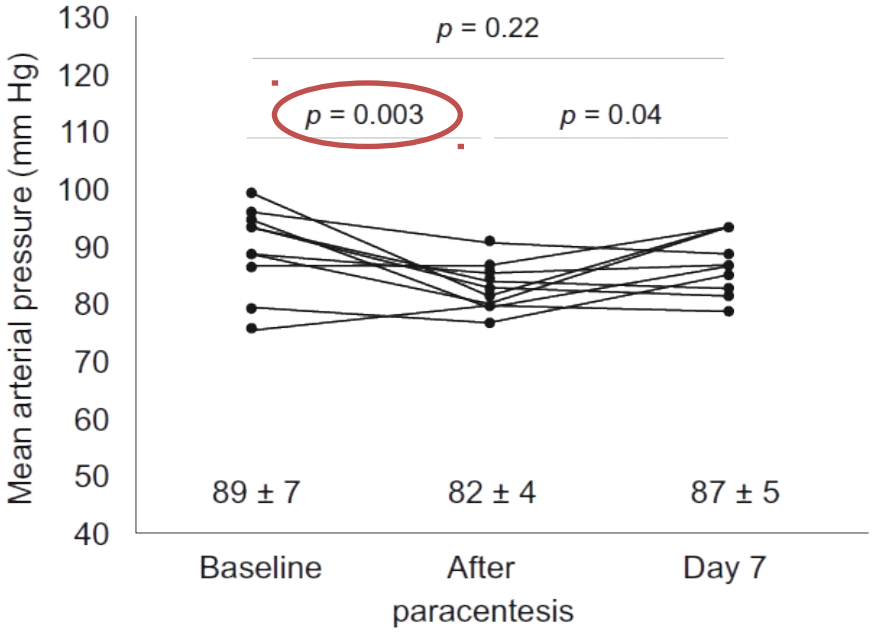


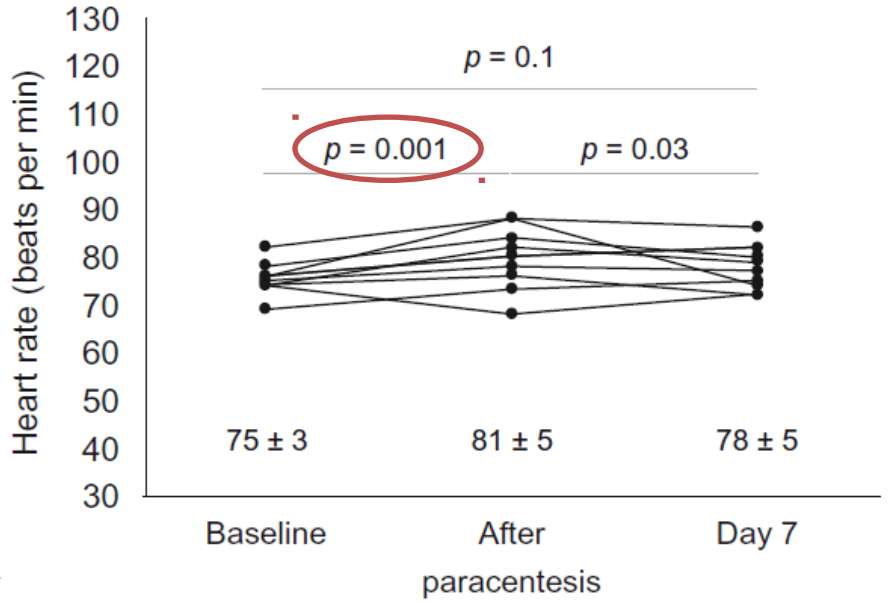


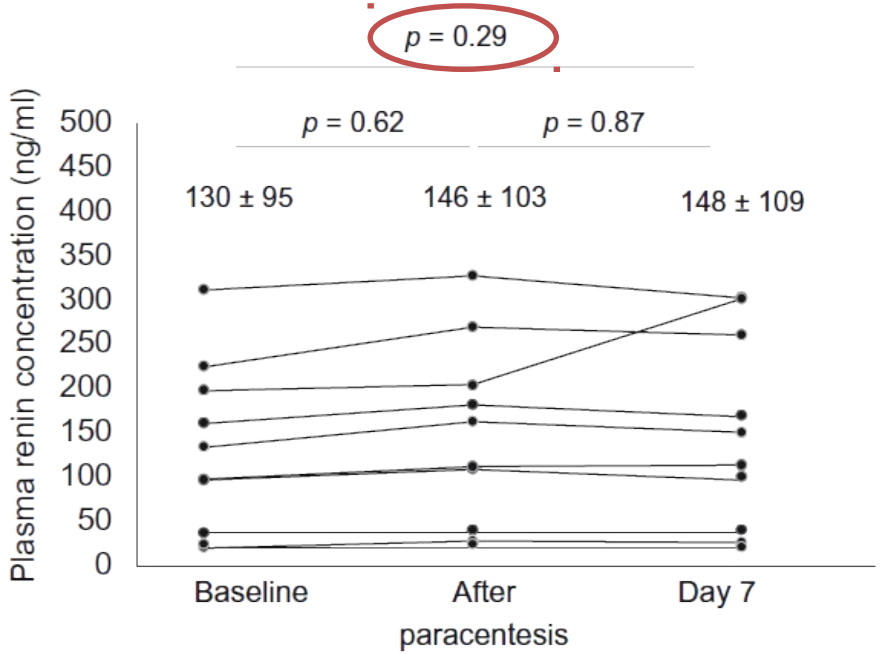


Sersté et al. *J Hepatol* 2011

Assessment of PICD after discontinuation of beta-blockers

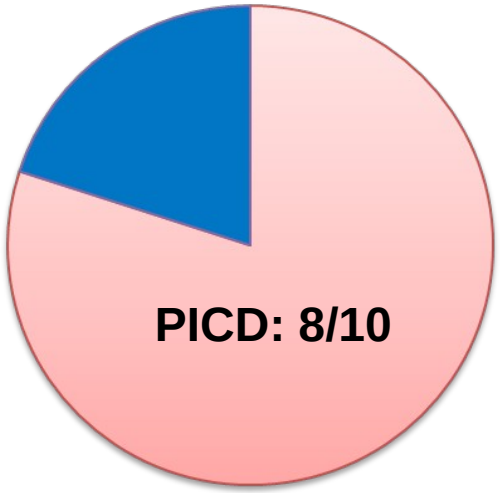






Sersté et al. *J Hepatol* 2011

Assessment of PICD in cirrhotic patients with refractory ascites



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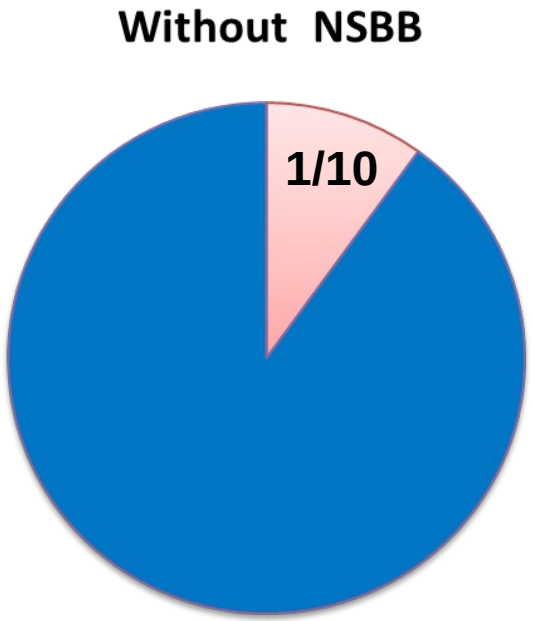


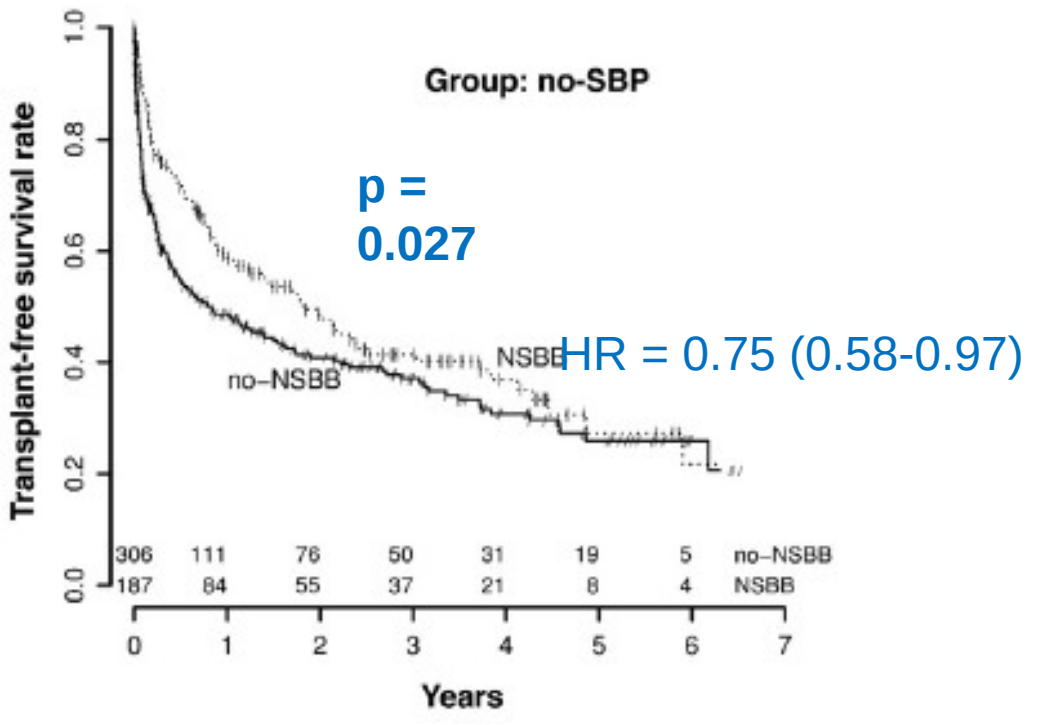
The inability of the circulatory system to increase cardiac output
in cirrhotic patients given NSBB increases the risk of PICD

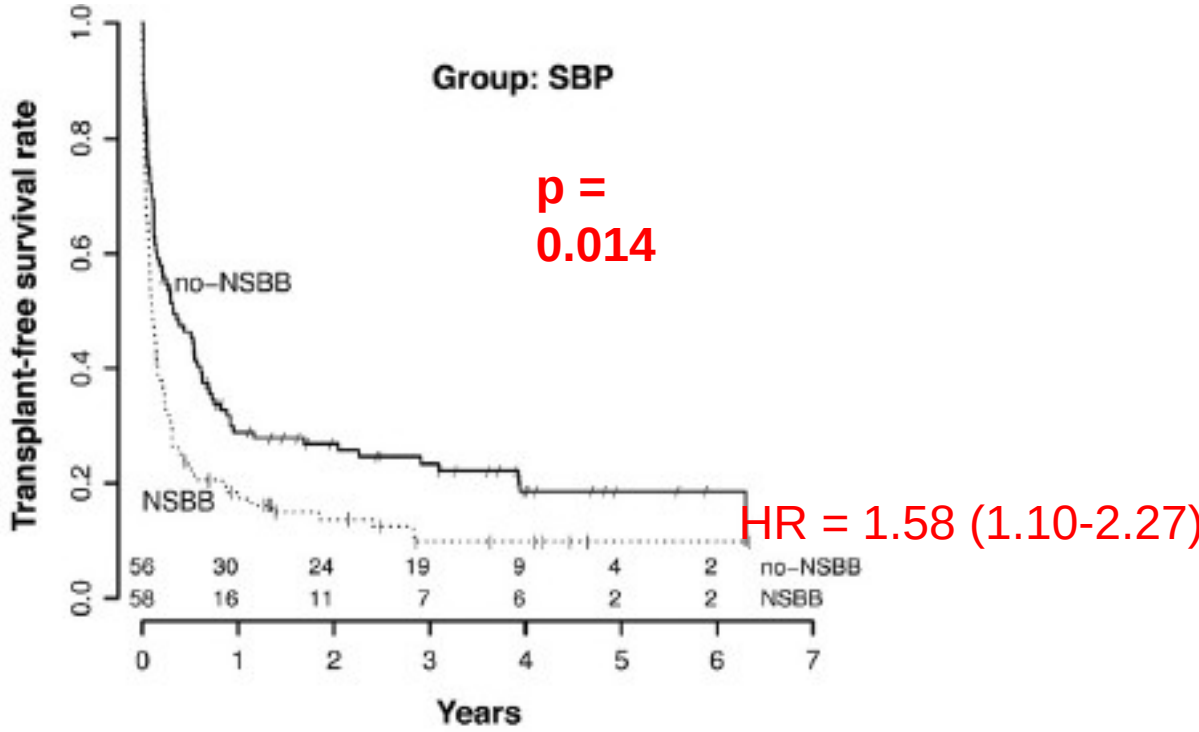
Sersté et al. *J Hepatol* 2011

Beta-blockers impact on survival in cirrhotics with spontaneous bacterial peritonitis (SBP)

- Retrospective analysis of 607 consecutive cirrhotic patients who had their first paracentesis

  - 182 developed SBP (first episode) during follow-up and among them 86 (47.3 %) received NSBB

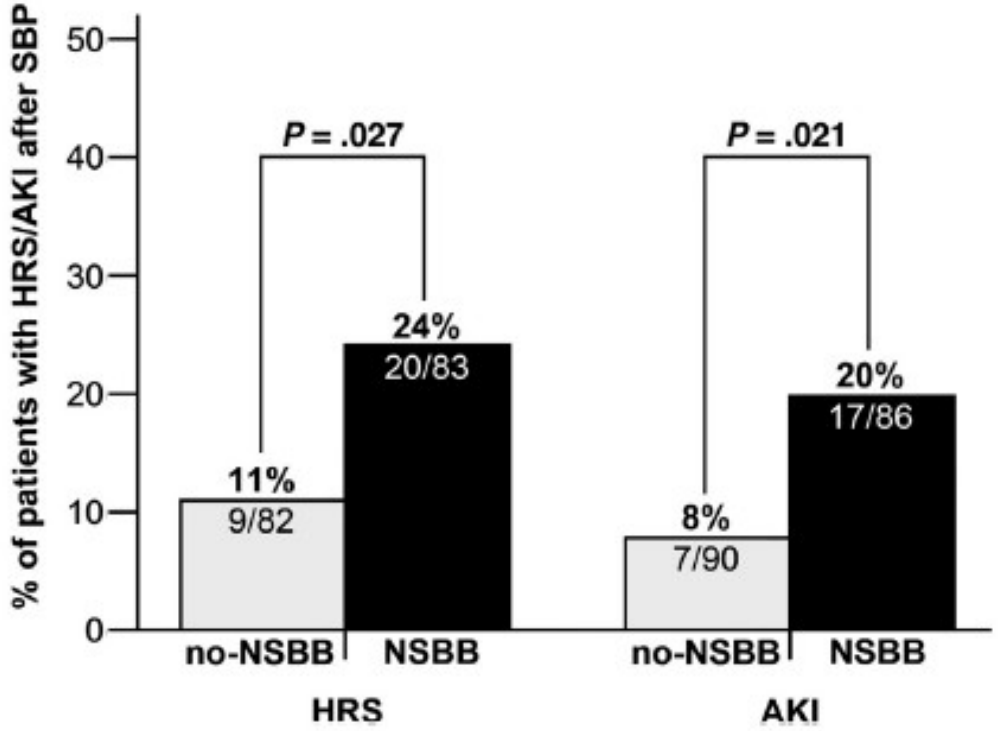




Mandorfer et al. *Gastroenterology* 2014

NSBB treatment and risk of HRS and AKI in cirrhotic patients with SBP

- Influence of NSBB treatment on hepatorenal syndrome (HRS) and grade C Acute kidney injury (AKI) development within 90 days after the first SBP diagnosis



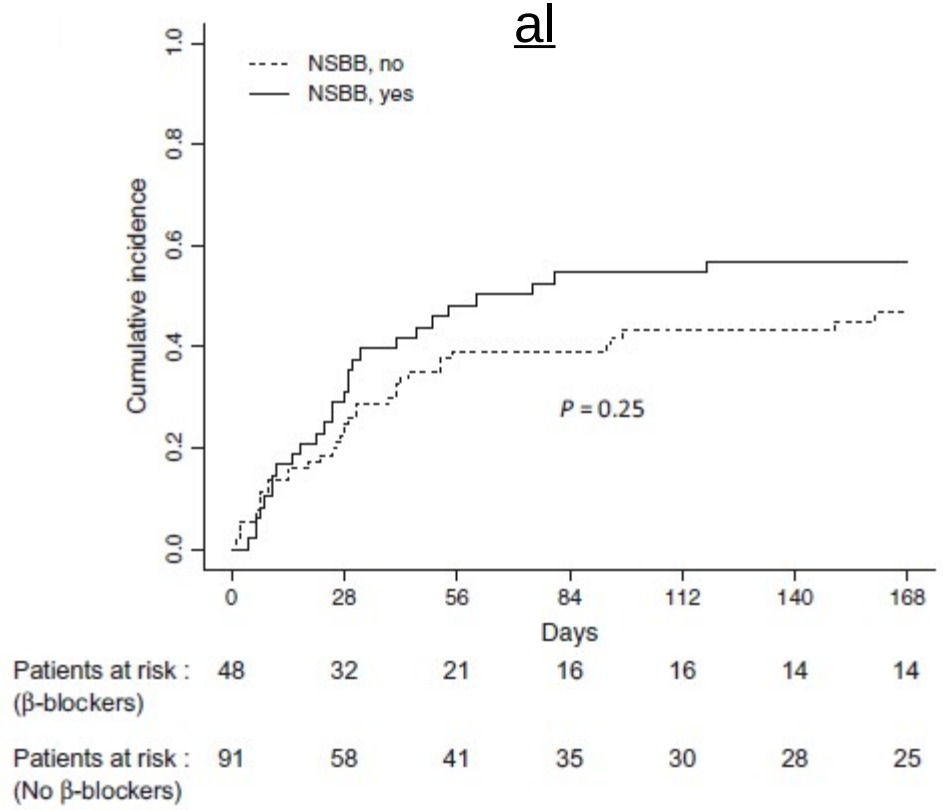
Among cirrhotics **with SBP**, NSBBs increase the risks for AKI and HRS and reduce transplant-free survival

Mandorfer et al. *Gastroenterology*

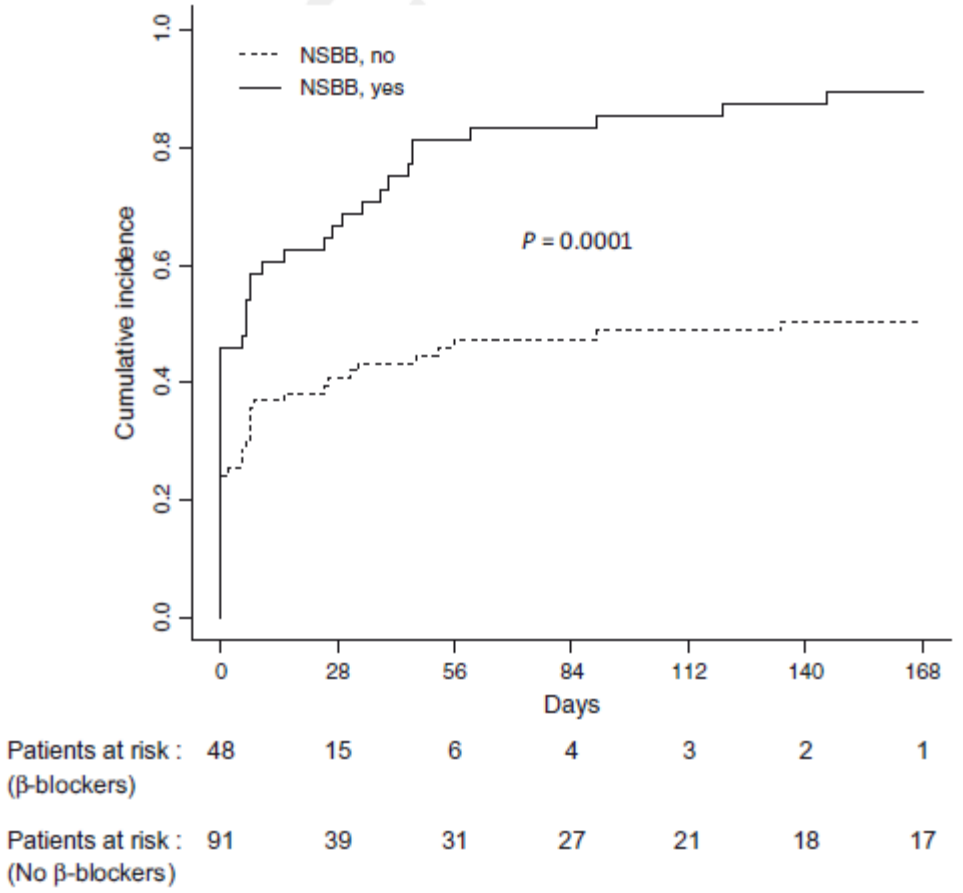
NSBB treatment and risk of AKI in cirrhotic patients with severe alcoholic hepatitis

- 139 cirrhotic patients with severe alcoholic hepatitis histologically confirmed
  - 51 (46.8 %) had NSBB

Surviv
al



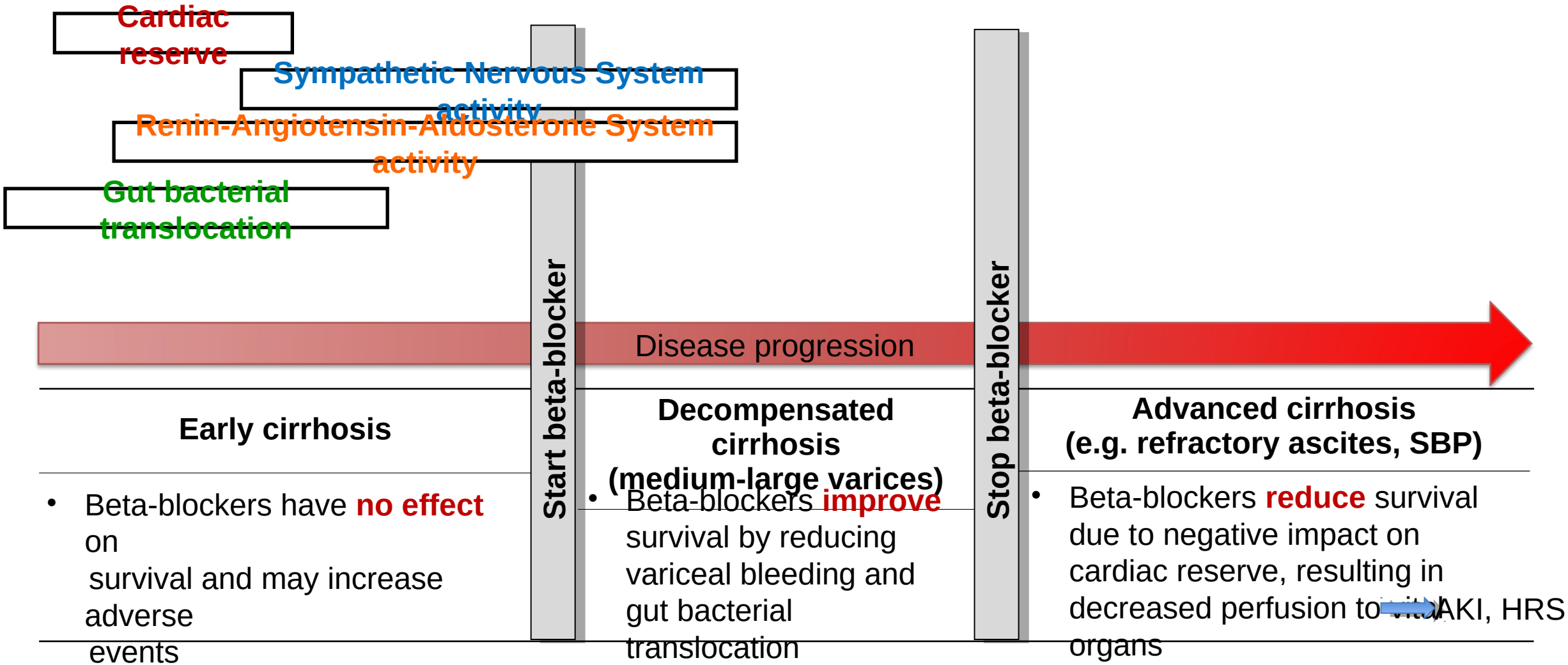
AKI



Sersté et al. *Liver Int*

3) Which subset of cirrhotic patients could benefit the most from beta-blocker therapy?

Appropriate timing for beta-blocker therapy: "The window hypothesis"



Krag et al. *Gut* 2012
Ge 2012 *J Hepatol* 201

Conclusions

- Beta-blockers (nonselective) are part of the cornerstone of the medical management
  of primary and secondary prevention of variceal hemorrhage

- Beta-blockers are not indicated to prevent the development of varices in early cirrhosis

- Beta-blockers should be tapered and discontinued when patients develop end-stage cirrhosis with refractory ascites or SBP as decreased cardiac output results in decreased renal perfusion and increased risk for AKI, HRS and mortality

  - Beta-blockers should be promptly discontinued in the setting of either sepsis or HRS

Ge et al. *J Hepatol* 2014

Acknowledgments

- Dr. Thomas Sersté (UMC Saint Pierre, Brussels and C.U.B. Hôpital Erasme, Brussels, Belgium)

For your attention…

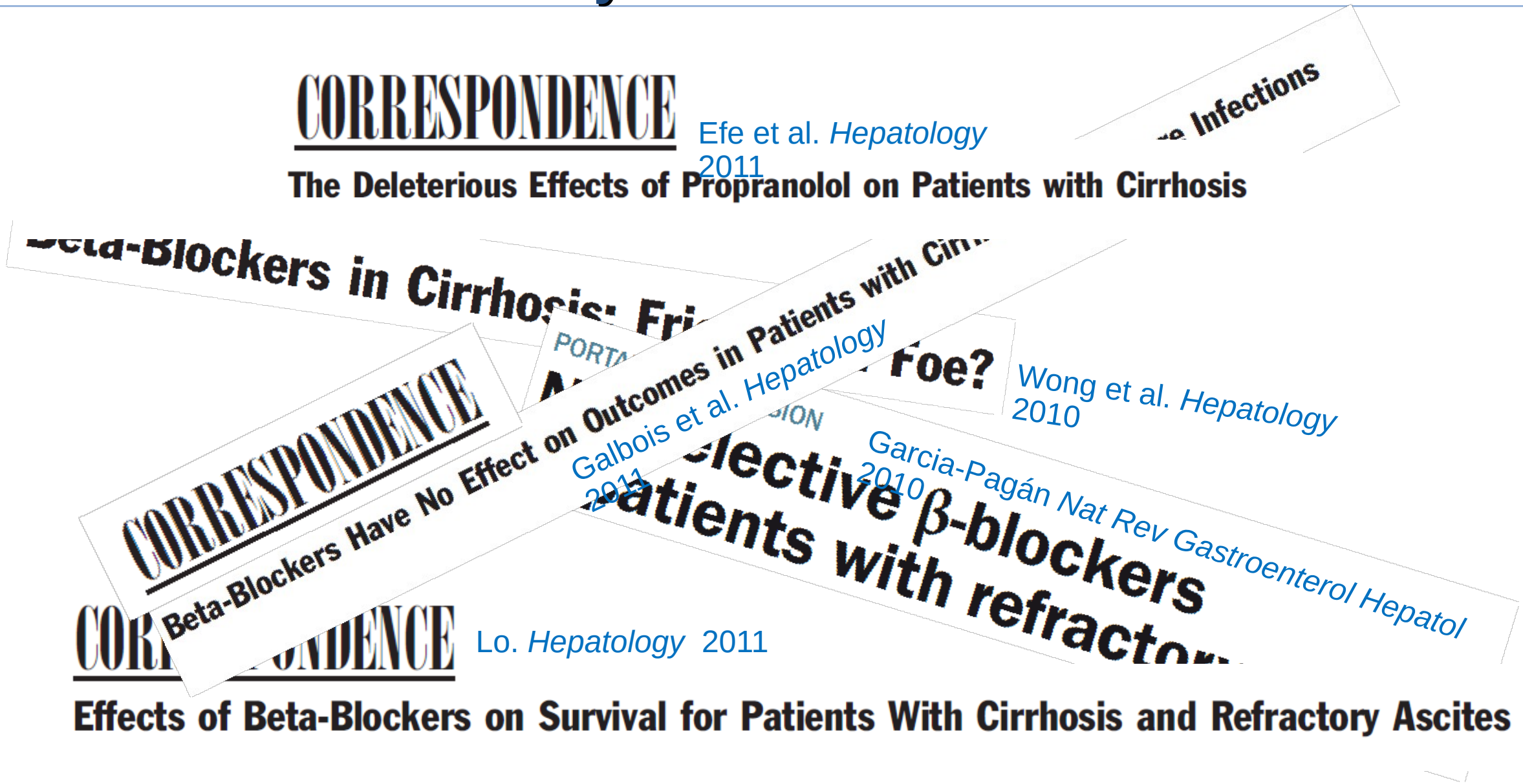
Additional research questions concerning beta-blocker therapy

- Appropriate dosing of NSBB in cirrhosis?
  - Previous studies used increasing doses until the heart rate was reduced by approximately 25%,
    with doses ranging from 20 to 180 mg given twice a day
  - ↓ hepatic venous pressure gradient (HVPG) to <12 mmHg or by >20% from baseline

- Further evaluation of newer-generation of NSBB
  - Studies on carvedilol are inconclusive

- Additional studies to evaluate the role and safety of beta-blockers in patients with advanced cirrhosis notably with refractory ascites and/or SBP are critically needed
  - Original RCTs excluded the subset of patients with refractory ascites!

Safety of NSBB in refractory ascites: A lively debate…



Efe et al. *Hepatology* 2011

Wong et al. *Hepatology* 2010

Galbois et al. *Hepatology* 2011

Garcia-Pagán *Nat Rev Gastroenterol Hepatol* 2010

Lo. *Hepatology* 2011