Rethinking the role of non-selective beta blockers in patients with cirrhosis and portal hypertension

Alberto Ferrarese, Alberto Zanetto, Giacomo Germani, Patrizia Burra, Marco Senzolo

Alberto Ferrarese, Alberto Zanetto, Giacomo Germani, Patrizia Burra, Marco Senzolo, Multivisceral Transplant Unit, Department of Surgery, Oncology and Gastroenterology, Padua University Hospital, 35128 Padua, Italy

Correspondence to: Dr. Marco Senzolo, MD, PhD, Multivisceral Transplant Unit, Department of Surgery, Oncology and Gastroenterology, Padua University Hospital, via Giustiniani 2, 35128 Padua, Italy. marcosenzolo@hotmail.com
Telephone: +39-04-98218726
Fax: +39-04-98218727

Abstract

Non-selective beta blockers (NSBB) are commonly used to prevent portal hypertensive bleeding in cirrhotics. Nevertheless, in the last years, the use of NSBB in critically decompensated patients, especially in those with refractory ascites, has been questioned, mainly for an increased risk of mortality and worsening of systemic hemodynamics. Moreover, even if NSBB have been reported to correlate with a higher risk of renal failure and severe infection in patients with advanced liver disease and hypotension, their use has been associated with a reduction of risk of spontaneous bacterial peritonitis, modification of gut permeability and reduction of bacterial translocation. This manuscript systematically reviews the published evidences about harms and benefits of the use of NSBB in patients with decompensated cirrhosis.

Key words: Beta blockers; Ascites; Cirrhosis; Portal hypertension

Core tip: In this review, we've critically analyzed the recent evidence on the role played by non-selective beta blockers in patients with decompensated liver disease.

INTRODUCTION

Cirrhosis is among the leading causes of death worldwide and hepatocellular carcinoma and complications of portal hypertension (PH) represent the most frequent causes of death.

PH is characterized by a systemic hyperdynamic

circulation, with increase of cardiac output (CO) and heart rate (HR), and reduction of mean arterial pressure (MAP) and systemic vascular resistances[1]. The degree of PH correlates with the severity of hyperdynamic circulation, while the absence of hemodynamic imbalance (*i.e.*, preserved right heart preload) is associated with better prognosis[2].

Ascites, esophageal varices, encephalopathy and/ or jaundice are the main features of decompensated cirrhosis. Ascites represents the first clinical sign of decompensation in 30%-50% of patients, being the incidence about 50% within 10 years[3]. Refractory ascites occurs in 5% to 10% of cases, leading to a significant shortening in survival[4]. Oesophageal varices occur in about 50% of cirrhotic patients[5] being the incidence of first variceal bleeding estimated to be about 12%-15% per year, and the mortality of 15%-20% for every episode[6]. Varices mainly develop due to increased PH, but Fernandez *et al*[7] reported that their formation was also modulated by active angiogenesis, and not by a simple mechanism of vasodilation.

Moreover, several external factors, such surgery, bacterial infections or bleeding, represent severe trigger factors for derangement of hemodynamic; for instance, infection seemed more frequent in those patients who developed an acute-on-chronic liver failure (32.6% *vs* 21.8%, *P* < 0.01)[8]. Phillip *et al*[9] showed that removal of > 5 L of ascites determined a significant reduction of MAP and SVR, which is usually associated with a counterbalancing increase of CO[10]. The hemodynamic imbalance after LVP led to an increased risk of renal dysfunction, and subsequently to an increased mortality, according to the well-defined Paracentesis Induced Circulatory Dysfunction (PICD)[11].

Heart dysfunction has been shown in decompensated cirrhosis[12], being caused both by organic (*i.e.*, alcoholic or septic cardiomyopathy) and/or functional [*i.e.*, cirrhotic cardiomyopathy (CM)] factors. CM is mainly due to chronic increase of pro-inflammatory cytokines, impairment of systemic and regional hemodynamic, and beta-adrenergic receptor desensitization, with reversible impairment of systolic contractility, diastolic function and electrophysiological activity[1,13]. The impaired CO may also contribute to a decrease in renal perfusion: For instance, Krag *et al*[14] demonstrated that a lower cardiac index was associated with an increased development of hepatorenal syndrome within 3 mo (43% *vs* 5%, *P* = 0.04). Although it's difficult to determine the prevalence of CM since it's usually masked at rest, it could be an important cause of multi-organ failure and death during stressing conditions, as infection or liver transplantation[15].

ROLE OF NON-SELECTIVE BETA BLOCKERS IN THE TREATMENT OF PH
Non-selective beta blockers and variceal bleeding
Non-selective beta blockers (NSBB) act reducing portal flow and PH by decreasing CO (through β1 receptors) and determining splanchnic vasoconstriction (through β2 receptors)[16]. In 1981 Lebrec *et al*[17] demonstrated for the first time the effectiveness of NSBB for variceal bleeding; the re-bleeding rate was 4% in the treated group, compared to 50% in the placebo group.

Several randomized studies confirmed that NSBB represent the preferred option in primary prophylaxis against no intervention[18] and in preventing re-bleeding in combination with endoscopic band ligation[19]. Furthermore, a Cochrane metanalysis[20] confirmed that NSBB were as effective as endoscopic band ligation for reducing bleeding related mortality [29/567 (5.1%) *vs* 37/585 (6.3%); RR = 0.85; 95%CI: 0.53 to 1.39].

However, identification of hemodynamic response to NSBB still remains challenging for the hepatologists. Heebøll *et al*[21] demonstrated that only 51/124 (40%) of patients with cirrhosis who underwent measurement of gradient between portal and hepatic veins (HVPG) presented a significant hemodynamic improvement (reduction greater than 20% or > 12 mmHg) after NSBB use. Moreover, authors did not demonstrate a significant association between improvement of HVPG and change of HR (*P* = 0.8), which is commonly used parameter to tailor propranolol therapy.

Importantly, all the trials often ruled out cirrhotics with decompensated liver disease (*i.e.*, those with refractory ascites) from the analysis.

NSBBS IN DECOMPENSATED CIRRHOTICS
Serstè *et al*[22] showed for the first time in 2010 that the median survival was extremely reduced in 151 patients with cirrhosis and refractory ascites treated with propranolol (20.0 mo *vs* 5.0 mo; *P* = 0.00001); other factors associated with higher mortality were Child-Pugh class C, hyponatremia and renal failure. These data raised several concerns amongst hepatologists[23-25] about the use of NSBB in cirrhotics with more advanced liver disease.

First, the group receiving NSBB comprises obviously sicker patients, because of higher prevalence of oesophageal varices (77/77 *vs* 3/74; *P* = 0.001) and higher serum bilirubin (56 mg/dL *vs* 48 mg/dL, *P* = 0.01). Second, the propranolol dose of 160 mg/d was significantly higher (in about half of the patients) than the mean dose used in the previous RCTs. Third, mortality was extremely higher in the NSBB group (63/77, 85.1%, median survival time was 5 mo), and there was an increased prevalence of sepsis related mortality, which remain difficult to explain[25].

The French group hypothesized that NSBB use can worse hemodynamic after LVP; thus, reduced survival could be due to an increased incidence of PICD. A crossover study published in 2011[26] including 10 patients with refractory ascites, investigated the incidence of PICD after LVP when patients were taking NSBB and after

drug discontinuation. The authors showed that PICD was extremely decreased after propranolol discontinuation (1/10 *vs* 8/10; *P* = 0.01). The hypothesis was that propranolol use determined a reduction of CO and consequently an increase of counter-regulatory vasoconstriction systems, as renin angiotensin aldosterone, whose permanent hyper-activation could be associated with poorer renal function and reduced paracentesis-free interval time.

The link between NSBB and hemodynamic impairment was explained with the reduced MAP, which is a known negative prognostic factor for hyperdynamic circulation and progression of liver disease[27]. For instance, in the French study by Serstè *et al*[22], the cohort receiving propranolol did have lower MAP (90 mmHg *vs* 83 mmHg). Nevertheless, NSBB have been shown not to reduce MAP after acute *i.v.* administration[28], and the detrimental effects which were seen by the authors could have been due to the dose related side effect made by propranolol. CO is not usually reduced by NSBB introduction[29].

The following clinical studies failed to find any association between the use of NSBB and increased risk of deaths in decompensated cirrhotics (Table 1). Leithead *et al*[30] analyzed a subgroup of 117 patients with refractory ascites listed for LT, receiving a median dose of propranolol of 80 mg/d. They demonstrated that NSBB were independently associated with reduced waitlist death (adjusted HR = 0.35, *P* = 0.022), without higher prevalence of sepsis related mortality. Moreover, an equal survival between patients with refractory ascites taking NSBB and patients without NSBB (12/38 *vs* 8/23; *P* = 0.79) was shown in another smaller single center retrospective analysis[31].

Bossen *et al*[32] not only confirmed similar mid-term mortality between 258 patients with refractory ascites receiving NSBB and a control group of 330 patients (30.8% *vs* 30.5%; adjusted HR = 1.02, 95%CI: 0.74-1.39) retrospectively evaluated, but also showed that discontinuation of NSBB was associated with an higher mortality (adjusted HR = 5.13, 95%CI: 2.28-11.55).

In addition, new data seemed to confirm the absence of correlation between mortality and NSBB. Pereira *et al*[33] included 163 patients with infection, of whom 104 were on NSBB. Use of NSBB was associated with lower frequency of sepsis (21% *vs* 42%, *P* = 0.03), being 3-mo survival not different between cohorts (59% *vs* 63%; *P* = ns). Mallawaarachchi *et al*[34] showed that 75 patients treated with NSBB (67 with carvedilol and 8 propranolol) presented equal mortality after a median follow-up time of 28.0 mo (60.0% *vs* 66.7%; *P* = 0.10); in those with moderate or severe ascites, survival was similar in both groups (*P* = 0.67), while it was better in NSBB patients in mild ascites (*P* = 0.02).

In a large multicentric cohort, Bhutta *et al*[35] confirmed that survival was significantly greater in patients on NSBB at admission with a median survival of 58 d compared to 32 d in patients not on NSBB (*P* = 0.033). No difference was found between those who did or did not discontinue NSBB (*P* = 0.91), being only systolic arterial pressure and acute renal failure independent predictors of death.

Onali *et al*[36] evaluating 316 patients (126 with refractory ascites), showed that those on NSBB (*n* = 128, 40.5%) had a higher frequency of previous variceal bleeding (50% *vs* 21%, *P* < 0.001) and spontaneous bacterial peritonitis (27% *vs* 17%, *P* = 0.025), but were at lower risk of death (16% *vs* 32%; *P* = 0.002). At multivariate analysis use of NSBB was associated with reduced mortality (HR = 0.511, 95%CI: 0.3-0.87, *P* = 0.014).

Finally, in a recent study provided on 349 acute-on chronic patients with cirrhosis, Mookerjee *et al*[37] demonstrated a significantly lower short term mortality in patients on NSBB compared to those without NSBB (24% *vs* 34%, *P* = 0.048). Interestingly, patients on NSBB had less severe progression to the stages of acute-on-chronic liver failure, and those who discontinued NSBB had a higher mortality (37% *vs* 13%), even if it might be due to an independently higher presence of circulatory dysfunction.

The association between increased mortality and NSBB could be explained with the worsening of an already impaired hemodynamics, especially in those who experience a greater decrease of cardiac function (*i.e.*, of CO) and of MAP. However, in the study by Karagiannakis *et al*[15] in which the decrease of CO (and subsequently of cardiac index) has been correlated with a lower survival, the used cut-off (1.5 L/m per square meter) is not diffusely seen in cirrhotics, even when decompensated[38].

Simultaneous presence of several cofactors, as infection, could contribute to the change of clinical scenario, being patients at higher risk of hemodynamic derangement if NSBB are not withdrawn.

Mandorfer *et al*[39] showed that 245 patients with refractory ascites but without infection, taking NSBB, experienced a significant reduction in hospitalization rate (19.4 d *vs* 23.9 d per person-year); at multivariate analysis, NSBB treatment correlated with higher transplant-free survival (HR = 0.771; 95%CI: 0.598-0.993; *P* = 0.04). The Authors demonstrated a correlation between mortality and NSBB only in patients experiencing a previous episode of spontaneous bacterial peritonitis (SBP), with a significant difference in length of hospitalization (NSBB: 33.4 d per person-year; 95%CI: 31.9-34.9 *vs* no-NSBB: 28.8 d per person-year; 95%CI: 27.6-29.9), and impaired transplant-free survival (HR = 1.644; 95%CI: 1.145-2.361). These data may confirm that NSBB could negatively influence hemodynamic status in patients with infection, but not that NSBB represented a trigger for infection.

However, Galbois *et al*[40] showed that cirrhotics admitted to intensive care unit for sepsis or septic shock who were receiving NSBB were not at increased risk of early or mid-term mortality (15/26 *vs* 26/42, *P* = 0.8; and 21/26 *vs* 28/42; *P* = 0.27, respectively).

In summary, latest studies seem not to confirm correlation between NSBB and mortality. Another meta-

Table 1 Available literature on the potential correlation between non-selective beta blockers and mortality in patients with cirrhosis

Ref.	Patients	Refractory ascites	Propranolol dose/day	Follow-up	Mortality	Sepsis
Serstè *et al*[22]	74	100%	40 mg (9); 80 mg (31); 120 mg (1); 160 mg (36)	8 mo	63/77 (*P* < 0.0001 *vs* No NSBB)	NA
Galbois *et al*[40]	26	14 (53.8%)	NA	6 mo	21/26 (80.8%)	100%
Robins *et al*[60]	36	100%	48.9	10 mo	18/36 (50%) survival 18 mo	NA
Mandorfer *et al*[39]	245	100%	40 mg (20-120)	660 persons/year	Higher transplant free survival (HR = 0.771, *P* = 0.044)	No correlation between NSBB and SBP (HR = 0.728, *P* = 0.211)
Kimer *et al*[31]	23	100%	80 mg (40-200)	Retrospective	15/23 (65.2%)	NA
Leithead *et al*[30]	159 (119 on propranolol)	NA	80 mg (10-240)	Retrospective	35/159 (22%)	NA
Bossen *et al*[32]	559	46%	NA	12 mo	125/559 (22.5%)	NA
Mookerjee *et al*[37]	164 (propranolol 111; nadolol 6; carvedilol 16; other 31)	NA	40 (20-80; propranolol)	NA	40/164 *vs* 63/184 (24.4% *vs* 34.1%, *P* = 0.048) Similar 6 and 12-mo mortality between groups (*P* = 0.64 and 0.35 respectively)	NA
Pereira *et al*[33]	104	NA	NA	NA	67% *vs* 69% (*P* = ns)	21% *vs* 42% (*P* = ns)
Mallawaarachchi *et al*[34]	75 (8 propranolol)	NA	NA	28 mo	60% *vs* 66% (*P* = ns)	NA
Bhutta *et al*[35]	308 (nadolol 155; propranolol 64; carvedilol 72, other 62)	NA	NA	NA	Mean survival: 58 d in NSBB group (*vs* 32 d of control group; *P* = 0.033)	NA
Onali *et al*[36]	126	100%	NA	4 mo	20 *vs* 60 (16% *vs* 32%; *P* = 0.002)	NA

NA: Not available; NSBB: Non-selective beta blockers; SBP: Spontaneous bacterial peritonitis; ns: No significance.

analysis[41], which comprised 23 and 28 RCTs on primary and secondary prophylaxis for variceal bleeding, for a total of 4481 patients included (39.8% with ascites), extensively confirmed the absence of increased mortality for patients on NSBB. In primary prophylaxis, 215/955 patients died for bleeding-unrelated causes, in a proportion not different between those who were or were not on treatment with NSBB (OR = 0.91, 95%CI: 0.73-1.15). Similarly, in secondary prophylaxis RCTs, bleeding-unrelated deaths did not differ between groups (189/1143 *vs* 225/1208; OR = 0.90, 95%CI: 0.67-1.23). These data were confirmed in the subgroup taking 120 mg/d or more of propranolol (48/374 *vs* 57/309, OR = 1.01, 95%CI: 0.55-1.84), and in those with severe ascites (124/595 *vs* 151/627, OR = 0.93, CI: 0.61-1.43).

SECOND GENERATION OF BETA BLOCKERS: CARVEDILOL

Carvedilol is a NSBB with mild anti-α1-adrenergic activity. It has been shown to be more effective than propranolol in reducing HVPG due to the α-1 blockage, which reduces intra-hepatic resistances. Its role was investigated for the first time more than 20 years ago[42], as a potential tool for reducing PH in patients with cirrhosis, with promising results. Since then, several studies demonstrated its effectiveness in terms of HVPG decrease, after acute administration and after chronic treatment[43].

In 2002, Bañares *et al*[44] demonstrated that 26 patients receiving carvedilol experienced a greater reduction of HVPG than 25 patients taking propranolol (-19% ± 2% *vs* -12% ± 2%; *P* < 0.001); the decrease of HVPG was higher in patients with more severe liver disease (Child-Pugh class B and C *vs* Child-Pugh class A: -25% ± 2% *vs* -14% ± 3% respectively).

Previous studies showed that, in patients with cirrhosis, acute administration of carvedilol could enhance hypotension and effective hypovolemia, reducing renal blood flow and consequently glomerular filtration rate. In the study by Bañares *et al*[44], renal function remained stable (glomerular filtration rate from 90 mL/min ± 4 mL/min to 84 mL/min ± 5 mL/min; *P* = ns) in both groups, suggesting a potential chronic hemodynamic adjustment in response to arterial hypotension. Furthermore, the authors confirmed that reductions of HR and CO were lower with carvedilol than with propranolol. However, MAP was significantly reduced only in the carvedilol group (91.4 mmHg ± 2.5 mmHg *vs* 81.2 mmHg ± 2.9 mmHg; *P* < 0.05; propranolol: 88.6 mmHg ± 4.5 mmHg *vs* 83.8 mmHg ± 3.1 mmHg; *P* = ns). Thus, despite promising data, the use of carvedilol as first choice drug remains controversial[19], especially in those patients with severely impairment of hemodynamic (*i.e.*, refractory ascites), because further reduction of MAP could be detrimental for organ perfusion. In fact in a recent metanalysis[45] on 5 studies which analyzed the role of carvedilol in a total of 90 patients, the number of patients achieving a reduction in HVPG to ≥ 20% was markedly higher with carvedilol (57/94 *vs* 33/87), but hypotension occurred in one-third

more patients than with propranolol.

NON-HEMODYNAMIC EFFECTS OF NSBBS IN PH

Several pleiotropic effects of NSBB have been recently demonstrated beyond their hemodynamic role[46].

In 2003 Abraldes *et al*[47] compared the incidence of complications due to PH in 28 patients responders to NSBB; after a follow-up of 8 years, they found that the risk of developing ascites ($P = 0.025$), hepatorenal syndrome ($P = 0.026$), and encephalopathy ($P = 0.024$) were significantly lower than in the 45 patients non-responders. Another study of Hernández-Gea *et al*[48] demonstrated that an effective treatment (*i.e.*, significant reduction of HVPG) with NSBB for primary prophylaxis was associated with reduced risk of ascites development (19% *vs* 57% at 3 years, $P < 0.001$).

Since bacterial translocation has been widely considered an important trigger factor for worsening of PH, also for the lack of response of immune system in cirrhosis[49], and since selective bacterial decontamination seems to partly reverse the hemodynamic derangement in cirrhosis[50], several studies tried to investigate whether NSBB could contribute to PH reduction through a modification of the protean interactions between the gut and the liver.

Propranolol seems to play a role in reduction of bacterial translocation, probably increasing bowel motility through a sympatholytic action[51]. After the confirmation that intestinal permeability was significantly impaired in cirrhotic than in controls (lactulose/mannitol ratio: 0.026 *vs* 0.014, $P = 0.001$); we demonstrated that NSBB introduction determined a significant improvement of intestinal permeability, and reduction of hyper-vascularization at confocal microscopy[52]. Also Reiberger *et al*[53] showed a reduction of intestinal permeability after introduction of NSBB, and a contemporary reduction of bacterial translocation [LPS-binding protein: -16% ($P = 0.018$); interleukin-6: -41% ($P < 0.0001$)]; interestingly, the Authors showed equal effectiveness also in those whose HVPG did not significantly reduced after NSBB introduction.

Although a retrospective study on 134 patients with cirrhosis and ascites[54] did not show a reduction of SBP during therapy with NSBB (6/33 *vs* 33/101; OR = 0.46, $P = 0.17$), a meta-analysis performed on 4 studies demonstrated a significant difference (12.1%, $P < 0.001$) in favor of propranolol in preventing SBP[55].

Bacterial translocation is the main trigger factor for infection in cirrhosis, and infection is a known trigger for variceal bleeding[46]. Merli *et al*[56] demonstrated that in 140 patients with cirrhosis who experienced infection, those on NSBB showed a trend towards a lower incidence of sepsis (40% *vs* 57%), septic shock (8% *vs* 15%), hepatorenal syndrome (14% *vs* 17%) and mortality (15% *vs* 40%).

CONCLUSION AND FUTURE PERSPECTIVES

To date, NSBB remain the treatment of choice for primary and secondary prophylaxis for portal hypertensive bleeding, even though new drugs, as statins[57], or new generation beta blockers, as carvedilol, may increase the rate of hemodynamic response. NSBB use has been associated with several pleiotropic characteristics, *i.e.*, reduction of bacterial translocation, prevention of spontaneous bacterial peritonitis - different from prevention of bleeding, suggesting a pleiotropic role in decompensated cirrhosis. Contrasting data on the use of NSBB in sickest patients with decompensated cirrhosis made their use controversial. A recent survey[58] about 629 physicians highlighted the high heterogeneity across centers. For instance, refractory ascites was considered a contraindication to NSBB use for 36% of responders, while for the 61% NSBB have to be withdrawn during HRS, highlighting a general lack of consensus across all the issues of the survey. A window hypothesis for therapy with NSBB in the natural history of cirrhosis was made by Krag *et al*[59]; according to this view, NSBB could play a detrimental role for cirrhotics at the earlier stage (*i.e.*, for pre-primary prophylaxis) and in the "extremely decompensated" phase, in those patients with MAP lower than 80 mmHg, decreased baseline CO of those with concomitant infections[19].

Since infected cirrhotics are those at greater risk of variceal bleeding and HVPG has been increased also after the resolution of infection[38], attention should be paid to a potential increase in the risk of portal hypertensive bleeding. In addition, the interplay between propranolol and sepsis has to be further investigated with future larger studies.

REFERENCES

1   **Møller S**, Henriksen JH. Cirrhotic cardiomyopathy. *J Hepatol* 2010; **53**: 179-190 [PMID: 20462649 DOI: 10.1016/j.jhep.2010.02.023]

2   **Møller S**, Hobolth L, Winkler C, Bendtsen F, Christensen E. Determinants of the hyperdynamic circulation and central hypovolaemia in cirrhosis. *Gut* 2011; **60**: 1254-1259 [PMID: 21504996 DOI: 10.1136/gut.2010.235473]

3   **Pessione F**, Ramond MJ, Peters L, Pham BN, Batel P, Rueff B, Valla DC. Five-year survival predictive factors in patients with excessive alcohol intake and cirrhosis. Effect of alcoholic hepatitis, smoking and abstinence. *Liver Int* 2003; **23**: 45-53 [PMID: 12640727 DOI: 10.1034/j.1600-0676.2003.01804.x]

4   EASL clinical practice guidelines on the management of ascites, spontaneous bacterial peritonitis, and hepatorenal syndrome in cirrhosis. *J Hepatol* 2010; **53**: 397-417 [PMID: 20633946 DOI: 10.1016/j.jhep.2010.05.004]

5   **D'Amico G**, Garcia-Tsao G, Pagliaro L. Natural history and prognostic indicators of survival in cirrhosis: a systematic review of 118 studies. *J Hepatol* 2006; **44**: 217-231 [PMID: 16298014 DOI: 10.1016/j.jhep.2005.10.013]

6   **Garcia-Tsao G**, Sanyal AJ, Grace ND, Carey W. Prevention and management of gastroesophageal varices and variceal hemorrhage in cirrhosis. *Hepatology* 2007; **46**: 922-938 [PMID: 17879356 DOI: 10.1002/hep.21907]

7   **Fernandez M**, Vizzutti F, Garcia-Pagan JC, Rodes J, Bosch J. Anti-VEGF receptor-2 monoclonal antibody prevents portal-

systemic collateral vessel formation in portal hypertensive mice. *Gastroenterology* 2004; **126**: 886-894 [PMID: 14988842]

8   **Moreau R**, Jalan R, Gines P, Pavesi M, Angeli P, Cordoba J, Durand F, Gustot T, Saliba F, Domenicali M, Gerbes A, Wendon J, Alessandria C, Laleman W, Zeuzem S, Trebicka J, Bernardi M, Arroyo V. Acute-on-chronic liver failure is a distinct syndrome that develops in patients with acute decompensation of cirrhosis. *Gastroenterology* 2013; **144**: 1426-1437, 1437.e1-e9 [PMID: 23474284 DOI: 10.1053/j.gastro.2013.02.042]

9   **Phillip V**, Saugel B, Ernesti C, Hapfelmeier A, Schultheiß C, Thies P, Mayr U, Schmid RM, Huber W. Effects of paracentesis on hemodynamic parameters and respiratory function in critically ill patients. *BMC Gastroenterol* 2014; **14**: 18 [PMID: 24467993 DOI: 10.1186/1471-230X-14-18]

10   **Sagarad SV**, Chawla YK, Dhiman RK. Portal hemodynamics after large-volume paracentesis in patients with liver cirrhosis and tense ascites. *Dig Dis Sci* 1998; **43**: 2470-2472 [PMID: 9824136]

11   **Ginès A**, Fernández-Esparrach G, Monescillo A, Vila C, Domènech E, Abecasis R, Angeli P, Ruiz-Del-Arbol L, Planas R, Solà R, Ginès P, Terg R, Inglada L, Vaqué P, Salerno F, Vargas V, Clemente G, Quer JC, Jiménez W, Arroyo V, Rodés J. Randomized trial comparing albumin, dextran 70, and polygeline in cirrhotic patients with ascites treated by paracentesis. *Gastroenterology* 1996; **111**: 1002-1010 [PMID: 8831595 DOI: 10.1016/S0016-5085(96)70068-9]

12   **Farr M**, Schulze PC. Recent advances in the diagnosis and management of cirrhosis-associated cardiomyopathy in liver transplant candidates: advanced echo imaging, cardiac biomarkers, and advanced heart failure therapies. *Clin Med Insights Cardiol* 2014; **8**: 67-74 [PMID: 25657603]

13   **Krag A**, Møller S, Burroughs AK, Bendtsen F. Betablockers induce cardiac chronotropic incompetence. *J Hepatol* 2012; **56**: 298-299 [PMID: 22173037 DOI: 10.1016/j.jhep.2011.04.033]

14   **Krag A**, Bendtsen F, Henriksen JH, Møller S. Low cardiac output predicts development of hepatorenal syndrome and survival in patients with cirrhosis and ascites. *Gut* 2010; **59**: 105-110 [PMID: 19837678 DOI: 10.1136/gut.2009.180570]

15   **Karagiannakis DS**, Papatheodoridis G, Vlachogiannakos J. Recent advances in cirrhotic cardiomyopathy. *Dig Dis Sci* 2015; **60**: 1141-1151 [PMID: 25404411 DOI: 10.1007/s10620-014-3432-8]

16   **Kroeger RJ**, Groszmann RJ. Increased portal venous resistance hinders portal pressure reduction during the administration of beta-adrenergic blocking agents in a portal hypertensive model. *Hepatology* 1985; **5**: 97-101 [PMID: 2857150]

17   **Lebrec D**, Poynard T, Hillon P, Benhamou JP. Propranolol for prevention of recurrent gastrointestinal bleeding in patients with cirrhosis: a controlled study. *N Engl J Med* 1981; **305**: 1371-1374 [PMID: 7029276 DOI: 10.1056/NEJM198112033052302]

18   **Hayes PC**, Davis JM, Lewis JA, Bouchier IA. Meta-analysis of value of propranolol in prevention of variceal haemorrhage. *Lancet* 1990; **336**: 153-156 [PMID: 1973480]

19   **de Franchis R**. Expanding consensus in portal hypertension: Report of the Baveno VI Consensus Workshop: Stratifying risk and individualizing care for portal hypertension. *J Hepatol* 2015; **63**: 743-752 [PMID: 26047908 DOI: 10.1016/j.jhep.2015.05.022]

20   **Gluud LL**, Krag A. Banding ligation versus beta-blockers for primary prevention in oesophageal varices in adults. *Cochrane Database Syst Rev* 2012; **8**: CD004544 [PMID: 22895942 DOI: 10.1002/14651858.CD004544.pub2]

21   **Heebøll S**, Villadsen GE, Aagaard NK, Grønbæk H, Vilstrup H, Keiding S. Propranolol treatment of portal hypertension in cirrhosis patients is better the higher the untreated pressure: a single-centre prospective experience. *Scand J Gastroenterol* 2013; **48**: 969-973 [PMID: 23755897 DOI: 10.3109/00365521.2013.805811]

22   **Sersté T**, Melot C, Francoz C, Durand F, Rautou PE, Valla D, Moreau R, Lebrec D. Deleterious effects of beta-blockers on survival in patients with cirrhosis and refractory ascites. *Hepatology* 2010; **52**: 1017-1022 [PMID: 20583214 DOI: 10.1002/hep.23775]

23   **Efe C**, Purnak T, Ozaslan E. The deleterious effects of propranolol on patients with cirrhosis. *Hepatology* 2011; **53**: 371-372 [PMID: 20726015 DOI: 10.1002/hep.23881]

24   **Wong F**, Salerno F. Beta-blockers in cirrhosis: friend and foe? *Hepatology* 2010; **52**: 811-813 [PMID: 20812354 DOI: 10.1002/hep.23852]

25   **Senzolo M**, Nadal E, Cholongitas E, Burroughs AK. Is hydrophobia necessary for the hepatologist prescribing nonselective beta-blockers in cirrhosis? *Hepatology* 2011; **53**: 2149-2150 [PMID: 21400554 DOI: 10.1002/hep.24176]

26   **Sersté T**, Francoz C, Durand F, Rautou PE, Melot C, Valla D, Moreau R, Lebrec D. Beta-blockers cause paracentesis-induced circulatory dysfunction in patients with cirrhosis and refractory ascites: a cross-over study. *J Hepatol* 2011; **55**: 794-799 [PMID: 21354230 DOI: 10.1016/j.jhep.2011.01.034]

27   **Llach J**, Ginès P, Arroyo V, Rimola A, Tító L, Badalamenti S, Jiménez W, Gaya J, Rivera F, Rodés J. Prognostic value of arterial pressure, endogenous vasoactive systems, and renal function in cirrhotic patients admitted to the hospital for the treatment of ascites. *Gastroenterology* 1988; **94**: 482-487 [PMID: 3335320]

28   **Villanueva C**, Albillos A, Genescà J, Abraldes JG, Calleja JL, Aracil C, Bañares R, Morillas R, Poca M, Peñas B, Augustin S, Garcia-Pagan JC, Pavel O, Bosch J. Development of hyperdynamic circulation and response to β-blockers in compensated cirrhosis with portal hypertension. *Hepatology* 2016; **63**: 197-206 [PMID: 26422126 DOI: 10.1002/hep.28264]

29   **Sharma P**, Kumar A, Jha S, Mishra SR, Sharma BC, Sarin SK. The haemodynamic response to propranolol in cirrhosis with arterial hypertension: a comparative analysis with normotensive cirrhotic patients. *Aliment Pharmacol Ther* 2010; **32**: 105-112 [PMID: 20345511 DOI: 10.1111/j.1365-2036.2010.04308.x]

30   **Leithead JA**, Rajoriya N, Tehami N, Hodson J, Gunson BK, Tripathi D, Ferguson JW. Non-selective β-blockers are associated with improved survival in patients with ascites listed for liver transplantation. *Gut* 2015; **64**: 1111-1119 [PMID: 25281417 DOI: 10.1136/gutjnl-2013-306502]

31   **Kimer N**, Feineis M, Møller S, Bendtsen F. Beta-blockers in cirrhosis and refractory ascites: a retrospective cohort study and review of the literature. *Scand J Gastroenterol* 2015; **50**: 129-137 [PMID: 25113796 DOI: 10.3109/00365521.2014.948053]

32   **Bossen L**, Krag A, Vilstrup H, Watson H, Jepsen P. Nonselective β-blockers do not affect mortality in cirrhosis patients with ascites: Post Hoc analysis of three randomized controlled trials with 1198 patients. *Hepatology* 2016; **63**: 1968-1976 [PMID: 26599983 DOI: 10.1016/S0168-8278(15)30087-8]

33   **Pereira GH**, Baldin C, Victor L, Piedade J, Guimarães L, Rocha T, Pereira L. Use of non-selective beta blockers (nsbb) in cirrhotic patients with bacterial infections is associated with lower frequency of sepsis, but not of acute-on-chronic liver failure (ACLF) or survival. Results of a prospective study. *J Hepatol* 2016; **64** (S2): S263

34   **Mallawaarachchi N**, Sinha R, Hayes P. Does the use of non-selective beta-blockers in cirrhosis patients with ascites result in increased mortality? *J Hepatol* 2016; **64** (S2): S278-279

35   **Bhutta AQ**, Garcia-Tsao G, Reddy R, Tandon P, Wong F, O'Leary JG, Bajaj J. Beta-blocker use in hospitalized cirrhotic patients with ascites is associated with a lower MELD, less inflammation and an improved survival. *J Hepatol* 2016; **64** (S2): S245

36   **Onali S**, Kalafateli M, Majumdar A, Westbrook M, O'Beirne J, Patch D, Tsochatzis E Non-selective beta blockers (NSBBS) use is associated with improved survival in cirrhotic patients with ascites: a single centre retrospective study. *J Hepatol* 2016; **64** (S2): S668

37   **Mookerjee RP**, Pavesi M, Thomsen KL, Mehta G, Macnaughtan J, Bendtsen F, Coenraad M, Sperl J, Gines P, Moreau R, Arroyo V, Jalan R. Treatment with non-selective beta blockers is associated with reduced severity of systemic inflammation and improved survival of patients with acute-on-chronic liver failure. *J Hepatol* 2016; **64**: 574-582 [PMID: 26519600 DOI: 10.1016/j.jhep.2015.10.018]

38   **Ruiz-del-Arbol L**, Urman J, Fernández J, González M, Navasa M, Monescillo A, Albillos A, Jiménez W, Arroyo V. Systemic, renal, and hepatic hemodynamic derangement in cirrhotic patients with spontaneous bacterial peritonitis. *Hepatology* 2003; **38**: 1210-1218 [PMID: 14578859 DOI: 10.1053/jhep.2003.50447]

39   **Mandorfer M**, Bota S, Schwabl P, Bucsics T, Pfisterer N, Kruzik M, Hagmann M, Blacky A, Ferlitsch A, Sieghart W, Trauner M, Peck-Radosavljevic M, Reiberger T. Nonselective β blockers increase risk for hepatorenal syndrome and death in patients with cirrhosis and spontaneous bacterial peritonitis. *Gastroenterology* 2014; **146**: 1680-1690.e1 [PMID: 24631577 DOI: 10.1053/j.gastro.2014.03.005]

40   **Galbois A**, Das V, Thabut D, Maury E, Ait-Oufella H, Housset C, Guidet B. Beta-blockers have no effect on outcomes in patients with cirrhosis and severe infections. *Hepatology* 2011; **53**: 1412-1413 [PMID: 21480358 DOI: 10.1002/hep.24053]

41   **Ferrarese A**, Germani G, Rodriguez-Castro KI, Nadal E, Zanetto A, Bortoluzzi I, Russo FP, Burra P, Burroughs AK, Senzolo M. Bleeding-unrelated mortality is not increased in patients with cirrhosis and ascites on treatment with β-blockers: A meta-analysis. *Digest Liver Dis* 2014; **46** (Suppl 1): e31 [DOI: 10.1016/j.dld.2014.01.072]

42   **Forrest EH**, Bouchier IA, Hayes PC. Acute haemodynamic changes after oral carvedilol, a vasodilating beta-blocker, in patients with cirrhosis. *J Hepatol* 1996; **25**: 909-915 [PMID: 9007720]

43   **Berzigotti A**, Bosch J. Pharmacologic management of portal hypertension. *Clin Liver Dis* 2014; **18**: 303-317 [PMID: 24679496 DOI: 10.1016/j.cld.2013.12.003]

44   **Bañares R**, Moitinho E, Matilla A, García-Pagán JC, Lampreave JL, Piera C, Abraldes JG, De Diego A, Albillos A, Bosch J. Randomized comparison of long-term carvedilol and propranolol administration in the treatment of portal hypertension in cirrhosis. *Hepatology* 2002; **36**: 1367-1373 [PMID: 12447861 DOI: 10.1053/jhep.2002.36947]

45   **Sinagra E**, Perricone G, D'Amico M, Tinè F, D'Amico G. Systematic review with meta-analysis: the haemodynamic effects of carvedilol compared with propranolol for portal hypertension in cirrhosis. *Aliment Pharmacol Ther* 2014; **39**: 557-568 [PMID: 24461301 DOI: 10.1111/apt.12634]

46   **Thalheimer U**, Bosch J, Burroughs AK. How to prevent varices from bleeding: shades of grey--the case for nonselective beta blockers. *Gastroenterology* 2007; **133**: 2029-2036 [PMID: 18054573 DOI: 10.1053/j.gastro.2007.10.028]

47   **Abraldes JG**, Tarantino I, Turnes J, Garcia-Pagan JC, Rodés J, Bosch J. Hemodynamic response to pharmacological treatment of portal hypertension and long-term prognosis of cirrhosis. *Hepatology* 2003; **37**: 902-908 [PMID: 12668985 DOI: 10.1053/jhep.2003.50133]

48   **Hernández-Gea V**, Aracil C, Colomo A, Garupera I, Poca M, Torras X, Miñana J, Guarner C, Villanueva C. Development of ascites in compensated cirrhosis with severe portal hypertension treated with β-blockers. *Am J Gastroenterol* 2012; **107**: 418-427 [PMID: 22334252 DOI: 10.1038/ajg.2011.456]

49   **Mehta G**, Gustot T, Mookerjee RP, Garcia-Pagan JC, Fallon MB, Shah VH, Moreau R, Jalan R. Inflammation and portal hypertension - the undiscovered country. *J Hepatol* 2014; **61**: 155-163 [PMID: 24657399 DOI: 10.1016/j.jhep.2014.03.014]

50   **Rasaratnam B**, Kaye D, Jennings G, Dudley F, Chin-Dusting J. The effect of selective intestinal decontamination on the hyperdynamic circulatory state in cirrhosis. A randomized trial. *Ann Intern Med* 2003; **139**: 186-193 [PMID: 12899586]

51   **Pérez-Paramo M**, Muñoz J, Albillos A, Freile I, Portero F, Santos M, Ortiz-Berrocal J. Effect of propranolol on the factors promoting bacterial translocation in cirrhotic rats with ascites. *Hepatology* 2000; **31**: 43-48 [PMID: 10613726]

52   **Nadal E**, Buda A, Pizzuti D, Nai L, Burra P, Senzolo M. Functional study of the intestinal barrier in patients with cirrhosis and portal hypertension. *J Hepatol* 2011; **54** (s1): 247-248 [DOI: 10.1016/S0168-8278(11)60612-0]

53   **Reiberger T**, Ferlitsch A, Payer BA, Mandorfer M, Heinisch BB, Hayden H, Lammert F, Trauner M, Peck-Radosavljevic M, Vogelsang H. Non-selective betablocker therapy decreases intestinal permeability and serum levels of LBP and IL-6 in patients with cirrhosis. *J Hepatol* 2013; **58**: 911-921 [PMID: 23262249 DOI: 10.1016/j.jhep.2012.12.011]

54   **Cholongitas E**, Papatheodoridis GV, Manesis EK, Burroughs AK, Archimandritis AJ. Spontaneous bacterial peritonitis in cirrhotic patients: Is prophylactic propranolol therapy beneficial? *J Gastroenterol Hepatol* 2006; **21**: 581-587 [PMID: 16638103]

55   **Senzolo M**, Cholongitas E, Burra P, Leandro G, Thalheimer U, Patch D, Burroughs AK. beta-Blockers protect against spontaneous bacterial peritonitis in cirrhotic patients: a meta-analysis. *Liver Int* 2009; **29**: 1189-1193 [PMID: 19508620 DOI: 10.1111/j.1478-3231.2009.02038.x]

56   **Merli M**, Riggio O. Interaction between infection and hepatic encephalopathy. *J Hepatol* 2015; **62**: 746-747 [PMID: 25450708 DOI: 10.1016/j.jhep.2014.10.028]

57   **Abraldes JG**, Albillos A, Bañares R, Turnes J, González R, García-Pagán JC, Bosch J. Simvastatin lowers portal pressure in patients with cirrhosis and portal hypertension: a randomized controlled trial. *Gastroenterology* 2009; **136**: 1651-1658 [PMID: 19208350 DOI: 10.1053/j.gastro.2009.01.043]

58   **Thorhauge KH**, Lindvig KP, Laleman W, Angeli P, Singh SP, Krag A. Lack of consensus for usage of β-blockers in end-stage liver disease. *Gut* 2016; **65**: 1058-1060 [PMID: 26933172]

59   **Krag A**, Wiest R, Albillos A, Gluud LL. The window hypothesis: haemodynamic and non-haemodynamic effects of β-blockers improve survival of patients with cirrhosis during a window in the disease. *Gut* 2012; **61**: 967-969 [PMID: 22234982 DOI: 10.1136/gutjnl-2011-301348]

60   **Robins A**, Bowden A, Watson W, Smith F, Gelson W, Griffiths W. Beta-blockers in cirrhosis patients with refractory ascites. *Hepatology* 2014; **59**: 2054-2055 [PMID: 23929786 DOI: 10.1002/hep.26676]

Baishideng®