Grand Rounds

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Beta adrenergic blockade and decompensated cirrhosis

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Summary

Non-selective betablockers (NSBBs) remain the cornerstone of medical treatment of portal hypertension. The evidence for their efficacy to prevent variceal bleeding is derived from prospective trials, which largely excluded patients with refractory ascites and renal failure. In parallel to the increasing knowledge on portal hypertension-induced changes in systemic hemodynamics, cardiac function, and renal perfusion, emerging studies have raised concerns about harmful effects of NSBBs. Clinicians are facing an ongoing controversy on the use of NSBBs in patients with advanced cirrhosis. On the one hand, NSBBs are effective in preventing variceal bleeding and might also have beneficial non-hemodynamic effects, however, they also potentially induce hypotension and limit the cardiac reserve. An individualized NSBB regimen tailored to the specific pathophysiological stage of cirrhosis might optimize patient management at this point. This article aims to give practical recommendations on the use of NSBBs in patients with decompensated cirrhosis.

Keywords: Beta blockers; Ascites; Liver cirrhosis; Decompensation; Hypertension, portal; Esophageal and gastric varices; Gastrointestinal hemorrhage.

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Key point

Non-selective betablockers (NSBBs) represent the cornerstone of pharmacological treatment of portal hypertension.

Clinical vignette

Clinical scenario 1

A 42-year-old male patient with cirrhosis due to hereditary hemochromatosis with large esophageal varices at endoscopy has been treated with propranolol 120 mg/d for primary prophylaxis of variceal bleeding for 4 years. The patient is undergoing regular phlebotomies to maintain serum ferritin levels of 50–100 μg/L. He presents at the outpatient clinic and reports dizziness and reduced exercise capacity together with weight gain. Edema and new-onset ascites were noted at clinical examination. The heart rate was 58 beats per minute (bpm) and the arterial blood pressure was 95/52 mmHg. Investigations (including diagnostic paracentesis) revealed no evidence of bacterial infection. The patient tells the physician that dizziness is most pronounced after propranolol intake.

Q1: Should the primary prophylaxis with propranolol be interrupted or discontinued in this patient with new-onset ascites and symptomatic arterial hypotension?

Clinical scenario 2

A 55-year-old female patient with cirrhosis due to alcoholic liver disease was referred for evaluation for liver transplantation, as she had developed refractory ascites. Following a variceal bleeding two years ago, the patient has been receiving propranolol 160 mg/d and repeated endoscopic band ligations (EBLs). The last EBL was performed 3 months ago, and the last upper gastrointestinal (GI) endoscopy two days after referral only showed small varices and portal-hypertensive gastropathy. Blood pressure and heart rate were 125/80 mmHg and 59 bpm, respectively. A therapeutic large volume paracentesis was performed and the ascitic fluid polymorphonuclear (PMN) cell count was 78 cells/μL. The patient had a stable serum creatinine of about 1.3 mg/dL over the past 12 months.

Q2: Should the propranolol dose in secondary prophylaxis be lowered or treatment discontinued in this patient with refractory ascites?

Pathophysiology (Fig. 1)

Both increased intrahepatic vascular (sinusoidal) resistance and increased portal blood flow contribute to the elevated portal pressure in patients with cirrhosis. Clinically significant portal hypertension (CSPH) is defined by a hepatic venous pressure gradient (HVPG) of ⩾10 mmHg. In these patients, porto-systemic collaterals (e.g., esophageal varices)

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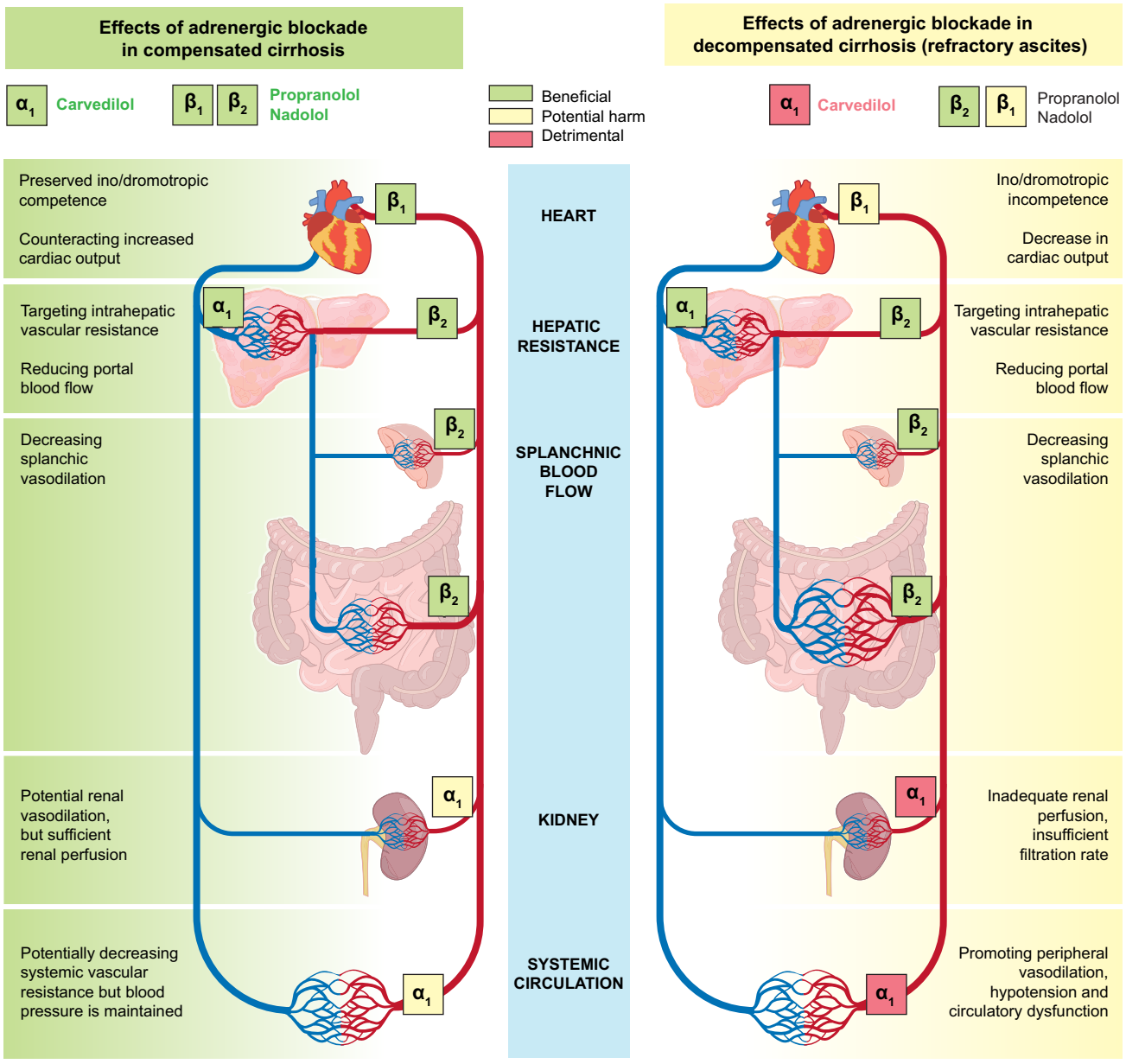

Fig. 1. The effects of adrenergic blockage in compensated and decompensated cirrhosis.

and ascites may develop. Due to progressive splanchnic and peripheral vasodilation, portal hypertension ultimately leads to a hyperdynamic circulation with compensatory increases in heart rate and cardiac output. These changes characterize the hyperdynamic (or hyperkinetic) portal-hypertensive syndrome [1,2].

Importantly, β-adrenergic blockade leads to a more pronounced decrease in HVPG in patients with CSPH, since these patients have splanchnic vasodilatation and hyperdynamic circulation [3]. This explains why NSBBs are not generally effective in preventing the development of varices in patients with cirrhosis [4,5], but might be able to prevent progression from small to large varices in patients with CSPH [6,7]. The hemodynamic effects of NSBBs, thus, depend on the severity of the hyperdynamic state, since mechanistically NSBB act by decreasing heart rate and inhibiting splanchnic vasodilation. This would suggest, that achieving a HVPG-response to NSBBs is more likely in patients with pronounced hyperdynamic circulation (e.g., refractory ascites) [8]. Due to increased resting heart rates, higher doses of NSBBs might be necessary to achieve the same target heart rates in patients with decompensated, when compared to patients compensated disease. This would indeed impact both beneficial effects

on splanchnic hemodynamics and detrimental effects on systemic hemodynamics.

The upregulation of the sympathetic nervous system (SNS) activity associated with adrenergic-mediated increase in cardiac output represents a compensatory adaption to the decrease in effective circulatory blood volume. In situations when cardiac reserve is critical, for example plasma volume depletion after large volume paracentesis, massive blood loss during variceal bleeding, or infections such as spontaneous bacterial peritonitis (SBP), patients with cirrhosis frequently develop a progressive impairment in systemic hemodynamics, which leads to acute kidney injury (AKI) and other organ failures [9]. NSBBs might impair the β-adrenergic-mediated increase in cardiac output [10], which is essential for maintaining the systemic and renal perfusion in advanced cirrhosis [11,12]. The critical role of the SNS to maintain a sufficient systemic circulation during SBP is also underlined by the beneficial effects of noradrenaline in hepatorenal syndrome (HRS) [13] and indirectly by the deleterious effects of NSBBs on renal function if arterial hypotension occurs [14].

Diagnostic and prognostic biomarkers

Currently, invasive measurement of HVPG is the only accurate method for diagnosis of portal hypertension [15]. Clinical signs that indicate CSPH are the presence of collaterals on imaging, varices in upper GI endoscopy, or ascites [16]. However, some patients might have CSPH without varices or ascites. Biomarkers such as liver stiffness [17] and spleen stiffness [18] measured by elastography, spleen diameter [19,20], von-Willebrand factor [21], or simply the platelet count be can used as surrogates for CSPH. Incorporating these markers into composite scores has been shown to be useful for the non-invasive assessment of the risk for CSPH and might also rule out varices needing treatment [19,22].

There are no established non-invasive biomarkers for the evaluation of the 'hemodynamic' efficacy of NSBBs. Up until now, there has been no non-invasive way to predict the hemodynamic response to NSBBs apart from HVPG measurements prior to (without) and during NSBB treatment [23]. Acute response to i.v. propranolol can be used as an excellent surrogate for long-term response, but the HVPG measurement itself remains invasive [24]. However, some patients may lose their initial hemodynamic response to NSBBs, mainly due to modifications of NSBB dose, alcohol intake [25], and worsening of liver function [26].

With progression of liver disease and increasing HVPG, the activation of the SNS, and thus hyperdynamic circulation, gets more pronounced [1,11]. Due to limited availability of HVPG measurement, NSBBs are usually titrated to achieve a certain target heart rate (e.g., 60 bpm [27] or even 50–55 bpm [28]). The use of this strategy might imply that patients with more pronounced hyperdynamic circulation, such as patients with (refractory) ascites, are likely to receive higher doses of NSBBs. Indeed, almost half of the patients (46.7%) in the study by Serste *et al.* [29], who first reported a deleterious effect of NSBBs on mortality in patients with refractory ascites received propranolol at a dose of 160 mg/day. The high doses used in this French study were due to the use of a long-lasting propranolol formulation, which makes titration difficult. Importantly, a nationwide study from Denmark showed that the dose of propranolol is an important determinant of its net impact in cirrhotic patients with SBP (n = 81): while low propranolol doses (80 mg/d or less) were associated with reduced mortality (HR: 0.56), patients on high propranolol doses (160 mg/d) showed increased mortality after SBP (HR: 2.27 in unadjusted analysis) [30]. However, there is no standardized practice of NSBB dosing as underlined by the results of a recent survey among physicians (predominantly hepatologists and gastroenterologists from academic or tertiary care centers [31]): The most popular strategy was to use doses that result in a 25% decrease in heart rate (about one third of responses). Thus, there was (and still is) no consensus on an optimal titration protocol [31].

Ultimately, more mechanistic studies are needed to identify biomarkers in patients with decompensated liver disease that indicate beneficial effects of NSBBs and situations where NSBBs might be harmful. An increasing body of evidence suggests, that there is no detrimental effect of NSBBs in patients with ascites in general [32–34]. However, the use of NSBBs should be based on a critical risk/benefit evaluation in patients with refractory ascites and signs of systemic circulatory dysfunction [16,35]. Severe hyponatremia [35], low arterial blood pressure [36] or cardiac output [37], and increasing serum creatinine as a marker of renal failure [9] indicate a worse prognosis in patients with decompensated cirrhosis, in whom a dose reduction or (temporal) discontinuation of NSBB treatment might be considered [16]. Thus, in the last Baveno VI consensus [16], the panel of Drs. Reiberger, Moreau, Ripoll, Albillos, Augustin, Salerno, Abraldes and Garsia-Tsao proposed that in patients with refractory ascites and (i) systolic blood pressure <90 mmHg, or (ii) serum creatinine >1.5 mg/dL, or (iii) hyponatremia <130 mmol/L the NSBB dose should be reduced or NSBB treatment discontinued.

The longitudinal assessment of prognostic scores reflecting liver dysfunction (i.e., the model for end-stage liver disease [MELD] and the Child-Pugh scores) is used to identify patients who have progressed to a more advanced stage. In the decompensated stage, these prognostic scores together with a relative decrease in cardiac index and the presence of left ventricular dysfunction represent important

Table 1. Current evidence for NSBB effects in patients with decompensated cirrhosis.

Study	Type of patients	Conclusion	Strengths	Limitations
Leithead et al. Gut 2015 [1]	Cirrhosis and ascites listed for OLT; N = 159 NSBB, N = 163 w/o NSBB	NSBBs reduced waiting list mortality in patients with ascites including those with refractory ascites	Propensity score matching Large sample size	Retrospective Short follow-up Transplant setting
Mookerjee et al. J Hepatol 2016 [2]	ACLF; N = 155 NSBB, N = 185 w/o NSBB	History of/ongoing NSBB treatment reduced mortality in case of ACLF development	Prospective Large sample size Low NSBB doses	Lower ACLF grades in NSBB patients 78/185 patients stopped NSBBs before developing ACLF
Aday et al. Am J Med Sci 2016 [3]	Cirrhosis and ascites/varices or both ascites and varices; N = 1039 NSBB, N = 1380 w/o NSBB	Among patients with ascites, including those with severe ascites, mortality was lower in the NSBB-treated group	Large sample size	Retrospective
Bang et al. Liver Int 2016 [4]	Cirrhosis and ascites; N = 3075 mildly decompensated, N = 644 severly decompensated; 20% NSBB	Reduced mortality risk with propranolol doses <160 mg/day only but not with higher doses	Large sample size Propensity score matching	Potential underreporting within the registry
Galbois et al. Hepatology 2011 [5]	Cirrhosis and sepsis; N = 36 NSBB, N = 42 w/o NSBB	No difference in ICU mortality (NSBBs were discontinued during hemodynamic instability) 6-month mortality was higher in ICU survivors on NSBBs	Well characterized patients (ICU)	Retrospective Small sample size
Robins Hepatology 2014 [6]	Cirrhosis and severe ascites, N = 114	No difference in survival	Low propranolol doses	Retrospective
Mandorfer et al. Gastroenterology 2014 [7]	Cirrhosis and ascites; N = 245 NSBB, N = 362 w/o NSBB	NSBBs decreased hospitalization and increased survival in patients with ascites NSBBs increased risks for AKI/HRS and mortality after SBP	Large sample size	Retrospective Carvedilol included
Kimer et al. Scand J Gastroenterol 2015 [8]	Cirrhosis and refractory ascites; N = 23 NSBB, N = 38 w/o NSBB	No difference in mortality between patients with and without NSBBs		Retrospetive Small sample size
Bossen et al. Hepatology 2016 [9]	Cirrhosis and severe ascites; N = 559 NSBB, N = 629 w/o NSBB	NSBBs did not affect mortality in patients with severe ascites including patients with refractory ascites NSBBs were stopped in 29% due to safety concerns	Prospectively collected data Large sample size	*Post-hoc* analysis
Njei et al. Gut 2016 [10]	Cirrhosis and ascites; Meta-analysis	Carvedilol but not propranolol/nadololol increased mortality	Large sample size for propranolol	Not all relevant studies were considered Small sample size for nadolol/carvedilol Susbtantial heterogeneity between studies
Serste et al. Hepatology 2010 [11]	Cirrhosis and refractory ascites; N = 77 NSBB, N = 74 w/o NSBB	Propranolol was associated with increased mortality	Prospectively collected data 'True' refractory ascites (high doses of diuretics)	High propranolol doses
Serste et al. J Hepatol 2011 [12]	Cirrhosis and refractory ascites; N = 10	Propranolol increased the risk of paracentesis-induced circulatory dysfunction	Prospective Cross-over design	Small sample size High propranolol doses
Serste et al. Liver Int 2015 [13]	Severe alcoholic hepatitis; N = 48 NSBB, N = 91 w/o NSBB	Propranolol was associated with a higher incidence of AKI in severe alcoholic hepatitis	Prospectively collected data	*Post-hoc* analysis
Kalambokis et al. Gut 2016 [14]	Primary prophylaxis, small varices without red spots, Child-Pugh 7-13 points; N = 53 NSBB, N = 41 w/o varices	Propranolol was associated with increased risks of HRS and mortality in Child-Pugh C patients (but not in Child-Pugh B)	Well-defined population and setting	Retrospective Small sample size and subgroups

ACLF, acute-on-chronic liver failure; AKI, acute kidney injury; HRS, hepato-renal syndrome; ICU, intensive care unit; NSBB, non-selective beta-blocker; OLT, orthotopic liver transplantation; SBP, spontaneous bacterial peritonitis.

predictors of mortality [38]. Recent data presented at the International Liver Congress™ (ILC) in Barcelona showed that systolic ventricular dysfunction was more prevalent in patients with higher MELD scores, and NSBBs may impact on cardiac contractility only in very severe disease, i.e., MELD score >25 [39]. Thus, further studies investigating the value of echocardiography for identifying patients in whom NSBBs might be harmful are warranted.

On the other hand, it seems that markers of systemic inflammation (e.g., white blood cell count) could be indicative of beneficial effects of NSBBs, as suggested by an analysis of the CANONIC study by Mookerjee *et al.* [40] Intestinal transit time [41] and markers of bacterial translocation [42] during NSBB treatment might serve as additional biomarkers to monitor non-hemodynamic effects of NSBBs in patients with cirrhosis.

Current management with supporting evidence

Non-selective β-blockers (NSBBs) have been shown to effectively reduce the risk of variceal bleeding [43–45] and rebleeding [46,47] due to a reduction of portal pressure. Thus, Baveno VI [16] and AASLD [48] guidelines recommend NSBBs for primary prophylaxis and for secondary prophylaxis (in combination with EBL) of variceal bleeding in patients with cirrhosis and esophageal varices.

The absolute risk reduction to prevent first variceal bleeding with NSBB treatment (*vs.* no treatment) is -10%, thus, ten patients (number needed to treat, NNT) have to receive NSBBs to prevent one episode of bleeding within a 2-year period [49]. When only patients with medium-large varices are treated with NSBB in primary prophylaxis, the absolute risk reduction is -16%; the corresponding NNT is six patients [49]. However, NSBBs do not decrease mortality in patients with medium-large varices in the setting of primary prophylaxis [49]. Interestingly, there is only a non-significant trend of a -9% absolute risk reduction of first variceal bleeding in patients with medium-large varices *and* ascites (from 31% to 22%) [49].

In contrast, the absolute risk reduction of recurrent variceal bleeding (secondary prophylaxis) is -21% with a NNT of only five patients. In secondary prophylaxis, NSBB treatment does also decrease mortality by -7% with a number needed to treat of 14 patients [49].

Guidelines and recommendations are based on evidence from high-quality randomized controlled trials that have largely excluded patients with refractory ascites, renal failure, or infections such as SBP. However, the development of ascites is the most common first decompensating event [50]. While NSBBs have been used to reduce the risk of variceal bleeding and rebleeding for more than two decades, the last 5 years have been dominated by discussions among experts about the net effect of NSBBs on survival in patients with decompensated cirrhosis. While the pathophysiological mechanisms involved in the portal-hypertensive syndrome have yet to be fully explored, the net effect of NSBBs on the outcome of patients in certain stages of cirrhosis is being assessed in clinical studies. The discussion about potential harmful effects in advanced liver disease, i.e., decompensated cirrhosis, was triggered by the study of Serste *et al.* [29] that reported increased mortality in patients with cirrhosis and refractory ascites treated with NSBBs. The window hypothesis [11], proposed by Krag and co-workers is consistent with these results and implies the existence of a therapeutic window for NSBB treatment, which closes late in the natural course of cirrhosis. Since then, several other studies have reported conflicting results.

NSBBs are more than portal pressure-lowering drugs, as demonstrated by the amelioration of bacterial translocation [42], as well as the reduction of SBP development, which were independent of hemodynamic response [51]. In patients with acute-on-chronic liver failure (ACLF) – a distinct pathophysiological syndrome different from decompensated cirrhosis [52] – NSBBs use was associated with lower white blood cell count and improved survival [40]. This data was obtained from a large prospective multicenter trial (the CANONIC study [52]). In this study, the rate of ACLF development was similar in patients discontinuing NSBB treatment after inclusion and in patients with continuous NSBB use (13% *vs.* 17%). However, in patients who went on to develop ACLF, the 28-day mortality was lower among NSBB users (24% *vs.* 34%). The significance of these findings [40] are limited by the lack of a uniform definition of refractory ascites and a higher severity of ACLF (more ACLF stage 2/3) in patients without NSBB treatment. Moreover, almost half of patients (77 of 148 patients) discontinued NSBB treatment prior to ACLF development. In contrast, in severe alcoholic hepatitis, which is a common precipitating event of ACLF, NSBBs were associated with development of AKI [53].

Key point

Endoscopic band ligation is a safe and effective strategy for primary prophylaxis of variceal bleeding in case of intolerance to NSBBs.

Key point

NSBBs also exert non-hemodynamic beneficial effects in patients with cirrhosis and seem to increase survival patients with ACLF.

The latter findings indicate that patients with severe liver disease are not the same, and the mere presence of ascites in decompensated cirrhosis, ACLF, or severe alcoholic hepatitis should not be regarded as an absolute contraindication for the use of NSBBs to prevent variceal bleeding and rebleeding.

We have summarized the studies that have specifically assessed the safety of NSBB in patients with ascites (see Table 1), also discussing their strengths and limitations. The type of patients studied and the clinical scenario in which NSBBs were used were not uniform across the studies, which might explain the discrepant results.

Yet, some of these studies deserve special attention: Leithead *et al.* [54] analyzed a cohort of n = 322

patients with cirrhosis and ascites being listed for liver transplantation. They included a subgroup of n = 117 patients with refractory ascites and found a reduced risk of waiting list mortality if patients were on NSBB treatment. The study was well-designed and statistically sound, since analyses were controlled for relevant confounding factors and repeated using propensity-score matching. However, data such as blood pressure, or causes of mortality could not be obtained in all patients. Moreover, the median follow-up was less than 3 months, which significantly limits the generalizability of their findings. In addition, the population on the liver transplant waiting list represents a highly-selected cohort of patients including a significant number of patients with a history of variceal bleeding (32%), and thus, on secondary prophylaxis. According to the concept of risk-benefit-stratification, beneficial effects of NSBBs are more pronounced in secondary prophylaxis than in primary prophylaxis: As mentioned previously, the NNT to avoid one episode of variceal bleeding is only five in secondary prophylaxis *vs.* ten in primary prophylaxis. An important finding of this study was the 'intermediate' effect of carvedilol (*vs.* propranolol) in reducing mortality in patients with ascites[54], indicating that additional α1-adrenergic blockade is 'less benefical', when compared to traditional NSBBs. A detrimental role for carvedilol in patients with ascites was also observed in a recent meta-analysis, which also included data from the Leithead *et al.* [54] study, suggesting that carvedilol but not propranolol or nadolol increase mortality in cirrhotic patients with ascites [55]. While we and others have generally found beneficial effects of NSBB on hospitalization rates [14] and in-hospital mortality [56] in cirrhotic patients with ascites, close clinical monitoring of NSBB safety is needed in patients with refractory ascites requiring repetitive paracenteses in close intervals [12,29], and in cases of SBP-associated arterial hypotension and AKI [14].

Key point

NSBBs should be used in secondary prophylaxis of variceal bleeding since they reduce mortality.

Strong evidence against an increased mortality with NSBBs in ascites was created by a recent individual patient data-based analysis of three randomized controlled trials on satavaptan including 1198 patients with cirrhosis and ascites [34]. NSBB users had a lower prevalence of Child-Pugh stage C cirrhosis, less hyponatremia and a lower proportion had refractory ascites, but Cox regression was performed to adjust for these factors. The safety of NSBBs was further confirmed in a subgroup of n = 588 patients with refractory ascites [34].

Thus, in general, ascites is not a contraindication for NSBB treatment and NSBBs can be used for primary prophylaxis and should be used in secondary prophylaxis of variceal bleeding.

Key point

Ascites *per se* is not a contraindication for NSBB treatment.

Areas of uncertainty

Are NSBBs effective and safe in cirrhotic patients with ascites?

There is no prospective study that assessed the efficacy and safety of NSBBs to prevent variceal bleeding or rebleeding specifically in patients with cirrhosis and ascites. As mentioned previously, most studies on primary and secondary prophylaxis excluded patients with refractory ascites and renal failure. Even if a small number of patients with ascites were included, this does not necessarily imply that NSBBs are as effective and safe in patients with cirrhosis and ascites. We would like to emphasize that achieving a hemodynamic response to NSBBs is associated with a decreased risk of development of ascites and its complications, i.e., SBP and HRS [57]. It is unclear whether NSBBs can reduce complications in patients who have already developed ascites. However, a nationwide study based on Danish registers confirmed the association between NSBB treatment and lower risk of SBP development in patients who had already developed ascites [58]. We continue to use NSBBs for primary prophylaxis of variceal bleeding in patients with ascites but tend to switch to EBL in case of systolic blood pressure <90 mmHg, serum creatinine >1.5 mg/dl, or hyponatremia <130 mmol/L. In secondary prophylaxis we try to maintain NSBB treatment but in case of refractory ascites we avoid carvedilol and high doses of propranolol (>80 mg/d).

Can NSBB therapy prevent the development/recurrence of SBP?

Despite meta-analyses [51], it is still not entirely clear if NSBB treatment can prevent the occurrence of SBP in patients with cirrhosis who have already developed ascites. Both experimental [41] and clinical [42] studies suggest that NSBB treatment is associated with decreased bacterial translocation. Bacterial translocation happens mostly at the decompensated stage after ascites has developed, giving another reason in favor of the use of NSBBs in patients with ascites. It is unknown whether NSBBs can prevent recurrent SBP, if the SBP episode has already occurred under NSBB treatment. Current guidelines [16,28] do not support the use of NSBBs in patients without varices just for prevention of SBP.

Systemic inflammation – potentially triggered by bacterial translocation – plays a key role in further decompensation and development of organ failure in cirrhosis [59]. NSBBs might exert additional anti-inflammatory effects in patients with cirrhosis [40], which could be attributed to a reduction of bacterial translocation [42] or an improvement of endothelial dysfunction [60]. A recent study has proposed that propranolol is able to prevent

Table 2. Recommendations for clinical practice.

Clinical scenario	Recommendation
Decompensation	• Evaluate the patient for liver transplantation
First decompensation with ascites (primary prophylaxis)	• Screen for varices if not already done • Medium-large varices: Start primary prophylaxis with either NSBB or EBL according to local expertise and patient preference • Ascites *per se* is not a contraindication for NSBBs • If ascites is severe or refractory avoid high doses of propranolol (>80 mg/d) and do not use carvedilol
Variceal bleeding and ascites (secondary prophylaxis)	• Treat variceal bleeding according to recommendations of the Baveno VI consensus • Establish secondary prophylaxis with a combination of EBL and NSBB • Ascites *per se* is not a contraindication for NSBBs • If ascites is severe or refractory avoid high doses of propranolol (>80 mg/d) and do not use carvedilol • If a patient is on terlipressin/vasopressors (e.g., variceal bleeding, AKI/HRS, or shock) interrupt NSBB treatment – but try to re-establish NSBB treatment • If variceal bleeding occurs while on adequately dosed NSBB treatment, the patient is considered a 'clinical' NSBB non-responder and should be evaluated for TIPS
Progressive arterial hypotension or intolerance of NSBB treatment	• Treat other reasons of arterial hypotension (i.e. infections) • Reduce NSBB dose or discontinue NSBB treatment and monitor changes in blood pressure • Consider switching from carvedilol to propranolol • Consider plasma expansion with albumin in case of severe hypoalbuminemia (i.e., serum albumin levels <25 g/dL) • Primary prophylaxis: Consider switching from NSBBs to EBL • Secondary prophylaxis: Try to maintain NSBB treatment at a lower dose
NSBB Intolerance	• Up to 20% of patients with cirrhosis show intolerance to NSBBs • Try to initiate NSBBs at a low dose (carvedilol: 6.25 mg/d, propranolol 40 mg/d) and follow a slow dose increasing titration protocol until intolerance occurs • Consider switching from carvedilol to propranolol or use low doses of propranolol (⩽80 mg/d) • Primary prophylaxis: Switch to EBL • Secondary prophylaxis: Consider TIPS, especially if the patient has severe or refractory ascites
Refractory ascites	• Reduce dose of NSBB or discontinue NSBBs in patients with (i) systolic blood pressure <90 mmHg, or (ii) serum creatinine >1.5 mg/dL, or (iii) hyponatremia <130 mmol/L • Primary prophylaxis: Consider switching from NSBBs to EBL • Secondary prophylaxis: Try to maintain NSBB treatment at a lower dose • Avoid high doses of propranolol (>80 mg/d) and do not use carvedilol • Evaluate the patient for TIPS
Spontaneous bacterial peritonitis	• Reduce NSBB dose or interrupt NSBB treatment in case of (i) systolic blood pressure <90 mmHg, or (ii) serum creatinine >1.5 mg/dL, or (iii) hyponatremia <130 mmol/L • In the setting of septic shock when terlipressin or vasopressors are needed maintain arterial blood pressure stop NSBB treatment and carefully monitor renal function to detect AKI/HRS • Primary prophylaxis: Consider switching from NSBBs to EBL • Secondary prophylaxis: Try to re-establish NSBB treatment, eventually at a lower dose • Establish antibiotic prophylaxis for recurrent SBP
AKI/HRS	• Stop diuretics and perform plasma expansion with albumin to establish the diagnosis of HRS-AKI • Stop NSBBs if terlipressin/vasopressors are needed • Consider re-establishing NSBBs after AKI/HRS has resolved • Evaluate the patient for TIPS

EBL, endoscopic band ligation; AKI, acute kidney injury; HRS, hepatorenal syndrome; NSBB, non-selective beta-blocker; TIPS, transjugular intrahepatic portosystemic shunt.

inflammation-driven endothelial exhaustion in cirrhosis [61]. However, these potential non-hemodynamic effects and anti-inflammatory aspects of NSBBs [40] including respective biomarkers have to be explored in further studies.

What is the best dose titration strategy when NSBB treatment is initiated?

A slow NSBB dose titration is recommended in order to assess and improve tolerance and reduce dose-dependent side effects of NSBBs in patients with cirrhosis. Guidelines recommend titrating NSBBs until the highest tolerated dose or until heart rate decreases to 55–60 bpm [16,28]. For primary prophylaxis in patients with compensated cirrhosis we would recommend to start carvedilol at a dose of 6.25 mg/d for one week and increase the dose to 12.5 mg/d after the second week [62,63]. Higher doses of carvedilol (>12.5 mg/d) might not be more effective in decreasing portal pressure, but are likely to worsen arterial hypotension [63]. Only compensated patients who still present with hypertensive arterial blood pressure levels might be treated with higher doses of carvedilol, since they need anti-hypertensive medication anyway. With regard to propranolol, we would recommend a dose titration strategy as following: first week: propranolol 20 mg in the morning and in the evening; second week: 20 mg in the morning and 40 mg in the

Key point

Carvedilol should not be used in patients with severe ascites due to higher risk of inducing arterial hypotension.

Grand Rounds

evening, third week: 40 mg b.i.d. (twice a day); fourth week (if well tolerated): 40 mg morning, 20–40 mg at lunchtime, 40 mg in the evening. In our experience, a significant proportion of patients do not achieve hemodynamic response to propranolol doses <80 mg/d while 80–120 mg/d are generally well tolerated in most patients and yield higher hemodynamic response rates. For patients with severe ascites we prefer propranolol to carvedilol.

Is arterial hypotension a contraindication to NSBB therapy according to the drug label?

On first sight, there is an obvious answer: Yes, a drug that is also used for treatment of arterial hypertension is contraindicated in patients with arterial hypotension. Thus, discontinuation of NSBB treatment is common in patients with cirrhosis due to the development of an intolerance to NSBBs or arterial hypotension, with rates up to 29% reported in the study by Bossen *et al.* [34] While the combined α1, β1/β2-blocker carvedilol decreases arterial blood pressure in patients with cirrhosis and ascites, the effects of traditional β1/β2-blockers on arterial blood pressure are modest if not used at high doses. Nevertheless, we and others [64] recommend to reduce the dose or to discontinue NSBBs in cirrhotic patients who develop arterial hypotension (systolic blood pressure <90 mmHg).

Key point

Patients with sepsis, SBP and HRS who are in need for vasopressor treatment should have their NSBBs treatment interrupted.

Key point

Low doses of propranolol (⩽80 mg per day) seem to be safe and effective in patients with severe or refractory ascites.

When should we stop NSBB therapy?

In clinical scenarios where the associated risks and side effects outweigh the potential benefits of NSBB therapy we recommend to discontinue NSBBs. As outlined above, the effect size of NSBB treatment is larger in secondary than in primary prophylaxis and NSBB also seem to reduce mortality in secondary prophylaxis [49]. This concept of risk stratification requires evaluation of the predominating risk factor and knowledge on the pathophysiology of the portal-hypertensive syndrome: NSBBs decrease cardiac output and thus splanchnic blood flow by blocking β1-adrenergic receptors on the myocardium that are stimulated by an upregulation of the SNS. This therapeutic approach aims to decrease the consequences of a progressive portal-hypertensive state by decreasing portal pressure and the risk of variceal bleeding. In clinical scenarios where the underlying liver disease persists and portal hypertension aggravates, or if there is an additional hit such as bacterial translocation or a severe infection (i.e., SBP), systemic vascular resistance decreases [59]. In patients without NSBB treatment, this is compensated by a further increase in heart rate and cardiac output aiming at maintaining systemic circulation and adequate perfusion of vital organs including the kidneys. Elegant studies have shown that in advanced cirrhosis, cardiac output becomes critically dependent on the heart rate [65]. Thus, development of arterial hypotension (systolic blood pressure <90 mmHg), or renal failure (serum creatinine >1.5 mg/dl) during NSBB treatment are clinical signs indicative of circulatory dysfunction and detrimental effects of NSBBs in decompensated patients.

Thus, treatment decisions must consider the whole picture of the patient and be based on careful risk/benefit assessment. For example, patients on primary prophylaxis with NSBBs with ascites, side effects related to β-adrenergic blockade (e.g., dizziness) and low arterial blood pressure should be switched to EBL (compare clinical scenario 1).

In knowledge of this complex pathophysiology, it seems rather counterintuitive to continue NSBB treatment although the endogenous SNS is needed to maintain adequate systemic circulation and perfusion, especially if terlipressin/vasopressors are used to prevent progressive renal failure and treat HRS. Thus, we recommend stopping NSBB treatment in patients with HRS and septic/hemorrhagic shock when terlipressin or vasopressors are needed to maintain arterial blood pressure. In absence of renal impairment and arterial hypotension, low doses of propranolol (⩽80 mg/d) seem safe but carvedilol should generally be avoided in patients with severe or refractory ascites.

Therapy beyond guidelines

Based on the currently available data, an individualized NSBB regimen tailored to the specific pathophysiological stage of cirrhosis is likely to be the best strategy to optimize patient management at this point [66]. Treatment recommendations are summarized in Table 2.

Primary prophylaxis: Several studies have demonstrated the superiority of carvedilol over propranolol in reducing portal pressure [63,67,68]. However, it is important to point out that carvedilol is also associated with a stronger decrease in arterial blood pressure [63,69], increased need for diuretics [69], and potentially less survival benefit (when compared to propranolol) in patients with cirrhosis and ascites on the transplant waiting list [54]. While we prefer to use carvedilol in primary prophylaxis for compensated patients [63], we avoid the use of carvedilol in patients with severe or refractory ascites, as well as patients with progressive arterial hypotension [55]. For primary prophylaxis in patients with severe ascites we would recommend low doses of propranolol (⩽80 mg/d) or repetitive EBL until variceal eradication. This strategy is supported by meta-analysis data showing similar survival with EBL or NSBB in primary prophylaxis [70,71] and a potentially higher risk of HRS and mortality in patients with ascites treated with NSBBs if they develop hypotension [14] or have advanced liver dysfunction [72].

Secondary prophylaxis: If there is a strong indication for the use of NSBBs (secondary *vs.* primary prophylaxis), the effectiveness of NSBBs is probably more pronounced than in other scenarios. In clinical scenario 2, NSBB treatment does not only decrease the risk of rebleeding [73] but might also exert non-hemodynamic effects [42,51]. At the same time, there is no convincing evidence of detrimental effects in uncomplicated (non-refractory, no SBP) ascites [34,74]. Thus, we recommend to maintain NSBB treatment in secondary prophylaxis for patients with ascites, but to avoid high doses of propranolol (>80 mg/d) and carvedilol in patients with severe or refractory ascites. Ultimately, patients with refractory ascites and a history of variceal bleeding should be evaluated for transjugular intrahepatic portosystemic shunt (TIPS), since covered stents may improve survival in these patients [75], as well as liver transplantation.

In conclusion, NSBBs can be used for primary prophylaxis in patients with ascites and should be used for secondary prophylaxis of variceal bleeding. However, careful monitoring of blood pressure and renal function, as well as screening for infections should be performed to identify scenarios in which NSBB doses should be reduced or treatment discontinued. Due to the higher risk of inducing arterial hypotension, carvedilol should not be used in patients with severe or refractory ascites. In contrast, low doses of conventional NSBBs seem to be safe in patients with cirrhosis and severe or refractory ascites.

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Conflict of interest

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Authors' contributions

Literature search (T.R., M.M.), concept of the article (T.R., M.M.), extraction of data (T.R., M.M.), drafting of the manuscript (T.R., M.M.), revision for important intellectual content (T.R., M.M.).

Key point

Patients should be evaluated for TIPS in case of NSBB intolerance in secondary prophylaxis especially if refractory ascites is present as well.

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