



Beta-blockers in cirrhosis: Evidence-based indications and limitations

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Summary

Non-selective beta-blockers (NSBBs) are the mainstay of treatment for portal hypertension in the setting of liver cirrhosis. Randomised controlled trials demonstrated their efficacy in preventing initial variceal bleeding and subsequent rebleeding. Recent evidence indicates that NSBBs could prevent liver decompensation in patients with compensated cirrhosis. Despite solid data favouring NSBB use in cirrhosis, some studies have highlighted relevant safety issues in patients with end-stage liver disease, particularly with refractory ascites and infection. This review summarises the evidence supporting current recommendations and restrictions of NSBB use in patients with cirrhosis.

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Introduction

Almost 40 years ago, non-selective beta-blockers (NSBBs) emerged in the field of cirrhosis and portal hypertension (PH), as propranolol was shown to prevent recurrent variceal bleeding.¹ For the following 3 decades, several randomised controlled trials (RCTs) demonstrated the efficacy of NSBBs for preventing primary and secondary bleeding from oesophagogastric varices^{2–5} and portal hypertensive gastropathy (PHG).⁶ Additionally, NSBBs reduce bacterial translocation and the risk of spontaneous bacterial peritonitis (SBP), and increase survival independent of bleeding events.^{7,8} NSBBs have also been suggested to decrease the risk of hepatocellular carcinoma.⁹

Interestingly, at the time of the first publication in 1980, a letter alerted readers to potentially severe hypotension induced by NSBBs in patients with ascites related to their effect of on the renin-angiotensin system.¹⁰ However, the tide began to turn on NSBBs 30 years later when Sersté *et al.* suggested that patients with refractory ascites on NSBBs could have increased mortality.¹¹ This has led to a discussion on the safety of NSBBs in patients with ascites, infection or renal injury. Since then, a plethora of mostly observational data emerged and gave rise to the “therapeutic window” hypothesis, which questioned NSBB use in early cirrhosis without medium-large varices and cautioned to avoid them in patients with end-stage liver disease and refractory ascites.¹²

This controversy has been tempered as more recent and larger studies support the safety of NSBBs in most indications, provided they are used carefully. The scenario has been further

changed by the introduction of a new NSBB, carvedilol, which has a greater effect on reducing portal pressure than traditional NSBBs and has significant clinical benefit in new indications in compensated cirrhosis.¹³ However, data on how well carvedilol is tolerated compared with traditional NSBBs requires further assessment. Furthermore, in the last 5 years, various studies have demonstrated the safety and survival benefit of NSBB use in decompensated cirrhosis, putting into question some of the current guideline recommendations.

Two systematic searches on Medline and Embase were performed to assess i) the efficacy of NSBBs in patients with cirrhosis and PH and ii) the role of NSBBs on mortality in patients with decompensated liver cirrhosis. This review aims to provide a balanced summary of the existing evidence on the indications for and the potential limitations of beta-blockers in cirrhosis.

Brief overview of the pathophysiological basis for using beta-blockers in cirrhosis

Portal venous pressure increases in the setting of liver cirrhosis, first, due to increased resistance to portal blood inflow at the hepatic circulation. This has a mechanical component related to distortion of liver microvascular architecture and a dynamic component related to endothelial dysfunction, which results in decreased availability of endogenous vasodilators, mainly nitric oxide (NO), and increased release of vasoconstrictors (prostanoids, endothelins and angiotensin), leading to an increased hepatic vascular tone. At a later stage, portosystemic collaterals develop because of

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dilatation of pre-existing vascular conduits caused by increased portal pressure, as well as vascular endothelial growth factor-mediated angiogenesis.¹⁴ This heralds splanchnic vasodilation with increased blood inflow to splanchnic organs and the portal system. Splanchnic vasodilation leads to systemic vasodilation; the ensuing effective hypovolemia triggers expansion of the plasma volume and increases the cardiac output. This hyperkinetic circulation further increases the blood flow to splanchnic organs, which contributes to an additional increase in portal pressure.

The effects of NSBBs are summarised in Fig. 1. NSBBs, via β_1 -adrenergic blockade, reduce heart rate and cardiac output with a decrease in flow of about 20%. Whereas via β_2 -adrenergic blockade, NSBBs cause splanchnic vasoconstriction due to unopposed adrenergic tone, with a subsequent additional decrease in portal-collateral blood flow of about 15%, for a total 35% reduction in portal venous inflow. This is the mechanism by which NSBBs decrease the portal pressure by approximately 15%. Via an unopposed adrenergic tone, NSBBs cause a mild increase in peripheral and hepatic resistance, which explains why patients under NSBB do not develop arterial hypotension and why the effect on portal pressure is relatively mild. Carvedilol is a NSBB that has an intrinsic anti- α_1 adrenergic effect, which causes intrahepatic vasodilatation and further decreases portal pressure. Although carvedilol is more effective in reducing hepatic venous pressure gradient (HVPG) than propranolol or nadolol, at relatively high doses (over 25 mg/d) it may decrease mean arterial pressure (MAP).¹⁵ At low doses (6.25–12.5 mg/d) carvedilol does not cause hypotension but decreases portal pressure significantly more than propranolol. Low doses cause only a moderate decrease in cardiac output and heart rate. This could explain why carvedilol has been better tolerated than therapeutic doses of propranolol, established after titration according to heart rate, arterial pressure and clinical tolerance.¹³

Key points

- Non-selective beta-blockers (NSBBs) are the established cornerstone of treatment for prevention of first bleeding and rebleeding of oesophageal varices in patients with cirrhosis.
- NSBBs include propranolol, nadolol, and timolol. Carvedilol is a new NSBB that is increasingly used; it has a greater portal pressure reducing effect than propranolol and is safe in patients with compensated and decompensated cirrhosis.
- New trials should focus on NSBBs for the prevention of decompensation (ascites) in compensated cirrhosis and prevention of mortality and liver transplantation in decompensated cirrhosis.
- Fixed doses of NSBBs are discouraged. Rather, the dose should be titrated individually. Adherence and doses of NSBBs should be re-evaluated whenever there are significant changes in the clinical condition of the patient, especially low blood pressure.
- Refractory ascites, spontaneous bacterial peritonitis and acute-on-chronic liver failure are not contraindications for NSBB treatment. Doses should be carefully tapered, with a temporary reduction or discontinuation in patients who develop signs of decreased organ perfusion or significant hypotension. Re-initiation and titration of NSBBs should be performed once the acute event is resolved.

Clinical benefit from NSBBs stems from a significant reduction in the portal pressure gradient, determined clinically at hepatic vein catheterisation as the HVPG. The gradient must decrease by at least 10% of baseline (preferably by at least 20%) or below 12 mmHg to prevent first variceal bleeding (or liver decompensation).¹⁶ To prevent rebleeding, it should drop by at least 20% or below 12 mmHg.^{2,13,17–20} Although this is achieved in about 50% of patients receiving propranolol,²¹ the proportion of responders increases to about 75% when using carvedilol (even in propranolol non-responders).¹⁹

Satisfactory responses to NSBBs are associated with a decreased risk of bleeding, as well as a lower risk of ascites, SBP, hepatorenal syndrome (HRS) and a better survival rate,

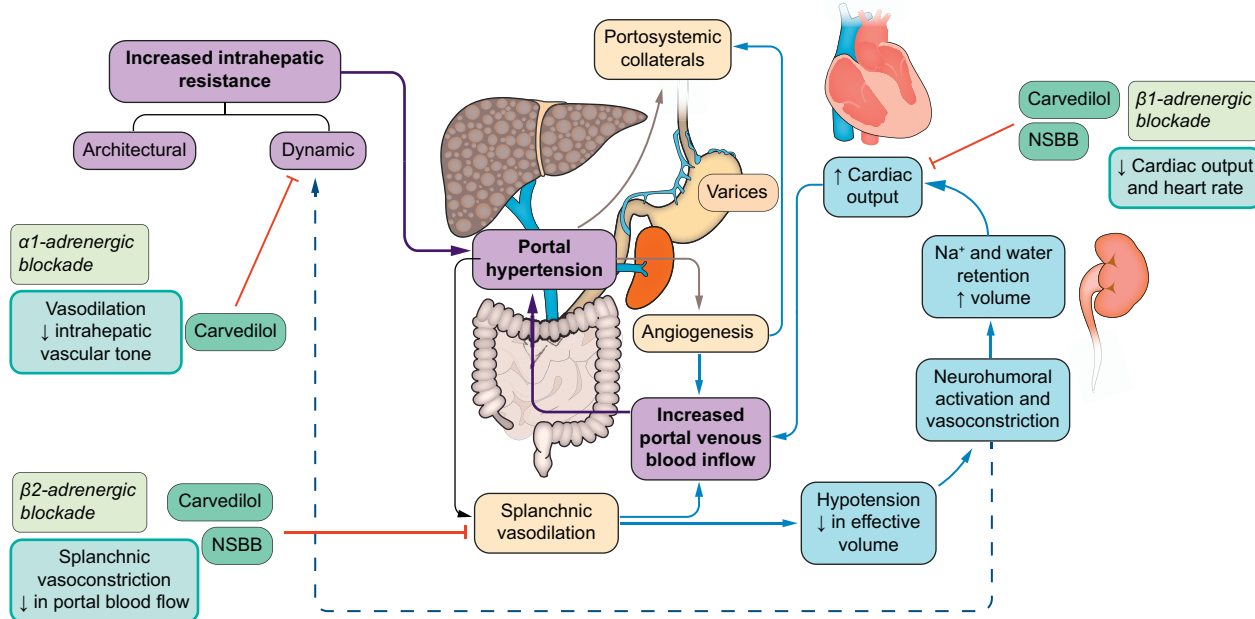


Fig. 1. Pathophysiology of portal hypertension in cirrhosis and mechanisms and sites of action of non-selective beta-blockers. NSBB, non-selective beta blocker.

Pre-primary prophylaxis	Prevention of decompensation	Prevention of first variceal bleeding	Prevention of variceal rebleeding	Gastric varices	Portal hypertensive gastropathy
>1 RCT failed to show prevention of large varices and more adverse events	1 RCT in compensated patients with CSPH	Various RCT meta-analyses: - Decreases bleeding - Improves survival	Various RCT meta-analyses: - Decreases rebleeding - Improves survival	Prevention of first bleeding GOV1-2, IGV1: III;2 Indication	1 RCT: - Decreases rebleeding No RCT designed for prevention of first bleeding:
I;1 GRADE 1 Level 1b	I;1 GRADE 1 Level 1b	Compensated and high-risk varices: I;1 Decompensated and high-risk varices: I;1	Patients without and with ascites and previous variceal bleeding: I;1 GRADE 1 Level 1a	Prevention of rebleeding: cyanoacrylate superior (RCT) and no additional benefit from NSBB GRADE 2, Level III	I;1 GRADE 1 Level 1b
No indication to prevent varices or progression	Indication	Both GRADE 1 Level 1a Indication	Indication	No strong evidence of indication	Indication

Indications for beta-blockers in cirrhosis: levels of evidence and grade of recommendation

Fig. 2. Levels of evidence for non-selective beta-blockers in cirrhosis according to indication. CSPH, clinically significant portal hypertension; GOV1-2, gastroesophageal varices type 1/2; IGV1, isolated gastric varices type 1; NSBB, non-selective beta blocker; RCT, randomised controlled trial.

reflecting a favourable impact on the natural history of the disease; this is one of the advantages of NSBBs compared to endoscopic therapy. The level of evidence for NSBB use in the main indications of cirrhosis is summarised in Fig. 2.

Indications

Prevention of first variceal bleeding (primary prophylaxis)

Patients with high-risk varices and compensated cirrhosis

Currently, NSBBs and endoscopic band ligation (EBL) are considered equally effective in preventing first bleeding in patients with high-risk varices,^{22–24} i.e. medium to large varices or small varices with red wale marks or in patients with decompensated cirrhosis (Child-Pugh B/C).^{22,25} NSBBs are favoured over endoscopic therapy in patients with small, high-risk varices, given the size of the varices.²²

In patients with compensated cirrhosis and high-risk varices, the primary goal of therapy is not limited to bleeding prevention (that is not the most common event), but must also focus on preventing decompensation of cirrhosis (ascites, variceal bleeding or hepatic encephalopathy). However, the vast majority of studies were only designed to evaluate reductions in the risk of haemorrhage and subsequent bleeding-related death. Moreover, most studies included both compensated and decompensated patients. As stated above, it is now preferred to consider therapy according to the stage of the disease; treating compensated patients to prevent decompensation and decompensated patients to prevent liver transplantation and death.

Considering this, pharmacological therapy may be a better approach than endoscopic treatment, given its ability to prevent decompensation. It is well known that ascites may be prevented in haemodynamic responders to NSBBs,¹³ while this is not possible with endoscopic treatments.

NSBBs are effective in preventing first bleeding event in patients with cirrhosis, independent of disease severity.²⁶ In 1999, a meta-analysis of RCTs selected 8 studies including patients with medium-large varices. This meta-analysis compared NSBBs (propranolol/nadolol) to placebo or nonactive treatment and demonstrated a clear reduction in absolute risk of bleeding and bleeding-related mortality, but not overall mortality.²⁷ The

absolute risk reduction of first variceal haemorrhage within 2 years of follow-up was –10% in patients with NSBBs vs. placebo. A small decline in absolute mortality rate, of –4% was found, approaching statistical significance. When the analysis was stratified to patients with high-risk varices, the bleeding rate in treated patients diminished significantly, by –16%.²⁷

In 2012, a meta-analysis of 19 trials suggested that EBL was slightly superior to NSBBs for primary prophylaxis of variceal bleeding (risk ratio [RR] 0.67; 95% CI 0.46–0.98; $p = 0.037$). However, on further analysis, no significant differences were found either in bleeding-related or overall mortality compared with NSBBs in high-quality trials. Complications or side effects associated with EBL are less frequent, but more severe and potentially fatal.^{28,29}

Regarding carvedilol, the first RCT comparing carvedilol to EBL³⁰ reported that carvedilol had lower rates of the first variceal bleed (10% vs. 23%, $p = 0.04$), with no significant differences in overall mortality (35% vs. 37%, $p = 0.71$), and bleeding-related mortality (3% vs. 1%, $p = 0.26$), but did not report data on other events. Thirty percent of patients in both arms dropped out and per-protocol analysis revealed no significant differences in outcomes; in addition, the study was underpowered. Another study showed that, in propranolol non-responders, carvedilol could effectively decrease HVPG; during a 2-year follow-up, bleeding rates for propranolol were 11% compared to 5% with carvedilol and 25% with EBL ($p = 0.04$).¹⁹ A further trial in Pakistan showed that both EBL and carvedilol monotherapy groups had comparable variceal bleeding (8.5% vs. 6.9%), bleeding-related mortality (4.6% vs. 4.9%) and overall mortality rates (12.8% vs. 19.5%), respectively.³¹ An additional study comparing EBL vs. propranolol and carvedilol showed comparable rates of bleeding prevention.³² Again, these studies provide no data on prevention of other complications of PH. Presently, there is still insufficient data showing superiority of either EBL or carvedilol therapy in primary prevention of bleeding. The ongoing CALIBRE multicentre UK trial is designed to compare carvedilol to EBL in prevention of bleeding.³³ These results are awaited, particularly regarding impact on preventing other liver-related complications.

A network meta-analysis using data combining direct and indirect evidence from 32 RCTs including 3,362 patients with

cirrhosis with high-risk varices assessed the effect of different treatment modalities on first episode of variceal bleeding and mortality. Regarding bleeding prevention, on direct meta-analysis, EBL monotherapy reduced the risk of first variceal bleed compared to placebo (odds ratio [OR] 0.36; 95% CI 0.14–0.92), to NSBB (OR 0.52; 95% CI 0.35–0.78), and to isosorbide mononitrate (ISMN) (OR 0.25; 95% CI 0.07–0.93). EBL monotherapy was associated with a higher risk of overall mortality compared with NSBBs, although not significant (OR 1.35; 95% CI 0.98–1.86). Side effects were more common with NSBBs, leading to 10–13% rates of treatment discontinuation, but almost all of the serious adverse events were related to EBL.³⁴ Six RCTs within this meta-analysis compared combined EBL or ISMN and NSBBs to monotherapy and demonstrated that combination therapy significantly reduced first variceal bleeding compared with placebo (OR 0.34; CI 0.14–0.86). However, in the trials of combined therapy, adverse events were reported in 59% of patients receiving a combination of EBL and NSBBs, in 51% of patients receiving carvedilol monotherapy and ranged between 20–24% for those receiving other NSBBs or EBL or ISMN or combined NSBB+ISMN.³⁴ The 2 existing trials on combined endoscopic and NSBB therapy vs. monotherapy showed no added benefit.^{7,35} In 2017, a multicentre RCT from Korea reported that propranolol + EBL was more effective for primary prophylaxis in patients with high-risk varices. Moreover, combination therapy was more effective in the prevention of variceal recurrence after EBL eradication. Adverse event rates were not described.³⁶ It is still unclear whether combination therapy is more effective and safer for primary prophylaxis. Although current guidelines recommend either NSBBs or EBL as equivalent therapies for primary prophylaxis, recent evidence shows that NSBBs in patients with compensated cirrhosis and clinically significant portal hypertension (CSPH) can prevent first decompensation, namely ascites. Thus, since EBL is not likely to prevent ascites, NSBBs are emerging as the preferred option.¹³

Patients with high-risk varices and decompensated cirrhosis

The potential limitations of NSBBs in end-stage cirrhosis will be discussed later in a dedicated section. There is firm data supporting NSBB use in the prevention of first variceal bleeding event in both patients with and without ascites. An individual patient meta-analysis of 4 RCTs showed that NSBBs effectively prevent the first episode of variceal bleeding and reduce bleeding-related mortality independently of cirrhosis stage.²⁶ The 2-year bleeding rate was reduced by 9%. The risk decrease was observed in patients with ascites (–14%) and without ascites (–15%). According to the log-rank test on Kaplan-Meier cumulative estimates, the reduction in first bleeding episode was statistically significant (from 41% to 27%, $p = 0.002$).^{26,27}

Furthermore, a meta-analysis on prevention of first bleeding and rebleeding analysed both patients with cirrhosis with and without ascites, who responded to treatment with NSBB (based on reductions in HVPG), and demonstrated a reduced risk of liver-related events, death, or liver transplantation.³⁷

Following 2 observational studies, concerns regarding beta-blocker use in the context of ascites¹¹ or SBP³⁸ were raised. Since then, various studies questioned the validity of the findings and showed that in decompensated patients NSBB use improved survival^{39–43} or showed no difference.⁴¹ A retrospective study of 264 propensity score matched patients under

carvedilol use and decompensated cirrhosis, showed increased survival in the carvedilol group vs. non-carvedilol groups (24% vs. 2%, $p < 0.0001$). The long-term survival was significantly better in the carvedilol than the non-carvedilol group (log-rank $p < 0.001$).⁴⁴

Prevention of the formation or growth of varices (preprimary prophylaxis)

Patients with no varices or non-high-risk varices and compensated cirrhosis

Presently, there is not enough evidence to support the use of NSBBs to prevent the development or growth of varices in patients with cirrhosis without varices or with small varices without red wale signs. One French study evaluated the effect of propranolol on preventing the development of large oesophageal varices over 2 years in patients with or without small varices.⁴⁵ More than twice the patients assigned to propranolol developed varices compared to placebo, but one-third of the patients were lost to follow-up, in addition to those who suspended therapy because of intolerance. Bleeding and mortality rates were similar. A multicentre, single, double-blind RCT of timolol vs. placebo showed that, after 55 months, 39% and 40% of patients in the timolol and placebo groups, respectively, developed varices. Additionally, adverse events were more frequent in the timolol group. However, the study disclosed that the development of large varices, variceal bleeding, ascites, encephalopathy, and death did not occur when HVPG remained below 10 mmHg, and that varices developed much less frequently when HVPG was decreased by over 10% of baseline. A therapeutic benefit of timolol in preprimary prophylaxis could not be established.⁴⁶ Among possible causes are sample size distribution and inclusion of patients without CSPH (HVPG <10 mmHg). Around 50% of the patients did not have CSPH and, thus, had not fully developed a hyperdynamic circulatory state. At this stage, the effect of propranolol on portal pressure has been shown to be almost negligible.⁴⁷

More recently, Sarin *et al.* showed that in patients with cirrhosis and small oesophageal varices, NSBBs were unable to prevent the growth of varices, variceal haemorrhage, or mortality.⁴⁸ In contrast, 2 studies showed evidence in favour of beta-blockers to delay growth of small varices. One RCT comparing nadolol to placebo reported cumulative risks of variceal progression in 20% vs. 51%, for the nadolol and placebo groups, respectively. The cumulative probability of variceal bleeding was also lower in patients randomised to nadolol ($p = 0.02$). Survival was not different and adverse effects resulting in withdrawal were more common in the nadolol group.⁴⁹ Carvedilol was tested in another RCT against placebo to assess the delay in small varices progression; this study showed that 79% of patients in carvedilol group vs. 61% of patients in placebo group were free from progression to large varices ($p = 0.04$). No differences were found regarding bleeding events, mortality or adverse side effects.⁵⁰ A meta-analysis of 6 RCTs including patients with no or small varices found no significant benefit for NSBBs compared to placebo for the prevention of large varices, first variceal bleeding and death.⁵¹ Overall, the evidence is conflicting regarding an impact of beta-blockers on slowing the progression of small varices to large varices in patients with cirrhosis. At this stage, treatment should be centred on eliminating or controlling the cause of liver disease to attempt regression of architectural changes and reduction of intrahepatic resistance. Furthermore, it is currently accepted

that at such an early stage, treatment in patients with compensated cirrhosis should be aimed at preventing a first episode of clinical decompensation, the most frequent being ascites.

Prevention of decompensation

Data from trials demonstrating the effect of NSBBs on the prevention of clinical decompensation were non-existent. Previous trials illustrated that decompensation risk was concentrated almost exclusively in patients with a baseline HVPG ≥ 10 mmHg, the threshold defining CSPH.⁵² Moreover, patients with CSPH exhibit a greater HVPG response to NSBBs than those without, suggesting that NSBBs may be an effective option to prevent decompensation, and that compensated patients with CSPH, but without high-risk varices, would be the ideal population to test this hypothesis.

The PREDESCI trial, a multicentre, double-blind, RCT adopted this set-up and investigated whether long-term treatment of patients with compensated cirrhosis and CSPH with NSBBs might prevent progression to clinical decompensation or death. Patients developing moderate-large varices in both arms received EBL. This is the first RCT to show that long-term treatment with NSBBs decreases clinical decompensation or liver-related death by half. This was mainly due to decreased rates of ascites, which is the most common decompensating event and for which there was previously no effective preventive drug therapy. There were no differences in the bleeding incidence in the study, probably due to the use of EBL in patients developing high-risk varices. One likely explanation is that the study showed that NSBBs, but not placebo, significantly reduced the HVPG at each yearly control, and that reductions of at least 10% from baseline or to below 10 mmHg conferred marked protection from decompensation and death during follow-up.¹³

Prevention of rebleeding and death (secondary prophylaxis)

The main goal of treating patients with cirrhosis after an acute variceal haemorrhage, as first decompensating event, has been to prevent recurrent variceal bleeding. However, these patients very frequently show additional manifestations of decompensation, such as ascites or hepatic encephalopathy, and have a poor prognosis. Thus, since Baveno VI, the aim of therapy in these cases should be liver transplantation and death prevention, while decreasing further decompensation rates would represent a secondary endpoint. Nonetheless, to date, trials have aimed primarily at recurrent variceal bleeding prevention, so the available data on outcomes, as per Baveno VI, are limited. Baveno VI recommends a combination of NSBBs (propranolol or nadolol) and EBL for rebleeding prevention.²²

A meta-analysis of 12 RCTs comparing NSBBs vs. placebo showed a mean absolute reduction of rebleeding of 21% in the NSBB group.⁵³ Nine RCTs comparing propranolol and sclerotherapy were analysed. Sclerotherapy was more effective in preventing variceal rebleeding, but with significantly higher adverse event rates, and no difference in survival rates.⁵³ In a meta-analysis, the combination of NSBBs and low-dose ISMN was not significantly better than NSBBs alone, but had a higher rate of adverse events.⁵⁴ In 2012, a meta-analysis of 9 trials assessed the effects of EBL plus NSBBs \pm ISMN vs. monotherapy (EBL or NSBBs \pm ISMN) for secondary prevention of recurrent bleeding. Combination therapy reduced mortality related to

rebleeding (RR 0.52; number needed to treat = 33) and the risk of recurrent bleeding from oesophageal varices (RR 0.68; number needed to treat = 8).⁹

Four trials comparing drugs alone (NSBB+ISMN) or associated with EBL, including 409 patients, demonstrated that variceal rebleeding decreased with combined therapy ($p < 0.01$), but rebleeding from oesophageal ulcers increased ($p = 0.01$). Overall, there was a trend towards lower rebleeding (RR 0.76; 95% CI 0.58–1.00) without significant effects on mortality (RR 1.24; 95% CI 0.90–1.70). Combination therapy (NSBB+ISMN) was only slightly more effective than drug monotherapy.⁵⁵ An individual patient data meta-analysis of 7 trials comparing combined EBL + NSBB vs. monotherapy (either NSBBs or EBL) showed that compared with EBL alone, EBL + NSBB reduced rebleeding in both Child-Pugh A and B/C patients, with a significant reduction in mortality in Child-Pugh B/C patients (incidence rate ratio [IRR] 0.46; 95% CI 0.25–0.85), whereas NSBBs alone performed as well as combination therapy. This study highlighted the independent role that NSBBs play in modifying survival, particularly in patients with advanced liver failure (Child-Pugh B/C).⁵⁶ Thus, it has been suggested that patients with contraindications or who cannot tolerate NSBBs should be considered for transjugular intrahepatic portosystemic shunt (TIPS), particularly in the presence of another indication, *i.e.* difficult to treat or refractory ascites.

Regarding carvedilol, 1 trial compared the safety and efficacy of carvedilol to nadolol plus ISMN in preventing variceal rebleeding. The treatments were equally effective with similar mortality rates, but the carvedilol group had significantly less adverse events (3% vs. 46%, $p < 0.0001$).⁵⁷ A multicentre RCT with 64 patients compared carvedilol and EBL and reported no difference for rebleeding and a trend towards reduced mortality for carvedilol (27% vs. 52%, $p = 0.110$).⁵⁸ More recently, a meta-analysis compared the efficacy and safety of carvedilol plus EBL vs. traditional NSBBs plus EBL in preventing variceal rebleeding. Carvedilol decreased rebleeding rates ($p < 0.001$) and drug-related adverse events ($p < 0.001$) more than traditional NSBBs. No difference was noted with respect to mortality. Nevertheless, these findings must be interpreted cautiously given the overall suboptimal quality of the eligible studies and the lack of HVPG.⁵⁹

Gastric and ectopic varices

Gastric and ectopic varices are particularly more frequent in presinusoidal PH compared to patients with cirrhosis. Thus, RCTs are scarce and include small samples and patients with differing disease states: either with or without cirrhosis, or with gastric and oesophageal varices. Therefore, the degree of evidence is much less firm than in patients with cirrhosis.

Gastroesophageal varices type 1 (GOV1) are the most common (around 75% of gastric varices) and are oesophageal varices extending below the cardia into the lesser curvature. These are most frequently associated with bleeding, although less severe than cardiofundal variceal bleeding, and are managed like oesophageal varices.²² GOV type 2 (GOV2) extend to the fundus and tend to be longer and more tortuous. Isolated gastric varices type 1 (IGV1) are located in the fundus, while IGV type 2 are found elsewhere in the stomach. Cardiofundal varices (GOV2 and IGV1) bleed less frequently, but are generally more severe, more difficult to control and show a higher risk of bleeding recurrence and mortality compared to oesophageal varices.^{60,61}

Prevention of first bleeding

The 2 most widely used treatments in this context are NSBBs and endoscopic variceal obliteration with tissue adhesive injection. Solid data from RCTs is too scarce to demonstrate superiority of cyanoacrylate variceal obliteration over NSBBs. One RCT reported a higher rate of first bleeding episodes in patients with cardiofundal varices (GOV2 and IGV1) in the group treated with NSBBs compared to cyanoacrylate injection (38% vs. 10%, $p = 0.003$), with similar survival rates (83% vs. 74%, $p = 0.113$).⁶² Guidelines advocate NSBBs for primary bleeding prophylaxis of GOV2 and IGV1 based on a potential lower risk of complications and the possibility of clinical decompensation prevention. GOV1 varices should be treated per guidelines for oesophageal varices (either NSBBs or EBL).^{22,23}

Management of acute bleeding and prevention of rebleeding

Medical treatment of acute bleeding from gastric varices is similar to oesophageal varices, except that the preferred endoscopic therapy for gastric varices is variceal obliteration with endoscopic cyanoacrylate injection.²³ Assessment is complicated by the fact that many studies have small samples and include patients with GOV1 varices and different aetiologies of PH, including some patients with extrahepatic portal vein occlusion or idiopathic PH. A single RCT with 95 patients concluded that adding NSBBs provided no additional benefit to obliteration with cyanoacrylate for the prevention of rebleeding and mortality.⁶³ Nevertheless, the study was powered to assess a 25% absolute decrease in risk of rebleeding, so a smaller reduction in absolute risk of bleeding could not be ruled out. One small trial compared TIPS to cyanoacrylate injection in 72 patients; TIPS proved more successful in preventing rebleeding from gastric varices, without significant differences regarding survival and adverse events.⁶⁴ However, TIPS might not be possible in some of the patients with extrahepatic portal vein occlusion. In these cases, other forms of percutaneous radiological intervention procedures, such as balloon-occluded retrograde transvenous obliteration of gastric varices, and variants of the technique, may be lifesaving. However, a detailed discussion of these procedures is beyond the scope of the current review.

Bleeding from ectopic varices is very rare in cirrhosis, but is more frequent in patients with extrahepatic portal vein occlusion, overall representing between 1 and 5% of all gastrointestinal haemorrhage in patients with PH.^{65–67} Ectopic varices are dilated portovenous vessels located outside of the oesophagus or the stomach. Anatomic mapping is essential and the heterogeneity in localisation limits the implementation of standard treatment. Current treatment options include endoscopic therapy, mostly with cyanoacrylate injection or endosonographic coil placement, TIPS with or without embolisation, and balloon-occluded retrograde transvenous obliteration.²⁴ There is no data from controlled trials assessing the role of NSBBs in patients with ectopic varices.

Portal hypertensive gastropathy

Data is lacking regarding beta-blockers for primary prophylaxis of bleeding from PHG.⁶⁸ Two previous studies demonstrated a reduced risk of PHG in patients under NSBBs compared to those treated only with EBL for bleeding prophylaxis.^{69,70} One study compared carvedilol vs. propranolol vs. EBL for primary prevention of variceal bleeding, and studied the effect of each treatment on PHG after 1 year. The carvedilol and propranolol

groups had a lower risk of PHG compared to those under endoscopic therapy.³²

In patients with previous acute or chronic bleeding, the benefit of beta-blockade is more established. Current guidelines recommend NSBBs as first line therapy in preventing recurrent bleeding from PHG.²² An RCT in patients with cirrhosis and PHG reported PHG-associated rebleeding rates of 65% in controls vs. 38% in patients under propranolol (doses 40–320 mg/d) ($p < 0.05$). At 30 months, over 50% of patients on propranolol did not experience rebleeding compared to less than 10% of controls.⁶ An earlier, smaller study involving 38 patients with PHG (14 with acute bleeding and 24 with nonbleeding PHG) described a decrease in the incidence of rebleeding and a reduction in PHG with propranolol.⁷¹

Acute bleeding associated with PHG is rare. A multicentre study reported a 2.5% rate of acute PHG-related bleeding during a mean follow-up period of 18 months.⁷² The evidence supporting NSBBs during bleeding events is very scarce.⁷¹ Current guidelines advocate beta-blockers for secondary prophylaxis after adequate bleeding control with faster-acting vasoactive drugs.²²

Beta-blocker contraindications, dosage and side effects

Contraindications and dosage

Absolute or relative contraindications for NSBBs are present in around 15% of patients because of coexisting conditions and, in another 15%, dose reduction or withdrawal may be necessary because of adverse effects⁷³ (Box 1). These limitations should not discourage patients and clinicians from using NSBBs for the indications previously described, given the firm evidence of their efficacy in cirrhosis and PH (Table 1).

Although limited data shows that there is no correlation between the decrease in HVPG and a decrease in heart rate,⁷⁴ current clinical practice recommends an approximate 25% decrease in heart rate as evidence of adequate beta-adrenergic blockade with NSBBs. It is usually advised that NSBBs be titrated until the maximum tolerated dose, provided the systolic blood pressure remains above 90 mmHg and heart rate above 55 bpm. Specific data on titration, frequency of administration, and maximum doses for each NSBB are provided in Table 2. Once started, NSBBs should be maintained for life. According to Baveno I-VI, no endoscopic surveillance is required once patients have achieved a stable maintenance dose.

Side effects

NSBBs can have a negative impact on a patient's quality of life. This is mainly due to adverse effects such as worsening fatigue, reduced exercise capacity and sexual dysfunction. These symptoms are unspecific and can be attributed to cirrhosis or depression. Therefore, dose reduction or switch to another NSBB (for instance, carvedilol if the patient was on propranolol or nadolol) is recommended rather than discontinuing therapy. After initiating NSBBs, they should be reevaluated periodically as intolerance or contraindications can develop later on. It is currently unknown which threshold of blood pressure and/or heart rate and cardiac output reduction can be considered safe, particularly in patients with decompensated cirrhosis. Specific studies examining this issue are warranted, although it is clear that adverse events are dose related. Table 2 indicates the dose

Box 1. Non-selective beta-blocker contraindications and adverse effects.**Absolute contraindication**

Second- or third-degree AV block (in the absence of a permanent pacemaker)
 Critical limb ischemia
 Asthma
 Cardiogenic shock
 Cocaine-induced coronary vasospasm
 Known hypersensitivity

Relative contraindication

Uncontrolled diabetes mellitus and hypoglycemia
 Raynaud syndrome

Consider reducing the dose or discontinuing the NSBB

Hypotension (systolic blood pressure <90 mmHg or mean arterial pressure <65 mmHg)
 Development of acute kidney injury/ hepatorenal syndrome
 Hyponatremia (serum sodium <130 mEq/L)

Commonly reported adverse effects

Weakness
 Shortness of breath
 Dizziness
 Hypotension
 Gastrointestinal symptoms (nausea, constipation)
 Sexual and erectile dysfunction

AV, atrioventricular; NSBB, non-selective beta-blocker.

limits for each beta-blocker. Furthermore, since propranolol is exclusively metabolised by the liver, the dose should be reassessed for tolerance when liver failure progresses in a given patient.

Potential limitations*Ascites and refractory ascites*

In an observational study, Sersté *et al.* questioned the use of NSBBs in 151 patients with advanced cirrhosis and suggested that NSBBs decreased survival in patients with refractory ascites.¹¹ However, a more severe underlying liver disease, higher bilirubin, lower serum sodium, higher prevalence of Child-Pugh class C, and higher prevalence of high-risk varices in the group with NSBBs might justify these differences. Subsequent studies provided evidence on the safety of NSBBs for patients with refractory ascites.^{39,40,44,75–80} The deleterious effect of NSBBs reported by Sersté *et al.*^{11,81} could also have been related to high doses of propranolol: nearly half of the patients were receiving 160 mg/d (and 7 out of 10 patients in the consecutive crossover study). A nationwide study based on Danish registers evaluated 3,719 patients with cirrhosis and ascites. Propranolol doses >160 mg/d were associated with higher mortality than doses <160 mg/d.⁴⁰ Since propranolol is metabolised exclusively by the liver, its dose should be restricted in advanced cirrhosis. These patients should probably not receive propranolol doses >80 mg/d.⁷⁸ As for carvedilol, high doses (over 25 mg/day) were associated with worse outcomes in patients with refractory ascites.^{42–44,77,80} As already stated, the recommended dose of carvedilol for PH is 6.25–12.5 mg/day, as increasing the dose does not enhance the fall in portal pressure but may cause systemic hypotension. Only the presence of concomitant arterial hypertension in well-compensated cirrhosis – something increasingly observed due to the increased prevalence of non-alcoholic fatty liver disease – justify the use of higher doses of

carvedilol in order to correct both the arterial and the PH. A recent study retrospectively assessed the interaction between NSBBs and cardiac function on outcomes in patients on a transplant waiting list (n = 584), which included 32.5% of patients with refractory ascites. The study showed that refractory ascites and NSBB use in patients with compromised cardiac reserve (lower left ventricular stroke work index <64.1 g.m/m²) were associated with increased waiting list mortality in the overall group of patients. Nevertheless, the effect of NSBBs on mortality in the subset of patients with refractory ascites was not addressed.⁸²

Table 3 summarises studies on NSBB use in patients with ascites and refractory ascites. Attention will be focussed on the most recent and largest studies. Bossen *et al.* did not find differences in survival between patients taking or not taking NSBBs in a *post hoc* analysis of 1,198 patients with cirrhosis and ascites (588 with refractory ascites).⁷⁶ Patients with systolic blood pressure <80 mmHg or creatinine >150 µmol/L were not included in the study, which may have increased the perception of safety of NSBBs. Bhutta *et al.* retrospectively analysed prospective data from 717 hospitalised patients with cirrhosis and ascites, including 366 (51%) patients with refractory ascites, revealing no association between NSBBs and a worse outcome.⁷⁷

Aligned with the aforementioned studies, a retrospective study of 2,419 patients studied the impact of NSBBs on in-hospital mortality. Patients were classified according to the presence of varices, ascites or both. In a multivariable model, NSBBs were significantly associated with increased survival, and indicated a survival benefit in all groups of patients, including those with severe ascites. These results were confirmed in a propensity score matching of a subgroup of 865 patients.³⁹ Onali *et al.*⁷⁹ analysed a retrospective cohort of 316 patients with cirrhosis and ascites considered for liver transplantation (40% with refractory ascites). Patients were classified according

Table 1. Summary of the meta-analyses of randomised trials on prevention of first oesophageal variceal bleeding and rebleeding in patients with cirrhosis treated with NSBBs.

Study Author, year (reference)	Arms	Patient and study number	Main results
Prevention of first bleeding			
Poynard <i>et al.</i> 1991 ²⁶	NSBB vs. control	Studies: 4 trials Patients: 589 (286 NSBB vs. 303 placebo) Disease stage: most Child-Pugh B8; 18–37% with ascites	Bleeding: NSBB 78±3% vs. control 65±3% ($p = 0.002$). Overall mortality (2 year): NSBB 71 ±3% vs. control 68±3% survived ($p = 0.34$). Bleeding-related mortality: NSBB 90±2% vs. control and 82±3% survived ($p = 0.01$)
D'Amico <i>et al.</i> 1999 ²⁷	NSBB vs. placebo or non-active treatment NSBB vs. ISMN NSBB + ISMN vs. NSBB NSBB + spironolactone vs. NSBB NSBB vs. SCL (see rebleeding section below)	Studies: 11 trials Patients: 1,189 Disease stage: most Child-Pugh A and B; 4 included patients with ascites	Bleeding: NSBB vs. controls 15% vs. 25%; ARD: -10% (95% CI -16 to -5; NNT = 10) Overall mortality: ARD: -4% (95% CI -9% to 0%)
Tripathi <i>et al.</i> 2007 ⁸⁹	EBL vs. NSBB	Studies: 9 trials Patients: 734 (356 EBL vs. 378 NSBB) Disease stage: most Child-Pugh A and B; Child-Pugh C: 10–30%	Bleeding: EBL vs. NSBB: RR 0.63 (CI 0.43–0.92), NNT=13 Overall mortality: EBL vs. NSBB: RR 1.09 (95% CI 0.86–1.38) Bleeding-related mortality: EBL vs. NSBB: RR 0.71 (95% CI 0.38–1.32) Adverse events: EBL vs. NSBB: RR 0.24 (95% CI 0.12–0.47; NNT=10)
Gluud <i>et al.</i> 2012 ²⁹	NSBB vs. EBL	Studies: 12 trials Patients: 1,504 773 NSBB vs. 731 EBL	Bleeding: EBL vs. NSBB: RR 0.67 (95% CI 0.46 to 0.98) Overall mortality: EBL vs. NSBB: RR 1.09 (95% CI 0.92–1.30) Bleeding-related mortality: EBL vs. NSBB: RR 0.85 (95% CI 0.53–1.39) Adverse events: Both interventions were associated with adverse events
Bai <i>et al.</i> 2014 ⁹⁰	NSBB±ISMN vs. EBL/SCL vs. combined NSBB + EBL/SCL	Studies: 12 trials Patients: 1,571 3 EBL/SCL + NSBB vs. NSBB 4 ISMN + NSBB vs. NSBB 1 EBL/SCL + NSBB vs. EBL/SCL vs. NSBB vs. no therapy; 1 EBL/SCL+ NSBB vs. EBL/SCL; 1 Spironolactone + NSBB vs. NSBB; 1 probiotics + NSBB vs. norfloxacin + NSBB vs. NSBB Disease stage: most Child-Pugh B7–8 Child-Pugh A6–C11	Bleeding: All combined therapies: no significant improvement in prevention of variceal bleeding, non-variceal bleeding Overall mortality: no difference Adverse events: more frequent for combined therapy; EBL/SCL + NSBB vs. NSBB: OR 6.07 (CI 2.27–16.20; $p < 0.001$); ISMN + NSBB vs. NSBB: OR 2.29 (CI 1.58–3.33; $p < 0.001$)
Zacharias <i>et al.</i> 2018 ⁹¹	Prevention of first bleeding and rebleeding Carvedilol vs. other NSBB NSBB: propranolol (n=9), or nadolol (n=1)	Studies: 10 trials 3 First bleeding 3 Rebleeding 4 Bleeding and rebleeding Patients: 810	Bleeding and rebleeding: Carvedilol vs. NSBB: RR 0.77 (95% CI 0.43–1.37) Overall mortality: Carvedilol vs. NSBB: RR 0.86 (95% CI 0.48–1.53) Adverse events (serious): Carvedilol vs. NSBB: RR 0.97 (95% CI 0.67–1.42)
Sharma <i>et al.</i> 2019 ³⁴	Direct and network meta-analysis	Studies: 32 trials 5 NSBB vs. placebo 4 EBL vs. placebo 12 EBL vs. NSBB 3 ISMN vs. NSBB 1 ISMN vs. placebo 2 EBL vs. carvedilol 2 EBL+NSBB vs. NSBB 1 EBL+NSBB vs. EBL 1 NSBB+ISMN vs. EBL 2 NSBB+ISMN vs. NSBB Patients: 3,362 Disease stage: Child-Pugh B7 – Child-Pugh C 11 (most Child-Pugh B 8)	Bleeding: Carvedilol vs. placebo: OR 0.21 (95% CI 0.08–0.56) EBL vs. placebo: OR 0.33 (95% CI 0.19–0.55) EBL vs. NSBB: OR 0.51 (95% CI 0.34–0.76) EBL + NSBB vs. placebo: OR 0.34 (95% CI 0.14–0.86) NSBB vs. placebo: OR 0.64 (95% CI 0.38–1.07) Overall mortality: NSBB mono: OR 0.70 (95% CI 0.49–1.00) EBL + NSBB: OR 0.49 (95% CI 0.23–1.02) ISMN + NSBB: OR 0.44 (95% CI 0.21–0.93) Adverse events: EBL higher serious adverse events than NSBBs
Dwinata <i>et al.</i> 2019 ⁹²	Carvedilol vs. EBL (see rebleeding section below)	Studies: 4 trials Patients: 742 368 vs. 374 Disease stage: Child-Pugh A (most) & Child-Pugh C	Bleeding: Carvedilol: RR 0.74 (95% CI 0.37–1.49) Fixed-effects model: RR 0.38 (95% CI 0.15–0.93) All-cause mortality: RR 1.10 (95% CI 0.76–1.58) Bleeding-related mortality: RR 1.02 (95% CI 0.34–3.10) Adverse events: RR 4.18 (95% CI 2.19–7.95)

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Table 1 (continued)

Study Author, year (reference)	Arms	Patient and study number	Main results
Malandris <i>et al.</i> 2019 ⁵³	Carvedilol vs. other NSBB or EBL (see rebleeding section below)	Studies: 7 trials 4 EBL, 3 NSBB Patients: 984 Disease stage: most Child-Pugh A and B; Child-Pugh C: 10–49%	Bleeding: Carvedilol vs. EBL: RR 0.74 (95% CI 0.37–1.49) Carvedilol vs. propranolol: RR 0.76 (95% CI 0.27–2.14)
Prevention of rebleeding			
Bernard <i>et al.</i> 1997 ⁵³	NSBB vs. SCL	Studies: 12 trials Patients: 769 389 NSBB vs. 380 SCL Disease stage: most Child-Pugh A and B, Child-Pugh C: 0–35%	Rebleeding: NSBB: OR 2.3 (95% CI 1.7–3.0, $p < 0.001$) Overall mortality: survival NSBB: OR 1.4 (95% CI 1.0–1.9, $p = 0.04$) Bleeding-related mortality: survival NSBB: OR 1.65 (95% CI 1.1–2.4, $p = 0.01$) Adverse events: free of adverse events higher in NSS vs. SCL: mean difference: 22% (95% CI 6–38%, $p = 0.007$)
D'Amico <i>et al.</i> 1999 ²⁷	NSBB vs. placebo/no treatment NSBB vs. SCL NSBB vs. NSBB + SCL	Studies: 25 trials Patients: 1,698 Disease stage: most Child-Pugh B, Child-Pugh C: 0–47%	Rebleeding: NSBB vs. placebo: ARD = –21% (95% CI –30% to –13%, NNT= 5) NSBB vs. SCL: ARD = 7% (95% CI –2% to 17%) NSBB vs. NSBB+SCL: ARD = 19%; (95% CI 8%–30%) Overall mortality: NSBB: ARD = –7% (95% CI –12% to –2%; NNT = 14) NSBB vs. NSBB + SCL: ARD 15% (95% CI – 1% to 32%) Adverse events: NSBB: ARD –22% (95% CI –38% to –6; NNH = 4)
Cheung <i>et al.</i> 2009 ⁹⁴	EBL vs. NSSB±ISMN vs. EBL+ NSSB±ISMN	Studies: 12 trials 6 EBL vs. NSSB±ISMN 4 EBL vs. EBL+ NSSB±ISMN 2 EBL+NSSB±ISMN vs. NSSB±ISMN Patients: 1,381 EBL vs. NSBB: 698 Combined vs. EBL: 404 Combined vs. NSSB±ISMN: 279 Disease stage: Child-Pugh B/C 70–80%	Rebleeding: EBL vs. NSSB±ISMN: RR 1.00 (95% CI 0.73–1.37) EBL vs. NSSB±ISMN when NSBB dose <80 mg/d: RR 0.67 (95% CI 0.49–0.91) EBL+ NSSB±ISMN vs. EBL; RR 0.57 (95% CI 0.31–1.08) EBL+ NSSB±ISMN vs. NSSB±ISMN: RR 0.76 (95% CI 0.56–1.03) Mortality: not significantly different Adverse events: events between EBL vs. NSSB±ISMN, but was higher with EBL+ NSSB±ISMN vs. EBL.
Funakoshi <i>et al.</i> 2010 ⁹⁵	EBL+ NSBB vs. EBL SCL+NSBB vs. SCL	Studies: 19 trials 4 SCL and 3 EBL Patients: 1,483 Disease stage: most Child-Pugh B; Child-Pugh C: 5–35%	Rebleeding: lower EBL group: OR 2.06 (95% CI 1.55–2.73, $p < 0.0001$) NSBB + SCL/EBL vs. only EBL/SCL reduced rebleeding: OR 2.20 (95% CI 1.69–2.85) Overall and Bleeding-related mortality: No significant difference Combination therapy lower overall mortality: OR 1.43 (95% CI 1.03–1.98) Adverse events (serious): NSBB: OR 2.61 (95% CI 1.60–4.40, $p < 0.0001$)
Thiele <i>et al.</i> 2012 ⁹	EBL + NSBB±ISMN vs. monotherapy (EBL or medical therapy alone)	Studies: 9 trials Patients: 955 442 combination vs. 513 monotherapy Disease stage: most Child-Pugh B; Child-Pugh C: 8–22%	Rebleeding: Combination therapy: RR 0.68 (95% CI 0.54–0.85, NNT: 8) Overall mortality: Combination: RR 0.89 (95% CI 0.65–1.21) Bleeding-related mortality: RR 0.52 (95% CI 0.27–0.99; NNT: 33). Adverse events: Combination: RR 1.38 (95% CI 1.13–1.68) Adverse events (serious): RR2.02 (95% CI 1.14–3.56)
Puente <i>et al.</i> 2014 ⁵⁵	EBL + NSBB± ISMN vs. either treatment alone	Studies: 9 trials 5 EBL vs. EBL + NSBB± ISMN; 4 NSBB± ISMN vs. EBL + NSBB± ISMN Patients: 885 476 + 409 Disease stage: most Child-Pugh B; Child-Pugh C: 13–31%	Rebleeding: Combination vs. EBL mono: RR 0.44 (95% CI 0.28–0.69) Combination vs. NSBB mono: RR 0.76 (95% CI 0.58–1.00) Overall mortality: Combination vs. EBL mono: RR 0.58 (95% CI 0.33–1.03) Combination vs. NSBB mono: RR 1.24 (95% CI 0.90–1.70) Adverse events: Combination: rebleeding from oesophageal ulcers increased ($p = 0.01$)

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Table 1 (continued)

Study Author, year (reference)	Arms	Patient and study number	Main results
Albillos <i>et al.</i> 2017 ⁵⁶	EBL+ NSBB vs. EBL or NSBB, stratified by cirrhosis severity (Child-Pugh A vs. B/C)	Studies: individual patient meta-analysis: 7 trials 3 EBL + NSBB vs. NSBB 4 EBL + NSBB vs. EBL Patients: 805 389 (vs. NSBB) + 416 (vs. EBL) Disease stage: Child-Pugh B/C: 54–89%	Rebleeding: EBL + NSBB vs. NSBB: IRR 1.00 (95% CI 0.68–1.47; $p = 0.996$), Child-Pugh A: IRR 0.40 (95% CI 0.18–0.89, $p = 0.025$); Child-Pugh B/C: IRR 1.36; (95% CI 0.87–2.14, $p = 0.180$) EBL + NSBB vs. EBL: IRR 0.36 (95% CI 0.21–0.59, $p < 0.001$) Overall mortality: EBL + NSBB vs. NSBB: IRR 1.19 (95% CI 0.76–1.87; $p = 0.449$) EBL + NSBB vs. EBL: IRR 0.50 (95% CI 0.28–0.89, $p = 0.019$)
Zacharias <i>et al.</i> 2018 ⁹¹	Information presented above in prevention of first bleeding		
Dwinata <i>et al.</i> 2019 ⁹²	Carvedilol vs. EBL	Studies: 3 trials Patients: 230 112 vs. 118 Disease stage: Child-Pugh B 9 (median)	Bleeding: Carvedilol: RR 1.10 (95% CI 0.75–1.61) Overall mortality: RR 0.51 (95% CI 0.33–0.79)
Malandris <i>et al.</i> 2019 ⁹³	Carvedilol vs. propranolol OR NSBB+ISMN OR EBL	Studies: 7 trials 3 EBL, 2 NSBBs + ISMN, 2 NSBB Patients: 614 Disease stage: most Child-Pugh B7–9	Rebleeding: Carvedilol vs. EBL: RR 1.10 (95% CI 0.75–1.61) vs. NSBBs+ISMN: RR 1.02 (95% CI 0.70–1.51) vs. propranolol: RR 0.39 (95% CI 0.15–1.03) Overall mortality: compared to EBL (3 RCTs), RR 0.51 (95% CI 0.33–0.79) Adverse events: No significant differences for safety compared with EBL and NSBBs

ARD, absolute risk difference; EBL, endoscopic band ligation; IRR, incidence rate ratio; ISMN, isosorbide mononitrate; NNH, number needed to harm; NNT, number needed to treat; NSBB, non-selective beta-blocker; OR, odds ratio; RR, risk ratio; SCL, sclerotherapy.

to whether they were receiving NSBBs or not at the time of transplant. NSBBs were associated with reduced mortality (HR 0.511; CI 0.3–0.87; $p = 0.014$).

Regarding studies including carvedilol, Leithead *et al.* evaluated 322 patients with ascites listed for liver transplantation and found a significantly lower waitlist mortality in NSBB users.⁴² The subgroup of patients receiving carvedilol (median

dose 6.25 mg/d) had a mortality risk between those on propranolol and those not receiving NSBBs. Sinha R *et al.*⁴⁴ analysed 264 patients with cirrhosis and ascites, 132 treated with carvedilol (median dose 12.5 mg), showing that long-term use of carvedilol was associated with a 41% mortality reduction in patients with mild ascites. In the subset of patients with moderate or severe ascites, carvedilol did not reduce mortality, but

Table 2. Appropriate dosing, targets and follow-up of available NSBBs for prevention of first bleeding episode in patients with high-risk varices and liver cirrhosis.

Beta-blocker	Dosing	Target	Follow-up
Propranolol	<ul style="list-style-type: none"> ✓ Start 20–40 mg orally <u>twice</u> a day ✓ Increase by 20 mg twice a day steps every 2–3 days until target; reduce gradually if intolerant ✓ Maximal dosage: <ul style="list-style-type: none"> - 320 mg/d (no ascites) - 160 mg/d (if evident ascites present) 	<ul style="list-style-type: none"> ✓ Resting heart rate of 55–60 bpm ✓ Avoid systolic pressure <90 mmHg ✓ Final dose tolerated 	<ul style="list-style-type: none"> ✓ Assess target heart rate and tolerance at each visit ✓ Lifelong, assess compliance ✓ No follow-up endoscopy required
Nadolol	<ul style="list-style-type: none"> ✓ Start 20–40 mg orally <u>once</u> a day ✓ 20 mg <u>once</u> a day increments every 2–3 days until target; reduce gradually if intolerant ✓ Maximal dosage: <ul style="list-style-type: none"> - 160 mg/d (no visible ascites) - 80 mg/d (visible ascites) 		
Carvedilol	<ul style="list-style-type: none"> ✓ Start with 6.25 mg <u>once</u> a day ✓ After 3 days increase to 6.25 mg <u>twice</u> a day ✓ Maximal dose: <ul style="list-style-type: none"> - 12.5 mg/d (if arterial hypertension, consider 25 mg/d) 	<ul style="list-style-type: none"> ✓ Avoid systolic blood pressure <90 mmHg ✓ Final dose tolerated 	<ul style="list-style-type: none"> ✓ Lifelong, assess compliance ✓ No follow-up endoscopy required

Table 3. Summary of the studies for and against NSBB use in different scenarios of advanced chronic liver disease.

Against NSBB use	For NSBB use
<p>Refractory ascites and ascites Sersté et al. Hepatol 2010¹¹ Population: 151 (77 NSBB) patients with cirrhosis and refractory ascites Aetiology: 56% alcoholic cirrhosis Dose NSBB (mean): propranolol (160 mg/d in 46.7% patients) Follow-up: 72 days Main result: Propranolol significantly associated with higher mortality rate. <i>Limitations:</i> High doses of Propranolol, single-centre <i>Strengths:</i> Prospective cohort</p>	<p>Leithead et al. Gut 2015⁴² Population: 322 (149 NSBB) patients with cirrhosis and ascites listed for transplantation Aetiology: 56% alcoholic cirrhosis Dose NSBB (median): propranolol (80 mg/d) carvedilol (6.25 mg/d) Follow-up: 72 days Main result: NSBB use reduced significantly transplant-free mortality <i>Limitations:</i> Retrospective, transplant setting <i>Strengths:</i> Propensity score matching</p>
<p>Sersté et al. J Hepatol 2011⁸¹ Population: 10 NSBB patients with cirrhosis and refractory ascites Aetiology: 7 patients with alcoholic cirrhosis Dose NSBB: 7 patients propranolol (160 mg/d) Follow-up: 9.9 months Main result: NSBB increase the risk of paracentesis-induced circulatory dysfunction but not to adverse clinical outcomes <i>Limitations:</i> small simple size, high doses propranolol <i>Strengths:</i> Prospective</p>	<p>Robins et al. Hepatol 2014⁷⁸ Population: 114 (34 NSBB) patients with cirrhosis and ascites Aetiology: 58% alcoholic cirrhosis Dose NSBB (mean): propranolol (48.9 mg/d) Follow-up: 10 months Main result: No significant difference in mortality between propranolol group and no propranolol group. <i>Limitations:</i> Retrospective, small sample <i>Strengths:</i> Appropriate doses of NSBB</p>
<p>Kalambokis et al. Hepatol 2016⁹⁶ Population: 171 (53 NSBB) patients with cirrhosis and ascites Aetiology: 64% alcoholic cirrhosis Dose NSBB: NR Follow-up: 3 years Main result: Propranolol was associated with increased mortality <i>Limitations:</i> Retrospective, unmatched <i>Strengths:</i> Long-term of follow-up</p>	<p>Bang et al. Liver Int 2016⁴⁰ Population: 3,719 (743 NSBB) patients with mildly and severely decompensated cirrhosis Aetiology: 97% alcoholic cirrhosis Dose NSBB (median): propranolol (97 mg/d) Follow-up: 24 months Main result: Significant reduced mortality was found for doses of propranolol lower than 160 mg/d only <i>Limitations:</i> Retrospective register <i>Strengths:</i> Large sample size</p>
<p>Kim et al. Liver Transpl 2017⁹⁷ Population: 205 (94 NSBB) patients developed AKI in waitlist register were matched to a case-control study Aetiology: 48% ALD/NASH patients Dose NSBB (median): propranolol 40 mg/d Follow-up: 12.8 months Main result: NSBB use in patients with ascites was associated with increased risk of AKI <i>Limitations:</i> Retrospective, many potential confounders <i>Strengths:</i> Appropriate doses propranolol</p>	<p>Bossen et al. Hepatol 2016⁴¹ Population: 1,198 (559 NSBB) cirrhosis patients with ascites (49% refractory ascites) Aetiology: 56% alcoholic cirrhosis Dose NSBB: NR Follow-up: 12 months Main result: NSBBs did not increase significantly cirrhosis-related mortality. <i>Limitations:</i> Post hoc analysis. <i>Strengths:</i> Prospective and Large sample size</p>
	<p>Aday et al. Am J Med Sci 2016³⁹ Population: 2,419 (1,039 NSBB) cirrhosis patients with varices or ascites Aetiology: 44% alcoholic cirrhosis Dose NSBB: NR Follow-up: NR Main result: Mortality was significantly lower in patients with cirrhosis taking NSBB than in those not taking NSBB <i>Limitations:</i> Retrospective <i>Strengths:</i> Large sample size</p>
	<p>Sinha et al. J Hepatol 2017⁴⁴ Population: 264 (132 NSBB) patients with cirrhosis and ascites from mild to severe Aetiology: 70% alcoholic cirrhosis Dose NSBB (median): carvedilol (12.5 mg)</p>

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Table 3 (continued)

Against NSBB use	For NSBB use
	<p>Follow-up: 27.6 months Main result: In mild ascites, use of carvedilol was associated with 43% reduction in mortality. In severe ascites, carvedilol use did not influence mortality <i>Limitations:</i> ascites severity was based on radiology reports. <i>Strengths:</i> Long-term of follow-up, carvedilol use</p>
	<p>Onali et al. Liver Int 2017⁷⁹ Population: 316 (128 NSBB) patients with cirrhosis and ascites (39% refractory ascites) on a transplant waiting list Aetiology: 42% alcoholic cirrhosis Dose NSBB (median): propranolol (180 mg/d) Follow-up (mean): 7 months Main result: NSBB use was associated with significantly reduced mortality <i>Limitations:</i> Retrospective, short follow-up <i>Strengths:</i> Well characterised population</p>
	<p>Bhutta et al. Aliment Pharmacol Ther 2018⁷⁷ Population: 717 (307 NSBB) patients with cirrhosis and ascites (51% refractory ascites) Aetiology: 33% alcoholic cirrhosis Dose NSBB (median): propranolol (40 mg/d), nadolol (20 mg/d) and carvedilol (12.5 mg/d) Follow-up (mean): 15 days Main result: NSBB use was not associated with an increased mortality. <i>Limitations:</i> Short follow-up <i>Strengths:</i> Large sample size</p>
	<p>Tergast et al. Aliment Pharmacol Ther 2019⁸⁰ Population: 624 (255 NSBB) cirrhosis patients with ascites Aetiology: 47 % alcoholic cirrhosis Dose NSBB (median): propranolol (30 mg/d) - carvedilol (12.5 mg/d) Follow-up: 28 days Main result: NSBBs were associated with a significant higher 28-day transplant-free survival. <i>Limitations:</i> Retrospective, short follow-up <i>Strengths:</i> Well characterized patients</p>
<p>Spontaneous bacterial peritonitis Mandorfer et al. Gastroenterol 2014³⁸ Population: 182 (86 NSBB) patients at the first diagnosis of SBP Aetiology: 60% alcoholic cirrhosis in NSBB group vs. 44% in non-NSBB group Dose NSBB: NR Follow-up: 9.6 months Main result: NSBBs increase risks for HRS and AKI, and reduced transplant-free survival. <i>Limitations:</i> Retrospective, unmatched. <i>Strengths:</i> Large sample</p>	<p>Bang et al. Liver Int 2016⁴⁰ Population: 361 patients with first peritonitis episode Aetiology: 97% alcoholic cirrhosis Dose NSBB (median): propranolol (97 mg/d) Follow-up: 24 months Main result: Significantly reduced mortality was observed in the propranolol group <i>Limitations:</i> Retrospective register <i>Strengths:</i> Large sample size</p>
	<p>Tergast et al. Aliment Pharmacol Ther 2019⁸⁰ Population: 257 patients developed SBP during hospitalisation Aetiology: 47% alcoholic cirrhosis Dose NSBB (median): propranolol (30 mg/d) - Carvedilol (12.5 mg/d) Follow-up: 28 days Main result: NSBB was associated with a higher 28-day transplant-free survival and only patients with SBP and MAP <65 mmHg was associated with renal impairment.</p>

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Table 3 (continued)

Against NSBB use	For NSBB use
Acute-on-chronic liver failure	<p><i>Limitations:</i> Retrospective, short follow-up</p> <p><i>Strengths:</i> Well characterized patients</p> <p>Mookerjee et al. J Hepatol 2016⁴³</p> <p>Population: 349 (155 NSBB) patients with ACLF</p> <p>Aetiology: 54% alcoholic cirrhosis</p> <p>Follow-up: 28 days</p> <p>Dose NSBB (median): propranolol (40 mg/d) - Carvedilol (12.5 mg/d)</p> <p>Main result: NSBB treatment was associated with significantly reduction in 28-day mortality</p> <p><i>Limitations:</i> NSBB group had lower grades of ACLF</p> <p><i>Strengths:</i> Prospective cohort, Large sample</p>

ACLF, acute-on-chronic liver failure; AKI, acute kidney injury; ALD, alcohol-related liver disease; HRS, hepatorenal syndrome; MAP, mean arterial pressure; NASH, non-alcoholic steatohepatitis; NR, not reported; NSBBs, non-selective beta-blockers; PH, portal hypertension; SBP, spontaneous bacterial peritonitis.

did not worsen prognosis. In the most recent study, 624 patients with ascites were analysed retrospectively.⁸⁰ Patients receiving NSBBs had a significantly higher 28-day transplant-free survival than patients not receiving NSBBs ($p = 0.014$). Results did not differ between patients on propranolol (median 30 mg/d) and those on carvedilol (median 12.5 mg/d). These results support that carvedilol at low doses (6.25–12.5 mg/d) is safe in patients with decompensated cirrhosis. In a more detailed analysis, the beneficial effect of NSBBs on survival was attenuated in patients with a low MAP (<82 mmHg) and was absent in patients with ascites and a MAP <65 mmHg; moreover, the latter group had increased rates of renal impairment. Thus, despite the benefits of NSBBs, patients with hypotension should be closely monitored and NSBB dose reduced or withdrawn if hypotension is severe.

Three recent meta-analyses of the mostly observational studies previously mentioned further concluded that NSBB use is not associated with increased mortality, including patients with mild and refractory ascites.^{83–85} There was significant heterogeneity across these studies. In summary, current evidence from observational studies does not support withdrawing NSBBs in patients with ascites or refractory ascites.^{76–78} Indeed, most studies observed a benefit, with increased survival in patients with refractory ascites treated with NSBBs.^{39,40,75,79,80}

At Baveno VI, when part of the aforementioned data was still unavailable, it was recommended that the NSBB dose should be reduced or discontinued in the case of hypotension (systolic blood pressure <90 mmHg), hyponatremia (serum sodium <130 mEq/L) or the development of acute kidney injury (AKI).²² It was further suggested that discontinuation of NSBBs should be temporary and that they should be carefully reinstated after resolution of the event.

Current EASL guidelines recommend that propranolol should not exceed daily doses >80 mg/d based on observational data⁽²³⁾. Although they do not recommend carvedilol in patients with ascites, several recent studies have emerged to support its use and safety at low doses (6.25–12.5 mg/d) in these patients.^{42–44,77,80} In light of the available evidence, in patients with refractory ascites, carvedilol can probably be used safely at low doses (6.25–12.5 mg/day), provided the patient maintains a systolic blood pressure over 90 mmHg. Nevertheless, the limits both for doses and for “safe” circulatory parameters are not currently evidence based, so further prospective studies assessing NSBB use in patients with

decompensated liver cirrhosis are still warranted to ascertain whether adverse effects are related to dosage or mainly depend on haemodynamic factors.

Spontaneous bacterial peritonitis

In a retrospective study including 607 patients at their first paracentesis, Mandorfer *et al.*³⁸ analysed 182 patients at the first diagnosis of SBP, suggesting that NSBB use was associated with poor outcomes in the subgroup of patients with SBP. These patients had more episodes of HRS and AKI, and decreased transplant-free survival. However, in this study, the subset of patients with SBP taking NSBBs also had higher total bilirubin levels and lower arterial blood pressure, as well as including a higher proportion of patients with Child-Pugh C cirrhosis. It is entirely speculative to ascribe NSBB use to the increased mortality rate, since this could well reflect end-stage liver disease, severe infection or a combination of different non-identified factors. In contrast, other studies failed to confirm a worse prognosis of patients under NSBBs.^{43,76,77} Bang *et al.*⁴⁰ analysed the largest series, with 361 patients with SBP and reported that NSBB use was associated with increased survival. Moreover, among patients with severely decompensated cirrhosis, NSBBs were associated with a lower risk of developing SBP. Thus, the data is controversial and no firm conclusions can be obtained. However, it is wise to carefully assess patients with SBP if they are receiving NSBBs and reduce their dose or stop their administration in cases of severe hypotension or severe AKI. Of note, NSBBs decrease the incidence of SBP, so they should not be prohibited in patients with ascites, even in those with previous SBP episode(s).⁸

Acute-on-chronic liver failure

Patients with ACLF present an inflammatory status that can be associated with renal failure and circulatory dysfunction, so a concern was raised with regards to NSBB use since these patients frequently have sepsis or AKI. Nevertheless,⁴³ a sub-analysis of the CANONIC study with 349 hospitalised patients with ACLF, showed that NSBB administration improved 28-day survival in patients with ACLF. A potential mechanism could be increased gut motility and reduced bacterial translocation known to be caused by beta-blockade, which in turn may decrease systemic inflammation. More recently, Tergast *et al.*⁸⁰ reported better survival in 254 patients with ACLF under NSBBs. NSBB use remained a positive prognostic factor after adjusting for potential confounders in a multivariate model,

while early interruption of NSBBs was associated with lower 28-day transplant-free survival. Consequently, there is no evidence for NSBB withdrawal in ACLF.

Table 3 describes the results, strengths and limitations of most recent studies for and against NSBB use in refractory ascites, SBP and ACLF in advanced cirrhosis. Most of the evidence comes from observational studies, as no specific RCT of NSBB use has been carried out in these scenarios. As a result, these studies are prone to many potential biases: short follow-up duration (median 28 days to 27 months); heterogeneous population (discrepant definitions for refractory ascites and AKI, and different NSBB doses); lack of information on titration strategy, and policy for stopping/resuming NSBBs.

Moreover, these studies have an important inherent bias when comparing patients receiving NSBBs or not. Patients on NSBBs tend to have more advanced cirrhosis and higher prevalence of high-risk varices than those not receiving NSBBs. This bias is difficult to avoid without randomisation, despite the use of propensity scores or multivariate analysis.⁸⁶ Nevertheless, evidence from these studies strongly suggests that NSBBs are not absolutely contraindicated in patients with ascites, refractory ascites, SBP and ACLF,^{76–78} and 3 independent meta-analyses confirmed this data.^{83,84,87}

Non-response to non-selective beta-blockers

Currently with carvedilol as an alternative to propranolol, only a small proportion of patients remain haemodynamic non-responders. Since measurements of HVPG are not done routinely in clinical practice, the decision to use NSBBs is based on its known beneficial effects and the absence of

contraindications. The advent of agents more effective than propranolol, such as carvedilol, could potentially render haemodynamic monitoring unnecessary even in clinical trials. Non-invasive markers to monitor beta-blocker response are still currently unavailable.

For secondary prophylaxis, in patients receiving NSBBs plus EBL (complemented or not with low doses of a lipophilic statin, such as simvastatin), TIPS is the best rescue treatment. Primary prophylaxis failures treated with either NSBBs or EBL have no current recommended treatment option due to the lack of RCTs in this setting. De Souza *et al.*⁸⁸ analysed 89 patients and found an increased risk of rebleeding and death in patients with an index bleed while under NSBBs. These patients (clinical NSBB non-responders) might benefit from more aggressive therapy, such as TIPS, particularly if the patients have high-risk features, namely, ascites or portal vein thrombosis, and an absence of contraindications.²⁴

Conclusions

In summary, the indication to start NSBBs has expanded recently beyond the setting of PH-associated bleeding to prevention of decompensation in patients with compensated cirrhosis. Doses must be titrated and re-evaluated in all patients, particularly those with decompensated cirrhosis and with deteriorating liver failure. Data from observational studies are contradictory regarding the safety of NSBBs in patients with refractory ascites or infection. Future RCTs should include patients with decompensated cirrhosis to assess efficacy, dose tolerance limits, and safety.

Abbreviations

ACLF, acute-on-chronic liver failure; AKI, acute kidney injury; ALD, alcohol-related liver disease; ARD, absolute risk difference; AV, atrio-ventricular; EBL, endoscopic band ligation; GOV, gastroesophageal varices; HRS, hepatorenal syndrome; HVPG, hepatic venous pressure gradient; IGV, isolated gastric varices; IRR, incidence rate ratio; ISMN, isosorbide mononitrate; MAP, mean arterial pressure; NASH, non-alcoholic steatohepatitis; NNH, number needed to harm; NNT, number needed to treat; NR, not reported; NSBBs, non-selective beta-blockers; OR, odds ratio; PH, portal hypertension; PHG, portal hypertensive gastropathy; RCT, randomised controlled trials; RR, risk ratio; SBP, spontaneous bacterial peritonitis; SCL, sclerotherapy; TIPS, transjugular intrahepatic portosystemic shunt.

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Conflict of interest

The authors declare no conflicts of interest that pertain to this work.

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Authors' contributions

SGR and YPM performed the systematic review of the literature and drafted the manuscript. JB supervised, drafted and revised the manuscript.

Supplementary data

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