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REVIEW

Non-selective beta-blockers in cirrhosis: Current concepts and controversies

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Abstract

Non-selective beta-blockers (NSBBs) have been at the forefront in the management of portal hypertension in liver cirrhosis for the last three decades, a trusty component in the armamentarium of the Hepatologist. The role of beta-blockers has been cemented for years in cardiac disease including angina, hypertension and in heart failure, however NSBBs with their non-selective effects on β1 and β2 receptors have led to them fondly being termed "the hepatologist's aspirin". NSBBs' role in reduction of portal pressure in the setting of primary and secondary prophylaxis for variceal haemorrhage has been well established. NSBBs include propranolol, nadolol and carvedilol - with the latter having been shown to be effective in patients who often fail to demonstrate a haemodynamic response to propranolol. Recent observational studies however have served for the Hepatology community to question the beneficial role of NSBBs in portal hypertension, especially in advanced cases with refractory ascites. The deleterious effect in patients with refractory ascites in a few studies led to a U-turn in clinical practice, with some in the Hepatology community withdrawing their usage in patients with advanced cirrhosis. This also led to the "window hypothesis" suggesting there may be only be a finite time frame when NSBBs have a beneficial effect in portal hypertension. The window hypothesis proposed the window for the benefits of NSBBs is closed in early portal hypertension, opening as portal hypertension progresses with it closing in advanced liver disease. The window was proposed to close in conditions such as refractory ascites or spontaneous bacterial peritonitis when patients may not necessarily mount a compensatory haemodynamic response when on NSBBs. Some centres however have continued the practice of NSBBs in advanced cirrhosis with published data challenging the scepticisms of other groups who stop NSBBs. Thus the debate, like the window hypothesis has opened, with more questions to be answered about NSBB's mechanism of action not only in reducing portal hypertension but also their effects on systemic haemodynamics and on the pro-inflammatory pathways often activated in cirrhosis especially in advanced disease. This article serves to review the role of NSBBs in the management of portal hypertension/cirrhosis and concentrate on current concepts and controversies in this field.

Key words: Variceal haemorrhage; Non-selective beta-

blockers; Portal hypertension; Liver cirrhosis

Core tip: This article serves to discuss the changing role of non-selective beta-blockers in liver disease and portal hypertension. For many years non-selective beta-blockers have been at the forefront in reducing portal hypertensive complications such as variceal haemorrhage, however recent data has questioned their role in advanced liver disease. This article reviews their role in portal hypertension, discusses recent advances in the field and reviews the controversy recently generated regarding their role in advanced liver disease.

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INTRODUCTION

Liver cirrhosis is a major cause of morbidity and mortality throughout the world[1,2], with the advent of portal hypertension one of the key defining steps leading to the complications that can develop in advanced liver disease. The role of non-selective beta-receptor antagonists [non-selective beta-blockers (NSBBs)] has been well established over the years in the Hepatologist's armamentarium against portal hypertension and its consequences. NSBBs have been used routinely in practice with beneficial roles in primary and secondary prophylaxis in patients with medium to large oesophageal varices[3-5]. The development of portal hypertension is the key defining step leading to complications that can occur in patients with liver cirrhosis irrespective of aetiology. Consequences can include variceal haemorrhage, ascites formation [and thereafter a risk of the development of spontaneous bacterial peritonitis (SBP)] and hepatic encephalopathy. Portal hypertension develops from a combination of a rise in the intrahepatic resistance but also from splanchnic vasodilatation and the hyperdynamic circulation that occurs in cirrhosis. It has been shown that rupture of varices is related to tension on the variceal wall, with the tension dependent on the radius[6]. There has been no linear relationship found between the severity of portal hypertension and the risk of variceal haemorrhage however a hepatic venous pressure gradient (HVPG) > 12 mmHg has become an accepted threshold for variceal bleeding[7,8]. As liver disease progresses and portal hypertension worsens, ascites can form, bacterial translocation from the gut occurs and patients can become prone to complications such as infection that can in turn lead to increases in portal pressure and thus variceal haemorrhage. Thus reduction of portal pressure is key in preventing complications of cirrhosis including reduction of ascites, hepatic encephalopathy and variceal haemorrhage[9-11]. Whilst portal hypertension can be reduced by radiological methods such as transjugular intrahepatic portosystemic shunts (TIPSS), NSBBs have been the key pharmacological therapy in reduction of portal pressure over the years. The role of selective beta-blockers in cardiac disease has been cemented for years, including in acute coronary syndrome[12], hypertension[13] and congestive cardiac failure[14]. NSBBs used in liver disease however act by dual blockage of β1 and β2 receptors unlike their cardio-selective counterparts. NSBBs reduce cardiac output (CO) and splanchnic blood flow *via* blockade of the β1 receptor, and by blocking β2 result in a splanchnic vasoconstriction *via* unopposed α1 activity[15]. NSBBs have been used to decrease the incidence of 1st variceal haemorrhage in patients with cirrhosis (*i.e.,* primary prophylaxis)[3-5] and then to prevent rebleeding after a variceal haemorrhage (*i.e.,* secondary prophylaxis)[16-18]. Propranolol has been the mainstay of NSBBs used in chronic liver disease for years, however more recently carvedilol, with its intrinsic α1-adrenergic activity has been studied and found to be useful even in settings where patients have failed to demonstrate an appropriate haemodynamic response to propranolol[19] thus providing an additional or alternative therapy for reduction of portal pressure.

There has however been a recent concern about the role of NSBBs in advanced liver disease and especially in patients with refractory ascites, with one group raising concerns showing an increase in mortality in this setting[20]. This issue led to the "window" hypothesis, suggesting that there may be a finite time frame when NSBBs have a favourable effect in chronic liver disease, with their effects becoming deleterious and the window closing in advanced disease states[21]. However, recent data from our own centre has argued against this, with beneficial findings of NSBBs in patients with ascites on a liver transplant waiting list even in those patients with refractory ascites[22]. Furthermore, favourable data on the role of NSBBs in alcoholic hepatitis[23] and acute on chronic liver failure (ACLF) has recently emerged[24]. Thus, there still remains controversy of how safe and effective are NSBBs in advanced cirrhosis, with further studies required to address this debate.

A PubMed search was performed using the following keywords: "non-selective beta-blockers" and "variceal haemorrhage cirrhosis". From this search 2965 articles were found. This search was complemented by a search of the keywords using www.google.com™. One hundred and eighteen papers/abstracts were studied for the preparation and writing of this review article. This review article serves to explore the role of NSBB in portal hypertension and liver cirrhosis, to review their mechanism of action and to review the favourable and negative data pertaining to their roles in liver disease. The article will review the recent controversies with NSBB in advanced liver disease, and proposes some thoughts on future directions of NSBB usage and studies potentially required to answer the question if NSBBs can remain as the Hepatologist's aspirin?

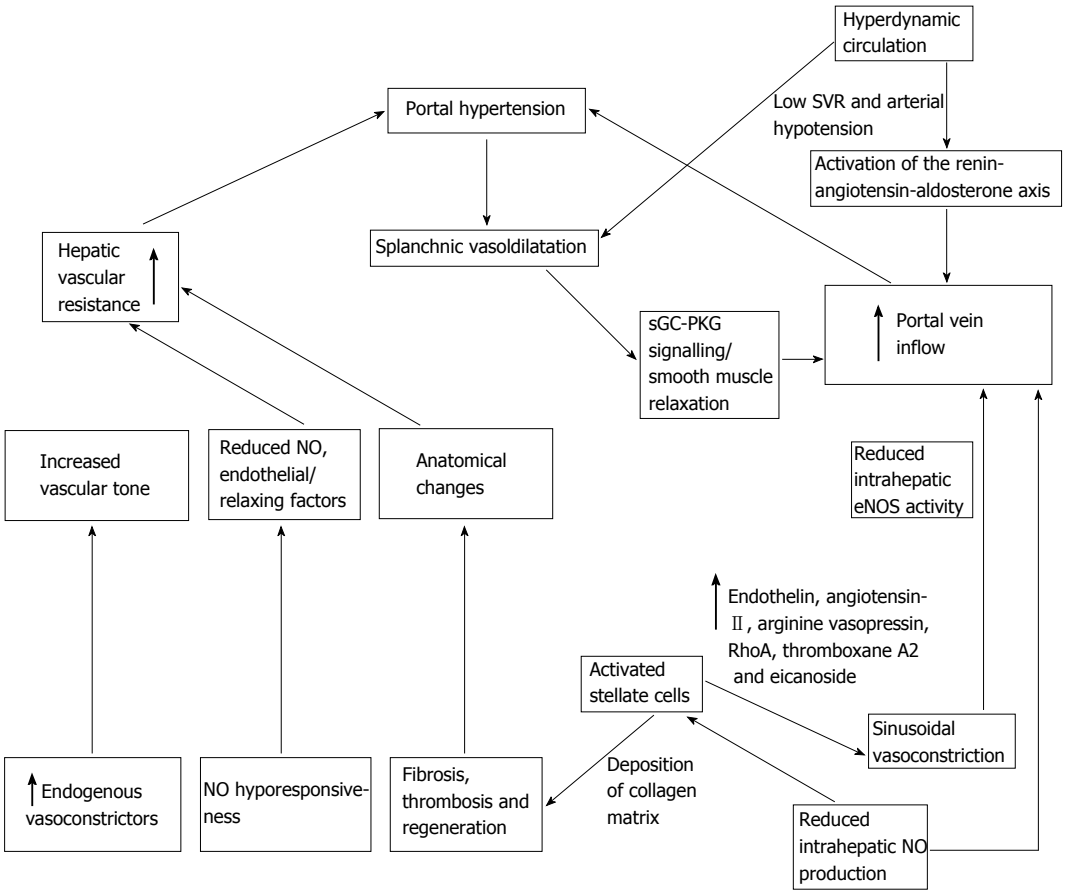

Figure 1 Factors involved in the pathogenesis of portal hypertension. A mechanical obstruction due to fibrosis or regenerative nodules results increased resistance to flow and a rise in hepatic vascular resistance. Contraction of sinusoidal and extra sinusoidal contractile cells (stellate cells) with intrahepatic imbalance between vasoconstrictors (such as endothelin-1 and angiotensin) and vasodilators (*e.g.*, NO) leads to reduced intrahepatic eNOS activity leading to an increase resistance to portal inflow. Portosystemic collaterals develop with the aim of decompressing the portal circulation. However, the opposite occurs, with splanchnic vasodilatation in response to a relatively ischaemic liver or extrahepatic excess of NO, with sGC-PKG signalling and smooth muscle cell relaxation. The increased portal blood flow maintains portal hypertension. A hyperdynamic circulation results due to these haemodynamic changes in cirrhosis and portal hypertension. eNOS: Endothelial nitric oxide synthase; NO: Nitric oxide; SVR: Systemic vascular resistance; sGC-PKG: Soluble guanylyl cyclase-cGMP-dependent protein kinase.

PORTAL HYPERTENSION: THE KEY TARGET FOR NSBBS

The development of portal hypertension is the key factor leading to decompensation of liver disease such as variceal haemorrhage, ascites formation (with the inherent risk of development of SBP thereafter) and also hepatic encephalopathy[25]. Portal hypertension results from 2 major events: An increase in the intra-hepatic vascular resistance and also an increase on portal venous inflow (Figure 1). Increased intrahepatic resistance can result of a number a pathophysiological mechanisms occurring in liver disease. Structural fixed anatomical changes can result in up to 70% of the cause of intrahepatic resistance increasing[26] with the suggestion that the other 30% the result of an increase in vascular tone. Anatomical disruption within the liver develops by the activation of stellate cells, which in turn, leads to sinusoidal capillirisation. Stellate cells are found in the perisinusoidal space (Space of Disse) within the liver. These cells are the major cell subset involved in liver fibrosis. In health, stellate cells are in an inactivated quiescent state, however when the liver is injured the stellate cells become activated and secrete collagen scar tissue. A reduction in the nitric oxide (NO) production by sinusoidal endothelial cells furthermore causes activation of stellate cells. The stellate cells once activated are the key mediator in the extracellular matrix production[27]. Over time, the formation of fibrous septae and also nodular regeneration leads to alteration of the hepatic architecture, and micro-portal and hepatic venule thrombosis also leads to an increase in the intra-hepatic resistance[28]. All these factors lead to a fixed component of the rise in portal pressure. It is clear that anatomical changes at present are a fixed component in the development of portal hypertension, abrogated by either replacement of full liver tissue (*e.g.,* by liver transplantation), or by bypassing the fixed anatomical restriction (*e.g.,* by a TIPSS). Research strategies are ongoing to modulate the scarring/fibrosis pathways to try to address this "fixed" component at present of portal hypertension[29].

The other more dynamic component to the development of portal hypertension is the change in the vascular tone and portal inflow increase. In cirrhosis activated stellate cells cause sinusoidal vasoconstriction due to an increase in

Table 1 Changes in measurement of portal haemodynamic pressures with different types of portal hypertension

Type of portal hypertension	Example	FHVP	WHVP	HVPG
Pre-hepatic	Portal/splenic vein thrombosis	Normal	Normal	Normal
Pre-sinusoidal	Primary biliary cirrhosis, schistosomiasis, sarcoidosis	Normal	Normal	Normal
Sinusoidal	Alcoholic hepatitis, NASH/alcoholic/viral cirrhosis	Normal	Increased	Increased
Post-sinusoidal	Sinusoidal obstruction syndrome	Normal	Increased	Increased
Post-hepatic	Budd Chiari[1]	-	-	-
	Heart failure	Increased	Increased	Normal

[1]Denotes hepatic vein not cannulated to measure. NASH: Non-alcoholic steatohepatitis; HVPG: Hepatic venous pressure gradient; FHVP: Free hepatic vein pressure; WHVP: Wedged hepatic vein pressure.

vasoconstrictive mediators such as endothelin, angiotensin-Ⅱ, arginine vasopressin, RhoA, thromboxane A2 and eicanoside[30-33]. There is also decrease in the vasodilators at a sinusoidal level such as NO - a key vasodilatory mediator in the portal venous system[34] and glucagon. Thus an imbalance exists leading to a reduction of intrahepatic endothelial Nitric Oxide synthase activity, leading to an increase in portal inflow. This mechanism is modifiable *via* NSBBs as is the other major component in the development of portal hypertension - the increased portal inflow (Figure 1).

Ohms law states that the change in pressure (P1-P2) along a blood vessel is a function of the resistance (R) and the rate of blood flow (Q), expressed as P1-P2 = R × Q. In healthy individuals, the liver accommodates changes in blood flow throughout the day and the liver itself is a very low resistance organ. The liver accommodates changes in blood flow without increasing the portal pressure by reducing the pressure in the liver by the recruitment of additional hepatic sinusoids. Thus (P1-P2) does not increase as Q increases but R falls. When Ohms law is applied in advancing liver disease, there is an increase in (intra-hepatic) resistance (R) leading to a rise in pressure (P1-P2), and the formation of porto-systemic collaterals to decompress the higher pressure. Also due to a hyperdynamic circulation there can be an increase in Q, again leading to an increase in (P1-P2) in Ohms law.

Splanchnic vasodilatation occurs as a response to a relatively ischaemic liver or due to extrahepatic excess of NO. This results in soluble guanylyl cyclase-cGMP - dependent protein kinase signalling and smooth muscle cell relaxation[35]. The resultant increased portal blood flow maintains portal hypertension and the hyperdynamic circulation results due to these haemodynamic changes in advancing liver disease. This manifests as a high CO with low systematic vascular resistance (SVR) and arterial hypotension[36]. The hyperdynamic splanchnic circulation (leading to increased portal inflow) is thus one of the key factors involved in the maintenance of portal hypertension and an area where NSBB have a key mechanism of action. The circulatory disturbances that arise (including reduction in CO, increase in heart rate and decrease in mean arterial pressure (MAP) and a reduction in the SVR) can lead to activation of the sympathetic nervous system and also the renin-angiotensin system in an attempt to counteract low arterial pressure[37]. There is an increase thus in not only sodium retention but also total body water retention (often leading to a dilutional hyponatraemia) and plasma/blood volume. Despite this, patients with cirrhosis and advanced disease have a reduced effective arterial blood volume[38,39] which can lead to organ hypoperfusion and problems with hepatorenal syndrome (HRS), or when infection takes hold with further arterial vasodilatation. Also patients can thus encounter problems with paracentesis-induced circulatory dysfunction (PICD) when ascitic fluid is removed without adequate plasma expansion replacement. With this pathophysiology, it is here that NSBBs indeed may have a beneficial effect in portal hypertension but also may worsen advanced systemic haemodynamic changes in end stage disease[40].

Markers for NSBB effectiveness not only include clinical endpoints such as prevention of variceal haemorrhage or rebleeding from varices, but reductions of portal pressure. Portal pressure measurements can be directly derived from the HVPG (normal range 1-5 mmHg). The HVPG can be measured by advancing a catheter either by a transfemoral or transjugular route into the hepatic vein and here a free hepatic vein pressure (FHVP) is measured. A balloon is then used to wedge the catheter in the hepatic vein and a second pressure is taken [the wedged hepatic vein pressure (WHVP)]. The WHVP reflects sinusoidal pressure. Thereafter the HVPG can be calculated (HVPG = WHPG - FHVP)[41]. The differences between these components depending on the type of portal hypertension are summarised in Table 1. Varices have been shown to be more likely to develop when the HVPG > 10 mmHg[42]. To effectively reduce the risk of variceal haemorrhage, the drop in portal pressure (as measured by the HVPG) must be reduced to < 12 mmHg or by 20%[43] thus allowing a surrogate marker for NSBB effectiveness in any clinical trial or occasionally in clinical practice when indicated.

NSBB - MECHANISM OF ACTION AND FAVOURABLE EFFECTS IN CHRONIC LIVER DISEASE

NSBB: Mechanism of action

NSBBs and their use in liver disease stems back over 3 decades[3] with a well understood mechanism of action

in reducing portal hypertension. NSBBs effects are not only *via* a β1-receptor to reduce the cardiac output and splanchnic blood flow[44,45] but also an additional action *via* β2 receptor blockade, blocking the adrenergic dilatory tone in mesenteric arterioles, thus resulting in an unopposed α-adrenergic vasoconstriction and subsequent reduction in portal blood flow. This "β-2" effect occurs after chronic usage[4]. This dual action is very much different to their counterparts used in cardiac disease such as metoprolol or atenolol that have been shown to be less effective than the NSBBs and thus not recommended in portal hypertension[46,47]. NSBBs include propranolol, nadolol and carvedilol. Propranolol has been used since the original study by Lebrec *et al*[48] in the 1980s however its effect of HVPG reduction can be variable with up to 31% reduction seen in some studies[15]. Up to a third of patients however do not have an adequate haemodynamic response to propranolol despite reductions in azygous flow[49]. Nadolol is another NSBB used with a longer half-life than propranolol due to low lipid solubility and hepatic metabolism[50] which allows for a once-a-day regime as appose to the twice a day of propranolol. It has a similar haemodynamic effect as propranolol[51]. Timolol is another NSBB like nadolol with low lipid solubility, and a greater affinity for β-1 and β-2 receptors[50]. However there is a paucity of comparative data in the setting of this drug in portal hypertension[52].

Carvedilol is one of the new generations of NSBBs with promising data in the setting of portal hypertension. It has an additional vasodilating action due to unopposed alpha-1-receptor blockade. This additional blockade results in a reduction of portocollateral resistance, and a reduction of intrahepatic resistance *via* an effect on hepatic stellate cells[15]. It has been found to be 2-4 times more potent action compared to other NSBBs at a receptor blockade[15]. Carvedilol is protein bound thus in patients with cirrhosis and hypoalbuminaemia there can be an increased bioavailability of it. It has anti-inflammatory, anti-oxidant[53] properties and also an antifibrotic effect[54] along with other roles in enhancing insulin sensitivity and improving mitochondrial function[55]. The role of carvedilol in reducing portal pressure has been compared to other NSBBs. It has been found after chronic usage to reduce HVPG[56] with more patients having a haemodynamic response when compared to propranolol[57]. In another study from Reiberger *et al*[19] the benefits of carvedilol were established in those not responding to propranolol. In this study, 56% of patients who did not respond to propranolol showed a haemodynamic response to carvedilol. There was a drop in HVPG of -19% in the carvedilol group *vs* -12% in the propranolol group. Thus there may indeed be a subset of patients deemed propranolol "haemodynamic non-responders" who are at risk of bleeding despite being on NSBB. Further studies are thus required to assess if carvedilol should be used as first line, or whether all patients on propranolol should have (ideally non-invasive) an assessment for haemodynamic response in the clinical setting and then switched to carvedilol if indeed a "non-responder". Carvedilol has also been compared to variceal band ligation (VBL) in the prevention of 1st variceal haemorrhage with medium or large varices[58]. The NSBB group had lower rates of 1st variceal bleed of 10% *vs* 23% in the band ligation group on intention-to-treat analysis, although there was no difference in mortality or bleeding related mortality between the groups. In this study carvedilol was well tolerated[58] at dose of 12.5 mg and higher doses have shown to have no additive effect in reduction of portal pressure from this dose[19].

Another area of benefit of NSBBs in patients with portal hypertension may indeed include reducing in bacterial translocation. In mice models, propranolol treated mice have been shown to not only have significantly lower portal pressures, but faster intestinal transit times and also lower rates of bacterial overgrowth and translocation[59]. In a meta-analysis by Senzolo *et al*[60], 644 patients (257 propranolol-treated) were evaluated (73% with ascites). The end-point of advent of SBP was used in the 3 randomised controlled trials (RCTs) and 1 primary prophylaxis study, and a statistically significant difference of 12.1% ($P < 0.001$) in favour of propranolol in preventing SBP was found. The beneficial effects were found irrespective of fall of portal pressure measurements thus suggesting an independent effect of NSBB in prevention of SBP irrespective of their benefits in reduction of portal pressure. Reiberger *et al*[61] have recently shown that NSBB therapy decreases intestinal permeability and plasma LPS-binding protein (LBP - a soluble acute phase response protein) and interleukin-(IL-)6 (a pro-inflammatory cytokine related to fever generation and related to such conditions as Systemic Lupus Erythymatosis and Rheumatoid arthritis[62,63]) with higher levels of IL-6/LBP associated with a higher risk of variceal bleeding on follow-up but not mortality. Thus NSBBs have a number of different mechanisms whereby they may indeed have benefit in patients with portal hypertension especially when varices develop (Table 2).

Clinical indications: Oesophageal varices

In the seminal Phase-Ⅲ study of NSBBs in patients with oesophageal varices by Lebrec *et al*[3] 74 patients who had a variceal 1st (index) bleed were randomised to either treatment with propranolol orally or placebo with 96% of the NSBB group free from bleeding at 1 year compared to 50% patients in the placebo group ($P \leq 0.0001$). The role of NSBBs in prevention of 1st variceal haemorrhage (*i.e.,* primary prophylaxis) was studied with Pascal *et al*[4] randomising 230 patients with large oesophageal varices (with no history of previous bleeding) to propranolol or placebo and finding 74% *vs* 39% free from bleeding at 1 year respectively ($P < 0.05$). There was also a survival advantage in the NSBB arm (72% *vs* 51% placebo, $P < 0.05$) thus showing a definite role in primary prevention, echoed thereafter in a number of studies including other NSBBs such as nadolol[64,65]. A meta-analysis of 9 placebo-controlled trials (964 patients) found the -11% (95%CI: -21% to -1%) for bleeding and -9% (95%CI: -18% to -1%) for death when propranolol was

Table 2 Types of non-selective beta-blocker used in cirrhosis

	Propanolol	Carvedilol	Nadalol
Proposed mechanism of action	β-1 activity to reduce cardiac output and reduce portal blood flow through splanchnic vasoconstriction *via* β-2 blockade	β-1 activity to reduce cardiac output and reduce portal blood flow through splanchnic vasoconstriction *via* β-2 blockade. Additional intrinsic α1-adrenergic activity	β-1 activity to reduce cardiac output and reduce portal blood flow through splanchnic vasoconstriction *via* β-2 blockade
Side efffects/cautions[1]	Hypotension, bradycardia, caution in peripheral vascular disease/asthma. To be discontinued at time of SBP, renal impairment and hypotension[1]	Hypotension (more profound than others), bradycardia, caution in peripheral vascular disease/asthma. To be discontinued at time of SBP, renal impairment and hypotension[1]	Hypotension, bradycardia, caution in peripheral vascular disease/asthma. To be discontinued at time of SBP, renal impairment and hypotension[1]
Indications	Primary prophylaxis of variceal haemorrhage (Level 1A, grade A). In combination with VBL for secondary prevention (Level 1a, grade A)[2]	Primary prophylaxis of variceal haemorrhage (Level 1a, grade A). In combination with VBL for secondary prevention (Level 1b, grade B)[2]	Primary prophylaxis of variceal haemorrhage (Level 1a, grade A). In combination with VBL for secondary prevention (Level 1a, grade A)[2]
Dose	40 mg BD if tolerated or once HR < 50-55 bpm	12.5 mg OD if tolerated or once HR < 50-55 bpm	40mg OD (maximum dose 240 mg) or once HR < 50-55 bpm
Mode of administration	Oral	Oral	Oral

[1]For consideration of re-introduction after acute event and depending on clinical judgement; [2]NSBB combined with VBL as standard of care in secondary prevention[23,65]. BD: Bi-daily; OD: Once daily; SBP: Spontaneous bacterial peritonitis; VBL: Variceal band ligation; NSBB: Non-selective beta-blocker.

compared to placebo[66]. Primary prophylaxis of variceal haemorrhage with a NSBB is thus recommended at present in patients with medium/large varices[25,67].

The role of NSBBs in primary prophylaxis in patients with no varices or small varices has also been studied. In a RCT patients with small varices were studied and in the group receiving NSBB actually developed more varices in the NSBB arm[68]. In another trial[69], nadolol reduced the incidence of variceal bleeding when compared to placebo but had no survival benefit and more side effects. In another study of NSBBs in an unselected group of patients with chronic liver disease (without cirrhosis or varices in some patients) no benefit was found in the use of NSBBs[70] in prevention of 1st variceal bleed or survival. Another RCT looked at the role of Timolol *vs* placebo in patients without varices but portal hypertension (HVPG > 6 mmHg) and found no difference in variceal bleeding rates, and in fact more side effects of patients on NSBBs[42]. In a meta-analysis of 6 RCTs of cirrhotic patients with small or no varices, incidence of large varices, 1st upper gastrointestinal bleed and death were similar between placebo and NSBB groups[71]. Thus NSBB are not currently recommended for primary prophylaxis in patients without endoscopic evidence of varices or small varices[25,67]. Combination of NSBB and Isosorbide Mononitrate (ISMN - another vasodilator used in patients with angina) has been studied in the setting of primary prophylaxis for variceal bleeding. Nadolol alone *vs* nadolol and ISMN was studied in a RCT, with combination therapy leading to reduced frequency of bleeding however no significant differences in mortality[72]. These findings were not echoed however in a double-blind RCT comparing propranolol and ISMN *vs* propranolol and placebo[73]. With a potential for increased side effects due to hypotension, this strategy is thus currently not recommended for primary prophylaxis[67].

The role of NSBBs in secondary prevention of variceal haemorrhage after an index (1st) variceal bleed has become established over the years[74-76]. A meta-analysis of NSBB (nadolol or propranolol in 12 trials) compared to no treatment found a significant reduction in rebleeding but no mortality benefit[77,78]. The addition of ISMN in a secondary prophylaxis role has shown improved varcieal rebleeding rates in one study[79], but no survival benefit. In a meta-analysis of ISMN alone *vs* ISMN with NSBB or endoscopic therapy showed there was no mortality benefit from combination of ISMN/NSBB than NSBB monotherapy[80]. There have been a number of studies and meta-analysis comparing combined endoscopic VBL and NSBB and monotherapy with either. A large meta-analysis of 23 trials of either VBL or injection sclerotherapy in combination with NSBB concluded that combination therapy led to reduced rebleeding than either NSBB alone or endoscopic therapy alone, however no difference in mortality was found[81]. There has been a number of meta-analysis of numerous trials since then with differing results on combination therapy affecting mortality but a clear benefit in reduction of rebleeding[17,82-84]. A recent multicentre RCT from Stanley *et al*[85] compared carvedilol to VBL in rebleeding and although found a tendency towards improved survival in the carvedilol arm, there was no statistically significant difference in rebleeding rates or mortality (P = 0.857 and P = 0.110, respectively). Combination therapy of VBL and NSBB (propranolol or nadolol) is however now recommended for prevention of variceal rebleeding[25,67].

NSBBs clinical indications: Gastric varices

NSBBs have also been studied in the setting of gastric varices, which historically are known to bleed at a lower portal pressure than their oesophageal counterparts with poorer outcomes[86]. Mishra *et al*[87] studied the role of NSBB (*vs* glue therapy) in primary prophylaxis, comparing them to injection therapy with N-Butyl-2-

Cyanoacrylate glue therapy in the prevention of rebleeding of gastric varices. In 67 patients, the group receiving injection therapy after index bleed had a lower rebleeding rate and lower mortality when compared the NSBB group (15% *vs* 55%, $P = 0.004$ and 3% *vs* 25%, $P = 0.024$ respectively). In another paper in the setting of gastric varices, Hung *et al*[88] compared the effects of endoscopic injection obturation therapy alone compared to that of obturation combined with NSBB in 95 patients after a gastric variceal haemorrhage. Overall rebleeding and survival rates were not different between the two groups ($P = 0.336$ and 0.936, respectively), thus the optimal role of NSBB in patients after an index gastric variceal haemorrhage remains in question. The British Society of Gastroenterology (BSG) recent guidelines[67] stated that NSBB treatment could be considered in selected high risk patients with large gastro-oesophageal type 2[86] (extending down from the oesophagus below the gastro-oesophageal junction into the fundus) after "taking into account the patient's preferences and clinical judgment".

NSBB: THE CURRENT CONTROVERSIES

NSBBs: A deleterious role in advanced cirrhosis?

With the role of NSBBs in portal hypertension and variceal haemorrhage prevention established, the tide however has changed in the last few years with a series of high profile publications questioning their safety in advanced cirrhosis[20,21,89,90]. The detrimental effect of NSBB in patients with ascites was initially provoked in a study by Bañares *et al*[57] with the aim of the study to explore the role of NSBBs in reducing HVPG when patients randomized to carvedilol or propranolol, with the former showing a greater reduction in HVPG (19% ± 2% *vs* -12% ± 2%, $P = 0.001$). There was however a tendency towards an increase in the dose of diuretics required in the carvedilol arm (27% *vs* 8%, $P = 0.07$), suggesting that carvedilol may worsen ascites. As cirrhosis progresses after the development of varices, ascites later can form as the disease gets more advanced as proposed by D'Amico *et al*[75]. Thus with a suggestion of ascites being worsened by NSBB in the study by Bañares *et al*[57], the role of NSBBs in advancing cirrhosis was studied in more detail.

The potential detrimental effect of NSBB in the setting of patients with ascites undergoing a large volume paracentesis (LVP) was studied by Sersté *et al*[89]. In this cross over trial of 10 patients, haemodynamics and plasma renin levels were assessed pre-, immediately post- and 7 d post- LVP in patients on propranolol. The NSBB was phased out and then measurements repeated in a similar fashion. When on NSBB immediately post-LVP the HR did not change ($P = 0.61$) however the MAP significantly fell ($P = 0.007$). When off NSBB, immediately post-LVP the MAP significantly fell again ($P = 0.003$) however with a significant rise in HR ($P = 0.001$). The authors proposed that immediately post-LVP that NSBB may indeed cause a PICD with a lack of rise of compensatory HR in patients on NSBB, which may account for a degree of tissue hypoperfusion. Thus it was proposed that NSBB may indeed contribute to PICD in patients on NSBBs. It is however worth noting that these findings were not replicated in another study[91] exploring the relationship between changes in HVPG induced by NSBB and the development of ascites in compensated cirrhosis (with severe portal hypertension). Eighty-three patients without any previous decompensation of cirrhosis, HVPG ≥ 12 mmHg and large oesophageal varices were included. Haemodynamic studies prior to NSBB (nadolol) were performed and then repeated at 1-3 mo later. This group showed that patients in whom NSBB reduced HVPG by ≥ 10% ("NSBB-responders") indeed had a lower probability of developing ascites (19% *vs* 57% at 3 years, $P < 0.001$), refractory ascites ($P = 0.007$), and HRS ($P = 0.027$). It is worth noting however that these two studies[90,91] were not directly comparable due to slightly different patient cohorts in that one had decompensated patients and the other compensated cirrhotic patients.

The role of NSBBs in refractory ascites has further been questioned by the same French group in a high impact publication[20] out-with the paracentesis setting. In this prospective landmark study, 151 patients were studied (77 on propranolol) with refractory ascites. The 1-year survival was indeed worse than those receiving propranolol [19% (95%CI: 9%-29%) *vs* 64% (95%CI: 52%-76%), $P < 0.0001$)]. Along with NSBB, hyponatraemia, Childs C class and renal dysfunction were predictors of mortality on multivariant analysis. It was concluded that NSBBs are contraindicated in patients with refractory ascites and led to a change in the use of NSBBs in cirrhosis in some parts of the international Hepatology community.

In advanced cirrhosis when bacterial translocation is high, and patients are prone to infections, the role of prophylactic antibiotics is clear but the place of NSBBs has been cast into some doubt. Mandorfer *et al*[90] explored in a retrospective cohort of 607 patients the effects of NSBBs in advanced cirrhosis. NSBBs were shown to improve transplant-free-survival in patients without SBP - HR = 0.75; 95%CI: 0.581-0.968; $P = 0.027$). On development of SBP however, NSBBs were associated with haemodynamic compromise (systolic arterial pressure < 100 mmHg 38% *vs* 18% those not on NSBB, $P = 0.002$), but more importantly increased incidence of HRS (24% *vs* 11%, $P = 0.027$), and reduced transplant free survival (HR = 1.58, 95%CI: 1.098-2.274, $P = 0.014$). This along with the data from a meta-analysis by Senzolo *et al*[60] showing NSBB preventing SBP potentially suggests NSBBs are indeed beneficial in prevention of SBP until late on when infection sets in and patients have difficulty mounting a compensatory cardiac/organ perfusion response on NSBBs.

NSBBs and the window hypothesis

Following on from the Sersté *et al*[20,89] studies, it was proposed that NSBBs were only beneficial during a set time window in the progression of cirrhosis with portal hypertension[21]. The "window hypothesis" proposed

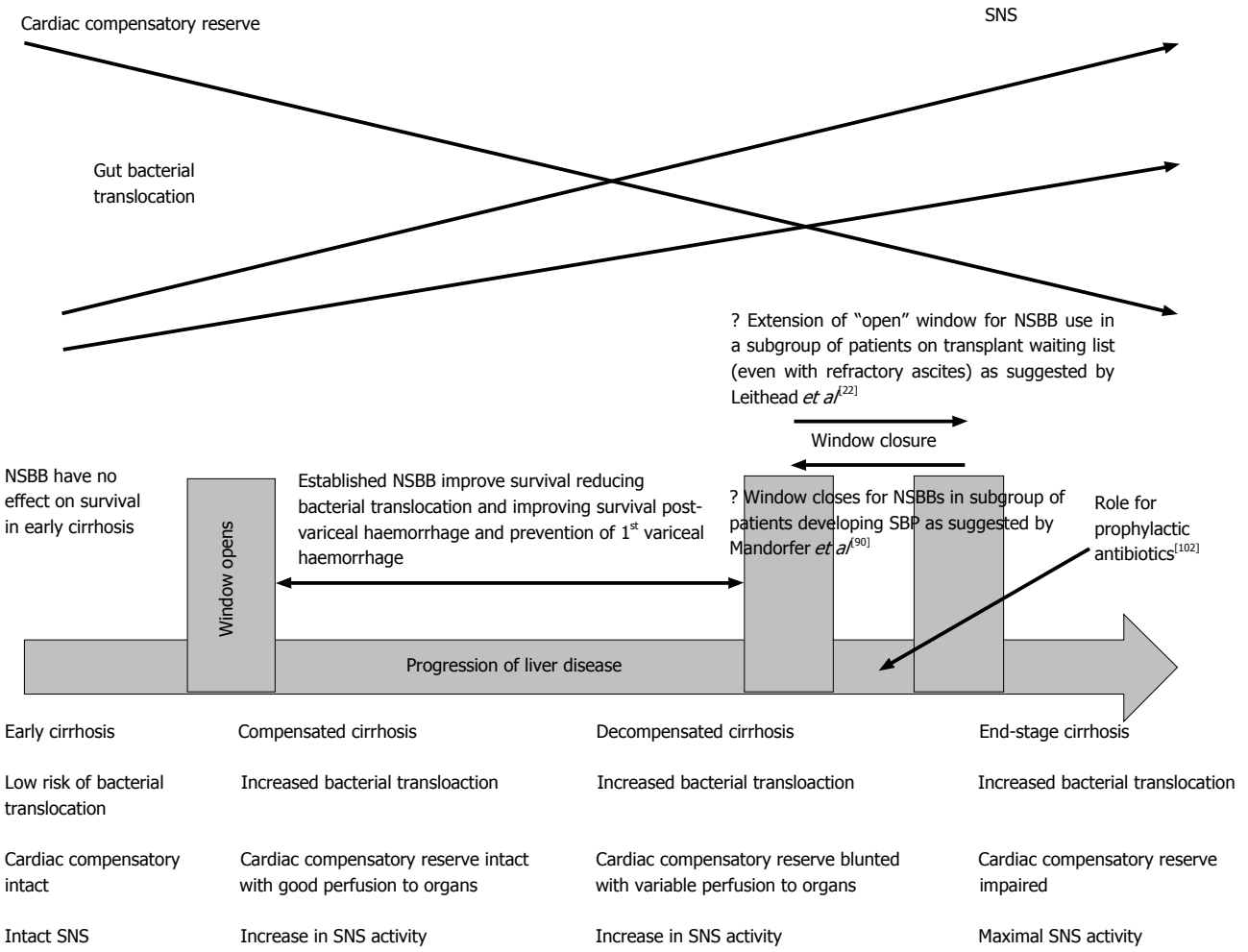

Figure 2 Extended - "window hypothesis" adapted and revised from Krag *et al*[21]. The window hypothesis illustrates that in early portal hypertension when low risk of bacterial translocation and adequate cardiac compensatory reserve, NSBBs have no effect on survival[25,67]. As disease progresses and varices enlarge there is clear benefit of NSBB in primary and secondary prophylaxis in improving mortality and also reducing rebleeding rates. The original widow hypothesis[21] commented that the window for benefit of NSBBs then may indeed close in decompensated cirrhosis (*e.g.*, patients with refractory ascites[20]) however the data from Leithead *et al*[22] would suggest the window may indeed remain open even in such patients for a period of time. This window however may indeed close once patients have developed an episode of SBP[90]. SNS: Sympathetic nervous system activity; NSBB: Non-selective beta-blocker; SBP: Spontaneous bacterial peritonitis.

that there may be no benefit in early cirrhosis when there is less risk of bacterial translocation, no increase in the sympathetic nervous system activity, and when the cardiac compensatory reserve is preserved, *i.e.,* a milder splanchnic and systemic haemodynamic state[42] (Figure 2). In advancing cirrhosis however there is an up-regulation of the renin-angiotensin-aldosterone axis with salt and water preservation to attempt to compensate for a reduced effective arterial circulation (due to splanchnic vasodilatation)/cardiac output[92]. This leads to salt and water retention, and ascites formation and a loss of compensatory reserve with often hypoperfusion to organs as a result. The maintenance of effective perfusion to organs is critical especially in the face of infection, at it was proposed that at this stage the window closes and NSBBs may indeed be detrimental[21]. As cirrhosis develops however, NSBB were felt to be beneficial in reducing variceal haemorrhage and reducing bacterial translocation with an increasing sympathetic nervous system drive. The window was then felt to close as cirrhosis progresses, patients develops refractory ascites and NSBBs were thought to exert a negative impact on the cardiac compensatory reserve. With MAP being found to be an independent predictor of survival in patients with cirrhosis and ascites[93] it was proposed[21] that NSBBs by lowering MAP may indeed contribute further to hypoperfusion of organs (especially in the context of further sepsis-induced vasodilatation) leading to an increase in mortality or HRS - well known to be associated with arterial underfilling from splanchnic vasodilatation[94].

NSBB-refractory ascites cessation: The rebuttal?

The data from Sersté *et al*[20] is indeed compelling, with a change of practice recommended following years of usage of NSBBs in cirrhosis and advanced disease. One important comment is that to date there has been no RCT showing a deleterious effect of NSBBs in patients with cirrhosis and refractory ascites. There were a number of criticisms of the landmark study raised from

sections of the Hepatology community from the paper by Sersté *et al*[20]. On exploring the patient demographics in more detail, all patients who had NSBBs had confirmed varices, however in the group not receiving them only 4.1% had varices. Patients in the NSBB arm were indeed sicker with a difference in bilirubin levels (56 *vs* 48 mg/dL, $P = 0.01$), lower sodium levels and more encephalopathy which may have influenced outcome. Furthermore, the NSBB arm had more Child Pugh Grade C patients and also more patients with hepatocellular carcinoma (HCC). There was no comment in the paper about the alcohol intake of the patient cohorts, and with similar MELD and Child Pugh scores, that there may have been a potential for patients in the NSBB arm having acute alcoholic hepatitis thus accounting for the hyperbilirubinaemia, a condition with a poor prognosis. Alcohol alone has been shown to cause microvasculature obstruction and capillarization of hepatic sinusoids may lead to rises in portal pressure[95] thus introducing some potential variability into the study. Other variables between the patient cohort was that the NSBB has a lower arterial pressures ($P < 0.0001$) - which rather than secondary to the effects of NSBBs may have indeed reflected a sicker cohort of patients with lower cardiac output or indeed an impaired cardiac compensatory reserve even prior to NSBB institution. In the subset of patients (39%) who had HVPG monitoring, there was no significant difference in the HVPG in these patients 20 ($\pm$ 4.5) mmHg in the NSBB group *vs* 19.1 ($\pm$ 5) mmHg in those without NSBB. Again this leads evidence that rather than NSBB having a deleterious causative effect, the differences in patient characteristics may have had more to do with the outcomes. The next major area of interest in this paper, was that on multivariant analysis apart from use of NSBB, class of Child Pugh, HCC, aetiology of refractory ascites, renal impairment and hyponatraemia were all independent predictors of death. Interestingly however MELD score did not come out as a predictor of death despite its use in scoring patients to predict mortality[95-98] in patients with cirrhosis and on waiting lists for liver transplantation.

Recently the question of NSBB and their effects in advanced portal hypertension was studied from our own group in the United Kingdom. Leithead *et al*[22] examined the role of NSBBs on patients listed for adult liver transplantation in a single centre. In this retrospective study, 322 patients listed for liver transplantation were studied - with all patients having ascites (34.8% had refractory ascites). In a multivariate competing risk Cox model, patients on NSBB had reduced mortality compared with matched non-NSBB patients (HR = 0.55, 95%CI: 0.32-0.95, $P = 0.032$). Similarly, in the subgroup of patients with refractory ascites ($n = 117$), NSBB remained independently associated with less wait-list death (adjusted HR = 0.35; 95%CI: 0.14-0.86, $P = 0.022$). The strengths of this study included a well matched patient group, large numbers, advanced liver disease patients on the liver transplant waiting list abstinent from alcohol. It should be noted that the study groups were indeed different from that in the study from Sersté *et al*[20] with patients in this study being highly selected group, listed for liver transplantation. The study however had some criticisms including the retrospective single centre design. Selection bias must be considered in any non-randomised trial. To counter this, the study group used propensity risk score matching to try to mimimise selection bias. Patients were on lower doses of NSBB when compared to the study of Sersté *et al*[20] however another criticism was a was a lack of haemodynamic measurements in this study[22].

Leithead *et al*[22] proposed that the benefit of NSBB this may indeed be due to the reduction of bacterial translocation in patients listed for liver transplantation with ascites, and that NSBB may indeed reduce low level of the systemic inflammatory response in such patients, which in effect may reduce portal pressure too. Systemic inflammatory response (SIRS) is increasingly recognised as a pathogenetic factor in the circulatory dysfunction of advanced cirrhosis; patients with child-pugh class C disease have a greater frequency of bacterial translocation, and patients (who have ascites) with evidence of endotoxemia have more pronounced circulatory dysfunction[96,97]. Leithead *et al*[22] proposed that the window hypothesis may actually stay longer open for a subset of patients with refractory ascites. A retrospective series from another large United Kingdom transplant centre[98] reviewed patients who had refractory ascites attending for LVP. Of 114 consecutive patients, 36 patients were receiving a NSBB with no differences in survival found between the groups ($P = 0.93$). Doses of propranolol used in this study were between 40-80 mg. One important way to add information to the argument regarding the safety, efficacy and benefit of NSBBs in advanced liver disease/cirrhosis and patients with ascites would be through a meta-analytical approach. A recent review by Kimer *et al*[99] rather than perform a meta-analysis reviewed studies and their characteristics reported on the heterogeneity of the study designs and definitions of ascites. Following this, they reported on their own experience in 61 patients with cirrhosis and refractory ascites with no increase in mortality in patients on NSBBs. In the 2015 AASLD meeting, Chirapongsathorn *et al*[100] reported on a meta-analysis of 4 RCTs and 8 observational studies including 2486 patients with ascites. When compared to patients not on NSBBs, the use of NSBBs was found not to increase mortality in patients with ascites (RR = 0.94; 95%CI: 0.6-1.47, $P = 0.77$) or with refractory ascites (RR = 0.86, 95%CI: 0.47-1.57; $P = 0.63$). The use of NSBBs was not associated with death at 6 mo, 1 year or 2 years. A notable limitation is the heterogeneity of the studies included in such meta-analyses. Some patients may be late in the advanced liver cirrhosis stage (such as the cohort in our own study listed for liver transplantation[22]) and others earlier on in the window hypothesis where there indeed is a degree of cardiac compensatory reserve, and may be less likely to suffer major haemodynamic disturbances when an insult occurs such as infections (Table 3).

In a recent study by Bossen *et al*[101], data from 3 trials

Table 3 Summary of studies/recent guidelines with non-selective beta-blocker in advanced cirrhosis

Ref.	Year, country	Study design	Findings/recommendations	Strenghts/weaknesses of study (if applicable)
Bañares *et al*[57]	2002, Spain	Randomised controlled trial	More favorable reduction of HVPG comparing carvedilol with propranolol however an increase in diuretic requirement in patients on carvedilol suggesting potential worsening of ascites	Increased requirement of diuretic not a hard end-point
Sersté *et al*[20]	2010, France	Single centre observational prospective case study	Patients on NSBB in refractory ascites having higher 1-year mortality than those not on NSBB	Non-randomised Lack of haemodynamic data. No competing risk analysis
Mandorfer *et al*[90]	2014, Australia	Single centre retrospective study	NSBB associated with higher transplant free survival but increase in renal dysfunction and mortality following episode of SBP	Groups not well matched at baseline with NSBB group having higher bilirubin in subgroup analysis
Leithead *et al*[22]	2015, United Kingdom	Single centre, retrospective case study	NSBB associated with reduced wait-list mortality and a higher likelihood of survival to transplantation	Lack of haemodynamic measurements. Non randomized. Well matched groups
Tripathi *et al*[67]	2015, United Kingdom	British guidelines	NSBB to be continued till episode of SBP, hypotension of renal failure (based on level 2b, Grade B evidence)	National guidelines based on all available evidence
Kimer *et al*[99]	2015, Denmark	61 patients with cirrhosis and ascites (following a review of 14 trials)	No survival difference in patients on/not NSBBs in patient cohorts with ascites	Small retrospective analysis
de Franchis[25]	2015, International	Meeting consensus statements	NSBB dose reduction or discontinuation can be considered if hypotension/ hyponatraemia or renal function impairment in patients with refractory ascites. If a clear precipitant for these (*e.g.*, SBP), NSBB can be restarted once parameters normalised	International consensus statements based on evidence
Robins *et al*[98]	2014, United Kingdom	Letter - retrospective review of 114 patients undergoing LVP	No significant difference in survival comparing patients on NSBB and those not	Small retrospective series
Bossen *et al*[101]	2015, Denmark and France	Post-hoc analysis of 3 RCTs	NSBBs not associated with increase in mortality in patients with cirrhosis and ascites Cessation of NSBB linked thereafter to increase in mortality due to liver decompensation events	Multicentre trials, 3 RCTs, large data set and reflective of real world experience. Lack of haemodyamic studies and assessment of severity of portal hypertension. NSBBs stopped during admission so? true reflection of their effects on mortality

HVPG: Hepatic venous pressure gradient; SBP: Spontaneous bacterial peritonitis; LVP: Large volume paracentesis; NSBB: Non-selective beta-blocker; RCTs: Randomised controlled trials.

of 1198 patients was reviewed in a post-hoc analysis to assess the effect of the use of NSBBs on mortality in patients with cirrhosis including the subgroup who had ascites. A cox-regression analysis was performed to assess for mortality once correcting for variables between groups of patients on NSBBs (n = 559) compared to those not (n = 629). The data were taken from 3 trials conducted to assess the safety of satavaptan in treating ascites. Two hundred and forty patients had diuretic refractory ascites requiring regular paracentesis - although the definition and categorization of refractory or diuretic responsive ascites was down to independent clinicians per site. The important finding from such a well-constructed, rigorous and clinically relevant study/ analysis was that NSBBs did not increase mortality or hospitilisation in patients with cirrhosis or in the subgroup of those with refractory ascites. Although there were no portal pressure measurements performed and a lack of data on the presence of varices (thus lack of markers of severity of portal hypertension), this was a real world practice/experience. The authors also tried to address the sub-groups who have differences in systemic haemodynamics within the window hypothesis based on MAP with no obvious effect on mortality between groups. Interestingly during the follow-up period, 29% of those on NSBB at the beginning of entry to trials stopped these, reflecting possible current day practice. This cessation of NSBB was thereafter linked to a sharp increase in mortality and coincided with not only hospitalization but also variceal bleeding, bacterial infection, and/or development of the HRS. Despite being a well conducted trial with actual clinical data, it should be noted that only 133 patients had a MELD score > 18, thus may not actually have been further down the window hypothesis pathway. Furthermore, as the NSBBs were stopped mid-way through study/admission it is difficult to conclude mortality would/would not have differed if they had actually been continued to the end-points stated. Patients on NSBBs had a median MAP of 83 mmHg which was similar to the group who were

not on a NSBB and therefore are not representative of the group previously shown to be harmed by the use of NSBBs. The authors concluded that discontinuation of NSBBs increased the mortality by over 5 times. It is more biologically plausible that this increase is due to the reasons NSBBs were discontinued in the first place, *i.e.,* hospitalization, infections and bleeding. It is likely that NSBBs would have impaired the cardiovascular reserve during these episodes thus contributing to the higher mortality. This relationship could have been demonstrated by close monitoring of MAP of patients on NSBBs after their discontinuation. This is a major limitation of studies performing post hoc analysis.

RECENT ADVANCES AND FUTURE DIRECTIONS OF NSBBs IN LIVER DISEASE

NSBBs: Bacterial translocation and effect in infections

The role of NSBBs in advanced cirrhosis certainly needs further evaluation. A large multicentre trial looking at the beneficial or deleterious effects of NSBBs in outcome of patients with advanced portal hypertension, especially in patients with ascites is clearly required. With the data suggesting that NSBBs have a deleterious effect after 1st episode of SBP[90], but with conflicting animal data suggesting NSBBs may indeed reduce bacterial translocation across the gut[59] the optimal timing of administration of NSBBs and their role in infection prevention or clinical deterioration needs to be clarified. Another issue is whether in patients who are at high risk of SBP as per the criteria outlined by Fernández *et al*[102] (child-pugh score ≥ 9 points with serum bilirubin level ≥ 3 mg/dL) or impaired renal function (serum creatinine level ≥ 1.2 mg/dL, blood urea nitrogen level ≥ 25 mg/dL, or serum sodium level ≤ 130 mEq/L) in whom primary prophylaxis is recommended should have their NSBBs discontinued or not, and also the optimal timing thereafter for reintroduction? Current BSG guidelines[67] suggest that NSBB are indeed discontinued at time of first advent of SBP however the lead up to this in those at high risk is not clear, and the potential benefits of NSBB in prophylaxis of variceal haemorrhage and reduction of potential low-grade SIRS/bacterial translocation need to be weighed up against the development of SBP. Clinical judgment however is required with reintroduction of NSBB once an acute septic hit has resolved. In patients with refractory ascites, the Baveno Ⅵ guidelines[25] state that NSBBs should be discontinued if hypotension (systolic blood pressure < 90 mmHg, hyponatraemia (< 130 mEq/L) or AKI. They state if a clear precipitant such as SBP (or gastrointestinal bleed) than NSBB should be considered to be restarted once the parameters cited normalise - however the grading of evidence for these statements was 5:D (expert opinions based on non-systematic reviews) - thus it should be interpreted with caution. Also cessation of NSBB in infective states such as SBP should be done with caution as SBP can increase portal pressure itself *via* bacterial translocation and thus a pro-inflammatory release at a sinusoidal level with consequent rise in portal pressure[103]. Rather than cessation of NSBB completely, in the author's opinion continuation with close observation may be a preferable strategy, although further trials are warranted for this approach. Potentially stratifying patients into risk of SBP based on not only the Fernández *et al*[102] criteria, but using variceal assessment and HVPG (or non-invasive portal pressure studies) may allow a future study to look into randomising patients to NSBB alone, NSBB with primary prophylaxis of antibiotics or antibiotics alone, and then following patients up for the advents of SBP and variceal haemorrhage.

NSBBs and portal vein thrombosis

Another area to be studied is the effect of NSBBs on portal blood flow, and whether this could lead to portal vein thrombosis (PVT) due to stagnant blood flow within the portal vein. Qi *et al*[104] discussed the hypothesis of NSBB potentially causing a reduction of portal vein inflow however with a lack of any large trials this area is still hypothetical. To date, one small unpublished study[105] found in 56 cirrhotic patients (with no HCC) who had an ultrasound every 6 mo on follow-up, on multivariant analysis the use on NSBB was an independent predictor of PVT (OR = 3.3, 95%CI: 1.4-6.8, $P < 0.001$). In another study published in abstract form retrospectively studied a large cohort of 568 patients assessing for factors predictive of the development of PVTs[106]. Although only 23 patients developed PVT, on mutlivariant analysis NSBBs were a risk factor for development of PVT (OR = 4.3, 95%CI: 1.4-12.6; $P = 0.01$). Larger published studies however are needed to explore this association in more detail, with ideally HVPG measurements.

NSBBs and HVPG

One area pertaining to NSBB research is indeed the measurement of HVPG and guided response when using any medical therapies - especially NSBBs. This modality is only reserved in specialist centres, often in a research setting only. The absence of assessment of haemodynamic response remains a criticism levelled at multiple research papers in the field, even those that have suggested changes in clinical practice in patients on NSBBS[20,22]. The role of NSBB - especially carvedilol with its more potent effect than propranolol in primary prophylaxis in small varices or even the prevention of variceal formation is not clear as yet, and longitudinal studies are required in this field, to see if the NSBB window for opening can be extended earlier in the disease course. Also studies comparing carvedilol with the other NSBBs are required in both a primary and secondary prophylaxis setting and in patients with advanced cirrhosis. If patients are diagnosed with non-invasive evidence of portal hypertension from imaging, blood work or elastography methods (after endoscopic verification of no varices or small varices)[107] a RCT is needed to assess intermittently the development of

varices comparing propranolol, carvedilol, nadolol and placebo. A recent systematic review and meta-analysis of 5 studies comparing carvedilol and propranolol suggested better haemodynamic reduction profile of carvedilol however commented on the lack of "quality" of the trials[108].

Other areas of interest include the role of combined different types of NSBB with VBL after a variceal haemorrhage compared to NSBB alone, to attempt to show what is the optimal therapy for prevention of rebleeding. In a trial from Egypt[109] published in abstract form, propranolol was studied in the prevention of recurrence of varices after endoscopic eradication. Ninety patients who had varices eradicated (primary and secondary prophylaxis) were divided into just follow-up alone (n = 43) or propranolol (n = 47). Propranolol use was associated with a delay in time to recurrence of varices, but not in the recurrence of varices. Also teasing out which NSBB reduces rebleeding rates superiorly is indeed required in a potential trial. A combined or an additive approach needs to be studied further, where if there is a failure to reduce size of varices (or reduce HVPG) by either banding or NSBBs alone, and assessing whether an addition of the other modalities improves HVPG reduction and rebleeding rates. To explore these issues in more detail, well-constructed likely multicentre RCTs large studies are required. This not only applies to oesophageal varices but gastric varices as well when patients cannot be entered necessarily into a band ligation programme after a herald bleed, thus more interest in NSBB could be applicable in prevention of gastric variceal rebleeding - and comparison of different NSBBs.

NSBBs and alcoholic hepatitis and ACLF

Another potential area of interest could be the role of NSBBs in patients with acute alcoholic hepatitis, one of the most florid manifestations of liver disease. Although in the studies from Plevris *et al*[70] there was no benefit in prevention of 1st variceal bleed in a cohort of patients with chronic liver disease, assessment of levels of pro-inflammatory cytokines, and even gut bacterial translocation rates in experimental models of alcoholic hepatitis when NSBBs administered and when not would be interesting. As the mice models have shown, NSBBs can significantly lower portal pressures, but also speed up intestinal transit times and also lower rates of bacterial overgrowth and translocation[59]. In this study propranolol was used, thus the role of carvedilol would be interesting. This could then be translated to an alcoholic hepatitis patient cohort with measurements of portal pressure and pro-inflammatory cytokine release, and to assess if NSBBs had a role in prevention of HRS or worsening of it. A recent retrospective study from Sersté *et al*[23] tried to answer this question, identifying 139 biopsy proven patients with alcoholic hepatitis with 34.5% receiving a NSBB. These patients had lower heart rates, MAP but comparable MELD cores and Maddrey discriminant functions to the non-NSBB arm. There was a higher 168-d cumulative incidence of AKI found in the NSBB group (P = 0.0001) however similar 168-d transplant free survival between the groups. Thus it may well be that patients with Alcoholic Hepatitis and a marked SIRS component with marked systemic vasodilatation may not indeed benefit from NSBBs, whereas another subgroup where bacterial translocation (in the earlier stages of disease) can be reduced may benefit having NSBBs continued. The effect of NSBBs on SIRS was studied in a high profile study from Mookerjee *et al*[24], this time in patients with ACLF. In this prospective observational study, 349 patients were studied with 47% receiving NSBBs. The advent of ACLF was observed with lower rates of ACLF in patients at presentation (P = 0.047) who were on NSBBs. On follow-up patients on NSBBs had a better 28-d survival [estimated risk reduction 0.596 (95%CI: 0.361-0.985; P = 0.0436)] and improvement in survival was associated with a significantly lower white cell count [NSBB: 8.5 (5.8); no NSBB: 10.8 (6.6); P = 0.002] suggesting those on NSBBs may either be more effective in those patients who have lower levels/grade of SIRS or may potentially reduce SIRS *via* effects on bacterial translocation in ACLF patients. A major limitation of this study is the lack of methods to control for differences in baseline characteristics between NSBBs and non-NSBBs groups, such as propensity score matching. A significant proportion of patients discontinued NSBBs for reasons that are not clear.

NSBBs and HCC

NSBBs, by way of potential reducing bacterial translocation and also reducing levels of SIRS may indeed have a hypothetical benefit in reducing the portal load of danger signals/molecules from the gut to the liver, with a potential benefit in altering the cascade in development of HCC. HCC is known to be linked to bacterial translocation and liver inflammation through Toll-like receptor signalling[110], thus one could propose NSBBs may have a beneficial effect in preventing signalling and translocation. There is a clear association between the inflammatory cascade and HCC formation[111] thus reducing the bacterial translocation stimulus for inflammation could be an important step in cancer prevention. At experimental level, NSBBs have also been shown to inhibit key processes involved in tumour development such as decreasing angiogenesis by inhibiting vascular endothelial growth factors, and by blocking adrenergic-mediated stimulation that can promote angiogenesis[112]. Beta-blockers too may block cell proliferation, migration, invasion, resistance to programmed cell death and metastasis too[113,114] and have been shown to improve the effect of some chemotherapeutic agents[115]. To this end a systematic review from Thiele *et al*[116] recently examined 23 trials on 2618 patients with cirrhosis to see if there was a link between patients on NSBB and reduction in incidence of HCC. The study found that NSBBs did not reduce HCC related mortality. Of the 47 of 694 (NSBB arm) developed HCC *vs* 65 of 697 controls (risk difference -0.026; 95%CI: -0.052 to -0.001; number needed to treat 38 patients). This area certainly requires further research.

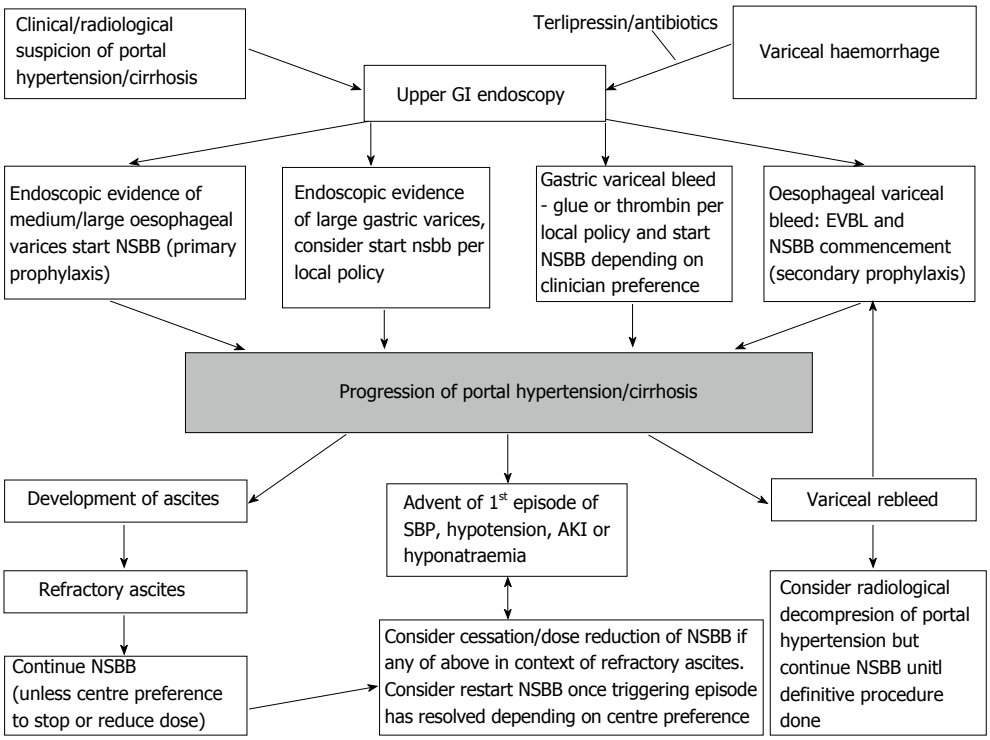

Figure 3 Proposed algorithm of Non-selective beta-blocker usage based on current guidelines and recent papers. NSBB: Non-selective beta-blocker; GI: Gastrointestinal; SBP: Spontaneous bacterial peritonitis.

NSBBs and stratification of patients per window hypothesis

Further complex mathematical modelling may indeed be required to retrospectively delineate cohorts of patients however this will be very difficult given the trials/study designs and captured data already gained. A well designed RCT however with long term follow-up assessing for markers of SIRS, portal pressure assessments, physiological parameter assessments, recording of septic insults, and cardiac function studies (ideally non-invasively) may add more information in the future. In a recent abstract the role of myocardial dysfunction was investigated by Giannelli *et al*[117]. In 583 patients undergoing liver transplantation assessment, 34% had refractory ascites. Patients had invasive cardiac assessment in including a right heart catheterization (right and left ventricular stroke work index assessments). Patients with refractory ascites had a significantly lower MAP, heart rate and a higher HVPG than those without refractory ascites as well as lower right and left heart stroke work index assessments. NSBBs were associated with a significant drop in the left ventricular stroke work index in patients with refractory ascites compared to those not on NSBBs, however there was no difference noted between the 2 groups in patients without refractory ascites. These findings may support the original window hypothesis[21] that NSBBs may indeed have a negative effect on the cardiac compensatory reserve in advanced cirrhosis (listed for transplantation in the study from Giannelli *et al*[117]. For future studies non-invasive modalities measuring cardiac function (*e.g.,* functional Magnetic resonance imaging) in cirrhosis may be more helpful to tease out the cardiovascular shifts occurring as liver disease progresses in patients with ascites and on NSBBs.

The effect of NSBBs in patients with cirrhosis affecting acute insults such as the development of HRS or AKI is an important area following on from the Mandorfer *et al*[90] study. Future studies describing or assessing outcomes of patients on NSBBs within different phases of the window hypothesis clearly need to examine these acute insults that lead to hospital admission of patients. In a recent multicenter study[118] from the North American Consortium for the Study of End Stage Liver Disease, 981 patients with cirrhosis admitted to hospital were studied. It was found that patients on NSBBs developed AKI compared to those not on NSBBs (49% *vs* 41%, $P = 0.019$), however whilst NSBBs were indeed found by backward elimination regression analysis to be associated with development of AKI during admission, there was no association with death during admission. The advent of infection in those admitted and on a NSBB was associated with AKI compared to those without infection ($P < 0.05$). Thus as per recommendation within Baveno Ⅵ, there may indeed be value to temporarily stop NSBBs in patients who are admitted with a complication of cirrhosis to avoid the issue of hypoperfusion of the kidneys in the face of a potentially impaired compensatory cardiac reserve, thus avoiding the advent of AKI and development of HRS (Figure 3).

CONCLUSION

In conclusion, it is an exciting time for NSBBs in patients

with liver disease. Their role has been firmly established over the years in prevention of variceal haemorrhage and rebleeding. It has however become clear that in certain stages of liver disease their benefit may become outweighed by their deleterious effects on systemic haemodynamics. It is clear that in a subset of patients, continuing NSBBs may indeed be appropriate to prevent variceal haemorrhage, SBP and improve outcomes, however when patients begin to deteriorate with sepsis in later disease or other evidence of end-organ hypoperfusion, then that may indeed be the time that the NSBB window closes. More studies are indeed required to tease out this exact timing for cessation, and also to expand the potential beneficial roles for NSBBs in the future. Not only does the window for NSBBs' beneficial effects open, but with the recent conflicting data as their role in advanced cirrhosis, the debate as to when to stop NSBBs has indeed opened too. There is an urgent need for well designed prospective studies of NSBBs in patients with advanced liver and in the setting of SBP to define clinical parameters for the safe administration of these indispensable treatments for portal hypertension.

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