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REVIEW

Non-selective beta-blockers in patients with ascites: The complex interplay among the liver, kidney and heart

Luis Téllez | Agustín Albillos

Department of Gastroenterology and Hepatology, Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas (CIBERehd), Instituto Ramón y Cajal de Investigación Sanitaria (IRYCIS), Hospital Universitario Ramón y Cajal, Universidad de Alcalá, Madrid, Spain

Correspondence
Luis Téllez, Ctra. Colmenar Viejo, Km 9,100, 28034, Madrid, Spain.
Email: luis.tellez@salud.madrid.org

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Abstract

Non-selective beta-blockers (NSBBs) are the cornerstone of the primary and secondary prophylaxis of variceal bleeding in cirrhotic patients. They additionally prevent ascites development and death in compensated patients with clinically significant portal hypertension. After ascites onset, NSBBs remain beneficial for preventing further decompensations. However, as the cirrhosis progresses, the inflammation increases, systemic vasodilatation worsens, ascites turns refractory and cardiodynamic equilibrium becomes extremely fragile. In this scenario, NSBBs can critically impair the cardiac reserve and facilitate a haemodynamic breakdown, imperilling renal perfusion. Consequently, NSBB treatment should be carefully monitored or even avoided in such patients, and other options for portal hypertension management should be considered. In the present review, we explore the effects of NSBBs in patients with ascites and discuss the complex interplay among their hepatic, systemic and renal haemodynamic effects in this scenario.

KEYWORDS
ascites, cirrhosis, non-selective beta-blockers, refractory ascites, renal injury

1 | INTRODUCTION

Four decades have passed since Lebrec et al published the first results demonstrating the efficacy of propranolol, a non-selective beta-blocker (NSBB), in reducing portal pressure in patients with cirrhosis and previous gastrointestinal bleeding.[1] This revolutionary observation spearheaded a titanic amount of research work in the coming years, resulting in the accumulation of robust evidence from numerous randomized clinical trials (RCTs) and several meta-analyses supporting the safety and usefulness of propranolol in treating cirrhosis.[2] As a result of these studies, we now know that NSBBs prevent the first and recurrent episodes of portal hypertension-related bleeding.[3-19] More importantly, because of their portal pressure-reducing effect, NSBBs are the only non-aetiological drugs shown to prevent cirrhosis decompensation and improve survival, both in compensated and decompensated patients.[20-22]

Thirty years after their seminal report, the same French group raised an alarm concerning the deleterious effect of NSBBs in cirrhotic patients with refractory ascites.[23] In an observational cohort study of 151 patients with refractory ascites, the authors showed that treatment with NSBBs was independently related to mortality. These results challenged the indication for NSBBs in such patients and spurred the scientific community to question their effects on other end-stage complications of cirrhosis, such as bacterial infection and acute kidney injury (AKI). Consequently, considerable observational data have emerged in the last decade, resulting in the 'window hypothesis' theory.[24] This hypothesis suggests that the beneficial effects of NSBBs are lost in end-stage cirrhosis when

Abbreviations: AKI, acute kidney injury; HVPG, hepatic venous pressure gradient; MAP, mean arterial pressure; NSBBs, non-selective beta-blockers; RCT, randomized clinical trial; SAP, systolic arterial pressure; SBP, spontaneous bacterial peritonitis; TIPS, transjugular intrahepatic portosystemic shunt.

the cardiac compensatory reserve is exhausted. NSBBs are cardio-inhibitory and reduce cardiac output, which has been associated with the development of hepatorenal syndrome and harms survival.[25,26] Although the controversy has tempered in recent years, new studies have mechanistically supported this hypothesis.[27-29] The use of sophisticated methods for estimating systolic cardiac function and renal perfusion has led to a more accurate description of the impact of NSBBs in end-stage cirrhosis.[30,31]

The present review examines the effects of NSBBs in patients with ascites and their 'pros' and 'cons' and analyses the complex interplay among their hepatic, systemic and renal haemodynamic effects in this scenario.

Key points

- NSBBs effectively reduce portal pressure and prevent variceal haemorrhage in patients with ascites, improving survival.
- Refractory ascites is a distinctive haemodynamic state of cirrhosis in which sympathetic activation and systolic function are upregulated as an adaptive response to maintain renal perfusion despite extreme vasodilation.
- When ascites becomes refractory, β-blockade blunts the sympathetic overdrive, critically diminishes the cardiodynamic reserve and imperils renal perfusion and function.
- In patients with refractory ascites, NSBBs should be used with caution or even avoided, and other treatments for portal hypertension, such as TIPS or liver transplantation, should be considered as a priority.

2 | HOW DO NON-SELECTIVE BETA-BLOCKERS IMPROVE SURVIVAL IN CIRRHOSIS?

In cirrhosis, portal hypertension results from increased hepatic resistance to portal blood flow and high portal venous inflow.[32] At early stages, the primary mechanism underlying its pathogenesis is the distortion of liver microvascular architecture because of fibrosis.[33] However, as the portal pressure increases, the systemic inflammation rises in parallel, leading to peripheral vasodilatation, which triggers the expansion of plasma volume, sympathetic hyperactivation and increased cardiac output.[34,35] This hyperkinetic circulation perpetuates and aggravates portal hypertension by increasing splanchnic inflow.[36] At this stage, the dilatation of pre-existing vessels secondary to portal hypertension and the angiogenesis mediated by endothelial growth factor promotes the development of portosystemic venous collaterals.

As shown in Figure 1, NSBBs induce significant haemodynamic changes in patients with portal hypertension. The blockade of β-1 receptors in the heart promotes a negative inotropic and chronotropic effect, decreasing cardiac output and splanchnic blood flow. Through the blockade of β-2 receptors, NSBBs also counterbalance mesenteric vasodilatation, facilitating an unopposed α-adrenergic vasoconstrictor effect in the splanchnic (and peripheral) vasculature. Consequently, both β-1 and β-2 blockades ameliorate the splanchnic vascular inflow, reducing portal pressure and portosystemic collateral blood flow. Thus, the hypotensive effect of NSBBs on portal pressure mainly relies on the attenuation of the increased portal inflow, which is a consequence of the hyperdynamic circulation. Indeed, in patients with cirrhosis and mild portal hypertension (ie a hepatic venous pressure gradient [HVPG] of 6–10 mmHg), the hyperdynamic syndrome is still underdeveloped and NSBBs are ineffective.[40,41] Distinctively, carvedilol is a NSBB with an additional α-1 anti-adrenergic effect that promotes intrahepatic vasodilatation and further decreases portal pressure. Consequently, carvedilol is more effective at reducing portal pressure than propranolol, but the α-1 blockade facilitates significant decreases in mean arterial pressure (MAP).[37-39]

When clinically significant portal hypertension is reached (HVPG ≥10 mmHg), NSBB-induced reductions in the HVPG of at least 10% from baseline are sufficient to prevent the first episode of variceal bleeding and the appearance of ascites.[42] To prevent rebleeding, more significant decreases of at least 20% from baseline (or a HVPG <12 mmHg) are recommended.[2,41,43] However, these haemodynamic responses only succeed in approximately 50% of patients receiving propranolol and 75% of patients on carvedilol.[2,39] Interestingly, we know that the beneficial clinical effects of NSBBs are present even in non-responders, suggesting the involvement of additional mechanisms. In particular, NSBBs seem to exert systemic anti-inflammatory activity, which is more pronounced in decompensated cirrhosis and independent of the HVPG response.[44-46] These non-haemodynamic effects have been proposed as mechanisms for reducing bacterial translocation, thereby decreasing the risk of spontaneous bacterial peritonitis (SBP), and some reports even ascribe them an anticarcinogenic effect.[19,47]

3 | EFFICACY OF NON-SELECTIVE BETA-BLOCKERS IN PATIENTS WITH ASCITES

Ascites is the most frequent complication in the natural history of cirrhosis, occurring in 50% of patients within 10 years of diagnosis. Its development is an ominous landmark in the progression of chronic liver disease.[48,49] The clinical efficacy of NSBBs in preventing variceal bleeding in patients with large oesophageal varices with and without ascites has largely been explored in several prospective RCTs and meta-analyses,[3,9] which concluded that they should be chosen ahead of endoscopic band ligation for primary prophylaxis.

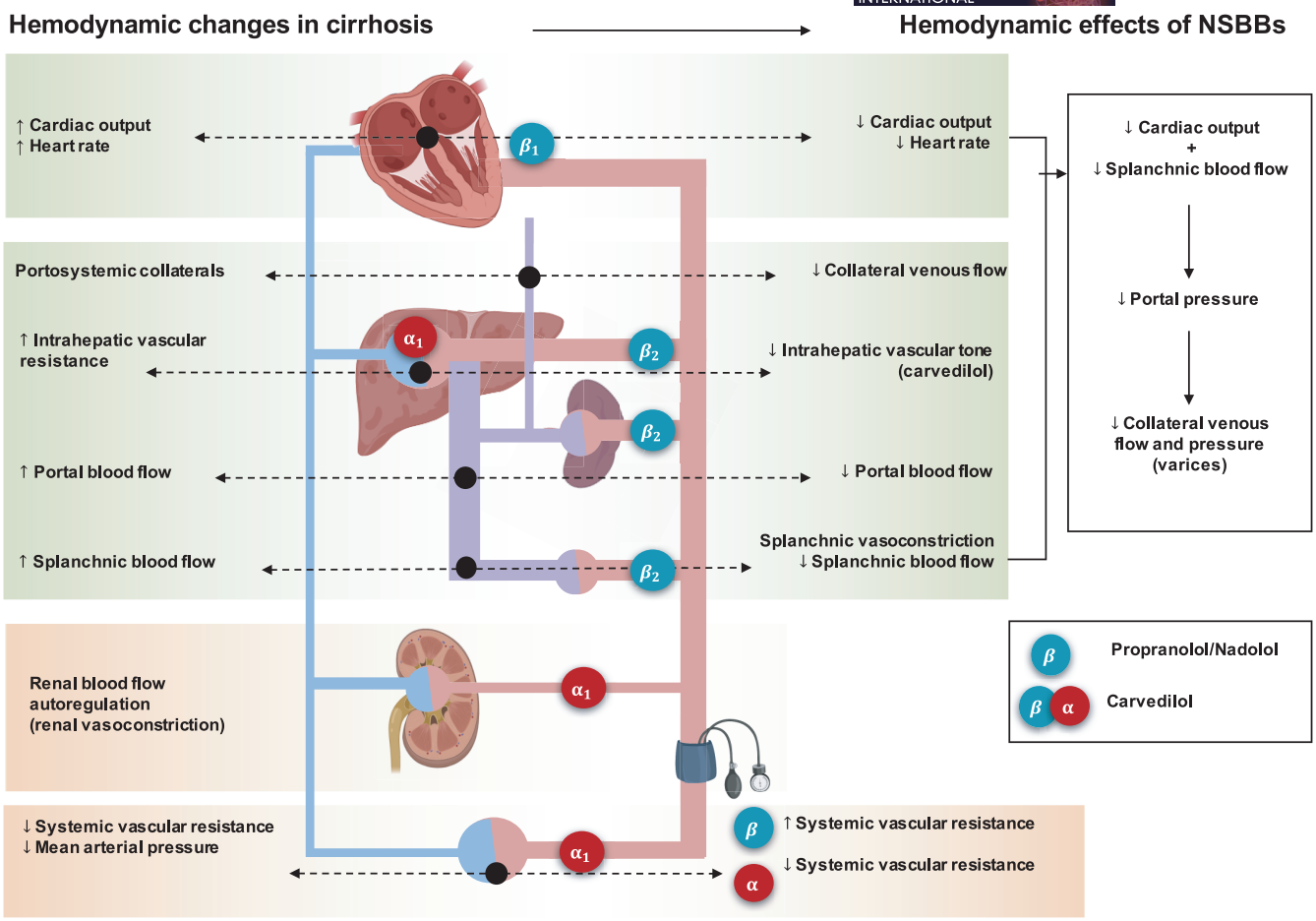

FIGURE 1 Haemodynamic changes in cirrhotic portal hypertension and mechanisms of action of NSBBs. NSBBs, non-selective beta-blockers

Turco et al analysed 15 clinical studies in their most recent publication, including 452 patients with ascites. This meta-analysis showed that, after β-blockade, the portal pressure, as measured by the HVPG, significantly decreased from 19.9 mmHg at baseline to 17.2 mmHg at follow-up in patients with ascites, with this reduction exceeding 20% from baseline in 42% of patients.[22] Remarkably, the mean drop in the HVPG was greater in compensated than in decompensated patients, despite the greater developed hyperdynamic circulation in the latter. This distinct haemodynamic response may be partly related to collateralization, which is more developed in decompensated cirrhosis. Once collaterals have developed, NSBBs, in addition to reducing portal venous inflow, may also increase portal-collateral resistance, which partially offsets the effect on portal pressure.[41] Such a worse response to NSBBs may also be related to a more severe vascular dysfunction in decompensated patients, with hypo-contractility induced by dysregulation of vasoactive proteins,[50] which can be more evident in patients with refractory ascites.[51] Nonetheless, it is essential to highlight that patients with ascites show higher HVPG values at baseline and thus represent a very high-risk group for variceal bleeding and other life-threatening complications. Notably, the haemodynamic changes achieved by NSBBs (mostly propranolol or nadolol) in decompensated patients have been associated not only with a lower rate of further decompensation (defined as the development of variceal haemorrhage, refractory ascites, hepatic encephalopathy, SBP or hepatorenal syndrome), but also with a decrease in the combined endpoint of death or liver transplantation.[22] Indeed, the greatest reduction in risk of death or liver transplantation was mainly seen in patients with a history of variceal haemorrhage (secondary prophylaxis), who likely represent a sicker population.[2,22] Accordingly, in an individual data-based meta-analysis focussed on patients in secondary prophylaxis, NSBB use, but not endoscopic therapy (ie band ligation), was associated with significantly increased survival in decompensated cirrhosis (ie Child-Pugh B and C).[15]

Importantly, the beneficial effects of NSBBs in patients with ascites are not restricted to patients treated with classical NSBBs (propranolol and nadolol). For example two recent studies of patients with ascites showed that carvedilol used in primary prophylaxis also improves survival compared with endoscopic band ligation.[52,53]

These results confirm that propranolol, nadolol and carvedilol are useful in patients with ascites and high-risk varices. They should thus be considered the first-line therapy for preventing variceal bleeding.[54,55] However, patients with severe and refractory decompensated liver disease manifesting as intractable ascites or tense ascites

resistant to diuretic treatment and those at high risk of renal failure were systematically excluded from most of the above-mentioned RCTs. Consequently, the current recommendations cannot be automatically extrapolated to patients with severely decompensated cirrhosis, a population with a clearly distinctive haemodynamic state.[56,57]

4 | CAN NON-SELECTIVE BETA-BLOCKERS BE HARMFUL IN PATIENTS WITH ASCITES?

NSBBs have several potential adverse effects that negatively impact patients' quality of life and adherence.[58] NSBBs can result in symptomatic bradycardia, trigger airway resistance in patients with bronchial hyperreactivity, exacerbate peripheral artery disease and hamper insulin-induced hypoglycaemia recovery in patients with diabetes mellitus. Additionally, cirrhotic patients on NSBBs frequently report depression, fatigue and sexual dysfunction. These adverse effects have led to treatment discontinuation in approximately 15% of the patients included in clinical trials.[59] This phenomenon may be more frequent in cases of severely decompensated cirrhosis, such as patients with refractory ascites. In a meta-analysis of three RCTs addressing the efficacy of tolvaptan in patients with refractory ascites, NSBBs were discontinued because of adverse effects in up to 30% of patients, highlighting their worse tolerance at this stage of cirrhosis.[60]

In 2010, Sersté et al conducted an observational study of 151 patients with decompensated cirrhosis and refractory ascites. They demonstrated that patients on propranolol had a dramatically lower median survival (5 months, with a survival rate of 19% at 1 year) than patients not taking propranolol (20 months, with a survival rate of 64% at 1 year). In multivariate analysis, NSBBs were independently and significantly associated with a 2.6-fold increased risk of death (95% confidence interval, 1.6–4.2).[23] Three pathophysiological factors could explain the negative impact of NSBBs on this population. Firstly, the lower arterial pressure in patients on NSBBs may at least partially explain the higher mortality rate in the treated group, which is in line with previous observations of worse 1-year survival rates in patients with ascites and MAP <80 mmHg.[26,61] Notably, in a larger cohort of patients with ascites listed for liver transplantation, the survival benefits of NSBBs were markedly attenuated in patients with MAP <82 mmHg and ultimately lost in those with MAP <65 mmHg.[62] Secondly, the high dose of propranolol used in the Sersté study (mean dose, 160 mg/day) may have influenced survival. This hypothesis is supported by a retrospective analysis of a well-characterized cohort of mildly and severely decompensated patients, where individuals treated with doses below 160 mg/day showed lower mortality risk than those who did not take NSBBs. In contrast, doses above 160 mg/day had no beneficial effect on survival.[63] Finally, all patients included in the Sersté study were regularly treated with large volume paracentesis and intravenous albumin. In this regard, NSBBs, by inhibiting the compensatory increase in heart rate in response to increased vasodilation, have been linked to a greater incidence of paracentesis-associated circulatory dysfunction, a complication associated with low survival in patients with cirrhosis and tense ascites.[64-66]

Other recent publications have linked the use of NSBBs with an increased risk of renal injury in decompensated cirrhosis. In a cohort of severely decompensated patients (Child-Pugh C), β-blockade increased the risk of AKI and hepatorenal syndrome by three-fold vs untreated patients.[67] Interestingly, when patients listed for liver transplantation were analysed, the effect of NSBBs on risk of AKI was dependent on whether they had experienced ascites. In compensated patients, NSBB use was associated with an 80% reduction in AKI incidence, whereas, once ascites was present, the risk of AKI increased more than three-fold.[68] Similar conclusions were also made in patients at high risk of AKI, such as those admitted for the first time with SBP. In this scenario, NSBBs increased the risks of hepatorenal syndrome and AKI and reduced transplant-free survival in the months following discharge.[69] Conversely, these results were not further replicated in a larger cohort with a longer follow-up.[63] According to specific analysis, high doses of NSBBs may also play a critical role also in patients admitted for SPB.[70]

As shown in Table 1, many retrospective studies addressing mixed populations of outpatients and hospitalized patients failed to identify significant differences in mortality and probability of AKI between patients with ascites treated or untreated with NSBBs.[45,60,71-73] However, the theoretical population at risk of harmful effects because of β-blockade (ie patients with systolic pressure <80 mmHg, creatinine >150 μmol/L or refractory ascites) is not well represented, which may have influenced the perception of NSBB safety.

Other observations suggest that the disparities in mortality and risk of renal injury reported in patients on NSBBs may be related to the type of NSBB: traditional NSBBs (propranolol or nadolol) vs those with additional α-1 anti-adrenergic activity (carvedilol). In a meta-analysis of nine observational studies, neither propranolol nor nadolol increased all-cause mortality in patients with diuretic-responsive and refractory ascites. However, carvedilol was associated with a significant increase in mortality (relative risk, 1.75; 95% confidence interval, 1.1–2.9). The added α-blocking activity significantly reduces MAP more than propranolol, which may explain the differences.[74]

The most robust evidence is summarized in the three recently published meta-analyses, which conclude that NSBB use is not associated with increased mortality in patients with ascites. However, there was significant heterogeneity among the included studies.[75-77] Before firm conclusions are made, some considerations should be noted. Firstly, each study included a different population and mostly mixed patients at various stages of decompensated cirrhosis (mild, moderate, severe and strictly refractory ascites) with short and varying follow-up durations. Secondly, the dose and type of NSBB (propranolol/nadolol or carvedilol) were not homogeneous.[68,77] Thirdly, the prevalence of high-risk varices is higher in patients treated with NSBBs, probably reflecting their greater severity of portal hypertension. Fourthly, the diagnosis of refractory ascites currently relies only on clinical criteria and may be overestimated or underestimated

in retrospective analyses. Finally, the results of the most recent retrospective and observational studies may be influenced by the evidence from the first reports and the recommendations included in current clinical guidelines, meaning that patients at a high risk of complications may not be fully represented.

In summary, the current evidence from observational studies merely allows us to work diligently with different hypotheses, which deserve a pathophysiological demonstration and eventual clinical evaluation in prospective RCTs.

5 | DO NON-SELECTIVE BETA-BLOCKERS BREAK THE FRAGILE CARDIORENAL INTERPLAY IN REFRACTORY ASCITES?

In 1980, Harold O. Conn wrote an editorial highlighting that, 'conceivably the administration of propranolol to patients with a propensity to develop the hepatorenal syndrome might well give rise to a new and even more complex disorder, the hitherto unknown cardiohepatorenal syndrome'.[78]

Cirrhosis advances from compensated to decompensated stages and then onto further decompensated stages (ie refractory ascites) as the portal pressure, systemic inflammation and peripheral vasodilation progressively worsen.[57] As cirrhosis progresses, the gradual recruitment of compensatory cardiac mechanisms (ie enhanced left ventricular function) can counteract the progressive hypotensive state and maintain renal perfusion.[30] In patients with diuretic-responsive ascites, the heart can adequately respond to vasodilation-driven sympathetic activation by increasing cardiac output. However, this haemodynamic equilibrium becomes disrupted when decompensated cirrhosis progresses to refractory ascites, and the inflammatory state reaches its maximum.[76] At this stage, cardiac function is unable to increase further and compensate for the worsened arterial underfilling, leading to reduced organ perfusion.[29] This phenomenon can be explained by the presence of a latent cirrhotic cardiomyopathy, characterized by decreased density and function of myocardial β-receptors, changes in cardiomyocyte membrane composition and myocardial fibrosis mediated by extreme systemic inflammation and bacterial translocation.[79-85] Importantly, these alterations render cardiac output more sensitive to β-blockade, as shown in two recent cohorts of decompensated patients.[27,30] In this complex setting, the negative cardiac and inotropic effects of NSBBs may fully exhaust the already compromised cardiac reserve, aggravating the arterial underfilling and critically reducing organ perfusion.[24,28]

Renal autoregulation guarantees that the kidneys receive a constant blood flow, regardless of daily fluctuations in blood pressure.[86] Given a hypotensive state, several mechanisms ensure a stable renal blood flow, such as activation of the sympathetic nervous system, enhanced systolic function and the myogenic response mediated by tubuloglomerular feedback.[85,87] However, renal autoregulation only operates at a renal perfusion pressure greater than 65 mmHg, and renal blood flow decreases in proportion to renal perfusion pressure below this critical threshold.[88] Renal perfusion pressure is the result of the difference between the MAP (input) and inferior vena cava pressure (output) and is therefore highly dependent on systemic vascular resistances and central venous (cardiac overloading) and intra-abdominal pressures, which are increased in patients with tense ascites.[89] Consequently, in patients with refractory ascites and maximal sympathetic activation, renal perfusion is critically reduced and renal blood flow becomes highly dependent on MAP and the enhanced left ventricular systolic function (Figure 2).[88,90]

A mechanistic proof-of-concept and prospective study using sophisticated and load-independent diagnostic methods compared the effect of NSBBs (propranolol) on cardiac and renal haemodynamics in two well-characterized cohorts of patients with diuretic-responsive and refractory ascites.[29] β-blockade significantly reduced left ventricular contractility to values close to the range of healthy controls, but the resulting cardiac output could not maintain renal perfusion pressure above 65 mmHg in most patients with refractory ascites. These effects were not limited to systolic function but extended to diastolic function, resulting in central volume overload and further decreased renal perfusion pressure. Patients with critically compromised renal perfusion (below 65 mmHg) had significantly increased creatinine levels, leading to hepatorenal syndrome in 20%. Interestingly, these detrimental changes were only seen in patients with refractory ascites and not in those with diuretic-responsive ascites, in which the beneficial effects of NSBBs were noticeably maintained. The specificity of the impact of NSBBs on systolic function in refractory ascites confirms the extreme dependence of systolic function and sympathetic hyperactivation on maintaining a constant renal blood flow at this stage, which is hampered by β-adrenergic blockade. In line with these results, Giannelli et al observed increased mortality in refractory ascites patients on the liver transplant waiting list who were on NSBBs and had a left ventricular stroke work index below 64.1 g × m/m^2.[28] In addition, greater reductions in cardiac output (cardiac output <5 L/min) in patients with decompensated cirrhosis on NSBBs have also been related to lower survival rates.[27] In summary, the results from these three studies using a highly refined and state-of-the-art cardiac evaluation support the belief that the therapeutic window of NSBBs in cirrhosis precedes refractory ascites. The confirmation of the hypothesis suggested by Conn 40 years ago reinforces the critical role of cardiac function in hepatorenal syndrome pathophysiology and provides the mechanistic explanation for the increased mortality seen in patients with refractory ascites.

6 | NON-SELECTIVE BETA-BLOCKERS IN CIRRHOSIS AND ASCITES: CURRENT RECOMMENDATIONS AND FUTURE DIRECTIONS

Current evidence supports the use of NSBBs in patients with cirrhosis and ascites, especially diuretic-responsive ascites. At this stage, NSBBs prevent first variceal bleeding, rebleeding, SBP episodes, the

TABLE 1 Summary of effect of non-selective beta-blockers in observational studies including patients with ascites

Ref.	Follow-up (months)	Population	Group	Median dose of NSBB (mg/day)	Patients (*n*)	Refractory ascites (%)
Sertsé, 2010[23]	8.0	Refractory ascites	NSBB	P: 160	77	100
			Control		74	100
Sertsé, 2011[65]	9.9	Refractory ascites	NSBB	P: 160	10	100
			Control		10	100
Galbois, 2011[97]	6.0	Severe sepsis	NSBB	—	26	54
			Control		42	41
Mandorfer, 2014[69]	9.6	Admitted with SBP	NSBB	P: 80; C: 12.5	86	—
			Control		96	—
Leithead, 2014[98]	2.4	Ascites in waiting list for LT	NSBB	P: 80; C: 6.25	159	35
			Control		169	37
Robins, 2014[99]	10.0	Ascites under LVP	NSBB	P: 49	34	100
			Control		78	100
Kimer, 2014[100]		Ascites under LVP	NSBB	P: 80	23	100
			Control		38	100
Kalambokis, 2016[67]	36.0	Child-Pugh B-C	NSBB	—	53	—
			Control		41	—
Bang, 2016[63]	24.0	"Severely" decompensated	NSBB	P: 96	129	—
			Control		515	—
Bossen, 2016[60]	12.0	Ascites	NSBB	—	562	46
			Control		636	53
Mookerjee, 2016[45]	1.0	ACLF	NSBB	P: 40; C: 12.5	155	—
			Control		185	—
Aday, 2016[72]	—	Cirrhosis with or without ascites	NSBB	—	1039	—
			Control		1380	—
Sinha, 2017[53]	28.0	Ascites	NSBB	C: 12.5	132	—
			Control		132	—
Kim, 2017[68]	12.8	Waiting list for LT	NSBB	P: 40	170	—
			Control		240	—
Onali, 2017[73]	7.0	Ascites	NSBB	P: 80; C: 6.25	128	32
			Control		188	44
Scheiner, 2017[101]	36.0	Cirrhosis and varices	NSBB	P: 96; C: 19	93	0
			Control		83	0
Bhutta, 2018[71]	0.5	Hospitalized with ascites	NSBB	P: 40; C: 12.5	307	54
			Control		411	48
Tergast, 2019[62]	1.0	Hospitalized with ascites	NSBB	P: 30; C: 12.5	255	44
			Control		369	45
Giannelli, 2020[28]	4.7	Evaluated for LT	NSBB	P: 80	291	34
			Control		293	31

Abbreviations: ACLF, acute on chronic liver failure; AKI, acute kidney injury; C, carvedilol; HRS, hepatorenal syndrome; ICU, intensive care unit; LT, liver transplantation; LVP, large volume paracentesis; MAP, mean arterial pressure; MELD, model for end-stage liver disease; NSBB, non-selective beta-blockers; P, propranolol; RA, refractory ascites LVSWI, left ventricular systolic work index.

*$p < 0.05$.

development of refractory ascites and improve survival. However, when ascites becomes difficult to treat and the MAP decreases, NSBBs can impair the fragile cardiodynamic equilibrium and harm renal perfusion (Figure 3). At this stage, if NSBBs are prescribed, a low dose of propranolol is probably preferable to carvedilol, given its lower hypotensive effect. Notably, at end-stage cirrhosis, the bioavailability of propranolol is significantly increased because of its predominant liver metabolism. Consequently, NSBBs should be

Previous variceal bleeding (%)	MELD score	MAP (mmHg)	AKI/HRS risk in NSBB group	Mortality risk in NSBB group	Global effect
–	19	103	41% vs. 27%	OR 2.6 (1.6–4.2)*	NSBBs increased mortality in refractory ascites
–	19	123*			
–	18	81	–	–	NSBBs increased LVP-induced dysfunction
–	16	89			
–	23	72	–	55% vs 13%* (In ICU-discharged)	NSBBs increased 6-month mortality in ICU discharged patients
–	24	80			
18	22	77	24% vs 11%	HR 1.6 (1.1–2.3)*	NSBBs increased the risk of AKI/HRS and death after SBP
15	20	83*			
40	17	89		HR 0.4 (0.1–0.9)*	NSBBs reduced transplant-free mortality
25	16	86			
69	NR	NR	–	–	NSBBs did not increase mortality
32	NR	NR			
–	15	NR	45% vs 43%		NSBBs did not increase mortality
–	16	NR			
–	–	–	65% vs 20%*	51% vs 11%*	NSBBs increased mortality and the risk of AKI in Child-Pugh C patients
–	–	–			
33	–	–	HR 0.4 (0.3–0.6)*	HR 0.5 (0.2–1.6)*	Dose of $p < 160$ mg/day did not increase mortality
22	–	–			
30	12	85	–	HR 1.0 (0.7–1.4)	NSBBs did not increase mortality, but they were stopped in 30%
13	11	83			
43	27	79	–	OR 0.6 (0.4–1.0)*	NSBBs decreased mortality, but they were stopped in 50%
17	29	78			
–	–	–	–	6.5 vs 16.2%*	NSBBs decreased mortality in patients with cirrhosis
–	–	–			
32	13	–	–	HR 0.6 (0.4–1.1)	Carvedilol did not increase mortality in mild to moderate ascites
34	14	–			
–	–	–	HR 3.3 (1.6–7.0)*	–	NSBBs increased risk of AKI in patients with ascites
–	–	–			
50	14	80	–	HR 0.2 (0.1–0.7)	NSBBs reduced mortality, but subanalysis in RA was not made
21	15	86*			
33	12	101	HR 0.5 (0.2–1.3)	HR 0.3 (0.1–0.8)*	NSBBs did not increase risk of AKI, but patients with RA were not included
31	13	97			
33	20	86	–	13% vs 14%	NSBBs did not increase mortality (Increasing trend in RA)
16	20	86			
26	18	77	–	HR 0.6 (0.4–0.9)*	NSBBs decreased mortality in patients with MAP >65 mmHg
5	19	78			
–	16	–	–	HR 7.7 (1.7–34.2)*	NSBBs increased mortality in patients with LVSWI <64.1 g.m/m^2
–	15	–			

carefully titrated in patients with ascites and the use of high and fixed dosing is strongly discouraged. In patients with refractory ascites, the careful monitoring is advisable of changes in cardiac function, systemic arterial pressure and renal function. Based on a post hoc analysis of the previously reported cohort of patients with diuretic-sensitive and refractory ascites treated with NSBBs,[29] the latest Baveno VII expert consensus recommended that, in cases of persistent arterial hypotension (MAP <65 mmHg or systolic arterial

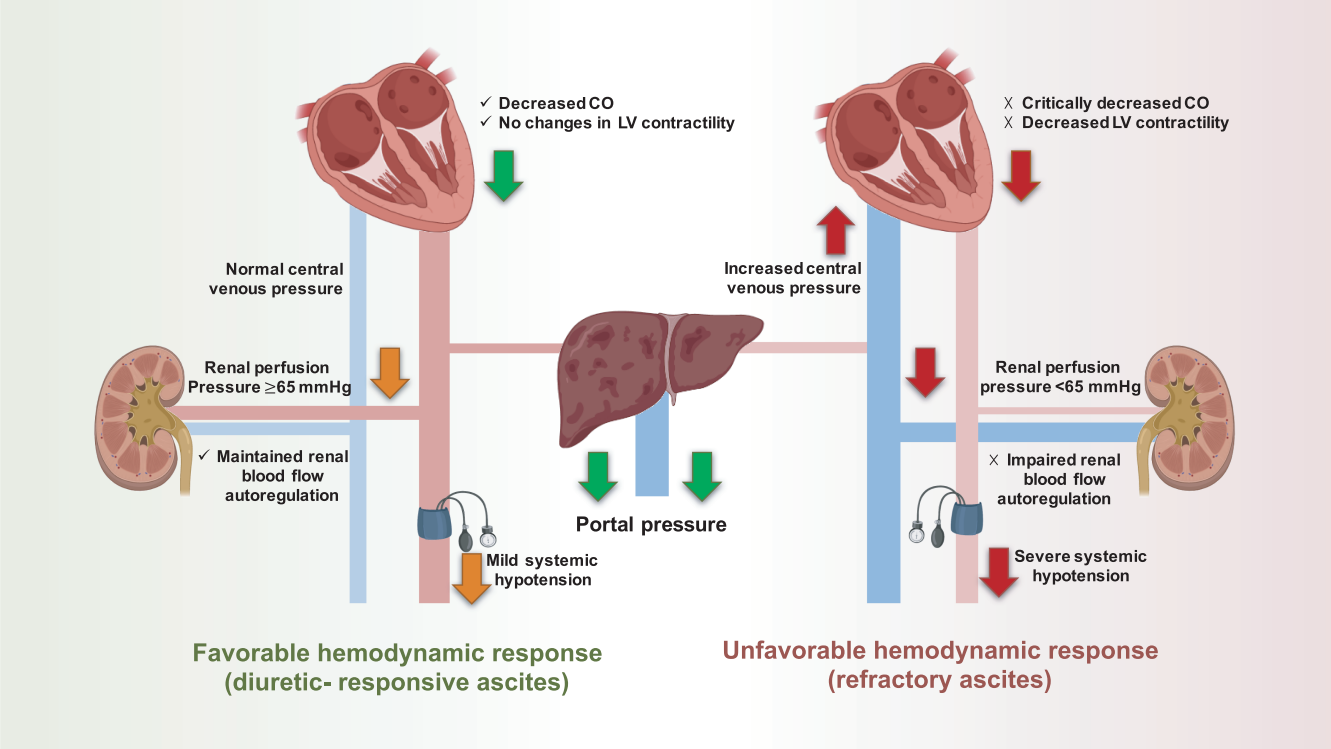

FIGURE 2 Different haemodynamic responses to NSBBs in diuretic-responsive and refractory ascites. NSBBs induce a similar haemodynamic response in portal pressure in patients with diuretic-responsive and refractory ascites. When ascites becomes refractory and systemic vasodilation peaks, NSBBs hamper cardiac output, lower renal perfusion pressure below the critical threshold (65 mmHg) and increase the risk of hepatorenal syndrome. CO, cardiac output; LV, left ventricular

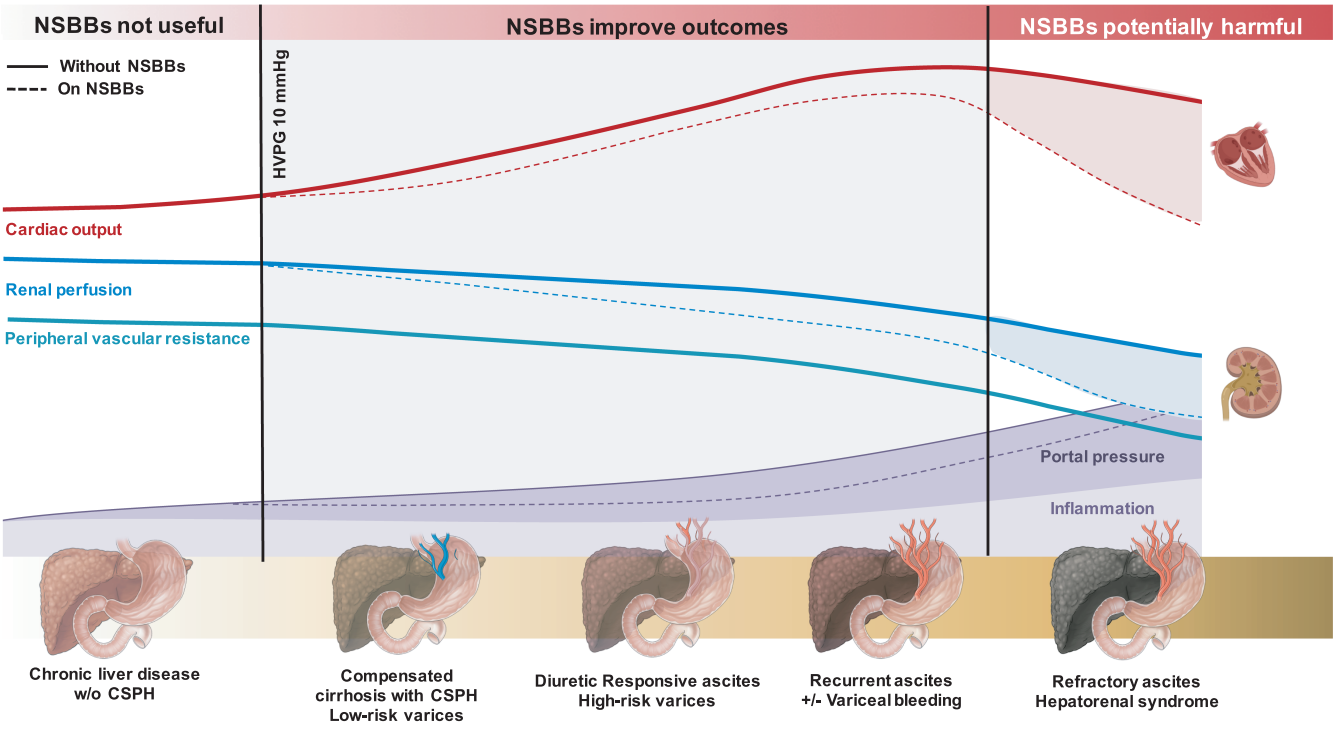

FIGURE 3 Haemodynamic effects of NSBBs across all cardiodynamic states in cirrhosis. CSPH, clinically significant portal hypertension; NSBBs, non-selective beta-blockers

pressure <90 mmHg) or hepatorenal syndrome, NSBBs should be discontinued and reintroduced at lower doses with careful monitoring. NSBBs should be immediately stopped in all patients admitted with ascites and AKI, even in the absence of a definitive recognized cause of AKI. Irrespective of the AKI stage, NSBBs discontinuation is recommended to prevent AKI progression and hepatorenal syndrome development.[54] The updated practical recommendations for NSBBs included in the current international clinical practice guidelines and position documents are summarized in Table 2.

In any case, other treatments for portal hypertension should be considered in this scenario, because refractory ascites is an accepted indication for liver transplantation. If liver transplantation is not feasible or the predicted waiting list time is too long, insertion of a transjugular intrahepatic portosystemic shunt (TIPS) should be

TABLE 2 Summary of recommendations for NSBBs use in patients with cirrhosis and ascites based on current clinical practice guidelines

Recommendations

When are NSBBs indicated in patients with ascites?
• Prevention of oesophageal variceal haemorrhage (primary prophylaxis):
  • Patients with ascites and low (<5 mm, no red signs, not Child-Pugh C) or high risk (≥5 mm, or red signs or Child-Pugh C) oesophageal varices propranolol or carvedilol should be used to prevent first variceal haemorrhage. NSBBs are preferred over EBL because they also exert other potentially beneficial effects in addition to lowering portal pressure.[55]
• Prevention of gastric and ectopic variceal haemorrhage (primary prophylaxis):
  • For prevention of first variceal bleeding from gastric and ectopic varices, NSBBs can be used, although the data are not as strong as for oesophageal varices.[102]
• Prevention of recurrent portal hypertension-related haemorrhage (secondary prophylaxis):
  • First-line therapy for the prevention of recurrent variceal haemorrhage is the combination of propranolol or carvedilol and EBL.[54,55,102]
  • NSBBs are first-line therapy in preventing recurrent bleeding from portal hypertensive gastropathy.[55]

Which is the NSBB of choice in patients with ascites? • In patients with ascites, either propranolol or carvedilol may be used to prevent first variceal haemorrhage.[55] • Carvedilol might be deleterious in patients with ascites as it is more likely to cause a systemic haemodynamic depressive effect.[54] • In patients with severe or recurrent/refractory ascites, propranolol is the NSBB of choice and carvedilol is not recommended.[54]
Which are the procedures indicated before NSBBs initiation? • Patients in whom ascites develops should have upper gastrointestinal endoscopy performed to screen for gastro-oesophageal varices unless previously diagnosed and treated.[54,55,102] • The decision to treat with NSBBs should be taken when clinically indicated, independently of the possibility of measuring HVPG.[55] • An electrocardiogram should be available to rule out the presence of a second or third atrioventricular blockade since they are absolute contraindications for the use of NSBBs (in the absence of peacemaker). • Resting heart rate and blood pressure should be measured more than twice in the seated position.

How NSBBs dose should be titrated in patients with ascites?
• Propranolol[102]
  • Initiation dose: 20–40 mg orally twice a day
  • Treatment goal: 55–60 beats per minute with SAP >90 mmHg or MAP >65 mmHg
  • Dose-adjustment: Every 2–3 days until treatment goal
  • Maximal daily dose: 160 mg/day
• Carvedilol[102]
  • Initiation dose: 6.25 mg once a day
  • Treatment goal: Maintaining SAP >90 mmHg or MAP >65 mmHg
  • Dose-adjustment: After 3 days, increase to 12.5 mg/day
  • Maximal daily dose: 12.5 mg/day

Follow-up and retitration of NSBBs in patients with ascites • In general, guiding NSBBs therapy according to the HVPG response is not needed but can be considered (if available) in high-risk settings.[54,55] • At every outpatient visit, ensure that heart rate is on target and SAP >90 mmHg or MAP >65 mmHg. [55,102] • NSBBs should be dose reduced or discontinued in case of persistently low blood pressure (more than two resting measurements). Once blood pressure returns to baseline, NSBBs can be reinitiated at lower dose or retitrated.[55]
When NSBBs should be discontinued? • In patients with ascites (especially if recurrent/refractory) and progressive hypotension (SAP <90 mmHg or MAP <65 mmHg), or in patients who develop an acute intercurrent condition such as bleeding, sepsis or SBP, NSBBs should be discontinued.[54,55] • When a diagnosis of AKI is made, NSBBs as well other drugs that could be associated with the occurrence of AKI should be immediately stopped.[54] • After recovery, reinstatement of NSBBs can be attempted at lower doses with careful monitoring.[54,55]
Which are the therapeutic alternatives in patients with ascites intolerant to NSBBs? • When NSBBs are not tolerated or any contraindication persist, patient bleeding risk can be managed by EBL.[54,55] • In patients with recurrent ascites (>3 paracenteses in 1 year) or refractory who cannot tolerate NSBBs TIPS should be considered.[55]

Abbreviations: AKI, acute kidney injury; EBL, endoscopic band ligation; HVPG, hepatic vein pressure gradient; MAP, mean arterial pressure; NSBBs, non-selective beta-blockers; SAP, systolic arterial pressure; SBP, spontaneous bacterial peritonitis; TIPS, transjugular intrahepatic portosystemic shunt.

contemplated. In these patients, TIPS will not only be able to control ascites in a high proportion of cases (about 40%–75%), but will also improve renal function and systemic inflammation and prevent first and further gastrointestinal bleedings.[91-93]

In short, the efficacy of NSBBs and the safety profile deserve long-term and prospective analyses. The impact of NSBBs on survival across various settings in patients with cirrhosis and ascites needs further research. For this purpose, more extensive RCTs using sophisticated cardiac and renal diagnostic tests will provide a better risk stratification of poor outcomes after β-blockade and could identify the subgroups of patients with a clear contraindication for treatment. New strategies based on non-invasive biomarkers, such as miRNA signatures, could also help us to identify patients more likely to benefit NSBBs.[94]

Finally, with the emerging incidence of non-alcoholic steatohepatitis cirrhosis, we will probably face new models of portal hypertension with some haemodynamic peculiarities.[95,96] Moreover, liver disease and cardiovascular comorbidities (diabetes mellitus, obesity, arteriosclerotic coronary disease and essential hypertension) usually coexist and can modify cardiac and kidney function. Consequently, a redefinition of the role of NSBBs in such a new population should be promptly addressed.

7 | CONCLUSIONS

NSBBs are the cornerstone to prevent first or recurrent variceal haemorrhage in patients with cirrhosis and ascites. However, in patients with refractory ascites and a high risk of renal failure, NSBBs can deteriorate the fragile cardiodynamic equilibrium. At this stage, NSBBs should be discontinued or carefully tapered to safer doses. An exhaustive follow-up is recommended of patients with refractory ascites.

DISCLOSURES

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ORCID

Luis Téllez https://orcid.org/0000-0002-9254-3891

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