Use of Non-selective Beta blockers in Decompensated Cirrhosis and ACLF

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Abstract

Purpose of Review Our understanding of beta blockers in liver cirrhosis has transformed over the last 40 years. However, questions remain over their safety in acute decompensation and acute on chronic liver failure. Since these conditions are associated with significant morbidity and mortality, a critical appraisal of recent literature is imperative to help guide clinicians.
Recent Findings The latest BAVENO guidelines now recommend carvedilol in all patients with clinically significant portal hypertension to prevent decompensation. There is significant data which shows safety of beta blocker use in decompensated cirrhosis but concerns remain in refractory ascites. There is also a short-term mortality benefit demonstrated in acute on chronic liver failure.
Summary With the latest guidelines and recent evidence, it seems beta blocker use will continue to increase. Future studies should aim to identify biomarkers that can determine who will benefit from beta blockers and help guide therapy.

Keywords Beta blockers · Decompensated cirrhosis · ACLF

Introduction

It was just over 40 years ago that the landmark study by Lebrec et al. demonstrated for the first time that propranolol significantly reduced portal hypertension (PH) in liver cirrhosis and therefore could prevent recurrent variceal bleeding [1]. Since then, there has been a wealth of published literature showing the efficacy of non-selective beta-blockers (NSBBs) in primary and secondary prevention of variceal bleeding, reducing the occurrence of spontaneous bacterial peritonitis (SBP), providing survival benefit and potentially reducing hepatocellular carcinoma (HCC) [2,3,4,5,6].

However, Sersté et al.raised concerns that NSBBs could increase mortality in individuals with cirrhosis and refractory ascites [7]. Subsequent research led to the development of the "therapeutic window hypothesis" which suggested

that NSBBs should not be used in early cirrhosis without significant varices where sympathetic nervous system activity (SNS) is near normal. In addition, they should not be used in end-stage cirrhosis where they could increase mortality by reducing cardiac contractility and mean arterial pressure (MAP) [8]. However, in recent years, several studies have suggested that NSBBs can be used safely in these settings and possibly provide survival benefit in most scenarios in decompensated cirrhosis [9, 10].

This paints the picture for the current controversy of NSBBs in cirrhosis. Questions exist over whether NSBBs should be used in advanced cirrhosis and in all individuals with clinically significant portal hypertension (CSPH), which is defined as a portal pressure ≥ 10 mmHg [11]. Furthermore, uncertainty remains over whether it is safe to continue NSBBs in acute decompensation (AD) and acute-on-chronic liver failure (ACLF), and if so, what criteria should be used to stop and when to re-start therapy? Once on treatment, the optimal method to monitor NSBB response has not been determined. Whilst there is increasing acceptance that invasive monitoring in the form of hepatic venous pressure gradient (HVPG) cannot be used routinely, questions remain over the accuracy of non-invasive monitoring. This review will aim to address some of these issues by focussing on

recent research in the last 3 years and will highlight important questions that still remain unanswered.

Role of NSBBs in Preventing Decompensation

One of the most significant recent publications is the PREDESCI trial, which was a multi-centre, double-blind, randomised controlled trial (RCT) that aimed to determine whether NSBBs provided benefit in terms of preventing decompensation and mortality in individuals with compensated cirrhosis and CSPH [12••]. The study involved 201 patients with a follow-up over 37 months. It is the first study to demonstrate that treatment with NSBBs was associated with a significant reduction in decompensation or death compared to placebo (16% vs 27%, $p = 0.041$). This was predominantly through a reduction in the development of ascites (9% vs 20%), which is the most prevalent decompensating event and for which, until now, there has been no preventative pharmacotherapy. Carvedilol was shown to have greater portal pressure-reducing effects compared to traditional NSBBs (16% vs 10%, $p = 0.04$), despite being in the group that did not respond to IV propranolol at time of HVPG measurement. Indeed, the recent BAVENO VII guidelines now advocate that NSBBs should be considered for all patients with CSPH to prevent decompensation [13••]. With such a significant recommendation to change practice, one could query whether these changes go too far. Questions have been raised over the applicability of the PREDESCI findings to clinical practice. The study involved invasive HVPG monitoring to diagnose CSPH. In addition, the aetiology for most patients in this study was hepatitis C and questions remain over whether these findings hold true for other populations that have predominantly alcohol- and non-alcohol steatohepatitis (NASH)–related cirrhosis.

McDowell et al.performed a retrospective analysis of 152 patients that had been recruited to an RCT of carvedilol versus variceal band ligation (VBL) in preventing first variceal bleed [14•]. Whilst median survival was significantly higher in the carvedilol cohort (7.8 years vs 4.2 years, $p = 0.03$), no difference was noted between transplant free-survival, liver-related mortality and decompensation events suggesting that the survival benefit observed in the patients treated with carvedilol was not purely liver related. These intriguing findings warrant prospective studies.

Previous studies have suggested that there may be a role for NSBBs in preventing HCC. Of note, Wijarnpreecha et al. performed a retrospective cohort study comprising 107,428 patients with cirrhosis. The 100-month cumulative incidence of HCC was lower in all NSBB groups: carvedilol (11.2%) vs no NSBB (15.7%) and propranolol (26.2%) vs no NSBB (28.8%) [15•]. A subgroup analysis of patients with

decompensated cirrhosis showed that the protective effect of NSBBs remained. The underlying mechanism is not known but hypothesised to be through inhibition of angiogenesis and carcinogenesis pathways. Future prospective studies should assess whether this benefit is observed across all severities of liver disease.

Given the current evidence, whilst some clinicians are reluctant, there is a strong argument for the use of NSBBs in all compensated patients with CSPH. However, future studies are needed to evaluate the role of NSBBs in a population more weighted with alcohol and NASH aetiologies. In addition, they should make use of non-invasive measures as opposed to HVPG to guide therapy and determine potential benefits.

Role of NSBBs in Decompensated Cirrhosis

As previously highlighted, the upper limit of the therapeutic window of NSBB in treating patients with decompensated cirrhosis remains controversial. Tergast et al.attempted to define this with a retrospective study of 624 patients with decompensated cirrhosis and ascites [16••]. They showed that patients with a MAP ≥ 65 mmHg had a superior 28-day transplant-free survival on NSBB ($p = 0.021$), but this benefit was lost in patients with a MAP < 65 mmHg. Indeed, early discontinuation of NSBB was associated with lower survival in patients with a MAP ≥ 65 mmHg ($p = 0.004$). A subset of the population with SBP was also analysed, and in those with a MAP ≥ 65 mmHg a survival benefit was observed with NSBBs ($p = 0.008$). A non-significant trend was also noted towards increased incidence of acute kidney injury (AKI) in those with SBP on NSBBs (HR: 2.957, $p = 0.085$), but this was not the case in those with a MAP ≥ 65 mmHg. A subsequent analysis showed that using a cut-off for systolic blood pressure of > 90 mmHg was comparable to a MAP threshold of 65 mmHg, which is consistent with current guidelines [17]. A limitation of this study is that 58% of the patients on NSBBs were on propranolol with a median dose of 30 mg/day. Other studies which have shown increased mortality with NSBBs have used higher doses of propranolol which may have skewed the positive findings seen here.

Ngwa et al. performed a retrospective analysis of 170 patients and observed a trend towards lower 90-day mortality in the NSBB cohort versus the non-NSBB group (6% vs 15% p = 0.06), despite having statistically higher Child Pugh and MELD scores [18]. An increased risk of AKI was noted in the NSBB group (22% vs 11%, $p = 0.048$). In the study, 44 patients had refractory ascites or a history of SBP and there was no difference in 90-day mortality and AKI between this cohort and the rest of the population. The study showed no survival benefit of NSBB beyond 90 days. Whilst a small study, this seems to demonstrate safety data of NSBBs in

patients with refractory ascites. In contrast, the study by Tellez et al.provided different results. They performed a prospective study of 18 patients with diuretic responsive ascites (DRA) and 20 with refractory ascites (RA) [19••]. Patients were treated with propranolol for 4 weeks with baseline and repeat measurements performed of Doppler echocardiography, as well as haemodynamic assessments of hepatic, kidney and cardiopulmonary systems. The study assessed overall systolic function using the ejection intraventricular pressure difference (EIVPD) as a load-independent marker. Propranolol caused a significant reduction in EIPVD in the RA compared to DRA cohorts (-20% vs -2%, $p < 0.01$). Renal perfusion pressure (RPP) reduced in both groups but dropped below 65 mmHg, the threshold for autoregulation in 55% in the RA group vs 12% in the DRA group ($p = 0.01$). This was reflected by a significant decrease in eGFR and increase in creatinine in the RA group (0.24 mg/dl, $p = 0.01$). This study suggests that in refractory ascites, NSBBs may blunt cardiac output and impair renal perfusion and therefore should be avoided. Whilst the study and haemodynamic measurements involved were robust, the numbers were small.

A recent meta-analysis also aimed to provide further clarity about the safety of NSBBs in decompensated cirrhosis and ascites [20]. In total, 8 studies with a total of 3267 patients were analysed. A sub-cohort analysis of patients with severe or refractory ascites showed similar mortality in the NSBB group (33.3%) compared with the non-NSBB group (32.1%). Three studies were deemed to be good quality and 5 fair quality. However, there was significant study heterogeneity ($I^2 = 87\%$) which led the authors giving a GRADE rating of the evidence as "very low". Hence, data from this meta-analysis are not possible to interpret.

Overall, whilst some studies have demonstrated safety of NSBBs in decompensated cirrhosis including in SBP, the literature would suggest ongoing concern for its use in patients with refractory ascites, particularly with regard to renal impairment. A MAP of 65 mmHg/systolic of 90 mmHg should be used to reduce or withhold NSBBs. Prospective studies should address whether NSBBs prevent further decompensation events in already decompensated patients.

Role of NSBBs in ACLF

Clinicians are understandably cautious to use NSBBs in ACLF given that it is a hyperinflammatory condition associated with circulatory dysfunction and multiorgan failure. Mookerjee et al. previously showed that in patients receiving NSBBs at the time of hospitalisation with ACLF, 28-day survival was significantly higher than those that were not receiving NSBBs [21]. More recently, the study by Tergast et al.which has been previously discussed also

studied 254 (41%) individuals with ACLF.[16••] Patients receiving NSBBs prior to hospitalisation had an increased 28-day transplant-free survival in a multivariate analysis ($p = 0.004$). As per the decompensated cirrhosis cohort, a MAP ≥ 65 mmHg conferred survival benefit with no difference observed with a MAP < 65 mmHg. Early discontinuation of NSBB in the whole cohort led to reduced survival ($p = 0.004$) and there was no association with renal impairment. This study also showed some positive impact of NSBBs with regard to lung and coagulation failure, suggesting benefits beyond purely reducing portal pressure. There is increasing evidence of the anti-inflammatory properties of NSBBs, reflected in this study. The NSBB cohort had lower white blood cells (WBC) ($p = 0.014$). However, no difference in CRP was noted. Further limitations of this study are its retrospective nature and that ACLF was only assessed at two time points. Therefore, some patients may have been missed out of the analysis.
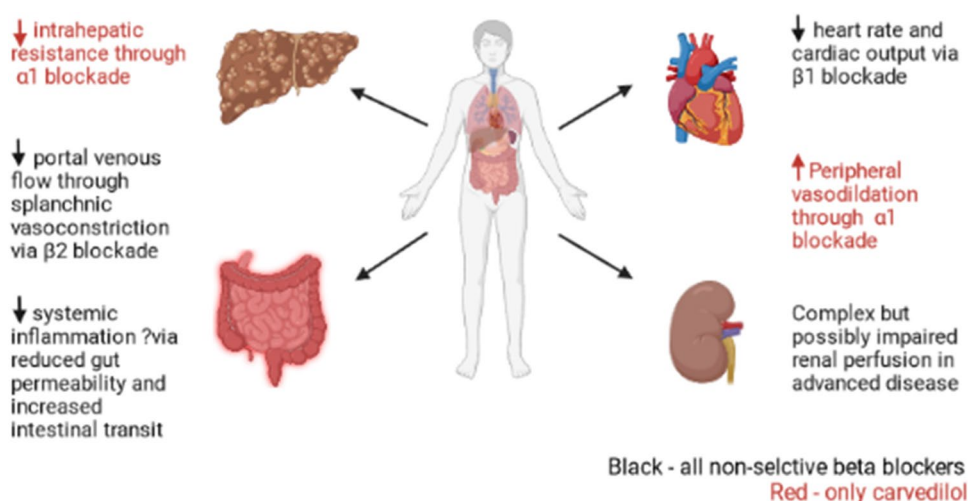
The Sarin group was the first to do prospective randomised control trial of NSBBs in ACLF [22••]. A total of 136 patients with ACLF and HPVG ≥ 12 mmHg were randomised to either carvedilol or placebo. When the carvedilol group was compared to the control group censored at 28 days, there was a reduction in (i) mortality (10.6% vs 24.3%, $p = 0.044$), (ii) AKI development (13.6% vs 35.7%, $p = 0.012$), (iii) development of SBP (6.1% vs 21.4%, $p = 0.013$) and (iv) variceal progression (11.1% vs 32.6%, $p = 0.021$). In the 2 weeks after commencing treatment, increases in ACLF grade were noted in 22.9% of controls and 6.1% of those on carvedilol ($p = 0.007$). However, this benefit was lost at 90 days [21]. Although this data is interesting, it is difficult to understand how this effect was achieved by carvedilol and before this data is used in clinical practice, further adequately powered, multicentre trial data are needed.

Preference of Type of NSBB and Dose Titration

The mechanisms of how NSBBs work in cirrhosis patients is demonstrated in Fig. 1 [23]. Sharma et al. conducted a post hoc analysis of a RCT comparing carvedilol with propranolol following an acute variceal bleed [24]. They demonstrated reduced incidence of ascites in the carvedilol group (40% vs 69.5%, $p = 0.04$). However, there were only 25 patients in the carvedilol arm and 23 in the propranolol arm. Therefore, the results should be interpreted with caution.

A recent meta-analysis by Sharma et al. compared carvedilol, traditional NSBBs and VBL as individual and combination therapies [25]. Whilst traditional NSBBs were associated with a higher odds ratio for bleeding than carvedilol (OR 3.05 [CI 1.20–7.74]), no difference was

Fig. 1 Effects of non-selective beta-blockers in liver cirrhosis

↓ intrahepatic resistance through α1 blockade

↓ portal venous flow through splanchnic vasoconstriction via β2 blockade

↓ systemic inflammation ?via reduced gut permeability and increased intestinal transit

↓ heart rate and cardiac output via β1 blockade

↑ Peripheral vasodildation through α1 blockade

Complex but possibly impaired renal perfusion in advanced disease

Black - all non-selctive beta blockers
Red - only carvedilol

observed in mortality. However, the authors do note there was a lack of RCTs including carvedilol and suggested a need for more prospective studies.

There is one recent prospective RCT carried out by Kalambokis et al.involving 96 patients on propranolol for variceal bleeding prophylaxis [26••]. Patients were randomised in a 2:1 ratio to switch to carvedilol at 12.5 mg/day ($n = 64$) or continue propranolol ($n = 32$). At 12 months, the carvedilol group showed a significant improvement in systemic vascular resistance, glomerular filtration rate and renal blood flow with significant decreases in plasma renin activity and plasma noradrenaline. After 2 years, the incidence of further decompensation was lower in carvedilol group compared to the propranolol group (10.5% vs 35.9%, $p = 0.003$). This was associated with improved survival (86% vs 64.1%, $p = 0.01$). However, the numbers are small with ascites being the most common decompensation event in

follow-up and this only being detected in 5 patients in the propranolol group and 2 in the carvedilol group.

Therapeutic heart rate reduction and blood pressure still seem to be the mainstay of titrating NSBBs, as well as the main outcome measures used in clinical trials to determine adequate dosing. Previous studies have demonstrated that lowering HR to 55–65 beats per minute (BPM) can improve myocardial oxygen demand and coronary perfusion with independent effects on portal hypertension [27]. Indeed, a previous meta-analysis showed a therapeutic of 5 bpm with NSBBs could provide a 14% reduction in mortality [28]. More recent data suggests the importance of monitoring blood pressure in guiding therapy rather than heart rate. Table 1 shows some potential options to help guide NSBB therapy in the future.

In summary, based on the current evidence, the first choice NSBB should therefore be carvedilol titrated to a maximum of 12.5 mg/day. Higher doses may lack addi-

Table 1 Potential parameters that can be used to guide NSBB therapy

Management	Tests	Findings/thresholds	References
Starting NSBBs	US/CT imaging	Presence of varices/ portal-systemic collaterals	Garcia-Tsao et al. [29]
	Fibroscan	LS > 25 kPa **or** LS > 20–25 kPa and platelets < 150×10^9/L	Garcia-Tsao et al. [29]
	Splenic stiffness	> 34.16kPA	Stefanescu et al. [36]
Titrating NSBBs	Heart rate	Reduction to 55–65	Bosch et al. [27]
	Splenic stiffness (SS)	1. Aim for ≥ 10% reduction in SS	Marasco et al. [42]
		2. Model incorporating change in SS with target threshold of 0.530	Kim et al. [30]
	Wet biomarkers	Aim reduction WBC ≥ 15%	Jachs et al. [33••]
Stopping NSBBs	Haemodynamic	Systolic BP < 90 mmHg (MAP < 65 mmHg)	Tergast et al. [16••] BAVENO guidelines [13••]
	Cardiac indices	1. Cardiac output < 5L/min	Alvarado-Tapias et al. [34•]
		2. Left ventricular stroke work index < 64.1 g-m/m^2	Giannelli et al. [35•]
	Wet biomarkers	Reduction in VWF < 5% on NSBBs	Jachs et al. [40••]

tional portal pressure reduction, whilst compromising

tolerability due to potential systemic hypotension [12••]. Indeed, the BAVENO VII guidelines advise carvedilol as the preferred choice of NSBB in compensated cirrhosis due to (i) superior reduction in HPVG, (ii) greater benefit in preventing decompensation and (iii) greater tolerability [13••].

Stopping and Re-starting NSBBs

There is limited literature addressing outcomes of stopping and re-starting NSBBs. Bhutta et al.performed a retrospective study of 716 patients of which 43% were on NSBB and 51% had refractory ascites [9]. They showed that NSBB use in hospitalised patients with ascites was not associated with increased mortality. Forty-nine percent of patients discontinued NSBBs during admission because of low blood pressure in the context of infection or AKI with no increase in mortality. This cohort had a mean systolic blood pressure of 103 mmHg at discontinuation of NSBB, compared to 114 mmHg on admission, which is higher than the EASL recommendation of 90 mmHg for reducing or stopping NSBBs [17]. However, there was a higher incidence of infection and renal impairment in those that discontinued NSBBs, and it is likely that there was a combination of factors which led to NSBB discontinuation. Forty percent of patients were re-commenced on NSBB prior to discharge which was predominantly driven by an increase in mean MAP to 84mmg (± 11) at re-initiation. However, mean follow-up for the study was only 14 ± 24 days and therefore long-term effects of this strategy are not known.

There is increasing evidence that cardiac indices could be used to guide NSBB therapy. Alvarado-Tapias et al.performed a retrospective analysis and demonstrated that in a cohort of patients with cirrhosis ($n = 190$), those who died had significantly lower cardiac output (CO) on NSBB and that CO could independently predict death (C-index 0.74) [34•]. The authors determined a cut off CO of 5L/min, below which a significantly higher mortality was observed (HR 0.44, $p = 0.004$), with a sensitivity of 81% and specificity of 60%. Indeed, this was retrospective study with no control arm and only 1–3-month follow-up. A further study by Giannelli et al.retrospectively analysed 584 patients, of whom 50% were receiving NSBBs and 33% had refractory ascites [35•]. Right heart catheterisation was performed to determine left ventricular stroke work index (LVSWI) which considers not only cardiac output but also arterial pressure providing a global assessment of cardiac function. In a multivariate analysis, they observed that receiving NSBBs with LSWI cut-off < 64.1 g-m/m led to higher risk of waiting list mortality than those not on NSBBs ($p = 0.0008$). Whilst these data provide guidance regarding withdrawal of NSBBs, this is a single-centre study and

LVSWI has not been studied extensively in cirrhosis and needs further validation. In addition, both studies discussed here required invasive measurements via cardiac catheterisation. Future studies should prospectively analyse cardiac indices using non-invasive techniques such as 2D echocardiography or MRI.

Future Research

The role Systemic Inflammation as a Target

It is known that ACLF and decompensated cirrhosis are associated with significant systemic inflammation and that this is associated with the severity of liver disease, portal hypertension–associated complications and mortality [37, 38]. Several studies have demonstrated that NSBBs can reduce systemic inflammation [21, 39]. It has been speculated that their mechanism may involve reducing gut permeability by reducing splanchnic blood flow and hence intestinal wall oedema, as well as increasing intestinal transit. Jachs et al. recently performed a retrospective study of 307 patients including 231 patients with decompensated disease [33••]. They showed a significant reduction in WBC with NSBB therapy (median: -2×10^9, $p = 0.011$), independent of HPVG response and this was most pronounced in Child–Pugh C patients. These changes significantly correlated with a reduction in CRP, procalcitonin and IL-6. The group also showed that a reduction of WBC $\geq$ 15% was associated with a reduced risk of further decompensation (HR 0.694, $p = 0.038$) and liver-related mortality (HR 0.561, $p = 0.013$). However, prospective, long-term studies with control arms are required to develop our understanding and potential therapeutic targets of systemic inflammation.

HCC and Portal Vein Thrombosis (PVT)

As stated previously in the review, retrospective studies have showed that NSBBs may reduce the incidence of HCC. Whilst not the focus of this review, some historic studies have suggested that NSBBs can increase incidence of PVT, although the prospective PREDESCI study did not show this [12••]. More data are needed to substantiate these findings.

Non-invasive Biomarkers/Imaging

A robust biomarker for non-haemodynamic response and guiding NSBB therapy remains elusive. Recently Jachs et al.performed a retrospective analysis of 159 patients with clinically stable decompensated cirrhosis [40••]. The patients had paired HVPG/von Willebrand factor (VWF) measurements prior to and then subsequently whilst they

were receiving NSBBs. Those who had a ≥ 5% decrease in VWF were deemed as "VWF-responders" versus those who did not, "VWF-non-responders". The VWF responders had significantly reduced CRP and procalcitonin levels compared with the non-responders suggesting reduced inflammation. In a multivariate analysis, the VWF-responder group was associated with a reduced risk of; decompensation (adjusted hazard ratio [aHR] 0.55, $p = 0.20$), ACLF (aHR 0.40, $p = 0.007$), AKI (aHR 0.37, $p = 0.01$) and liver-related death (aHR 0.332, $p < 0.001$). This suggests vWF may be a useful biomarker to guide who will benefit from NSBB therapy. The limitations of this study are its retrospective nature. In addition, the vWF responders had a significantly higher proportion of patients on carvedilol and it is unclear how much of the benefit seen was due to NSBB class.

There is a wealth of data addressing the utility of imaging in assessing fibrosis progression and portal hypertension [41, 36]. Some recent evidence suggests that whilst liver stiffness (LS) is well validated, it may not be as effective as splenic stiffness (SS) in determining NSBB response. Marasco et al. performed a prospective study to assess haemodynamic response in patients on NSBBs [42]. They showed that changes in HVPG did not correlate with LS ($r = 0.12$, $p = 0.65$) but did correlate with SS ($r = 0.78$, $p < 0.0001$). A reduction in SS ≥ 10% correlated with being a HVPG responder (HVPG reduction ≤ 10% or < 12 mmHg). However, the study was small with only 20 patients included with no multivariate analysis. These findings were supported by a larger study done by Kim et al. assessing 106 patients on carvedilol using acoustic radiation forced impulse (ARFI) [30]. Baseline and repeat measurements of HVPG, LS and SS on carvedilol demonstrated in a multivariate analysis that only a change in SS was a predictor of haemodynamic response to NSBBs (≈80%).

Potential biomarkers for future studies include copeptin and asymmetric dimethylarginine (ADMA). Copeptin has demonstrated a predictive role in ascites formation, HE and survival, and ADMA has shown correlation with portal hypertension and mortality [31, 32]. Future studies should be prospective in nature and aim to validate biomarkers/imaging and help guide the following treatment decisions: who to treat with NSBBs, titrating dosages and defining when to stop/re-start treatment.

Future of NSBB Use

Currently, screening endoscopy is recommended in individuals at risk of high-risk varices defined by liver stiffness (LS) ≥ 20 kPa or platelet count ≤ 150×10^9/L [13••]. A new paradigm proposed by *Garcia-Tsao* et al. involves non-invasive measures to identify those with CSPH (either LS > 25 kPa or LS > 20–25 kPa and

platelets < 150×10^9/L, or presence of varices or portal-systemic collaterals on imaging). Those who fulfil criteria would be treated with carvedilol with the aim of preventing all-cause decompensation. Those who did not fulfil the criteria would have annual LS and platelet measurements [29]. Many countries were forced to do this during the pandemic due to resource limitation. Not only would this be cost-effective in terms of reducing screening endoscopies but it would also be preferable to patients. The exceptions to this would be individuals who are intolerant of NSBBs or present with decompensated cirrhosis for which the initial paradigm stands. Whilst a cut-off LS > 25 kPa is valid for alcohol related liver disease, hepatitis B and C, it performed poorly in obese patients with non-alcoholic steatohepatitis (detecting only 62.8% of CSPH) and in patients with cholestatic disorders such as primary biliary cholangitis [43].

The jury on the universal use of carvedilol 12.5 mg OD in all individuals with CSPH to prevent decompensation is out and is a matter of ongoing debate despite the Baveno VII guidance. Whilst there is significant safety data in decompensated cirrhosis and we would advocate carvedilol use, concerns remain for patients with refractory ascites and risk of AKI. It is clear that NSBBs should be held and/or reduced when the MAP is < 65 mmHg or systolic blood pressure is < 90 mmHg and re-introduced cautiously as the blood pressure improves.

Conclusion

This review highlights that we are in a new era of NSBB management. Recent evidence has shown safety in clinical settings where historic literature would suggest stopping therapy. However, we must not become overzealous, and concern does remain in certain scenarios that have been discussed in this paper. The golden ticket for researchers in this field remains a non-invasive biomarker to guide NSBB therapy. It is an exciting time, and we look forward to future studies that will hopefully clarify the unanswered questions that remain.

Declarations

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Papers of particular interest, published recently, have been highlighted as:
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