β-blockers in advanced cirrhosis: more friend than enemy

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Abstract

Nonselective beta-adrenergic blocker (NSBB) therapy for the prevention of initial and recurrent gastrointestinal bleeding in cirrhotic patients with gastroesophageal varices have been used for the past four decades. They are considered the treatment cornerstone for varices and have
become the standard of care. However, a 2010 study from the group that pioneered β-blocker therapy suggested a detrimental effect of NSBBs in decompensated cirrhosis, especially in patients with refractory ascites. Since then, numerous additional studies have incompletely resolved whether NSBBs are deleterious, although more recent evidence weighs against a harmful effect. The possibility of a ‘therapeutic window’ has also been raised. We aimed to review the literature to analyze the pros and cons of NSBBs in patients with cirrhosis, not only with respect to bleeding/mortality but other potential benefits and risks. β-blockers are highly effective to prevent first bleeding and recurrent bleeding. Furthermore, NSBBs improve congestion/ischemia of the gut mucosa, decrease intestinal permeability, and therefore indirectly alleviate systemic inflammation. β-blockers shorten the electrocardiographic prolonged QTc interval and also may decrease the incidence of hepatocellular carcinoma. On the other hand, the possibility of deleterious effects in cirrhosis has not been completely eliminated. NSBBs may be associated with an increased risk of portal vein thrombosis, although this could be correlative artefact. Overall, we conclude that β-blockers in cirrhosis are much more friend than enemy.

Key words: cirrhosis, non-selective beta-adrenergic receptor blocker, portal hypertension, varices, bleeding, refractory ascites, end stage liver disease.
“Keep your friends close, but your enemies closer”


**Introduction**

Nonselective beta-adrenergic blockers (NSBBs) have been used in the management of portal hypertension in patients with cirrhosis for four decades \(^1\), \(^2\). Lebrec and colleagues in 1980 conducted a randomized trial and found that propranolol at doses reducing the heart rate by 25% significantly decreased portal pressure in cirrhotic patients with portal hypertension \(^1\). They speculated that the portal-hypotensive effect of propranolol might be useful in the prevention of recurrent bleeding caused by esophageal varices. This seminal study helped usher in the ‘golden age’ of cardio-hepatology, the study of cardiovascular anomalies in liver disease and vice-versa. Nowadays NSBBs are established as standard of care to prevent variceal bleeding and rebleeding \(^3\).

What was not to like about \(\beta\)-blockers in cirrhosis? Numerous studies clearly demonstrated their efficacy in reducing the incidence of a first variceal bleed (primary prophylaxis) and rebleeding (secondary prophylaxis), with relatively few serious adverse effects (reviewed in: \(^4\)-\(^7\)). The theoretical risk of reducing cardiac output and thus inducing arterial hypotension and tissue ischemia proved to be generally unfounded as the chronic \(\beta\)-blockade allowed unopposed \(\alpha\)-adrenergic vasoconstriction to offset the reduction in cardiac output and maintain arterial pressure in most patients \(^4\), \(^8\). Only a small percentage of cirrhotic patients showed significant hypotension after starting \(\beta\)-blockade. Furthermore, known adverse effects such as precipitation/worsening of asthma, increasing electrocardiographic first-degree heart block and reduced exercise tolerance were clinically insignificant in the vast majority of patients.
It was therefore surprising to the liver world a decade ago when Lebrec’s group published a study suggesting that β-blocker therapy in patients with advanced cirrhosis and refractory ascites was associated with significant harms including decreased survival. Coming from the acknowledged ‘founding father’ of β-blockers in portal hypertension, this study received great attention and several centres attempted to confirm or refute this hypothesis.

β-blockers may exert harmful effects in cirrhotic patients by several potential mechanisms: 1) decrease in mean arterial pressure (MAP), heart rate and ventricular contractility, thus diminishing organ perfusion; 2) precipitate acute kidney injury; 3) trigger paracentesis-induced circulatory dysfunction after large-volume paracentesis; 4) the portal-hypotensive effect may increase the risk of occlusive portal vein thrombosis. Besides the effects on variceal bleeding and the kidney, other potential benefits and harms have been suggested (Table 1). Herewith we review the pros and cons of nonspecific β-blockers in patients with cirrhosis.

**NSBBs reduce portal pressure**

It is well known that β-adrenoceptors increase cardiac conduction, heart rate and contractility, and thereby increase cardiac output. Patients with cirrhosis are characterized by decreased arterial pressure and increased cardiac output, which is called hyperdynamic circulation. Among the multiple causes of hyperdynamic circulation, the adrenergic system plays a critical role and the cardiovascular β-adrenoceptor is overdriven. Blockade of β-receptors should protect the heart from damage due to sympathetic overactivation, ie, catecholamine cardiotoxicity. On the other hand, portal venous hypertension derives from the increased blood flow resistance in the liver and portal vein (backward flow theory), and increased mesenteric blood flow
(forward flow theory). The hydrodynamic formula $P = Q \times R$ (portal pressure = mesenteric blood flow x liver resistance), implies that blockade of $\beta_1$-receptors decreases cardiac output which reduces mesenteric blood flow and portal pressure. Another target of NSBBs is the $\beta_2$-adrenergic receptor which vasodilates the mesenteric circulation. Blockade of $\beta_2$-receptors allows an unopposed vasoconstrictive $\alpha$-adrenergic effect in the splanchnic vasculature $^{12}$, which also decreases blood flow and thus pressure in the portal vein.

Poynard and colleagues analyzed four randomized controlled trials (RCTs) and found that in two years of follow-up, 78% of $\beta$-blocker treated-patients (2 RCTs used propranolol, 2 nadolol) did not have upper gastrointestinal bleeding; this percentage was 65% in controls ($P < 0.01$). About 90% of the patients on NSBB treatment had no fatal bleeding; this percentage was 82% in patients without NSBB treatment ($P = 0.01$). 62% of the survivors in the NSBB group did not experience variceal hemorrhage after two years; this percentage was 53% in patients without NSBB treatment ($P < 0.05$). After adjustment for the cause, severity of cirrhosis, ascites and variceal size, NSBB groups still had fewer total bleeds ($P < 0.01$) and fatal bleeds ($P < 0.01$) compared with placebo controls. The authors concluded that $\beta$-blockers are effective on preventing first bleeding and reducing the mortality rate associated with gastrointestinal bleeding, regardless of the cirrhosis severity $^{13}$.

Patients with acute-on-chronic liver failure (ACLF) who present with variceal bleeding represent a special subpopulation. In that group, a recent study reported by Shin and colleagues from the Korean ACLF consortium demonstrated that the presence of ACLF was associated with significantly increased mortality compared to those without ACLF$^{14}$. 
Furthermore, Kumar and colleagues demonstrated that NSBB improves survival, and decreases the number of acute kidney injury (AKI) and spontaneous bacterial peritonitis events in patients with ACLF\textsuperscript{15}. Therefore, NSBB may be a useful therapeutic agent for ACLF patients with variceal bleeding.

It is documented that a sizable minority, approximately 30-50\% of patients with cirrhosis, do not respond to NSBB therapy hemodynamically with a significant drop in portal pressure\textsuperscript{4,5,7}. Interestingly, NSBBs remain effective in the prevention of variceal hemorrhage in a large proportion of hemodynamic nonresponders\textsuperscript{4,5,7}. This suggests that NSBBs may prevent other triggers of variceal bleeding, such as inflammation and infection\textsuperscript{16}.

**NSBBs alleviate systemic inflammation**

Moreau and colleagues investigated the relationship between systemic inflammation in patients with acute-on-chronic liver failure (ACLF) and found that the intensity of systemic inflammation (as judged by markers such as high leukocyte count and plasma C-reactive protein (CRP) concentration) parallels the severity of ACLF\textsuperscript{17}. The degree of inflammatory reaction was an independent predictor of post-enrolment development of ACLF and ACLF-associated mortality. Jalan et al. also found that, in patients with ACLF, the ability to resolve inflammation (reduce CRP) was correlated with prognosis\textsuperscript{18}. Cazzaniga and coworkers studied not only patients with ACLF, but also cirrhotic patients consecutively admitted to the hospital and found that systemic inflammation is closely associated with the severity of liver disease, portal hypertension-related complications and poor survival\textsuperscript{19}.
The underlying mechanism underlying these changes may be the so-called ‘inflammatory phenotype’ of cirrhosis. Patients with cirrhosis are prone to develop increased levels of bacteria and bacterial toxins in the circulation. In part, this is due to defective innate immune function in cirrhosis, including defective bactericidal and opsonic activities, chemotaxis, phagocytosis, monocyte function and low serum complement levels. In addition, the combination of portal hypertension congesting the gut mucosa and impaired bowel motility leads to increased intestinal permeability and bacterial overgrowth. These factors thus induce gut translocation of bacteria and endotoxin and unleash a humoral and cell-mediated inflammatory response, the ‘inflammatory phenotype’. In cirrhosis, the inflammatory phenotype may be involved in pathogenesis of several cardiovascular complications including cirrhotic cardiomyopathy.

Several studies found that NSBBs alleviate systemic inflammation. β-blockers may exert this effect by reducing mesenteric venous congestion as well as directly decreasing intestinal permeability. Mookerjee and coworkers demonstrated that NSBB treatment was associated with lower grades of ACLF, and significantly more patients with ongoing β-blocker treatment improved. This improvement was associated with a considerably lower white cell count. In comparison, patients not treated with β-blocker tended towards worsening of ACLF during their hospital stay. Furthermore, the patients that discontinued NSBBs had significantly higher 28-day and 3-month mortality rates.

NSBB decrease electrocardiographic QT intervals

The QT interval on an electrocardiogram (ECG) is a measure of ventricular depolarization and repolarization. The QT interval must be corrected for heart rate (QTc) and there are several
methods for doing this, but the commonly-used Bazett formula should be avoided in favor of the more stringent Friedericia method. Approximately 30-60% of patients with cirrhosis have a prolonged QTc interval.

Two studies reported that cirrhotic patients with prolonged QTc had significantly lower survival rates than those with a normal QTc interval. However, these interesting results must be confirmed by larger prospective observational studies, because this association may merely reflect that QT intervals generally correlate with degree of liver dysfunction, ie, more advanced cirrhosis shows greater prolongation of QTc. Peter and colleagues demonstrated that QTc, serum Na⁺ concentration and β-blocker use predicted development of hepatorenal syndrome in 78 consecutive patients admitted with variceal bleeding. However, as there were only 14 cases of hepatorenal syndrome (HRS), this small study needs to be confirmed by larger trials.

β-blockers decrease the QTc interval. Henriksen and colleagues found that acute β-blockade reduced cardiac output, heart rate, hepatic venous pressure gradient (HVPG) and QTc 90min after an oral dose of propranolol. The decrease of QTc was observed only in cirrhotic patients with prolonged QTc, not controls. Furthermore, the percentage decrease in QTc correlated with reduction in HVPG and cardiac output. Zambruni et al. showed a similar result with nadolol dosed chronically over 1-3 months; only those patients with prolonged QTc showed a decrease.

Although prolonged QTc has been associated with increased risk of ventricular arrhythmias and even sudden cardiac death in several noncirrhotic heart diseases, whether this still holds true in patients with cirrhosis is doubtful. To date there is no convincing evidence that prolonged QT interval in cirrhosis remains anything more than an electrophysiological curiosity, nor whether correcting the prolonged QT interval conveys any definite clinical benefit.
NSBB and hepatocellular carcinoma (HCC)

There are several possible theoretical pathways by which an NSBB may reduce the incidence of HCC: 1) NSBBs decrease portal pressure. Ripoll and colleagues demonstrated that HVPG is an independent predictor of HCC development. They divided patients into two groups based on a cutoff line of 10 mmHg of HVPG and found that patients whose HVPG are more than 10 mmHg have a 6-fold increase in the HCC incidence; 2) β-blockers inhibit the effect of catecholamines. It is well known that catecholamines can stimulate cancer cell migration, invasiveness and proliferation. Studies have demonstrated that NSBBs prevent or have therapeutic effects on different cancers such as gastric, pancreatic and breast cancers; 3) β-blockers inhibit the inflammatory phenotype. Inflammation is a key driver of malignant transformation in hepatocytes; 4) β-blockers have anti-angiogenic effects.

Herrera and colleagues reported on 173 HCV-related cirrhotic patients for a median of 11 years follow up in a Spanish national registry. Seventy-three were treated with NSBBs. They reported that the likelihood of HCC diagnosis was significantly higher in patients who were not taking β-blockers. The multivariate survival analysis using a Cox regression model showed that chronic treatment with β-blockers was the only independent predictor for the development of HCC (hazard ratio=0.30, 95% confidence interval=0.12–0.79; P=0.015). These results, although promising, must be interpreted cautiously because the two groups were not randomized, and selection bias cannot be ruled out. For example, one can easily imagine that patients on long term NSBB are monitored more regularly and closely than those not taking any vasoactive drug therapy. It is possible that closer monitoring of one group may have improved the outcomes.
A meta-analysis in 2015 of 12 trials showed that NSBB reduced HCC incidence by a statistically significant but tiny margin (-2.6%). Therefore the number needed to treat to prevent one case of HCC was 38. It remains unclear if this tiny reduction in incidence is biologically meaningful. Moreover the meta-analysis was severely underpowered because there were not enough patients nor HCC cases. Of 1391 patients, only 112 developed HCC. The authors estimated that a robustly powered meta-analysis would require approximately 3700 patients. Therefore they emphasized that more clinical trials are necessary.

**NSBB and portal vein thrombosis**

Xu and colleagues performed a meta-analysis to examine the question of β-blockers increasing the risk of portal vein thrombosis (PVT). The theoretical underpinning for this hypothesis is that a decrease in portal venous pressure and blood flow may cause turbulent or sluggish flow in this vessel and thus increase the risk of clotting. These authors analyzed a total of 9 studies, after eliminating more than 6400 (!) case reports and studies. They concluded that there is a significant 4.6-fold increased risk of PVT in patients taking β-blockers. However the quality of the studies is relatively low and there was significant heterogeneity in the available dataset.

This issue will therefore need to be answered by a large controlled prospective observational study. However, even a perfect meta-analysis cannot answer the key question of why such an association exists. Is the association truly cause-and-effect or a correlational artefact? We believe the latter; the association simply reflects the nature of the population being treated with β-blockers, those with advanced cirrhosis. The risk of PVT is also known to correlate with the...
stage of liver failure. Therefore it may be that β-blockers do not actually cause PVT but both are simply a correlational association of advanced liver disease.

**NSBB and survival in advanced cirrhosis**

In the portal hypertension world, probably the major scientific ‘shockwave’ of 2010 was the aforementioned study from Lebrec’s group. Sersté et al. reported that NSBB was associated with a deleterious mortality effect in patients with refractory ascites. The median survival time was 20 months in patients not treated with propranolol and 5 months in those treated with propranolol (95% CI, 4.8-35.2 vs 3.5-6.5 months, P < 0.01). Furthermore, the one-year survival rate was significantly lower in propranolol-treated patients compared with untreated subjects (64% vs 19%, 95% CI: 52%-76% vs 9%-29%, P < 0.01). However, this study was retrospective and not randomized, which raises a significant possibility of selection bias. In particular, an issue that may explain the survival difference was the variceal status in the two groups. All the NSBB-treated patients had esophageal varices, while this percentage in the NSBB-untreated group was only 4%. The third issue is that liver function (total bilirubin) was worse in the β-blocker treated group.

Following on from this study, other centers tried to test the hypothesis of possible harm. To date, the literature on the effect of NSBBs on outcomes remains incompletely clarified, at least if one simply reviews the large number of conflicting studies individually (table 2). Some studies showed beneficial effects, no difference, or deleterious effects. We believe that the large literature dataset is best examined by systematic reviews and meta-analyses. Two
technically well-performed meta-analyses have been published in the past five years and these will be discussed.

A 2016 meta-analysis by Chirapongsathorn and colleagues included studies up to January 2015, and examined 3 RCTs and 8 observational studies. There were 1206 deaths in the total cohort of 3145 patients with ascites. All-cause mortality was similar in the two groups (taking or not taking NSBB) in the overall cohort, as well the subgroups with non-refractory ascites and refractory ascites. Survival rates were similar in the two cohorts, whether examined at 6, 12, 18 or 24 months of follow up. Evidence quality was low in the observational studies, but good in the 3 RCTs.

In 2019, Wong and coworkers performed another meta-analysis. This analysis included 8 studies including the 3 RCTs and 3627 total patients with any grade of ascites. They reported that there was no significant increase in all-cause mortality in patients treated with β-blockers. Subgroup analysis of only patients with severe or refractory ascites also showed no significant mortality differences. Only the 3 RCTs were graded to be good quality, 5 were considered only fair quality.

Given that two independent and technically well-performed meta-analyses within the past 5 years have both shown a similar lack of harmful effect of β-blockers on survival in patients with ascites, we believe this issue, at least in cirrhosis with ascites, can now be ‘laid to rest’. β-blockers are not an enemy in this population.

What about the subgroup of patients with compensated cirrhosis? In that regard, Villanueva and colleagues recently reported the results of a randomized, placebo-controlled, multicentric Spanish trial (PREDESCI) in patients with compensated cirrhosis but clinically significant portal
hypertension, defined as HVPG >9 mmHg\textsuperscript{52}. Patients were randomized to either propranolol or carvedilol depending on if they demonstrated an adequate portal-hypotensive response to an intravenous test dose of propranolol, or not, respectively. Patients were maintained on chronic drug or placebo therapy over a median of 36 months of followup, and the main endpoints were decompensation events defined as onset of variceal bleeding, ascites or encephalopathy. Survival was also tracked.

This study found that long-term treatment with NSBBs improved decompensation-free survival, mainly by decreasing ascites onset\textsuperscript{52}. During the follow up period, heart rate, cardiac index and HVPG were significantly decreased in the \(\beta\)-blocker group compared to the placebo group. Compensated cirrhotic patients with clinically significant portal hypertension, even those who had no or small varices, gradually progressed to develop decompensation. The early use of \(\beta\)-blockers for these patients reduced the number of decompensation events\textsuperscript{52}. This carefully-conducted RCT argues in favour of long term NSBB therapy to prevent disease progression and improve survival in patients with compensated cirrhosis and portal hypertension, but needs confirmation by other studies.

**NSBB and kidney function**

In 2015, Sersté et al. reviewed 139 patients with severe alcoholic hepatitis and found that 86 patients (62\%) developed AKI. Patients with NSBBs had comparable MELD scores, Maddrey scores and medical histories. 43 out of 48 NSBB users (90\%) experienced AKI within 168 days, compared to 50\% in non-NSBB users (\(P = 0.0001\)). They concluded that NSBB is an independent risk factor for AKI in these patients\textsuperscript{10}. Mandorfer and colleagues found that \(\beta\)-blockers significantly increased the risk of hepatorenal syndrome in cirrhotic patients with
spontaneous bacterial peritonitis. In a cohort of patients with advanced cirrhosis and ascites referred for transplantation, Kim and coworkers also reported that NSBBs are associated with AKI.

Sheiner et al investigated compensated cirrhotic patients. During a 3 year followup period, they found that the renal function was comparable between patients with and without NSBB treatment; the incidence of AKI was similar, even when the patient had ascites and MAP <90 mmHg.

Ngwa and colleagues recently reported on a cohort of 170 consecutive patients referred for liver transplant evaluation to their center. 38 patients were taking β-blockers. There was an increased risk of AKI in the group taking β-blockers compared to those who were not (22% vs 11%, P<0.05). However, AKI episodes were mild stage 1, and all patients recovered. Short-term mortality at 90 days was actually superior in the NSBB group (6% vs 15%; p<0.05).

As all these studies are nonrandomized and retrospective, the conclusions must be regarded with caution. At present, there is insufficient evidence to conclude that NSBBs increase the risk of AKI or HRS in patients with ascites.

A related question is whether β-blockers cause paracentesis-induced circulatory dysfunction (PICD) in patients with cirrhosis and refractory ascites. PICD is usually defined as >50% increase in plasma renin activity after large volume paracentesis. In 2011, a hemodynamic study from the Lebrec group showed that PICD developed in 8 of 10 patients with refractory ascites after large volume paracentesis. The same patients acted as their own controls and had repeated haemodynamic and blood testing after being weaned off β-blockers after their varices had been adequately treated. When these patients were no longer on β-blockers, only 1 of 10 developed PICD.
Ferrarese and coworkers reported discordant results compared to the above study. These authors studied 10 patients with refractory ascites before and after starting NSBB therapy. They found that before β-blockers, large volume paracentesis significantly decreased the systemic vascular resistance (1896 to 1348 dyn·s·cm⁻⁵; \( p = 0.028 \)) and peripheral vascular resistances (measured in the forearm) (47 to 30 mmHg·min·dl·ml⁻¹; \( p = 0.04 \)); cardiac output also increased, but did not reach statistical significance (3.9 to 4.5 L/min; \( p = 0.06 \)). When patients were taking NSBB, large volume paracentesis did not significantly decrease systemic vascular resistance (2002 vs 1798 dyn·s·cm⁻⁵; \( p = 0.1 \)) or increase cardiac output (3.4 to 3.8 L/min; \( p = 0.13 \)). Only 2 patients before taking β-blockers developed PICD; this rose to 3 after drug was started (p=NS). The authors suggested that the negative inotropic effect of NSBB may be compensated by a milder decrease of vascular resistance after paracentesis. Thus this study concluded that β-blockers do not increase the incidence of paracentesis-induced circulatory dysfunction.

We conclude that the scant size of the available literature on PICD with β-blockers precludes any definitive conclusion at present. Moreover, PICD is a laboratory definition that may have relatively little direct clinical relevance. We believe it is more important to track clinical and measurable hemodynamic outcomes such as MAP, cardiac output, hyponatremia, glomerular filtration rate and occurrence of AKI/HRS.

**Window theory**

The window theory is based on the concept that the sympathetic nervous system activity is nearly normal in the early stages of cirrhosis, so NSBBs will exert only modest effects at this stage. However, at the later endstage, although the sympathetic system is highly active, NSBBs by reducing cardiac contractility and arterial pressure, may cause tissue hypoperfusion and
death, especially when patients have refractory ascites. β-blockers are the only vasoactive drugs shown to improve survival in cirrhosis and this beneficial effect may be limited to the window phase, ie, the middle phase between mild and decompensated cirrhosis. However, exactly when this middle phase window should be opened and closed remains unclear.

Krag et al proposed that the indications for NSBB usage should be: 1) HVPG ≥10 mmHg, 2) development of medium-to-large esophageal varices and 3) ascites. D’Amico et al divided patients with cirrhosis into four stages: stage 1: no varices or ascites; stage 2: varices, no ascites, stage 3: ascites ± varices; stage 4: bleeding ± ascites. Stages 1 and 2 are considered compensated, whereas stages 3 and 4 are decompensated. Whether we can combine the window theory with the cirrhotic stage concept needs further study.

A further debate is whether the therapeutic window even exists. Leithead et al. evaluated 322 patients with endstage liver disease and ascites awaiting liver transplantation, of whom about half were on NSBB treatment. The MELD score, frequency of hepatocellular carcinoma and refractory ascites were comparable between the two groups (taking or not taking NSBB). These authors demonstrated that patients on β-blockers had lower mortality compared with non-NSBB patients. The beneficial effects on survival were even demonstrated in the subgroup of patients with refractory ascites.

**β-blockers in cirrhosis: friend or foe?**

We believe that although the initial studies seemed to show deleterious effects of beta blockers in patients with refractory ascites, these suffered from important methodological limitations including the retrospective and nonrandomized study designs. On the other hand, more recent
studies including carefully conducted prospective randomized trials and several meta-analysis have either shown no deleterious effect of beta blockers on survival or even improved survival. Furthermore, the concept of a therapeutic window, while interesting and theoretically attractive, is frustratingly difficult to actually test in any kind of clinical study design. The subgroup question of whether β-blockers impair renal function in patients with moderate or advanced cirrhosis remains unresolved. There are no RCTs in this topic, and the few available studies suffer from significant methodological limitations. The prudent approach espoused by almost all clinicians is to stop β-blockers in the relatively small percentage of patients who experience a significant drop in arterial pressure. It is likely that this is the group at risk of developing renal dysfunction on NSBB therapy. Our overall conclusion is that β-blockers are probably not deleterious and in fact may even exert beneficial effects on survival and reducing decompensation. Accordingly the benefits probably significantly outweigh potential harms.

**Carvedilol**

Carvedilol is discussed separately because it is a β-blocker with additional intrinsic α-1-blocking effects, which may be superior to traditional NSBBs in reducing portal pressure and risk of variceal bleeding. However, because of the additional α-blockade, it is much more prone to cause hypotension, so doses need to start low and be carefully titrated upwards. Current guidelines recommend the use of NSBBs, carvedilol or variceal band ligation (VBL) for primary prevention of variceal bleeding. Carvedilol is effective for primary prevention of variceal bleeding, and some patients who do not respond to traditional NSBBs may respond to carvedilol.
In a recent Cochrane meta-analysis to compare carvedilol with traditional NSBBs, which included 10 RCTs with 810 participants with esophageal varices, there were no clear beneficial or harmful effects of carvedilol versus traditional NSBBs on mortality, upper gastrointestinal bleeding and adverse events. A systematic review with network meta-analysis by Sharma compared the efficacy of NSBBs, carvedilol and VBL in the primary prevention of variceal bleeding and overall survival. Even though each treatment decreased all-cause mortality and variceal bleeding risk, none were clearly superior to the others due to a lack of adequately powered studies. The ongoing CALIBRE trial will compare carvedilol vs VBL as primary prophylaxis in patients with medium to large esophageal varices, with preliminary results perhaps available in late 2021.

Sinha and coworkers evaluated the effects of long-term carvedilol therapy on mortality in 325 patients with ascites. The long-term overall survival was significantly better in the carvedilol group (n=132) than the no-carvedilol group (adjusted HR 0.59; 95% CI 0.44-0.80). However the survival benefit was no longer significant in patients with moderate or severe ascites. Unfortunately, like many other studies, this was a nonrandomized retrospective analysis, so possible selection bias significantly limits the robustness of any conclusions.

Recently, Premkumar and coworkers prospectively evaluated the effects of carvedilol on cardiac function and survival in patients with cirrhosis. Carvedilol alone or carvedilol combined with a novel drug ivabradine were administered to achieve the target heart rate, defined as heart rate reduction to 55-64 beats/min. Ivabradine selectively inhibits the cardiac pacemaker ion current and thus reduces heart rate without affecting blood pressure. This study found that left ventricular diastolic dysfunction was reversed in the carvedilol+ivabradine group. Various neurohormones, such as norepinephrine, N-terminal brain natriuretic peptide (BNP), plasma
renin activity, and aldosterone levels were reduced in patients who achieved the target rate reduction. The achievement of the rate reduction target reduced the risk of encephalopathy and acute kidney injury, and improved overall survival. Combination therapies, especially with new drugs, therefore show great promise and need further investigation.

Conclusion

In conclusion, the ‘friendly’ qualities of NSBB in the treatment of cirrhosis include prevention of primary and recurrent variceal hemorrhage, mitigation of systemic inflammation and possibly decreasing the progression of compensated cirrhosis to decompensated. β-blockers may also slightly decrease the incidence of HCC, although more studies are needed. The unfriendly aspects include the usual known adverse drug effects such as asthma, heart block, decreased exercise tolerance, as well as potentially more serious effects such as hypotension and worsening of renal function. There is possibly an association with β-blockers and risk of portal vein thrombosis.

Considering the indisputable proof of efficacy in variceal bleeding and the probability or possibility of significant other benefits, we conclude that β-blockers are much more friend than enemy. Indeed to quote the most famous line from ‘The Godfather’, β-blockers in patients with cirrhosis should be considered “an offer you can’t refuse”.

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References

12. Mookerjee RP, Mehta G. All beta-blockers are created equal, but some beta-blockers are more equal than others. *Liver Int*. 2013;33:501-503


Table 1. Summary of Possible Effects of β-adrenergic Blockers

<table>
<thead>
<tr>
<th>Beneficial Effects</th>
<th>Deleterious Effects</th>
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<tr>
<td>Decrease variceal bleeding risk</td>
<td>Decrease survival in decompensated cirrhosis?</td>
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<tr>
<td>a) Primary prophylaxis</td>
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<td>b) Secondary prophylaxis</td>
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<tr>
<td>Decrease portal hypertensive gastropathy</td>
<td>Decrease renal perfusion</td>
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<tr>
<td>Decrease prolonged QTc interval</td>
<td>Increase portal vein thrombosis?</td>
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<tr>
<td>Decrease systemic inflammation?</td>
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<tr>
<td>Decrease hepatocellular carcinoma risk?</td>
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Table 2. NSBB and Survival in Patients with Cirrhosis

NSBBs decrease survival

<table>
<thead>
<tr>
<th>First author</th>
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<th>Drug dose</th>
<th>Study design</th>
<th>Sample size</th>
<th>Authors’ conclusion</th>
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<td>Serste et al. 9</td>
<td>Cirrhotic patients with refractory ascites</td>
<td>Propranolol 113±46 mg</td>
<td>Retrospective</td>
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<td>de Souza et al. 73</td>
<td>Cirrhotic patients with acute variceal bleeding</td>
<td>Propranolol (40 mg to start); nadolol (20 mg to start)</td>
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<td>Kalambokis et al. 74</td>
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<td>Child-Pugh B (n=96), Child-Pugh C (n=75)</td>
<td>Decreased survival in 2 yr followup in Child-Pugh B group; and in 6 mo followup in Child-Pugh C group</td>
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NSBBs have no effect on survival

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<td>Sarin et al. 75</td>
<td>Consecutive cirrhotic patients</td>
<td>Propranolol 20-360mg</td>
<td>RCT</td>
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<td>No effect on variceal growth, bleeding, or mortality.</td>
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<td>Bhutta et al. (2018)</td>
<td>Hospitalized patients with cirrhosis and ascites</td>
<td>Nadolol 20mg, propranolol 40mg, carvedilol 12.5mg</td>
<td>Multicentre database; retrospective</td>
<td>718, (307/411) (with/without β-blocker)</td>
<td>No effect on survival overall, nor refractory ascites subgroup</td>
</tr>
<tr>
<td>Tripathi et Grade II or larger</td>
<td>Carvedilol</td>
<td>RCT</td>
<td>152</td>
<td>Prevented the first variceal bleedings</td>
<td></td>
</tr>
<tr>
<td>Study</td>
<td>Condition</td>
<td>Treatment</td>
<td>Study Type</td>
<td>N</td>
<td>Result/Outcomes</td>
</tr>
<tr>
<td>-------------------</td>
<td>------------------------------------------------</td>
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<tr>
<td>Leathead et al. 61 (2015)</td>
<td>Ascites and refractory ascites on transplant waitlist</td>
<td>Propranolol 80 mg (10-240); Carvedilol 6.25mg (3.125-12.5)</td>
<td>Retrospective</td>
<td>322</td>
<td>NSBB reduces waitlist death</td>
</tr>
<tr>
<td>Mookerjee et al. 26 (2016)</td>
<td>Acute-on-chronic liver failure</td>
<td>Propranolol 40 mg (20-80); Nadolol 40 mg (20-80); Carvedilol 12.5mg (6.25-25)</td>
<td>Prospective, observational</td>
<td>349</td>
<td>Increased survival probability</td>
</tr>
<tr>
<td>Sheiner et al. 55 (2017)</td>
<td>Compensated 68.7%</td>
<td>Propranolol/60 (95.6 ± 31.2) Carvedilol/30 (19.2 ± 11.0)</td>
<td>Retrospective</td>
<td>176</td>
<td>Improved TIPS-/transplant-free survival</td>
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<tr>
<td>Onali et al. 77 (2017)</td>
<td>Assessed for LT suitability</td>
<td>Propranolol 118 median 80mg Carvedilol 10 median 6.25mg</td>
<td>Retrospective</td>
<td>316</td>
<td>Improved overall survival; no effect on survival in patients with refractory ascites</td>
</tr>
<tr>
<td>Sinha et al. 45 (2017)</td>
<td>Consecutive cirrhotic patients</td>
<td>Carvedilol 12.5mg</td>
<td>Retrospective</td>
<td>325</td>
<td>Increased overall survival, and in patients with mild ascites; no effect in</td>
</tr>
<tr>
<td>Study</td>
<td>Patient Characteristics</td>
<td>Treatments</td>
<td>Study Design</td>
<td>Participants</td>
<td>Findings</td>
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<tr>
<td>Sharma et al. [69] (2019)</td>
<td>Large varices, no prior history of bleeding</td>
<td>NSBB, isosorbide-mononitrate, carvedilol</td>
<td>Systematic review with network meta-analysis</td>
<td>3,362</td>
<td>Decreased mortality and first variceal bleeding with a lower risk of serious complications</td>
</tr>
<tr>
<td>Villanueva et al. [52] (2020)</td>
<td>Compensated, significant portal hypertension without high-risk varices</td>
<td>Propranolol (&lt; 160 mg); carvedilol (≤25 mg/day) for non-responders</td>
<td>RCT</td>
<td>201</td>
<td>Increase decompensation-free survival; reduce the incidence of ascites</td>
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<tr>
<td>Premkumar et al. [71] (2020)</td>
<td>Single-center cirrhosis clinic Carvedilol (6.25-25 mg/day)+/-ivabradine (5-15mg/day)</td>
<td>RCT</td>
<td>189</td>
<td>improved LV diastolic dysfunction; reduced decompensation risk; improved survival</td>
<td></td>
</tr>
<tr>
<td>Ngwa et al. [56] (2020)</td>
<td>Candidates for liver transplantation</td>
<td>Propranolol (20mg/day)</td>
<td>Retrospective</td>
<td>170</td>
<td>improved short-term survival</td>
</tr>
</tbody>
</table>

**Figure legend**

Mechanisms underlying effects of β-adrenergic blockade in cirrhotic patients. CO: cardiac output; HR: heart rate; PV: portal vein; AKI: acute kidney injury.