Review

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The changing role of beta-blocker therapy in patients with cirrhosis

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Summary

Cirrhosis is a leading cause of death in the United States and worldwide. Beta-blockers have been established in numerous studies as part of the cornerstone of the medical management of cirrhosis, particularly in the primary and secondary prevention of variceal hemorrhage. However, new evidence has cautioned the use of beta-blockers in patients with end-stage cirrhosis and refractory ascites. In this article, we review the beneficial effects of beta-blocker therapy, the potential harms of aggressive beta-blocker therapy, and provide suggestions regarding the appropriate use of this class of medications in patients with cirrhosis.

Introduction

Cirrhosis is a leading cause of mortality in the United States and worldwide [1,2]. Within the developed world, the leading causes of cirrhosis include alcoholic liver disease, hepatitis C, and more recently, non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH). Ever since NASH was described as a cause for cryptogenic cirrhosis [3], there has been increasing recognition that NASH may become the most common cause of advanced liver disease in the coming decades [4]. It is projected that between 2015 and 2030, NASH cirrhosis will overtake hepatitis C cirrhosis as the most common indication for liver transplantation in the United States [5]. Studies have also implicated NASH risk factors including metabolic disease as being co-morbid with chronic hepatitis C [6] and alcoholic liver disease [7]. Some patients have all three insults to their liver.

Given the comorbidity of hypertension, metabolic syndrome, and NASH cirrhosis, increasing numbers of patients with chronic liver disease are now on antihypertensives for essential hypertension. In a study of outpatient antihypertensive prescribing behavior, ambulatory visits by adults having uncomplicated essential hypertension increased 33% from 29.8 million visits in 1993 to 39.6 million visits in 2004 [8]. Beta-adrenergic antagonists ("beta-blockers") have been established as part of the cornerstone of the medical management of hypertension [9], as well as acute coronary syndrome [10], and congestive heart failure [11].

Beta-blockers have also been well established in the prevention of variceal hemorrhage in patients with cirrhosis [12–15]. The use of non-selective beta-blocker therapy in the secondary prevention of variceal hemorrhage was first introduced in 1981 [12]. Subsequent studies expanded the role of non-selective beta-blockers to include primary prevention of variceal hemorrhage in patients with known cirrhosis and large esophageal varices [13]. Beta-blocker therapy has been demonstrated to be cost-effective [16–18], and may be also beneficial in the prevention of other complications of cirrhosis and portal hypertension, including bleeding from portal hypertensive gastropathy [19,20], and the development of spontaneous bacterial peritonitis [21]. However, new studies have cautioned the use of beta-blockers in patients with decompensated cirrhosis [22,23]. Updated recommendations are therefore needed regarding the appropriate use of beta-blockers in patients with cirrhosis.

Beta-blockers in cirrhosis

In its early stages, liver disease is often asymptomatic. As cirrhosis advances, portal hypertension develops, resulting in ascites, hepatic encephalopathy, and variceal hemorrhage. Ascites is the most common major complication of cirrhosis, occurring in 50% of patients within ten years of diagnosis [24]. The presence of ascites is an ominous landmark in the progression of cirrhosis, as 15% of patients with ascites will succumb within 1 year, and 44% within 5 years [25]. Over one third of patients diagnosed with cirrhosis develop esophageal varices within three years of diagnosis [26].

Circulatory disturbances also develop, including increased cardiac output and heart rate, decreased systemic vascular resistance, and decreased mean arterial blood pressure. The most widely accepted explanation of the hemodynamics in cirrhosis, the peripheral arterial vasodilatation hypothesis [27], states that systemic vasodilatation from reduced systemic vascular resistance leads to arterial underfilling, which together with the sequestration of fluid into the peritoneal cavity, activates

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salt-retaining mechanisms and neurohormonal systems such as the sympathetic nervous system and the renin-angiotensin-aldosterone system to counteract low arterial blood pressures [28]. As a result, although plasma and blood volume is increased in cirrhosis, patients with decompensated cirrhosis and ascites have a decreased effective arterial blood volume [27–30]. Paracentesis further induces arteriolar vasodilation and results in additional decrease in effective arterial blood volume [31].

It is in this pathophysiological context that beta-adrenergic blockade has both theoretical benefits as well as adverse effects. Non-selective beta-blockers such as propranolol and nadolol achieve their effects through the dual mechanism of reducing cardiac output via beta-1 adrenergic blockade, and reducing portal blood flow through splanchnic vasoconstriction via beta-2 adrenergic blockade [32]. Both mechanisms are clearly necessary for these medications to be safe and effective in cirrhosis; selective beta-1 antagonists such as metoprolol and atenolol have been shown to be less effective and are not recommended for the prophylaxis of variceal hemorrhage [33,34].

Benefits of beta-blocker therapy

The use of non-selective beta-blocker therapy was first introduced by Lebrec and colleagues in 1981 [12]. In their study, 74 patients presenting with a first episode of variceal bleeding were randomized to either placebo or oral propranolol targeted to a 25% reduction in heart rate. They found that 96% of patients in the propranolol group were free of recurrent gastrointestinal bleeding at one year, compared to 50% of patients in the placebo group [12]. The findings from this and additional studies established the role of non-selective beta-blockers in the secondary prevention of gastrointestinal hemorrhage [35].

Subsequent studies expanded the role of non-selective beta-blockers. Pascal and colleagues in 1987 studied the role of propranolol in the prevention of a first upper gastrointestinal bleeding event in patients with known cirrhosis [13]. In their study, 230 patients with large esophageal varices without previous episodes of bleeding were randomized to either placebo or propranolol targeted to a 20–25% reduction in heart rate. They found that 74% of patients in the propranolol were free of variceal bleeding at one year, compared to 39% in the placebo group, suggesting that propranolol has a role in decreasing the incidence of the first episode of upper gastrointestinal bleeding in patients with cirrhosis [13]. Similarly, two year survival was 72% in the propranolol group, compared to 51% in the placebo group, demonstrating a significant survival benefit in the use of propranolol in patients with cirrhosis and large esophageal varices [13]. A meta-analysis from Poynard and colleagues in 1991 analyzed four randomized clinical trials [13,36–38], and determined that non-selective beta-blockers are effective in preventing first bleeding episode and reducing the mortality rate from gastrointestinal bleeding among patients with cirrhosis [14]. Additional meta-analyses have since established the use of non-selective beta-blockers as first-line pharmacotherapy in both primary and secondary prevention of variceal hemorrhage (Table 1) [15,39].

Adverse effects of beta-blocker therapy

Despite the proven clinical effectiveness of beta-blocker therapy, its success is limited by potential adverse effects and suboptimal treatment adherence. Studies in the cardiology literature have shown that patient adherence to beta-blocker therapy following myocardial infarction decline substantially over time [40]. Similarly, studies in the hepatology literature have suggested that despite well established guidelines and recommendations, as few as 6–22% of patients with known medium or large varices received primary prophylaxis with beta-blockers [41]. Side effects led to treatment discontinuation in approximately 15% of patients in the various beta-blocker trials in patients with cirrhosis [32].

Beta-blocker therapy can result in both cardiac as well as non-cardiac adverse effects. The decrease in cardiac output from beta-1 antagonism may cause major cardiac side effects. Despite the central role of beta-blockers in the management of congestive heart failure, beta-blockers may also exacerbate heart failure, or even precipitate heart failure in patients with pre-existing cardiac dysfunction and borderline compensation who are reliant upon sympathetic drive [42]. Beta-blockers also significantly decrease chronotropy, depressing conduction through the atrioventricular node. This can result in symptomatic bradycardia, or even high grade heart block [43].

The acute withdrawal of beta-blocker therapy can lead to serious morbidity and potential mortality [44]. Abrupt cessation of beta-blocker therapy can result in accelerated angina, myocardial infarction, and sudden death, even in patients who do not previously have coronary artery disease [45,46]. These symptoms are presumably due to rebound sympathetic activity resulting in a hyperadrenergic state, which is more likely to occur with shorter-acting medications such as propranolol [47].

Most of the major non-cardiac adverse effects of beta-blockers result from the non-selective beta-adrenergic blockade. Non-selective beta-blockers can result in increased airways resistance in patients with bronchospasm, and therefore should be avoided in patients with known bronchospastic diseases [48]. Nonselective beta-blockers can also cause exacerbations of peripheral artery disease due to the reduction of cardiac output and blockade of beta-2-adrenergic skeletal muscle vasodilation, resulting in local vascular insufficiency. Initial studies of patients with peripheral artery disease taking propranolol showed complications of claudication, cold extremities, absent pulses, cyanosis, and impending gangrene [49]. Additionally, in patients with diabetes mellitus, glucose recovery from insulin-induced hypoglycemia is dependent on epinephrine-mediated beta-adrenergic mechanisms, which can be dangerously impaired by the use of non-selective beta-blockers such as propranolol [50]. Finally, commonly reported side effects from beta-blockers also include depression, fatigue, and sexual dysfunction [51]. It has been previously hypothesized that these symptoms are associated with central nervous system effects of older generation lipophilic beta-blockers such as propranolol, however a meta-analysis of clinical trials showed no increased risk of depression and small increases in fatigue and sexual dysfunction, without significant differences by the degree of beta-blocker lipid solubility [52].

Studies of beta-blockers in the cardiology literature have almost uniformly suggested that side effects are decreased with selective beta-1 antagonists. However, selective beta-1 antagonists such as metoprolol and atenolol have been shown to be less effective in portal hypertension and are not recommended for the prophylaxis of variceal hemorrhage [33,34]. Additional studies focused on adverse effects of non-selective beta-blockers have been generally lacking. It should be noted that adverse effects

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Table 1. Key studies supporting beta-blocker usage.

Ref No.	Author	Year	Type of Trial	Results	*p* value	Mortality	*p* value
[12]	Lebrec *et al.*	1981	Propranolol *vs.* placebo for secondary prevention of variceal bleeding	Free of recurrent GI bleeding 96 *vs.* 50%	<0.0001	Not studied	
[13]	Pascal *et al.*	1987	Propranolol *vs.* placebo for primary prevention of variceal bleeding	Free of first variceal bleeding 74 *vs.* 39%	<0.05	Two year survival 72 *vs.* 51%	<0.05
[36]	Lebrec *et al.*	1988	Nadolol *vs.* placebo for primary prevention of variceal bleeding	Free of first variceal bleeding 97 *vs.* 77%, only statistically significant in subgroup of compliant patients	<0.02	Not studied	
[37]	Ideo *et al.*	1988	Nadolol *vs.* placebo for primary prevention of variceal bleeding	Free of first variceal bleeding 94 *vs.* 70%	<0.02	No significant difference	
[38]	Italian multicenter project	1989	Propranolol *vs.* placebo for primary prevention of variceal bleeding	Free of first variceal bleeding 74 *vs.* 59%	n.s.	42 month survival 51 *vs.* 59%	n.s.
				In subset of patients without ascites, free of first variceal bleeding in 83 *vs.* 61%	0.028	42 month survival 65 *vs.* 66%	n.s.

n.s., not significant.

of beta-blockers have mostly been reported in the cardiology literature, rather than the hepatology literature. In clinical trials and meta-analyses in the hepatology literature, beta-blockers have not shown decreased survival, and have almost consistently shown benefit. It is therefore not clear whether the lack of reported adverse effects are due to existing studies not having been specifically designed to uncover adverse effects, the inability to generalize results from the cardiology literature to patients with cirrhosis, or other immeasurable factors such as patient non-compliance or type II statistical error.

The differential effect of beta-blockers in cirrhosis

Recent studies suggest that beta-blockers may be effective only within a particular clinical window of advanced liver disease [26]. Outside of this window, beta-blockers may be ineffective in early cirrhosis with some increase in adverse events, and potentially harmful in advanced cirrhosis (Table 2 and Fig. 1).

In patients with early cirrhosis, the ineffectiveness of beta-blocker therapy can be attributed to a milder splanchnic and systemic hyperdynamic circulatory state [53]. This was suggested in a large multicenter clinical trial from Groszmann and colleagues in 2005, which showed the non-selective beta-blocker timolol to be ineffective in preventing the development of varices in unselected patients with cirrhosis and portal hypertension [53]. In their study, 213 patients with cirrhosis and portal hypertension confirmed with hepatic venous pressure gradient (HVPG) measurements were randomized to receive either placebo or timolol targeted to a 25% reduction in heart rate or a goal heart rate of 55 beats per minute. At a median follow-up period of 54.9 months,

Table 2. Key studies suggesting potential harm from beta-blocker usage.

Ref No.	Author	Year	Type of trial	Major findings
[53]	Groszmann *et al.*	2005	Timolol *vs.* placebo for prevention of gastrointestinal varices	No statistically significant difference in development of gastrointestinal varices. Adverse events 18% in timolol group *vs.* 6% in placebo group ($p = 0.006$)
[58]	Krag *et al.*	2010	CI and MAP in cirrhosis and ascites	6 month survival 50% and 1 year survival <40% when CI <1.5 L/min/m^2
				6 month survival >90% and 1 year survival >70% when CI >1.5 L/min/m^2
				6 month survival 60% and 1 year survival <40% when MAP ≤80 mmHg
				6 month survival >80% and 1 year survival >70% when MAP >80 mmHg
[22]	Serste *et al.*	2010	Propranolol in patients with cirrhosis and refractory ascites	1 year survival 19% in patients treated with propranolol, 1 year survival 64% in patients not treated with propranolol (p <0.0001)
[23]	Serste *et al.*	2011	Propranolol and development of paracentesis-induced circulatory dysfunction	Significant decrease in MAP after paracentesis with development of paracentesis-induced circulatory dysfunction among patients given propranolol, decreased development of paracentesis-induced circulatory dysfunction after discontinuation of propranolol

CI, cardiac index; MAP, mean arterial pressure.

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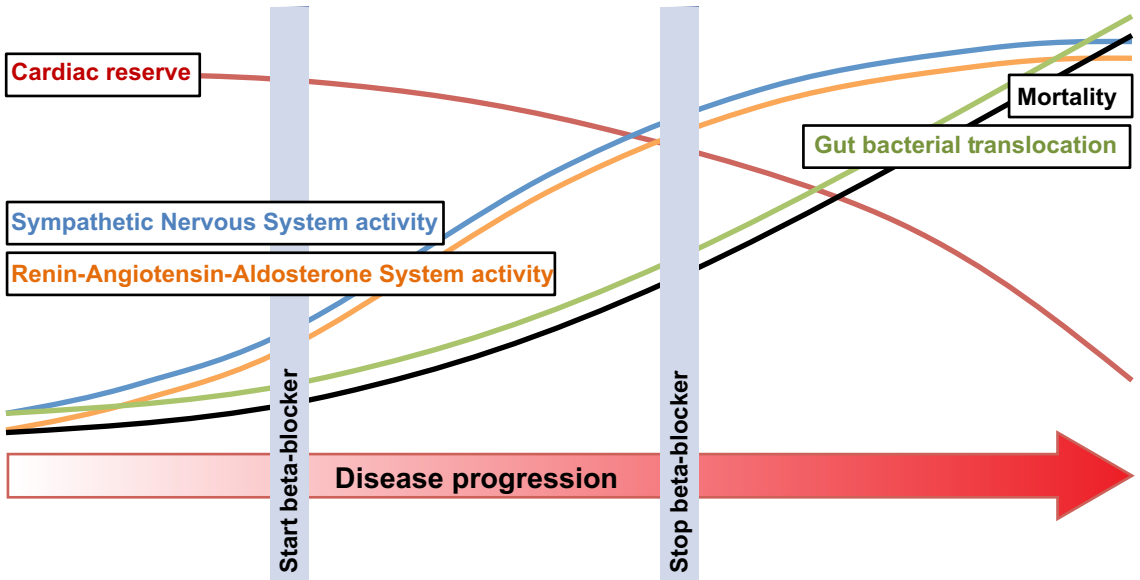

Early cirrhosis	Decompensated cirrhosis (medium-large varices)	End-stage cirrhosis (refractory ascites)
• Beta-blockers have **no effect** on survival, may increase adverse events	• Beta-blockers **improve** survival by reducing variceal bleeding and gut bacterial translocation	• Beta-blockers **reduce** survival due to negative impact on cardiac reserve, resulting in decreased perfusion to vital organs during periods of stress and precipitation of hepatorenal syndrome
• May use beta-blocker for cardiovascular indications		
• Cardiac reserve intact	• Cardiac reserve intact but steadily declining	• Cardiac compensatory reserve critically impaired, with baseline hypotension
• SNS and RAAS activity at baseline	• SNS and RAAS activity increased but not maximal	• SNS and RAAS maximally stimulated, can no longer maintain adequate blood pressure
• Low risk of gut bacterial translocation	• Increased risk of gut bacterial translocation	• High risk of gut bacterial translocation
• Low risk of mortality	• Increased risk of mortality	• High risk of mortablity

Fig. 1. The differential effect of beta-blockers in cirrhosis. Modified with permission from: Krag A, Wiest R, Albillos A, Gluud LL. The window hypothesis: haemodynamic and non-haemodynamic effects of beta-blockers improve survival of patients with cirrhosis during a window in the disease. Gut 2012;61:967–969. Copyright © 2012 BMJ Group.

the trial showed no significant difference in the development of gastrointestinal varices or variceal bleeding. However, the study demonstrated a statistically significant increase in the number of adverse events (48% in the timolol group *vs.* 32% in the placebo group), which included bradycardia, fatigue, shortness of breath, syncope, claudication, and impotence. It was noted that drug intolerance limited the ability to further up-titrate timolol dosing, as patients were reluctant to tolerate its side effects. The study concluded that the use of beta blockers cannot be widely recommended because of the increased incidence of serious side effects [53].

In advanced cirrhosis, a number of circulatory changes occur, including the up-regulation of the sympathetic nervous system [54,55] and of the renin-angiotensin-aldosterone system [56,57]. These circulatory changes, along with the development of sodium and water retention and the formation of ascites, are aimed at maintaining adequate cardiac output and organ perfusion. They reflect an adaptive response to the peripheral vasodilation, effective hypovolemia, and arterial hypotension that accompanies advanced cirrhosis. However, as cirrhosis progresses, the cardiovascular system eventually loses its compensatory ability. It is at this stage that the maintenance of blood pressure and cardiac output is paramount in prolonging overall survival, and there is evidence that the hemodynamic effects of beta-blockers in reducing blood pressure and cardiac output may actually result in decreased survival in this subset of patients [22,26,58].

Blood pressure and survival

The correlation between blood pressure and survival in patients with cirrhosis was suggested by Llach and colleagues in 1988 [59]. In their survival analysis of 139 patients with cirrhosis and ascites, mean arterial pressure was found to be an

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independent predictor of survival [59]. Mean arterial pressure of ⩽82 mmHg was the single variable most strongly correlated with shortened survival; the survival probability rate of patients with mean arterial pressure ⩽82 mmHg was approximately 20% at 24 months and 0% at 48 months, in contrast with approximately 70% at 24 months and 50% at 48 months among patients with mean arterial pressure >82 mmHg [59]. It was also observed that patients with ascitic fluid protein ⩽1 g/dl correlated with a significantly shorter survival, similar to previous observations that patients with low ascitic fluid protein levels are predisposed to developing spontaneous bacterial peritonitis [60]. The study concluded that the increased activity of the renin-angiotensin-aldosterone and sympathetic nervous systems in patients with cirrhosis with ascites is a homeostatic response to maintain arterial pressures near or within normal range, and that mean arterial pressure is possibly itself a reflection of the degree of alteration of the splanchnic and portal circulation [59].

A hyperdynamic circulation with arterial underfilling from splanchnic vasodilation also results in the development of hepatorenal syndrome, a major cause of mortality in patients with cirrhosis [61]. Krag and colleagues demonstrated that a low cardiac output state predicts the development of hepatorenal syndrome and subsequent survival in patients with cirrhosis and ascites [58]. In their study of 24 patients with cirrhosis and ascites, patients with a cardiac index below 1.5 L/min/m^2 had significantly decreased survival compared to those with a cardiac index above 1.5 L/min/m^2 [58]. The study also showed that cumulative survival in patients with mean arterial pressure below 80 mmHg was 60% at 6 months and <40% at 12 months; in contrast, survival in patients with mean arterial pressure above 80 mmHg was >80% at 6 months and >70% at 12 months [58]. The study concluded with a suggestion that in patients with low cardiac indices and ascites, beta-blockers and/or other methods of decreasing systemic pressures may worsen hemodynamics, resulting in the development of hepatorenal syndrome and subsequent mortality [58].

Midodrine

Additional evidence confirming the importance of maintaining cardiac output in patients with advanced cirrhosis has been suggested among studies of midodrine, an alpha-1 adrenergic agonist [62–66]. Angeli and colleagues in 1998 demonstrated that midodrine has a preferential effect on the splanchnic circulation, and its acute administration overall improves systemic hemodynamics, renal function, and sodium excretion in non-azotemic patients with ascites [62]. Their findings were followed by subsequent studies, which introduced the combination of octreotide and midodrine as a treatment for type 1 hepatorenal syndrome [67,68]. In a recent randomized controlled study from Singh and colleagues, midodrine therapy was shown to result in a significant increase in urinary volume, urinary sodium excretion, and mean arterial pressure; with decrease in plasma renin activity and in overall mortality [66]. The study concluded that midodrine improved systemic hemodynamics without causing renal or hepatic dysfunction [66].

ACE inhibitors

Studies investigating the effects of angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) in patients with cirrhosis have likewise shown that reducing cardiac index and mean arterial pressures results in worsened outcomes in patients with advanced cirrhosis and ascites [69–72]. The latest clinical practice guidelines from both the American Association for the Study of Liver Diseases and the European Association for the Study of the Liver on the management of adult patients with ascites due to cirrhosis recommend against the use of ACE inhibitors and ARBs in patients with ascites due to concerns of hypotension and renal failure [73–75].

Carvedilol

Similarly, studies of newer-generation beta-blockers such as carvedilol concluded that while carvedilol has a potent portal hypotensive effect that may be superior to propranolol, it has greater potential to cause systemic hypotension, especially in patients with cirrhosis and ascites [76–79]. Thus far, evidence supporting the use of carvedilol for portal hypertension has been limited [80]. In one study from Banares and colleagues, 35 patients were randomized to carvedilol, propranolol, or placebo [77]. Carvedilol was found to markedly reduce HVPG greater than propranolol; patients receiving carvedilol achieved HVPG <12 mmHg or >20% decrease from baseline HVPG in a greater proportion than propranolol (64% *vs.* 14%, p <0.05). However, carvedilol also caused significant arterial hypotension with average decrease in mean arterial pressure of −17.2% in the carvedilol group *vs.* −3.4% in the propranolol group [77]. In a follow-up study, 51 patients were randomized to long-term carvedilol or propranolol [78]. Carvedilol was shown to cause a greater decrease in HVPG than propranolol, with a greater proportion of patients achieving an HVPG reduction of >20% or <12 mmHg. However, the study again showed a significant decrease in mean arterial pressure of −11% in the carvedilol group *vs.* −5% in the propranolol group. Patients receiving carvedilol also had significant increases in plasma volume, body weight, and worsening of pre-existing ascites [78].

More recently, Tripathi and colleagues compared carvedilol *vs.* variceal band ligation in a randomized controlled trial of 152 patients with medium or large esophageal varices [79]. The carvedilol group was found to have lower rates of first variceal bleeding of 10% *vs.* 23% in the variceal band ligation group. There were no significant differences in overall mortality or bleeding-related mortality. The study concluded that carvedilol is effective for primary prophylaxis of variceal bleeding in patients with high-risk esophageal varices [79]. Thus, while initial studies concluded that the clinical applicability of carvedilol is limited by its systemic hypotensive effects, more recent studies suggest a potential role for carvedilol in the primary and secondary prevention of variceal bleeding. However, the data at present is inconclusive at best and merits additional investigation.

Despite the central role of beta-blockers in the treatment of hypertension, acute coronary syndrome, and congestive heart failure, recent concerns have been raised by the cardiology community regarding the use of beta-blockers. Several studies have suggested that no evidence existed that beta-blockers prevent first episodes of cardiovascular events in patients with hypertension, and in some trials, beta-blockers actually had worse outcomes compared to other classes of antihypertensives [81]. One meta-analysis concluded that beta-blockers were associated with a higher risk of death from cardiovascular causes when compared to renin-angiotensin blockade [82]. Newer guidelines no longer

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recommend the use of beta-blockers in the initial treatment of hypertension [83,84]. Furthermore, data from the POISE trial studying the effects of perioperative metoprolol in patients undergoing non-cardiac surgery found that although metoprolol decreased the risk of myocardial infarction, cardiac revascularization, and atrial fibrillation, it also resulted in an excess risk of death, stroke, and clinically significant hypotension and bradycardia [85].

Beta-blockers in refractory ascites

The challenges and adverse effects of beta-blockers appear to be most pronounced in patients with advanced cirrhosis and refractory ascites. In 2010, almost 30 years following their landmark article on the use of propranolol for the prevention of recurrent variceal bleeding [12], Lebrec and colleagues (Serste *et al.*) showed in a prospective observational study that the use of beta-blockers in patients with refractory ascites may be associated with poor survival, suggesting that beta-blockers should be contraindicated in this subclass of patients [22], Their study included 151 patients with cirrhosis and refractory ascites, who all regularly underwent large-volume paracentesis and intravenous albumin administration. The overall mean survival was 10 months, with a 41% probability of survival at 1 year. However, the median survival was dramatically lower in patients treated with propranolol (5 months, with 19% probability of survival at 1 year), as compared to the median survival in patients who were not treated with propranolol (20 months, with 64% probability of survival at 1 year) [22]. This four-fold decrease in median survival with the administration of propranolol in patients with refractory ascites was highly statistically significant [22]. In their editorial regarding this study, Wong and Salerno stated that although there were methodological concerns to the study, an important question was raised as to the safety of propranolol in patients with cirrhosis and refractory ascites [86].

A subsequent self-controlled cross-over study by Lebrec and colleagues (Serste *et al.*) showed that beta-blockers are associated with the development of paracentesis-induced circulatory dysfunction, further suggesting that beta-blockers are correlated with poor survival in this group of patients [23]. In this study involving 10 patients in a cross-over design, patients given propranolol experienced a significant decrease in mean arterial pressure with no significant change in heart rate following paracentesis, with the development of paracentesis-induced circulatory dysfunction in eight of the ten patients [23]. After discontinuation of beta-blockers, patients experienced a significant increase in heart rate with no significant change in mean arterial pressure following paracentesis, with the development of paracentesis-induced circulatory dysfunction in only one of the ten patients. The study concluded that among patients with cirrhosis and refractory ascites, beta-blockers may be associated with an increased risk of paracentesis-induced circulatory dysfunction, which although may be clinically silent in itself, is associated with shortened survival [87].

One important observation mentioned by Lebrec and colleagues in their recent study [22] is that the effects of beta-blockers in the subset of patients with cirrhosis and refractory ascites had actually never been studied. Even the original studies, which demonstrated a clear and convincing survival advantage of beta-blockers in patients with cirrhosis and esophageal varices, excluded the subset of patients with refractory ascites. One of the specific inclusion criteria in the original study by Lebrec and colleagues in 1981 was that "*ascites was absent or mild and transient*" [12]. In the study by Pascal and colleagues in 1987, patients were included only if they had a Child-Pugh score of less than 14 [13]. In the meta-analysis from Poynard and colleagues in 1991 of four trials of beta-blockers in the primary prevention of esophageal variceal bleeding, advanced cirrhosis and the presence of ascites were independently associated with death in both patients receiving propranolol and not receiving propranolol [14]. However, patients with refractory ascites were again excluded from any of the trials used in the meta-analysis [14]. Certainly additional research is needed to fully study the effects of beta-blockers in this population; however, based on the available evidence, it is likely that such studies will show a detrimental effect of beta-blockers in patients with advanced cirrhosis and refractory ascites.

At present, due to the paucity of available studies, we have determined that although recent studies are suggesting harm in the use of beta-blockers in patients with advanced cirrhosis and refractory ascites, there exists insufficient evidence to draw definitive conclusions. The existing studies do not share enough homogeneity for pooled analysis or meta-analysis to be reliably and confidently performed. Additional studies to evaluate the role and safety of beta-blockers in patients with advanced cirrhosis and refractory ascites are critically needed; however developing a large randomized controlled trial to answer aspects of this question is certain to be difficult especially as beta-blockers are increasingly becoming generic.

Table 3. Beta-blocker dosing-regimens.

Ref No.	Author	Year	Type of trial	Dosing regimen
[12]	Lebrec *et al.*	1981	Propranolol *vs.* placebo for secondary prevention of variceal bleeding	Propranolol titrated to reduce resting heart rate by 25%, dose ranged from 20-180 mg given twice daily
[13]	Pascal *et al.*	1987	Propranolol *vs.* placebo for primary prevention of variceal bleeding	Propranolol titrated to reduce resting heart rate by 20-25%, starting dose 20 mg given twice daily, increased as required to maximum dose of 160-320 mg long-acting propranolol given once daily
[36]	Lebrec *et al.*	1988	Nadolol *vs.* placebo for primary prevention of variceal bleeding	Nadolol titrated to reduce resting heart rate by 25%, starting dose 80-160 mg given once daily
[37]	Ideo *et al.*	1988	Nadolol *vs.* placebo for primary prevention of variceal bleeding	Nadolol given at dose from 40-120 mg once daily
[38]	Italian multicenter project	1989	Propranolol *vs.* placebo for primary prevention of variceal bleeding	Propranolol titrated to reduce resting heart rate by 25%, dose ranged from 10-480 mg daily

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Additional challenges affecting beta-blocker therapy

There are several additional challenges to beta-blocker therapy in cirrhosis. First, the appropriate dosing of beta-blockers in cirrhosis can be problematic and demands further investigation. The current propranolol dosing regimen was established by several of the early non-selective beta-blocker clinical trials (Table 3), without explanation to the origin or scientific validity of such a dosing regimen. Lebrec's original study called for propranolol to be given at increasing doses until the heart rate was reduced by approximately 25%, with doses ranging from 20 to 180 mg given twice a day [12]. Subsequent clinical studies evaluating the hemodynamic effects of propranolol continued to utilize this dosing regimen [88–90]. Additional investigations regarding the dosing of beta-blockers have since escaped scientific study.

A number of the beta-blocker trials determined that a decrease in portal pressure during chronic treatment, as measured by a decrease in the hepatic venous pressure gradient (HVPG) to <12 mmHg or by >20% from baseline, was a strong predictor of clinical effectiveness [19,91]. Studies have shown that assessment of hemodynamic response with the HVPG may be the best predictor of clinical efficacy in patients being treated with beta-blockers [53,92]. However, dosing to HVPG goals is problematic as this method is invasive, impractical, and not routinely performed in most institutions in the United States except in clinical research studies [93].

Second, previous studies have implicated patients' unwillingness to tolerate the side effects of beta-blockers as a factor in treatment failure [53]. Regardless of whether or not the side effects have been confirmed in rigorous meta-analyses, in our anecdotal experience patients routinely complain of side effects including fatigue, lightheadedness, and erectile dysfunction, and many unilaterally discontinue or dose-reduce the medication without reporting this to their physician [94]. It is therefore not surprising that an increasing amount of evidence suggests that many patients fail to receive evidence-proven treatments [41,95].

Third, the limited therapeutic window during which beta-blockers provide a survival benefit demands close follow-up to minimize the risk of causing harm to the patient, and to ensure that beta-blockers are discontinued when the patient's disease progresses beyond this window. In our experience, we increasingly encounter patients with cirrhosis on multiple antihypertensives who invariably develop azotemia, hypotension, and end-organ damage as their cirrhosis progresses. Beta-blockers should not be recommended to patients who have poor follow-up or who have issues with non-compliance; the initiation and continuation of beta-blockers demands meticulous follow-up, ideally with home monitoring of blood pressure by patients and frequent clinic visits with the physician. The hemodynamic effects of these medications are significant and may become dangerous as these patients develop worsening cirrhosis.

Fourth, discontinuity of care is an increasingly challenging issue in modern medicine. The widely popular hospitalist movement has separated the outpatient physician from the inpatient physician, creating discontinuity at a critical juncture in patient care. Patients may be started on beta-blockers during their initial hospitalization for a life-threatening variceal bleeding event, only to be left in an "autopilot" state upon discharge. They may either subsequently present to an emergency department months later with systemic hypotension and azotemia, potentially at a different hospital which has no records for the patient, or may develop symptoms or side effects and unilaterally discontinue their medication. This concern is supported by a recent study, which showed that the increasing involvement of hospitalists was associated with a significant decrease in continuity of care [96]. Recent studies aimed at care coordination may help to decrease the discontinuity of care and improve outpatient follow-up and medication compliance [97].

Table 4. Summary of recommendations for beta-adrenergic antagonists in patients with cirrhosis.

Clinical situation	Recommendation for beta-blockers
Early cirrhosis	
Without medium-large esophageal varices	Not indicated for cirrhosis, however may be indicated for concurrent cardiovascular disease (e.g. coronary artery disease, congestive heart failure, atrial fibrillation, etc.).
Compensated cirrhosis	
With medium-large esophageal varices	Indicated to prevent first episode of variceal bleeding. Caution should be taken to avoid systemic hypotension.
Decompensated cirrhosis	
Initial episode of variceal bleeding	Indicated to prevent recurrent variceal bleeding. Caution should be taken to avoid systemic hypotension.
With sepsis or hepatorenal syndrome	Discontinue existing beta-blockers.
End-stage cirrhosis	
With refractory ascites	Not indicated due to decreased cardiac output and risk for hypotension and renal failure. Existing beta-blockers should be tapered and then discontinued. Consider alternative treatment modality such as endoscopic band ligation. Consider midodrine to increase blood pressure.
Other clinical scenarios	
Patients with poor compliance or inadequate follow-up care	Not indicated as risks of causing harm may substantially outweigh potential benefits.
Routine office visit for patient with good medical compliance	Adjust beta-blockers based on serial blood pressure measurements over time. Titrate to 25% reduction in baseline heart rate, or goal heart rate 55 beats/minute, as blood pressure and side effects tolerate. Home monitoring of pulse and blood pressure is superior to a single clinic measurement.

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Review

Recommendations and conclusions

One of the few benefits of advanced cirrhosis may be that cirrhosis effectively cures hypertension. The emerging prevalence of NAFLD and NASH cirrhosis, our society's ongoing struggles with metabolic syndrome and its comorbid diabetes mellitus and essential hypertension, and the changing healthcare environment in the United States draws new implications regarding the use of beta-blocker therapy in patients with cirrhosis. Our overall recommendations for the use of beta-blockers are summarized in Table 4 and Fig. 2.

Perhaps the most appropriate timing for beta-blocker therapy was outlined in a recent hypothesis from Krag and colleagues known as the "window hypothesis" (Fig. 1), which suggests that beta-blockers improve survival only in a narrow clinical window in the course of cirrhosis [26]. In early cirrhosis, beta-blockers have no effect on survival, increase adverse events and do not prevent the formation of varices [53]. In this early stage, the initiation of beta-blockers is not recommended for the purpose of preventing gastrointestinal bleeding, although they may be indicated for cardiac comorbidities such as coronary artery disease and congestive heart failure.

As portal pressures increase and the sympathetic nervous system becomes increasingly activated, medium to large esophageal varices develop, and there is increased risk of variceal bleeding and bacterial translocation from the gut [98]. Ascites also begins to develop at this stage. From a cardiovascular perspective, systemic hemodynamics is still relatively preserved, cardiovascular reserve is intact, and blood pressure and cardiac output are maintained to deliver adequate end-organ perfusion. In this middle stage of cirrhosis, beta-blockers have been shown in numerous trials to have survival benefit [12,14,15,26]. Beta-blockers are

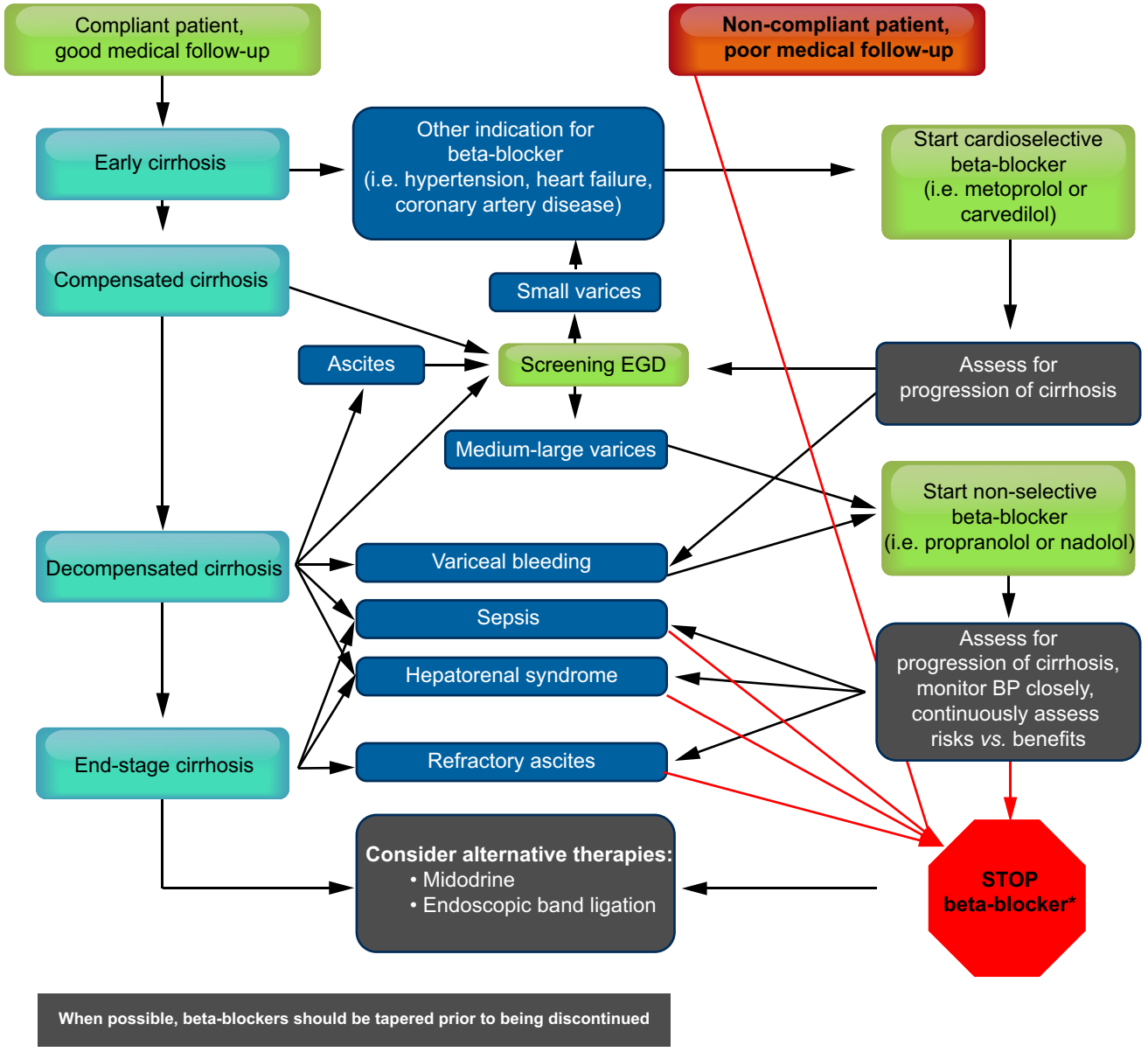

Fig. 2. Algorithmic approach for beta-adrenergic antagonists in patients with cirrhosis. BP, blood pressure; EGD, esophagogastroduodenoscopy.

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therefore indicated and recommended for the primary and secondary prevention of gastrointestinal bleeding, although they should be promptly discontinued in the setting of either sepsis or hepatorenal syndrome.

However, as cirrhosis progresses and cardiovascular reserve becomes impaired, the sympathetic nervous system is maximally stimulated to maintain cardiac output and end-organ perfusion. Additional complications such as cirrhotic cardiomyopathy may also develop [99]. In this advanced stage of cirrhosis, generally reflected by refractory ascites, the evidence now suggests that beta-blockers reduce survival. The inability of the circulatory system to increase cardiac output via the beta-adrenergic system during situations of increased physiological stress results in decreased mean arterial pressures, decreased perfusion to vital organs, azotemia, and subsequent increased risk for hepatorenal syndrome and end-organ damage [22,23,26,58]. In this final stage of decompensated cirrhosis, beta-blockers should neither be recommended nor initiated. Additionally, beta-blockers should be tapered and discontinued in those patients who develop refractory ascites, worsening hypotension, or worsening azotemia [73,74]. Endoscopic band ligation of varices can be considered as a substitute treatment to prevent variceal hemorrhage [13,100]. Consideration should also be given to agents such as midodrine that increase cardiac output and blood pressure [62]. One potential option in patients with end-stage cirrhosis that merits additional investigation would be to consider simultaneously using non-selective beta-blockers for the prevention of variceal bleeding, and midodrine to improve systemic hemodynamics.

Many questions remain with regards to the exact therapeutic parameters of beta-blockers in patients with cirrhosis, and additional studies on the optimal timing and dosage of beta-blockers are certainly needed. An increasing amount of evidence supports the limited use of beta-blockers in only a certain subset of patients with cirrhosis. Outside this limited window of clinical opportunity, the global harm of beta-blockers may ultimately exceed its global benefit.

Key Points

- Beta-adrenergic antagonists ("beta-blockers") are part of the cornerstone of the medical management of cirrhosis, particularly in the primary and secondary prevention of variceal hemorrhage
- New evidence cautions using beta-blockers in patients with end-stage cirrhosis, and supports their use only in a certain subset of patients with cirrhosis
- Beta-blockers are not indicated to prevent development of varices in early cirrhosis
- Beta-blockers should be tapered and discontinued when patients develop end-stage cirrhosis with refractory ascites, as decreased cardiac output results in decreased renal perfusion, azotemia, and increased risk for hepatorenal syndrome and mortality
- Beta-blockers should not be initiated in patients with poor medical follow-up or poor medical compliance, as the limited therapeutic window during which beta-blockers provide a survival benefit demands close follow-up

Conflict of interest

The authors declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

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