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Primary prophylaxis of variceal bleeding in patients with cirrhosis: A comparison of different strategies

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Abstract

Patients with cirrhosis and esophageal varices bleed at a yearly rate of 5%-15%, and, when variceal hemorrhage develops, mortality reaches 20%. Patients are deemed at high risk of bleeding when they present with medium or large-sized varices, when they have red signs on varices of any size and when they are classified as Child-Pugh C and have varices of any size. In order to avoid variceal bleeding and death, individuals with cirrhosis at high risk of bleeding must undergo primary prophylaxis, for which currently recommended strategies are the use of traditional non-selective beta-blockers (NSBBs) (*i.e.*, propranolol or nadolol), carvedilol (a NSBB with additional alpha-adrenergic blocking effect) or endoscopic variceal ligation (EVL). The superiority of one of these alternatives over the others is controversial. While EVL might be superior to pharmacological therapy regarding the prevention of the first bleeding episode, either traditional NSBBs or carvedilol seem to play a more prominent role in mortality reduction, probably due to their capacity of preventing other complications of cirrhosis through the decrease in portal hypertension. A sequential strategy, in which patients unresponsive to pharmacological therapy would be submitted to endoscopic treatment, or the combination of pharmacological and endoscopic strategies might be beneficial and deserve further investigation.

Key Words: Cirrhosis; Esophageal varices; Primary prophylaxis; Non-selective beta-

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Core Tip: Variceal hemorrhage still is an important cause of death among patients with cirrhosis, and primary prophylaxis against variceal bleeding is of the utmost importance. Traditional non-selective beta-blockers, carvedilol or endoscopic variceal ligation are currently recommended for primary prophylaxis, and the superiority of one alternative over the others is controversial. This review will provide a comparison of the strengths and weaknesses of the different strategies for primary prophylaxis against variceal bleeding, so that practitioners make an informed decision when choosing among them.

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INTRODUCTION

In patients with compensated cirrhosis, esophageal varices develop in an annual rate of 7%-8%, characterizing state 2 in the natural history of the disease. Once they develop, they will bleed in 5%-15% of patients *per year*, marking their transition to decompensated cirrhosis (state 3 in the natural history of cirrhosis). When patients bleed, the mortality rate reaches 20% [1,2].

In order to avoid bleeding and death, individuals with cirrhosis should be screened for esophageal varices, and primary prophylaxis against their rupture is recommended to patients at higher risks [3-6]. The Baveno VI consensus recommends that patients with cirrhosis and medium-large varices should be submitted to prophylaxis with either traditional non-selective beta-blockers (NSBBs) (*i.e.*, propranolol or nadolol), carvedilol (a beta-blocker with an alpha-adrenergic blocking effect) or endoscopic variceal ligation (EVL). Patients with small varices should also be submitted to prophylaxis with NSBBs as long as they are classified as Child-Pugh C or have varices with red signs [3]. The most important medical associations in the field of hepatology support these recommendations [4,5]. Nevertheless, there are divergences in medical literature regarding the superiority of one prophylactic alternative over the others [7-9].

This article aims at reviewing the main strategies for primary prophylaxis against variceal hemorrhage, as well as comparing their strengths and weaknesses (Table 1). Knowing the characteristics of each prophylactic strategy will enable physicians to make better decisions when choosing among them in the management of particular patients.

TRADITIONAL NSBBs

NSBBs are considered the main pharmacological intervention in the treatment of portal hypertension since Lebrec *et al* [10] demonstrated that propranolol administration effectively reduced the hepatic venous pressure gradient (HVPG) in patients recovering from an acute episode of gastrointestinal bleeding due to ruptured esophageal varices. This reduction was associated with a significant decrease in portal blood flow, which is usually increased in patients with cirrhosis due to significant splanchnic arterial vasodilation. Later studies confirmed that NSBBs-induced portal blood flow reduction is caused by the activity of these drugs on beta-1 cardiac receptors, determining a negative chronotropic response and a reduced cardiac output, and, most importantly, by their effects on beta-2 receptors of the splanchnic vascular bed, resulting in splanchnic vasoconstriction [11,12].

Table 1 Strengths and weaknesses of the different strategies for primary prophylaxis of variceal bleeding in cirrhosis

	NSBBs	Carvedilol	EVL
Prevention of mortality	+	+?	+?
Prevention of bleeding	+	+	++
Prevention of other complications of cirrhosis	+	+	-
Reduction in HVPG	+	++	-
Adverse effects	--	--	-
Serious adverse effects	-	-	--

The plus sign (+) indicates strength. The minus sign (-) indicates weakness. The question mark (?) indicates uncertainty. NSBBs: Traditional non-selective beta-blockers; EVL: Endoscopic variceal ligation; HVPG: Hepatic venous pressure gradient.

When NSBBs are used in primary prophylaxis of variceal bleeding, the hemodynamic goal is to achieve an HVPG reduction $\geq 20\%$ of the baseline levels or a decrease in absolute levels to under 12 mmHg. Below those thresholds, patients would be protected from variceal bleeding[13]. Even a reduction $\geq 10\%$ is likely to be clinically relevant for primary prophylaxis[3]. Nevertheless, only 33%-50% of patients undergoing NSBB prophylaxis achieve the proposed hemodynamic goals[8].

Different randomized controlled trials (RCTs) have evaluated the role of NSBBs in primary prophylaxis against variceal bleeding. A meta-analysis evaluating 6 of these studies and including 811 patients with cirrhosis and medium or large varices demonstrated that primary prophylaxis with NSBBs was more effective than placebo, with 2-year bleeding rates of 30% in the control group and 14% in the NSBB group[14].

In clinical practice, the most commonly used NSBBs are propranolol and nadolol, and treatment with these drugs should begin with low doses that are gradually increased to the maximum tolerated dose or to a heart rate target around 55-60 beats *per minute*. Propranolol can be started at 20-40 mg twice a day, and maximal daily dose should be 320 mg/d in individuals without ascites or 160 mg/d in those with ascites[4] (80 mg/d for patients with severe or refractory ascites according to the European Association for the Study of the Liver[5]). Nadolol can be started at 20-40 mg once a day, and maximal daily dose should be 160 mg/d in patients without ascites or 80 mg/d in those with ascites[4].

Some concern has been shown regarding the use of NSBBs by patients with end-stage cirrhosis. According to the window hypothesis, the therapeutic window for the use of NSBBs would close at end-stage cirrhosis, particularly with the development of refractory ascites, because these drugs would not only be less effective in that stage, but also might lead to a higher risk of hepatorenal syndrome and mortality due to a negative impact on the cardiac compensatory reserve[15]. This hypothesis was based on an observational study of 151 individuals with cirrhosis and refractory ascites, in which those using propranolol had a shorter survival[16]. Later on, other observational studies associated the use of NSBBs to a higher risk of hepatorenal syndrome and a lower transplant-free survival among patients with spontaneous bacterial peritonitis[17] and to a higher risk of acute kidney injury among those with severe alcoholic hepatitis[18]. Nevertheless, the methodological limitations of these observational studies should be noticed, and a meta-analysis of 11 studies (3145 patients) failed to demonstrate evidence of a negative impact of NSBBs on the mortality of individuals with ascites (including a subgroup analysis focused on patients with refractory ascites)[19].

Therefore, considering existing evidences, the current recommendations are that NSBBs should be reduced or discontinued (or should not be initiated) in patients with systolic blood pressure < 90 mmHg, with acute kidney injury or with serum sodium < 130 mEq/L[3-5]. In the settings of acute decompensation of cirrhosis with spontaneous bacterial peritonitis, sepsis or bleeding, NSBBs should be discontinued. If NSBBs cannot be reinitiated after 3-6 d, EVL should be considered[5].

As previously mentioned, international guidelines recommend the use of either NSBBs or EVL as first-line options with similar effectiveness for primary prophylaxis of variceal bleeding[3]. Yet, some issues should be considered when choosing between these options in clinical practice. Firstly, NSBBs work by reducing portal hypertension through a decrease in splanchnic blood flow. Theoretically, this could benefit patients in relation to the prevention of other complications of portal hypertension, such as

ascites, hepatic encephalopathy or infections[20]. Indeed, a recent RCT on the role of NSBBs in patients with clinically significant portal hypertension (individuals who did not have an indication for primary prophylaxis against variceal bleeding) has demonstrated that those receiving propranolol or carvedilol had a lower risk of developing the primary endpoint (cirrhosis decompensation or death, hazard ratio of 0.51, $P = 0.041$). Interestingly, the benefit was predominantly related to the lower incidence of ascites among individuals receiving the intervention (hazard ratio of 0.42, $P = 0.03$)[21]. Of course, this is not an expected effect of EVL, which works mechanically on the obliteration of varices.

Another important aspect that might influence the choice of the method of prophylaxis is the occurrence of adverse events. Usually, studies suggest that there are more side effects with NSBBs (around 15% of patients require dose reduction due to fatigue or hypotension), although they are more severe with EVL (pain, esophageal ulcers, strictures, and bleeding). In addition, NSBBs are cheap and easy to manage, while EVL requires more complex resources and permanent endoscopic surveillance to monitor the recurrence of varices[4].

Finally, although strong evidence is lacking in medical literature, prophylaxis against the rupture of small varices is recommended for individuals classified as Child-Pugh C or for those who have red wale marks on the surface of the varices[22]. These red signs reflect increased tension on the vessel wall and imminent risk of rupture. Currently, the recommendation for these patients is that primary prophylaxis should be performed with NSBBs, since the use of EVL for these varices can be technically complex[3-5].

CARVEDILOL

Carvedilol is a NSBB with an additional activity on alpha-1 cardiac receptors. Therefore, aside from reducing cardiac output (beta-1 blocking effect) and from leading to splanchnic vasoconstriction (beta-2 blocking effect), it promotes sinusoidal vasodilation (alpha-1 blocking effect). For this reason, most authors believe that carvedilol promotes greater reductions in HVPG than NSBBs, leading to better hemodynamic response rates during primary prophylaxis against variceal bleeding [23]. However, the superiority of carvedilol over NSBBs regarding portal hypertension improvement is still not consensual[24].

Four RCTs evaluated the role of carvedilol in the primary prophylaxis against variceal bleeding. Two of them demonstrated that this drug was superior to EVL in preventing first variceal bleeding[25,26]. On the other hand, the other 2 RCTs failed to identify a benefit of carvedilol when compared to EVL[27] or to either EVL or propranolol[28]. The largest RCT on this issue is currently in progress and will hopefully put an end to this controversy[29].

While that trial is not published, another recent study contributed with data on the comparison between NSBBs and carvedilol. The study evaluated patients with a past history of ascites who were undergoing both primary or secondary prophylaxis against variceal bleeding with propranolol. Subjects were randomized either to switch to carvedilol or to remain under propranolol. When compared to individuals remaining on propranolol, patients switching to carvedilol had significant decreases in plasma renin activity, plasma aldosterone and serum noradrenaline, as well as significant increases in systemic vascular resistance and glomerular filtration rate. Moreover, patients on carvedilol had fewer decompensating events at 2 years than their counterparts (10.3% *vs* 37.5%, $P = 0.002$), as well as lower liver-related mortality (64.1% *vs* 86%, $P = 0.01$). It must be highlighted, though, that an intention-to-treat approach was not used in this study[30].

In clinical practice, carvedilol should be started at a dose of 6.25 mg/d and increased to 12.5 mg/d after three days, as long as systolic blood pressure does not fall below 90 mmHg[4]. The adverse effects profile of carvedilol does not seem to be different from that of NSBBs, but doses should not be increased over 12.5 mg/d, except in patients with persistent systemic arterial hypertension[4,23]. Heart rate should not be used as a target while titrating the dose of carvedilol. Non-invasive methods of verifying the response to carvedilol have been studied as an alternative to HVPG. In a recent prospective cohort study, the difference between baseline and post-treatment spleen stiffness measured by acoustic radiation force impulse elastography was able to predict hemodynamic response to carvedilol during primary prophylaxis with areas under the receiver operating characteristic curve over 0.8. This might become a useful tool for verifying response to carvedilol after further validation[31].

EVL

EVL was first described in 1986[32]. Ten years later, the first RCT on the efficacy of EVL for primary prophylaxis against variceal bleeding was published. In that trial, in which 62 individuals with cirrhosis and 6 with non-cirrhotic portal hypertension were included, EVL was associated with a significantly lower incidence of first variceal bleeding when compared to no treatment (8.5% *vs* 39.4%, $P < 0.01$). There was also a trend towards lower bleeding-related mortality favoring EVL (2.9% *vs* 15.2%, $P = 0.08$) [33]. In the following years, EVL also was compared with NSBBs, with evidence suggesting that the endoscopic treatment was associated with a significant lower probability of variceal bleeding, which did not translate into lower mortality[34].

EVL has replaced injection sclerotherapy as the endoscopic therapy of choice not only for the prevention of the first variceal hemorrhage, but also for the treatment of acute variceal bleeding and for secondary prophylaxis. This was due to lower rates of mortality[35], recurrent hemorrhage and adverse events[35,36] with EVL when compared to sclerotherapy. Because of mounting evidence showing an increase in mortality in subjects submitted to sclerotherapy for the prevention of variceal hemorrhage[35-38], most experts and international associations no longer recommend sclerotherapy for primary prophylaxis[3-5,39]. Moreover, there does not seem to be a role for combined EVL and sclerotherapy in order to improve variceal eradication[40]. EVL has also been compared to tissue adhesive injection for primary prophylaxis with varying results, but there is no evidence-based recommendation advocating the latter over the former, not even in Child-Pugh C patients[32]. Thus, up to this moment, EVL should be considered the best endoscopic therapy to prevent the first bleeding from medium to large esophageal varices and it is considered as a first line option for primary prophylaxis, along with NSBBs and carvedilol[3-5,39].

According to the American Association for the Study of Liver Diseases (AASLD), EVL should be performed every 2-8 wk until esophageal varices eradication is achieved. Then, first follow-up esophagogastroduodenoscopy (EGD) would be repeated in 3-6 mo and every 6-12 mo thereafter. If esophageal varices reappear during follow-up, EVL should be reinitiated[4]. We believe, however, that a shorter interval of time between each EVL session (2-4 wk) could be advisable in order to avoid bleeding from occurring while varices are not eradicated, and that first follow-up EGD should be ideally performed at 3 mo[39].

Small esophageal varices and gastroesophageal varices type 1 (GOV1) are less likely to bleed unless in the presence of red signs or advanced Child-Pugh C cirrhosis. In this scenario, EVL is not considered to be the best option[3-5,39] since it may not be technically feasible and might be more prone to induce complications[32]. Moreover, despite anecdotal reports, EVL is not considered the procedure of choice for gastric or ectopic varices, because those vessels tend to have large diameters and to lay deep in the submucosa, making them not amenable to fully entrapment under suction to perform banding. Tissue adhesive injection is instead the procedure of choice for gastric or ectopic varices[32].

OTHER STRATEGIES FOR PRIMARY PROPHYLAXIS AGAINST VARICEAL BLEEDING

As previously mentioned, NSBBs, carvedilol or EVL are first line options for primary prophylaxis against esophageal varices hemorrhage. These options are recommended in monotherapy, and the choice should take into account the status of cirrhosis (compensated or decompensated), individual preferences, local resources and expertise, contraindications, potential complications of each strategy and their costs[3-5]. Nevertheless, combining therapies in order to achieve a greater reduction in the risk of the first episode of bleeding has been examined in the literature. An RCT comparing the combination of propranolol and EVL *vs* EVL alone for primary prophylaxis failed to demonstrate differences in the incidence of bleeding or death between groups. On the other hand, combination therapy was associated with a higher number of side effects[41]. Another RCT compared primary prophylaxis with carvedilol, EVL or the combination of both in 270 individuals with cirrhosis classified as Child-Pugh B or C. In that study, the probability of the first bleeding was lower with combination therapy when compared to either carvedilol or EVL alone (8.9%, 37.8% and 22.2% respectively)[42].

Considering that pharmacological therapy has beneficial effects on other complications of portal hypertension aside from preventing variceal bleeding, the combination of pharmacological agents has also been studied in order to promote greater reductions in portal pressure. The combination of NSBBs and nitrates, for instance, has resulted in conflicting evidences. In a long-term study, 146 patients assigned to receive nadolol monotherapy or nadolol along with isosorbide mononitrate were followed up for a median of 55 mo. Cumulative risk of bleeding was 29% and 12% respectively, and authors concluded that nadolol plus isosorbide mononitrate was significantly more effective than nadolol alone in the long-term use[43]. In contrast, another RCT could not demonstrate the benefits of combination therapy. A total of 349 subjects were randomized to receive either propranolol plus placebo or propranolol plus isosorbide mononitrate, and no significant differences in 1- and 2-year actuarial probabilities of variceal bleeding were observed between the groups (monotherapy 8.3% and 10.6% respectively; combination therapy 5% and 12.5% respectively)[44].

It was also hypothesized that adding statins to carvedilol could improve its effects on portal hypertension. The rationale for this lies on the fact that statins could decrease intrahepatic vascular resistance due to a reduction in stellate cells contractility, an increase in the levels of nitric oxide and thrombomodulin and a reduction in the levels of endothelin-1. Nevertheless, in the only RCT on the addition of simvastatin to carvedilol for primary prophylaxis against variceal bleeding, there was no significant benefit of the combined prophylaxis regarding either hemodynamic or clinical outcomes[45].

Other strategies for primary prophylaxis against variceal bleeding have been studied, particularly focused on specific clinical settings. Gastric varices, for instance, are less common in patients with cirrhosis and seem to bleed less frequently, but bleeding episodes are usually more severe and difficult to control when compared to those originating in esophageal varices. No single method has yet been established and there are no robust recommendations for the prophylaxis against the first bleeding from gastric varices. Despite the lack of strong evidences, GOV1 should be approached as esophageal varices. Aside from NSBBs, which are the suggested prophylaxis for gastroesophageal varices type 2 (GOV2) and isolated gastric varices type 1 (IGV1), endoscopic variceal obliteration with cyanoacrylate and balloon occluded retrograde transvenous obliteration (BRTO) have been evaluated[3-5].

Data from a single RCT suggested that endoscopic variceal obliteration with cyanoacrylate might be more effective than NSBBs in preventing the first bleeding episode from GOV2 or IGV1, despite increasing portal pressure during the follow-up. However, the risk of thromboembolic events and increasing the size of esophageal varices represents a serious concern[46]. More data are required for establishing recommendations in this regard[3].

BRTO is a radiological technique for obliteration of gastric varices both for prophylaxis and for treatment of bleeding. It is a much more popular modality in Asian countries than in Western ones. It requires the patency of a large gastro-renal shunt, which is accessed to delivery sclerosant or oblitative agents and coils. Preliminary data suggest that it is safe and effective for the prevention of bleeding in the subset of patients with high-risk gastric varices in connection with large shunts [47]. Transjugular intrahepatic portosystemic shunt (TIPS) is another radiological technique, which is more widely used than BRTO in the treatment of portal hypertension. However, studies specifically evaluating the efficacy of TIPS in the setting of primary prophylaxis are lacking, and there is a concern regarding the increased risk of hepatic encephalopathy induced by this technique. Currently, neither BRTO nor TIPS are recommended by AASLD for primary prophylaxis against variceal bleeding[4].

COMPARATIVE ANALYSIS

Several meta-analyses have compared NSBBs, carvedilol and EVL[7-9,48,49]. Li *et al* [48] performed a meta-analysis of 12 RCTs on this issue. Authors only included RCTs that were peer-reviewed and fully-published, and there was no evidence of significant differences between pharmacological therapy and EVL regarding the prevention of gastrointestinal bleeding, all-cause mortality or bleeding-related deaths.

In the following year, the Cochrane group published a meta-analysis, including 19 RCTs, which compared NSBBs, including propranolol (17 trials), nadolol (1 trial) and carvedilol (1 trial), to EVL. In the main analysis, the authors found a lower rate of bleeding favoring EVL, with no effect on mortality. Nevertheless, in subgroup

analyses excluding trials of lower quality, the benefit of EVL could not be confirmed [7].

In the former meta-analyses, NSBBs and carvedilol were considered together as beta-blockers. This is why another systematic review by the Cochrane group aimed at comparing NSBBs and carvedilol for both primary or secondary prophylaxis against variceal bleeding. Eleven RCTs were included in the systematic review, and 10 in the meta-analysis. Carvedilol led to a significantly greater decrease in HVPg when compared to NSBBs, but there was no evidence of a significant benefit of carvedilol regarding the achievement of a satisfactory hemodynamic response. Moreover, there was no evidence of significant difference between NSBBs and carvedilol regarding mortality, upper gastrointestinal bleeding and serious adverse events [8].

More recently, one further meta-analysis compared carvedilol to EVL. Seven RCTs met the inclusion criteria, 4 of which were focused on primary prophylaxis, while the other 3 assessed secondary prophylaxis. Considering studies on primary prophylaxis, there was no evidence of difference between carvedilol and EVL regarding the incidence of the first bleeding episode, bleeding-related mortality or all-cause mortality. The risk of side effects, though, was significantly higher with carvedilol [risk ratio (RR): 4.18, 95% confidence interval (CI): 2.19-7.95]. On the other hand, EVL seemed to be associated with more severe complications than carvedilol [49].

The most relevant and comprehensive comparative study on this matter, however, is a network meta-analysis, which included 32 RCTs and evaluated NSBBs, carvedilol, isosorbide mononitrate, EVL and their combinations in the primary prophylaxis of variceal bleeding among individuals with cirrhosis. Regarding mortality (the primary outcome), NSBBs in monotherapy [odds ratio (OR): 0.70, 95%CI: 0.49-1.00] or in combination with EVL (OR: 0.49, 95%CI: 0.23-1.02) or with isosorbide mononitrate (OR: 0.44, 95%CI: 0.21-0.93) were significantly better than placebo or no intervention, but none of the evaluated therapies was significantly superior to another active treatment. Concerning the prevention of first variceal bleeding, EVL was significantly superior to NSBBs (OR: 0.51, 95%CI: 0.34-0.76), any active treatment was significantly better than isosorbide mononitrate alone, and any active treatment was significantly superior to placebo, except for isosorbide mononitrate alone or in combination with NSBBs [9].

It is important to highlight that the benefits of NSBBs regarding mortality might probably result not only from the prevention of variceal bleeding, but also from the prevention of other life-threatening complications of cirrhosis and maybe particularly those related to ascites [21]. Such advantages are especially noticed in those subjects achieving hemodynamic response to NSBBs [50]. Since EVL does not act on the pathophysiology of portal hypertension, but directly on its consequence (esophageal varices), it is not reasonable to expect that it could prevent other complications of cirrhosis. In this context, the combination of NSBBs and EVL might be a quite interesting alternative, since it would add the systemic effects of these drugs to the local effects of the endoscopic therapy. Nevertheless, it must be stressed that there is no recommendation for this association at the moment.

Evidences are still scarce regarding the best approach for patients with intolerance or no hemodynamic response to NSBBs. Carvedilol seems to be more potent and better tolerated than other NSBBs and might be considered as an alternative for individuals both intolerant or unresponsive to these drugs. In these circumstances or in patients also intolerant or unresponsive to carvedilol, EVL could be a good option [51]. In this context, Reiberger *et al* [52] proposed an interesting strategy, using NSBBs, carvedilol or EVL sequentially according to the hemodynamic response to the previous treatment. The authors evaluated a cohort of 104 individuals with cirrhosis who were initially treated with propranolol. Ten patients were intolerant to propranolol, while 37 achieved a satisfactory hemodynamic response. The 57 patients who were propranolol non-responders and 10 individuals who were intolerant to the drug received carvedilol, to which 38 were hemodynamic responders. Finally, the 29 patients unresponsive to either propranolol or carvedilol were submitted to EVL. In this study, carvedilol was superior to propranolol in decreasing HVPg (-19% *vs* -12% respectively, $P < 0.001$). Moreover, there was no additional benefit when the dose of carvedilol was increased over 12.5 mg/d. First variceal bleeding occurred in 11% of patients under propranolol, in 8% of those receiving carvedilol and in 24% of the individuals submitted to EVL ($P = 0.0429$). Transplant-free survival was higher with propranolol or carvedilol than with EVL ($P = 0.0455$). Hemodynamic responders to either of these drugs also developed less ascites than individuals requiring EVL ($P = 0.031$). Despite worse outcomes among patients undergoing EVL, it must be highlighted that only individuals unresponsive to propranolol and carvedilol were treated with EVL, so that it is likely that this was a more severely ill population [52].

CONCLUSION

Primary prophylaxis against variceal bleeding is of the utmost importance for patients with cirrhosis and high-risk varices. Currently recommended strategies include NSBBs, carvedilol or EVL. While EVL might be superior to pharmacological therapy regarding the prevention of the first bleeding episode, pharmacological therapy seems to prevent different complications of liver disease and probably play a more prominent role concerning mortality reduction. The sequential use of these alternatives or their combination should be further studied so that patients might benefit from the best aspects of each strategy.

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