



# Primary Prophylaxis of Variceal Bleeding is Combined Prophylaxis More Effective?



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## Introduction

One of the most common and life-threatening complications of portal hypertension is gastrointestinal bleeding secondary to oesophageal varices (OV). Estimates of the annual bleeding risk range from 10%-30% [1,2]. Despite advances in management, mortality remains high; 6-week mortality is around 15%, especially in patients with advanced liver dysfunction. Management is also resource and cost intensive, often requiring intensive care or high dependency unit admission, blood transfusion, vasoconstrictor therapy, endoscopic treatment and antibiotic prophylaxis [1,3].

Portal hypertension develops from increased intrahepatic vascular tone caused by dysfunction of stellate cells and sinusoidal endothelial cells and by activation of portal and septal myofibroblasts. Decreased intrahepatic bioavailability of nitric oxide, a potent vasodilator, along with increased levels of vasoconstrictors such as thromboxane A2 contributes to the increased intrahepatic vasoconstriction. Increased blood flow through the portal venous system also contributes and the presence of angiogenic factors, such as vascular endothelial growth factor and angiopoietin, facilitates the formation of collateral vessels, including oesophageal varices, which develop through the opening of pre-existing vessels or through de novo angiogenesis [3,4].

Diagnostic screening oesophago-gastro-duodenoscopy (OGD) is necessary to detect the presence of oesophageal varices in patients with cirrhosis. Patients with clinical decompensation of portal hypertension, such as ascites, should undergo screening OGD. The latest Baveno VI Consensus recommend that patients with compensated cirrhosis with liver stiffness <20kPa and platelet count >150,000 have a very low risk of varices requiring treatment and can avoid screening OGD. They also recommend that if liver stiffness increases or platelet count declines, these patients should undergo screening OGD [5]. Probably, those patients with compensated cirrhosis but with radiological signs of portal hypertension, such as radiological ascites, splenomegaly, collateral circulation, portal vein dilatation or biphasic or reverse portal flow should undergo screening OGD as well.

## Assessing the Risk of Bleeding

The risk of bleeding is clearly related to the presence of the following factors: variceal size, the presence of red wale marks and the degree of liver dysfunction. The presence of these factors has an additive effect on the risk of bleeding. The classic study of the North Italian Endoscopic Club (NIEC) showed that Child C patients with small varices without red wale marks have a high 1-year risk of bleeding, at 20%. This study also showed that the risk of bleeding can be as high as 76% in Child C patients with large varices and severe red wale marks [6]. Thus, patients who have oesophageal varices and indicators of high risk of bleeding should receive prophylactic treatment. When prophylaxis is offered to patients who have never bled it is called primary prophylaxis.

## Primary Prophylaxis or Prevention of First Variceal Bleeding

Experts recommend the use of prophylaxis in those patients with small oesophageal varices with red colour signs or with advanced liver dysfunction (Child-Pugh C) [5,7]. Non-selective beta-blockers (NSBB), including propranolol and nadolol showed a reduction in first variceal bleeding event compared to placebo (30% vs. 14%). There is contradictory data on the effect of NSBB or carvedilol in delaying the growth of small varices [7].

In patients with medium or large size varices there is a similar efficacy between NSBB, such as propranolol or nadolol, and endoscopic band ligation (EBL). Thus, current guidelines recommend the use of either beta-blockers, including carvedilol, or EBL indistinctively [5,7]. There are studies showing that carvedilol is more effective than propranolol and nadolol in reducing the portal pressure, probably due to the additional alpha blocker effect on top of its action on  $\beta_1$  and  $\beta_2$ -receptors.

There are contradictory data regarding the use of NSBB in the setting of advanced circulatory dysfunction such as refractory ascites or during an episode of spontaneous bacterial peritonitis. Experts recommend carefully monitoring the systemic blood

pressure and renal function of these patients and reduce the dose early in case of clinical deterioration [3].

## Combined Prophylaxis for Patients with Large Oesophageal Varices

### EBL alone versus combined prophylaxis

Two studies have compared endoscopic band ligation versus endoscopic band ligation plus propranolol. Both studies showed that combined prophylaxis reduced the rate of recurrence of OV. The first study included 72 patients in each arm with a median follow up of 12.2±10.7 months [9]. There was no significant difference in the rate of first bleeding episode (7% vs. 11%) or in mortality (8% vs. 15%) but the probability of recurrence of OV was lower in the group which received combined prophylaxis (19% vs. 33%,  $p=0.03$ ). The second study included 32 and 34 patients in each arm with a median follow up of 11.6 and 13.7 months [10]. Again, it did not show any significant difference in rate of bleeding (6% vs. 3%) or mortality (6% vs. 12%), but it showed a reduction in the rate of recurrence of OV (9% vs. 38%,  $p=0.003$ ). In both studies all cases of bleeding occurred before obliteration of OV. Although authors of both studies concluded that EBL and combined EBL plus propranolol were equally effective as primary prophylaxis, the fact that combined prophylaxis reduces the rate of OV recurrence suggests a difference in the bleeding rate might be observed in longer follow-up.

### NSBB alone versus combined prophylaxis

Two prospective trials compared NSBB alone versus NSBB plus EBL. There was a difference in the degree of liver cirrhosis between the patients included in these two studies and the studies showed different results. The first study included patients with advanced liver dysfunction; all participants were on the liver transplant waiting list, their medium MELD score was 20.7, and 63% of the patients had a Child-Pugh C score [11]. There was not a single patient with Child-Pugh A score. Patients were randomized to propranolol alone or to propranolol plus EBL, There were 36 patients in each arm. Patients on combined prophylaxis presented a much lower rate of bleeding at 18 months of follow-up (6% vs. 31%,  $P=0.03$ ). Patients on combined prophylaxis also had a lower mortality rate, but it did not reach statistical significance (11% vs. 31%,  $P=0.12$ ).

A second single-centre study, including 70 patients in each arm, did not show differences in rate of bleeding (26% vs. 18%,  $p=0.42$ ) or in mortality (23% vs. 21%). Furthermore, it showed a higher incidence of adverse events in the combined group (69% vs. 40%,  $P=0.06$ ). The characteristics of the patients differed from the previously described study; only 16% of patients had Child Pugh C score [12]. These two studies reported contradictory findings. The study showing no benefit in combined prophylaxis included twice as many patients as the positive study, although it still was a small single-centre study. The characteristics of the patients differed between studies; the study with positive results included patients

with more advanced liver dysfunction. The selection of patients with different disease severity may explain the contradictory results.

### NSBB alone versus EBL alone versus combined prophylaxis

Recently, the largest multicentre prospective study to-date compared all three approaches to primary prophylaxis. 260 patients with high-risk varices (F2 or F3 according to the Japanese Research Society for Portal Hypertension classification) were randomised to propranolol alone, EBL alone or propranolol plus EBL. The majority of patients (95.3%) in this study had Child A or B cirrhosis. Two-year OV bleeding rate was lowest in the combined prophylaxis group (3.4%) compared with propranolol alone (3.4% vs 14.0%,  $p=0.013$ ) and EBL alone (3.4% vs 14.9%,  $p=0.007$ ). OV recurrence was also lower with combined prophylaxis compared with EBL alone ( $p=0.004$ ). However, 2-year mortality did not differ significantly between the three groups [13].

### Conclusion

There are no conclusive data to recommend the use of combined primary prophylaxis, with NSBB plus EBL, to prevent first episode of variceal bleeding and only a few small trials have been conducted comparing monotherapy with combined therapy. When comparing EBL alone with combined prophylaxis, three trials showed a reduced rate of OV recurrence but this did not translate in to statistically significant changes in mortality rates. For NSBB alone versus combined prophylaxis, findings were contradictory with two studies reporting lower bleeding rates with combined prophylaxis and one reporting no reduction but increased adverse events in this group. Again, no change in mortality was observed.

Around 15% of patients have a bleeding episode despite primary prophylaxis with NSBB alone and De Souza et al showed that these patients also have a worse long-term outcome [14]. Villanueva et al. defined acute hemodynamic response as a reduction in hepatic venous pressure gradient (HVPG)  $\geq 10\%$  from baseline. His study showed that when acute hemodynamic response was not achieved after administration of intravenous propranolol, the risk of bleeding was 46% [15]. Moreover, a recent study showed that patients already on NSBB who have an episode of variceal bleeding have an increased risk of re-bleeding (48% vs. 24%,  $P=0.01$ ) and lower rate of transplantation-free survival (66% vs. 88%,  $P=0.02$ ) [14]. There are also studies demonstrating that, as we would expect, patients on NSBB who were not titrated have a higher risk of bleeding [16].

Therefore, there is a subgroup of patients, such as those without acute hemodynamic response to intravenous propranolol, who have a very high risk of bleeding despite prophylaxis with NSBB. Probably, the presence of red wale marks and advanced liver dysfunction increases this risk. The strategy of waiting for the first episode of variceal bleeding to occur before starting combined prophylaxis is suboptimal for obvious reasons. Therefore, large multicentre studies addressing this relevant clinical question are clearly needed.

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