(Pre)Primary Prophylaxis: Where Were We and Where Are We Heading?

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Introduction

The concept of preprimary prophylaxis refers to the administration of beta-blockers to avoid the development of varices [1]. This idea was supported by experiments in animal models of portal hypertension (schistosomiasis) in which administration of beta-blockers led to less collateral circulation as determined by microsphere technique [2].

In order to test this hypothesis in the clinical setting, a large multicenter randomized controlled trial was designed [3]. This study included 213 patients with compensated cirrhosis with portal hypertension as defined by a hepatic venous pressure gradient (HVPG) over 6 mmHg without varices at baseline. Patients were randomized to placebo or timolol (a nonselective beta-blocker). The main endpoint was a composite endpoint, which included the development of varices and/or variceal bleeding. Unfortunately, no differences were observed between the two treatment groups. Many possible explanations for this negative result were suggested. One of the main explanations was that only highly compensated patients were included with a mean Child-Pugh score of 5.4 points, and almost 90 % of these patients were in Child-Pugh class A [3], so that perhaps the prophylactic treatment was given to patients who may have actually had a low risk of developing the event.

Indeed, as a consequence of this study, the last two Baveno meetings [1, 4] stated that the administration of beta-blockers in the setting of preprimary prophylaxis was not recommended. This contrasts with the results of the questions posed to the faculty members of Baveno VI, in which the concept of preprimary prophylaxis was still considered as a possibility in patients with cirrhosis in half of those who

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answered (Fig. 10.1); nevertheless most of these suggested that the phenomenon to prevent should be the development of decompensation, rather than the development of varices (Fig. 10.2). This is not the classical definition of preprimary prophylaxis. This change may be due to recent studies in which different risk groups among compensated patients for clinical decompensation could be identified [5–7].

Traditionally, patients with compensated cirrhosis have been divided in patients without varices (in whom the concept of preprimary prophylaxis would apply) and those patients with varices (in whom the concept of primary prophylaxis would apply) [4, 7]. These two groups have a different mortality risk as well as a different risk for decompensation [5, 6, 8]. Varices develop only in patients who achieve a threshold of clinically significant hepatic venous pressure gradient [9], which is an estimation of portal pressure. Nevertheless, although all patients with varices have clinically significant portal hypertension, not all patients without varices have an HVPG below this threshold. Indeed, there may be compensated patients without varices who already have clinically significant portal hypertension [5, 6].

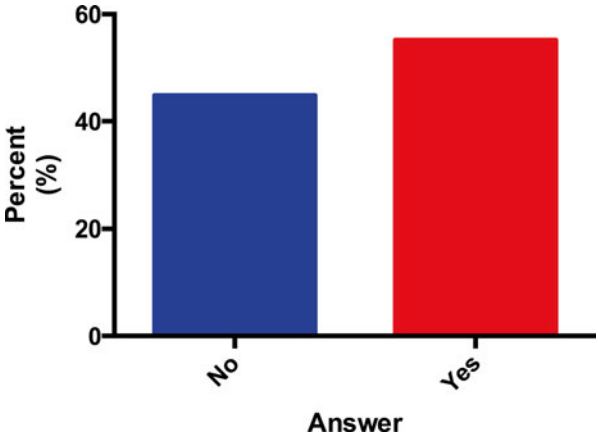

Fig. 10.1 Result of the questionnaire of the faculty of Baveno VI: do you consider preprimary prophylaxis?

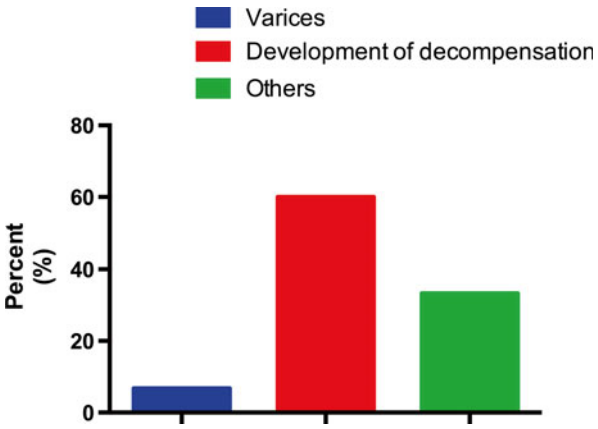

Fig. 10.2 Result of the questionnaire of the faculty of Baveno VI: what would be the relevant endpoint?

In this sense, in a secondary analysis of the abovementioned RCT (timolol study) [3], a cutoff value of 10 mmHg of hepatic venous pressure gradient was identified as an independent predictor for clinical decompensation (unadjusted HR 5.7 (95 % CI 2.7–12)) in this group of compensated cirrhosis with portal hypertension although without varices at baseline [6]. Patients with an HVPG value below this threshold had a 90 % probability of not developing decompensation with a median follow-up of 4 years. These data were confirmed in a latter study in which compensated patients with and without varices were included [10]. In this study, 98 % who developed decompensation during the follow-up had clinically significant portal hypertension at baseline. Patients with clinically significant portal hypertension have not only an increased risk for decompensation but also have an increased risk for death [5].

These results led to the theory that among compensated patients, one can identify a subgroup of patients with an increased risk of decompensation according to the presence of clinically significant portal hypertension. These patients with clinically significant portal hypertension are those who may have the most benefit from prophylactic treatment. Up to date, data supporting this strategy are lacking. Nevertheless, a decreased incidence of ascites was observed among patients who had response to acute administration of beta-blockers in the setting of primary prophylaxis. There is currently a Spanish multicenter trial ongoing aimed at evaluating the use of nonselective beta-blockers in this population group to prevent the development of decompensation.

Taking this into account, one could divide patients with compensated cirrhosis into two groups, firstly those who have clinically significant portal hypertension and who may benefit from the administration of nonselective beta-blockers and secondly those who do not have clinically significant portal hypertension, in whom the treatment should be mainly focused at managing the underlying etiology for the liver disease to avoid further progression (Fig. 10.3).

The definition of clinically significant portal hypertension requires the performance of the hepatic venous pressure gradient measurement, which is an invasive procedure [11]. However, there are promising noninvasive tools that may be useful to identify those patients with clinically significant portal hypertension among the patients with compensated cirrhosis. Among these, using liver stiffness to measure changes in chronic liver disease is the most promising one. Unfortunately, the measurement is dependent on the etiology of the liver disease, so that different cutoffs for detection of advanced fibrosis and presence of varices are identified for different etiologies [12]. However, in a recent meta-analysis, each unit increase in liver stiffness measurement was associated with a 7 % higher risk of decompensation, and this effect was stable across different etiologies of cirrhosis and therefore robust [13]. Nevertheless, although liver stiffness can detect clinically significant portal hypertension with a high sensitivity of around 92 %, it has a low specificity (around 65 %) and therefore cannot replace the measurement of HVPG [12, 13].

Other noninvasive approaches to identify the presence of clinically significant portal hypertension have combined measurements from different methods, for example, the combination of liver stiffness with spleen size and platelet count

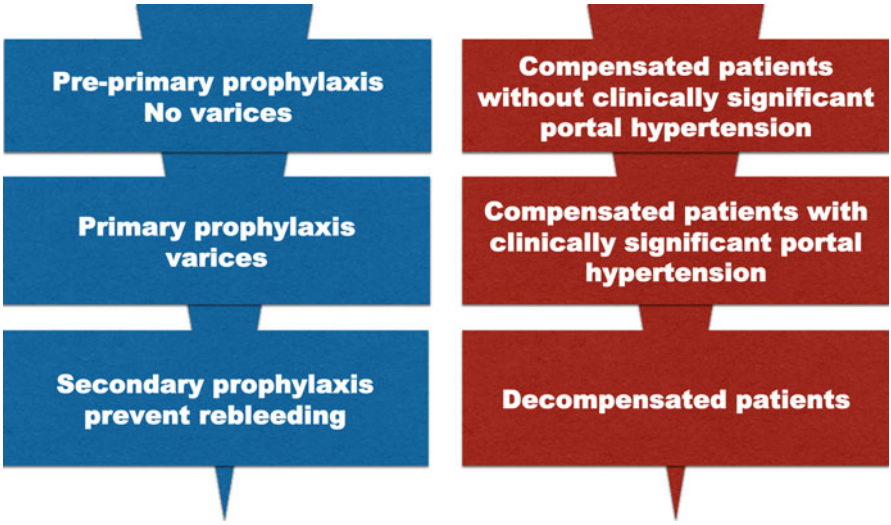

Fig. 10.3 *Left side* shows the progression of varices and variceal hemorrhage. *Right side* shows the progression of compensated patients to decompensated patients

(LSPS) [14]. This combination accurately detected clinically significant portal hypertension in compensated patients with an area under the ROC curve of 0.92. Using a cutoff from 1.72, the LSPS was able to classify correctly 84 % of the patients, while only 16 % were misclassified [14]. This cutoff was then validated in another cohort in whom almost 86 % were correctly classified.

In conclusion, the concept of preprimary prophylaxis is obsolete. Patients with compensated cirrhosis can be divided into those with and without clinically significant portal hypertension. In patients without clinically significant portal hypertension, etiological treatment seems to be the relevant step to avoid disease progression (i.e., development of clinically significant portal hypertension). On the other hand, compensated patients with clinically significant portal hypertension are at risk for decompensation and therefore may be those who can most benefit from prophylactic therapy. Upcoming studies will provide data on whether this new approach is clinically useful.

References

1. de Franchis R (2005) Evolving Consensus in Portal Hypertension Report of the Baveno IV Consensus Workshop on methodology of diagnosis and therapy in portal hypertension. J Hepatol 43:167–176
2. Sarin SK, Groszmann RJ, Mosca PG, Rojkind M, Stadecker MJ, Bhatnagar R et al (1991) Propranolol ameliorates the development of portal-systemic shunting in a chronic murine schistosomiasis model of portal hypertension. J Clin Invest 87:1032–1036
3. Groszmann RJ, Garcia-Tsao G, Bosch J, Grace ND, Burroughs AK, Planas R et al (2005) Beta-blockers to prevent gastroesophageal varices in patients with cirrhosis. N Engl J Med 353:2254–2261

4. de Franchis R (2010) Revising consensus in portal hypertension: report of the Baveno V consensus workshop on methodology of diagnosis and therapy in portal hypertension. J Hepatol 53:762–768
5. Zipprich A, Garcia-Tsao G, Rogowski S, Fleig WE, Seufferlein T, Dollinger MM (2012) Prognostic indicators of survival in patients with compensated and decompensated cirrhosis. Liver Int 32:1407–1414
6. Ripoll C, Groszmann R, Garcia-Tsao G, Grace N, Burroughs A, Planas R et al (2007) Hepatic venous pressure gradient predicts clinical decompensation in patients with compensated cirrhosis. Gastroenterology 133:481–488
7. D'Amico G, Garcia-Tsao G, Pagliaro L (2006) Natural history and prognostic indicators of survival in cirrhosis: a systematic review of 118 studies. J Hepatol 44:217–231
8. D'Amico G, Pasta L, Pasta L, Morabito A, D'Amico M et al (2014) Competing risks and prognostic stages of cirrhosis: a 25-year inception cohort study of 494 patients. Aliment Pharmacol Ther 39:1180–1193
9. Garcia-Tsao G, Groszmann RJ, Fisher RL, Conn HO, Atterbury CE, Glickman M (1985) Portal pressure, presence of gastroesophageal varices and variceal bleeding. Hepatology 5:419–424
10. Rincón D, Iacono Lo O, Tejedor M, Hernando A, Ripoll C, Catalina M-V et al (2013) Prognostic value of hepatic venous pressure gradient in patients with compensated chronic hepatitis C-related cirrhosis. Scand J Gastroenterol 48:487–495
11. Zipprich A, Winkler M, Seufferlein T, Dollinger MM (2010) Comparison of balloon vs. straight catheter for the measurement of portal hypertension. Aliment Pharmacol Ther 32:1351–1356
12. Castera L, Pinzani M, Bosch J (2012) Non invasive evaluation of portal hypertension using transient elastography. J Hepatol 56:696–703
13. Singh S, Fujii LL, Murad MH, Wang Z, Asrani SK, Ehman RL et al (2013) Liver stiffness is associated with risk of decompensation, liver cancer, and death in patients with chronic liver diseases: a systematic review and meta-analysis. Clin Gastroenterol Hepatol 11:1573–1584. e1–2; quiz e88–e89
14. Berzigotti A, Seijo S, Arena U, Abraldes JG, Vizzutti F, Garcia-Pagan JC et al (2013) Elastography, spleen size, and platelet count identify portal hypertension in patients with compensated cirrhosis. Gastroenterology 144:102–111.e1