Abstract

In liver cirrhosis, variceal bleeding is the last in a chain of events initiated by the increase in portal pressure (estimated in clinical practice by the hepatic venous pressure gradient). When hepatic venous pressure gradient goes above 10 mmHg the patient is at risk of developing varices, and when hepatic venous pressure gradient reaches 12 mmHg variceal bleeding might develop. Currently, there is not any effective therapy for the prevention of the development of varices. When varices are small, beta-adrenergic blockers might prevent the enlargement of the varices, and may reduce the risk of variceal bleeding. In patients with medium to large varices, beta-blockers are clearly effective in reducing the risk of variceal bleeding. Endoscopic band ligation might be more effective than beta-blockers, but available evidence is still very weak.

Keywords: Banding ligation; Beta-blockers; Cirrhosis

1. Introduction

Portal hypertension is a common clinical syndrome consequence of liver cirrhosis, the end stage of any chronic liver diseases. It is defined by a pathologic increase of portal pressure, in which the gradient between portal vein and inferior vena cava pressure is increased above the upper normal limit of 5 mmHg. The importance of this syndrome is defined by the frequency and severity of its complications (porto-systemic collaterals, variceal haemorrhage, ascites, hepato-renal syndrome, portosystemic encephalopathy, hepato-pulmonary syndrome); the appearance of these complications defines the progression from compensated to decompensated cirrhosis.

The most important and direct consequence of portal hypertension is the formation of porto-systemic collaterals and, in particular, the formation of gastro-oesophageal varices, the rupture of which is responsible for the main and most lethal complication of portal hypertension, variceal bleeding. Even with current treatments, the morbidity and mortality associated with this condition is high, which emphasizes the need of effective preventive therapy [1].

The present article reviews the established and potential therapeutic strategies for preventing the development and rupture of oesophageal varices.

2. Natural history and prognosis

Variceal bleeding is the last step of a chain of events initiated by an increase in portal pressure, followed by the development and progressive dilation of varices until these finally rupture and bleed. According to recent data, the appearance of varices in compensated patients indicates a change from a clinical stage with a very low risk of death at 1 year (stage 1; 1% risk) to an intermediate risk stage (stage 2; 3.4% risk). The occurrence of variceal bleeding is a dreadful event, marking the progression to decompens-
sation of the liver disease to a stage of very high risk of death (stage 4; 57% risk) [2]. Because the development of complications of cirrhosis marks a threshold beyond which survival prognosis changes considerably, a recent study by Ripoll et al. [3] investigated which markers might predict clinical decompensation (ascites, variceal bleeding, hepatic encephalopathy) in patients with compensated cirrhosis without gastro-oesophageal varices. HVPG, MELD-score and albumin were independent predictors of the development of clinical decompensation. Patients with an HVPG <10 mmHg had a 90% probability of remaining compensated after a median follow-up of 4 years. Besides, this study showed that for every 1 mmHg increase in HVPG there was an 11% increase in the risk of clinical decompensation [3].

2.1. Prevalence and formation of oesophageal varices

When cirrhosis is first diagnosed, varices are present in about 30–40% of compensated patients and in 60% of decompensated patients [4–6]. In cirrhotic patients without varices at first endoscopy, the annual incidence of new varices is 5–10% in published series [7–9]. Variceal formation results from interaction of haemodynamic, anatomical and angiogenic factors: increased portal pressure is the initial and most important factor leading to the opening of pre-existing vascular embryonic channels, that connect the portal and the systemic circulation at several locations, and it is likely to be also the signal for increased expression of angiogenic factors, like VEGF expression in the splanchnic vasculature. In fact recent studies demonstrate that angiogenesis contributes to collateral formation in portal hypertension [10,11] and also indicate that angiogenesis is involved in the maintenance of increased splanchnic blood flow and hyperdynamic circulation [12,11]. Gastro-oesophageal varices are the most frequent and clinically relevant collaterals.

Clinical-haemodynamic correlations have shown that varices may appear when HVPG increases to above 10 mmHg [4,13]. An HVPG over 10 mmHg is a strong predictor for the development of varices [4], confirming that portal pressure plays a pivotal role as the driving force for the development of collaterals. Because of this, an increased HVPG is at present the most important risk factor for the development of varices.

2.2. Progression of oesophageal varices from small to large

Once developed, varices increase in size from small to large before they eventually rupture and bleed. Studies assessing the progression from small to large varices show rates of progression ranging from 5% to 30% per year [8,14,9,15]. The most likely reasons for such variability are differences in patient selection and follow-up endoscopy schedule [15]. Several factors may contribute to the growth of varices. Among them the factor that has been most consistently associated with variceal progression is Child–Pugh class [9,14,16,8]. However, since portal hypertension progresses in parallel to parenchymal liver disease, it is likely that the factor that plays the most important role in the growth of varices is still the increased portal pressure. Other factors include alcoholic aetiology of cirrhosis and presence of red wale markings [9,15]. Improvement in liver function and abstinence from alcohol may result in decrease or even disappearance of varices [16].

2.3. Incidence and risk indicators of first bleeding from oesophageal varices

The incidence of the first variceal bleeding is variable: in patients with no varices the risk of bleeding is about 2% per year and increases to about 5% per year in those with small varices, up to 15% per year in patients with medium–large varices [6].

The probability of bleeding from oesophageal varices is variable and depends on cirrhotic status, but can be estimated according to some risk indicators.

2.3.1. Clinical and endoscopic risk indicators

Variceal size, severity of liver dysfunction expressed by the Child–Pugh classification, and presence of red wale marks – parameters combined in the NIEC (North Italian Endoscopic Club) index – are significantly associated with the risk of bleeding [17]. Although this index has been validated, its predictive accuracy is far from satisfactory (74% sensitivity and 64% specificity) [18]. Moreover, less than 50% of the patients presenting a first variceal bleeding episode would have been classified “a priori” as high-risk patients according to the NIEC index [19].

2.3.2. Haemodynamic risk indicators

The mechanism of variceal rupture is at present explain with the so-called “explosion theory”. This hypothesis suggests that the main factor implicated on the risk of rupture and bleeding is the variceal wall tension. According to Frank’s modification of Laplace’s law, wall tension (WT) increases both with the increase of variceal transmural pressure (that is the difference between intravariceal pressure $P_i$ and oesophageal lumen pressure $P_e$) and variceal radius $(r)$ both with the decrease of thickness of the variceal wall $(w)$.

$$\text{WT} = \frac{(P_i - P_e)r}{w}$$

Variceal size and red wale markings are associated with increased bleeding risk because they reflect two of these three parameters of this equation: radius and wall thickness.

However the variceal pressure, the third factor implicated in wall tension, is the most important one, since it provides the driving force for the dilatation of varices and, as the varices dilate, their wall becomes thinner which further contributes to increase wall tension. Variceal pressure is a function of portal pressure. Many studies have shown that variceal bleeding does not occur if the HVPG does not reach a threshold value of 12 mmHg [20,13,21]. Conversely, if the
HVPG is substantially reduced (below 12 mmHg or by more than 20% of baseline levels) there is a marked reduction in the risk of bleeding [20,22]. This is of outstanding importance, since demonstrates that the portal hypertension syndrome is reversible by pharmacological treatment effectively decreasing portal pressure.

3. Screening for oesophageal varices: how and when

Although several non-invasive tests, in particularly platelet count, the presence of splenomegaly, the ratio of both [23] or data obtained from abdominal ultrasonography (such as increased portal vein diameter >13 mm), and more recently transient elastography [24], have been suggested to be useful in selecting patients with a high risk of having large oesophageal varices, none of these tests, alone or in combination, is accurate enough to completely discard the presence of oesophageal varices when non-invasive indicators are negative [25]. Thus, current recommendation is that all patients at the time of initial diagnosis of cirrhosis should undergo an upper gastrointestinal endoscopy for the screening of oesophageal varices (to assess appearance, number, size and presence of red color signs) [26].

Since endoscopy is unpleasant for the patient, and screening in all cirrhotic patients is a substantial burden, empirical beta-blocker therapy for all patients has been proposed. Two studies suggest that this strategy is cost-effective [27,28], but a third suggested that empiric beta-blockers are cost-effective only in patients with decompensated cirrhosis [29]. The lack of effectiveness of beta-adrenergic blockers preventing the development of varices, and the high rate of side effects observed in well-compensated patients [4] questions the use of beta-adrenergic blockers without screening.

In patients without varices at initial endoscopy, a follow-up evaluation should be performed after 2–3 years to detect the development of varices before they bleed. This interval should be decreased in patients who have an initial HVPG >10 mmHg. Once developed, varices may increase in size. Reported progression rates in prospective studies ranges from 5–20% per year with a median of 12% [30]. Accordingly, in Report progression rates in prospective studies ranges from >10 mmHg. Once developed, varices may increase in size. Should be decreased in patients who have an initial HVPG the development of varices before they bleed. This interval should be performed after 2–3 years to detect the progression of small varices, while the beneficial effects of beta-blockers are less clear in patients with small varices [36]. However, the classification of varices according to their size is very subjective. In fact, in the recent Baveno IV consensus conference it was not possible to agree on a definition of small and big varices [31,32,9,33]. A potentially more acceptable way of screening for varices is the use of capsule endoscopy, although more information is required and its cost still is too high for wide scale use.

4. Prophylactic therapy

4.1. Patients without varices: pre-primary prophylaxis

The observation that non-selective beta-blockers allowed to attenuate or delay the development of collaterals in experimental models of portal hypertension [34,35], prompted studies to investigate whether these agents could prevent the development of oesophageal varices in patients with cirrhosis.

Unfortunately this was not confirmed in a recent study by Groszmann et al. [4]. This study randomized 213 patients with cirrhosis and portal hypertension but without varices to receive timolol (a non-selective beta-adrenergic blocker) or placebo for a median of 55 months [4]. The primary end point was development of oesophageal varices or variceal haemorrhage and the secondary end point was the incidence of complications (i.e. ascites, encephalopathy, liver transplantation or death). The rate of development of the primary endpoint did not differ between the two treatment groups (intention to treat) and the incidence of secondary end-points was also not different. Adverse events were more frequent in the timolol group. Therefore, beta-blockers cannot be recommended for the prevention of the development of oesophageal varices. This study, however, showed that a baseline HVPG lower than 10 mmHg, or a decrease in HVPG greater than 10% of baseline or below 10 mmHg, were the only independent predictors of remaining free of oesophageal varices. Such a reduction in HVPG was achieved more frequently under timolol that under placebo, and this was indeed statistically significant.

Recent studies have shown that blockade of the VEGF signalling cascade is highly effective reducing the formation of collaterals in experimental models [10,11], but no study has explored this clinically.

A different approach, which is already available, is to prevent the progression of cirrhosis (i.e. abstinence in alcoholics, antivirals in viral cirrhosis, lifestyle change in NASH, corticosteroids in autoimmune hepatitis, phlebotomies in hemochromatosis and copper chelators in Wilson’s disease).

4.2. Patients with varices: primary prophylaxis

4.2.1. Who to treat

In the past only patients with medium to large varices were considered for prophylactic treatment of variceal bleeding. This was due to the fact that most studies with beta-adrenergic blockers were performed in patients with medium to large varices, while the beneficial effects of beta-blockers are less clear in patients with small varices [36]. However, the classification of varices according to their size is very subjective. In fact, in the recent Baveno IV consensus conference it was not possible to agree on a definition of small and big varices [26]. On the other hand, it is well established that small varices with red signs or in Child–Pugh C class patients have a bleeding risk similar to that of big varices [17]. Additionally, two controlled studies have evaluated the role of non-selective beta-blockers preventing the increase in size of small varices. The study by Cales et al. [16] showed no benefit of long acting propranolol vs. placebo in preventing the development of large varices in a group of 206 cirrhotic patients who either had no varices or small varices. This study has been criticized
because the risk of developing large varices in the propranolol group was greater than in the placebo group (31% vs. 14%), but this was not matched by an increased risk of bleeding. This unexpected finding may be due to some undetected bias, perhaps in part attributable to the great proportion of patients lost from follow-up (30%). By contrast, the study by Merkel et al. [8] including 161 cirrhotic patients, all with small varices, showed a significantly lower rate of increase in the size of the varices in patients receiving nadolol than in those receiving placebo. Additionally, the bleeding risk at the end of follow-up was significantly lower in the nadolol group (12%) compared to 22% in the placebo group [8]. Based on these data, the last Baveno consensus conference concluded that “prophylactic treatment with non-selective beta-blockers could be considered in patients with small esophageal varices (without associated risk factors for bleeding) with the primary aim to reduce variceal growth. However, further studies are required before this suggestion can be accepted as a formal recommendation”.

In patients with small varices who are at high risk for bleeding (with advanced liver disease and/or presence of red weal marks) prophylaxis with beta-blockers to prevent first variceal bleeding should be used. In those patients who choose not to take beta-blockers endoscopy should be performed every 2 years and annually in the setting of decompensation [26,37].

4.2.2. How to treat

4.2.2.1. Pharmacologic therapy. Pharmacologic prophylaxis is aimed at preventing the first bleeding episode and at improving survival by reducing bleeding-related death.

The efficacy of non-selective beta-adrenergic blockers for the prevention of first bleeding have been compared with that of placebo or non-active treatment in 11 RCTs. Meta-analysis of these studies has been shown to reduce the risk of first variceal bleeding (from 24% with non active treatment to 15% with beta-blockers after a median follow-up 2 years) [36]. Mortality was also lower in the beta-blockers group and this difference has recently been shown to be statistically significant [38]. Once initiated, therapy with beta-adrenergic blockers should be maintained indefinitely, since the bleeding risk comes back to baseline if the treatment is withdrawn [39]. It is important to note that beta-blockers are among the safest and cheapest drugs worldwide. Propranolol and nadolol are the two most widely used non-selective beta-blockers [36]. Nadolol is easier to administrate because it has longer half-life allowing once-a-day administration. In addition it has a low-lipid solubility, so it does not cross the blood-brain barrier and for this reason may have lower potential for central side effects [40]. Propranolol is commonly initiated at a dose of 20 mg twice a day, while nadolol is initiated at a dose of 40 mg once a day. A decrease in HVPG <12 mmHg essentially eliminates the risk of bleeding and improves survival [20], while reductions >20% from baseline [41] or even >10% from baseline [42] significantly decrease the risk of first variceal bleeding. Since HVPG measurement is not widely available, in the majority of the published studies, the dose of beta-blockers was titrated to decrease the heart rate 25% from baseline. However, since a reduction in heart rate dose not correlate with reduction in HVPG [43], the dose of beta-adrenergic blockers is adjusted to maximal tolerated doses. So, the dose is titrated by stepwise increases until reaching the maximum tolerated dose, within the limit of 160 mg twice a day for propranolol or 240 mg once a day for nadolol. The median maximum tolerated dose is about 80 mg twice daily for propranolol and 80 mg once daily for nadolol.

The most common side effects of beta-blockers are light-headedness, fatigue, shortness of breath, impotence and sleep disorders. Although these are usually not severe, may require reductions in the dose of beta-blockers or result in lack of compliance. Around 10–15% of side-effects result in treatment discontinuation [44]. In addition, approximately 15% of patients have contraindications to the use of beta-blockers [45]. Absolute contraindications include congestive heart failure, asthma, severe chronic obstructive pulmonary disease, 2nd or 3rd degree heart block, severe aortic stenosis and peripheral vascular disease. Insulin-dependent diabetes and sinus bradycardia are relative contraindications.

Circa 25% of cirrhotic patients with medium/large esophageal varices may have either contraindications for the administration of non-selective beta-blockers or can not tolerate these drugs, and the degree of protection afforded (about 40% relative risk reduction) is far from ideal, which has stimulated the search for alternative treatments.

Nitrates decrease portal pressure mainly through a reduction in intrahepatic and portal-collateral resistance [30]. However, all available vasodilators have a systemic hypotensive effect and the decrease in portal pressure may be more related to hypotension than to a decrease in resistance [46]. Among long-acting nitrates only isosorbide mononitrate (ISMN) has been evaluated in clinical trials for the prevention of variceal bleeding. ISMN administered alone is ineffective in the prevention of variceal bleeding [45], and could increase the morbidity, specially in patients with advanced cirrhosis and ascites [47]. The combination of non-selective beta-blockers and ISMN have been shown to significantly enhance the long-term HVPG response to beta-adrenergic blockers [48]. However, it is less clear whether the greater effect of this combination on portal pressure translates into a greater clinical efficacy in primary prophylaxis. An open trial comparing nadolol vs. nadolol + ISMN demonstrated a significant lower rate of first bleeding in the combination group, but without improving survival [49,50]. However, a subsequent double-blind, placebo controlled study including a large number of patients failed to confirm these results. Furthermore, more side effects were observed in the combination group [44]. Therefore, the association of ISMN with non-selective beta-blockers is not recommended as a standard therapy in the primary prophylaxis of variceal bleeding.
bleeding [26]. The same limitations apply to the association of propranolol or nadolol with other vasodilators. Spironolactone and low-sodium diet have been shown to reduce portal pressure in patients with compensated cirrhosis by diminishing the increased plasma volume and splanchnic blood flow [51]. However, the combination of nadolol plus spironolactone failed to improve the clinical efficacy of nadolol alone in primary prophylaxis [52]. As a conclusion, non-selective beta-blockers remain as the only pharmacological treatment with proven efficacy for the primary prophylaxis of oesophageal variceal bleeding.

Another question is whether HVPG monitoring should be performed in patients on pharmacological therapy. Three longitudinal studies have demonstrated that a sufficient HVPG decrease (to 12 mmHg or below or of more than 20% from baseline) is associated with an effective protection from first variceal bleeding [20,53,41]. This leads to the question on whether HVPG measurements should be used to monitor portal pressure response to drug treatment in clinical practice. Two simulation analyses have yielded conflicting results; one suggesting that HVPG monitoring might be cost-effective in primary prophylaxis [54], and the other arriving to the opposite conclusion [55]. The main problem is that the assumptions of these analyses (i.e. how to manage non-responders to medical treatment) have never been tested in randomized controlled trials. A study of HVPG guided therapy suggested that the shift of non-responders from beta-blockers to EBL does not improve the outcome [56]. The issue will remain hypothetical until HVPG guided therapy is proven better than empirical approaches in randomized controlled trials.

4.2.2.2. Endoscopic therapy. It is widely accepted that banding ligation is nowadays the endoscopic method of choice for the primary prevention of variceal bleeding since it is more effective and it is associated with fewer side-effects than endoscopic injection sclerotherapy (EIS) [57,58]. Banding ligation is repeated until the varices are obliterated, which usually requires two to four ligation sessions. Minor complications such as transient dysphagia and chest discomfort are relatively frequent. The shallow ulcers that develop at the site of ligation can bleed, but less frequently than the ulcers that form after sclerotherapy. Mechanical complications, which range from mucosal tears that cause bleeding to complete oesophageal perforation, are less frequent now that multiple-band ligating devices are coming into widespread use [30].

There is no agreement on how frequently the varices should be ligated in the initial course of eradication. Some authors wait a minimum of one month between banding procedures [59], while others perform EBL on a weekly basis [60]. Reported frequency of complications with the former strategy was lower than with the latter. A recent trial evaluated the effectiveness and complications of EBL performed every two weeks vs. every 2 months. This trial included patients with and without previous bleeding [61]. The 2-month interval scheme obtained a higher total eradication rate and lower recurrence rate. No patient in either group developed variceal bleeding. However, other studies favour shorter intervals (1–2 weeks). Follow-up endoscopies should be performed every 6 months and varices should be re-eradicated upon recurrence. This is in marked contrast with prophylaxis with beta-blockers, in which no follow-up endoscopies are needed.

4.2.2.3. Pharmacologic vs. endoscopic therapy: beta-blockers vs. banding ligation. Sixteen trials have been reported comparing endoscopic band ligation with beta-adrenergic blockers as first line option for primary prophylaxis of variceal bleeding. Only 10 have been fully published [62,63,60,64–72,59,73]. The meta-analysis of these trials (both including or excluding the studies published in abstract) shows an advantage of endoscopic band ligation over beta-adrenergic blockers in terms of prevention of first bleeding, without differences in mortality [74,75].

These results, however, have several problems. One of them is that most trials were underpowered or lacked any sample size calculation (11 out of 16 included less than 100 patients). The sample size that would be needed to detect a decrease in the incidence of variceal bleeding (at 2 years) from a 20% under beta-blockers (a rather pessimistic estimate) to a 12% with banding ligation (a rather optimistic hypothesis), under a two-sided hypothesis (alpha 5%, beta 20%) would be of 658 patients. The largest trial to date included only 152 [60]. Additionally, four of the trials were prematurely stopped after an interim analysis, due to futility in three cases [60,68,73] or to an apparently significant benefit of banding in a small study [59]. When a cumulative meta-analysis of the 10 fully published studies is performed by ordering them by sample size, results are far from significance after the four trials with 100 or more patients, and become significant only after the inclusion of trials with 62 patients or less (Fig. 1).

<table>
<thead>
<tr>
<th>Study name</th>
<th>Sample Size</th>
<th>Cumulative RR</th>
<th>CI</th>
<th>p-Value</th>
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<td>Schepke 2004</td>
<td>152</td>
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<td>0.524 to 1.506</td>
<td>0.653</td>
</tr>
<tr>
<td>Liu 2002</td>
<td>110</td>
<td>0.814</td>
<td>0.501 to 1.326</td>
<td>0.404</td>
</tr>
<tr>
<td>Lo 2004</td>
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<td>0.499 to 1.236</td>
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<tr>
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<td>0.553 to 1.132</td>
<td>0.206</td>
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<tr>
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<td>89</td>
<td>0.722</td>
<td>0.514 to 1.103</td>
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<tr>
<td>Nobile 2007</td>
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<td>0.505 to 0.977</td>
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<tr>
<td>Paleopoulus 2005</td>
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<tr>
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<td>0.492 to 0.931</td>
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<td>De 1999</td>
<td>30</td>
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<td>0.504 to 0.947</td>
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Fig. 1. Cumulative meta-analysis of the 10 fully published studies, performed by ordering them by sample size. Results are far from significance after the four trials with 100 or more patients, and become significant only after the inclusion of trials with 62 patients or less.
Another controversial result of the meta-analysis is that adverse events requiring treatment discontinuation were significantly more frequent in patients treated with non-selective beta-blockers [75]. However, the type and severity of side effects was different between the two therapies [74]. Indeed, most side effects related to beta-blockers (hypotension, tiredness, breathlessness, poor memory, insomnia) were subjective and were easily managed by adjusting the dose or discontinuation of beta-blockers, did not require hospital admission and no fatalities were observed. In contrast, side effects related to EBL included 12 bleeding episodes related to EBL and one oesophageal perforation. In most cases, these complications required hospitalization and blood transfusion and resulted in three deaths [60,73]. Further, because of the short duration of follow-up in most of these studies, the long-term safety and benefits of prophylactic endoscopic band ligation are still uncertain. On the contrary, long-term safety and efficacy of non-selective beta-adrenergic blockers is well established [39,41]. Bleeding episodes after discontinuing beta-blockers because of side effects have also been considered as an argument against its use as first choice. However, most of these bleedings occurred months or years after beta-blockers were withdrawn, suggesting that if an alternative therapy, as EBL, had been offered to these patients, some of these bleeding episodes could have been prevented.

The cost-effectiveness of EBL vs. beta-blockers for primary prophylaxis has been compared in three decision-

![Algorithm for the prevention of first bleeding in patients with cirrhosis (CSPH: clinically significant portal hypertension).](image-url)
analysis studies. Different assumptions on the incidence of variceal bleeding, quality of life with each treatment, mortality or other portal hypertensive complications lead to conflicting conclusions [29,27,76].

The recommendation made at the 2005 Baveno consensus conference (and that, in our view, still stands) is that non-selective beta-blockers should be considered as first-choice treatment to prevent first variceal bleeding, while EBL should be offered to patients with medium/large varices and contraindications or intolerance to beta-blockers [26]. Even in this case a recent trial shed some doubts in the use of EBL. In that trial EBL was compared with no treatment in patients with contraindications to beta-blockers. The trial was prematurely stopped due to a high rate (12%) of iatrogenic bleeding in the band ligation group [77]. However, the early termination of the trial frustrated the possibility of obtaining clear-cut evidence to support a recommendation.

The combination of pharmacology and endoscopic therapy was also investigated with contrasting results. In the study of Sarin et al. [78] endoscopic band ligation plus beta-adrenergic blockers appears to offer no benefit in terms of prevention of first bleeding when compared to endoscopic band ligation alone. However, in the study of Gheorghe et al. [79] combination therapy significantly reduced the occurrence of the first episode of variceal bleeding and improved bleeding-related survival in a group of cirrhotic patients with high-risk oesophageal varices in the waiting list for liver transplantation [79]. There was a lower rate of recurrence of varices in patients treated with endoscopic band ligation plus propranolol but at the expense of more side effects. Probably more studies would be required, although these are unlikely to be performed due to the very large number of patients that would be needed.

5. Summary (Fig. 2)

The evidence from prophylactic trials indicates that endoscopic screening for varices should be part of routine clinical practice in patients with cirrhosis and should be done when the diagnosis of cirrhosis is made.

If endoscopy shows that patient has no varices, there is no evidence to support starting on non-selective beta-blockers to prevent the development of varices (pre-primary prophylaxis). Similarly there is no clinical evidence for strategies based on the use of anti-angiogenic agents. In these patients it is recommended to repeat endoscopy after 2–3 years, if they have compensated cirrhosis, or at the moment of hepatic decompensation and then annually. Surveillance should be closer in those with an HVPG >10 mmHg.

In patients with small varices with increased risk of bleeding (Child–Pugh score B/C or presence of red wale marks) non-selective beta-blockers should be used for the prevention of first variceal bleeding (primary prophylaxis). In those patients with small varices but without increased risk of bleeding, non-selective beta-blockers can be used with the aim of prevent variceal growth, although their long term benefit have not been established.

In patients with medium-large varices with criteria for increased risk of haemorrhage (Child–Pugh score B/C or presence of red wale marks) non-selective beta-blockers or endoscopic banding ligation is recommended for the prevention of first variceal bleeding (primary prophylaxis). In patients with medium-large varices but without increased risk of haemorrhage, beta-blockers are preferred and banding ligation should be considered if there are contraindications, intolerance or non-compliance to beta-blockers.

In patients who take beta-blockers as primary prophylaxis, the drug should be adjusted to the maximal tolerated dose; endoscopic follow-up is unnecessary. If patients are treated with banding ligation, endoscopy should be repeated every 1–2 weeks until obliteration, 1–3 months after obliteration and then every 6–12 months to check for variceal recurrence. More information is needed on the long-term benefit from prophylactic banding ligation and on the association of beta-blockers and banding ligation.

Available data do not support the use of nitrates (either alone or in combination with beta-blockers) or endoscopic sclerotherapy.

### Practice points

- Patients without varices should be screened endoscopically for the appearance of varices every 2–3 years. In patients with small varices it is indicated to repeat endoscopy every 1–2 years. The interval should be shortened in patients with HVPG ≥10 mmHg.
- Patients with moderate/large varices should be treated with a non-selective beta-blocker if there are no contraindications.
- Patients with small varices with red signs or with advanced liver failure (Child–Pugh C) are at similar risk of bleeding as those with moderate/large varices and should be considered for preventive therapy.
- Patients with moderate/large varices with contraindications to or who cannot tolerate beta-blockers should be offered endoscopic band ligation. Band ligation might be used as first choice in patients with moderate/large varices depending on patient’s preferences and local resources.
- If no bleeding occurs treatment should be maintained for life (unless the liver disease improves and significant portal hypertension disappears).
Research agenda

- Further refinement is needed in non-invasive tools for selecting cirrhotic patients at risk of having varices.
- Studies for the pre-primary prophylaxis should focus on patients with HVPG \( \geq 10 \) mmHg, and should include longitudinal HVPG measurements.
- New drugs more effective decreasing portal pressure than beta-adrenergic blockers are required.

Conflict of interest statement
None declared.

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