Portal Hypertensive Bleeding in Cirrhosis: Risk Stratification, Diagnosis and Management - 2016 Practice Guidance by the American Association for the Study of Liver Diseases

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A. Purpose and Scope of the Guidance

This guidance provides a data-supported approach to risk stratification, diagnosis, and management of patients with cirrhosis and portal hypertension. A guidance document is different from a guideline. Guidelines are developed by a multidisciplinary panel of experts who rate the quality (level) of the evidence and the strength of each recommendation using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system. A guidance document is developed by a panel of experts in the topic, and guidance statements, not recommendations, are put forward to help clinicians understand and implement the most recent evidence.

This guidance focuses on portal hypertension, varices, and variceal hemorrhage, and statements are based on the following: (1) review of the recent literature using PubMed, giving more weight to large, well-designed prospective trials and well-performed meta-analyses; (2) several consensus conferences among experts; and (3) the authors' years of experience caring for patients with cirrhosis and varices. Management of ascites and encephalopathy is addressed in other documents.

When little or no data exist from well-designed prospective trials, emphasis is given to results from large series and reports from recognized experts. In this case, clinical studies needed to clarify management are specified in a section on future research.

Practice guidelines for the diagnosis and treatment of gastroesophageal variceal hemorrhage were published in 1997, endorsed by the American Association for the Study of Liver Diseases, American College of Gastroenterology, American Gastroenterological Association, and

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American Society of Gastrointestinal Endoscopy (1). Since then, a number of randomized controlled trials have advanced our approach to managing variceal hemorrhage. Additionally, 4 international consensus conferences were held since then, where experts in the field evaluated the changes in pathophysiology, diagnosis and management of varices and variceal hemorrhage. These include 2 American Association for the Study of Liver Diseases/European Association for the Study of the Liver single-topic conferences in 2007 (many of the recommendations from this conference were incorporated into the aforementioned guidelines) (2) and in 2013, and 2 Baveno consensus conference in 2010 (3) and in 2015 (4). In this updated practice guidance, recommendations derived from these consensus conferences were also incorporated, particularly those from the latest Baveno conference that took place in Baveno, Italy, in April 2015.

Perhaps the most relevant change in these recommendations has been the recognition of the different stages of cirrhosis (5), so that recommendations are now focused on risk stratification and individualizing care for portal hypertension.

Intended for use by healthcare providers, this guidance identifies preferred approaches to the diagnostic, therapeutic, and preventive aspects of care of patients with portal hypertension. As with other guidance documents, it is not intended to replace clinical judgment but rather to provide general guidance applicable to the majority of patients. They are intended to be flexible, in contrast to formal treatment recommendations or standards of care, which are inflexible policies designed to be followed in every case. Clinical considerations may justify a course of action that differs from this guidance.

B. Risk Stratification

Cirrhosis is a chronic condition with a high mortality. It constitutes the fifth leading cause of adult deaths and ranks eighth in economic cost among the major illnesses (6).

Cirrhosis is a heterogeneous disease that cannot be studied or managed as a single entity and is classified in 2 main prognostic stages: compensated and decompensated cirrhosis (5, 7). This

classification depends on the presence or absence of clinically evident decompensating events (specifically ascites, variceal hemorrhage, and encephalopathy), with a median survival in the compensated stage that exceeds 12 years, while it is only 1.8 years in patients who develop decompensation (8). The Child-Turcotte-Pugh (CTP) classification has been used to stratify patients with cirrhosis. Patients with cirrhosis belonging to CTP-A class are compensated, while those in CTP-B/C class are mostly decompensated.

Portal hypertension is the initial and main consequence of cirrhosis and is responsible for the majority of its complications. In fact, it has been shown that portal pressure, determined by the hepatic venous pressure gradient (HVPG), is better than liver biopsy in predicting the development of complications of cirrhosis in patients with chronic liver disease without cirrhosis on liver biopsy (9). Therefore, a new entity denominated "compensated advanced chronic liver disease" has been proposed, emphasizing that portal hypertension may occur before a formal anatomical diagnosis of cirrhosis is established (4). This entity would encompass patients with cirrhosis and those with advanced liver fibrosis with portal hypertension (HVPG >5 mmHg). For ease of understanding, in the rest of this guidance the entity of compensated advanced chronic liver disease will be referred to as compensated cirrhosis, both terms being interchangeable and acceptable by consensus (4).

The stage of compensated cirrhosis is asymptomatic, and it is the longest stage. Pathophysiological mechanisms are evolving at this stage, and, therefore, several sub-stages are being recognized. Based on portal pressure, patients with compensated cirrhosis can be divided into those with mild portal hypertension (HVPG >5 but <10 mmHg) and those with "clinically significant portal hypertension" (CSPH), defined by an HVPG ≥ 10 mmHg. CSPH is associated with an increased risk of developing varices (10), overt clinical decompensation (ascites, variceal hemorrhage, hepatic encephalopathy) (11), post-surgical decompensation (12), and hepatocellular carcinoma (13). This sub-staging is not only prognostically important, but, as mentioned below, the mechanisms maintaining portal hypertension at these sub-stages are different, and therefore their therapeutic approach will be different.

CSPH is present in about 50%-60% of patients with compensated cirrhosis without gastroesophageal varices (GEV) (10). Patients with GEV have, by definition, CSPH, because patients with GEV have an HVPG of at least 10 mmHg (14, 15). Prognosis is worse in patients with compensated cirrhosis with GEV compared to those without GEV (16, 17). Therefore, among patients with CSPH, 2 sub-stages are recognized based on the absence or presence of GEV.

It is important to recognize that although portal hypertension and its direct consequences (varices) form the bases of staging in compensated cirrhosis, liver insufficiency even at this stage plays an important role, as serum albumin and the Model for End-Stage Liver Disease (MELD) score are also independent predictors of decompensation (11).

Variceal hemorrhage constitutes a decompensating event, but its mortality differs whether it presents as an isolated complication of cirrhosis (20% 5-year mortality) or whether it presents in association with other complications (over 80% 5-year mortality) (8).

While in the past, emphasis had been placed on managing the direct complications of portal hypertension, varices, and variceal hemorrhage, it is now clear that these complications cannot be considered in an isolated manner. Rather, they should be considered in the context of advances in the staging of cirrhosis and in the context of other complications of cirrhosis that may occur concomitant or subsequent to the development of varices and variceal hemorrhage (4).

Stages of portal hypertension in cirrhosis are depicted in Figure 1, and goals of therapy at each stage are shown in Table 1.

Guidance statements

- **Cirrhosis should be described, analyzed, and managed in 2 distinct clinical stages, compensated and decompensated, defined by the presence or absence of overt clinical complications of cirrhosis (ascites, variceal hemorrhage, hepatic encephalopathy).**

- **Patients with compensated cirrhosis should be sub-staged into those with mild portal hypertension and those with clinically significant portal hypertension, an entity that predicts the development of more advanced stages.**
- **Patients with CSPH are sub-staged into those with and without gastroesophageal varices.**
- **The treatment of portal hypertension differs depending on the stage and sub-stages of cirrhosis, because prognosis and mechanisms of disease (and therefore therapeutic targets) are different.**

C. Epidemiology and Associated Conditions

GEV are present in approximately 50% of patients with cirrhosis, but this depends on the clinical stage. In patients with compensated cirrhosis, GEV are present in 30%-40%, while they can be present in up to 85% of patients with decompensated cirrhosis (18, 19). In patients with compensated cirrhosis, varices develop at a rate of 7%-8% per year (10), and progression from small to large varices occurs at a rate of 10%-12% per year, with decompensated cirrhosis being an independent predictor of progression (20). Variceal hemorrhage occurs at a rate of around 10%-15% per year and depends on the severity of liver disease, the size of varices, and the presence of red wale marks (areas of thinning of the variceal wall) (21, 22). Six-week mortality, which is now recognized as the primary endpoint to assess the impact of therapies for acute variceal hemorrhage (4), ranges between 15% and 25% (23-25).

Other factors associated with poor outcomes in patients with variceal hemorrhage are the presence of bacterial infections and an HVPG >20 mm Hg, which is mostly observed in patients belonging to CTP-C class. (26, 27). If untreated, recurrent variceal hemorrhage occurs in 60% of patients, usually within 1-2 years of index hemorrhage (28).

Obesity and alcohol use are associated conditions of prognostic relevance in patients with cirrhosis, independent of etiology. Obesity has been shown to predict worsening of liver fibrosis, cirrhosis decompensation, and lack of regression of cirrhosis in patients with viral cirrhosis (29-31), while even moderate alcohol intake can lead to worsening portal pressure and has been shown to

worsen prognosis of HCV (hepatitis C)- and NASH (nonalcoholic steatohepatitis)-related cirrhosis (32, 33). Therefore, although beyond the scope of this guidance, weight loss and alcohol abstinence are important considerations in patients with cirrhosis.

D. Pathophysiological bases of therapy

As shown in Figure 2, portal pressure increases initially as a consequence of an increased intrahepatic resistance to portal flow due to structural mechanisms (eg, fibrous tissue, vascular distortion from regenerative nodules, microthrombi). This "structural" component, which explains about 70% of the increased intrahepatic resistance, could be targeted by treating the etiology of cirrhosis, the use of antifibrotic agents, and even anticoagulants (34). However, at least one-third of the increased intrahepatic resistance is due to an increased intrahepatic vascular tone, which, in turn, is due to endothelial dysfunction resulting mostly from reduced nitric oxide bioavailability (35). This "functional" component is amenable to vasodilators (such as nitrates, alpha-adrenergic antagonists, angiotensin-2 blockers) (36). These drugs should not be used alone, as they also cause systemic vasodilatation, decrease arterial blood pressure, and may worsen sodium retention. A conceptually more appealing approach to ameliorate the functional component is to use drugs that will reduce portal pressure by improving endothelial dysfunction, such as statins (37). An added advantage of these drugs is that by causing intrahepatic vasodilatation, they may improve hepatic blood flow and liver function. Statins in particular also have anti-fibrotic properties (34).

One of the initial consequences of portal hypertension is the formation of porto-systemic collaterals, the most important being those that develop through the coronary or the short gastric veins and constitute gastroesophageal varices. Although the formation of collaterals had been assumed to be the result of dilatation of pre-existing vascular channels, research studies have implicated a process of neoangiogenesis (38). Concomitant or even prior to the development of collaterals, splanchnic vasodilatation occurs, leading to increased flow into the gut and into the portal venous system. Therefore, even when portal flow is entirely diverted through collaterals, portal hypertension persists (39). Increased splanchnic nitric oxide production is the main factor that leads to vasodilatation and increased splanchnic blood flow.

Hyperglucagonemia and neoangiogenesis further contribute to the increased splanchnic blood flow that maintains the portal hypertensive state (38).

Vasodilation occurs not only in the splanchnic but also in the systemic circulation (manifested clinically as arterial hypotension), leading to activation of neurohumoral and vasoconstrictive systems, sodium and water retention, increased blood volume, and increased cardiac output, that is, a hyperdynamic circulatory state that further increases portal venous inflow and portal pressure. Additionally, norepinephrine, angiotensin-2, and antidiuretic hormone (activated neurohumoral and vasoconstrictive systems) further contribute to intrahepatic vasoconstriction.

Drugs that act by causing splanchnic vasoconstriction, such as non-selective beta-blockers (propranolol, nadolol, carvedilol), vasopressin and its analogue terlipressin, and somatostatin and its analogues (octreotide, vapreotide) are known to reduce portal pressure and constitute the current mainstay in the treatment of varices and variceal hemorrhage. Since these drugs act by decreasing flow to the splanchnic circulation and the liver, an improvement in liver function would not be expected. β-1 adrenergic blockade decreases portal flow through a decrease in cardiac output, and β-2 blockade decreases portal flow through splanchnic vasoconstriction via unopposed α-adrenergic activity. Therefore, it is essential that beta-blockers used in the treatment of portal hypertension be non-selective. Importantly, the effect of non-selective beta-blockers (NSBB) in decreasing flow is more related to their β-2 blocking effect rather than to their β-1 effect (40) and explains the lack of correlation between decreases in portal pressure and decreases in heart rate (41). Carvedilol, a non-selective beta-blocker with anti-α_1 adrenergic (vasodilator) activity, acts as an NSBB decreasing portal flow but also acts as a vasodilator (intrahepatic circulation). HVPG response is greater with carvedilol than with propranolol or nadolol, but, given its vasodilatory properties, carvedilol is associated with a greater decrease in mean arterial pressure (42).

It has been recently shown that patients with mild portal hypertension (HVPG >5 but <10 mmHg) have a normal cardiac index (ie, they have not yet developed the hyperdynamic

circulatory state), while those with CSPH, especially if varices are present, have already developed a hyperdynamic state. Accordingly, the response to NSBB in patients with mild portal hypertension is suboptimal compared to that of patients with CSPH (43), indicating that there is no role for NSBB in this setting.

Endoscopic variceal ligation (EVL) is a local therapy that consists of placing rubber bands around esophageal varices in repeated sessions until they become obliterated. Because it is a local therapy that has no effect on portal hypertension, recurrence of varices is the rule, and patients require indefinite endoscopic monitoring.

Local therapies for the management of gastric (mostly cardiofundal) varices consist of (1) the transendoscopic obturation by injection of cyanoacrylate glue into the varices or (2) the transvenous obliteration by instilment of sclerosants and/or liquid embolic agents into a gastro/splenorenal collateral via the left renal vein aided by balloon occlusion, that is, balloon occluded retrograde transvenous obliteration (BRTO) (44).

In patients with decompensated cirrhosis, placement of the transjugular intrahepatic portosystemic shunt (TIPS) by interventional radiological techniques that consist of connecting the hypertensive portal vein with a normotensive hepatic vein via a coated stent causes a significant decrease and even normalization of portal pressure. Therefore, in patients with functional TIPS stents, there is no need for other therapies for portal hypertension (eg, NSBB, EVL).

E. Diagnosis and Monitoring

Portal hypertension is defined as a portal pressure gradient (the difference in pressure between the portal vein and the hepatic veins) greater than 5 mmHg.

The best method to assess portal pressure is through the catheterization of the hepatic vein with determination, via a balloon catheter, of the HVPG, which is the difference between the

wedged (or occluded) hepatic venous pressure and the free hepatic venous pressure (45). Normal HVPG is 3-5 mmHg.

It should be underlined that the wedged (occluded) pressure (and consequently the HVPG) is a measure of sinusoidal pressure and does not provide useful data in pre-hepatic or pre-sinusoidal portal hypertension (Table 2). An HVPG over 5 mmHg identifies patients with compensated advanced chronic liver disease/compensated cirrhosis secondary to conditions associated with sinusoidal hypertension (Table 2). As mentioned above, portal hypertension is further defined as mild portal hypertension (HVPG >5 but <10 mmHg) and as clinically significant portal hypertension (HVPG ≥10 mmHg). Above this threshold of 10 mmHg all the complications of portal hypertension are more likely to appear (varices, clinical decompensation).

In patients with gastroesophageal varices (who by definition have CSPH), an HVPG >12 mm Hg identifies bleeding risk, mostly because there is clear evidence that shows that reducing the HVPG to levels of 12 mmHg or below is associated with protection from variceal bleeding (28). An HVPG >16 mmHg indicates a higher risk of death (46). As mentioned previously, an HVPG ≥20 mm Hg predicts failure to control bleeding, early rebleeding, and death during acute variceal hemorrhage (27, 47), and in patients with cirrhosis awaiting liver transplantation, each 1 mm Hg increase in HVPG predicts a 3% increase in the risk of death in a median follow-up of 19 months (48).

Despite the crucial role of HVPG in the determination of CSPH and other outcomes, HVPG measurements require specific expertise, are invasive, relatively expensive, and not available in all centers. Therefore, HVPG measurements are not considered standard of care for every patient with cirrhosis, particularly because non-invasive or surrogate indicators are increasingly utilized at most centers.

a) Non-invasive tests (NIT) in the diagnosis of clinically-significant portal hypertension

In a stepwise diagnostic approach, specific signs of portal hypertension should be first looked for on physical examination. They include spider nevi or visible abdominal porto-systemic collaterals. The absence of physical signs cannot be used to rule out CSPH.

Among laboratory data, a low platelet count is the most common laboratory sign of portal hypertension; it correlates slightly with HVPG and with the presence of GEV. However, taken alone, it is not accurate enough to either diagnose or exclude CSPH or GEV. On the other hand, the combination of platelet count with other unrelated non-invasive tests (NITs) improves the non-invasive diagnosis of CSPH (49).

Ultrasound provides safe and inexpensive imaging evidence of morphologic abnormalities associated with cirrhosis and portal hypertension. The presence of porto-collateral circulation on ultrasound, CT, or MRI (recanalized paraumbilical vein, spontaneous spleno-renal circulation, dilated left and short gastric veins) or the finding of a reversal of flow within the portal system is 100% specific for CSPH (50) and is sufficient to diagnose CSPH. Several other sonographic signs of portal hypertension have been described, such as dilatation of portal vein and the reduction of portal vein velocity (or their combination as congestion index of the portal vein) (51, 52). Although splenomegaly taken alone is a sensitive but non-specific sign of portal hypertension, the size of the spleen should be routinely reported because, when combined with platelet count and liver stiffness, it provides accurate data on the presence of CSPH/varices (49, 53).

The ability to assess liver stiffness (LS), a physical property of liver tissue influenced by the amount of liver fibrosis content, has represented a major advance in this field. LS by transient elastography (FibroScan®) has proved very accurate for discriminating patients with and without CSPH, with a mean AUROC of 0.93 in a recent meta-analysis (based on 5 studies including 420 patients) (54) and can be currently considered the backbone of the non-invasive diagnosis of portal hypertension. However, most of the data have been obtained in patients with untreated viral cirrhosis and alcoholic cirrhosis. Data regarding other etiologies and data in patients who have eliminated HCV require further investigation.

Most studies have shown that the best LS cutoff to detect CSPH is >20-25 mmHg, with a diagnostic accuracy over 90% (55, 56). In a prospective study, HVPG ≥10 mmHg and LS ≥ 21 kPa were equally effective in predicting decompensation (57).

In a large study, an LSPS (liver stiffness [in kPa] x spleen size [in cm]/platelet count [in number/mm^3] score) >2.06 was 90% specific in ruling in CSPH with a positive predictive value of >90% (49). Importantly, these measures/scores have to be considered in the context of clinical parameters. In this sense, a recent prospective study described a sequential screening-diagnostic strategy based on liver stiffness measurements assessed in the context of the presence of any ultrasound abnormality and/or a platelet count <150,000/mm^3 and identified the subgroup of patients with compensated cirrhosis in whom CSPH would be more likely (56).

Spleen stiffness (SS) measurement by transient elastography has been recently proposed as a novel parameter more tightly related to portal hypertension, with promising results (58, 59). In fact, SS >54 kPa was better than LS and similar to HVPG in predicting first clinical decompensation in one study. However, SS cannot be measured by transient elastography without a separate ultrasound exam and cannot be measured if the spleen is not significantly enlarged. Therefore, SS measurements by transient elastography cannot be recommended in clinical practice.

Newer sonoelastographic methods allow direct visualization of the liver and spleen, facilitating SS measurement. Evidence is still limited, but point shear wave elastography (ARFI, Siemens, Germany) (60) and 2-dimensional real-time shear wave elastography (Aixplorer, Supersonic Imagine, France) (61, 62) show promising results with higher applicability and similar accuracy in the prediction of CSPH.

Magnetic resonance elastography is an emerging technique that provides data on liver and spleen stiffness of much larger areas of the liver and spleen compared to ultrasound-based techniques. Although magnetic resonance elastography has been shown to be accurate in the staging of liver fibrosis (63), data regarding its diagnostic performance in the diagnosis of CSPH are still very limited, with one study showing that LS determined by magnetic resonance elastography

predicted the onset of clinical decompensation in patients with compensated cirrhosis (64). More studies are needed in this field.

Guidance statements

- **HVPG measurement is the gold-standard method to assess the presence of clinically significant portal hypertension (CSPH), defined as an hepatic venous pressure gradient (HVPG) ≥10 mmHg.**
- **CSPH can be identified by non-invasive tests. LS > 20-25 kPa, alone or combined with platelet count and spleen size. The presence of porto-systemic collaterals on imaging is sufficient to diagnose CSPH.**
- **Patients with gastroesophageal varices on endoscopy have, by definition, CSPH.**

b) Non-invasive tests (NIT) in the diagnosis of gastroesophageal varices (GEV)

Determining the presence and size of varices and the presence of red wale marks requires esophago-gastro-duodenoscopy (EGD), an invasive and expensive procedure that is not free of risks. Many studies have looked for non-invasive ways of determining the presence of high-risk varices (medium/large varices, ie, those requiring prophylactic therapy) so as to circumvent the need for screening endoscopy.

The discriminative accuracy of non-invasive tests in predicting the presence of any GEV is limited (AUROC between 0.71 and 0.84) (55), and the use of non-invasive tests to diagnose GEV is not recommended. However, NITs are accurate to rule-out high-risk varices in patients with compensated cirrhosis. In particular, LS combined with platelet count correctly identifies patients at very low risk (<5%) of having high-risk varices (56, 65). This data has been obtained mostly from patients with untreated viral cirrhosis. Data in patients with NASH cirrhosis, cholestatic liver disease, and in patients with HCV-related cirrhosis achieving sustained virological response are needed.

By consensus among experts, and after review of the literature, it was proposed that patients with compensated cirrhosis with liver stiffness <20 kPa (determined by transient elastography)

and a platelet count >150,000/mm^3 were very unlikely to have high-risk varices (<5%), and endoscopy could be safely avoided in them (4). Unpublished studies have validated these cutoffs and report that 20%-25% of EGDs can be circumvented.

In patients with cirrhosis secondary to hepatitis B, an LSPS (liver stiffness [in kPa] x spleen size [in cm]/platelet count [in number/mm^3] score) <3.5 was accurate in ruling out high-risk varices (53). Whether this cutoff can be applied to patients with cirrhosis due to other etiologies remains to be established.

Because measurements of spleen stiffness are more feasible with ARFI, irrespective of spleen size, this technology is a promising tool in diagnosing and ruling out high-risk varices and compares favorably to other NIT in Asian studies (60); however, data in European and American patients are lacking.

Guidance statements

- **Patients with a LS <20 kPa and platelet count >150,000/mm^3 have a very low probability (<5%) of having high-risk varices, and EGD can be circumvented.**
- **In patients who do not meet these criteria, screening endoscopy for the diagnosis of gastroesophageal varices is recommended when the diagnosis of cirrhosis is made.**

c) Monitoring the development of CSPH, varices, high-risk varices

Patients without evidence of CSPH should be monitored to identify the onset of the syndrome. Even if data on this specific aspect is lacking, data from published abstracts suggest that LS and platelet count monitoring could be useful. The appearance of new porto-systemic collaterals during follow-up has been shown to be associated with variceal formation and growth (66), as is progressive spleen enlargement (67). Therefore, when performing screening for hepatocellular carcinoma, imaging evidence of worsening portal hypertension should be specifically sought.

Patients without varices on screening endoscopy constitute an area of uncertainty, since their natural history has not yet been fully elucidated, particularly with the emergence of therapies that eliminate the etiologic agent (68). Experts' opinion suggests that if liver injury is ongoing (eg, active drinking in alcoholics and lack of sustained virological response in HCV) and/or co-factors of disease are present (eg, obesity, alcohol), surveillance endoscopy should be repeated at 2-year intervals. Otherwise, in the absence of ongoing injury, 3-year intervals are considered sufficient (4). Although probably reasonable, there is no data to support discontinuing screening endoscopies if several of them are negative for varices.

In patients with small varices on screening endoscopy who are not candidates for primary prophylaxis (see below), repeat endoscopy is recommended. It has been suggested that if the liver injury is ongoing (eg, active drinking in alcoholics and lack of sustained virological response in HCV) and/or co-factors of disease are present (eg, obesity), surveillance endoscopy should be repeated at yearly intervals. Otherwise, in the absence of ongoing injury, 2-year intervals are considered sufficient (4).

Because development of decompensation could indicate worsening of portal hypertension and liver dysfunction with a higher incidence of cirrhosis, patients with no or small varices on screening endoscopy should have a repeat endoscopy performed when and if decompensation develops.

d) Monitoring changes in HVPG

Changes in HVPG, spontaneous or during pharmacological therapy, have been shown to be predictive of outcomes. In patients with a history of variceal hemorrhage, a decrease in HVPG to less than 12 mmHg or a decrease greater than 20% from baseline significantly reduces the risk of recurrent hemorrhage, ascites, encephalopathy, and death (69, 70). In patients with compensated cirrhosis, reductions in HVPG >10% from baseline have been associated with a reduction in the development of varices (10), first variceal hemorrhage, and death (71).

Recent studies show that the need for separate HVPG procedures to assess response to therapy can be obviated by assessing the acute hemodynamic response to intravenous propranolol (0.15 mg/kg) during a single procedure, but this requires further investigation (71, 72).

Unfortunately, there have been no non-invasive tests (eg, Doppler, liver stiffness) that correlate with changes in HVPG.

Guidance statements

- **Patients with compensated cirrhosis without varices on screening endoscopy should have endoscopy repeated every 2 years (with ongoing liver injury or associated conditions such as obesity and alcohol use) or every 3 years (if liver injury is quiescent, eg, after viral elimination, alcohol abstinence).**
- **Patients with compensated cirrhosis with small varices on screening endoscopy should have endoscopy repeated every year (with ongoing liver injury) or every 2 years (if liver injury is quiescent, eg, after viral elimination, alcohol abstinence).**
- **Patients with compensated cirrhosis without varices or with small varices who develop decompensation should have a repeat endoscopy when this occurs.**
- **Monitoring changes in HVPG should not be performed routinely (outside clinical trials). Non-invasive tests do not correlate well with changes in HVPG.**

F. Management

As mentioned above, therapy of varices and variceal hemorrhage should be stratified according to the different clinical stages of cirrhosis and portal hypertension that are shown in Table 1. The objective of therapy for patients at an early stage is to prevent the development of later stages. Varices and variceal hemorrhage should be managed in the context of the presence (or absence) of other complications of cirrhosis/portal hypertension (eg, ascites, encephalopathy), and therefore the status (compensated or decompensated) of the patient with varices/variceal hemorrhage should be always considered in the selection of the different therapies. In the compensated patient, the ultimate objective is to prevent decompensation; that is, the

objective is not only to prevent varices or variceal hemorrhage but also to prevent the other complications of cirrhosis.

In addition to specific therapies that will be outlined below, in the compensated patient every effort should be taken to eliminate the etiologic agent and to correct associated aggravating conditions such as alcohol, obesity, and drug-induced liver injury, since these measures in themselves can decrease portal pressure and reduce the risk of decompensation.

a) Patients with compensated cirrhosis and mild portal hypertension

This stage is defined by an HVPG >5 but <10 mmHg. Patients in this stage do not have varices or other complications of portal hypertension and are known to have a very low risk of clinical decompensation in the following 5 years. Therefore, the goal of therapy is to prevent the development of CSPH, which clinically would translate to the prevention of GEV and clinical decompensation. Patients at this stage of cirrhosis have not yet reached the threshold portal pressure that predicts the development of complications, and they have not yet fully developed a hyperdynamic circulatory state (43). Therefore, because increased intrahepatic resistance is the main mechanism leading to portal hypertension in this stage, the mainstay of therapy has to be directed towards the etiology of cirrhosis. Livers of patients in this stage of cirrhosis are more likely to have thin fibrous septa compared to patients with CSPH (73). Because thin septa are considered more susceptible to resorption/degradation, patients in this stage are the most likely to show regression to a non-cirrhotic stage with treatment of etiology (74), as has been demonstrated in patients with HBV (hepatitis B) cirrhosis (31).

In addition to eliminating or suppressing the etiological agent (eg, HBV, HCV, alcohol, iron), a number of drugs have been shown to have “antifibrotic” properties in pre-clinical studies, and some are currently being investigated in randomized clinical trials in patients mostly with compensated NASH cirrhosis (with and without CSPH) (75).

Statins decrease hepatic fibrogenesis, improve intrahepatic endothelial dysfunction, reduce portal pressure, and improve liver perfusion and liver function (76). In patients with

compensated HCV cirrhosis, a propensity score-matched study showed that statin users had lower incidence of decompensation (ascites and variceal hemorrhage) and lower mortality than non-users (77). However, prospective randomized trials of statins in patients with compensated cirrhosis are lacking. Although statins appear to have a beneficial effect at all stages of cirrhosis (76), the specific stage of cirrhosis that will be associated with maximal benefit from statins remains to be determined. This also applies to new antifibrotic agents.

Unfortunately, current non-invasive tests are not useful in ruling out CSPH. Therefore, the only way of confirming the absence of CSPH in patients without varices is by performing HVPG measurements. However, these measurements are not recommended in clinical practice, particularly since treatment of etiology is the only currently recommended therapy in these patients, independent of sub-stage. The specific identification of these patients by HVPG should be confined to clinical trials, in which the efficacy of targeted therapies and the significance of reductions in HVPG to 5 mmHg (or below) or the magnitude of HVPG reductions from baseline should be explored.

Guidance statements

- **In patients in the earliest stage of compensated cirrhosis (patients with mild portal hypertension), the objective of treatment is to prevent the development of CSPH/decompensation and perhaps even to achieve regression of cirrhosis.**
- **Elimination of the etiologic agent is the current mainstay of therapy.**
- **Drugs that act on portal flow, such as nonselective beta-blockers, will be mostly ineffective in this sub-stage, as the hyperdynamic circulatory state is not fully developed.**

b) Patients with compensated cirrhosis and CSPH but without gastroesophageal varices (GEV)

CSPH is defined as HVPG ≥10 mmHg and is a hallmark in compensated cirrhosis as it heralds the development of varices and clinical decompensation, among other outcomes. Livers of patients

in this stage of cirrhosis mostly have thick fibrous septa and smaller nodules compared to those with mild portal hypertension (73).

Until recently, it was considered that the aim of therapy at this stage of cirrhosis was to prevent the development of GEV ("pre-primary prophylaxis"). In this regard, a large, multicenter, randomized, placebo-controlled trial showed no differences between placebo and NSBB (timolol) in the prevention of varices (10). Therefore, no specific portal pressure-reducing treatment to prevent the formation of varices is recommended in this setting. Even though at the time it was considered that the study included a very homogeneous patient population (patients with cirrhosis without GEV), two distinct populations were identified: those with and without CSPH. The response to NSBB is different between groups; patients without CSPH (mild portal hypertension) have not yet developed a hyperdynamic circulatory state and therefore the reduction in portal pressure observed in response to beta-blockers is significantly smaller n these patients than in those with CSPH (43). Negative results of the timolol study are partly explainable because roughly half the patients did not have CSPH.

This study also showed that a decrease in HVPG >10% from baseline identified patients unlikely to develop varices (10). More importantly, changes in HVPG in this setting could be surrogates of the development (or not) of clinical decompensating events. While reduction or maintenance of HVPG to levels below 12 mmHg likely prevents patients from developing variceal hemorrhage and ascites, the percent reduction in HVPG from baseline associated with decreased risk of clinical outcomes remains to be determined.

It is now considered that the objective of therapy in patients at this stage is not only to prevent GEV but, more importantly, to prevent decompensation. Drugs that will decrease intrahepatic resistance and/or decrease splanchnic blood flow are reasonable at this stage. Results of ongoing trials using NSBB and exploring this objective are eagerly awaited.

Guidance statements

- **In patients with cirrhosis and CSPH but without varices, the objective of treatment should no longer be to prevent varices, but to prevent clinical decompensation.**
- **There is no evidence at present to recommend the use of NSBBs in preventing the formation of varices.**

c) Patients with compensated cirrhosis and gastroesophageal varices (GEV)

Patients at this stage have endoscopically proven GEV and have, by definition, CSPH, because the lowest HVPG in these patients is 10-12 mmHg (14, 15). This clinical setting was previously described as "primary prophylaxis of variceal hemorrhage," and the main objective was to prevent the first episode of variceal hemorrhage. In this setting, a reduction in HVPG to ≤12 mm Hg or ≥20% from baseline was shown to be protective of the development of variceal hemorrhage and constitutes an "optimal response" to NSBB (70). It is important to emphasize that changes in heart rate do not correlate with changes in HVPG and that noninvasive tests are not useful in assessing changes in HVPG. Additionally, the beneficial effect of NSBB may go beyond their portal-pressure reducing effect and therefore monitoring changes in HVPG should not be performed routinely.

As already mentioned, prevention of clinical decompensation is probably the most appropriate endpoint at this stage because ascites, not variceal bleeding, is the most common decompensating event (11), and patients with varices, compared to those without varices, are more likely to decompensate (16).

Therapies that would act on the pathophysiological mechanisms of portal hypertension/hyperdynamic circulatory state would theoretically prevent not only variceal hemorrhage but other complications of cirrhosis, while local therapies such as EVL, which may prevent variceal hemorrhage but would not prevent the other complications, would only play a role in patients intolerant to pathophysiologically targeted therapies.

In fact, reductions in HVPG >10% induced by the use of NSBB in the prevention of first hemorrhage are associated not only to a lower incidence of first variceal hemorrhage but also to a lower incidence of ascites and death (71, 78). A decreased incidence of clinical decompensation has also been observed with reductions in HVPG >20% from baseline or to levels below 12 mm Hg (79). However, these findings are not consistent (80).

Other than these post-hoc analyses, there are no prospective studies specifically designed to assess therapies to prevent decompensation in patients with esophageal varices. Therefore, current recommendations are only pertinent with regards to prevention of first variceal hemorrhage and are applicable to patients with both compensated and decompensated cirrhosis.

Primary prophylaxis of variceal hemorrhage is indicated in patients at a high risk of bleeding. These are (a) patients with medium/large varices; (b) patients with small varices with red wale signs; and (c) decompensated patients with small varices (81). Table 2 shows the recommended doses, therapeutic goals, and follow-up procedures for each of the recommended therapies.

c.1. Prevention of first variceal hemorrhage in patients with medium/large esophageal varices

The most recent meta-analyses of 8 randomized controlled trials (RCT) comparing NSBB to no therapy/placebo (22) showed a benefit of NSBB in preventing first variceal hemorrhage. A meta-analysis of 19 RCTs (including unpublished abstracts) comparing NSBB to EVL (82) showed that EVL was associated with lower rates of upper gastrointestinal bleeding and variceal bleeding, without differences in mortality. The beneficial effect of EVL on bleeding was not confirmed in subgroup analyses limited to 7 trials with adequate bias control or to 12 fully published studies (82, 83). Therefore, it has been recommended by consensus that either NSBB (propranolol, nadolol) or EVL can be used to prevent first variceal hemorrhage in patients with

medium/large varices and that the choice of treatment should be based on local resources and expertise, patient preference and characteristics, contra-indications and adverse events (3, 4).

Based on 2 trials comparing EVL to carvedilol that showed either a greater efficacy of carvedilol (84) or comparable efficacy (85), carvedilol was added to the list of NSBB that can be used in this setting (Table 2) (4).

Advantages of NSBB include low cost, ease of administration, and not requiring specific expertise. In addition, and as mentioned previously, hemodynamic responders to NSBB have a lower incidence of decompensation and death.

Importantly, because clinical trials proving the benefit of NSBB did not routinely repeat EGD, and those that did showed no clear modification in variceal size, once a patient is on NSBB there is no need for repeat EGD.

Disadvantages of NSBBs are that approximately 15% of patients may have absolute or relative contraindications to therapy, and another 15% require dose reduction or discontinuation due to common side effects (eg, fatigue, weakness, shortness of breath) that resolve upon discontinuation but that may discourage patients and their physicians from using these drugs (86).

In cases in which NSBBs have to be discontinued because of intolerance, the patient can be switched to carvedilol, as it is generally perceived as being better tolerated than traditional NSBBs. Dosing of carvedilol is also easier, as it is not guided by heart rate and is at a start dose of 3.125 mg twice daily and increased to a maximum dose of 6.25 mg twice daily (Table 2). In

patients intolerant to even the lowest dose of carvedilol, treatment should be switched to serial EVL.

Advantages of EVL are that it can theoretically be done in the same session as screening endoscopy and has few contraindications. Disadvantages are the risks associated with sedation, plus the risk of causing dysphagia, esophageal ulcerations, strictures, and bleeding. Although the number of side effects is greater with NSBB, the severity of side effects is greater with EVL, with reports of deaths resulting from EVL-induced bleeding ulcers. In addition, because EVL is a local therapy that does not act on the pathophysiology of portal hypertension, not only is it unable to prevent complications other than variceal hemorrhage, but, after variceal eradication, surveillance endoscopies are necessary to detect variceal recurrence, which approaches 90%.

Subjective factors influence the physician's choice in selecting NSBB versus EVL, as illustrated in a recent study in which gastroenterologists who spent at least half their time performing endoscopy were more likely to choose EVL, while physicians had a less procedural-based practice were more likely to choose NSBB (87).

There is only one RCT comparing the combination of NSBB plus EVL versus EVL alone in the prevention of first variceal hemorrhage that showed no differences in the incidence of bleeding or death between groups, with an expectedly higher number of side effects in the combination therapy group (88). Combination therapy is therefore not recommended in this setting.

Based on evidence obtained from trials of prophylactic surgical shunt therapy that show a significantly higher rate of encephalopathy and a tendency for a higher mortality in patients randomized to shunt surgery, TIPS (a shunt therapy) is not recommended in this setting (89).

Guidance statements

- **Either traditional NSBB (propranolol, nadolol), carvedilol, or endoscopic variceal ligation (EVL), is recommended for the prevention of first variceal hemorrhage (primary prophylaxis) in patients with medium or large varices (Table 2 for doses and schedules).**
- **The choice of treatment should be based on patient preference and characteristics.**
- **Patients on NSBB or carvedilol for primary prophylaxis do not require monitoring with serial EGD.**
- **Combination therapy NSBB plus EVL is *not* recommended in this setting.**
- **TIPS placement is not recommended in the prevention of first variceal hemorrhage.**

c.2. Prevention of first variceal hemorrhage in patients with small esophageal varices

The treatment of patients with small varices depends on whether they are at a high risk of hemorrhage (with red wale marks and/or occurring in a CTP-C patient) or whether they lack these characteristics (ie, low risk of bleeding) (21).

Regarding high-risk small varices, although there is no study that specifically addresses this issue (mainly because it is rare to find patients with high-risk small varices), the recommended treatment is NSBBs, because performing EVL in these varices and defining eradication may be challenging.

Regarding low-risk small varices, there is evidence that shows that NSBB or carvedilol may delay the growth of small varices (90, 91), but this is controversial (92, 93). Further evidence is required to confirm a benefit from starting therapy at this stage.

Guidance statement

- **NSBB is the recommended therapy for patients with high-risk small esophageal varices (Table 3 for doses).**

d) Patients presenting with acute esophageal variceal hemorrhage

Patients at this stage are considered decompensated, but 5-year mortality is very different, depending on whether the patient with cirrhosis presents with variceal hemorrhage as an isolated decompensating event (20%) or whether the patient presents with other complications of cirrhosis (ascites or encephalopathy) (over 80%) (8).

In this setting, imaging studies aimed at ruling out hepatocellular carcinoma and portal vein thrombosis, which can further increase portal pressure and lead to variceal haemorrhage and could modify the therapeutic strategy, should be considered or performed.

In this setting, risk stratification is essential. Indeed, there is data to suggest different therapeutic approaches based on this stratification. As mentioned previously, HVPG ≥20 mm Hg (measured within 24 hours of admission) is a strong predictor of early rebleeding and death (47) and could be used to stratify risk. However, recognizing that these measurements are unavailable at most centers, a study looking at clinical variables showed a strong association between the CTP class and an HVPG ≥20 mmHg, with more than 80% of CTP-C patients having an HVPG ≥20 mmHg (27). Recent studies have confirmed the value of CTP class in stratifying risk (24, 25, 94), and a recalibrated MELD score has been recently proposed (23).

The immediate goal of therapy in these patients is to control bleeding, to prevent early recurrence (within 5 days) and to prevent 6-week mortality, which is considered, by consensus, the main treatment outcome (4).

Acute variceal hemorrhage is a medical emergency requiring intensive care. As in any patient with any hemorrhage, it is essential to first assess and protect the circulatory and respiratory status of the patient. Volume restitution should be initiated to restore and maintain hemodynamic stability. A recent RCT including patients presenting with gastrointestinal bleeding showed that a “restrictive” packed red blood cell (PRBC) transfusion strategy (initiating PRBC transfusion at a hemoglobin threshold of 7 g/dL and maintaining it at 7-9 g/dL) was

associated with a significant decrease in mortality compared to a "liberal" transfusion strategy (initiating PRBC transfusion at a hemoglobin threshold of 9 g/dL and maintaining it at 9-11 g/dL) (95). In a subgroup of patients with cirrhosis, significantly lower early rebleeding and mortality rates were observed in patients randomized to restrictive PRBC transfusion, particularly in those with CTP class A and B. Notably, HVPG was measured before and after transfusion in some patients, and, while it increased with liberal transfusion, it did not change in those randomized to restrictive transfusion. Transfusion/volume expansion in the individual patient should take into account other factors such as age, cardiovascular disorders, ongoing hemorrhage, and hemodynamic status.

Regarding correction of coagulopathy, randomized controlled trials of recombinant factor VIIa have not shown a clear benefit (96, 97), and therefore correcting the INR by the use of fresh frozen plasma or factor VIIa is not recommended, particularly since INR is not a reliable indicator of coagulation status in cirrhosis. No recommendations can be given regarding platelet transfusion in patients with variceal hemorrhage.

Patients with cirrhosis presenting with gastrointestinal hemorrhage are at a high risk of developing bacterial infections, and the use of antibiotic prophylaxis has been shown in RCT to lead to a decrease in the development of infections, recurrent hemorrhage, and death (98, 99). Studies have recognized that rates of infection and death are low in CTP-A cirrhotic patients admitted with GI hemorrhage (26, 100); however, there are no prospective studies that evaluate the need of antibiotic prophylaxis in these patients. Regarding the type of antibiotic, intravenous ceftriaxone has been shown to be more effective in preventing infection compared to oral norfloxacin (101). However, most of the difference was explained by a high rate of infections by quinolone-resistant organisms. The specific antibiotic recommended should be based on individual patient risk characteristics and local antimicrobial susceptibility patterns, with ceftriaxone (1 g/24 h) being the first choice in patients with advanced cirrhosis, in those on quinolone prophylaxis, and in hospital settings with high prevalence of quinolone-resistant bacterial infections (4). Norfloxacin is no longer available in the United States and is not available in most inpatient formularies. Therefore, the antibiotic of choice in most centers is

intravenous ceftriaxone at a dose of 1 g every 24 hours. Duration of antibiotic prophylaxis is short-term, for a maximum of 7 days.

A meta-analysis of 30 RCTs shows that the use of vasoactive agents in acute variceal hemorrhage is associated with lower 7-day all-cause mortality and lower transfusion requirements (102); therefore, they should be started as soon as possible, together with antibiotics and prior to diagnostic endoscopy. All vasoactive drugs used in the control of acute hemorrhage are used in intravenous infusion. A recent study comparing the three most utilized worldwide (somatostatin, octreotide, terlipressin) found no significant differences among them, although terlipressin was used at doses lower than recommended (103). Octreotide is the only vasoactive drug available in the United States, and in a meta-analysis of 11 trials, it was shown to significantly improve control of acute hemorrhage (102). Table 4 shows the recommended doses, therapeutic goals, and follow-up procedures for vasoactive drugs used in acute variceal hemorrhage.

Endoscopy is done as soon as possible and not more than 12 hours after presentation. If a variceal source is confirmed, EVL should be performed. The diagnosis of variceal hemorrhage is considered certain when active bleeding from a varix is observed or when a sign of recent bleeding, such as a “white nipple,” is observed. Variceal hemorrhage should be inferred when varices are the only lesion found, and either blood is present in the stomach or endoscopy is performed after 24 hours of hemorrhage.

Once endoscopy and EVL have been performed, RCTs have shown that, compared to standard therapy, “early” (pre-emptive) TIPS (placed within 72 hours of admission) is associated with significantly lower treatment failure and mortality rates in carefully selected high-risk patients. These have been defined in one trial (which used uncovered TIPS stents) as those with an HVPG >20 mmHg (104), and in a second trial (which used currently recommended covered TIPS stents) as those with CTP class C cirrhosis with a score of 10-13 and those with CTP class B with active bleeding on endoscopy despite intravenous vasoactive drug therapy (105). The latter trial had many exclusion criteria, including CTP class A, CTP class B without active bleeding at

endoscopy, CTP-C patients with a score of 14 and 15 points, age >75 years, hepatocellular carcinoma outside Milan criteria, a creatinine level greater than 3 mg/dL, previous combination pharmacological plus endoscopic treatment to prevent rebleeding, bleeding from isolated gastric or ectopic varices, total portal-vein thrombosis, and heart failure. Patients included in the study constituted <20% of those admitted for variceal hemorrhage. Notably, observational studies have not confirmed the effect of early TIPS on survival (106, 107), and further studies are necessary.

Patients who do not belong to the “high-risk” categories defined above should continue standard therapy with vasoactive drugs continued for up to 5 days depending on control of bleeding and severity of liver disease. Persistent bleeding, or severe rebleeding despite combined pharmacological and endoscopic therapy, is best managed by PTFE-covered TIPS. If rebleeding is modest, a second session of endoscopy therapy can be attempted.

Up to 20% of variceal hemorrhage episodes can be refractory to standard therapy and are associated with a high mortality. A “bridge” therapy may be necessary in order to acutely control hemorrhage until a more definitive therapy such as TIPS can be performed. Balloon tamponade is still used as bridge therapy and provides hemostasis in up to 80% of patients, but is associated with a high rate of severe adverse events and a mortality rate near 20% (1). Balloon tamponade should not exceed 24 hours.

A recent small multicenter RCT compared balloon tamponade to endoscopically placed self-expandable metal stents in patients with cirrhosis and variceal hemorrhage refractory to medical and endoscopic treatment. Although no differences in survival could be demonstrated, control of bleeding was significantly greater and side effects were significantly lower with metal stents (108). Additionally, these stents can stay in place for up to 7 days, allowing more time for resuscitation and plans for definitive therapy.

Guidance statements

- **Packed red blood cell (PRBC) transfusion should be done conservatively, starting to transfuse when the hemoglobin reaches a threshold of around 7 g/dL with the goal of maintaining it between 7-9 g/dL.**
- **Short-term (maximum 7 days) antibiotic prophylaxis should be instituted in any patient with cirrhosis and GI hemorrhage.**
- **Intravenous ceftriaxone 1 g/24 h is the antibiotic of choice and should be used for a maximum of 7 days (consider discontinuing when hemorrhage has resolved and vasoactive drugs discontinued).**
- **Vasoactive drugs (somatostatin or its analogue octreotide; vasopressin or its analogue terlipressin) should be initiated as soon as variceal hemorrhage is suspected (Table 4 for recommended doses and schedules).**
- **EGD should be performed within 12 hours of admission and once patient is hemodynamically stable.**
- **If a variceal source is confirmed/suspected, EVL should be performed.**
- **In patients at high risk of failure or rebleeding (CTP class C cirrhosis or CTP class B with active bleeding on endoscopy) who have no contraindications for TIPS, an "early" (pre-emptive) TIPS within 72 hours from EGD/EVL may benefit selected patients.**
- **For patients in whom an early TIPS is not performed, intravenous vasoactive drugs should be continued for 2-5 days and NSBB initiated once vasoactive drugs are discontinued. Rescue TIPS is indicated in these patients if hemorrhage cannot be controlled or if bleeding recurs despite vasoactive drugs + EVL. In patients in whom TIPS is performed successfully, intravenous vasoactive drugs can be discontinued.**

e) Patients who have recovered from an episode of acute esophageal variceal hemorrhage

This clinical setting was previously described as "secondary prophylaxis of variceal hemorrhage." However, as mentioned previously, therapies have to be taken in the context of the presence or absence of other complications of cirrhosis. In patients with a low risk of death (those with variceal hemorrhage as the sole complication of cirrhosis), the objective of therapy should be the prevention of an additional complication, including variceal rebleeding, while in

patients at a high risk of death (those with variceal hemorrhage and other decompensating events), the objective of therapy should be to improve survival (4).

As these specific objectives have not been explored as main end-points in clinical trials until now, the following recommendations are only pertinent with regards to prevention of recurrent variceal hemorrhage. Patients who recover from the first episode of variceal hemorrhage have a high rebleeding risk (60% in the first year), with a mortality of up to 33%. Therapy to prevent rebleeding is therefore mandatory in these patients and should be instituted before the patients is discharged from the hospital.

Patients who had a TIPS performed during the acute episode do not require specific therapy for portal hypertension or varices but should be referred for transplant evaluation. TIPS patency should be assessed by Doppler ultrasounds every 6 months (at the same time as ultrasound is being performed for hepatocellular carcinoma screening). First-line therapy for all other patients (the majority) is the combination of NSBB (propranolol or nadolol) + EVL. A recent meta-analysis comparing combination therapy to monotherapy with EVL or drug therapy has demonstrated that combination therapy is significantly more effective than EVL alone in preventing all-source GI hemorrhage. However, combination therapy is only marginally more effective than drug therapy (NSBB + nitrates) alone, with a tendency for an increased survival with drugs alone (109). This suggests that pharmacological therapy is the cornerstone of combination therapy. Therefore, if NSBB are not tolerated, EVL should not be used as monotherapy and TIPS should be considered, particularly if the patient has another complication (eg, ascites) that could benefit from TIPS.

The combination of NSBB plus low-dose isosorbide mononitrate (ISMN) has a greater portal pressure-reducing effect than NSBB alone, but rate of side-effects is higher because of the added ones associated with ISMN, specifically headache and lightheadedness. In a meta-analysis, the combination of NSBB and ISMN was no different than NSBB alone regarding overall rebleeding or mortality, but had a higher rate of side effects (110).

In the setting of secondary prophylaxis of variceal hemorrhage, carvedilol has only been compared to EVL alone (111) or to NSBB + ISMN (112) but has not been compared to standard of care with the combination of NSBB + EVL. Therefore, there is not enough data to recommend carvedilol in the prevention of rebleeding. Additionally, carvedilol, particularly at doses >12.5 mg/day, may decrease arterial pressure (42) and should not be used in patients with refractory ascites (even in the setting of primary prophylaxis).

A recent multicenter placebo-controlled RCT showed that the addition of simvastatin (40 mg PO every day) was not associated with a reduction in rebleeding (compared to placebo) but was associated with a significant improvement in survival, mainly related to a decrease in deaths from bleeding or infections (113). However, there was a higher than expected incidence of rhabdomyolysis, limited to patients with severe liver dysfunction.

TIPS is the treatment of choice in patients that fail first-line therapy to prevent rebleeding (NSBB + EVL). Until recently, all trials comparing TIPS and endoscopic therapy had used uncovered TIPS stents (114). In a recent multicenter RCT, TIPS (using the currently recommended covered stents) was compared to EVL or glue injection plus NSBB, and showed a significantly lower rebleeding rate (0% versus 29%) in patients treated with covered TIPS with no differences in survival and with a higher incidence of early encephalopathy in the TIPS group (115).

The lowest rebleeding rates are observed in patients on secondary prophylaxis who are HVPG responders (defined as a reduction in HVPG below 12 mmHg or >20% from baseline) (28). Therefore, HVPG-guided therapy performed in centers where HVPG measurements are readily available would be a reasonable strategy. A recent RCT of covered TIPS versus HVPG-guided therapy (propranolol and isosorbide mononitrate) showed lower rebleeding rates in patients randomized to TIPS (7% versus 26%) without differences in survival and with a higher incidence of encephalopathy in the TIPS group (116).

Table 5 shows the recommended doses, therapeutic goals, and follow-up procedures for each of the first line recommended therapies.

Guidance statements

- **Combination of NSBB + EVL is first-line therapy in the prevention of rebleeding (Table 5 for recommended doses and schedules).**
- **Patients who have a TIPS placed successfully during the acute episode do not require NSBB or EVL.**
- **TIPS is the recommended rescue therapy in patients who experience recurrent hemorrhage despite combination therapy NSBB + EVL.**

G. Gastric varices

Gastric varices are present in about 20% of patients with cirrhosis. Sarin's classification is the most commonly used for risk stratification and management of gastric varices (117). Gastroesophageal varices type 1 (GOV1) are EV extending below the cardia into the lesser curvature and are the most common (75% of gastric varices). Gastroesophageal varices type 2 (GOV2) are those extending into the fundus. Isolated gastric varices type 1 (IGV1) are located in the fundus (IGV1). GOV2 and IGV1 are commonly referred to as "cardiofundal varices." Isolated varices type 2 (IGV2) are located elsewhere in the stomach but are extremely infrequent in patients with cirrhosis. The main factors associated with a higher risk of bleeding are localization (IGV1>GOV2>GOV1), large size, presence of red spots, and severity of liver dysfunction (117, 118).

Cardiofundal varices are much more frequent in patients with portal vein and/or splenic vein thrombosis, and the finding of these varices should prompt imaging to investigate the presence of such thromboses. In patients with bleeding cardiofundal varices, and because endovascular obliteration is an option in those with a large gastro- or splenorenal collateral, cross-sectional vascular imaging is preferred as it would investigate both thrombosis and the presence of such collaterals and would guide management accordingly.

The evidence to support recommendations for the management of gastric variceal hemorrhage is much less robust than that for esophageal varices. There are only a few controlled trials available, including a small sample size and, in most instances, without adequate stratification according to the type of varices or severity of liver disease.

a) Prevention of first hemorrhage from gastric varices

Only one randomized trial has been published on the primary prevention of gastric variceal bleeding. This study included 89 patients with large (≥10 mm) GOV2 and IGV1 that were randomized to endoscopic injection of cyanoacrylate (glue), NSBB, and observation (119). The number of patients with IGV1 was small (15%). Cyanoacrylate injection was associated with lower bleeding rates (10%) than NSBBs (38%) and observation (53%). Survival was higher in the cyanoacrylate group (93%) compared to observation (74%), but no different from those on NSBB (83%). Firm recommendations cannot be derived from this trial. The least invasive treatment is NSBB, and this could be recommended because, as mentioned previously, they could have beneficial effects in preventing other complications of cirrhosis.

Although no studies have specifically evaluated the efficacy of TIPS in preventing first hemorrhage from cardiofundal varices, results from trials of prophylactic surgical shunt therapy that show a significantly higher rate of encephalopathy and a tendency for a higher mortality in patients randomized to shunt surgery, TIPS is not recommended in this setting (89). The efficacy of BRTO in preventing first hemorrhage in patients with cardiofundal varices has not been studied, and therefore this therapy cannot be recommended.

No studies have assessed primary prevention of bleeding from GOV1 varices. These are commonly managed following guidelines for esophageal varices (see above).

Guidance statements

- **For prevention of first variceal hemorrhage from GOV2 or IGV1, NSBB can be used, although the data is not as strong as for esophageal varices.**

- **Prevention of first bleeding from GOV1 varices may follow the recommendations for esophageal varices.**
- **Neither TIPS nor BRTO are recommended to prevent first hemorrhage in patients with fundal varices that have not bled.**

b) Management of acute hemorrhage from gastric varices

The initial treatment of gastric variceal bleeding is similar to that of esophageal variceal bleeding (volume resuscitation, vasoactive drugs, and antibiotics prior to diagnostic endoscopy).

In case of massive bleeding, balloon tamponade with the Linton-Nachlas tube may serve as a bridge to other treatments. If using the Sengstaken-Blakemore or Minnesota tubes, inflation of only the gastric balloon and anchoring it against the gastroesophageal junction could be sufficient to produce adequate tamponade.

b.1. Endoscopic therapy

Meta-analysis of 3 RCTs comparing cyanoacrylate injection versus EVL shows that both therapies are equally effective for initial hemostasis, but cyanoacrylate injection is associated with significantly lower rebleeding rates (120). The overall quality of the evidence is low given small sample sizes, and the meta-analysis was dominated by the larger study including only GOV1 varices (121). In addition, EVL should only be performed on small gastric varices in which both the mucosal and contralateral wall of the vessel can be suctioned into the ligator; otherwise, the band will fall off in several days, leaving an ulcer overlying the vessel, which can result in catastrophic rebleeding. Other endoscopic tools are rapidly emerging that may provide far greater safety and efficacy, such as the EUS-guided insertion of coils and cyanoacrylate (122).

The cyanoacrylate used in randomized trials has been N-butyl-2-cyanoacrylate; 2-octyl cyanoacrylate is an alternative with longer polymerization time (123) and has been used with success in acute gastric variceal bleeding (124). None of them is specifically approved for

treating gastric variceal bleeding in the United States. The technique has been recently reviewed by the American Society for Gastrointestinal Endoscopy in a technical report (125).

b.2.Transjugular intrahepatic portosystemic shunt (TIPS)

TIPS is very effective in the treatment of bleeding gastric varices, with more than a 90% success rate for initial hemostasis (126). It frequently requires additional embolization of spontaneous collaterals feeding the varices. TIPS has not been compared to endoscopic cyanoacrylate injection or to variceal ligation for the initial control of bleeding. In centers with expertise in cyanoacrylate injection, it would be reasonable to reserve TIPS for failures of medical (intravenous vasoconstrictors) plus endoscopic (glue) therapy. However, in the case of fundal varices, which have a higher early rebleeding rate, TIPS should be considered earlier than for other types of varices.

Guidance statements

- **Patients with acute bleeding from gastric varices should be initially managed in a similar fashion to those bleeding from esophageal varices (using a restrictive transfusion policy, vasoactive drug infusion, and antibiotic prophylaxis).**
- **In patients bleeding from GOV1 varices, either EVL (if technically feasible) or cyanoacrylate glue injection, if available, are the recommended endoscopic treatments.**
- **TIPS is the treatment of choice in the control of bleeding from cardiofundal varices (GOV2 or IGV1).**
- **Cyanoacrylate glue injection is an option for cases in which TIPS is not technically feasible, but it is not approved for the treatment of gastric varices in the United States and should be performed only in centers where the expertise is available.**

c) Prevention of rebleeding

c.1. Endoscopic therapy and NSBBs

In one RCT, repeated cyanoacrylate injection was superior to NSBB in the prevention of rebleeding and mortality in patients with cardiofundal varices (127). In another trial, also in

patients with cardiofundal varices, addition of NSBBs to cyanoacrylate injection did not improve the rebleeding or mortality rates compared to cyanoacrylate alone (128).

c.2. TIPS

A single randomized trial including patients with GOV1 and GOV2 varices showed that TIPS is more effective than glue injection in preventing rebleeding (129), but with higher rate of encephalopathy and without differences in survival.

c.3. BRTO

Balloon-occluded retrograde transvenous obliteration (BRTO) is a procedure for the treatment of fundal varices associated with a large gastro/splenorenal collateral (130). The technique involves retrograde cannulation of the left renal vein via the jugular or femoral vein, followed by balloon occlusion and slow infusion of sclerosant to obliterate the gastro/splenorenal collateral and fundal varices (44, 131). Several variations of the technique exist, such as balloon-occluded antegrade transvenous obliteration (BATO) (132) or occlusion of the collateral by the placement of a vascular plug (PARTO) (133) or coils (CARTO) (134). BRTO has the theoretical advantage over TIPS that it does not divert portal blood inflow from the liver. On the other hand, BRTO and its variations might increase portal pressure and might worsen complications such as ascites or bleeding from esophageal varices. For this reason, some centers will measure portal pressures and place a TIPS in cases in which the HVPG exceeds 12 mmHg post-BRTO. No randomized trials have compared BRTO with other therapies.

Guidance statements

- **In patients who have recovered from a GOV1 hemorrhage, the combination of NSBBs and endoscopic variceal therapy (EVL or cyanoacrylate injection) is the first-line therapy to prevent rebleeding.**
- **In patients who have recovered from GOV2 or IGV1 hemorrhage, TIPS or BRTO are first-line treatments in the prevention of rebleeding.**
- **Cyanoacrylate glue injection is an option for cases in which TIPS or BRTO are not technically feasible, but it is not approved for the treatment of gastric varices in the**

United States and should be performed only in centers where the expertise is available.

H. Ectopic varices

Bleeding from ectopic varices is very rare in cirrhosis, but it is a significant source of bleeding in patients with pre-hepatic portal hypertension (135, 136). Localization and anatomy are heterogeneous, which makes standardization of treatment difficult, and therefore cases should be evaluated/treated on a case-by-case basis and based on vascular anatomy. Diagnosis can be made with a thin-slice contrast-enhanced CT in the portal venous phase, using large-volume diluted water-soluble oral contrast. The most frequent locations are surgical stomas, duodenum, jejuno-ileum, and colon. Management requires a good definition of the vascular supply and local hemodynamics of the varices and a multidisciplinary approach involving endoscopists, hepatologists, interventional radiologists and surgeons. Treatment options include endoscopic therapy, mostly with cyanoacrylate injection or endosonographic coil placement, TIPS with or without collateral embolization, and BRTO. In the case of stomal varices, direct injection of sclerosant agents or cyanoacrylate under radiographic guidance can be very successful.

Guidance statement

- **The management of ectopic varices requires a thorough knowledge of the vascular supply to the varices and a multidisciplinary approach. Options are ligation, cyanoacrylate injection, endosonographic coil placement, TIPS with or without embolization, and BRTO.**

I. Special populations

a) Patients with refractory ascites or after spontaneous bacterial peritonitis

Recent observational studies raised concerns regarding the use of NSBBs in patients with advanced cirrhosis, either with refractory ascites or after an episode of spontaneous bacterial peritonitis. In the first study, the effect of NSBBs on mortality was prospectively assessed in 151 consecutive patients admitted for refractory ascites (137). After adjustment for severity of liver

disease, NSBB use was associated with increased mortality. Notably, patients on NSBB had a significantly lower systolic pressure compared to those not on NSBB. A follow-up small crossover study showed that, while on NSBB, a larger percentage of patients developed post-paracentesis circulatory dysfunction than while off NSBB (138). A second retrospective study showed that NSBBs improved survival in patients with ascites, but in a sub-analysis limited to those surviving an episode of spontaneous bacterial peritonitis episode, NSBB worsened survival and had a higher risk for hepatorenal syndrome (139). Again, patients on NSBBs had lower blood pressure.

These concepts have been challenged in 3 subsequent studies assessing large cohorts of patients with ascites (140-142), studies that have shown either no differences (141) or even improved survival (140, 142) in patients treated with NSBBs, including patients with refractory ascites. An additional study showed that ongoing treatment with NSBBs was associated with improved survival in patients with acute-on-chronic liver failure (143). In these studies, mean arterial pressure was not significantly different between patients on NSBB and those not on them.

Two recent observational studies found an association of the dose of NSBBs and outcomes. The first showed that in patients with decompensated cirrhosis, doses of propranolol above 160 mg/day were associated with worse survival, whereas doses up to 160 mg/day were associated with an improved survival (142). In the second study, focused on patients with spontaneous bacterial peritonitis , doses <160 mg/day of propranolol were associated with improved survival after adjustment for confounders, while doses of 160 mg/day or above were not (144).

In summary, current evidence from observational studies does not support a harmful effect of NSBBs in most patients with decompensated cirrhosis. In these patients, the dose of NSBBs should be carefully titrated. In patients with refractory ascites or spontaneous bacterial peritonitis, high doses of NSBBs should be avoided. NSBB dose should be reduced or discontinued in patients with refractory ascites with signs of severe circulatory dysfunction, such as severe hypotension (systolic blood pressure <90 mmHg), hyponatremia (serum sodium

< 130 meq/L), or unexplained deterioration in renal function) (4). NSBBs might be reintroduced after correction of renal function/circulatory state. This is particularly important when NSBB are used to prevent recurrent variceal hemorrhage.

Guidance statements

- **Refractory ascites and spontaneous bacterial peritonitis are *not* absolute contraindications for treatment with NSBBs. In these patients, high doses of NSBBs (over 160 mg/day of propranolol or over 80 mg/day of nadolol) should be avoided, as they might be associated with worse outcomes.**
- **In patients with refractory ascites and severe circulatory dysfunction (systolic blood pressure <90 mmHg, serum sodium <130 meq/L, or hepatorenal syndrome), the dose of NSBBs should be decreased or the drug temporarily held. NSBBs might be reintroduced if circulatory dysfunction improves.**

b) Prevention of rebleeding in patients experiencing the first variceal bleeding while on primary prophylaxis with NSBB or EVL

The widespread use of primary prophylaxis with NSBB or EVL has led to an increasing number of patients with cirrhosis who experience their first episode of variceal hemorrhage while on primary prophylactic therapy (NSBB or EVL). These patients, however, have been excluded in most trials evaluating current standard of care in the prevention of rebleeding. Therefore, the best approach to treat these patients is unknown. A recent cohort study assessing 89 patients on standard secondary prophylaxis showed that rebleeding and mortality were significantly higher in patients who had bled while on prophylactic NSBB compared to those that experienced variceal hemorrhage not having been on NSBB (145). These findings suggest that patients who bleed while on primary prophylaxis may need more aggressive therapy, such as TIPS. In the absence of RCTs, the optimal therapeutic strategy in this setting remains conjectural.

Guidance statement

- **Patients failing primary prophylaxis for variceal bleeding may be treated with the combination of NSBBs and EVL or, alternatively, with TIPS. Randomized trials are required in this group of patients to clarify the best therapeutic strategy.**

c) Prevention and treatment of variceal bleeding in patients with hepatocellular carcinoma

Most randomized trials for the prevention and treatment of variceal bleeding have excluded patients with hepatocellular carcinoma (HCC), and the few including HCC patients excluded those with advanced disease. Therefore, the optimal treatment for these patients remains unknown. Although observational data suggest that the risk of bleeding and prognosis of the bleeding episode might be worse in these patients (146-148), there is no data to suggest a decreased efficacy of treatments to prevent bleeding (NSBBs, EVL, or TIPS if technically feasible) as compared with no intervention. In a recent observational study, lack of secondary prophylaxis was frequent in patients with HCC recovering from acute variceal hemorrhage, and this was independently associated with mortality, after adjusting for HCC stage and liver dysfunction (148). This suggests that these patients should receive the same secondary prophylaxis as patients without HCC, including those who have portal vein thrombosis (tumoral or bland). In patients with advanced HCC, therapeutic decisions related to variceal bleeding should be framed within the context of the end-of-life care plan of the patient.

Guidance statement

- **Prevention and treatment of acute variceal bleeding in patients with hepatocellular carcinoma should follow the same principles as those for patients without hepatocellular carcinoma.**

J. Suggestions for Future Research

The following are important areas in the diagnosis and treatment of varices and variceal hemorrhage for which additional research/data are needed:

1. The role of noninvasive tests (eg, liver stiffness, spleen stiffness) in the diagnosis of CSPH in patients with etiologies other than viral/alcoholic cirrhosis

2. The role of noninvasive tests in evaluating hemodynamic response to different therapies and their relationship to clinical outcomes
3. Prospective studies evaluating the effect of therapies that act on pathophysiological mechanisms of portal hypertension in the prevention of clinical outcomes other than varices/variceal hemorrhage.
4. Effects of antifibrotic drugs preventing disease progression in patients with compensated cirrhosis.
5. Role of gut microbiota modulating the hemodynamic abnormalities of cirrhosis and portal hypertension and the response to medical therapy.
6. Clarify the role of preemptive ("early") TIPS in the management of acute variceal bleeding, refining the target population that will benefit from this treatment.
7. Data on clinical outcomes for statins and other potential targets not yet used clinically in this setting (eg, farnesoid X receptor agonists, enoxaparin).
8. Optimal prevention and treatment of bleeding from cardiofundal varices.

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Figure legends

Figure 1. Stages and sub-stages of cirrhosis. The 2 main stages are the compensated and decompensated stages. The latter is characterized by the presence of clinically overt complications: ascites, variceal hemorrhage, or hepatic encephalopathy (HE). The compensated stage is the longest stage, and it is asymptomatic. There are at least 2 main sub-stages of compensated cirrhosis with different prognostic and predominant pathophysiological mechanisms: patients with mild portal hypertension (PH) and those with clinically significant portal hypertension (CSPH). Patients in the latter stage are at risk of developing decompensation, particularly those who have gastroesophageal varices. The decompensated stage is much shorter and can rapidly progress to a stage of further decompensation in which renal failure, ie, hepatorenal syndrome (HRS) and liver failure (jaundice), develops, leading to a high mortality.

Figure 2. Pathogenesis of portal hypertension and sites of action of *currently* recommended therapies to reduce portal pressure or obliterate varices. In cirrhosis, portal pressure increases initially as a consequence of an increased intrahepatic resistance to portal flow due to structural mechanisms (eg, fibrous tissue, regenerative nodules) and an increased intrahepatic vascular tone (functional component). One of the initial consequences of portal hypertension is the formation of porto-systemic collaterals. Concomitant or even prior to the development of collaterals, splanchnic vasodilatation occurs, leading to increased flow into the gut and into the portal venous system. Vasodilation leads to activation of neurohumoral and vasoconstrictive systems, sodium and water retention, increased blood volume, and increased cardiac output; ie, a hyperdynamic circulatory state that further increases portal venous inflow and portal pressure. Additionally, activated vasoconstrictive systems further contribute to intrahepatic vasoconstriction. Etiological treatments, by ameliorating fibrosis/inflammation, target the mechanical component of the increased intrahepatic resistance. Vasodilators (like the α-adrenergic blocking effect of carvedilol) target its functional component (this is the site of action of statins). Non-selective beta-blockers (NSBB–β2-adrenergic blocking effect), somatostatin (SMT), and vasopressin (VP) act by causing splanchnic vasoconstriction, thereby

reducing portal venous inflow. NSBBs also act by decreasing cardiac output (β1-adrenergic blocking effect). The transjugular intrahepatic portosystemic shunt (TIPS) connects the hypertensive portal vein with a normotensive hepatic vein, thereby bypassing the site of increased resistance. Varices can be obliterated either endoscopically (endoscopic variceal ligation or cyanoacrylate injection) or via an endovascular approach (BRTO, or balloon occluded retrograde transvenous obliteration).

Table 1. Stages of portal hypertension in cirrhosis, clinical manifestations, and goals of therapy.

Disease Stage	**Compensated**			**Decompensated***		
HVPG	**<10 mmHg**	**≥10 mmHg (CSPH)**		**≥ 12 mmHg**		
Varices	Absent	Absent	Present	Present		
Complications of portal hypertension	Absent	Absent	Absent	Acute variceal hemorrhage	Previous variceal hemorrhage without other complications**	Previous variceal hemorrhage with other complications
Goals of therapy	Prevent CSPH	Prevent decompensation	Prevent decompensation (first bleeding episode)	Control bleeding, prevent early rebleeding and death	Prevent further decompensation (further bleeding) and other complications**	Prevent further decompensation and death/OLT

*Patients with decompensated cirrhosis (ascites, encephalopathy) without variceal hemorrhage (past or present) are not considered in this table/review; ** other complications = ascites, encephalopathy; HVPG=hepatic venous pressure gradient; CSPH=clinically significant portal hypertension.

Table 2. Hepatic vein pressure measurements in the different types of portal hypertension.

Type of Portal Hypertension*		Hepatic vein pressure measurement		
		Wedged (WHVP)	Free (FHVP)	Gradient** (HVPG)
Pre-hepatic (portal vein thrombosis)		normal	normal	normal
Pre-sinusoidal (cirrhosis due to cholestatic liver disease, schistosomiasis, idiopathic portal hypertension) ***		normal	normal	normal
Sinusoidal (cirrhosis due to alcohol / HCV / NASH)		↑	normal	↑
Post-sinusoidal	Sinusoidal obstruction syndrome	↑	normal	↑
	Budd-Chiari syndrome	Unable to catheterize hepatic vein		
Post hepatic	Right heart failure	↑	↑	normal

*Portal hypertension is classified by the site of increased resistance to blood flow; **Gradient or HVPG is calculated by subtracting the FHVP from the WHVP; ***In advanced stages of pre-sinusoidal causes of portal hypertension, the WHVP and HVPG will increase

WHVP=wedged hepatic venous pressure; FHVP=free hepatic venous pressure; HVPG= hepatic venous pressure gradient; HCV=hepatitis C; NASH=non-alcoholic steatohepatitis

Table 3. Management of patients with moderate/large varices that have not bled. Any of these 4 therapies can be used, but current data do not support the use of combination therapy.

Therapy	Recommended dose	Therapy goals	Maintenance/Follow-up

Propranolol	• 20-40 mg orally twice a day
	• Adjust every 2-3 days until treatment goal is achieved
	• Maximal daily dose:
	  ○ 320 mg/day in patients without ascites
	  ○ 160 mg/day in patients with ascites.
		• Resting heart rate of 55-60 beats per minute
		• Systolic blood pressure should not decrease <90 mmHg
			• At every outpatient visit make sure that heart rate is on target
			• Continue indefinitely
			• No need for follow-up EGD

Nadolol	• 20-40 mg orally once a day
	• Adjust every 2-3 days until treatment goal is achieved
	• Maximal daily dose:
	  ○ 160 mg/day in patients without ascites
	  ○ 80 mg/day in patients with ascites
		• Resting heart rate of 55-60 beats per minute
		• Systolic blood pressure should not decrease <90 mmHg
			• At every outpatient visit make sure that heart rate is on target
			• Continue indefinitely
			• No need for follow-up EGD

Carvedilol	• Start with 6.25 mg once a day • After 3 days increase to 6.5 mg twice daily • Maximal dose: 12.5 mg/day (except in patients with	• Systolic arterial blood pressure should not decrease <90 mmHg	• Continue indefinitely • No need for follow-up EGD

	persistent arterial hypertension)		
EVL	• Every 2-8 weeks until the eradication of varices	Variceal eradication (no further ligation possible)	First EGD performed 3-6 months after eradication and every 6-12 months thereafter

EVL=endoscopic variceal ligation; EGD=esophagogastroduodenoscopy

Table 4. Vasoactive agents used in the management of acute variceal hemorrhage.

Drug	Recommended Dose	Duration
Octreotide (somatostatin analogue)	Initial IV bolus of 50 micrograms (can be repeated in first hour if ongoing bleeding) Continuous IV infusion of 50 micrograms/hour	2-5 days
Vasopressin	Continuous IV infusion: 0.2-0.4 units/minute. Can be increased to 0.8 units/minute. It should always be accompanied by IV nitroglycerin at a starting dose of 40 mcg/minute, which can be increased to a maximum of 400 mcg/minute, adjusted to maintain a systolic blood pressure 90 mmHg.	24 hours
Somatostatin	Initial IV bolus 250 micrograms (can be repeated in the first hour if ongoing bleeding) Continuous IV infusion of 250 to 500 micrograms/hour	2-5 days
Terlipressin (vasopressin analogue)	Initial 48 hours: 2 mg IV every 4 hours until control of bleeding Maintenance: 1 mg IV every 4 hours to prevent rebleeding	2-5 days

IV= intravenous

Table 5. Treatments for the prevention of recurrent esophageal variceal bleeding. The combination of either propranolol or nadolol *plus* EVL is recommended. Carvedilol is not recommended in this setting.

Therapy	Recommended Dose	Therapy goals	Maintenance/Follow-up

Propranolol	• 20-40 mg orally twice a day
	• Adjust every 2-3 days until treatment goal is achieved
	• Maximal daily dose:
	  ○ 320 mg/day in patients without ascites
	  ○ 160 mg/day in patients with ascites
		• Resting heart rate of 55-60 beats per minute
		• Systolic blood pressure should not decrease <90 mmHg
			• At every outpatient visit make sure that heart rate is on target
			• Continue indefinitely.

Nadolol	• 20-40 mg orally once a day
	• Adjust every 2-3 days until treatment goal is achieved
	• Maximal daily dose:
	  ○ 160 mg/day in patients without ascites
	  ○ 80 mg/day in patients with ascites
		• Resting heart rate of 55-60 beats per minute
		• Systolic blood pressure should not decrease < 90 mmHg
			• At every outpatient visit make sure that heart rate is on target
			• Continue indefinitely.
			•

EVL	• Every 1-4 weeks until the eradication of varices	Variceal eradication (no further ligation possible)	First EGD performed 3-6 months after eradication and every 6-12 months thereafter

EGD=esophagogastroduodenoscopy