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Variceal Bleeding
Pharmacological Treatment and Prophylactic Strategies

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Contents

Abstract

Oesophageal varices and ascites may develop when the hepatic venous pressure gradient (HVPG) increases above 10 mmHg, and variceal bleeding may occur when the HVPG rises above 12 mmHg. Pharmacological therapy of portal hypertension may prevent bleeding by reducing the HVPG below 12 mmHg. Even if this threshold level is not reached, the risk of bleeding decreases markedly with reductions in HVPG that are >20% from baseline.

Endoscopic therapy is a local treatment that prevents bleeding by obliterating the varices, and has no effect on the pathophysiological mechanisms that lead to

portal hypertension and variceal rupture. When used together, both pharmacological and endoscopic therapies may have an additive effect, which has been demonstrated in different clinical settings. In acute oesophageal variceal bleeding, vasoactive drugs (either terlipressin or somatostatin) should be started as soon as possible (before diagnostic endoscopy) and maintained for 2–5 days. The efficacy of pharmacotherapy is improved with the addition of emergency endoscopic therapy. Adding endoscopic variceal ligation (EVL) improves the efficacy and safety achieved with the combination of emergency sclerotherapy and vasoactive drugs. Antibacterial prophylaxis should be an integral part of therapy in acute bleeding.

To prevent rebleeding, both EVL and the combination of β-adrenoceptor antagonists (β-blockers) and isosorbide mononitrate (ISMN) may be a valid first-line choice. Adding β-blockers improves the efficacy of EVL alone. Haemodynamic responders to β-blockers with or without ISMN (i.e. those with a decrease in HVPG to <12 mmHg or by >20% of baseline) have a reduction in the risk of haemorrhage to below 10% of patients and, consequently, will not need further treatment, while rescue therapies should be provided to nonresponders. Transjugular intrahepatic portosystemic shunts are the recommended rescue therapy when EVL and/or β-blockers with or without ISMN fail. β-Blockers significantly reduce the risk of a first haemorrhage in patients with large varices and improve survival. Compared with β-blockers, EVL reduces the risk of first bleeding without any differences in mortality and should be offered to patients with large varices who have contraindications or an intolerance to β-blockers.

Variceal bleeding is a medical emergency associated with a mortality rate that is still in the order of 20% at 6 weeks despite recent progress.[1-3] Available therapy allows the control of bleeding in nearly 85% of episodes, with an incidence of early rebleeding of about 20% within the first 6 weeks.[3] Late rebleeding occurs in around 60% of untreated patients within 1–2 years and death in 33%. Therefore, all patients surviving an acute variceal bleeding episode should be treated to prevent rebleeding. In recent years, many randomized controlled trials have advanced knowledge in the management of varices and variceal haemorrhage, and outcome has improved. This article discusses the currently available clinical evidence for the prevention and treatment of variceal bleeding. Full reports published in English-language journals and relevant abstracts from the American Association for the Study of Liver Diseases and the European Association for the Study of the Liver meetings were included in this review.

Portal hypertension is associated with the most severe complications of cirrhosis, including bleeding from gastro-oesophageal varices, ascites and hepatic encephalopathy. Oesophageal varices are present in approximately 50% of patients with cirrhosis.[4] Their presence correlates with the severity of liver disease.[5] The rate of formation of varices is about 5% per year and, consequently, on long-term follow-up they will develop in most patients.[6] The strongest predictor for development of varices in cirrhosis is an hepatic venous pressure gradient (HVPG) >10 mmHg.[6] Once varices have developed, the overall incidence of variceal bleeding is around 25% at 2 years.[7] Large variceal size is the most important predictor of haemorrhage.[8] The endoscopic presence of red wale marks on the variceal wall and the severity of liver dysfunction also increase the risk of bleeding.[8] Variceal bleeding is a major cause of death in patients with cirrhosis;[1-3] therefore, preventing this complication is essential.

1. Pathophysiology of Portal Hypertension and Variceal Bleeding

An increase in both intrahepatic vascular resistance and portal venous inflow contribute to portal hypertension in cirrhosis.[9] The increase in vascular resistance to portal blood flow is the initial factor and is mainly caused by the architectural disorder of the cirrhotic liver, as a result of fibrous tissue and regenerative nodules. However, there is also a dynamic component due to the active contraction of myofibroblasts, activated stellate cells and portal venules.[10,11] This active intrahepatic vasoconstriction is modulated by a deficit of nitric oxide and by the increased activity of endogenous vasoconstrictors such as endothelin, α-adrenergic stimulus, angiotensin and others.[10] The elevated portal pressure results in the formation of portosystemic collaterals and a concomitant splanchnic (and systemic) arteriolar vasodilatation, which is caused by an excessive release of endogenous vasodilators and leads to an increase in portal venous inflow that contributes to aggravate the increase in portal pressure.[12] Peripheral vasodilatation induces a decrease in effective blood volume and activation of endogenous antinatriuretic and vasoconstrictive systems (including the renin-angiotensin-aldosterone system, sympathetic nervous systems and antidiuretic hormone) that lead to sodium and water retention, and expansion of the plasma volume.[13] This results in the hyperdynamic circulatory syndrome associated with portal hypertension with systemic vasodilatation, increased cardiac index and hypervolaemia. These mechanisms provide the basis to treat portal hypertension using vasodilators, vasoconstrictors, low sodium diet and diuretics (figure 1).

Variceal wall tension is probably the key factor that determines variceal rupture and subsequent bleeding.[9] Variceal wall tension is the force generated by the vessel wall opposing intravascular distension, which is directly related to portal pressure.[9] Variceal wall tension also depends of vessel diameter (increasing when the size of the varix is larger) and is inversely proportional to the thickness of the vascular wall.[9] Because of its location in the lamina propria, oesophageal varices have a thin wall and lack of tissue support, which may facilitate a progressive dilation and eventually variceal rupture. Presence of red colour signs on the varices at endoscopy probably reflect a thin vascular wall.[5]

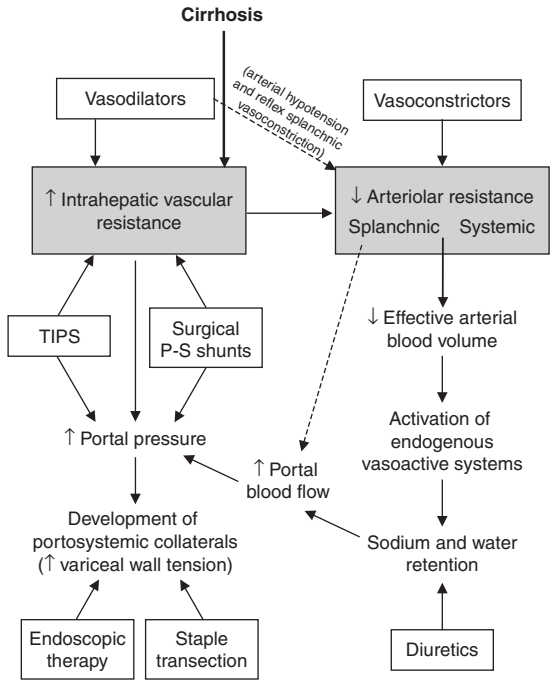

Fig. 1. Pathophysiology of variceal bleeding and therapeutic options. **TIPS** = transjugular intrahepatic portosystemic shunt; ↑ indicates increased; ↓ indicates decreased; dashed arrows indicate additional minor (of secondary relevance) effects.

2. Evaluation of Portal Hypertension

Portal pressure is commonly assessed by measuring the wedged venous pressure, which reflects portal pressure accurately both in alcoholic and viral cirrhosis.[12] The wedged pressure is obtained by placing a catheter in an hepatic vein and inflating a balloon to occlude a large branch. This pressure is corrected for increases in intra-abdominal pressure by subtracting the free hepatic vein pressure. The resultant is the HVPG. Although varices and ascites may develop when HVPG increases above 10 mmHg,[3,14] variceal bleeding does not appear until the HVPG increases above 12 mmHg.[15,16] The complications of portal hypertension may be corrected by reducing the HVPG below these

Table I. Drugs currently used in the treatment of portal hypertension

Drug	Haemodynamic effects	Efficacy in the treatment/prevention of bleeding[a]	Potential for adverse effects[b]
Vasodilators			
Nitric oxide donors (nitrates)	Reduce portal pressure Reduce variceal pressure	Combined with vasopressin (to treat acute bleeding) or with β-blockers (to prevent rebleeding)	Moderate
α_1-Adrenergic antagonist (prazosin)	Reduces portal pressure Increases hepatic blood flow	Not investigated	High
Renin-angiotensin system antagonists	No clear effect on HVPG Antifibrogenic	Not investigated	High
Calcium channel antagonists	No effect Increase collateral flow	Not investigated	High
Endothelin receptor antagonists	No clear effect	Not investigated	Moderate
Selective hepatic delivery of nitric oxide	Under investigation	Not investigated	Unknown
Vasoconstrictors			
Vasopressin	Reduces portal pressure	Effective to treat acute bleeding	High
Terlipressin	Reduces portal pressure Reduces variceal pressure	Effective to treat acute bleeding	Low
Somatostatin	Reduce portal pressure Avoid fluctuations in portal pressure	Effective to treat acute bleeding	Low
Somatostatin analogues (e.g. octreotide, vapreotide)	Avoid fluctuations in portal pressure	Effective to treat acute bleeding	Low
Nonselective β-blockers (e.g. propranolol, nadolol, timolol)	Reduce portal pressure Reduce variceal pressure	Effective to prevent first bleeding and rebleeding	Low
Diuretics			
Spironolactone	Reduces portal pressure	Not effective	Moderate
Combined therapies			
Vasopressin + nitrates	Reduce portal pressure	Effective to treat acute bleeding	Low
β-Blockers + ISMN	Reduce portal pressure	Effective to prevent rebleeding	Low
β-Blockers + prazosin	Reduce portal pressure	Not investigated	Moderate
Carvedilol[c]	Reduce portal pressure	Not investigated	Moderate
β-Blockers + spironolactone	Reduce portal pressure	Not effective	Moderate

a Efficacy in treating acute variceal bleeding or preventing first bleeding or rebleeding demonstrated by randomized controlled trials.

b Indicates the risk of adverse events. Such risk has been considered high when adverse effects that endangered the health or safety of the patients have been reported; moderate when the possibility of inducing such adverse effects is rare; and low when only minor adverse effects have been reported.

c Carvedilo is considered under combined therapies as it displays both nonselective β-blocking and α_1-adrenoreceptor blocking activities.

β-Blockers = β-adrenoceptor antagonists; **HVPG =** hepatic venous pressure gradient; **ISMN** = isosorbide mononitrate.

thresholds or preventing the increase.[12] In fact, clinical studies have shown that variceal bleeding does not occur when the HVPG is reduced below 12 mmHg.[15] Even if this threshold level is not reached, the risk of bleeding decreases markedly (to less than 10–15% of patients) with reductions in HVPG that are >20% from baseline.[16]

3. Effects of Pharmacological Therapy

The aim of the pharmacological treatment of portal hypertension is the reduction of portal pressure, which may be achieved by using drugs that reduce intrahepatic resistance (vasodilators), drugs that reduce portal venous inflow (vasoconstrictors) or both (table I).[17]

3.1 Vasoconstrictors

Various splanchnic vasoconstrictors, such as vasopressin and its derivatives, somatostatin and its analogues, and nonselective β-adrenoceptor antagonists (β-blockers), have shown efficacy in reducing portal pressure.[18] Some of these drugs, such as vasopressin or somatostatin, require intravenous administration and their use is restricted to the treatment of acute bleeding. Nonselective β-blockers are the mainstay for the long-term treatment of portal hypertension.[12,18]

3.1.1 Vasopressin

Vasopressin is a potent splanchnic vasoconstrictor, thereby leading to a reduction in portal inflow and pressure, as well as a reduction in collateral flow and variceal pressure.[19] However, its use is limited by the induction of adverse effects related to splanchnic and systemic vasoconstriction, such as bowel or myocardial ischaemia, arrhythmias or hypertension, requiring withdrawal of therapy in about 25% of patients.[4] The association of nitroglycerin with vasopressin enhances the reduction of portal pressure and decreases the incidence of adverse effects.[12]

3.1.2 Terlipressin

Terlipressin, or triglycyl-lysine vasopressin, is a synthetic vasopressin analogue that is slowly transformed into vasopressin by enzymatic cleavage of the glycyl residues.[12,18] This results in a continuous release of small amounts of vasopressin with prolonged biological effects (continuous infusion is unnecessary) and fewer complications. Haemodynamic studies have shown that terlipressin has a marked effect on decreasing portal pressure, portocollateral blood flow and variceal pressure.[20,21]

3.1.3 Somatostatin and its Analogues

Somatostatin and its analogues, such as octreotide, lanreotide or vapreotide, also induce splanchnic vasoconstriction at pharmacological doses and may decrease portal pressure without the adverse effects of vasopressin on systemic circulation.[22] The effects of somatostatin on splanchnic circulation have been attributed to a vasoconstrictor response mediated by the prevention of the release of vasoactive peptides.[18] However, a direct vasoconstrictive effect achieved by the potentiation of protein kinase C dependent vasoconstrictors has also been suggested.[23] Bolus injection of somatostatin produces a marked fall in HVPG that lasts only a few minutes, while the continuous infusion maintains a mild decrease.[24] This moderate effect is not uniform and the HVPG decreases more than 10% from baseline in only in approximately 50% of patients.[25] High doses of somatostatin (infusions of 500 μg/hour) may achieve a more consistent haemodynamic effect than the usual dose of 250 μg/hour, enhancing the decrease of HVPG.[24] In addition to the effect on portal pressure, recent studies have shown that somatostatin also has effects that may help to explain its clinical efficacy and that are probably linked to the prevention of the release of vasoactive peptides.[25] Somatostatin infusion has been shown to prevent secondary rises of portal pressure during the acute bleeding episode, which may favour further haemorrhage, such as those induced by the presence of blood in the gastrointestinal tract or by volume restitution.[25] As occurs with a meal, blood in the stomach induces splanchnic hyperaemia and a significant increase in portal pressure.[25] Blood volume restitution after an induced haemorrhage increases portal pressure beyond baseline value, probably as a consequence of raised portocollateral resistance. Somatostatin prevents these increments of portal pressure.[25] A recent study suggests that in patients in whom HVPG did not decrease by >10% from baseline with the usual somatostatin dose, both terlipressin and high-dose somatostatin infusion significantly decreased HVPG and increased the number of haemodynamic responders.[26] Such effects were greater with terlipressin.

3.1.4 Nonselective β-Adrenoceptor Antagonists

Nonselective β-blockers are the mainstay, long-term pharmacological treatment in the prevention of variceal bleeding (table II).[4] Nonselective β-blockers reduce portal pressure by decreasing cardiac output (blocking β_1 receptors) and by producing splanchnic vasoconstriction, thus decreasing portal

Table II. Choice of treatment for variceal bleeding in different clinical settings

Clinical setting	First-line therapy	Second-line therapy	Rescue therapy	Not recommended therapies
Prevention of first variceal bleeding	β-Blockers (EVL if contraindication/ intolerance)	EVL		ISMN β-Blockers + ISMN β-Blockers + spironolactone Sclerotherapy Portosystemic shunts
Treatment of acute bleeding	Vasoactive drugs (somatostatin or terlipressin) + endoscopic therapy (EVL) + antibacterials	Vasoactive drugs (octreotide, vapreotide) Endoscopic therapy (sclerotherapy)	Balloon tamponade TIPS Shunt surgery	Vasopressin
Prevention of variceal rebleeding	β-Blockers (± ISMN) + EVL	EVL alone (if contraindication/intolerance to β-blockers)	TIPS Shunt surgery	Sclerotherapy

β-Blockers = β-adrenoceptor antagonists; **EVL** = endoscopic variceal ligation; **ISMN** = isosorbide mononitrate; **TIPS** = tranjugular intrahepatic portosystemic shunt.

venous inflow (blocking β_2 receptors, which allows an unopposed α-adrenergic vasoconstriction).[18] The reduction in portal pressure induced by β-blockers is smaller than the decrease in portal venous inflow.[27] This is due to a concomitant increase in collateral resistance resulting from passive collapse (induced by the decreased flow) and active constriction.[27] The decrease in collateral blood flow and in variceal pressure also accounts for the protective effect of β-blockers in preventing variceal bleeding,[28,29] as may be the case with other nonhaemodynamic mechanisms. By increasing bowel motility and reducing bacterial overgrowth, β-blockers may reduce bacterial translocation (and infection) that may trigger bleeding.[30] A number of randomized controlled trials have compared nonselective β-blockers with untreated controls and with different therapeutic options, both in primary and secondary prevention of variceal bleeding (table III).

In practice, probably the best way to adjust the dose of β-blockers is by stepwise increases up to maximal tolerability but not allowing a heart rate below 55 beats/minute because reductions in heart rate and HVPG are not correlated.

3.2 Vasodilators

An imbalance between vasodilators and vasoconstrictor stimuli increases hepatic vascular resistance in cirrhosis.[12] The production of the vasodilator nitric oxide is decreased in the liver microcirculation and there is also an increased activity of endogenous vasoconstrictors such as adrenaline and angiotensin.[10] This provides the basis for administering drugs that increase the delivery of nitric oxide to the intrahepatic circulation, such as nitrates, drugs that block adrenergic activity, such as prazosin or clonidin, or drugs that block angiotensin, such as losartan or irbesartan.[12,18,31] Haemodynamic studies have shown that all of these drugs may decrease portal pressure.[31] However, available vasodilators act not only on the intrahepatic circulation but also on the systemic and portocollateral circulation, which may lead to arterial hypotension.[32] Such an arterial hypotension may induce a reflex splanchnic vasoconstriction that may contribute to a decrease in portal pressure by decreasing portal venous inflow.[32] However, arterial hypotension may also lead to a further decrease in effective arterial blood volume, which may finally result in sodium retention and accumulation of ascites and oedema, and may also lead to adverse effects on renal function.[32] Because of this potential for adverse effects, vasodilators alone should be used very cautiously in patients with advanced cirrhosis.[33]

3.3 Combined Drug Therapy with Vasoconstrictors and Vasodilators

Combined therapy of portal hypertension using intrahepatic vasodilators and splanchnic vasoconstrictors attempts to enhance the reduction in portal pressure that is achieved using vasoconstrictors alone.[34] Nonselective β-blockers induce an increase in portocollateral and intrahepatic resistance, which may hinder the reduction in portal pressure induced by the decrease of portal venous inflow.[35] The addition of vasodilators to β-blockers may counteract the increase in portohepatic resistance, thus enhancing the decrease of portal pressure.[36] Combined therapy decreases the HVPG and therefore maintains liver perfusion, in contrast with the significant reduction seen with β-blockers alone.[37] Furthermore, the association of nonselective β-blockers limits the untoward effects of vasodilators on arterial pressure and renal function because β-blockade increases peripheral vascular resistance and inhibits renin secretion.[37,38]

Combined therapy was introduced by adding nitrovasodilators to vasopressin in order to ameliorate its adverse effects.[34] It was noticed that, in addition to better safety profile, combined therapy also improved the reduction in portal pressure achieved using vasopressin alone.[34] Similarly, the combination of long-acting nitrates, mainly isosorbide mononitrate (ISMN), with nonselective β-blockers enhances the decrease in portal pressure achieved using β-blockers alone, without any adverse effects on renal function.[39-41] Furthermore, this combined therapy increases the rate of an adequate haemodynamic response from 30–40% using β-blockers alone to 40–50% with β-blockers plus ISMN.[36,42] β-Blockers have also been combined with other vasodilators, the most promising probably being the association with α_1-adrenergic antagonists (table I).[12] Carvedilol is a nonselective β-blocker with intrinsic anti-α_1-adrenergic activity[43] that achieves a greater reduction in portal pressure than β-blockers alone, increasing the rate of haemodynamic response to 55% of patients.[44-46] The reduction in portal pressure achieved with the combination of propranolol and prazosin (an α_1-adrenoceptor antagonist) is greater than that obtained with propranolol plus ISMN, increasing the rate of haemodynamic response to >80% in one study.[37] However, it

Table III. Efficacy of β-adrenoceptor antagonists (β-blockers) in randomized controlled trials on the prevention of variceal bleeding

Treatment	No. of studies	No. of pts receiving β-blockers/control	Median no. of pts with bleeding [%] (range)		Median mortality rate [%] (range)	
			β-blockers	control	β-blockers	control
Primary prevention						
β-Blockers vs nonactive treatment	11	590/600	12 (0–30)	22 (4–38)[a]	22 (7–43)	28 (6–44)[b]
β-Blockers vs EVL	12	429/410	16 (6–46)	11 (0–25)[a]	18 (3–43)	11 (0–45)[b]
β-Blockers vs β-blockers + ISMN	3	275/277	18 (10–37)	13 (10–17)[b]	18 (5–19)	10 (5–11)[b]
β-Blockers vs β-blockers + spironolactone	1	35/32	9	3	9	3
Secondary prevention						
β-Blockers vs nonactive treatment	13	410/399	38 (16–76)	63 (46–84)[a]	12 (0–45)	23 (4–44)[a]
β-Blockers vs sclerotherapy	10	398/413	54 (34–73)	48 (33–64)[c]	35 (23–42)	33 (22–53)[b]
β-Blockers vs β-blockers + sclerotherapy	3	135/138	55 (53–87)	38 (27–68)[a]	58 (35–81)	40 (26–55)[b]
β-Blockers vs β-blockers + ISMN	2	100/99	48 (39–57)	45 (40–51)[b]	18 (14–22)	28 (24–32)[b]
β-Blockers + ISMN vs EVL	6	357/356	35 (8–57)	42 (12–53)[b]	14 (12–17)	16 (11–32)[b]
β-Blockers + EVL vs EVL	2	97/105	18 (14–23)	42 (38–47)[a]	14 (12–17)	16 (11–32)[b]
β-Blockers + sclerotherapy vs sclerotherapy	10	307/243	23 (7–63)	39 (21–75)[c]	9 (3–35)	14 (0–26)[b]

a Significant difference according to meta-analysis of the studies.

b No significant difference according to meta-analysis of the studies.

c Significant difference but with heterogeneity.

EVL = endoscopic variceal ligation; **ISMN** = isosorbide mononitrate; **pts** = patients.

should be noted that the benefit of combined therapy in terms of portal pressure reduction is restricted to patients without haemodynamic responses to β-blockers alone.[37] A recent study suggests that the association of nadolol and prazosin may effectively rescue nonresponders to nadolol and ISMN, achieving a haemodynamic response rate >70% in these patients.[47] However, both carvedilol and the association of β-blockers plus prazosin may induce a decrease in arterial pressure, which may lead to fluid retention, and are also associated with other adverse effects, such as weakness or dizziness, that may prevent the long-term use.[33,44-46] An acceptable safety profile has been achieved by introducing prazosin when β-blockade had been reached, and by using a low dose very carefully titrated against blood pressure and tolerance.[47] Whether these or other combined therapies will significantly improve clinical outcomes should still be clarified in future studies.

4. Haemodynamic Monitoring of Pharmacological Treatment

HVPG monitoring provides strong prognostic information for the management of portal hypertension by adequately identifying patients who are effectively protected against the risk of bleeding.[48] Several randomized controlled trials and prospective cohort studies have shown that haemodynamic responders (i.e. those with a decrease in HVPG to <12 mmHg or by >20% of baseline) have a marked reduction in the risk of haemorrhage to below 10–15% of patients.[15,16,48] Furthermore, responders have a lower risk of developing other complications of portal hypertension, such as ascites, and have better survival.[49,50] With a low risk of bleeding comparable with that achieved with portal-systemic shunts, haemodynamic responders will not need further therapy.[51] Compared with responders, nonresponders have a significantly worse outcome both in primary and secondary prevention of variceal bleeding.[48] Even in patients who are treated only with endoscopic procedures to prevent rebleeding, those with a spontaneous haemodynamic response have a significantly lower probability of rebleeding, less chance of developing ascites and a better survival than those without this spontaneous response.[52,53] This emphasises the relevance of achieving a haemodynamic response. HVPG monitoring may be particularly useful in the high-risk setting of preventing variceal rebleeding. However, it may not be cost effective in primary prophylaxis because of the low rate of haemorrhage achieved with medical therapy.[48]

Achieving haemodynamic response may be considered an adequate target of pharmacological treatment for portal hypertension.[48,51] However, some issues should be resolved before HVPG monitoring may be recommended in routine clinical practice. The diagnostic accuracy of the procedure needs to be improved.[54] A critical point with HVPG monitoring is the low positive predictive value, particularly in primary prevention.[30] The commonly used target of a 20% reduction in HVPG maximizes sensitivity but is not very specific.[54] A recent study suggests that using a 10% threshold instead of 20% may be more appropriate in primary prevention.[55] This study also showed that assessing the acute response to β-blockers in a single haemodynamic study may provide accurate prognostic information on long-term risk.[55] In secondary prevention of variceal bleeding, a scenario with a much higher risk of haemorrhage, a 20% reduction in HVPG seems the best cut-off value to define response.[48,51] Identifying other prognostic indicators of rebleeding in nonresponders may be particularly relevant in these patients in order to restrict further therapies (mainly the most invasive) to those patients with a real risk of bleeding.

Another critical point with HVPG monitoring is the potential utility in clinical practice to guide therapeutic decisions. How to use the prognostic information obtained in order to improve patient outcome is a relevant issue, which has not been clarified.[56] Responders to β-blockers alone have no further decrease in HVPG with the addition of vasodilators, and the beneficial effects are restricted to nonresponders,[37] one-third of whom became responders with the addition of ISMN.[57] At present, it is not clear which rescue therapy may be effective

in patients who do not respond to this combination.[56] It has been suggested that combined treatment of β-blockers and prazosin may achieve response in a great proportion of these patients.[47] The efficacy of endoscopic variceal ligation (EVL) in this setting has been contradictory in uncontrolled studies.[57,58] EVL was not useful in a study in which nonresponders were switched from β-blockers to EVL.[57] However, better results were obtained in a study in which EVL was combined with β-blockers.[58] Whether or not these treatments or other rescue therapies, such as the transjugular intrahepatic portosystemic shunt (TIPS) or other drug combinations, may be effective in clinical practice needs to be clarified.[59,60]

5. Pharmacological Therapy in Clinical Practice

The current role of drug therapy in the management of portal hypertension should be analysed in different clinical settings and with patients who have different levels of risk. Patients bleeding from varices require therapies to stop acute haemorrhage and to prevent rebleeding. Patients who have never bled require treatment to prevent the first bleeding or even to prevent the development of varices.

5.1 Treatment of Acute Variceal Bleeding

Management of acute variceal bleeding should be undertaken in an intensive care setting because of the high mortality and morbidity associated with this medical emergency. Initial measures should be aimed at correcting hypovolaemia, preventing complications that may worsen the prognosis, such as bacterial infections or acute renal failure, and achieving haemostasis. The specific haemostatic treatment should aim to both control acute haemorrhage and prevent early rebleeding, which is particularly common within the first few days and is associated with increased mortality.[61]

5.1.1 General Management

Resuscitation of haemodynamically unstable patients is a first mandatory measure. Thus, an adequate peripheral venous access should be obtained. A cautious and conservative blood volume restitution is currently recommended, using saline or plasma expanders to maintain haemodynamic stability and packed red blood cells to maintain the haemoglobin at approximately 8 g/dL, depending on other factors such as patient co-morbidities, age, haemodynamic status and presence of ongoing bleeding.[62] Hypovolaemia should be avoided to prevent complications such as renal dysfunction. However, overtransfusion should also be avoided because of the inherent risk with blood transfusion, and also to avoid the risk of inducing an increase in portal pressure and the subsequent possibility of precipitating further bleeding.[33]

Endoscopy should be performed as soon as possible after resuscitation (within 12 hours from admission), especially in patients with clinically significant bleeding or in patients with features suggesting cirrhosis.[62] Emergency endoscopy is the main method for diagnosing variceal haemorrhage, excluding other potential sources of bleeding (about 15% of patients with cirrhosis bleed from causes not related to portal hypertension).[33] Tracheal intubation may be required for airway protection before endoscopy, particularly in patients with encephalopathy.

Antibacterial prophylaxis is an integral part of therapy for patients with cirrhosis (with or without ascites) presenting with gastrointestinal bleeding and should be instituted from admission.[63] This measure decreases the rate of bacterial infections, decreases the incidence of early rebleeding and significantly improves survival.[63,64] Oral norfloxacin is the first choice.[65] Intravenous fluoroquinolones may be given when oral administration is not possible.[33] A recent study suggests that in patients with advanced liver dysfunction, intravenous ceftriaxone may be more effective.[66]

Patients who present or develop encephalopathy should be treated for this condition. There are no studies evaluating the usefulness of lactulose/lactitol for the prevention of hepatic encephalopathy.[62]

5.1.2 Haemostatic Treatment of Acute Variceal Bleeding

When variceal bleeding is suspected, vasoactive drugs should be started as soon as possible and before diagnostic endoscopy (figure 2).[33,62] This is supported by several randomized controlled trials showing that early administration of vasoactive drugs reduces the rate of active bleeding during endoscopy, thus facilitating endoscopic procedures, improving the control of bleeding and possibly decreasing bleeding-related mortality.[67,68] Drugs should be maintained for 2–5 days to avoid early rebleeding.[32] Both terlipressin and somatostatin are effective and safe to use, and, consequently, the two drugs may be a valid first-choice therapy (table II).[4] Terlipressin has been shown to improve survival, while controlled trials comparing terlipressin and somatostatin have shown no significant differences between these drugs.[69] To avoid adverse effects, somatostatin may be the choice in patients with ischaemic heart disease or peripheral arterial disease. Results from a meta-analysis of trials of octreotide are controversial for when it is used alone without endoscopic therapy.[70]

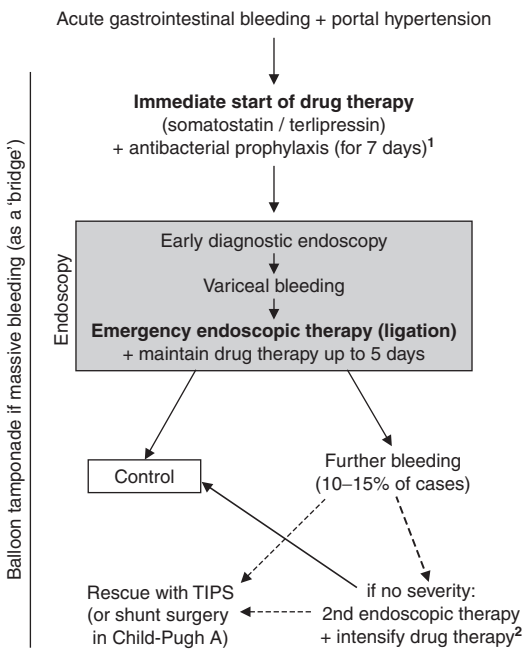

Fig. 2. Algorithm for the management of acute oesophageal variceal bleeding. **1**. Fluoroquinolone or ceftriaxone if advanced disease. **2**. Double somatostatin dose, change to terlipressin. **TIPS** = transjugular intrahepatic portosystemic shunt; dashed arrows indicate different options of management in cases of further bleeding.

A number of trials have compared the value of vasoactive drugs with emergency sclerotherapy (EST) for the treatment of the acute variceal bleeding episode. A meta-analysis of 15 trials, including more than 600 patients in each arm, has shown a similar efficacy with both treatments and fewer adverse effects associated with drugs.[71] The use of EST as first-line therapy for acute bleeding has therefore been questioned and it has been suggested that EST should be added only when the pharmacological intervention fails.[71] However, a randomized controlled trial has demonstrated that the efficacy of vasoactive drugs is significantly improved when EST is added, in patients both with and without active haemorrhage.[72] The main drawback with this approach is that EST also increases the incidence of adverse effects.[72]

Several randomized controlled trials have compared EST and EVL for actively bleeding varices without using vasoactive drugs.[73,74] No significant differences were found between these endoscopic treatments in the majority of these studies, the main aim of which was to investigate the value of these therapies in the long-term prevention of variceal rebleeding.[73,74] Two trials specifically compared EST and EVL in actively bleeding varices and conflicting results were found.[75,76] It has been claimed that emergency EVL may be difficult to perform because of factors such a reduced field of view as a consequence of the attachment of the banding device, which may fill with blood during active haemorrhage and hamper the appropriate placement of bands.[73] The use of multiple-shot ligation devices with transparent cylinders may overcome these difficulties. Furthermore, the technical performance of emergency endoscopic therapy may further ameliorate combining vasoactive drugs.[68] Administering drugs as soon as possible before emergency endoscopy, decreases the incidence of active variceal bleeding during endoscopy from up to 50% of patients when drugs are not used[69] to

only 20–25% of patients when they are used.[68] A recent randomized controlled trial has shown that adding emergency EVL to somatostatin (which was started before endoscopy and maintained for 5 days), significantly improved the efficacy and safety achieved compared with the addition of EST to somatostatin infusion.[77] This strongly supports the combination of vasoactive drugs and emergency EVL as first-line therapy for acute variceal bleeding.

The combination of both pharmacological and endoscopic therapy in the treatment of acute variceal bleeding is strongly supported by numerous trials showing that the efficacy of both EST and emergency EVL is significantly improved when they are combined with pharmacological treatment.[73,78] The meta-analysis of these studies showed that combined therapy improved the initial control of bleeding and 5-day haemostasis without differences in mortality or severe adverse events.[78]

5.1.3 Management of Therapeutic Failure

With the current recommended therapy of combining vasoactive drugs and emergency EVL, and adding antibacterial prophylaxis, 5-day therapeutic failure occurs in only 10–15% of patients (figure 2).[77,78] Therapeutic failure is best managed by TIPS, preferably with polytetrafluoroethylene covered stents.[79] Shunt surgery may be an option in Child-Pugh class A patients. Balloon tamponade should only be used in massive bleeding as a temporary 'bridge' until definitive treatment can be instituted.[62] When further bleeding is not severe, other rescue treatments may be considered. A second attempt at endoscopic therapy may be provided.[12] In some patients, more intensive pharmacological treatment may be considered.[26] A recent haemodynamic study suggests that either doubling the dose of somatostatin or switching to terlipressin can achieve a reduction in HVPG in previous non-responders to the standard somatostatin dose.[26] An increased clinical efficacy has been observed using higher doses of somatostatin in patients with active bleeding.[80] A recent study has also suggest that early TIPS placement may improve efficacy in high-risk patients (defined by an HVPG >20 mmHg).[81] Future trials should clarify the value of these approaches. The addition of recombinant factor VIIa to standard therapy did not improve the efficacy in a recent trial.[82] However, it should be clarified whether it may be of some value in patients who do not respond to standard therapy and who have severe coagulopathy and advanced liver disease (precluding other rescue therapies). A recent small study suggests that coated, self-expanding and removable oesophageal stents may be valuable in uncontrollable bleeding as first-line therapy (as an alternative to balloon tamponade).[32] The efficacy and safety profile of this procedure also needs to be clarified.

5.2 Treatment to Prevent Rebleeding

Given the high incidence of late rebleeding and death, all patients surviving an acute variceal bleeding episode should be treated for prevention of rebleeding. Patients with poor liver function should be considered for liver transplantation, and those who had required TIPS or shunt surgery to control the acute bleeding episode will not require further treatment to prevent rebleeding.

5.2.1 First-Line Therapy

Both nonselective β-blockers and EST have shown efficacy in preventing variceal rebleeding in randomized controlled trials (table III).[4,73] Untreated controls have a median rebleeding rate of 63% within 1–2 years, which is significantly reduced to 42% with β-blockers and to 50–55% with EST.[4,73] Ten randomized controlled trials have compared β-blockers with EST. The meta-analysis of these studies has shown similar rates of rebleeding and survival with both treatments, with more adverse effects associated with EST.[4] However, in more recent years, other options have achieved better results, taking in to account with pharmacological and endoscopic therapy.

Regarding endoscopic therapy, EVL has been shown to improve both the safety profile and efficacy that is achieved with EST in numerous studies.[74] The meta-analysis of 13 randomized controlled trials including more than 1000 patients showed that despite survival being similar with both endoscopic therapies, EVL significantly reduces rebleeding rate and the number of sessions required to

achieve the eradication of varices, as well as reducing complications.[73,74] EVL was better than EST in preventing rebleeding in all studies, although the difference was not significant in eight studies.[73,74] Therefore, EVL is the current endoscopic treatment of choice in the prevention of variceal rebleeding.[33,62] It is unclear whether variceal recurrence after initial eradication may be more common with EVL than with EST. It has been suggested that perforating veins that feed the varices are less affected with ligation.[73] Adding EST to EVL, to obliterate such perforating veins, was proposed to reduce variceal recurrence after EVL. However, no beneficial effects have been observed by combining these endoscopic treatments compared with using EVL alone.[83]

Pharmacological therapy has also been improved in recent years. The combination of nonselective β-blockers and ISMN showed a greater decrease in portal pressure than β-blockers alone.[36] This combined therapy with β-blockers and ISMN has been shown to be superior to β-blockers alone and to EST alone, with a higher efficacy to prevent rebleeding.[53,84] HVPG monitoring may identify haemodynamic responders to β-blockers with or without ISMN, who will not need any further treatment, while rescue therapies should be provided to non-responders who are still at high risk of bleeding.[48,85]

Six randomized controlled trials have compared combined pharmacological treatment with β-blockers plus ISMN versus EVL.[85-87] Our meta-analysis of these studies, including a total of 713 patients, shows that combined drug therapy and EVL have a similar efficacy to prevent variceal rebleeding (figure 3). The overall rate of adverse effects is similar with both therapies, although severe complications are more frequent with EVL. The meta-analysis also shows a trend towards better survival favouring drug therapy (figure 3). It should be noted that the trial that showed a greater trend towards better survival with pharmacotherapy, showed, in contrast, superiority of EVL to prevent rebleeding.[87] The median rebleeding rate achieved with combined drug therapy in these studies was 35% and with EVL was 42%.[85-87] In studies comparing EVL and EST, in which EVL was the experimental therapy, the median rebleeding rate with EVL was 24%.[73,74] Such a different efficacy in trials using EVL may be related to methodological factors such as differences in exclusion criteria or definition of rebleeding.

Three randomized controlled trials have compared EVL alone versus EVL combined with β-blockers to prevent variceal rebleeding. Our meta-analysis of these studies, including 373 patients, has shown that the addition of β-blockers significantly improves the efficacy of EVL alone, although with a similar mortality rate (figure 4). Variceal rebleeding, as well as recurrent bleeding from any source, and variceal recurrence after obliteration are significantly reduced by the addition of β-blockers to EVL.[91,92] This is in keeping with a recent meta-analysis showing that combining endoscopic therapy (either EST or EVL) and β-blockers reduces the risk of rebleeding achieved with either treatment alone.[93] On the other hand, the preliminary results of a recent multicentre trial suggest that the addition of EVL to combined drug therapy with β-blockers plus ISMN may decrease variceal rebleeding compared with drug therapy alone, although overall rebleeding was similar.[94] These studies support the association of EVL and pharmacological therapy as first-line therapy to prevent variceal rebleeding (figure 5).[33,62] This combination should be clearly recommended in patients who continue to bleed while receiving treatment with EVL or drugs alone. Patients with an adequate haemodynamic response to β-blockers with or without ISMN will not need further treatment.

5.2.2 Management of Therapeutic Failure

Before the introduction of EST, shunt surgery was used for years.[4] It was very effective in preventing rebleeding, but markedly increased the risk of encephalopathy and had no effect on survival. Compared with surgical shunts, TIPS has the advantage of lower mortality and morbidity from the procedure. However, TIPS is a calibrated shunt and has the disadvantages of deriving blood from the liver, such as enhancing encephalopathy and worsening liver failure. Numerous trials have compared

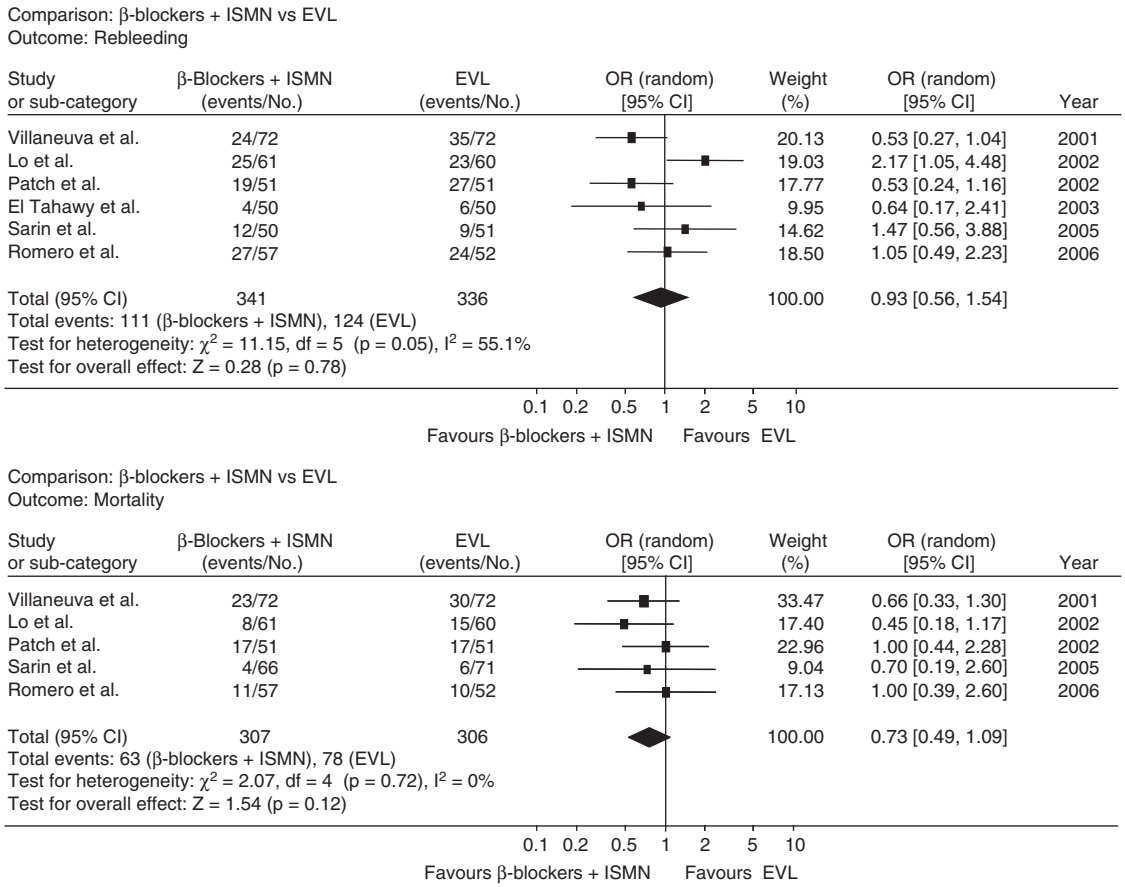

Fig. 3. Meta-analysis of randomized controlled trials (Villanueva et al.,[85] Lo et al.,[87] Patch et al.,[86] El-Tahawy et al.,[88] Sarin et al.[89] and Romero et al.[90]) comparing combined pharmacological treatment with β-adrenoceptor antagonists (β-blockers) and isosorbide mononitrate (ISMN) vs endoscopic variceal ligation (EVL) for the prevention of oesophageal variceal rebleeding. Both combined drug therapy and EVL have similar efficacy to prevent oesophageal variceal rebleeding with almost significant heterogeneity. There is a trend towards better survival favouring combined drug therapy, without heterogeneity. One study (Sarin et al.[89]) included patients with and without cirrhosis (26% of subjects). In one study (Romero et al.[90]), in the EVL group, one or two sessions of sclerotherapy were performed after the eradication of varices with EVL. One study (El-Tahawy et al.[88]) is only published as an abstract and included patients with schistosomal and hepatitis C virus coinfection. **OR** = odds ratio.

endoscopic therapy with TIPS. The meta-analysis of these studies has shown that TIPS is more effective at preventing rebleeding but is also associated with a higher incidence of encephalopathy, and survival is similar with both therapies.[96] These results are similar in studies using either EST or EVL for the endoscopic treatment of varices.[96] Furthermore, similar results have been observed in a trial comparing TIPS and combined drug therapy with β-blockers plus ISMN, in which drug therapy was less effective in preventing rebleeding, but was associated with less encephalopathy and produced identical survival.[97] Therefore, TIPS is not recommended as a first-choice treatment to prevent rebleeding, but as a rescue therapy (figure 5). Covered stents have shown a lower occlusion rate and lower incidence of encephalopathy than uncovered TIPS stents, with an improved clinical outcome.[33] Thus, covered stents should be used for performing TIPS. Surgical shunts (distal splenorenal shunt or 8 mm H-graft) may be an alternative for those with Child-Pugh class A cirrhosis.[98] Transplantation provides

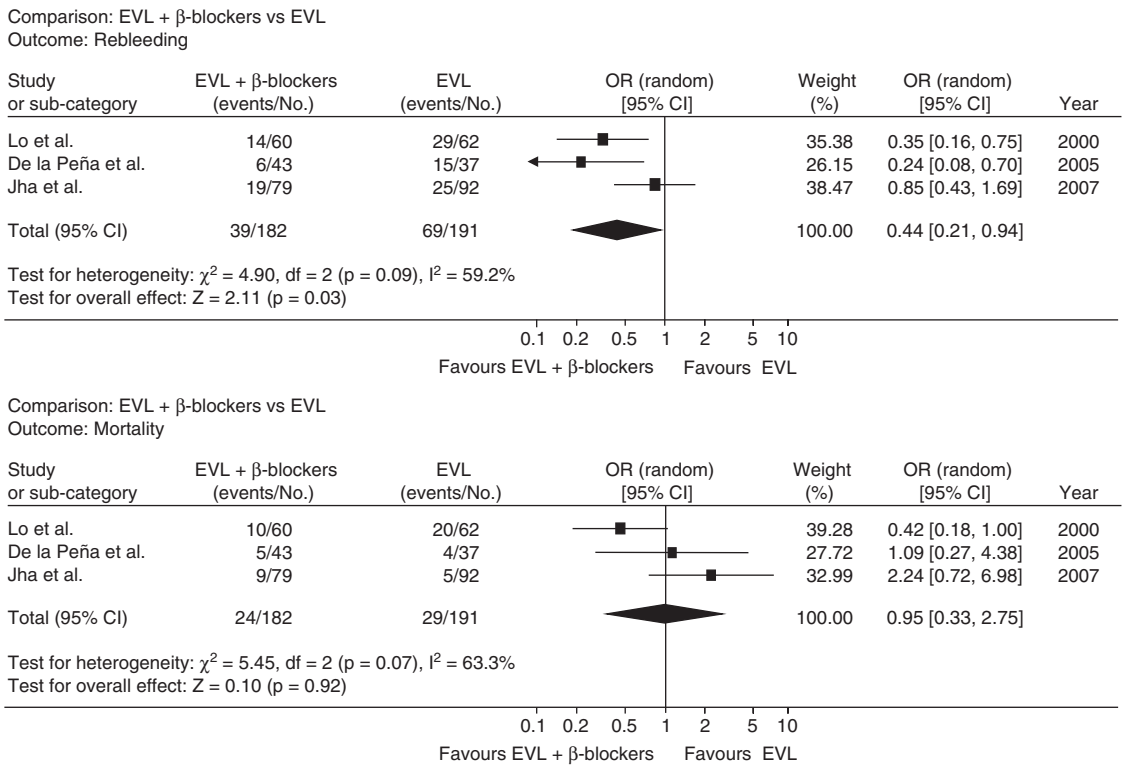

Fig. 4. Meta-analysis of randomized controlled trials (Lo et al.,[91] De la Peña et al.[92] and Jha et al.[95]) comparing endoscopic variceal ligation (EVL) alone or combined with β-adrenoceptor antagonists (β-blockers) for the prevention of oesophageal variceal rebleeding. Combined treatment with β-blockers and EVL is significantly better than EVL alone to prevent variceal rebleeding, without heterogeneity. However, survival was similar with both therapies. In one study, in the combined therapy group EVL was combined with nadolol and sucralfate.[91] One study (Jha et al.[95]) is only published as an abstract. **OR** = odds ratio; ← indicates the lower value of the 95% confidence interval was >0.1.[92]

good long-term outcomes in Child-Pugh class B/C cirrhosis and should be considered. TIPS may be used as a bridge to transplantation.

5.3 Treatment to Prevent the First Variceal Bleeding

Nonselective β-blockers were introduced more than 25 years ago for the treatment of portal hypertension.[99] Since then, a number of trials comparing β-blockers with placebo or non-active treatment have shown that β-blockers are useful in preventing the first variceal bleeding (table III). The meta-analyses of these studies, including more than 1000 patients, have shown that β-blockers significantly reduce the risk of a first haemorrhage in patients with large varices from 25% in controls to 15% in treated patients, and improve survival.[7,100] Therapy with β-blockers should be maintained indefinitely because the risk of bleeding recurs when treatment is stopped.[33]

More recently, randomized controlled trials have also shown the efficacy of prophylactic EVL in this setting.[101] Subsequently, different studies have compared the value of β-blockers and EVL in preventing the first bleeding in patients with large varices.[102] The meta-analysis of 14 trials, including 999 patients, showed that EVL significantly reduces the risk of first variceal bleeding, without differences in mortality.[103] The rate of adverse effects was higher with β-blockers, although EVL-associated adverse events were more severe with treatment-related mortality in some patients.[103] A small

study does not support the hypothesis that the addition of β-blockers to EVL may improve the efficacy of EVL alone in this setting.[104] Both β-blockers and EVL, but not combination therapy, are currently recommended as first-line treatment to prevent first variceal bleeding in patients with large varices (figure 6).[33,62] Interestingly, a recent multicentre, randomized, controlled trial suggests that carvedilol may be more effective than EVL in preventing a first variceal bleeding.[105]

Around 30% of patients with large varices have contraindications or intolerance to β-blockers that preclude their use.[106] EVL should clearly be offered to these patients. In the remaining patients who are able to take β-blockers, other issues should also be considered. Nonselective β-blockers reduce portal pressure, achieving an adequate haemodynamic response in the great proportion of patients.[69] In addition to a very low risk of bleeding, responders also have other benefits such a lower risk of developing ascites or spontaneous bacterial peritonitis.[85,107] These additional benefits of β-blockers should be adequately explored in future studies.

Present guidelines recommend classifying oesophageal varices into two grades (small and large), defining large varices as those with a diameter >5 mm.[33] Patients with small varices could be treated with nonselective β-blockers to prevent progression of varices and bleeding,[108] but further studies are recommended by experts because of the limited experience.[33,62] Patients with small varices with red wale signs or with Child-Pugh class C cirrhosis have an increased risk of bleeding and may benefit from treatment (figure 6).

A recent, double-blind, randomized, controlled trial failed to show a benefit of using nonselective β-blockers to prevent the development of varices in patients with cirrhosis and portal hypertension.[3] It has been suggested that this negative result may be partially due to the early stage of cirrhosis in these patients, with milder splanchnic and systemic hyperdynamic circulatory state, which is the main target of the action of β-blockers.[3]

Despite the greater effect on portal pressure, combined therapy with β-blockers plus ISMN has not improved the outcomes that are achieved when using β-blockers alone in primary prevention in

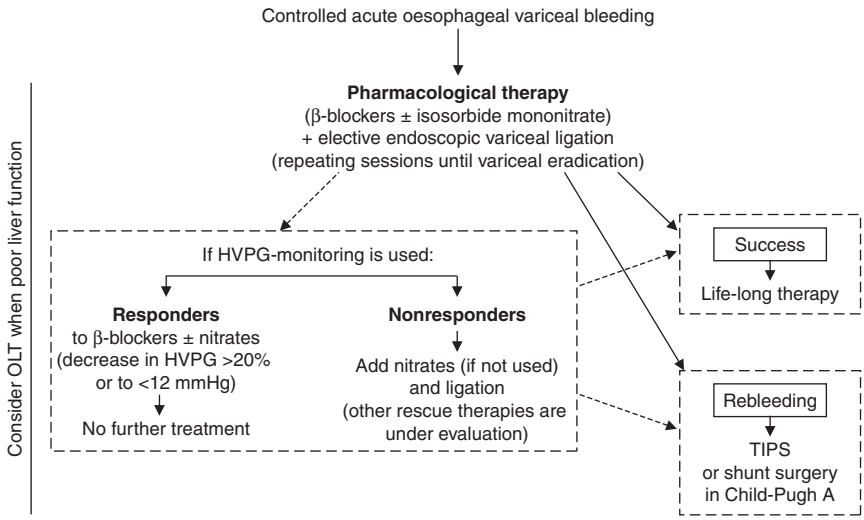

Fig. 5. Algorithm for the prevention of recurrent variceal bleeding. Hepatic venous pressure gradient (HVPG) monitoring, by measuring HVPG at baseline and again within the first month of starting treatment with β-adrenoceptor antagonists (β-blockers), to assess haemodynamic response, provides strong prognostic information when available. Patients with a decrease in HVPG >20% from baseline or to <12 mmHg (responders) have a low risk of rebleeding and will not require any further therapy. The best treatment to rescue nonresponders has not yet been established. **OLT** = orthotopic liver transplantation; **TIPS** = transjugular intrahepatic portosystemic shunt; dashed arrows are applicable when HVPG monitoring is used.

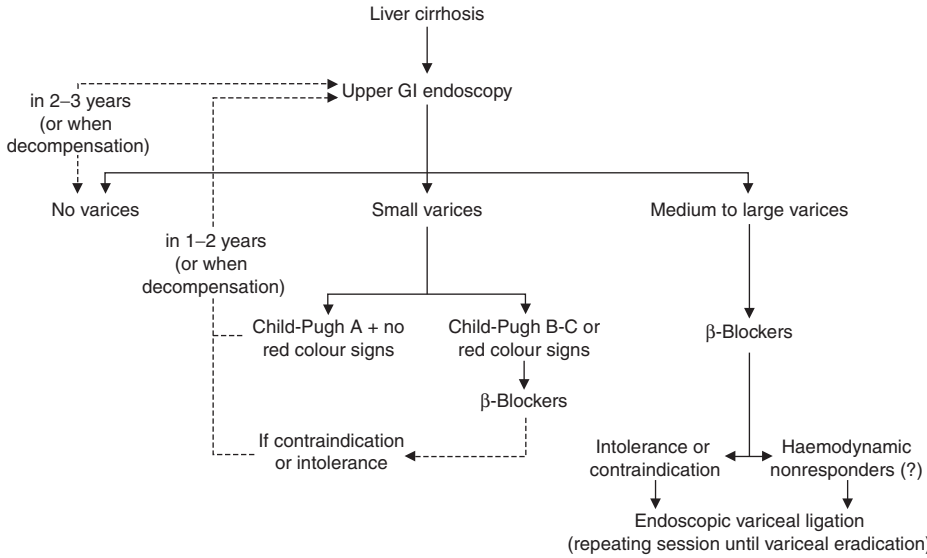

Fig. 6. Algorithm for primary prophylaxis of variceal bleeding. Haemodynamic nonresponders to β-adrenoceptor antagonists (β-blockers) are at high risk of bleeding and ligation may be a better option. However, whether or not this approach is actually useful should be established in future studies. Dashed arrows indicate recommended procedures using no therapeutic interventions.

double-blind, randomized, controlled trials (table II).[39] ISMN alone has been used in patients with contraindications or intolerance to β-blockers, but has been ineffective and has also increased adverse effects.[106] Furthermore, the long-term use of ISMN alone has been associated with a higher mortality than that observed with β-blockers in patients older than 50 years.[109] The combination of β-blockers and spironolactone has also been ineffective in the prevention of first variceal bleeding compared with β-blockers alone.[110]

5.4 Gastric Varices

Gastric varices are the source of 5–10% of bleeding episodes in patients with cirrhosis.[12] Few randomized controlled trials have been performed on the management of gastric variceal bleeding, probably as a consequence of the relatively low incidence. However, bleeding from this source may be more severe than that from oesophageal varices.[111] Large gastric varices are often associated with gastrorenal shunts, which can reduce portal pressure but not prevent bleeding.[111]

Gastric varices that constitute an extension of oesophageal varices along the lesser curvature of the stomach are treated the same as oesophageal varices.[33,62] Limited data is available on gastroesophageal varices that extend towards the fundus of the stomach. High rates of initial control of bleeding have been reported using EST with conventional sclerosants, although rebleeding is common.[73] In randomized studies, endoscopic variceal obturation of gastric varices with tissue adhesives has been more effective than EVL and EST.[112] Therefore, these glues are the current recommended endoscopic therapy for the management of fundal varices.[33,62] TIPS may also be effective in this setting and should clearly be used when endoscopic therapy is not possible or fails.[113] In these patients, TIPS may be associated with the embolization of collaterals feeding the varices.[12] Balloon tamponade with the Linton-Nachlas tube may serve as a bridge to TIPS in massive bleedings. Trials comparing endoscopic therapy with TIPS or with drugs, both in acute bleeding and to prevent rebleeding, are required to clarify the best management for fundal varices. Isolated fundal varices may be secondary to splenic vein thrombosis and thus splenectomy may

be indicated.[111] In the absence of specific controlled trials on primary prophylaxis of gastric variceal bleeding, endoscopic therapy should not be performed given the invasive nature of the procedure. Until results from these trials are available, nonselective β-blockers may be used for the prevention of the first bleeding episode.[12]

5.5 Portal Hypertensive Gastropathy

The incidence of portal hypertensive gastropathy (PHG) increases after oesophageal variceal eradication by endoscopic therapy.[73] Bleeding from PHG is uncommon, mainly occurs in patients with severe disease and is usually chronic.[114] When acute haemorrhage occurs, it is generally mild and can be controlled with vasoactive drugs.[12] However, the efficacy of this and other treatments for PHG has not been assessed in randomized controlled trials, probably because of the low frequency of this complication. The natural history of PHG is variable – it may remain stable, deteriorate, fluctuate or even improve spontaneously.[114] This fact limits the value of uncontrolled studies on treatments to prevent rebleeding. PHG should be distinguished from gastric antral vascular ectasia (GAVE) because it may have relevant therapeutic implications.[115] GAVE frequently occurs in patients without cirrhosis or portal hypertension.[115] However, in the setting of cirrhosis, GAVE can be difficult to differentiate from PHG. The distinction is relevant because, contrary to PHG, GAVE does not generally respond to portal hypotensive treatments such as β-blockers or TIPS.[115]

Treatment to prevent rebleeding from PHG includes pharmacological and endoscopic options as well as derivative procedures. Nonselective β-blockers have been shown to reduce recurrent bleeding from PHG[116] and may be considered the first-line therapy in this setting.[12] Furthermore, the role of derivative treatments is controversial. Both TIPS and shunt surgery have been shown to be effective in small studies.[10] Taking into account the limited evidence available and the invasive nature of such treatments, it seems advisable to consider TIPS only when β-blockers fail. Several small studies suggest that therapeutic endoscopy using injection therapy or thermal methods (including either contact or non-contact techniques) may be effective to treat GAVE-associated bleeding.[117] However, endoscopic therapy has rarely been investigated in PHG. A recent uncontrolled study suggested that endoscopic coagulation with argon gas may be effective in reducing recurrent bleeding in patients with PHG who are unresponsive to β-blockers and iron therapy.[118] Accordingly, it may be advisable to try endoscopic therapy before using derivative procedures, particularly when differentiation from GAVE is difficult.

6. Recommendations in Special Populations

There is a poor representation of special populations, such as children or the elderly, in randomized controlled trials on the treatment of variceal bleeding. Accordingly, few particular recommendations based on evidence may be provided regarding pharmacological treatment of portal hypertension in these special populations.

The leading cause of significant liver disease in children is biliary atresia, a disorder associated with prominent portal hypertension at disease stages where synthetic liver function is still preserved.[119] The progression of portal hypertension is related to the outcome after hepatoportoenterostomy. In clinical practice, paediatric hepatologists manage portal hypertension in the context of randomized controlled trials and meta-analyses performed in adults.[119]

When using medications in the elderly, some particularities should be considered. In the elderly, changes is the autonomic nervous system, the kidney and the liver may modify the metabolism and clinical effects of drugs.[120] Because of these and other factors, such as co-morbidity, elderly patients are also more susceptible to adverse effects. This should be considered when using medications with a narrow safety profile, such as vasopressin. There is an age-related decrease in intrinsic β-adrenoreceptor sensitivity and decreased responses to β-blockers are seen with ageing.[120] However, there is no evidence that these events alter the efficacy of β-blockers in the treatment of portal hypertension in the

elderly. In clinical practice, older patients do not tolerate β-blockers as well as younger individuals and may require other therapeutic strategies for the prevention of variceal bleeding.[121] Furthermore, lipophilic β-blockers, such as propranolol, cross the blood-brain barrier and affect the sleep pattern, and may worsen depression. This may favour the choice of hydrophilic β-blockers such as nadolol. These facts should be considered when treating portal hypertension in the elderly.

7. Conclusions

Pharmacological therapy of portal hypertension is mainly effective when the HVPG is reduced below 12 mmHg or at least by 20% from baseline. Endoscopic therapy may prevent bleeding by obliterating the varices, but does not decrease portal pressure. Used together, pharmacological and endoscopic therapies may have an additive effect, which has been demonstrated in different clinical settings. In acute variceal bleeding, vasoactive drugs (either terlipressin or somatostatin) should be started as soon as possible, before diagnostic endoscopy, and maintained for 2–5 days. The efficacy of drugs is improved by combining them with emergency endoscopic therapy. The addition of EVL to pharmacological therapy improves the efficacy and safety profile to a greater extent than is achieved with the addition of EST. Antibacterial prophylaxis should be an integral part of therapy in acute bleeding. To prevent rebleeding, both EVL and the combination of β-blockers and ISMN may be a valid first-line choice. Adding β-blockers improves the efficacy of EVL alone. Haemodynamic responders to β-blockers with or without ISMN have a low risk of haemorrhage and will not need further treatment, while rescue therapies should be provided to non-responders. Future studies should clarify the best therapeutic option in this high-risk subset of patients. TIPS are the recommended rescue therapy when EVL with or without drugs fails. β-Blockers significantly reduce the risk of a first haemorrhage in patients with large varices and improve survival. Compared with β-blockers, EVL reduces the risk of first bleeding without differences in mortality and should clearly be offered to patients with large varices who have contraindications or an intolerance to β-blockers.

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