

Acute variceal bleeding: Pharmacological treatment and primary/secondary prophylaxis

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Variceal bleeding is one of the most severe complications of portal hypertension related to liver cirrhosis. Primary prophylaxis is considered mandatory in patients with cirrhosis and high-risk oesophageal varices, and once varices have bled, every effort should be made to arrest the haemorrhage and prevent further bleeding episodes. In acute variceal bleeding, vasoactive drugs that lower portal pressure should be started even before endoscopy, and should be maintained for up to 5 days. The choice of vasoactive drug should be made according to local resources. Terlipressin, somatostatin and octreotide can be used; vasopressin plus transdermal nitroglycerin may be used if no other drug is available. In variceal bleeding, antibiotic therapy is also mandatory. In primary and secondary prophylaxis, beta-blockers are the mainstay of therapy. In secondary prophylaxis (but not in primary prophylaxis) these drugs can be combined with organic nitrates.

Key words: liver cirrhosis; therapy; prophylaxis; variceal bleeding.

Variceal bleeding is one of the most severe complications of portal hypertension associated with liver cirrhosis, carrying a mortality within 6 weeks in the order of 11–20%.

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Primary prophylaxis is therefore considered mandatory in patients with cirrhosis and oesophageal varices, and once varices have bled every effort should be made to arrest the haemorrhage and prevent further bleeding episodes.

Oesophageal variceal bleeding occurs only when there is a clinically significant portal hypertension, defined as hepatic vein pressure gradient (HVPG) >12 mmHg.^{1,2} Pathophysiologically, portal pressure depends on blood inflow and on resistance in the portal system. Therefore, to reduce portal pressure we can act on reducing portal blood flow by using splanchnic vasoconstrictors, and on the resistance in the portal system by using vasodilators. Some drugs (e.g. vasopressin and somatostatin) are short-acting, and therefore they are used in the setting of acute bleeding; others (e.g. non-selective beta-blockers) are long-acting and are used in primary and secondary prophylaxis.

In this chapter we will review the drugs used in the setting of acute haemorrhage and for primary and secondary prophylaxis of variceal bleeding.

ACUTE VARICEAL BLEEDING

The pharmacological treatment of acute bleeding aims at arresting the haemorrhage, preventing rebleeding, and reducing mortality. In cirrhotic patients, clinical studies^{3,4} and a meta-analysis⁵ have confirmed the beneficial effect of vasoactive drugs for variceal haemorrhage (Figure 1). Current guidelines⁶ recommend starting pharmacological therapy with vasoactive drugs as soon as possible – even during transfer to the hospital,³ since almost a quarter of deaths happen early⁷ – and maintaining it for up to 5 days, since this is the time frame in which early rebleeding is most frequent.⁶ Diagnostic and eventually therapeutic endoscopy is facilitated by the use of vasoactive drugs, and should be performed as soon as possible after admission.

Several drugs are available to treat acute variceal haemorrhage, and the choice should be made according to local resources, bearing in mind that the only drug shown

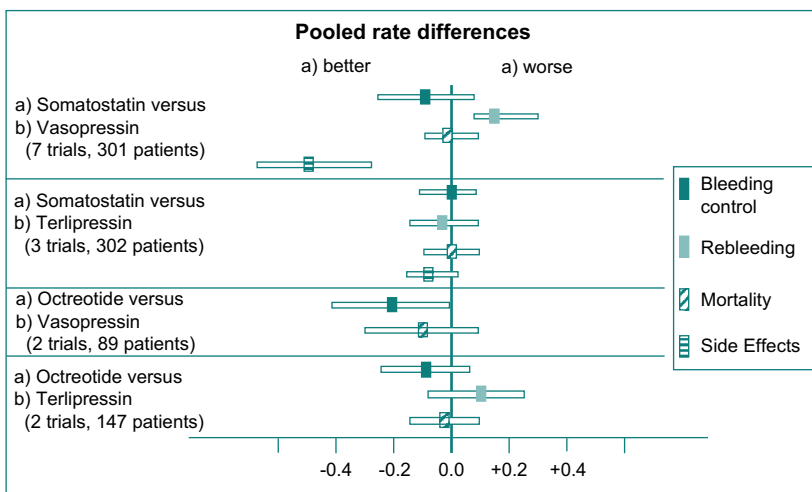


Figure 1. Comparison of vasoactive drug treatments for variceal bleeding in cirrhosis: a meta-analysis. From D'Amico et al (*Seminars in Liver Disease* 1999; **19**: 475–505) with permission.

to improve survival is terlipressin,³ and that somatostatin and octreotide have the same rate of arrest of bleeding but do not have an impact on survival.^{8,9} If none of these drugs is available, vasopressin plus transdermal nitroglycerin is a tolerable option.¹⁰

VASOACTIVE DRUGS

Vasopressin

Vasopressin is a powerful vasoconstrictor that effectively reduces portal pressure by reducing portal blood flow causing splanchnic vasoconstriction. It used to be the first drug in the treatment of variceal bleeding, but nowadays its use is allowed only if other drugs are not available because of severe adverse cardiovascular events (myocardial ischaemia or infarction, arrhythmias, mesenteric ischaemia, limb ischaemia, cerebrovascular accidents, and hyponatraemia due to its antidiuretic action). These adverse effects occur in 32–64% of patients^{11,12} and derive from increased peripheral vascular resistance and reduced cardiac output, heart rate and coronary blood flow. The adverse effects lead to discontinuation of therapy in about 25% of cases.^{13–15} Vasopressin should be infused at 0.4 U/min, with upward titration to a maximum rate of 1.0 U/min for up to 48 h, associated with transdermal nitroglycerin (20 mg/24 h) in order to enhance the portal hypotensive effect and to reduce the systemic side-effects. Vasopressin has been shown to significantly improve the control of variceal bleeding, although without a reduction in mortality.¹⁰

Terlipressin

Terlipressin (triglycyl-lysine vasopressin) is a long-acting derivative of vasopressin which is slowly transformed into vasopressin by enzymatic cleavage of the triglycyl residues by tissue peptidases.¹⁵ It has been hypothesised that the slow release of the active agent may account for the lower rate of side-effects with terlipressin than with vasopressin.¹⁵ Side-effects of terlipressin may occur in almost 25% of patients. They are usually relatively mild: abdominal cramps, diarrhoea, bradycardia and hypertension; severe side-effects – such as arrhythmias, angina, limb ischaemia – that require discontinuation of the drug occur in the order of 2–4%.^{16–18} Before starting terlipressin, an electrocardiogram (ECG) is mandatory, and cardiac monitoring is necessary for high-risk patients. Current guidelines recommend initiation of terlipressin at a dose of 2 mg/4–6 h for the first 48 h, and after this period the treatment can be maintained for up to 5 days at a dose of 1 mg/4–6 h to prevent early rebleeding.^{6,15,16} Terlipressin reduces portal pressure, and this effect is still significant 4 h after administration.¹⁹ Beside the effect in control of bleeding, there is indirect evidence that terlipressin might prevent bleeding-induced renal impairment, and it has been shown that in animals it protects the liver in cases of septic shock.²⁰

Clinical studies have shown that control of acute variceal bleeding is achieved in 75–80% of cases^{18,21} at 48 h and in 67% at 5 days without endoscopic therapy.¹⁶

Terlipressin versus placebo or non-active drugs

Several studies and a meta-analysis have shown that terlipressin improves both control of bleeding and 6-week survival^{3,10} compared to placebo^{10,21} or no active drug.^{15,17,21}

Terlipressin versus vasopressin

Five trials have shown that terlipressin is as effective as vasopressin (which was associated with sublingual nitroglycerin in two studies)¹⁰ in terms of control of bleeding, rebleeding or mortality,¹⁰ and that it is safer than vasopressin plus nitroglycerin.^{10,21}

Terlipressin versus somatostatin and endoscopic therapy

No differences have been found in comparison with somatostatin infusion and endoscopic therapy (i.e. sclerotherapy) in terms of control of variceal bleeding and prevention of early rebleeding.^{10,16,21,22} There is only one published randomised controlled trial (RCT) comparing terlipressin and sclerotherapy in terms of side-effects.¹⁶ In this trial side-effects were categorised as mild (chest pain, abdominal pain, dysphagia, skin lymphangitis, hyponatraemia, isolated fever, nausea), moderate (bacteraemia, oesophageal ulcers requiring therapy, dysphagia requiring therapy, auricular fibrillation, ischaemic change on ECG, bronchoaspiration), or severe (bleeding from oesophageal ulcers, aspiration pneumonia, sepsis from empyema, ischaemia of lower limbs, severe hyponatraemia, seizure), and a trend toward fewer side-effects for terlipressin (20% versus 30% for terlipressin and sclerotherapy, respectively; $P = 0.064$) was observed.

Somatostatin (SMT)

Somatostatin has been used in the treatment of acute variceal bleeding because of its ability to lower portal pressure and collateral blood flow^{23,24} by inhibition of the release of splanchnic vasodilatory peptides (i.e. glucagon) and facilitation of the effects of endogenous vasoconstrictor systems. Additionally, somatostatin blocks the postprandial increase in portal blood flow and portal pressure. Somatostatin is administered as an initial bolus of 250 µg (which can be repeated up to three times) followed by the infusion of 250 µg/h for up to 5 days to prevent early rebleeding²⁵ or until the achievement of a 24-h bleeding-free period. The reduction of portal pressure achieved with the bolus lasts less than 5 min due to the short half-life (1–3 min) of somatostatin.²⁴ Bolus injections of somatostatin have a vasoconstrictor effect in humans that is much greater than that caused by continuous infusions.²³ A double dose (500 µg/h) is associated with a greater decrease in HVP, and in clinical practice this dose has been shown to be effective in the subgroup of patients with active bleeding at emergency endoscopy.²⁶ Somatostatin side-effects are usually mild, consisting of bradycardia, hyperglycaemia, diarrhoea and abdominal cramps. The addition of nitroglycerin to SMT, in contrast to what happens with vasopressin, induces more adverse events and is not associated with increased efficacy.¹⁷

Somatostatin versus placebo or non-active drugs

Several RCTs have shown that, in comparison with placebo or non-active treatment,^{9,10} somatostatin significantly improves the rate of control of bleeding (63% versus 46% for somatostatin and placebo or non-active treatment, respectively) but has no effect on mortality.¹⁰

Somatostatin versus vasopressin

SMT is superior to vasopressin in the immediate control of bleeding and has less severe side-effects. SMT and vasopressin are equivalent for definitive control of bleeding and mortality.¹⁰

Somatostatin versus terlipressin

The three studies comparing SMT and terlipressin showed no significant differences in terms of failure to control bleeding, rebleeding and mortality.¹⁰ SMT showed fewer side-effects (21% versus 29%, not significant); severe side-effects that led to discontinuation of therapy were 4% with both drugs.¹⁰

Somatostatin analogues

Octreotide (OCT)

Octreotide is a synthetic octapeptide SMT analogue which has a longer half-life than SMT. Unfortunately, its longer half-life does not result in longer haemodynamic effects²⁷ because of the development of tachyphylaxis. Its beneficial effects may be related to the prevention of a postprandial increase in portal pressure.⁹ In clinical practice it is usually given as an initial bolus of 50 µg, followed by infusion of 25 or 50 µg/h⁹ maintained for 5 days to prevent early rebleeding. As for SMT, side-effects are not significant.

In clinical trials, octreotide has been shown to have little or no effect when used without endoscopic therapy. The results of four RCTs suggest that OCT may improve the efficacy of endoscopic therapy in terms of reduction of early rebleeding²⁸ but has no or little effect as a single therapy,¹⁰ especially when used as initial treatment,²⁹ probably because of tachyphylaxis. Octreotide has no effect on rebleeding or mortality.^{10,29}

In two RCTs OCT was better than vasopressin, and equivalent to terlipressin (two RCTs),¹⁰ for control of bleeding. Side-effects of OCT were less frequent and less severe, but the difference was significant only with vasopressin.¹⁰

In a study by Morales et al³⁰ in patients with cirrhosis, intravenous OCT for 48 h associated with sclerotherapy was not superior to sclerotherapy alone in terms of 7-day mortality, frequency of rebleeding, number of units of packed-red-blood-cell transfusion, and length of stay in intensive care.

Vapreotide and *Lanreotide* are other analogues of somatostatin. They have been shown to reduce portal pressure in animals, but their haemodynamic effects in cirrhotic patients are controversial.³¹

ANTIBIOTIC THERAPY

Up to 20% of cirrhotic patients hospitalised for gastrointestinal bleeding already have a bacterial infection on admission, and another 50% develop infections during hospitalisation.³² The most frequent infections in cirrhotic patients are spontaneous bacterial peritonitis, and/or spontaneous bacteraemia, urinary tract infections, and pneumonia. Gram-negative bacteria are the most commonly isolated microorganisms. In one study, admission for gastrointestinal bleeding and low serum albumin were identified as independent predictors of the development of bacterial infection.³³

Bacterial infections in the setting of variceal bleeding are associated with higher mortality and rebleeding rates (Figure 2), and therefore antibiotic prophylaxis is considered mandatory.⁶ A meta-analysis has shown that antibiotic prophylaxis significantly increases survival (mean improvement rate 9.1%) Figure 3.³⁴ On the basis of recent studies,^{35,36} current guidelines recommend instituting antibiotic prophylaxis on admission with oral quinolones (e.g. norfloxacin 400 mg/12 h) or intravenous cephalosporins, and maintaining this for 7 days.⁶ A recent study showed that intravenous ceftriaxone

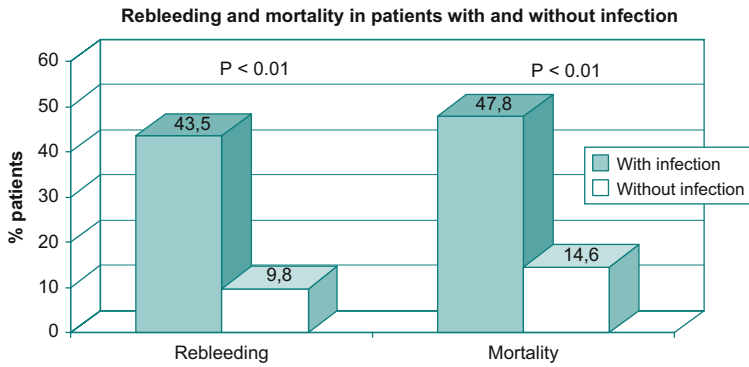


Figure 2. Prognostic significance of bacterial infection in bleeding cirrhotic patients. From Bernard et al (*Gastroenterology* 1995; **108**: 1828–1834) with permission.

is more effective than oral norfloxacin in the prophylaxis of bacterial infections in cirrhotic patients with variceal haemorrhage.³⁵ Aminoglycosides should be avoided because of their renal toxicity in cirrhotic patients.

TREATMENT OF COAGULATION ABNORMALITIES

Patients with cirrhosis often present with coagulation abnormalities that may play a role in the severity of variceal bleeding. Several drugs that act on coagulation and fibrinolytic pathways have been tested. *Desmopressin* (DDAVP), a drug that significantly decreases bleeding time in cirrhosis, has shown no clinical benefits in the setting of variceal bleeding.³⁷ The benefit of therapy with anti-fibrinolytic agents, useful in liver transplantation, has not been proven in clinical trials.³⁸ In the post-hoc analysis of

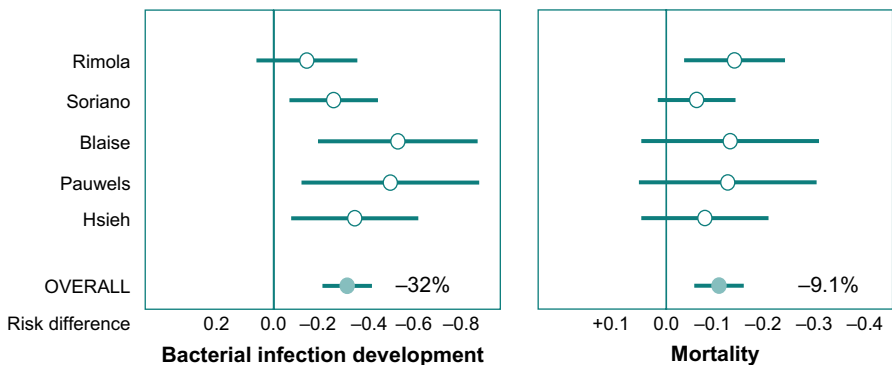


Figure 3. Effect of antibiotic treatment on the outcome of gastrointestinal bleeding in cirrhosis. The effect of antibiotic prophylaxis, mainly oral quinolones (norfloxacin, 400 g/12 h), on gastrointestinal bleeding outcome in cirrhotic patients is shown in this meta-analysis including 264 patients treated with antibiotics and 270 without antibiotic prophylaxis. Please note that antibiotic prophylaxis significantly increased the mean percentage of patients free of infection (mean improvement rate 32%), and also significantly increased the mean survival rate (9.1%). From Bernard et al (*Hepatology* 1999; **29**: 1655–1661) with permission.

the results of a recent multicentre randomised trial, administration of *activated recombinant factor VII* (rFVIIa) was shown to significantly improve the outcome of conventional therapy in patients with moderate and advanced liver failure (Child-Pugh class B and C).³⁹ Unfortunately, the results of a subsequent trial in patients with advanced cirrhosis and upper gastrointestinal bleeding did not show any effect of rFVIIa on control of bleeding and 5-day mortality (Figure 4).⁴⁰

PRIMARY AND SECONDARY PROPHYLAXIS

Patients with oesophageal varices at high risk of bleeding should be identified in order to start primary or (if bleeding as already occurred) secondary prophylaxis for bleeding. Independent predictors of the risk of bleeding include: degree of liver dysfunction, size of oesophageal varices, and presence of red signs on oesophageal varices. All these predictors are taken into consideration in the NIEC (New Italian Endoscopic Club) index.⁴¹ Current guidelines recommend giving primary prophylaxis to all patients with medium and large varices and patients with small varices with red wale signs or of Child class C.⁶ Patients with small varices without red wale signs and of Child class A or B may be treated with beta-blockers to prevent progression of varices and bleeding, but further studies are required.⁶ Patients surviving a first episode of variceal bleeding have a risk of recurrent bleeding of >60% within 1 year from the index bleeding, and should therefore receive active treatments for the prevention of rebleeding.⁴²

In the following paragraphs we will review the drugs used in current clinical practice and drugs that have been evaluated in clinical trials, but are not the standard of practice.

Non-selective beta-blockers

Non-selective beta-blockers (i.e. propranolol, nadolol, timolol) are the recommended first-line therapy for the primary prophylaxis of variceal haemorrhage in cirrhotic

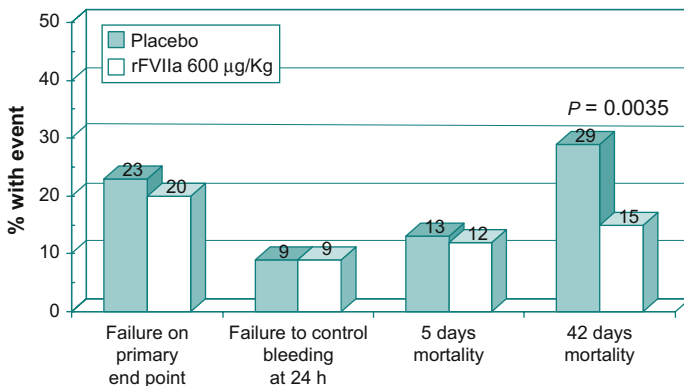


Figure 4. Recombinant factor VIIa (rFVIIa) for active variceal bleeding in patients with advanced cirrhosis: a multicentre randomised double-blind placebo-controlled trial. From Bosch et al (*Journal of Hepatology* 2007; **46**: S295) with permission.

patients with varices at high risk for bleeding.⁶ They cause a decrease in portal pressure and collateral blood flow, thus inducing a reduction in portal blood flow. This effect is achieved via the blockade of both the β_1 -adrenoreceptors, causing a reduction in cardiac output, and the β_2 -adrenoreceptors in the splanchnic vasculature, causing splanchnic vasoconstriction.^{43,44}

Beta-blockers reduce the 2-year incidence of first bleeding in these patients by 40%.¹⁰ Unfortunately, non-selective beta-blockers are not suitable for all patients because of contraindications (absolute: obstructive pulmonary disease, heart failure or aortic valve disease, second- and third-degree atrioventricular heart block, and peripheral arterial insufficiency; relative: sinus bradycardia and insulin-dependent diabetes mellitus). Such contraindications may be present in 5–20% of patients,⁴⁵ and 9–33% develop side-effects (symptomatic hypotension, severe bradycardia, severe fatigue, encephalopathy, loss of libido) that reduce compliance or lead to discontinuation of the treatment in 3–27% of cases.^{45,46} Nadolol can be administered only once daily, due to its longer half life, and has been suggested to have fewer side-effects because it does not cross the blood–brain barrier. Frequently, if side-effects develop with propranolol, they become less severe if the patient is shifted to nadolol or vice-versa.

Non-selective beta-blocker administration should be started at a low dose (i.e. 20 mg twice a day for propranolol and 40 mg once a day for nadolol) that should be increased stepwise with monitoring of the heart rate and blood pressure, reaching a maximum dose of 120 mg twice daily for propranolol and 160 mg once daily for nadolol. The dose of beta-blockers should be increased to achieve at least a 25% reduction in resting heart rate or development of symptoms.⁴⁷ Some but not all patients treated with beta-blockers achieving these targets will be protected from variceal bleeding, since there is no direct correlation between the degree of beta-blockade assessed by heart rate and the protection from variceal bleeding.⁶

Monitoring of the HVPG identifies patients with cirrhosis who will benefit from non-selective beta-blocker therapy. In fact, patients who achieve a reduction in the HVPG of ≤ 12 mmHg are totally protected from bleeding; in addition, when the HVPG, although still above 12 mmHg, is decreased by $\geq 20\%$ from baseline, the patients achieve a good degree of protection.^{48–50} However, since about 60% of patients who have never bled, treated with beta-blockers and not achieving these targets, will not bleed (for 2 years), HVPG monitoring cannot be recommended for primary prophylaxis. In secondary prophylaxis, assessment of haemodynamic response to drug therapy provides prognostic information about the rebleeding risk and should be performed.⁶

Beta-blocker therapy should be lifelong, and patients should be instructed not to discontinue the treatment abruptly because of the risk of 'rebound bleeding'.⁵¹

Primary prophylaxis

There are 12 RCTs comparing beta-blockers with placebo or non-active treatment,^{10,43,52} mostly including patients with medium or large oesophageal varices and with a median follow-up of almost 2 years. Meta-analyses of these studies showed a consistent reduction in the bleeding risk (non-active treatment versus beta-blockers: 25% versus 15%)^{10,53,54} with only a slight reduction in mortality (non-active treatment versus beta-blockers: 27% versus 23%) (Table 1).

However, in a recent study, timolol did not show any significant difference in comparison to placebo in preventing the formation of oesophageal varices and variceal haemorrhage.⁵⁵

Table 1. Meta-analysis of randomised controlled trials for the prevention of first variceal haemorrhage: placebo versus β -blockers.

Placebo	β -blocker	ARR	P	NNT
Failure rate: 24.7%	15.1	-9.6%	< 0.001	10.4
Death rate: 27.0%	23.0	-4.0%	=0.11	25.0

ARR, absolute risk reduction; NNT, number needed to treat.

Secondary prophylaxis

Current guidelines⁶ recommend using beta-blockers to prevent rebleeding, eventually in combination with endoscopic band ligation. Several RCTs compared beta-blockers with placebo or non-active treatments.⁵⁶⁻⁶² Meta-analyses of these studies confirmed the benefit from beta-blockers in terms of reduction in the rebleeding rate (non-treated group versus treated group: 68% versus 48%; absolute risk reduction [ARR] -21% [CI: -30% to -13%]; number needed to treat [NNT] 5) (see Table 2). Mortality for all causes was significantly reduced (non-treated group versus treated group: 27% versus 20%; ARR -7% [CI: -12% to -2%]; NNT 14),¹⁰ as was bleeding-associated mortality.⁶³

Two meta-analyses of ten studies comparing beta-blockers and sclerotherapy^{11,64} showed no significant differences between the two treatments concerning rebleeding for any cause (56% versus 53%, respectively) and survival (40% versus 37%, respectively). On the other hand, in the sclerotherapy group variceal rebleeding was significantly lower (beta-blockers versus sclerotherapy: 61% versus 45%, $P < 0.001$), but adverse events were significantly more frequent (beta-blockers versus sclerotherapy: 24% versus 44%, $P < 0.001$). The most frequent side-effects for propranolol were bronchospasm and fatigue, while the most severe were bradycardia and cardiac failure; in patients treated with sclerotherapy the most frequent adverse event was oesophageal ulceration, and the most severe adverse events were oesophageal stenosis, perforation and bleeding.

Organic nitrates

Long-acting nitrates – isosorbide dinitrate (ISDN) or isosorbide-5-mononitrate (ISMN) – decrease portal pressure by reducing intrahepatic and portal-collateral

Table 2. Meta-analysis of randomised controlled trials for the prevention of recurrent variceal haemorrhage: placebo versus β -blockers.

Placebo	β -blocker	ARR	P	NNT
Failure rate: 68.0%	48.0%	-20.0%	=0.001	5
Death rate: 27.0%	20.0%	-7.0%	=0.05	14.3

ARR, absolute risk reduction; NNT, number needed to treat.

resistance.¹³ ISMN should be started at 10 mg twice a day and titrated every other day up to 40 mg twice a day. Side-effects of nitrates are dose-dependent and include headache (20% of patients) and hypotension.^{64,65} Organic nitrates cause renal impairment and should not be used as single therapy.^{13,66}

Primary prophylaxis

ISMN has been compared to propranolol in three RCTs.^{67–69} Pooled results showed a non-significant increase in bleeding and mortality rate with ISMN. Moreover, in the long term a subgroup of ISMN-treated patients over 50 years of age had a higher mortality rate in comparison with propranolol-treated patients.⁶⁷ A more recent multicentre randomised trial conducted in the subgroup of patients who cannot receive beta-blockers showed no differences compared to placebo in the prevention of bleeding.⁶⁵

Combination therapy

Beta-blockers plus nitrates

The observation that, in the setting of acute variceal bleeding, the combination of a vasoconstrictor and a vasodilator (i.e. vasopressin and nitroglycerin) leads to a higher portal hypotensive effect and fewer side-effects has suggested the use of propranolol and ISMN as combination therapy^{70–73} for primary and/or secondary prophylaxis. Indeed, addition of ISMN to beta-blockers permits a higher reduction in portal pressure by preventing the increase in portal resistance caused by beta-blockers. This combination also allows a significant decrease in portal pressure in a subgroup of patients who are non-responders to beta-blockers. When nitrates are given in combination with beta-blockers, side-effects occur in 30–50% of patients and cause discontinuation of nitrates in 10–40%. In chronic treatment, ISMN in combination with beta-blockers does not cause impairment of renal function or sodium handling in cirrhotic patients.⁷⁰

Combination therapy has been compared to beta-blockers alone for primary prophylaxis in several studies.^{74–76} A meta-analysis of these studies showed no significant differences between the two drug therapies for bleeding and mortality rate, but showed a higher rate of side-effects with the combination therapy.¹⁰

In conclusion, in primary prophylaxis, monotherapy with ISMN is contraindicated, and the combination therapy between ISMN and beta-blockers cannot be recommended in clinical practice.⁷⁷

Two studies of ISMN associated with propranolol⁷⁸ or nadolol⁷⁹ versus the corresponding beta-blocker in secondary prophylaxis did not show a definitive benefit for the combination therapy. In fact, in both studies the combination therapy was not associated with a significant reduction of the 2-year rebleeding rate (combination therapy versus corresponding beta-blocker in the first study: 40.4% versus 57.4%; in the second study: 51% versus 39%). Furthermore, in the study with nadolol, there was a trend towards an increase in mortality with the combination therapy.

The combination of beta-blockers and ISMN has been shown to be superior to sclerotherapy in terms of rebleeding but not survival.⁸⁰ The four trials in which combination therapy was compared with band ligation have shown conflicting results:^{81–84} medical treatment was significantly better than band ligation in preventing rebleeding in one trial,⁸¹ significantly worse in the second,⁸² and not significantly different in the remaining two trials.^{83,84}

Compared with TIPS, the combination therapy is less effective for the prevention of rebleeding, but it is associated with similar mortality, significantly less encephalopathy, and lower costs.^{10,85}

Beta-blockers plus other drugs

Beta-blockers have been used in combination with other drugs in order to achieve a higher reduction in portal pressure. These associations (such as propranolol plus serotonin antagonists, propranolol plus spironolactone, propranolol plus clonidine, and propranolol plus prazosin)⁷² have been tested in animals and in the clinical setting, but have not gained wide usage in clinical practice.

Other drugs

Beside drugs associations, molecules that in themselves combine vasodilator and vasoconstrictor effects have been tested. The most important is *carvedilol*, a non-selective beta-blocker with intrinsic α_1 -adrenergic activity, whose haemodynamic effects mimic those of the combination therapy with beta-blocker plus prazosin.⁷² In a clinical study, carvedilol achieved a higher reduction in portal pressure than propranolol,⁸⁶ but at the expense of marked systemic hypotensive effects that may hamper its use in cirrhotic patients.

Anti-aldosterone diuretics such as *spironolactone* decrease portal pressure by reducing effective plasma volume and splanchnic blood flow.⁸⁷ In a trial comparing the additional effect of spironolactone and nadolol to nadolol alone in primary prophylaxis, similar HVPG reductions, bleeding rates, and 2-year mortality rates were observed.⁸⁸ According to current guidelines, there are insufficient data to recommend the use of the combination of spironolactone plus beta-blockers for primary prophylaxis.⁶

Angiotensin-II-receptor antagonists (i.e. losartan, irbesartan) have been studied in primary prophylaxis because of the results of an earlier trial showing that these drugs markedly reduced portal pressure.⁸⁹ In three subsequent randomised trials losartan and irbesartan did not cause a significant reduction in portal pressure,^{90–92} but caused marked arterial hypotension and impairment of renal function. In a fourth trial the effect of losartan on portal pressure was similar to that of propranolol.⁹³ Currently, angiotensin-receptor antagonists are not recommended in the setting of portal hypertension.

Other pharmacological agents (e.g. nitric oxide synthase inhibitors, statins, selective hepatic nitric oxide donors, molsidomine) capable of reducing portal pressure must be adequately tested before they can be proposed for clinical use.⁶

Practice points

- In suspected variceal bleeding, vasoactive drugs should be started as soon as possible and should be maintained for 2–5 days.
- Drug therapy should be chosen according to local resources. Terlipressin, somatostatin and octreotide should be used; vasopressin plus transdermal nitroglycerin is a tolerable option when no other drug is available.
- Antibiotic prophylaxis in patients with variceal bleeding is mandatory and should be instituted from admission.

- Patients with high-risk varices (i.e. medium and large oesophageal varices or small varices with red wale signs or of Child class C) should undergo primary prophylaxis for oesophageal variceal bleeding.
- Non-selective beta-blockers are the drugs of choice for both primary and secondary prophylaxis.
- Secondary prophylaxis should start as soon as possible after the discontinuation of the vasoactive drug used for the treatment of the bleeding episode.

Research agenda

- Other pharmacological agents capable of reducing portal pressure either in the setting of acute variceal bleeding or in primary/secondary prophylaxis should be evaluated.
- The optimal duration of vasoactive treatment in acute variceal bleeding should be determined.

SUMMARY

Variceal bleeding is one of the most severe complications of portal hypertension correlated with liver cirrhosis, with a 6-week mortality rate of 10–20%. Primary prophylaxis is mandatory in patients with cirrhosis and high-risk oesophageal varices, and when bleeding occurs every effort should be made to arrest the haemorrhage and prevent further bleeding episodes. In acute variceal bleeding, vasoactive drugs that lower portal pressure should be started even before endoscopy, and should be maintained for up to 5 days. The optimal duration of therapy with vasoactive drugs has not been clarified. The choice of vasoactive drug should be made according to local resources, but terlipressin should be the first choice, followed by somatostatin and octreotide, with vasopressin plus transdermal nitroglycerin as last choice by if no other drug is available. Since most variceal bleeders have a bacterial infection on admission, or become infected during the first week thereafter, antibiotic prophylaxis is mandatory. Cephalosporins appear to be the drugs of choice. In primary and secondary prophylaxis, beta-blockers are the mainstay of medical therapy because of their ability to lower portal pressure. However, a proportion of patients have contraindications to these drugs, and adverse events causing discontinuation of therapy do occur. In addition, adequate protection from bleeding can be achieved in only a proportion of patients. The search for better drugs should therefore continue. Beta-blockers, band ligation, or both should be used for the prevention of recurrent bleeding. In this setting, assessment of haemodynamic response to drug therapy provides prognostic information about rebleeding.

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