Published in final edited form as:
Gastroenterol Clin North Am. 2010 September ; 39(3): 681–695. doi:10.1016/j.gtc.2010.08.015.

Portal Hypertension

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Abstract

Portal hypertension is an increase in pressure in the portal vein and its tributaries. It is defined as a portal pressure gradient (the difference in pressure between the portal vein and the hepatic veins) greater than 5 mm Hg. Although this gradient defines portal hypertension, a gradient of 10 mm Hg or greater defines clinically significant portal hypertension, because this pressure gradient predicts the development of varices,[1] decompensation of cirrhosis,[2,3] and hepatocellular carcinoma.[4] The most direct consequence of portal hypertension is the development of gastroesophageal varices that may rupture and lead to the development of variceal hemorrhage. This article reviews the pathophysiologic bases of the different pharmacologic treatments for portal hypertension in patients with cirrhosis and places them in the context of the natural history of varices and variceal hemorrhage.

Keywords

Portal hypertension; Cirrhosis; Varices; Variceal hemorrhage; Hepatic venous pressure gradient; Portal pressure

Pathophysiology of Portal Hypertension

Anatomically, the portal vein is formed by the union of the superior mesenteric vein and the splenic vein. The mesenteric vein collects blood from the splanchnic circulation. Thus, portal venous inflow is determined by the state of constriction or dilatation of splanchnic arterioles.

The initial mechanism in the genesis of portal hypertension is an increase in vascular resistance that can occur at any level within the portal venous system. Portal hypertension is therefore classified as prehepatic (portal or splenic vein thrombosis); intrahepatic (cirrhosis), and posthepatic (Budd-Chiari syndrome). The most common cause of portal hypertension is cirrhosis. In cirrhosis, the increased resistance is mostly caused by hepatic architectural distortion (fibrosis and regenerative nodules) but about a third of the increased resistance is caused by intrahepatic vasoconstriction, amenable to vasodilators.[5] This is caused by the activation of stellate cells with active contraction of myofibroblasts and vascular smooth muscle cells in portal venules,[6] which in turn is caused by increased endogenous vasoconstrictors, such as endothelin, and reduced nitric oxide bioavailability.[7,8]

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Portosystemic collaterals develop as a consequence of the high pressure in the portal vein and ameliorate the increased resistance. However, even when portal blood flow is entirely diverted through collaterals, portal hypertension persists because of a concomitant increase in portal venous inflow, which in turn is caused by splanchnic vasodilatation,[9] mostly mediated by an increase in nitric oxide.[7]

The most important collaterals are those that constitute gastroesophageal varices. Although the formation of collaterals had been assumed to be the result of dilatation of preexisting vascular channels, recent studies have implicated a process of neoangiogenesis. This process has been shown to contribute not only to portal-systemic collaterals but also to increased splanchnic blood flow (arteriolar-capillary network).[10]

Measurement of Portal Pressure

Measurement of portal pressure in patients with portal hypertension is important in the evaluation of the efficacy of different portal-hypotensive pharmacologic therapies.

The most used method to assess portal pressure is the catheterization of the hepatic vein with determination, via a balloon catheter, of the hepatic vein pressure gradient (HVPG), which is the difference between the wedged (or occluded) hepatic venous pressure and the free hepatic venous pressure.[11] Normal HVPG is 3 to 5 mm Hg. In patients with compensated cirrhosis, an HVPG greater than or equal to 10 mm Hg predicts the development, not only of varices, but of complications that mark the transition from compensated to decompensated cirrhosis.1,2

Changes in HVPG during pharmacologic therapy have also been shown to be predictive of clinical outcomes. In patients with a history of variceal hemorrhage, a decrease in HVPG to less than 12 mm Hg or a decrease greater than 20% from baseline significantly reduces the risk of recurrent hemorrhage, ascites, encephalopathy, and death.12–14 In patients with compensated cirrhosis, even lower reductions in HVPG (>10% from baseline) have been associated with a reduction in the development of varices,1 first variceal hemorrhage,15 and ascites.15 Recent studies show that separate HVPG procedures to assess response to therapy can be obviated by assessing the acute hemodynamic response to intravenous (IV) propranolol (0.15 mg/kg) during a single procedure.15,16

Pharmacologic therapies should thus be ideally tailored to a target decrease in HVPG. Even though the HVPG procedure is simple and safe, its use is not widespread in the United States because it is invasive and because it has not been appropriately standardized.[17]

Pharmacologic Therapy for Portal Hypertension

Drugs that Act by Reducing Portal Flow

Increased portal venous inflow secondary to splanchnic vasodilatation can be corrected pharmacologically through the use of splanchnic vasoconstrictors. These drugs have been shown to decrease portal pressure in experimental and proof-of-concept hemodynamic studies. Vasoconstrictors effective in the chronic treatment of portal hypertension are nonselective β-adrenergic blockers (NSBB) (Table 1). Vasoconstrictors effective in the acute therapy for variceal hemorrhage are vasopressin and somatostatin and their respective synthetic analogues.

Recent studies in a rat model of prehepatic portal hypertension show that vascular endothelial growth factor blockade decreases portal pressure and concomitantly decreases the development of portosystemic collaterals and the hyperdynamic splanchnic circulatory

state.[18] Although no clinical studies are available, inhibition of angiogenesis may be a future target in the treatment of portal hypertension.

NSBB—These are the most widely evaluated and used drugs in the chronic treatment of portal hypertension (ie, in the prevention of variceal hemorrhage). Their mechanism of action is through both β-1 and β-2 blockade. Although β-1 blockade decreases portal flow through a decrease in cardiac output, β-2 blockade decreases portal flow through splanchnic vasoconstriction via unopposed α-adrenergic activity. As expected, NSBB (propranolol, nadolol, timolol) decrease HVPG to a greater extent compared with selective β-1 adrenergic blockers (atenolol, metoprolol) and are the preferred therapy.[19] The lack of correlation between the postpropranolol decrease in heart rate (β-1 effect) and the decrease in HVPG is further evidence that the β-2 effect plays a more important role.20

The most widely used NSBB are propranolol and nadolol. NSBB use is associated with a median reduction in HVPG of approximately 15%,[21] with 37% of the patients being hemodynamic responders (ie, achieving a reduction in HVPG to less than 12 mm Hg and/or a reduction >20% from baseline) (see Table 1).[13,15,22–37] The reduction in portal pressure induced by NSBB is lower than the β-blocker–induced reduction in portal blood inflow.38 This is because of a concomitant increase in collateral resistance secondary to a decrease in collateral flow and diameter.[38] This effect represents an added benefit of NSBB (not assessable by a reduction in portal pressure), which can explain their efficacy in randomized clinical trials (RCT) with only a modest portal pressure–reducing effect.

Although the recommended dosing of propranolol for the treatment of arterial hypertension in patients who are not cirrhotic is 4 times a day, in cirrhosis, because of a slower drug metabolism, twice a day dosing is sufficient. The starting dosage is 20 to 40 mg orally twice a day and this is gradually increased to a maximum of 160 mg twice a day. The lower starting dose (20 mg) is reserved for patients with a baseline low mean arterial pressure. In many RCT, the dose was adjusted to obtain a 25% decrease in heart rate; however, because a change in heart rate is not predictive of a decrease in portal pressure,[20] recent guidelines have recommended the adjustment of NSBB to the highest tolerated dose or to a heart rate of 50 to 55 beats/min.39 Nadolol has a longer half-life and can be used once daily, which may increase patient adherence. The initial dosage is 20 to 40 mg orally once daily, and this is adjusted to a maximum of 240 mg once daily in the same manner as described for propranolol. Nadolol may have fewer side effects than propranolol because it does not cross the blood-brain barrier, although head-to-head comparisons have not been performed.

The most frequent side effects related to NSBB reported in cirrhosis are lightheadedness, fatigue, and shortness of breath. Some of them disappear with time or after dose reduction. In clinical trials, side effects have led to the discontinuation of NSBB in approximately 15% of the patients. In a study comparing patient preferences between NSBB and band ligation (an endoscopic therapy), more than half the patients favored band ligation because of NSBB-related side effects.[40] In addition, up to 15% of the patients may have relative (sinus bradycardia, insulin-dependent diabetes) or absolute contraindications to NSBB, such as obstructive pulmonary disease, heart failure, aortic valve disease, second- and third-degree atrioventricular heart block, and peripheral arterial insufficiency.

Vasopressin and analogues—Vasopressin is the most potent splanchnic vasoconstrictor available, but it has been abandoned in the therapy for portal hypertension because of its numerous side effects. It is an endogenous nanopeptide that causes vasoconstriction (splanchnic and systemic) by acting on the V1 receptors within the arterial smooth muscle. Having a short half-life, vasopressin can only be administered as a continuous intravenous infusion, and therefore it is only used in an acute setting (ie, in the

management of acute variceal hemorrhage). Its continuous intravenous infusion is usually initiated at a dosage of 0.4 units/min that can be titrated up, based on the therapeutic response (cessation of bleeding) and, depending on the development of side effects, to a maximum of 0.8 to 1.0 units/min. Side effects can lead to drug withdrawal in up to 25% of patients, and can include arterial hypertension, myocardial ischemia, arrhythmias, ischemic abdominal pain, and limb gangrene.[41] Vasopressin should be used in combination with nitrates (see later discussion) to reduce side effects.

Terlipressin is a synthetic vasopressin analogue that releases its active form, lysine vasopressin, after 3 glycyl residues are cleaved by endogenous proteases. Because this is a gradual process, the hormone is released slowly, in a sustained manner, minimizing the rate and severity of side effects. It has a longer half-life than vasopressin and can thus be administered in intravenous boluses. Terlipressin is administered by intravenous boluses at a dosage of 2 mg IV every 4 hours for the first 48 hours and can be maintained for up to 5 days at a dosage of 1 mg IV every 4 hours to prevent early rebleeding.[42] The most common side effect of terlipressin is abdominal pain. Serious side effects, including peripheral and myocardial ischemia, occur in less than 3% patients.[42] Although terlipressin is preferred to vasopressin, it is currently not approved for use in the United States.

Somatostatin and analogues—Somatostatin and analogues (octreotide, vapreotide) cause splanchnic vasoconstriction not only through an inhibitory effect on the release of the vasodilator glucagon but also by a local mesenteric vasoconstrictive effect.[43] Intravenous boluses of somatostatin and octreotide cause significant transient reductions in portal pressure.44,45 However, although a mild reduction in portal pressure is maintained with the continuous infusion of somatostatin,44 the continuous infusion of octreotide does not result in a sustained reduction in portal pressure.45 One of the most important effects of somatostatin and analogues is a blunting of postprandial hyperemia,[46] which is useful in the setting of gastrointestinal bleeding when blood has the same effect as food. These drugs have a short half-life and are used in a continuous intravenous infusion in the setting of acute variceal hemorrhage. However, a recent placebo-controlled small study in 18 patients showed that the monthly subcutaneous administration of long-acting octreotide was associated with a significant (26%) decrease in HVPG at 3 months,[47] suggesting that this drug could be used in the chronic treatment of portal hypertension.

Somatostatin is initiated with a single intravenous bolus dose of 250 μg IV followed by a continuous intravenous infusion of 250 μg/h, which is maintained for 5 days. Higher dosages of somatostatin (500 μg/h) have been shown to further decrease HVPG and lower mortality in a subset of patients with bleeding at endoscopy that is difficult to control.[48] Both octreotide and vapreotide are used at an initial bolus of 50 μg intravenously followed by a continuous infusion of 50 μg per hour. As with somatostatin, therapy can be maintained for 2 to 5 days.

The absence of major side effects of somatostatin and analogues represents an important advantage compared with other vasoconstrictive agents. Minor side effects include nausea, vomiting, and hyperglycemia and can occur in up to 30% of patients.[48,49] Octreotide is the only vasoconstrictor available in the United States for control of acute variceal hemorrhage, although its use in this setting is off-label.

Drugs that Act by Reducing Resistance to Blood Flow

Vasodilators such as nitrates, prazosin, clonidine, angiotensin receptor blockers (ARBs) and angiotensin-converting enzyme inhibitors have resulted in significant reductions in HVPG.[21] In studies in which these agents have been administered for 7 days or more, the median reduction in HVPG is around 17%.21 However, these drugs not only act on the intrahepatic

circulation, they also exert a vasodilatory effect on the systemic circulation, leading to arterial hypotension that is frequently symptomatic.[50,51] In several of these studies, a direct correlation has been shown between the decrease in arterial pressure and the decrease in HVPG.[50] This suggests that vasodilators decrease portal pressure mainly through a decrease in portal blood flow secondary to reflex splanchnic vasoconstriction that occurs in response to arterial hypotension. Worsening vasodilatation can also lead to a further decrease in effective arterial blood volume, with consequent aggravation of sodium retention and renal vasoconstriction. Chronic administration of prazosin has been associated with the development of salt retention, ascites, and edema,[52,53] and administration of the ARB irbesartan has been associated with a decrease in creatinine clearance.[51] Furthermore, a trial of isosorbide mononitrate (ISMN) versus placebo in the prevention of first variceal hemorrhage showed a tendency for higher rates of bleeding and late mortality in patients randomized to ISMN.[54]

The use of vasodilators alone is currently not recommended. Nevertheless, a recent meta-analysis of individual patient data from studies that used ARBs and angiotensin-converting enzyme inhibitors shows that, in patients with Child A cirrhosis, these drugs reduce portal pressure with minimal side effects; whereas deleterious effects are mostly observed in patients with decompensated cirrhosis.[55] Future studies should determine the potential of these drugs as alternatives or adjuncts to NSBB in patients with compensated cirrhosis.

Other therapies have been shown, in experimental animals, to improve nitric oxide bioavailability in the liver and to reduce portal pressure. Of these, 2 have been translated to proof-of-concept hemodynamic studies in humans with cirrhosis. One of them is NCX-1000, a nitric oxide-releasing derivative of ursodeoxycholic acid that was found to have no effect on HVPG.[56] The other is simvastatin, which leads to the post-translational upregulation of endothelial nitric oxide synthase. In a small placebo-controlled study of 20 patients, simvastatin was associated with a significant reduction in HVPG, with 32% of hemodynamic responders.[57] Simvastatin was not associated with changes in blood flow, suggesting that it decreased hepatic vascular resistance by acting as a hepatic vasodilator.

Drugs that Act by Reducing Flow and Resistance

The combination of intrahepatic vasodilators and splanchnic vasoconstrictors results in an additive portal pressure–reducing effect (see Table 1). This effect was first shown in a hemodynamic study performed in patients with cirrhosis in whom the addition of nitroglycerin to vasopressin led to a further reduction in HVPG, not associated with a further decrease in portal flow[58] This observation suggested that the additional reduction in HVPG induced by nitrates resulted from a decrease in intrahepatic resistance.

This effect has also been observed when ISMN or prazosin are combined with NSBB, with an HVPG reduction of around 20% to 24% with combination therapy, compared with 15% with NSBB alone.[21,59] The rate of HVPG responders with NSBB+ISMN is 44%, [13,23,25,29–35,37] a rate that is significantly higher than that observed with NSBB alone (37%) (see Table 1). However, these combinations are associated with more side effects, specifically fluid retention and/or symptomatic hypotension.

Carvedilol is a nonselective β-blocker with weak anti-α_1 adrenergic (vasodilator) activity and therefore acts as a combination of NSBB and vasodilator. When used at a dosage of 25 to 30 mg/d, it has been associated with a significant reduction in HVPG (16%–19%), with 46% being HVPG responders (Table 2), which is similar to the response rate of a combination of NSBB and ISMN.[24,60,61] However, as for other combinations of vasoconstrictors and vasodilators, carvedilol at this dosage has been associated with a decrease in mean arterial pressure, fluid retention, and a high rate of patient withdrawal.[60,62]

Natural History of Varices and Variceal Hemorrhage

Gastroesophageal varices are present in approximately 50% of patients with cirrhosis, with a rate dependent on the severity of liver disease (42% of patients who are Child A vs 72% in Child B/C).63 Varices develop at a rate of 7% to 8% per year1 and the transition from small to large varices occurs at the same rate, more commonly among patients with Child B/C cirrhosis.64 Variceal hemorrhage occurs at a rate of 5% to 15% per year depending on the presence of risk factors, with variceal size, red wale marks on varices, and advanced liver disease (Child B or C) identifying patients at a high risk of variceal hemorrhage.65 Six-week mortality with each episode of variceal hemorrhage is still around 15% to 25% and also depends on the severity of liver disease.66,67 Late rebleeding occurs in approximately 60% to 70% of untreated patients, usually within 1 to 2 years of the initial hemorrhage.68

The pharmacologic therapy for portal hypertension has been evaluated at each of the stages in the natural history of varices/variceal hemorrhage.

Preprimary Prophylaxis (Prevention of Varices)

A large multicenter RCT of timolol, NSBB, versus placebo performed in patients with cirrhosis and portal hypertension but without varices, showed a similar rate of development of varices in both treatment groups, with a higher rate of adverse events in the timolol group. [1] Therefore, NSBB are not recommended for the prevention of varices.

Primary Prophylaxis (Prevention of First Variceal Hemorrhage)

Patients with medium/large varices are at a high risk of variceal hemorrhage and are the main subgroup of patients with cirrhosis without a previous episode of hemorrhage in whom prophylactic therapy is recommended. In this setting, NSBB have been shown to significantly reduce the risk of first variceal hemorrhage, from 24% to 15% in a median follow-up of 2 years.[41] Adding ISMN does not have an added beneficial effect in this setting, as shown in a double-blind, placebo-controlled trial.[69]

Although meta-analyses of studies comparing NSBB versus endoscopic variceal ligation (EVL) have shown a benefit for EVL, the evidence is weak, because subgroup meta-analysis of trials with adequate design and an acceptable sample size show no differences in the rate of first variceal hemorrhage between groups.70,71 As these therapies seem equal, choice should depend on local resources, patient preferences, and co-morbidities. It is reasonable to start with NSBB (which should be administered indefinitely) because they have other advantages, such as prevention of bleeding from other portal hypertension sources (portal hypertensive gastropathy and gastric varices) and prevention of ascites (Table 3).[15] In patients intolerant of, or with contraindications to, NSBB, EVL should be performed.

A recent single-center RCT showed a significantly lower rate of first variceal hemorrhage with carvedilol compared with EVL (10% vs 23%),[72] without differences in mortality. The dosage of carvedilol used (12.5 mg/d) was lower than that associated with an HVPG reduction (see Table 2) and with complications. Larger studies are necessary to evaluate its efficacy compared with NSBB and to determine its mechanism of action.

Patients with small varices with red signs or with advanced liver disease (Child C) are at a similar risk of first hemorrhage compared to those with moderate/large varices and should be treated with NSBB, because banding may be technically more challenging in these patients (see Table 3).

Acute Variceal Hemorrhage

A meta-analysis of RCTs for the specific management of acute variceal hemorrhage shows that a combination of endoscopic and pharmacologic therapy is significantly better than endoscopic therapy alone.[73] There are no apparent differences among vasoconstrictors. Notably, the most frequent pharmacologic agent used in these studies was octreotide, the only vasoconstrictor currently available in the United States. Terlipressin is the only vasoconstrictor that has been shown to improve survival[74] and, if confirmed in RCTs using current standard therapy, it would be the preferred vasoconstrictor. Vasoconstrictor therapy should be initiated as soon as possible, even before diagnostic endoscopy, because this has been shown to improve outcomes (Table 4).[75] General recommendations are to maintain vasoconstrictors for 3 to 5 days because this is the time period of highest risk for rebleeding, but this has not been well validated.

Another form of pharmacologic therapy recommended in patients with variceal hemorrhage is antibiotic prophylaxis. In a meta-analysis of 5 trials, antibiotics were associated not only with a decreased risk of infection but also a decreased mortality.[76] Their effect could be related in part to a decrease in the rate of early rebleeding.[77] The preferred antibiotic is oral norfloxacin at a dosage of 400 mg twice a day for 7 days, although IV ceftriaxone at a dosage of 1 g/d is preferable in patients with severe liver disease, particularly in settings of high prevalence of quinolone-resistant organisms.[78]

Other pharmacologic therapies, such as recombinant factor VIIa, have not been shown in RCTs to be of benefit in the management of acute variceal hemorrhage.[79,80]

Secondary Prophylaxis (Prevention of Recurrent Variceal Hemorrhage)

A recent meta-analysis shows that the combination of endoscopic plus pharmacologic therapy reduces overall gastrointestinal and recurrent variceal hemorrhage in patients with cirrhosis who have recovered from an episode of variceal hemorrhage, more than either therapy alone.[81] However, the long-term (82-month) follow-up of one of these studies showed that combination pharmacologic therapy (NSBB plus ISMN) is associated with a better survival compared with EVL.[82] However, this trial did not explore a combination of EVL+NSBB. A review of data obtained from published secondary prophylaxis randomized trials comparing EVL alone versus EVL+NSBB,[83,84] EVL alone versus NSBB+ISMN,[31,32,85,86] as well as 3 recent studies of EVL plus combination pharmacologic therapy (NSBB+ISMN) versus combination pharmacologic therapy[34,87] or versus EVL alone[88] shows that, at equivalent follow-up times, the combination of EVL plus drugs is associated with the lowest rates of recurrent variceal hemorrhage (14%), overall gastrointestinal hemorrhage (23%), and death (17%). Therefore, the current standard of care for secondary prevention is a combination of EVL and NSBB. In patients who are not candidates or who refuse EVL, the combination of NSBB plus ISMN should be attempted, although this combination is poorly tolerated (Table 5).

As mentioned earlier, the lowest rates of recurrent variceal hemorrhage (approximately 10%) are observed in patients who have a hemodynamic response to pharmacologic therapy, defined as a decrease in HVPG to less than 12 mm Hg or a decrease of greater than 20% from baseline levels.[14,68] The more rational approach would be to guide therapy based on the hemodynamic response. A recent RCT compared patients with HVPG-guided pharmacotherapy (nadolol plus ISMN or prazosin) with patients on nadolol+EVL.[35] As expected, patients in the HVPG-guided pharmacotherapy arm showed higher rates of hemodynamic response; however, the rates of recurrent hemorrhage were similar between groups (26% vs 23%). Additional data from larger studies are needed to more clearly define the role of HVPG in the secondary prophylaxis of variceal hemorrhage.

References

1. Groszmann RJ, Garcia-Tsao G, Bosch J, et al. Beta-blockers to prevent gastroesophageal varices in patients with cirrhosis. N Engl J Med 2005;353:2254–61. [PubMed: 16306522]
2. Ripoll C, Groszmann R, Garcia-Tsao G, et al. Hepatic venous pressure gradient predicts clinical decompensation in patients with compensated cirrhosis. Gastroenterology 2007;133:481–8. [PubMed: 17681169]
3. Bruix J, Castells A, Bosch J, et al. Surgical resection of hepatocellular carcinoma in cirrhotic patients. Prognostic value of preoperative portal pressure. Gastroenterology 1996;111:1018–22. [PubMed: 8831597]
4. Ripoll C, Groszmann RJ, Garcia-Tsao G, et al. Hepatic venous pressure gradient predicts development of hepatocellular carcinoma independently of severity of cirrhosis. J Hepatol 2009;50:923–8. [PubMed: 19303163]
5. Bhathal PS, Grossman HJ. Reduction of the increased portal vascular resistance of the isolated perfused cirrhotic rat liver by vasodilators. J Hepatol 1985;1:325–37. [PubMed: 4056346]
6. Pinzani M, Gentilini P. Biology of hepatic stellate cells and their possible relevance in the pathogenesis of portal hypertension in cirrhosis. Semin Liver Dis 1999;19:397–410. [PubMed: 10643625]
7. Wiest R, Groszmann RJ. The paradox of nitric oxide in cirrhosis and portal hypertension: too much, not enough. Hepatology 2002;35:478–91. [PubMed: 11826425]
8. Iwakiri Y, Groszmann RJ. Vascular endothelial dysfunction in cirrhosis. J Hepatol 2007;46:927–34. [PubMed: 17391799]
9. Sikuler E, Groszmann RJ. Interaction of flow and resistance in maintenance of portal hypertension in a rat model. Am J Physiol 1986;250:G205–12. [PubMed: 3953799]
10. Fernandez M, Vizzutti F, Garcia-Pagan JC, et al. Anti-VEGF receptor-2 monoclonal antibody prevents portal-systemic collateral vessel formation in portal hypertensive mice. Gastroenterology 2004;126:886–94. [PubMed: 14988842]
11. Groszmann RJ, Wongcharatrawee S. The hepatic venous pressure gradient: anything worth doing should be done right. Hepatology 2004;39:280–3. [PubMed: 14767976]
12. Feu F, Bordas JM, Luca A, et al. Reduction of variceal pressure by propranolol: comparison of the effects on portal pressure and azygos blood flow in patients with cirrhosis. Hepatology 1993;18:1082–9. [PubMed: 8225212]
13. Abraldes JG, Tarantino I, Turnes J, et al. Hemodynamic response to pharmacological treatment of portal hypertension and long-term prognosis of cirrhosis. Hepatology 2003;37:902–8. [PubMed: 12668985]
14. D'Amico G, Garcia-Pagan JC, Luca A, et al. HVPG reduction and prevention of variceal bleeding in cirrhosis: a systematic review. Gastroenterology 2006;131:1611–24. [PubMed: 17101332]
15. Villanueva C, Aracil C, Colomo A, et al. Acute hemodynamic response to beta-blockers and prediction of long-term outcome in primary prophylaxis of variceal bleeding. Gastroenterology 2009;137:119–28. [PubMed: 19344721]
16. La Mura V, Abraldes JG, Raffa S, et al. Prognostic value of acute hemodynamic response to i.v. propranolol in patients with cirrhosis and portal hypertension. J Hepatol 2009;51:279–87. [PubMed: 19501930]
17. Garcia-Tsao G, Bosch J, Groszmann RJ. Portal hypertension and variceal bleeding–unresolved issues. Summary of an American Association for the Study of Liver Diseases and European Association for the Study of the Liver single-topic conference. Hepatology 2008;47:1764–72. [PubMed: 18435460]
18. Fernandez M, Mejias M, Angermayr B, et al. Inhibition of VEGF receptor-2 decreases the development of hyperdynamic splanchnic circulation and portal-systemic collateral vessels in portal hypertensive rats. J Hepatol 2005;43:98–103. [PubMed: 15893841]
19. Mills PR, Rae AP, Farah DA, et al. Comparison of three adrenoceptor blocking agents in patients with cirrhosis and portal hypertension. Gut 1984;25:73–8. [PubMed: 6360815]
20. Garcia-Tsao G, Grace N, Groszmann RJ, et al. Short term effects of propranolol on portal venous pressure. Hepatology 1986;6:101–6. [PubMed: 3943775]

21. Garcia-Tsao G. Current management of the complications of cirrhosis and portal hypertension: varices and variceal hemorrhage, ascites and spontaneous bacterial peritonitis. Gastroenterology 2001;120:726–48. [PubMed: 11179247]
22. Groszmann RJ, Bosch J, Grace N, et al. Hemodynamic events in a prospective randomized trial of propranolol vs placebo in the prevention of the first variceal hemorrhage. Gastroenterology 1990;99(5):1401–7. [PubMed: 2210246]
23. Merkel C, Marin R, Sacerdoti D, et al. Long-term results of a clinical trial of nadolol with or without isosorbide mononitrate for primary prophylaxis of variceal bleeding in cirrhosis. Hepatology 2000;31:324–9. [PubMed: 10655253]
24. Banares R, Moitinho E, Matilla A, et al. Randomized comparison of long-term carvedilol and propranolol administration in the treatment of portal hypertension in cirrhosis. Hepatology 2002;36:1367–73. [PubMed: 12447861]
25. Turnes J, Garcia-Pagan JC, Abraldes JG, et al. Pharmacological reduction of portal pressure and long-term risk of first variceal bleeding in patients with cirrhosis. Am J Gastroenterol 2006;101:506–12. [PubMed: 16542287]
26. Sharma P, Kumar A, Sharma BC, et al. Early identification of haemodynamic response to pharmacotherapy is essential for primary prophylaxis of variceal bleeding in patients with 'high-risk' varices. Aliment Pharmacol Ther 2009;30:48–60. [PubMed: 19392862]
27. Merkel C, Bolognesi M, Berzigotti A, et al. Clinical significance of worsening portal hypertension during long-term medical treatment in patients with cirrhosis who had been classified as early good-responders on haemodynamic criteria. J Hepatol 2010;52:45–53. [PubMed: 19914730]
28. Feu F, Garcia-Pagan JC, Bosch J, et al. Relation between portal pressure response to pharmacotherapy and risk of recurrent variceal haemorrhage in patients with cirrhosis. Lancet 1995;346:1056–9. [PubMed: 7564785]
29. Villanueva C, Balanzo J, Novella MT, et al. Nadolol plus isosorbide mononitrate compared with sclerotherapy for the prevention of variceal rebleeding. N Engl J Med 1996;334:1624–9. [PubMed: 8628357]
30. McCormick PA, Patch D, Greenslade L, et al. Clinical vs hemodynamic response to drugs in portal hypertension. J Hepatol 1998;28:1015–9. [PubMed: 9672178]
31. Villanueva C, Minana J, Ortiz J, et al. Endoscopic ligation compared with combined treatment with nadolol and isosorbide mononitrate to prevent recurrent variceal bleeding. N Engl J Med 2001;345:647–55. [PubMed: 11547718]
32. Patch D, Goulis J, Gerunda G, et al. A randomized controlled trial of medical therapy versus endoscopic ligation for the prevention of variceal rebleeding in patients with cirrhosis. Gastroenterology 2002;123:1013–9. [PubMed: 12360462]
33. Villanueva C, Lopez-Balaguer JM, Aracil C, et al. Maintenance of hemodynamic response to treatment for portal hypertension and influence on complications of cirrhosis. J Hepatol 2004;40:757–65. [PubMed: 15094222]
34. Garcia-Pagan JC, Villanueva C, Albillos A, et al. Nadolol plus isosorbide mononitrate alone or associated with band ligation in the prevention of variceal rebleeding: a multicenter randomized controlled trial. Gut 2009;58:1144–50. [PubMed: 19218249]
35. Villanueva C, Aracil C, Colomo A, et al. Clinical trial: a randomized controlled study on prevention of variceal rebleeding comparing nadolol + ligation vs. hepatic venous pressure gradient-guided pharmacological therapy. Aliment Pharmacol Ther 2009;29:397–408. [PubMed: 19006538]
36. Escorsell A, Bordas JM, Castaneda B, et al. Predictive value of the variceal pressure response to continued pharmacological therapy in patients with cirrhosis and portal hypertension. Hepatology 2000;31:1061–7. [PubMed: 10796880]
37. Bureau C, Peron JM, Alric L, et al. "A La Carte" treatment of portal hypertension: adapting medical therapy to hemodynamic response for the prevention of bleeding. Hepatology 2002;36:1361–6. [PubMed: 12447860]
38. Kroeger RJ, Groszmann RJ. Increased portal venous resistance hinders portal pressure reduction during the administration of beta-adrenergic blocking agents in a portal hypertensive model. Hepatology 1985;5:97–101. [PubMed: 2857150]

39. Garcia-Tsao G, Sanyal AJ, Grace ND, et al. Prevention and management of gastroesophageal varices and variceal hemorrhage in cirrhosis. Hepatology 2007;46:922–38. [PubMed: 17879356]
40. Longacre AV, Imaeda A, Garcia-Tsao G, et al. A pilot project examining the predicted preferences of patients and physicians in the primary prophylaxis of variceal hemorrhage. Hepatology 2008;47:169–76. [PubMed: 17935182]
41. D'Amico G, Pagliaro L, Bosch J. Pharmacological treatment of portal hypertension: an evidence-based approach. Semin Liver Dis 1999;19:475–505. [PubMed: 10643630]
42. Escorsell A, Ruiz del Arbol L, Planas R, et al. Multicenter randomized controlled trial of terlipressin versus sclerotherapy in the treatment of acute variceal bleeding: the TEST study. Hepatology 2000;32:471–6. [PubMed: 10960437]
43. Wiest R, Tsai MH, Groszmann RJ. Octreotide potentiates PKC-dependent vasoconstrictors in portal-hypertensive and control rats. Gastroenterology 2000;120:975–83. [PubMed: 11231951]
44. Cirera I, Feu F, Luca A, et al. Effects of bolus injections and continuous infusions of somatostatin and placebo in patients with cirrhosis and portal hypertension. A double-blind hemodynamic investigation. Hepatology 1995;22:106–11. [PubMed: 7601400]
45. Escorsell A, Bandi JC, Andreu V, et al. Desensitization to the effects of intravenous octreotide in cirrhotic patients with portal hypertension. Gastroenterology 2001;120:161–9. [PubMed: 11208725]
46. Buonamico P, Sabba C, Garcia-Tsao G, et al. Octreotide blunts post-prandial splanchnic hyperemia in cirrhotic patients: a double-blind randomized echo-Doppler study. Hepatology 1995;21:134–9. [PubMed: 7806146]
47. Spahr L, Giostra E, Frossard JL, et al. A 3-month course of long-acting repeatable octreotide (sandostatin LAR) improves portal hypertension in patients with cirrhosis: a randomized controlled study. Am J Gastroenterol 2007;102:1397–405. [PubMed: 17488248]
48. Moitinho E, Planas R, Banares R, et al. Multicenter randomized controlled trial comparing different schedules of somatostatin in the treatment of acute variceal bleeding. J Hepatol 2001;35:712–8. [PubMed: 11738097]
49. Escorsell A, Bordas JM, Ruiz-del-Arbol L, et al. Randomized controlled trial of sclerotherapy versus somatostatin infusion in the prevention of early rebleeding following acute variceal hemorrhage in patients with cirrhosis. J Hepatol 1998;29:779–88. [PubMed: 9833916]
50. Blei AT, Garcia-Tsao G, Groszmann RJ, et al. Hemodynamic evaluation of isosorbide dinitrate in alcoholic cirrhosis: pharmacokinetic-hemodynamic interactions. Gastroenterology 1987;93:576–83. [PubMed: 3301517]
51. Schepke M, Werner E, Biecker E, et al. Hemodynamic effects of the angiotensin II receptor antagonist irbesartan in patients with cirrhosis and portal hypertension. Gastroenterology 2001;121:389–95. [PubMed: 11487548]
52. Albillos A, Lledo JL, Banares R, et al. Hemodynamic effects of a-adrenergic blockade with prazosin in cirrhotic patients with portal hypertension. Hepatology 1994;20:611–7. [PubMed: 7915703]
53. Albillos A, Lledo JL, Rossi I, et al. Continuous prazosin administration in cirrhotic patients: effects on portal hemodynamics and on liver and renal function. Gastroenterology 1995;109:1257–65. [PubMed: 7557093]
54. Garcia-Pagan JC, Villanueva C, Vila MC, et al. Isosorbide mononitrate in the prevention of first variceal bleed in patients who cannot receive beta-blockers. Gastroenterology 2001;121:908–14. [PubMed: 11606504]
55. Tandon P, Abraldes JG, Berzigotti A, et al. Renin-angiotensin-aldosterone inhibitors in the reduction of portal pressure: a systematic review and meta-analysis. J Hepatol 2010;53:273–82. [PubMed: 20570385]
56. Berzigotti A, Bellot P, De Gottardi A, et al. NCX-1000, a nitric oxide-releasing derivative of UDCA, does not decrease portal pressure in patients with cirrhosis: results of a randomized, double-blind, dose-escalating study. Am J Gastroenterol 2010;105:1094–101. [PubMed: 19920806]

57. Abraldes JG, Albillos A, Banares R, et al. Simvastatin lowers portal pressure in patients with cirrhosis and portal hypertension: a randomized controlled trial. Gastroenterology 2009;136:1651–8. [PubMed: 19208350]
58. Groszmann RJ, Kravetz D, Bosch J, et al. Nitroglycerin improves the hemodynamic response to vasopressin in portal hypertension. Hepatology 1982;2:757–62. [PubMed: 6815044]
59. Albillos A, Garcia-Pagan JC, Iborra J, et al. Propranolol plus prazosin compared with propranolol plus isosorbide-5-mononitrate in the treatment of portal hypertension. Gastroenterology 1998;115:116–23. [PubMed: 9649466]
60. Stanley AJ, Therapondos G, Helmy A, et al. Acute and chronic haemodynamic and renal effects of carvedilol in patients with cirrhosis. J Hepatol 1999;30:479–84. [PubMed: 10190732]
61. Bruha R, Vitek L, Petrtyl J, et al. Effect of carvedilol on portal hypertension depends on the degree of endothelial activation and inflammatory changes. Scand J Gastroenterol 2006;41:1454–63. [PubMed: 17101577]
62. Bañares R, Moitinho E, Piqueras B, et al. Carvedilol, a new nonselective beta-blocker with intrinsic anti-alpha$_1$-adrenergic activity, has a greater portal hypotensive effect than propranolol in patients with cirrhosis. Hepatology 1999;30:79–83. [PubMed: 10385642]
63. Kovalak M, Lake J, Mattek N, et al. Endoscopic screening for varices in cirrhotic patients: data from a national endoscopic database. Gastrointest Endosc 2007;65:82–8. [PubMed: 17185084]
64. Merli M, Nicolini G, Angeloni S, et al. Incidence and natural history of small esophageal varices in cirrhotic patients. J Hepatol 2003;38:266–72. [PubMed: 12586291]
65. North Italian Endoscopic Club for the Study and Treatment of Esophageal Varices. Prediction of the first variceal hemorrhage in patients with cirrhosis of the liver and esophageal varices. A prospective multicenter study. N Engl J Med 1988;319:983–9. [PubMed: 3262200]
66. Abraldes JG, Villanueva C, Banares R, et al. Hepatic venous pressure gradient and prognosis in patients with acute variceal bleeding treated with pharmacologic and endoscopic therapy. J Hepatol 2008;48:229–36. [PubMed: 18093686]
67. Augustin S, Muntaner L, Altamirano JT, et al. Predicting early mortality after acute variceal hemorrhage based on classification and regression tree analysis. Clin Gastroenterol Hepatol 2009;7:1347–54. [PubMed: 19699816]
68. Bosch J, Garcia-Pagan JC. Prevention of variceal rebleeding. Lancet 2003;361:952–4. [PubMed: 12648985]
69. Garcia-Pagan JC, Morillas R, Banares R, et al. Propranolol plus placebo versus propranolol plus isosorbide-5-mononitrate in the prevention of a first variceal bleed: a double-blind RCT. Hepatology 2003;37:1260–6. [PubMed: 12774003]
70. Gluud LL, Klingenberg S, Nikolova D, et al. Banding ligation versus beta-blockers as primary prophylaxis in esophageal varices: systematic review of randomized trials. Am J Gastroenterol 2007;102:2842–8. [PubMed: 18042114]
71. Bosch J, Berzigotti A, Garcia-Pagan JC, et al. The management of portal hypertension: rational basis, available treatments and future options. J Hepatol 2008;48(Suppl 1):S68–92. [PubMed: 18304681]
72. Tripathi D, Ferguson JW, Kochar N, et al. Randomized controlled trial of carvedilol versus variceal band ligation for the prevention of the first variceal bleed. Hepatology 2009;50:825–33. [PubMed: 19610055]
73. Banares R, Albillos A, Rincon D, et al. Endoscopic treatment versus endoscopic plus pharmacologic treatment for acute variceal bleeding: a meta-analysis. Hepatology 2002;35:609–15. [PubMed: 11870374]
74. Ioannou G, Doust J, Rockey DC. Terlipressin for acute esophageal variceal hemorrhage. Cochrane Database Syst Rev 2001;(1):CD002147. [PubMed: 11279753]
75. Levacher S, Letoumelin P, Pateron D, et al. Early administration of terlipressin plus glyceryl trinitrate to control active upper gastrointestinal bleeding in cirrhotic patients. Lancet 1995;346:865–8. [PubMed: 7564670]
76. Bernard B, Grange JD, Khac EN, et al. Antibiotic prophylaxis for the prevention of bacterial infections in cirrhotic patients with gastrointestinal bleeding: a meta-analysis. Hepatology 1999;29:1655–61. [PubMed: 10347104]

77. Hou MC, Lin HC, Liu TT, et al. Antibiotic prophylaxis after endoscopic therapy prevents rebleeding in acute variceal hemorrhage: a randomized trial. Hepatology 2004;39:746–53. [PubMed: 14999693]

78. Fernandez J, Ruiz d A, Gomez C, et al. Norfloxacin vs ceftriaxone in the prophylaxis of infections in patients with advanced cirrhosis and hemorrhage. Gastroenterology 2006;131:1049–56. [PubMed: 17030175]

79. Bosch J, Thabut D, Bendtsen F, et al. Recombinant factor VIIa for upper gastrointestinal bleeding in patients with cirrhosis: a randomized, double-blind trial. Gastroenterology 2004;127:1123–30. [PubMed: 15480990]

80. Bosch J, Thabut D, Albillos A, et al. Recombinant factor VIIa for variceal bleeding in patients with advanced cirrhosis: a randomized, controlled trial. Hepatology 2008;47:1604–14. [PubMed: 18393319]

81. Gonzalez R, Zamora J, Gomez-Camarero J, et al. Meta-analysis: combination endoscopic and drug therapy to prevent variceal rebleeding in cirrhosis. Ann Intern Med 2008;149:109–22. [PubMed: 18626050]

82. Lo GH, Chen WC, Lin CK, et al. Improved survival in patients receiving medical therapy as compared with banding ligation for the prevention of esophageal variceal rebleeding. Hepatology 2008;48:580–7. [PubMed: 18666235]

83. Lo GH, Lai KH, Cheng JS, et al. Endoscopic variceal ligation plus nadolol and sucralfate compared with ligation alone for the prevention of variceal rebleeding: a prospective, randomized trial. Hepatology 2000;32:461–5. [PubMed: 10960435]

84. de la Pena J, Brullet E, Sanchez-Hernandez E, et al. Variceal ligation plus nadolol compared with ligation for prophylaxis of variceal rebleeding: a multicenter trial. Hepatology 2005;41:572–8. [PubMed: 15726659]

85. Lo GH, Chen WC, Chen MH, et al. A prospective, randomized trial of endoscopic variceal ligation versus nadolol and isosorbide mononitrate for the prevention of esophageal variceal rebleeding. Gastroenterology 2002;123:728–34. [PubMed: 12198699]

86. Romero G, Kravetz D, Argonz J, et al. Comparative study between nadolol and 5-isosorbide mononitrate vs. endoscopic band ligation plus sclerotherapy in the prevention of variceal rebleeding in cirrhotic patients: a randomized controlled trial. Aliment Pharmacol Ther 2006;24:601–11. [PubMed: 16827811]

87. Lo GH, Chen WC, Chan HH, et al. A randomized, controlled trial of banding ligation plus drug therapy versus drug therapy alone in the prevention of esophageal variceal rebleeding. J Gastroenterol Hepatol 2009;24:982–7. [PubMed: 19638080]

88. Kumar A, Jha SK, Sharma P, et al. Addition of propranolol and isosorbide mononitrate to endoscopic variceal ligation does not reduce variceal rebleeding incidence. Gastroenterology 2009;137:892–901. 901. [PubMed: 19481079]

Table 1

Hemodynamic responders to long-term administration of different pharmacologic therapies in studies including at least 10 patients

First Author (Year)	Setting (Type of Prophylactic Study)	β-Blockers		β-Blockers+Nitrates		No Drugs	
		N treated	N responders (%)	N treated	N responders (%)	N treated	N responders (%)
Groszmann 1990[a,22]	Primary	45	14 (31)			39	7 (18)
Merkel 2000[23]	Primary	29	16 (55)	20	12 (60)	–	–
Banares 2002[24]	Primary	22	5 (23)				
Turnes 2006[25]	Primary	50	19 (38)	21	6 (28)	–	–
Villanueva 2009 [15]	Primary	73	25 (34)				
Sharma 2009[26]	Primary	56	21 (38)				
Merkel 2010[27]	Primary	37	13 (35)				
Feu 1995[28]	Secondary	69	25 (36)	–	–	–	–
Villanueva 1996[a,29]	Secondary	–	–	31	14 (45)	31	5 (16)
McCormick 1998[30]	Secondary	14	9 (64)	30	19 (63)	–	–
Villanueva 2001[a,31]	Secondary	–	–	49	25 (51)	46	7 (15)
Patch 2002[a,32]	Secondary	–	–	18	9 (50)	–	–
Abraldes 2003[13]	Secondary	29	11 (38)	44	17 (39)	–	–
Villanueva 2004[33]	Secondary	–	–	132	64 (48)	–	–
Garcia-Pagan 2009[a,34]	Secondary			135	48 (36)		
Villanueva 2009[a,35]	Secondary	22	7 (32)	27	10 (37)		
Escorsell 2000[36]	Mixed	47	19 (40)	–	–	–	–
Bureau 2002[37]	Mixed	34	13 (38)	21	7 (33)	–	–
Total		527	197 (37)[b]	528	231 (44)[b]	116	19 (16)

Hemodynamic response defined as a decrease in HVPG less than 12 mm Hg and/or a decrease in HVPG greater than 20% from baseline.

[a] Randomized controlled trial.

[b] Difference between NSBB and NSBB+ISMN: $P = .039$.

Table 2

Long-term effect of carvedilol on portal pressure in studies including at least 10 patients

Study	Setting	n	Mean Dosage (mg/d)	Mean Decrease in HVPG (%)	Hemodynamic Responders (%)
Stanley 1999[60]	Mixed	10	25	16	4 (40)
Banares 2002[a,24]	Primary	24	31	19	13 (54)
Bruha 2006[61]	Mixed	36	25	~16	15 (42)
Total		70			32 (46)

[a]Only comparative study with propranolol using a homogenous population of patients without a history of variceal hemorrhage and a baseline HVPG of 12 mm Hg or more. Mean decrease in HVPG with propranolol was 12% and rate of responders was 23% (see Table 1).

Table 3

Pharmacologic therapy in the prevention of first variceal hemorrhage (primary prophylaxis)

Medication	Dosage	Goals	
Propranolol	Initial: 20–40 mg by mouth twice a day Maximum: 160 mg by mouth twice a day	**1** **2**	Increase until maximum tolerated OR heart rate of 50–55 beats per minute Continue indefinitely. No need for follow-up EGD
Nadolol	Initial: 20–40 mg once daily Maximum: 240 mg once daily	**1** **2**	Increase until maximum OR heart rate of 50–55 beats per minute Continue indefinitely. No need for follow-up EGD

EGD, esophagogastroduodenoscopy.

Table 4
Pharmacologic therapy in the management of acute variceal hemorrhage

Medication	Dosage	Comments
Vasopressin + Nitroglycerin	0.4 units/min continuous IV infusion Intravenously (40 μg/min) or transdermally (10 mg in 24 h)	**1** Should always be used with nitroglycerin to avoid ischemic complications **2** Maximum duration should be 24 h at lowest effective dosage **3** Rarely used
Terlipressin	Initial 48 h: 2 mg IV every 4 h until control of bleeding Maintenance: 1 mg IV every 4 h for up to 5 d to prevent rebleeding	Unavailable in the United States
Somatostatin	Initial IV bolus: 250 μg (can be repeated in the first hour if ongoing bleeding) Maintenance: continuous IV infusion of 250–500 μg/h for 5 d	Unavailable in the United States
Octreotide	Bolus: 50 μg (can be repeated in the first hour if ongoing bleeding) Maintenance: continuous IV infusion of 50 μg/h for 5 d	Available in the United States (off-label use)
Vapreotide	Bolus: 50 μg Maintenance: continuous IV infusion of 50 μg/h for 5 d	Unavailable in the United States

Table 5

Pharmacologic therapy in the prevention of recurrent variceal hemorrhage (secondary prophylaxis)

Medication	Dosage	Comments	
Propranolol or nadolol	Same as Table 3	Same as Table 3	
Isosorbide mononitrate	Initial: 10 mg by mouth every night	**1**	Used only in combination with an NSBB
	Maximum: 20 mg twice a day	**2**	Increase until maximum tolerated dose and SBP>95 mm Hg

Abbreviation: SBP, systolic blood pressure.