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Prevention of Portal Hypertension: from Variceal Development to Clinical Decompensation

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Abstract

Pharmacological treatment of portal hypertension (PH) has been exclusively devoted to gastro-esophageal varices related events at different frameworks including prophylactic, emergency or preventive therapy. The goals of treatment are to avoid the first bleeding episode, stop active bleeding and prevent bleeding recurrence, respectively. The objective of pre-primary prophylaxis (PPP) is to avoid variceal development and therefore, it necessarily deals with cirrhotic patients at earlier stages of the disease. At these earlier stages, nonselective beta blocker (NSBB) have been ineffective in preventing the development of varices and other complications of PH. Therefore, treatment should not rely on NSBB. It is possible, that at these earlier stages, etiological treatment of liver disease itself could prevent the progression of PH.

This review will focus mainly on early treatment of PH, because if successful, it may translate into histological-hemodynamic improvements, avoiding not only variceal development but also other PH related complications, such as ascites and porto-systemic encephalopathy (PSE). Moreover, the advent of new therapies may allow not only the prevention of the complications of PH, but also the chance of a substantial degree of regression in the cirrhotic process with the possible prevention of hepatocellular carcinoma (HCC).

Introduction

Pharmacological therapy of variceal bleeding includes primary prophylaxis, for patients that never bled but are at risk of doing so; secondary prophylaxis, for patients surviving a bleeding episode and in order to prevent recurrent bleeding and emergency therapy, indicated for the acute bleeding episode (1). The latest chapter in this field is PPP (2). The therapeutic objective of PPP has evolved during the last 13 years, from its original definition as the “prevention of the formation and growth of varices” to the recent one, proposing that this therapy “should only include patients without gastroesophageal varices” (2). The old definition, by considering patients without and with already developed (although small) esophageal varices, involved a broader population of cirrhotic patients. While the newer one, not only simplifies the treatment end point (formation of varices) but also includes a wider

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option of treatment strategies in a less heterogeneous (at least endoscopically speaking) population.

Experimental background

Esophageal varices are difficult to generate in animal models of PH. However, in response to PH several animal species develop extensive porto-systemic collaterals including paraesophageal collaterals. These models have been useful to understand the pathophysiology and explore potential new treatments for PH (3). In liver cirrhosis, PH results from both increases in intrahepatic vascular resistance (IHVR) and in portal-collateral blood flow (3). IHVR is mainly due to a vascular obliterative process, with scar tissue and regenerative nodules both occluding and compressing vascular structures (3, 4). Concomitantly, a functional, non-structural component of IHVR is located at the sinusoidal circulation. This abnormality is due primarily to endothelial dysfunction, and is the consequence of disequilibrium between an increased release of vasoconstrictors [mainly endothelin-1 and cyclooxygenase-1-derived vasoconstrictive prostanoids] and a reduced bioavailability of vasodilators, mainly nitric oxide (NO) (3, 4). Simultaneously, splanchnic vasodilation, with an increased blood flow plays a crucial role in the development and maintenance of PH (3, 4). In the splanchnic circulation there is an overproduction of endogenous vasodilators (mainly NO). Intrahepatic endothelial dysfunction is already present at early stages of fatty liver disease (5). Moreover, mild increases in portal pressure (PP) upregulate endothelial NO synthase (eNOS) in the intestinal microcirculation of rats (6). Both abnormalities may coincide during early phases of human chronic liver diseases (CLD). PH is always initiated by an increased in IHVR. Angiogenesis and fibrogenesis are relevant mechanisms in PH pathophysiology (4). New vessel formation is involved in the development of portosystemic collaterals, in the maintenance of hyperdynamic circulation and in the progression of liver fibrosis. Intrahepatic vascular proliferation and collagen deposition are the consequence of over-expression of several growth factors, cytokines and metalloproteinases. Splanchnic and porto-collateral angiogenesis may also be driven by angiogenic factors. Accordingly, an increased expression of vascular endothelial growth factor (VEGF), VEGFR-2 and the endothelial cell marker CD31 has been observed in the splanchnic organs of PH animals (4). Of note, both early VEGF up-regulation and eNOS over-expression are contemporary events, as has been demonstrated in the rat intestinal microcirculation after mild increases in PP (6).

Experimental background as a basis for new therapeutic strategies Table 1

For each of the aforementioned mechanisms there is a related therapeutic proposal. Early investigation was based on the administration of vasoactive drugs, targeting the high splanchnic blood inflow. Non-selective beta blockers (NSBB) significantly decreased portal venous inflow (PVI), PP and PSS in different experimental models (3). Octreotide ameliorated vasodilatation and Na⁺ retention and decreased PP without affecting PSS in PVL rats (3). Later, experimental steps targeting splanchnic vasodilation were primarily based on the administration of NO synthesis inhibitors. Remarkable observations after NO inhibition in PH rats were: restoration of vascular reactivity to normal levels, amelioration of the hyperdynamic circulatory syndrome, reduction in plasma volume expansion and Na⁺ retention and reduction in PSS (3, 4).

Therapeutic attempts targeting endothelial dysfunction included “in vivo” NOS gene transfer to cirrhotic livers (4). Both an increased NO synthesis and a reduction in PP were observed after eNOS and neuronal NOS (nNOS) isoforms of NOS were transfected. Increased oxidative stress may also induce a decrease in NO bioavailability. Accordingly, both superoxide dismutase (SOD) gene transfer and reduction of superoxide activity have been shown to reduce PP in CCl₄ cirrhotic rats (4). Administration of a liver specific NO-donor (NCX-1000) improved liver vascular compliance and decreased the response to vasoconstrictors in cirrhotic rats (4). Another source of NO decreased bioavailability in cirrhotic livers might be the deficit of tetrahydrobiopterin (BH₄), an essential cofactor for the production of NO. Specifically, experimental supplementation of BH₄ improved endothelial dysfunction (4). Among the newest therapeutic strategies, statins may be the most intriguing option (7). In fact, simvastatin administration increases eNOS expression, Akt-dependent eNOS phosphorylation and cGMP liver content.

Finally, angiogenesis inhibition induces a significant improvement in experimental PH. Administration of agents interfering with the VEGF/VEGFR-2 and platelet derived growth factor (PDGF) signalling pathway improves PP, hyperdynamic circulation, splanchnic neovascularization and PSS in PH models (4). Moreover, the multi-targeted receptor tyrosine kinase inhibitor, sorafenib, causes a marked decrease in PSS, in splanchnic and hepatic neovascularization, and in liver fibrosis in experimental models of PH and cirrhosis (4).

Clinical background

The only trial (8) that completely follows the present definition for PPP included 213 patients without esophageal varices that were evaluated in order to investigate: a) the effects of timolol (a NSBB) in the prevention of the development of esophageal varices and variceal hemorrhage and b) the predictive value that sequential measurements of HVPg could have in the development of primary (development of varices/variceal hemorrhage), secondary (ascites/PSE) and terminating events (transplant or death). Only patients with cirrhosis and PH (i.e. HVPg >6 mmHg) were included. Hepatitis C virus (HCV) related cirrhosis accounted for 53%, alcohol for 20% and alcohol plus HCV for 15% of the study patients, respectively. Yearly endoscopies and HVPg measurements were performed and the median follow-up was 4.2 years. One hundred and eight patients received timolol (mean dose: 10.8 mg/day). The incidence of variceal formation (n=84; 39%) and of variceal haemorrhage (n=6; 7%), as well as other complications of PH (ascites n=46, encephalopathy n= 17 and terminating events n= 22) did not differ between drug and placebo. Moreover, no significant differences in HVPg were observed between the groups. An HVPg >10mmHg at baseline and at year 1 after inclusion was highly predictive of the development of primary, secondary and terminating events (p<0.0001). A significantly higher number of adverse events were reported in the timolol group.

An HVPg >10 mmHg is a powerful prognostic predictor of the development of complications of PH. Concomitantly, and theoretically related, the systemic hemodynamic profile in patients with HVPg <10 mmHg is more likely to be normal than hyperdynamic (9). Therefore, it is possible that at early stages of disease, the reduction in portal blood flow

(PBF) induced by NSBB, even though quantitatively similar to that produced in advanced PH, results in minimal or no effect on PP. This occurs because under these close to normal conditions the relation between PBF and portal-hepatic resistance is flat and reductions in PBF induced minor to insignificant changes in PP (10). None of the patient had esophageal varices upon entry into the study, the absence of “clinically significant portal hypertension” (CSPH) (11), manometrically defined, is by itself an important prognostic indicator in patients with cirrhosis. In summary, NSBB are not useful in preventing the development of varices/variceal hemorrhage and are associated with a higher proportion of adverse events in patients with cirrhosis without varices.

Two previous randomized, controlled trials performed according to the old PPP definition have been published. The first study (12) evaluated propranolol for the prevention of development of large esophageal varices in 206 patients. At inclusion, varices were absent in 79 and small in 127 patients. A fixed dose (160 mg/day) of long-acting propranolol was administered to 102 patients randomized to drug treatment versus a placebo. After 2 years of follow-up, large varices were present in 31% of the patients in the drug group vs. 14% of those in the placebo group ($p<0.05$). This difference lost significance at the third year (44% vs. 34%; respectively). Bleeding episodes and mortality did not differ between both treatment groups. The patients drop out rate and the administration of a fixed dose of propranolol may have influenced the negatives results. High abstinence rate among alcoholic patients (86% and 78% in each treatment group) was observed. Alcohol abstinence has been shown to decrease PP and variceal size, including its disappearance in some patients (13).

A second study (14) evaluated nadolol for the prevention of growth of small varices. One hundred and sixty one patients were included, with 83 randomized to nadolol and 78 receiving a placebo. Hepatic venous pressure gradient (HVPG) was measured at baseline and after 2 years in 19 patients (10 assigned to nadolol and 9 to placebo). Mean dose of nadolol varied from 60 ± 25 to 64 ± 25 mg/day and mean follow-up was 36 months. Nine patients receiving nadolol and 29 on placebo had variceal growth. Cumulative risk of variceal growth at 2, 3, 4 and 5 years were significantly lower for nadolol than for placebo ($p<0.001$). Cumulative probability of being free of variceal bleeding was 88% vs. 78% for nadolol and placebo respectively ($p<0.02$). Regression of varices occurred in 15 on nadolol and 5 patients on placebo (11 alcoholic vs. 9 non-alcoholic). Among alcoholic cirrhotic patients, regression (n: 11) was more frequent in abstainers. A high abstinence index was observed (64% and 69% for nadolol and placebo, respectively) (NS). HVPG decreased significantly at 2 years in the 10 patients receiving nadolol (from 12.2 ± 1.1 mmHg to 11.0 ± 1.5 mmHg) ($p<0.009$) while it showed a non-significant increase in the 9 patients receiving placebo. After 2 years the HVPG was lower in patients randomized to nadolol than to placebo (11.0 ± 1.5 mmHg vs. 12.5 ± 1.1 mmHg; respectively) ($p<0.03$). Survival did not differ between both groups. Therefore, pharmacological treatment seems to be successful not only in preventing variceal growth but also for inducing regression of varices (9 patients had variceal growth but 15 showed regression). It appears relevant that among alcoholic patients regression was more prevalent in abstainers. Another important finding is the significant decrease in HVPG induced by nadolol.

Clinically significant portal hypertension or the HVPG > 10 mmHg

CSPH is defined as an increase in HVPG gradient to a threshold above 10 mmHg. Clinically, the presence of varices, variceal hemorrhage and/or ascites is indicative of the presence of CSPH (11).

The natural history of cirrhosis may be considered as a dynamic process that includes the progression to successive stages. Early, compensated cirrhosis includes stage 1 patients (without esophageal varices, ascites or PSE) and stage 2 (esophageal varices without bleeding and without ascites or PSE). Advanced, decompensated cirrhosis includes stage 3 (ascites, without or with varices but no previous bleeding) and stage 4 (variceal bleeding, with or without ascites or PSE). Presence of sepsis and/or renal failure may determine an additional stage (stage 5) (15).

Of note, not all stage 1 patients (no varices, no ascites) have CSPH. In fact, during a time frame of their disease, they are within a period manometrically considered as “subclinical portal hypertension” (SPH) or portal hypertension that is “not clinically significant”. HVPG during SPH ranges between 6 and 10 mmHg. (8). As stated above, these patients were also refractory to the effect of NSBB on HVPG (8, 16).

CSPH as a predictive parameter of variceal formation

In compensated patients, CSPH is a strong predictor of variceal development and (8, 17). Moreover, during the same time period, a reduction of the HVPG by >10% or more was of significant benefit when related to the prevention of clinical decompensation (8, 17). Based on these results, a reduction in the HVPG by more than 10% and/or below 10 mmHg should be the goal of pharmacological prevention of PH related complications (8). However, it is important to emphasize that a reduction below 12 mmHg markedly reduces the risk of variceal haemorrhage and other complications of portal hypertension (22).

CSPH as a predictive parameter of clinical decompensation

Another remarkable observation is that, in previously compensated patients, CSPH is a strong predictor of clinical decompensation, ascites, PSE, and/or variceal hemorrhage. While varices may develop between 10 to 12 mmHg, it is only when the HVPG reaches 12 mmHg or more (severe portal hypertension) that the decompensated events are observed. Compensated patients with a HVPG value <10 mmHg had a 90% chance of not having any clinical decompensation in a follow-up of 4 years (17). Moreover, CSPH was an independent predictor of death within a group of 120 compensated patients, in which those at stage 1 had a significantly longer survival than those at stage 2 (18). In another study, performed in compensated HCV-related cirrhotics, CSPH was validated as a robust predictive parameter of clinical decompensation in stage 1 patients (19). Finally, within a group of compensated patients, the presence of CSPH showed a 6-fold increase in the incidence of HCC (20). In summary, CSPH is a strong predictor of clinical decompensation, HCC development and death in compensated cirrhotic patients. Therefore, we conclude that HVPG is a reliable surrogate of clinical events.

The potential target population for preventing the progression of PH; Table 2

Stage 1 patients have a low mortality rate (~1% yearly) and may progress to stage 2 (with varices) (mortality rate ~3.4% yearly) at an annual rate of ~6-8%. Nevertheless, a strict step-by-step progression may not always be the rule, as 4 to 6% of stage 1 patients may advance directly to stage 3 (ascites, without or with varices and no previous bleeding) (a yearly mortality rate of ~25%) (15). Therefore, although variceal development seems the most relevant therapeutic objective, a wider spectrum of treatment end-points might be considered in these patients. As previously stated, 2 different populations comprise stage 1 patients: those with and without CSPH (2, 8). This is not an arbitrary distinction, as CSPH is a well-known threshold for prognostic risks but also, and perhaps more importantly, for treatment response (21).

It was previously mentioned that a NSBB was no different than placebo in decreasing HVPg in compensated patients with cirrhosis and without varices (8). However, when the hemodynamic response was analyzed according to the presence/absence of CSPH, it was observed that patients with CSPH had a significant drop in HVPg, while those without CSPH did not (16). Responsiveness at this stage may depend on an already developed hyperdynamic circulation and collateralization of the portal venous system. Patients with CSPH respond both to NSBB or placebo with a significant reduction in HVPg. The placebo response in these patients was high, suggesting that other factors than NSBB were involved in the portal hypotensive effect observed. No effect on the HVPg was observed in the group of patients with HVPg < 10 mmHg (16). Etiological treatment may be useful in this last group of patients. In fact alcohol abstinence produced both significant liver function improvement and variceal regression in alcoholic cirrhotic patients (13). Although mostly observed in stage 2 patients, these beneficial effects may be considered more significant in patients with earlier disease. Response to treatment of HCV infection may also influence PP outcomes. Accordingly, in 20 patients with advanced fibrosis antiviral treatment induced a significant decrease in HVPg. Within the 11 included patients with CSPH, 9 of them had a 20% or greater reduction in HVPg (22). Moreover, among 47 compensated HCV-related cirrhotic patients, sustained virological response (SVR) was associated with a significant decrease in HVPg. Interestingly, a significant association between a hemodynamic response and both a histologic response and SVR was observed (22). More recently, successful treatment of HCV infection was reported to prevent esophageal varices development in compensated, stage 1, cirrhotic patients during a 12-year follow-up (23). Remarkably, a significant reduction in decompensating events was observed in these patients, when compared to those with non-SVR. Similarly, treatment of HBV infection in cirrhotic patients with CSPH may translate into significant clinical, humoral and hemodynamic improvement, as was observed in 19 patients (9 of them at stage 1) long-term treated with lamivudine (22). After 12 months, HVPg decreased in all but one patient. Finally, in compensated patients with cirrhosis, obesity is an independent risk factor for clinical decompensation (24). Therefore, weight loss should be a required treatment for any overweight, compensated patient with cirrhosis regardless of disease etiology. PH in cirrhosis without CSPH is mainly determined by intrahepatic factors. Therefore, intrahepatic resistance as determined by both “fixed” and “functional components seems the most amenable therapeutic target for this stage (3, 4).

Non-alcoholic steatohepatitis (NASH) is a variant of non-alcoholic fatty liver disease (NAFLD) that can progress to cirrhosis. It has been demonstrated that lifestyle intervention, in order to achieve body weight loss, leads to an improvement in liver histology. Among drugs assessed for NASH treatment, Vitamin E (α -tocopherol) and thiazolidinediones had been explored with mixed success (25).

Abstinence remains the most important therapeutic intervention at any stage of chronic alcoholic liver disease. Clinical, histological and hemodynamic improvement, together with an increased survival has been reported after sustained alcohol abstinence (13, 26).

There is evidence that SVR in patients with advanced fibrosis is associated with a significant decreased of clinical decompensation and HCC. Moreover, a remarkable histologic improvement, closely akin to cirrhosis reversal has been reported in a significant proportion of responders (27). New and more effective drugs are already available for the treatment of hepatitis C (28). No doubt they will be used in the future to prevent the complications of PH. The concept of fibrosis regression and disease reversal could be a reality (29).

HBV cirrhosis may also benefit from antiviral treatment (22, 30). Antiviral therapy can improve clinical outcomes in patients with advanced fibrosis who have maintained viral suppression. The use of potent nucleoside/nucleotide analogue therapy with very low risk of resistance, i.e. tenofovir or entecavir, is particularly relevant in this group of patients (30).

The best available treatment, not strictly related to etiology in all cases, may be beneficial for other forms of CLD, such as autoimmune hepatitis (31), primary biliary cirrhosis (32) and hemochromatosis (33). For each of these diseases, treatment efficacy has been shown for both advanced fibrotic and cirrhotic compensated stages.

As mentioned before, PH at this early stage is mainly due to an increased IHVR. Because impaired endothelial function has an important causal role in the pathophysiology of intrahepatic PH, the endothelium agonistic properties of statins could provide the necessary amount of intrahepatic relaxation to potentiate the PP reducing effects of the specific etiology based treatments (7). Interestingly, statins may also decrease the risk of HCC (24) and improve liver function (7). Other therapeutic measures targeting endothelial dysfunction may be considered. Among them, antioxidants, such as ascorbic acid, have been shown to improve endothelial dysfunction in PH patients with cirrhosis (4, 24). Moreover, given that dark chocolate improves endothelial dysfunction in patients with cirrhosis and that coffee might have an antifibrotic action, patients could be counseled to include them in their diet (24). These basic research advances might be progressively translated into clinical practice, not as single therapeutic agents, but as part of a combined therapeutic strategy, associated to specific disease treatment.

Summary

Pharmacological therapy of PH, as conceptually recognized in clinical practice, has been exclusively aimed at treating esophageal varices related events. The primary prophylactic treatment (patients with large varices) performed with NSBB, had shown significant efficacy in the prevention of variceal bleeding and in increased survival (1, 34).

PPP was proposed for patients with cirrhosis at earlier stages with a goal of preventing esophageal varices formation (2). As we know now, NSBB in PPP, are ineffective and induced adverse events in patients with early disease (8). Serious adverse events had also been observed in patients with cirrhosis and refractory ascites (35). However, another study does not seem to agree with the detrimental findings in refractory ascites (36). Additionally, prevention of the progression of PH should not rely on a single drug based therapy, but rather on a combined therapeutic strategy, targeting different components influencing both liver disease and PH. Prevention of esophageal varices formation may be associated with a decrease in other complications of portal hypertension (8, 17, 20, 23). The portal pressure that triggers decompensation is reached once the disease is quite advanced, and reaches a manometric level of severe portal hypertension (a HVPG >12 mmHg), at which time PH related complication/decompensation may be present (8,17). Therefore, prevention of PH progression should not be considered as a single end-point aimed therapy but as one devoted to prevention of a hemodynamic trigger points and the associated clinical consequences. Additionally, it may not rely on a single drug based therapy, but rather on a combined therapeutic strategy, targeting different components influencing both liver disease and PH evolution. An important remaining issue is the accurate diagnosis of Sub clinical PH, CSPH and severe PH. The necessary advent of new, non-invasive diagnostic methodologies will displace HVPG measurements, currently accepted as the gold standard for precisely establishing SPH, CSPH and severe PH (37).

In summary, the burden of liver diseases presents a challenge for new, earlier and more effective therapies oriented to interrupt/delay or, ideally revert, CLD progression. When possible treating the underlying etiology of the liver disease may be the best option to prevent or slowdown the progression of portal hypertension.

References

1. Thalheimer U, Bosch J, Burroughs AK. How to prevent varices from bleeding: Shades of grey-The case for non-selective β blockers. *Gastroenterology*. 2007; 133:2029–2036. [PubMed: 18054573]
2. Groszmann, RJ.; Merkel, C.; Dell'Era, A.; Merli, M.; Ripoll, C.; Vorobioff, J. Pre-primary and primary prophylaxis.. In: de Franchis, R., editor. *Portal Hypertension V. Proceedings of the Fifth Baveno International Consensus Workshop*. Wiley-Blackwell; Oxford: 2011. p. 59-74.
3. Groszmann RJ, Abraldes JG. Portal Hypertension. From bedside to bench. *J Clin Gastroenterol*. 2005; 39:S125–130. [PubMed: 15758647]
4. Bosch J, Abraldes JG, Fernández M, García-Pagán JC. Hepatic endothelial dysfunction and abnormal angiogenesis: New targets in the treatment of portal hypertension. *J Hepatol*. 2010; 53:558–567. [PubMed: 20561700]
5. Pasarin M, Abraldes JG, Rodríguez-Villarrupla A, LaMura V, García-Pagán JC, Bosch J. Insulin resistance and liver microcirculation in a rat model of early NAFLD. *J Hepatol*. 2011; 55:1095–1102. [PubMed: 21356259]
6. Abraldes JG, Iwakiri Y, Loureiro-Silva M, Haq O, Sessa WC, Groszmann RJ. Mild increases in portal pressure upregulate vascular endothelial growth factor and endothelial nitric oxide synthase in the intestinal microcirculatory bed, leading to a hyperdynamic state. *Am J Physiol*. 2006; 290:G980–G987.
7. Abraldes, JG.; La Mura, V.; Bosch, J. Statins in portal hipertensión.. In: de Franchis, R., editor. *Portal Hypertension V. Proceedings of the Fifth Baveno International Consensus Workshop*. Wiley-Blackwell; Oxford: 2011. p. 199-204.

8. Groszmann RJ, Garcia-Tsao G, Bosch J, Grace ND, Burroughs AK, Planas R, et al. Beta-blockers to prevent gastroesophageal varices in patients with cirrhosis. *N Engl J Med*. 2005; 353:2254–2261. [PubMed: 16306522]
9. Braillon A, Calès P, Valla D, Geoffroy P, Lebrec D. Influence of the degree of liver failure on systemic and splanchnic hemodynamics and on response to propranolol in patients with cirrhosis. *Gut*. 1986; 27:1204–1209. [PubMed: 3781335]
10. Groszmann, RJ.; Blei, A.; Atterbury, C. Portal hypertension.. In: Arias, IM.; Popper, H.; Jacoby, WB.; Schachter, DA.; Shafritz, DA., editors. *The liver: Biology and Pathobiology*. ed 2.. Raven Press; New York: 1988. p. 1147-1159.
11. D'Amico, G.; Garcia-Tsao, G.; Calès, P.; Escorsell, A.; Nevens, F.; Cestari, R., et al. Diagnosis of portal hypertension: How and when.. In: de Franchis, R., editor. *Portal Hypertension III. Proceedings of the third Baveno International Consensus Workshop on Definitions, Methodology and Therapeutic Strategies*. Blackwell Science; Oxford: 2001. p. 36-64.
12. Calès P, Oberti F, Payen JL, Naveau S, Guyader D, Blanc P, et al. Lack of effect of propranolol in the prevention of large oesophageal varices in patients with cirrhosis: a randomized trial. *Eur J Gastroenterol Hepatol*. 1999; 11:741–745. [PubMed: 10445794]
13. Vorobioff J, Groszmann RJ, Picabea E, Gamen M, Villavicencio R, Bordato J, et al. Prognostic value of hepatic venous pressure measurement in alcoholic cirrhosis: A ten year prospective study. *Gastroenterology*. 1996; 111:701–709. [PubMed: 8780575]
14. Merkel C, Marin R, Angeli P, Zanella P, Felder M, Bernardinello E, et al. A placebo-controlled clinical trial of nadolol in the prophylaxis of growth of small esophageal varices in cirrhosis. *Gastroenterology*. 2004; 127:476–484. [PubMed: 15300580]
15. D'Amico, G. Stages classification of cirrhosis: Where do we stand ?.. In: de Franchis, R., editor. *Portal Hypertension V. Proceedings of the Fifth Baveno International Consensus Workshop*. Wiley-Blackwell; Oxford: 2011. p. 132-139.
16. Qamar AA, Groszmann RJ, Grace ND, Garcia-Tsao G, Burroughs AK, Bosch J. Lack of effect of non-selective beta-blockers on the hepatic venous pressure gradient (HVPG) in patients with mild portal hypertension: a tail of two studies [Abstract]. *Hepatology*. 2010; 52(Suppl 1):1020 A.
17. Ripoll C, Groszmann RJ, García-Tsao G, Grace ND, Burroughs AK, Planas R, et al. Hepatic venous pressure gradient predicts clinical decompensation in patients with compensated cirrhosis. *Gastroenterology*. 2007; 133:481–488. [PubMed: 17681169]
18. Zipprich A, Garcia-Tsao G, Rogowski S, Fleig WE, Seufferlein T, Dollinger MM, et al. Prognostic indicators of survival in patients with compensated and decompensated cirrhosis. *Liver Int*. 2012; 32:1407–1414. [PubMed: 22679906]
19. Rincón D, Lo Iacono O, Tejedor M, Hernando A, Ripoll C, Catalina MV, et al. Prognostic value of hepatic venous pressure gradient in patients with compensated chronic hepatitis C-related cirrhosis. *Scand J Gastroent*. 2013; 48:487–495. [PubMed: 22871085]
20. Ripoll C, Groszmann RJ, García-Tsao G, Bosch J, Grace ND, Burroughs AK, et al. Hepatic venous pressure gradient predicts development of hepatocellular carcinoma independently of severity of cirrhosis. *J Hepatol*. 2009; 50:923–928. [PubMed: 19303163]
21. Grace N. Patients with clinically significant portal hypertension caused by hepatitis C virus cirrhosis respond poorly to antiviral therapy. *Clin Gastroenterol Hepatol*. 2011; 9:536–538. [PubMed: 21554988]
22. Rincon, D.; Ripoll, C.; Catalina, MV.; Bañares, R. A look into the future: New treatments in the horizon - Antiviral therapy.. In: de Franchis, R., editor. *Portal Hypertension V. Proceedings of the Fifth Baveno International Consensus Workshop*. Wiley-Blackwell; Oxford: 2011. p. 205-210.
23. Bruno S, Crosignani A, Facciotto C, Rossi S, Roffi L, Redaelli A, et al. Sustained virologic response prevents the development of esophageal varices in compensated, Child-Pugh class A hepatitis C virus–induced cirrhosis. A 12-year prospective follow-up study. *Hepatology*. 2010; 51:2069–2076. [PubMed: 20196120]
24. Tsochatzis EA, Bosch J, Burroughs AK. New therapeutic paradigm for patients with cirrhosis. *Hepatology*. 2012; 56:1883–1992.
25. Chalasani N, Younossi Z, Lavine JF, Diehl AM, Brunt EM, Cusi K, et al. The diagnosis and management of non-alcoholic fatty liver disease: Practice Guideline by the American Association

- for the Study of Liver Diseases, American College of Gastroenterology, and the American Gastroenterological Association. *Hepatology*. 2012; 55:2005–2023. [PubMed: 22488764]
26. O'Shea RS, Dasarathy S, McCullough AJ, the Practice Guideline Committee of the American Association for the Study of Liver Diseases and the Practice Parameters Committee of the American College of Gastroenterology. Alcoholic Liver Disease. *Hepatology*. 2010; 51:307–328. [PubMed: 20034030]
 27. Ghany G, Strader DB, Thomas DL, Seeff LB. AASLD Practice Guidelines. Diagnosis, management, and treatment of hepatitis C: an update. *Hepatology*. 2009; 49:1335–1374. [PubMed: 19330875]
 28. Pawlotsky JM. NS5A inhibitors in the treatment of hepatitis C. *J Hepatol*. 2013; 59:375–382. [PubMed: 23567084]
 29. Pinzani, M. Antifibrotic drugs.. In: de Franchis, R., editor. Portal Hypertension V. Proceedings of the Fifth Baveno International Consensus Workshop. Wiley-Blackwell; Oxford: 2011. p. 211-217.
 30. Lok ASF, McMahon BJ. AASLD Practice Guidelines. Chronic Hepatitis B. *Hepatology*. 2007; 45:507–539. [PubMed: 17256718]
 31. Czaja AJ, Carpenter HA. Decreased fibrosis during corticosteroid therapy of autoimmune hepatitis. *J Hepatol*. 2004; 40:646–65. [PubMed: 15030981]
 32. Huet PM, Vincent C, Deslaurier J, Coté J, Matsutani S, Boileau R, et al. Portal hypertension and primary biliary cirrhosis: Effect of long-term ursodeoxycholic acid treatment. *Gastroenterology*. 2008; 135:1552–1560. [PubMed: 18722374]
 33. Falize L, Guillygomarc'h A, Perrin M, Lainé F, Guyader D, Brissot P, et al. Reversibility of hepatic fibrosis in treated genetic hemochromatosis: a study of 36 cases. *Hepatology*. 2006; 44:472–477. [PubMed: 16871557]
 34. Simonetto DA, Shah VH, Kamath PS. Primary prophylaxis of variceal bleeding. *Clin Liver Dis*. 2014; 18:335–345. [PubMed: 24679498]
 35. Ge PS, Runyon BA. The changing role of beta-blocker therapy in patients with cirrhosis. *J Hepatol*. 2014; 60:643–653. [PubMed: 24076364]
 36. Ferrarese A, Germani G, Rodriguez-Castro KI, Nadal E, Zanetto A, Bortoluzzi I, et al. Bleeding-unrelated mortality is not increased in patients with cirrhosis and ascites on treatment with β -blockers: A meta-analysis. [Abstract]. *J Hepatol*. 2014; 60(Suppl 1):S385.
 37. Lim JK, Groszmann RJ. Transient Elastography for Diagnosis of Portal Hypertension in Liver Cirrhosis: Is There Still a Role for Hepatic Venous Pressure Gradient Measurement?. *Hepatology*. 2007; 45:1087–1090. [PubMed: 17464984]
 38. The 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. *N Engl J Med*. 1988; 319:983–989. [PubMed: 3262200]
 39. García-Pagán JC, Caca K, Bureau C, Laleman W, Appenrodt B, Luca A, et al. Early use of TIPS in patients with cirrhosis and variceal bleeding. *N Engl J Med*. 2010; 362:2370–2379. [PubMed: 20573925]
 40. Vilar Gomez E, Sanchez Rodriguez Y, Calzadilla Bertot L, Torres Gonzalez A, Martinez Perez Y, Arus Soler E, et al. The natural history of compensated HCV-related cirrhosis: A prospective, long-term study. *J Hepatol*. 2013; 58:434–444. [PubMed: 23111008]

Table 1
Prevention/Treatment of Portal Hypertension

Effects on the liver of different modes of treatment

	Liver fibrosis	Endothelial function	Angiogenesis reduction	Splanchnic blood flow	IHVR reduction	PP reduction
Etiological treatment	↓++*	?	?	?	↓++*	↓++*
Statins	↓+*	++*	?	?	↓+*	↓+*
Antioxidants	↓+•	↑++*•	?	—	↓+*•	↓+•
COX inhibitors	—	↑++•	?	?	↓+•	↓+•
Antifibrotics	↓+++•	?	?	?	?	?
Antiangiogenic	↓++•	?	↓+++•	↓++•	↓+•	↓+•
NSBB	—	—	↓+•	↓+++*•	—	↓+++*•
Vasodilators NOx donors	—	—	?	-↓•*	↓+++*•	↓+*•

Legends to the Table:

Supported by * Human studies • Experimental studies

IHV= Intrahepatic Vascular Resistance

↓ = reduction, ↑ = improvement, +=quantity, ? =unknown, -- no effect.

References: 1-4, 7-9, 12-14, 16, 22, 23, 25, 26, 29-33

Additional references supporting this Table are available at the Journal Website

Table 2

Stages of cirrhosis, risk of first variceal bleeding and death from variceal bleeding and bleeding risk reduction by NSBB

Stages of cirrhosis	Risk of variceal bleeding *	Risk of death from variceal bleeding	Bleeding risk reduction by NSBB *
Stage 1 (no varices, no ascites)	0.3 – 1.6 %	0.7 - 3%	None
Stage 2 (esophageal varices, no ascites, no bleeding)	7% for small varices 25% for medium/large varices	15 to 20%	~5% small varices ~10% large varices [#]
Stage 3 (ascites, with or without varices, no history of bleeding)	31%	25 to 35%	~10% large varices [#]
Stage 4 (gastrointestinal bleeding, with or without ascites)	-	-	-

References 8, 12, 14, 15, 17, 19, 20, 23, 34, 38-40

[#] significant

* Incidence is expressed at % per 2 years