Garbuzenko D.V., Arefyev N.O. Primary prevention of bleeding from esophageal varices in patients with liver cirrhosis: An update and review of the literature. J Evid Based Med. 2020; 13 (4): 313-324.

Received: 3 April 2020 | Accepted: 19 June 2020

DOI: 10.1111/jebm.12407

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REVIEW

Primary prevention of bleeding from esophageal varices in patients with liver cirrhosis: An update and review of the literature

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Funding information
Russian Foundation for Basic Research, Grant/Award Number: 18-315-00434

Abstract

All patients with liver cirrhosis and portal hypertension should be stratified by risk groups to individualize different therapeutic strategies to increase the effectiveness of treatment. In this regard, the development of primary prophylaxis of variceal bleeding and its management according to the severity of portal hypertension may be promising. This paper is to describe the modern principles of primary prophylaxis of esophageal variceal bleeding in patients with liver cirrhosis. The PubMed and EMbase databases, Web of Science, Google Scholar, and the Cochrane Database of Systematic Reviews were used to search for relevant publications from 1999 to 2019. The results suggested that depending on the severity of portal hypertension, patients with cirrhosis should be divided into those who need preprimary prophylaxis, which aims to prevent the formation of esophageal varices, and those who require measures that aim to prevent esophageal variceal bleeding. In subclinical portal hypertension, therapy should be etiological and pathogenetic. Cirrhosis with clinically significant portal hypertension should receive nonselective β-blockers if they have small esophageal varices and risk factors for variceal bleeding. Nonselective β-blockers are the first-line drugs for the primary prevention of bleeding from medium to large-sized esophageal varices. Endoscopic band ligation is indicated for the patients who are intolerant to nonselective β-blockers or in the case of contraindications to pharmacological therapy. In summary, the stratification of cirrhotic patients by the severity of portal hypertension and an individual approach to the choice of treatment may increase the effectiveness of therapy as well as improve survival rate of these patients.

KEYWORDS
bleeding, cirrhosis, esophageal varices, portal hypertension, primary prevention

1 | INTRODUCTION

Portal hypertension (PH) is one of the most common syndromes in liver cirrhosis. PH is characterized by a pathological increase in portal pressure of >5 mmHg. Its clinical importance is determined by the frequency and severity of complications, which are associated with disease progression. The most significant and direct consequence of PH is the formation of portosystemic collaterals, particularly esophageal varices. Their rupture leads to life-threatening bleeding. Moreover, bleeding-associated mortality remains high even if the existing treatment standards are followed, which underlines the necessity for the development of effective prophylactic therapy.[1]

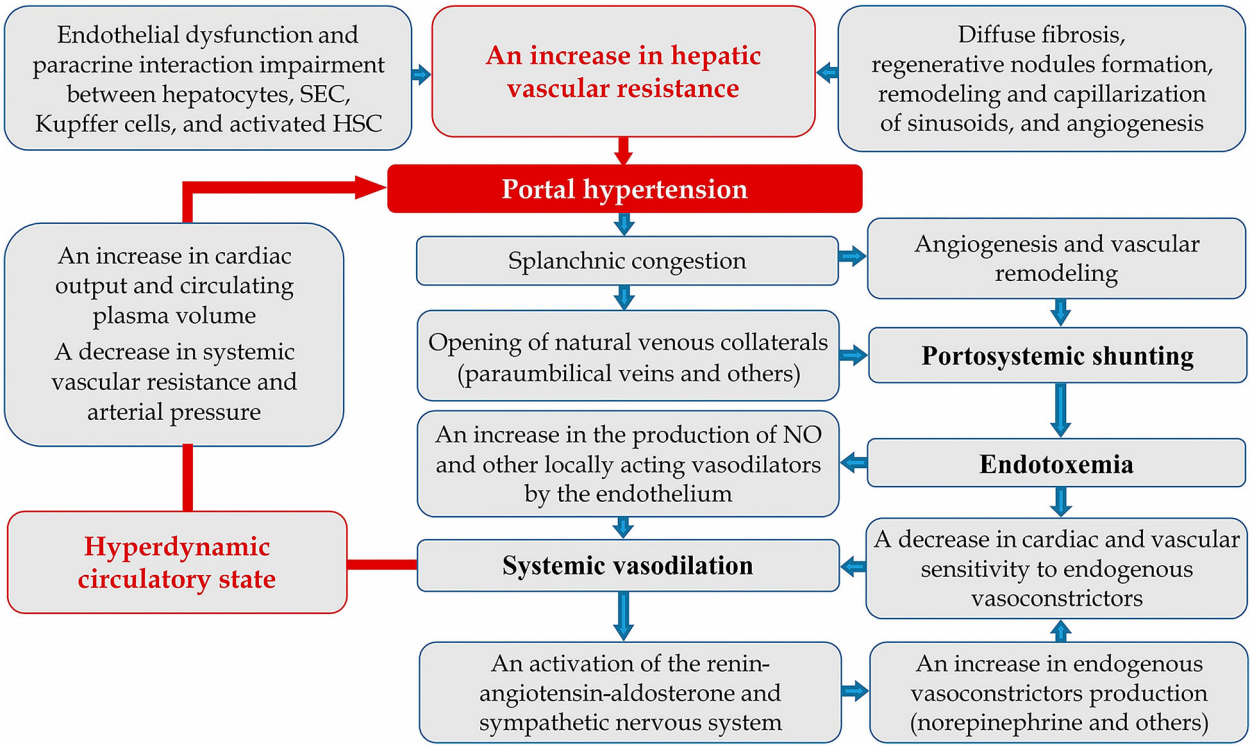

FIGURE 1 Potential mechanisms of portal hypertension pathogenesis in cirrhosis

Note: The newly formed blood vessels, which bypass sinusoids in response to the gross morphofunctional rearrangement of the liver in cirrhosis, fail to provide oxygen and nutrients to the tissues. With endothelial dysfunction and impaired paracrine interaction between hepatocytes, sinusoidal endothelial cells, Kupffer cells, and activated hepatic stellate cells, this increases hepatic vascular resistance to portal blood flow. Further progression of portal hypertension is a consequence of complex processes including angiogenesis, vascular remodeling, and endothelial dysfunction, which contribute to splanchnic congestion, systemic vasodilation, and portosystemic shunt formation. The subsequent hyperdynamic circulatory state worsens the course of the disease.

Abbreviations: HSC, hepatic stellate cells; SEC, sinusoidal endothelial cells

2 | METHODS

The PubMed and EMbase databases, the Web of Science platform, the Google Scholar retrieval system, the Cochrane Database of Systematic Reviews, and the reference lists from related articles were used to search for relevant publications. Articles corresponding to the aim of the review were selected for 1999–2019 using the keywords: "liver cirrhosis," "PH," "esophageal variceal bleeding," "prophylaxis," and "treatment." Primary prevention of esophageal variceal bleeding in patients with cirrhosis was the inclusion criterion.

3 | PATHOPHYSIOLOGICAL MECHANISMS OF PORTAL HYPERTENSION IN LIVER CIRRHOSIS

An increase in hepatic vascular resistance to portal blood flow underlies the development of PH in cirrhosis. Hepatic vascular resistance occurs partly because of diffuse fibrosis, the formation of regenerative nodules, and remodeling and capillarization of sinusoids. It has been discovered that endothelial dysfunction and impaired paracrine interaction among damaged hepatocytes, sinusoidal endothelial cells, Kupffer cells, and activated hepatic stellate cells also play a role in causing hepatic vascular resistance. Additionally, the newly formed blood vessels, which bypass sinusoids in response to the gross morphological and functional changes in the liver in cirrhosis, fail to provide oxygen and nutrients to the tissues. The lack of oxygen and nutrients worsens the course of the disease and contributes to the increase in hepatic vascular resistance to portal blood flow.[2] The complex processes of angiogenesis, vascular remodeling, and endothelial dysfunction result in subsequent splanchnic congestion, portosystemic shunt formation, and a developed hyperdynamic circulatory state. This leads to PH progression and the occurrence of related complications, particularly variceal bleeding (Figure 1).[3]

4 | THE ASSESSMENT OF PORTAL HYPERTENSION SEVERITY IN LIVER CIRRHOSIS

4.1 | Hepatic venous pressure gradient

Hepatic venous pressure gradient (HVPG) measurement is the "gold standard" for the assessment of PH severity in cirrhosis. HVPG normal values are from 1 to 5 mmHg. The values higher than 5 and up to 10 mmHg indicate PH usually without the development of any clinical

signs. Esophageal varices form when HVPG reaches 10-12 mmHg and the risk of variceal bleeding is greatly contributed by increasing HVPG values in PH.[4] Accordingly, patients with cirrhosis may have either subclinical PH (HVPG is limited to 6-10 mmHg) or clinically significant PH (CSPH) (HVPG is > 10 mmHg), which is divided into two subcategories: mild (the presence of esophageal varices or splenomegaly with thrombocytopenia) and severe (the presence of both esophageal varices and splenomegaly with thrombocytopenia).[5] Traditionally, esophageal varices are found during esophagogastroduodenoscopy. Their endoscopic severity correlates with HVPG and, accordingly, with the risk of variceal bleeding.[6]

HVPG measurement has an important diagnostic and prognostic value. However, its measurement is possible only in specialized centers. In addition, the invasiveness of this procedure and the need for repeated procedures elevate the risk of possible complications and increase the costs. These restrictions have contributed to the development of alternative methods of assessing PH severity.[7] Several biochemical tests and serum concentrations of inflammatory biomarkers, as well as imaging techniques are reported to correlate with CSPH.

4.2 | Biochemical tests

The following biochemical tests that reflect inflammation and liver fibrosis are reported to correlate with CSPH:

- risk scale (−0.193 + (−0.359 × albumin) + (−16.456 × INR) + (−0.016 × ALT)) > 0.06;[8]
- the aspartate aminotransferase/platelet ratio index > 1.09;[9]
- osteopontin concentration > 80 ng/mL;[10]
- Von Willebrand factor values ≥ 241%;[11]
- FibroTest values > 0.77;[12]
- biochemical plasma marker of true type V collagen formation Pro-C5 > 330 ng/mL;[13]
- the VITRO score (the Von Willebrand factor-Ag/platelet ratio) > 1.58;[14]
- the indocyanine green retention test at 15 minutes.[15]

Additionally, serum concentrations of IL-1β, IL-1R-α, Fas-R, VCAM-1, TNFβ, and HSP-70 correlate with HVPG values of <12 mmHg.[16]

4.3 | Doppler ultrasound

Changes in hepatic venous blood flow, although with moderate accuracy, may reflect the severity of PH.[17] Also, patients with a damping index (minimum velocity/maximum velocity of the hepatic vein waveform) of >0.6 are significantly more likely to have HVPG > 12 mmHg.[18] The subharmonic-aided pressure estimation of the hepatic vein could be useful to suspect PH.[19] The subharmonic-aided pressure estimation gradient and HVPG values had a linear correlation of .82 and even .97 for patients with an HVPG > 12 mmHg.[20] Contrast enhancement ultrasonography, a method that utilizes a microbubble contrast agent to measure its arrival time at the hepatic or splenic vein and artery and intrahepatic transit time,[21] was prospectively estimated in several studies and was able to distinguish CSPH. For that matter, a hepatic vein arrival time value of <14 seconds was used.[22] Intrahepatic transit time of 6 seconds was noted to be the most reliable and optimal value to diagnose severe PH.[23] The traveling time of microbubbles from the splenic artery to the splenic vein also corresponded to HVPG and was 13.5 seconds for HVPG > 10 mmHg and 14.5 seconds for HVPG > 12 mmHg.[24]

4.4 | Computed tomography

In several studies, computed tomography was used to investigate if the values of the liver and spleen volume may serve as predictors of CSPH. The following scale and prognostic models were developed:

- prognostic model (13.651 − 6.187 × ln (liver/spleen volume) + 2.755 × (classification of varices: small, 1; large, 2)) predicts HVPG > 12 mmHg;[25]
- prognostic model (18.726 − 0.324 (albumin) + 1.57 (aminotransferase-to-platelet ratio index) + 0.004 (liver volume) has an optimal cutoff value of 12.84;[26]
- scale (17.37 − 4.91 × ln (liver/spleen volume ratio) + 3.8 (in the presence of ascitic fluid in the perihepatic space) makes it possible to predict HVPG about 10 mmHg but does not have the same precision in patients with extreme HVPG values and has an unsatisfactory diagnostic performance for CSPH in patients with HBV-related cirrhosis;[27,28]
- virtual HVPG, a computational model based on computed-tomography angiography images, correlates with transjugular HVPG and is able to diagnose CSPH;[29]
- rHVPG, a radiomics signature, shows higher diagnostic performance than the imaging-based and serum-based noninvasive models including liver stiffness by FibroScan in HBV-dominant cirrhotic cohort.[30]

4.5 | Magnetic resonance imaging

Azygos blood flow rate of 4.4 mL/s by two-dimensional cine contrast-phase magnetic resonance imaging is a noninvasive marker of HVPG ≥16 mmHg.[31]

4.6 | Noninvasive measurements of liver and spleen stiffness

Different elastography techniques were used to assess the values of liver and spleen stiffness and proved to be valuable diagnostic tools for CSPH. In a meta-analysis of nine studies, the performance of point shear wave elastography for the diagnosis of CSPH was reasonably good, but standardization is needed due to significant heterogeneity in the imaging devices, protocols, liver stiffness measurement methods, and cutoff values used.[32] Two-dimensional shear wave elastography,

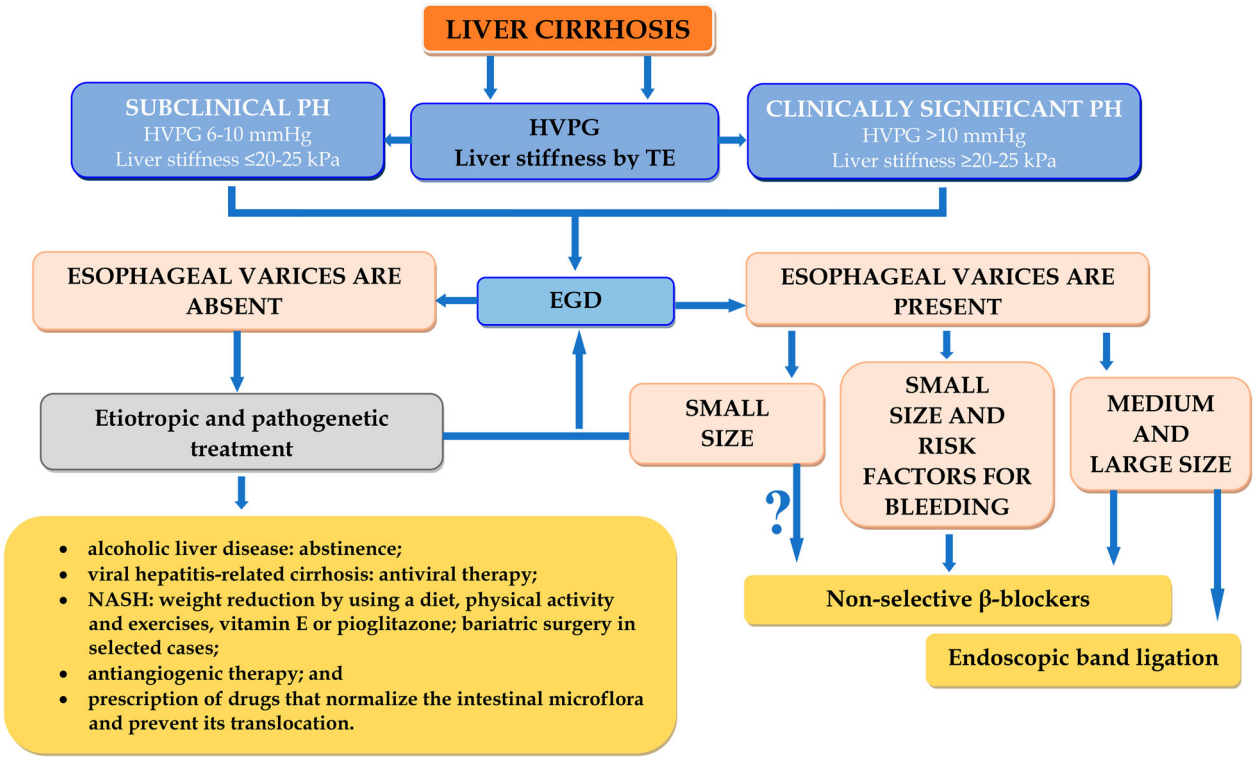

FIGURE 2 Proposed algorithm for the diagnosis and treatment of patients with cirrhosis who have not had bleeding from esophageal varices
Abbreviations: EGD, esophagogastroduodenoscopy; HVPG, hepatic venous pressure gradient; NASH, nonalcoholic steatohepatitis; PH, portal hypertension

unlike transient elastography, is considered a useful method for monitoring hemodynamic responses to drug therapy.[33] Its optimal cutoff values for the prediction of CSPH range from 15.2 to 24.6 kPa.[34] The values of liver stiffness by magnetic resonance elastography correlated with HVPG[35] and the values of spleen stiffness > 10.5 kPa reliably predicted CSPH.[36] Also, the combination of liver T1 relaxation time and splenic artery velocity measurements may increase the diagnostic effectiveness of magnetic resonance elastography.[37] However, all of the aforementioned methods require further validation and research. Currently, only transient elastography is recommended by the Baveno VI Consensus Workshop as a reliable noninvasive clinical tool to rule in CSPH. Liver stiffness values in the range of 20-25 kPa by transient elastography may be used to predict CSPH in patients with cirrhosis of viral etiology.[38] Liver stiffness values of 21.8 and 29.1 kPa in patients with alcoholic liver disease may refer to CSPH and severe PH, respectively.[39] At the same time, the combined liver stiffness measurement <20 kPa and platelet count >150 G/L algorithm is recommended to exclude CSPH.[40]

5 | PREPRIMARY PREVENTION OF VARICEAL HEMORRHAGE

Depending on the presence of subclinical PH or CSPH, patients with cirrhosis should be divided into those who need preprimary prophylaxis, which aims to prevent the formation of varices, and those who need measures aimed at variceal bleeding prevention (Figure 2).[41]

Nonselective β-adrenergic blockers (NSBBs) are the drugs of choice for primary prevention of bleeding from esophageal varices. Their ability to reduce cardiac output by blocking β1-adrenergic receptors and decrease splanchnic vasodilation by blocking β2-adrenergic receptors leading to a decrease in portal pressure. However, the absence of a hyperdynamic circulatory state makes it inappropriate to use them in cirrhotics with subclinical PH.[42] At this stage of the disease, therapeutic measures should be based on the etiological and pathogenetic approach.[43,44]

The leading causes of cirrhosis are alcohol and hepatitis B and C. Recently, nonalcoholic steatohepatitis has become a crucial etiology of cirrhosis. Primary biliary cholangitis, autoimmune hepatitis, Wilson's disease, and hereditary hemochromatosis also may make a contribution to cirrhosis development in particular patients.[45]

5.1 | Alcoholic liver disease

In patients with alcoholic liver disease, abstinence is the essential and fundamental treatment as it improves liver function, leads to liver fibrosis regression, and reduces portal pressure.[46]

5.2 | Viral hepatitis-related cirrhosis

With the advancement of antiviral therapy in the past decade, cirrhosis secondary to viral hepatitis has undergone a substantial

change in its natural course following antiviral therapy. A sustained virologic response has a positive effect on the histological structure of the liver and significantly decreases HVPG values.[47,48] Manolakopoulos et al[49] conducted a prospective study that proved that virologic and biochemical response at 12 months after lamivudine initiation (100 mg daily) correlates with a significant reduction of portal pressure in patients with HBV-induced cirrhosis whom also have CSPH. HVPG decreased >20% or below the 12 mmHg threshold in 10 of 13 patients with baseline HVPG ≥ 12 mmHg.

In a large-scale prospective study by Bruno et al,[50] a sustained virologic response after antiviral therapy with recombinant interferon (IFN)-α monotherapy or in combination with both pegylated IFN and ribavirin prevented the development of *de novo* esophageal varices in the long term in patients with compensated Child-Turcotte-Pugh (CTP) class A HCV-induced cirrhosis who did not have esophageal varices.

In a retrospective study by Mandorfer et al,[51] which involved patients with HCV-induced cirrhosis (CTP class A and B), sustained virologic response to IFN-free therapies improved PH. Patients received sofosbuvir (400 mg daily) in combination with ribavirin (weight-based doses ranged from 1000-1200 mg daily), simeprevir (150 mg daily), sofosbuvir or ledipasvir (400 mg and 90 mg daily respectively), or the 3D regimen (a once-daily dose of 12.5 mg of ombitasvir, 75 mg of paritaprevir, and 50 mg of ritonavir plus 250 mg of dasabuvir twice a day) with or without ribavirin. Treatment duration varied from 12 to 24 weeks. HVPG normalized to <6 mmHg in 63% of patients with a baseline HVPG between 6 and 9 mmHg. Moreover, no patients progressed to CSPH (HVPG ≥10 mmHg). However, in patients with HVPG > 15 mmHg, the effectiveness of these therapies was variable. Furthermore, 20% of patients had an increase in HVPG, even after reaching a sustained virologic response. This suggests that IFN-free therapy is more reliable and efficient in ameliorating subclinical PH.

Somewhat different results were obtained during an open clinical study conducted in nine international centers. The study involved 50 patients with HCV-induced cirrhosis (CTP classes A and B) who had esophageal varices and HPVG > 6 mmHg. All patients received 48 weeks of treatment with 400 mg of sofosbuvir daily and ribavirin (weight-based doses ranged from 1000 to 1200 mg daily). Of the nine patients with CSPH, who achieved a sustained virologic response, eight (89%) had a > 20% reduction in HVPG and three had their pressure reduced to < 12 mmHg.[52]

In addition, it was revealed that IFN-free therapy lessens PH in HIV/HCV-coinfected cirrhotic patients after a sustained virologic response. Patients were treated with sofosbuvir 400 mg daily plus daclatasvir 60 mg daily or weight-based ribavirin 1000-1200 mg twice a day, or received the fixed-dose combination of sofosbuvir/ledipasvir 400 mg/90 mg daily. In patients with CSPH, HVPG decreased from 14.1 ± 2.9 to 10.4 ± 3.9 mmHg and a hemodynamic response (HVPG decrease ≥10%) was observed in 73% of the patients.[53]

5.3 | Nonalcoholic steatohepatitis

The pathophysiological mechanisms of PH in nonalcoholic steatohepatitis have not yet been verified and are certainly diverse. Nevertheless, a persistent proinflammatory state may generate a fibrogenic and angiogenic response in the liver, contributing to an increase in hepatic vascular resistance to portal blood flow. In nonalcoholic steatohepatitis, an increase in portal pressure has been reported in the absence of significant fibrosis[54] with hepatocellular ballooning due to lipotoxicity and/or only mild perisinusoidal fibrosis.[55] Modern therapy for nonalcoholic steatohepatitis should concentrate on weight reduction, aerobic exercise, and vitamin E or pioglitazone in certain patients. In selected cases, bariatric surgery may be beneficial to patients with nonalcoholic steatohepatitis.[56] Ursodeoxycholic acid, immunosuppressive agents, and phlebotomy and/or iron chelators have been utilized clinically for the treatment of primary biliary cholangitis, autoimmune hepatitis, and hereditary hemochromatosis, respectively. All of these treatments can lead to remission or the delayed progression of these diseases.[57]

5.4 | Specific antifibrotic and antiangiogenic and therapy

Despite the importance of fibrogenesis and angiogenesis in the pathogenesis of PH in liver cirrhosis, only a small number of drugs have been investigated as possible antifibrotic and antiangiogenic therapy. Particularly, medicines that can modulate the activity of the coagulation cascade may be of interest in the light of recent data on the ability of coagulation proteins to activate hepatic myofibroblasts and accelerate fibrogenesis.[58] For example, Shi et al[59] noted a positive effect of low molecular weight heparin on liver fibrosis in patients with chronic viral hepatitis B. The improvements included a decrease in serum concentrations of hyaluronic acid and type IV collagen, as well as a decrease in collagen synthesis in the liver after treatment. In a pilot study by Dhar et al,[60] an 8-week course of warfarin, during which the international normalized ratio was maintained in the range of 2-3, significantly improved liver stiffness values in patients with chronic viral hepatitis C (the Ishak fibrosis score of 3-4) without serious side effects.

In general, there is not yet any specific treatment of liver fibrosis that is effective or approved for clinical use. Therefore, given the urgency of the problem, research in this direction is necessary. Research should take into account the recommendations adopted in 2014 at the AASLD conference on strategies and endpoints of antifibrotic drug trials in chronic liver disease. The most important provisions of the conference focused on the identification of potential unpredictable consequences and/or adverse outcomes associated with antifibrotic therapy implementation, such as the possibility of off-target toxicities.[61]

A number of experimental studies explored how angiogenesis inhibitors act and affect PH, but only sorafenib, a tyrosine kinase inhibitor, has been investigated as a possible antiangiogenic therapy for

PH.[62] The influence of sorafenib on the systemic and portal hemodynamics was first assessed by Coriat et al.[63] The study included seven patients with cirrhosis and hepatocellular carcinoma (CTP class A in five and CTP class B in two patients). Sorafenib was administered for 1 month at 400 mg twice daily. Side effects appeared in one patient, which led to the reduction of the daily dosage. Portal blood flow decreased by at least 36%, while the azygos vein and abdominal aorta blood flow did not change.

Pinter et al[64] investigated the influence of sorafenib on HVPG and systemic hemodynamics in a pilot study that included 13 patients with cirrhosis and hepatocellular carcinoma (10 patients had CTP class A and three patients had CTP class B). Sorafenib was applied at 400 mg twice daily for 2 weeks. HVPG was reduced by >20% from the baseline values in 4 of the 11 patients with PH. Nevertheless, the drug had no significant effects on portal pressure in a randomized double-blind placebo-controlled study that included nine patients with cirrhosis and hepatocellular carcinoma receiving the same dosage of sorafenib.[65] Moreover, administration of the drug caused the following adverse events: gastrointestinal (pain, diarrhea, nausea), cutaneous, and fatigue. The main shortcoming of tyrosine kinase inhibitors is hepatoxicity. Yet, their selective delivery to target cells, particularly hepatic stellate cells, seems to be a promising direction and requires further study.

5.5 | Targeting gut microbiota

In light of data on the role of endotoxemia in the pathogenesis of cirrhosis, PH, and its complications,[66] the drugs that influence the gut microbiota composition and prevent its translocation may be promising. Oral administration of norfloxacin (800 mg daily for 4 weeks) reduced portal pressure and improved the hyperdynamic circulation by decreasing serum endotoxin concentration in patients with alcohol-related liver cirrhosis.[67] Moreover, the long-term administration of norfloxacin (400 mg daily for 1 year) prevented hepatorenal syndrome development and improved the survival rate of decompensated patients.[68]

In a prospective study including patients with alcohol-related decompensated liver cirrhosis, the severity of endotoxemia and an 18% decrease in HVPG were achieved by decontaminating the intestine of patients with a nonabsorbable antibiotic rifaximin (1200 mg daily for 28 days).[69] Rifaximin administration for up to 5 years improved survival and reduced risk of developing complications of PH in these patients.[70] These positive effects of rifaximin on PH may be not only due to its action on the intestinal microflora but also the inhibition of the binding of lipopolysaccharide with TLR4 on the surface of the hepatic stellate cells. Therefore, rifaximin contributes to their inactivation and also may participate in the breaking of the fibronectin-mediated interaction between sinusoidal endothelial cells and hepatic stellate cells, eventually suppressing angiogenesis and fibrogenesis in the liver.[71]

The influence of propranolol monotherapy and its combination with rifaximin on HVPG was evaluated in an open pilot randomized controlled trial (RCT). Three-month-long treatment with rifaximin (1200 mg daily) and propranolol (starting at 40 mg daily titrated to a maximum of 320 mg daily to reduce heart rate by 25% or achieve a heart rate of 55 beats per minute) more effectively decreased HVPG than propranolol monotherapy (5.69 ± 4.19 vs. 3.48 ± 3.85 mmHg, respectively, $P = .057$).[72]

The therapeutic effect of probiotics in PH is less clear. In particular, the combined probiotic VSL#3 that contains eight different strains (*Bifidobacterium breve*, *Bif. longum*, *Bif. infantis*, *Lactobacillus acidophilus*, *L. plantarum*, *L. casei*, *L. bulgaricus*, *Streptococcus thermophilus*) is able to stabilize the intestinal epithelial barrier, reduce bacterial translocation, and reduce systemic endotoxemia. This reduces the production of proinflammatory cytokines and NO, eliminates endothelial dysfunction of mesenteric arteries caused by vascular oxidative stress, and inactivates the local renin-angiotensin system.[73] Monotherapy with the probiotic VSL#3 at a dose of 3600 billion CFU daily for 2 months had no significant impact on CSPH in a pilot study involving eight patients with compensated liver cirrhosis (CTP class A)[74] and in a randomized double-blind placebo-controlled study including seven patients with decompensated liver cirrhosis (CTP classes B and C).[75]

In a randomized double-blind placebo-controlled trial in parallel groups including 94 cirrhotic patients having large esophageal varices without variceal bleeding history, changes in HVPG were studied after administering propranolol as a monotherapy or in combination with either VSL#3 (900 billion CFU daily) or norfloxacin (400 mg daily). The treatment was carried out for 2 months. The initial propranolol dose of 40 mg daily was increased by 20-40 mg every 2 days (to the maximum of 320 mg daily) until the heart rate reached 55 beats per minute or side effects occurred. The combination of propranolol with probiotic or antibiotic was more effective in reducing portal pressure than the use of NSBB only by 19%, 18%, and 11%, respectively). Moreover, the combination therapy was safe and well tolerated by patients.[76]

Some studies noted the ability of ascorbic acid and dark chocolate to reduce the postprandial increase in portal pressure due to their antioxidant activity.[77,78] However, this requires further investigation.

6 | PRIMARY PREVENTION OF VARICEAL HEMORRHAGE

The goal of therapy for CSPH is to reduce HVPG values to <12 mmHg or make it 20% lower than the original value. Treatment should correct the hemodynamic disturbances characteristic of CSPH and, avoiding arterial hypotension, reduce the inflow of splanchnic blood into the portal vein while maintaining portal blood flow for adequate liver perfusion.[79]

6.1 | Nonselective β-blockers

The influence of NSBB on PH has been well studied.[80] A combination of NSBB and endoscopic band ligation showed a good ability to prevent recurrent variceal bleeding, which was approved in a recent meta-analysis.[81] Also, NSBB proved useful in primary prophylaxis of

bleeding from medium/large esophageal varices (≥5 mm).[82] On the other hand, their ability to prevent the formation of small esophageal varices (<5 mm) has not been conclusively determined.[83] In a recent meta-analysis, the majority of RCTs included in it did not reveal significant advantages in prescribing NSBB over placebo to reduce the growth of small varices, the risk of first bleeding, and mortality.[84] In contrast, in the RCT conducted by Bhardwaj et al,[85] carvedilol, an NSBB with a weak anti-α1-adrenergic activity applied at a dose of 12.5 mg daily, slowed the progression of esophageal varices during at least a 24-month follow-up period compared with placebo. However, there were no significant differences in the reduction of HVPG, the risk of first bleeding, and survival.

Notably, the size of esophageal varices is not enough to stratify the risk of bleeding. The additional adverse risk factors are severe liver dysfunction (CTP class B or C), an alcoholic etiology of liver disease, and the presence of "red wale signs" on varices during an initial esophagogastroduodenoscopy. Taking into account these circumstances, the current consensus decisions indicate that patients with small esophageal varices and the aforementioned risk factors have to receive prophylactic NSBB treatment and may even receive it in the absence of esophageal varices.[38] Moreover, patients who do not receive prophylaxis need to have endoscopic screening done every 1 or 2 years.[86] If medium and large varices are present, the need for prophylactic treatment is not in doubt because of the high probability of bleeding. In this case, the method of choice is either NSBB therapy or endoscopic band ligation.[87]

Propranolol was the first NSBB introduced into clinical practice for the treatment of PH. Currently, its impact on the portal and systemic hemodynamics is well studied. It was established that propranolol is able to reduce HPVG by 10% to 31%, azygous blood flow by 29% to 47%, cardiac output by 10% to 31%, average arterial pressure by 0% to 14%, and hepatic blood flow by 0% to 39%.[88] However, NSBB should be used with caution because a possible negative reaction of systemic hemodynamics increases the risk of severe complications including deaths that are not associated with variceal bleeding.[89] Therapy with propranolol should be started from a dose of 20-40 mg daily that may be further increased up to 320 mg daily in patients without ascites and up to 160 mg daily if ascites is present in order to reach target heart rate and systolic blood pressure. The maximum dose of nadolol, another representative of this pharmacological group, should not exceed 160 mg daily if ascites is absent and 80 mg daily in those with ascites.[90]

Although the meta-analysis by D'Amico et al[91] showed significant advantages of NSBB over placebo in preventing the first bleeding episode from esophageal varices (15% vs. 24%) after 2 years of treatment, NSBB clinical efficacy in PH is variable. In a number of studies, HVPG did not decrease by ≥20%. In the long-term period, a weakening of the therapeutic effect was noted in 50% to 70% of patients.[92] At the same time, an acute hemodynamic response in the form of a decrease in HVPG by ≥12% from a baseline value 20 minutes after intravenous administration of propranolol (0.15 mg/kg) indicates good prospects for further preventive therapy.[93]

In a pilot study, Reverter et al[94] presented a simple predictive model to identify HVPG-responders to intravenous propranolol based on metabolomic serum analysis. They have identified several lipid substances, most of which were nonesterified fatty acids and glycerophospholipids (plasmalogens), at significantly different concentrations between HVPG-responders and nonresponders.

Kim et al[95] developed a nomogram to estimate the risk of failure of primary prophylaxis with propranolol therapy. The nomogram scores for large varices, absence of ascites, and high liver volume index were 1, 0.64, and 0.62, respectively. Liver volume was measured in portal venous phase images of multidetector computed tomography. Discrimination analysis showed that patients with a nomogram score > 0.6 had a significantly higher incidence of prophylaxis failure compared to patients with low scores (subdistribution hazard ratio, 7.54; 95% CI, 2.88 to 19.73; $P < .001$).

Patients with cirrhosis who are nonresponsive to propranolol should receive carvedilol to prevent the first bleeding from esophageal varices if contraindications are absent.[96] The optimal dose of carvedilol is 12.5 mg daily.[97] Indeed, in the study by Reiberger et al,[98] the use of carvedilol (the average dose of 12.5 mg daily) made it possible to achieve a hemodynamic response in approximately 50% of patients who were not responsive to propranolol (the average dose of 100 mg daily). While mean arterial pressure and heart rate did not significantly differ between the groups, carvedilol reduced portal pressure significantly more than propranolol (19% vs. 12%). Within 2 years of follow-up, the first episode of esophageal variceal bleed was observed in 5% of patients taking carvedilol and in 11% of patients taking propranolol. Liver dysfunction was detected, respectively, in 26% and 38% of cases and mortality was 11% and 14%, respectively. In this study, NSBB doses were selected according to the recommended scheme, focusing on the change in pulse and systolic blood pressure. It was reported that, unlike propranolol, an increase in the dose of carvedilol from 6.25-12.5 mg daily to 25-50 mg daily resulted in a significant decrease in mean arterial pressure and a decrease in pulse without an additional effect on HVPG. These hemodynamic results suggest the use of low doses of carvedilol (6.25-12.5 mg daily) to avoid adverse events associated with arterial hypotension or bradycardia.

In a single-center prospective proof-of-concept cohort study, Kim et al[99] estimated a prediction model for hemodynamic response to prophylactic carvedilol therapy in cirrhotic patients with esophageal varices: ModelΔspleen stiffness = 0.0490 − 2.8345 × Δspleen stiffness with score = (exp(ModelΔspleen stiffness))/(1 + exp(ModelΔspleen stiffness)). If the threshold value of 0.530 was used, the model had an area under the receiver operating characteristic curve of 0.803. The sensitivity, specificity, accuracy, and positive and negative likelihood ratios for predicting hemodynamic response were 0.814, 0.745, 0.783, 3.192, and 0.250, respectively. The authors concluded that paired spleen stiffness measurements using acoustic radiation force impulse elastography may be a promising noninvasive tool for predicting hemodynamic response to carvedilol therapy applied as primary prophylaxis in patients with cirrhosis who have a high risk of bleeding from esophageal varices.

6.2 | NSBB and nitrates

The combined use of NSBB and nitrates for the prevention of the first episode of bleeding from esophageal varices has shown conflicting results. On the one hand, the effectiveness of this approach was noted in an RCT, in which 74 patients with cirrhosis received nadolol at a dose of 40-160 mg daily and 72 received nadolol (40-160 mg daily) along with isosorbide-5-mononitrate (10-20 mg three times a day) simultaneously. Long-term results traced over 7 years showed that the cumulative risk of bleeding from esophageal varices turned out to be 29% and 12%, respectively. Meanwhile, the accompanying mortality was 5.4% and 4.2%, and the overall mortality was 40.5% and 34.7%, respectively.[100]

In contrast, a multicenter prospective double-blind RCT by García-Pagán et al[101] did not reveal the benefits of combination therapy. Of the 349 patients with cirrhosis selected for prophylactic treatment, 174 received propranolol (the dose was adjusted until pulse reduction decreased by 25% from the initial value or became <55 beats per minute) with placebo and 175 received propranolol and isosorbide-5-mononitrate in the initial dose of 20 mg with an increase up to 40 mg two times a day in the absence of symptomatic hypotension or severe headache. The follow-up period did not exceed 2 years. The actuarial probability of bleeding from esophageal varices was 8.3% in the propranolol group and 10.6% in the combined group during the first year. For the 2-year period, it was 5% and 12.5%, respectively. The only independent predictor of variceal bleeding was the size of varices >5 mm. However, in patients with esophageal varices ($n = 196$), there were no differences in the frequency of bleeding between the groups. The actuarial probability of survival during the first year was 96% and 89% and during the 2 years was 95% and 88%, respectively.

6.3 | Endoscopic therapy

Endoscopic therapy is widely used as a part of the complex treatment and prophylaxis of acute hemorrhages from esophageal varices.[102] Given the low effectiveness of endoscopic sclerotherapy and the risk of associated complications, only endoscopic band ligation is recommended to prevent the first bleeding episode from esophageal varices.[103] In a multicenter RCT including 166 patients with cirrhosis (84 patients received endoscopic sclerotherapy and 82 were included into the control group), preventive endoscopic sclerotherapy did not reduce the incidence of bleeding from esophageal varices in patients with a low and moderate risk of their development and did not affect overall survival.[104] On the contrary, in a meta-analysis comparing prophylactic endoscopic band ligation with untreated controls among 601 patients in five homogeneous trials, relative risks of the first variceal bleeding, bleeding-related mortality, and all-cause mortality were 0.36 (0.26-0.50), 0.20 (0.11-0.39), and 0.55 (0.43-0.71) in endoscopic band ligation group and 4.1, 6.7, and 5.3 in controls, respectively.[105]

In a prospective cohort study by Dell'Era et al,[106] which included patients with cirrhosis who had contraindications, intolerance, or were nonresponsive to NSBB, endoscopic band ligation was no less useful in preventing the first bleeding from esophageal varices than NSBB in good responders.

In a meta-analysis involving 19 RCTs and a total of 1 504 patients with cirrhosis, 731 of whom underwent endoscopic band ligation and 773 received NSBB (patients were treated with propranolol in 17 RCTs, with nadolol in one RCT, and with carvedilol in one RCT), bleeding rates, including bleeding from esophageal varices, were significantly higher in patients receiving conservative treatment at 31%, while endoscopic intervention was 19%. However, the related mortality practically did not differ and was 6.3% and 5.1%, respectively. The typical complications after endoscopic band ligation were clinically significant bleedings from ulcers formed after the procedure and sternum pain. The complications from treatment with NSBB included dizziness, hypotension, impotence, apathy, and peripheral edema.[107]

In a recent systematic review with a network meta-analysis of 32 RCTs with a total of 3 362 patients with large esophageal varices without bleeding episodes, the authors evaluated the effectiveness of various preventive measures and overall survival with a minimum follow-up period of 12 months. NSBB (propranolol, nadolol, carvedilol), isosorbide-5-mononitrate, and endoscopic band ligation, either alone or in combination, were compared with each other or placebo. NSBB monotherapy reduced all-cause mortality and the risk of the first episode of bleeding from esophageal varices. In addition, it had a lower risk of serious complications compared to endoscopic band ligation.[108]

An important advantage of endoscopic band ligation is the eradication of esophageal varices. However, this technique also contributes to their recurrence and the development of bleeding as a result of an increase in portal pressure caused by repeated procedures. Theoretically, this can be avoided by using an NSBB. However, in a retrospective two-center study, the concomitant NSBB therapy neither decreased bleeding rates (log-rank: $P = .353$) nor mortality (log-rank: $P = .497$) as compared to endoscopic band ligation alone, which shows the inappropriateness of the combined treatment.[109]

Given that the effectiveness of NSBB and endoscopic band ligation is at least equivalent in preventing the first episode of bleeding from esophageal varices, the latest consensus recommends choosing a method primarily according to local resources, the experience of specialists working in a particular hospital, the patient's preference, contraindications, and side effects. However, they regard NSBB treatment as first-line therapy due to its low cost, ease of administration, and no need for specialized knowledge. Endoscopic band ligation is indicated if patients have intolerance or contraindications to NSBB. The disadvantages of this method include the risks associated with sedation, as well as possible complications such as dysphagia, the development of esophageal ulcers, strictures, and bleeding.[110]

7 | CONCLUSION

Given the urgency of the problem of bleeding from esophageal varices in patients with cirrhosis, medical tactics aimed at preventing these

severe complications of PH have been actively discussed in recent decades. Despite the fact that NSBB is considered the drugs of choice in this clinical situation, the optimal approach remains controversial. Notably, the modern consensus does not recommend the use of NSBB in subclinical PH. NSBBs have to be prescribed in patients with CSPH who have small esophageal varices and the risk factors for bleeding. NSBB may be prescribed in the absence of esophageal varices. The use of NSBB is also first-line therapy for the primary prevention of bleeding from medium and large esophageal varices. Patients who have contraindications to NSBB should undergo endoscopic band ligation. Thus, the stratification of patients with liver cirrhosis by the severity of PH and an individual approach to the choice of treatment that prevents the formation of esophageal varices and variceal bleeding may increase the effectiveness of therapy as well as improve the quality of life and survival rate of these patients.

FUNDING

This study was funded in full by Russian Foundation for Basic Research, grant number 18-315-00434.

CONFLICT OF INTEREST

Prof. Garbuzenko has nothing to disclose. Dr. Arefyev reports a grant from Russian Foundation for Basic Research (RFBR) during the conduct of the study.

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How to cite this article: Garbuzenko DV, Arefyev NO. Primary prevention of bleeding from esophageal varices in patients with liver cirrhosis: An update and review of the literature. *J Evid Based Med*. 2020;1-12.
https://doi.org/10.1111/jebm.12407