

# Chapter 7

## Pre-primary and Primary Prophylaxis of Variceal Hemorrhage

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### Introduction

Variceal hemorrhage is a life-threatening complication of portal hypertension. Depending on the degree of liver decompensation mortality averages around 20 % [1]. In our own studies, we found an esophageal variceal bleeding-related death rate of nearly 40 % [2, 3], although in-hospital death rate of variceal bleeding has dropped considerably within the last decades [1]. However, a rather high percentage of patients still die before they are admitted. Hence, despite the fact that bleeding is no longer the most frequent complication of liver cirrhosis, preventing bleeding from varices induced by portal hypertension remains a major treatment aim. The natural history of liver cirrhosis induced by chronic viral infection [4] shows an occurrence rate of ascites and hepatocellular carcinoma of around 2 % per year after diagnosis of compensated liver cirrhosis, while variceal bleeding occurred only in 5 % of patients within a time period of 10 years. Furthermore, bleeding is often more a bystander than a cause of severe liver decompensation. Nevertheless, variceal bleeding is a dramatic event and clinicians have been developing strategies for its treatment and prevention over decades.

This chapter reviews the main achievements and delineates new approaches to avoid first variceal bleeding which includes prevention of variceal formation.

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## **Pathogenesis of Varices and Bleeding**

The driving force for the formation of varices is portal hypertension [5] associated with hampered flow of the portal venous blood to the inferior caval vein. This induces formation of collaterals to drain the blood to the right heart, mainly via the superior vena cava. Portal hypertension is defined as portal pressure, which exceeds the pressure in the vena cava by more than 5 mmHg [6]. It is commonly assumed that varices develop once this pressure surpasses 10 mmHg; a pressure threshold established as significant portal hypertension. If this pressure is higher than 12 mmHg, esophageal varices may rupture and bleed [5, 6]. Most bleedings are intestinal, namely from esophageal varices and gastric varices, while large collaterals embedded in the paraintestinal tissue very rarely show spontaneous rupture.

At the distal part of the esophagus, the varices are only covered by a thin epithelial layer and often not by the muscularis mucosae [7, 8]. Furthermore, the transmural pressure gradient augments in the thoracic segments of the collaterals, where the luminal pressure is lower than in the abdomen [9]. This may explain why the region of the gastroesophageal junction or just above the lower esophageal sphincter is critical for the occurrence of bleeding.

## ***Risk Factors and Prognostic Signs***

According to La Place's law, tension of the wall is proportional to the radius of the vessel multiplied the transmural pressure, whereas it is inversely related to the thickness of the wall [10, 11]. This law can only partially be adapted to the situation of venous collaterals in humans but it provides indications. Thus, hemodynamic factors such as the esophageal variceal blood pressure or—indirectly—the portal blood pressure on the one hand and morphological characteristics of the vessel, such as size and properties of the wall, on the other hand [7, 9] possibly deliver indications about the risk of bleeding and therewith prognostic information. Another intrinsic factor may be deranged blood coagulation, e.g., triggered by infection [12].

Several clinical situations can precipitate or augment these risk parameters.

## **Hemodynamic Parameters**

The gradient of wedged hepatic venous pressure minus free hepatic venous pressure or minus the inferior vena cava pressure approximates the portal venous pressure measured directly [13]. In patients with previous variceal hemorrhage, this hepatic venous portal pressure gradient (HVPG) was nearly always greater than 12 mmHg. Yet, this pressure could in fact represent the threshold for formation of varices rather than serve as a good discriminator for bleeding, since many retrospective studies [14, 15] failed to find significant differences of the average HVPG between bleeders

and non-bleeders. Few data exist on the risk of diurnal pressure changes, e.g., induced by meals or physical activity, which can be quite remarkable [16]. Furthermore, portal flow may vary considerably between patients with a similar degree of portal hypertension.

There is some evidence that blood pressure within the varix or transmural pressure [17], which, however, is ideally assessed invasively, might be a better predictor of variceal bleeding [18].

The new technologies that determine liver stiffness noninvasively by measuring velocity of the propagation of vibration wave can quite accurately predict significant portal hypertension, i.e., HVPG >10 mmHg. Liver stiffness below 13.6 kPa rules out significant portal hypertension, while liver stiffness greater than 21.1 kPa is always associated with an HVPG above 10 mmHg [19]. Techniques to assess liver stiffness are increasingly integrated into ultrasound devices, and future equipments might allow estimation of portal blood flow, spleen size, diameter of the portal vein, as well as stiffness of the liver in one step. It remains to be seen whether these techniques will allow monitoring of the effect of drugs applied to lower portal pressure.

### **Morphological Features of the Vessels**

Although transmural pressure is the driving force that causes rupture and bleeding, morphological alterations of the wall may well support this event. Local erosions resulting in a reduction of wall thickness can be a precipitating event in large varices with high wall tension [7, 9]. These alterations are sometimes evident during endoscopy as the so-called white clot [20].

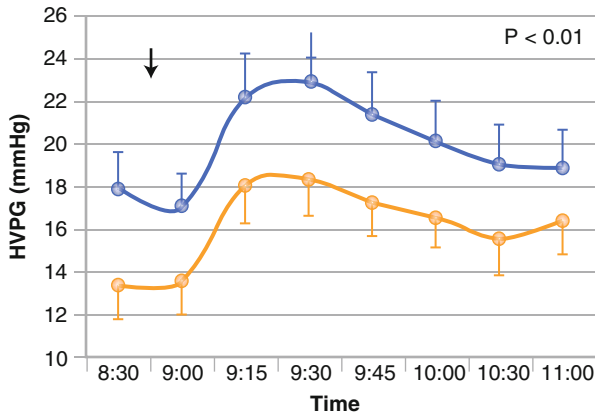
Furthermore, typical features of varices include red color signs (red wale markings, hematocystic spots) or size of varices that allow the prediction of variceal pressure and risk of bleeding [21, 22]. These parameters are part of one of the most relevant prognostic scores applied to calculate the risk of bleeding and to define patients for prophylaxis of first bleeding [21, 23–25].

### **Blood Coagulation**

Bleeding occurs more often in patients with decompensated cirrhosis independent of the macroscopic variceal characteristics. This may be partly due to an impaired coagulation following infections [12, 26].

### **Precipitating Events**

For prophylaxis of variceal bleeding, exact knowledge of events triggering bleeding is important [9]. If size of varices, wall characteristics [22–25, 27], portal as well as transmural variceal pressure, alcoholism [21], and degree of liver dysfunction are



**Fig. 7.1** Increase of the portal pressure after meal (arrow) as assessed by HVPG in 12 patients with liver cirrhosis (blue circles). Three-week treatment with propranolol ( $-25\%$  pulse rate, mean dosage  $93 \pm 13$  mg) significantly decreased portal pressure, but did not influence increase after meal (yellow circles). (Used with permission from Schiedermaier P, Koch L, Stoffel-Wagner B, Layer G, Sauerbruch T. Effect of propranolol and depot lanreotide SR on postprandial and circadian portal haemodynamics in cirrhosis. *Aliment Pharmacol Ther* 2003;18:777–784)

predictive for first bleeding, events that aggravate these parameters must be triggers for bleeding. These might include a sustained rise of portal pressure, e.g., induced by infection, alcoholism, or acute activation of contractile cells within the liver derived from the gut or elsewhere (pulmonary, urinary infection, or other foci of infection). Short-term increase of portal pressure due to meals (Fig. 7.1) or abdominal pressing have not consistently been found to trigger bleeding [16]. Erosions of the thin walls of large vessels could also be a trigger, but—again—only very few studies consider gastroesophageal reflux a risk factor for portal hypertensive bleeding [26].

According to the previously mentioned studies, strategies for pre-primary and primary prophylaxis of variceal hemorrhage should aim to:

- Prevent formation of varices mainly by reduction of intrahepatic resistance or by prevention of its increase.
- Prevent growth of varices.
- Prevent precipitating events if large varices are present, e.g., by reducing pressure and flow within the varices, by preventing infections, acute alcohol challenge, or other factors that lead to deterioration of liver function.
- Improve wall characteristics and/or reduce size of the vessels.

Pre-primary prophylaxis concentrates mainly on modulation/reduction of intrahepatic resistance, while primary prophylaxis with its available therapeutic options focuses more on modulation of the splanchnic vascular bed (e.g., application of nonselective  $\beta$ -blockers) and on direct alteration of the vascular segments at risk for bleeding (e.g., obliteration of varices using ligation).

## **Pre-primary Prophylaxis**

Patients with liver cirrhosis show esophageal varices in about 60 % of the individuals at the time of diagnosis [28]. In the remaining patients, the annual incidence of varices is about 7 % [28]. Although nonselective  $\beta$ -blockers are the standard treatment to prevent the first variceal bleeding, they have failed to retard the development of varices in cirrhotic patients [28, 29] despite encouraging experimental data [30].

Chronic liver disease is a result of a persisting hepatic injury with hepatocellular damage, inflammation, and fibrosis. During this process, many functional and structural changes, such as fibrosis, angiogenesis, hypocontractility of splanchnic vessels, and hyperreaction of contractile cells within the liver, take place and all contribute to the development of portal hypertension and formation of varices. The withdrawal of the underlying hepatic injury and different pharmacological approaches have been successfully tested in human and animal models to inhibit, attenuate, or reverse the processes associated with development of fibrosis, angiogenesis, or alterations of vascular responses. Since these processes interact during disease progression, a multimodal approach is preferred to offer new possibilities for future pre-primary prophylaxis.

### ***Withdrawal of the Underlying Hepatic Injury***

Until recently, established hepatic fibrosis was believed to be irreversible [31]. Today, however, many different studies show that elimination of the underlying cause may indeed reverse fibrosis and prevent the development of portal hypertension together with varices. Thus, different studies in patients with chronic viral hepatitis type B and C have shown that virus elimination leads to regression of fibrosis and cirrhosis [32–34], while other studies reported that drain of bile in chronic cholestasis ameliorated liver fibrosis as well as treatment of autoimmune hepatitis and weight loss in nonalcoholic steatohepatitis [35–37].

### ***Antifibrotic Strategies***

Although strategies to target the cause of the liver disease are mostly efficient, they may fail (e.g., treatment of chronic HCV infection or primary sclerosing cholangitis) or are initiated in a too advanced stage due to late diagnosis. In this situation, therapies that interrupt or attenuate fibrogenesis would be most helpful in order to decrease portal hypertension and its complications.

The key cells responsible for hepatic fibrosis are the hepatic stellate cells. They are activated and change their phenotype upon liver injury in that they transform towards cells that contract and produce extracellular matrix. Both phenomena

increase the intrahepatic resistance to portal flow. In the past, many approaches have been investigated in experimental models of fibrosis. Here, we focus on strategies that may be transferred to the human situation.

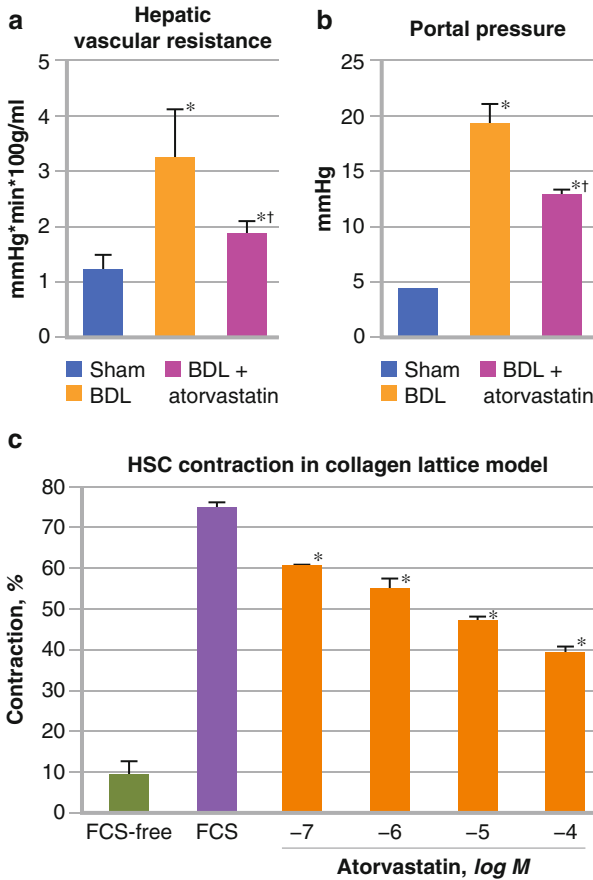
### **Activation of the Renin–Angiotensin System**

The renin–angiotensin system (RAS) is increasingly activated with decompensation of liver cirrhosis, probably as a reaction to systemic vasodilation [38, 39], while at the same time, tissue RAS, especially within the liver, may stimulate hepatic stellate cells via angiotensin 1 (AT1) receptors inducing fibrosis, vasoconstriction, and portal hypertension [40, 41]. In the past, many drugs, which modulate RAS have been validated and are now part of clinical routine in cardiovascular disorders.

Similarly, it has been shown in animal models of liver fibrosis that angiotensin type 1 receptors (AT1R) are upregulated within the liver together with angiotensin II formation. Blockade of this cascade via angiotensin-converting enzyme (ACE) or preventing angiotensin II binding to AT1 receptors attenuates fibrosis and decreases portal pressure [42–45]. Chronic administration of these available drugs might therefore play a role in the pre-primary prophylaxis of variceal bleeding. However, randomized trials are lacking to date. Around 10 years ago, a homologue to ACE, the so-called ACE2, has been described [46]. ACE2 degrades the active angiotensin II to angiotensin 1–7, which binds to the so-called MAS receptor. This receptor elicits contrary effects to AT1R-mediated processes; it blunts fibrosis and causes vasodilation. Thus, ACE2-deficient mice show more severe liver fibrosis, while the administration of recombinant ACE2 reduces experimental liver fibrosis [47, 48] and reduces portal hypertension via the degradation of angiotensin II to angiotensin 1–7 by dual effect prevention of AT1R stimulation and increased MAS receptor stimulation. Modulation of this system could also play a future role in pre-primary prophylaxis of variceal bleeding.

### **Statins**

HMG-CoA reductase inhibitors have effects that are independent from the lowering of serum cholesterol. These are mediated by the inhibition of the small GTPases [49–52]. Interestingly, statins decrease by this way accumulation of extracellular matrix within the liver, induce senescence in activated hepatic stellate cells and lead to relaxation of these cells (Fig. 7.2a–c) [49–52]. Such experimental data suggest an effect in the prevention and/or treatment of portal hypertension and thereby pre-primary prophylaxis of varices in chronic liver disease. As a proof of principle, it has already been shown in rather small studies that statins reduce portal pressure [53, 54] and possibly attenuate matrix formation [55–57]. Yet, again, large trials, especially regarding development of portal hypertension, are lacking.



**Fig. 7.2 (a–c)** Effect of 1-week atorvastatin feeding in rats with biliary cirrhosis as compared to controls. Mainly due to reduction of the intrahepatic resistance (a) the portal pressure decreases (b). This effect is caused by relaxation of activated hepatic stellate cells as shown in the in vitro experiment (c). (Used with permission from Trebicka J, Hennenberg M, Laleman W, Shelest N, Biecker E, Schepke M, Nevens F, et al. Atorvastatin lowers portal pressure in cirrhotic rats by inhibition of RhoA/Rho-kinase and activation of endothelial nitric oxide synthase. *Hepatology* 2007;46:242–253)

### Modulation of the Intestinal Microbiota

Liver cirrhosis is associated with small intestinal bacterial overgrowth, bacterial translocation, and change of the gut microbiota [58, 59]. All these factors can indirectly cause an increase in intrahepatic resistance (e.g., via activation of intrahepatic macrophages and hepatic stellate cells), hyperdynamic circulation and impairment of coagulation, derangements that may provoke portal hypertension and variceal

bleeding [60–63]. Thus, pathogen-free animals or those with interrupted pathways of innate immunity show considerably less hepatic fibrosis [64, 65]. Future will tell whether influencing intestinal microorganisms, the host immune response and the mucosal barrier will one day become a tool for the prophylaxis of variceal formation and variceal bleeding. A small trial showed that application of Rifaximin, a nonabsorbable antibiotic, indeed reduced portal pressure in humans [66].

### ***Antiangiogenic Approaches***

Antiangiogenic factors trigger and aggravate hepatic fibrogenesis [67] and it has been repeatedly shown, at least in animal models, that substances such as antibodies against vascular endothelial growth factor (VEGF) or tyrosine kinase inhibitors attenuate liver fibrosis [68–73]. Yet, as of today it remains open whether such strategies will translate into clinical hepatology for the prevention of varices.

Interestingly, angiogenesis also plays an important role in the de novo formation of portosystemic collaterals. Inhibition of angiogenesis in splanchnic vessels by inhibiting VEGF or PDGF resulted in the reduction of portal pressure and could possibly prevent the formation of varices [74–76]. One drug already used in clinical hepatology is sorafenib. Apart from its antiproliferative effect, it blunts angiogenesis as shown in portal hypertensive animals [71].

### ***Modulation of Hepatic and Extrahepatic Contractile Cells***

Portal hypertension is driven by the increased intrahepatic resistance—which is structural (fibrosis) and dynamic (intrahepatic activation of contractile cells)—and by an increased portal tributary blood flow resulting from splanchnic vasodilation [39, 77]. Both vessel beds are targets for drugs to prevent variceal bleeding or reverse portal hypertension.

### **Decreasing Hepatic Resistance**

Different approaches have been shown to lower portal pressure via reduction of intrahepatic resistance. An important target is the deactivation of stimulated hepatic stellate cells, Kupffer cells, or liver sinusoidal endothelial cells to facilitate portovenous blood flow through the liver. Drugs that blunt the basic mechanisms of contraction, e.g., the RhoA/Rho-kinase pathway, or enhance the delivery of vasodilative molecules, such as nitric oxide, effectively reduce intrahepatic resistance and portal pressure [49, 78–80]. Drugs that have been successfully tested for efficacy in this situation include AT1R antagonists [44, 45, 81, 82], amiloride [83], nitroflurbiprofen [84], nitrates [77], statins [49, 53, 54, 85],  $\beta$ 3-AR agonists [80], or MAS receptor agonists [86]. The following paragraphs will concentrate on clinical trials, which tested some of these drugs for prevention of variceal bleeding.



Unfortunately, medical treatments that reduce intrahepatic resistance may have considerable systemic side effects by further decreasing systemic arterial blood pressure and aggravating hyperdynamic circulation. Therefore, targeting specific cells within the liver might provide an answer. For example, a potent Rho-kinase inhibitor coupled to modified human serum albumin selectively decreased intrahepatic resistance without influencing systemic hemodynamics [87]. These molecules can also be used as a Trojan horse for the AT1R-blocker losartan [88].

### **Increasing Splanchnic Vascular Tone**

Increase of the splanchnic vessels tone decreases portal pressure via reduction of the portal tributary blood flow. Several animal studies have shown that low-dose AT1R-blockers and urotensin II receptor antagonists lower portal pressure via an increase of splanchnic vascular resistance and a decrease in the portal blood flow [45, 81, 89, 90]. Further compounds, such as neuropeptide Y, multi-kinase inhibitors, and MAS receptor blockers, exhibit a portal pressure lowering effect via correcting the deranged vasoconstrictile pathways and increasing the splanchnic vascular tone [39, 72, 86, 91–93]. Yet, at present, all these approaches to prevent and treat portal hypertension are experimental with the exception of the application of some vasoconstrictors such as terlipressin [94, 95].

### **Primary Prophylaxis**

Shunts, drugs, and endoscopic obliteration of varices prone to bleed have all been tested for prevention of first variceal hemorrhage in numerous clinical trials that are addressed in the following paragraphs.

#### ***Shunting Procedures***

Four randomized controlled trials [96–99] were performed in the 1960s and early 1970s. Variceal bleeding was prevented by insertion of a surgical shunt in the vast majority of patients, while first bleeding ranged between 20 and 40 % in the non-shunted individuals. However, during a follow-up period of 5–14 years, 44 % of the non-operated and 58 % of the operated patients died. This excess mortality was mainly due to operative mortality and a higher long-term hepatic failure rate in the shunted patients.

Since then, the surgical shunt has been considered a sacrilege in the prophylaxis of first variceal bleeding. TIPS has a much lower procedure-related trauma and can be easily occluded, but to date, no controlled trials have been initiated to test the value of TIPS for primary bleeding prophylaxis, despite the fact that such an approach has some theoretical basis in selected candidates.

## ***Local Treatment of Collaterals***

In 1939, Crafoord and Frenckner introduced sclerotherapy of esophageal varices [100]. In the early 1980s, first trials were conducted that favored sclerotherapy with respect to bleeding and survival. Numerous further trials, however, were less clear-cut [3, 101] or even showed an excess of bleeding. A large meta-analysis of 19 trials considered sclerotherapy unsettled for the prevention of first bleeding [102]. The results were too heterogeneous, which was mainly due to a large variation of the bleeding incidence in the control groups, although pooled odds ratios were in favor of sclerotherapy. The largest trial even found a higher death rate in the group of patients treated with sclerotherapy [103].

Later on ligation was introduced [104] and showed to have less adverse effects, especially in respect to procedure-related bleedings. Five trials compared prophylactic ligation with untreated controls comprising 601 patients. A meta-analysis found a homogenous beneficial effect with respect to reduction of first variceal bleed, bleeding-related mortality, and all cause mortality. Consequently, ligation has become the endoscopic procedure of choice in the prevention of first variceal bleeding [105]. Typically, 2–3 sessions of ligation are necessary. The interval between these sessions varies between the groups from 1 to 3 weeks, with 2–3 weeks [106] as possibly the best interval for the repetition of the procedure. Although ligation has been shown to be effective for prophylaxis of first bleeding, it has to be kept in mind that the procedure depends on the experience of the endoscopist and that it may induce life-threatening bleeding [2].

## ***Medical Treatment for Prophylaxis of First Bleeding***

### **Nonselective $\beta$ -Blockers**

Portal hypertension is caused on the one hand by an increased intrahepatic resistance and on the other hand by an augmented portal tributary blood flow—as first shown by Didier Lebrec and his group [107]. It is believed that the latter phenomenon contributes about one third to the degree of portal hypertension. The speculation by the French group of Clichy that portal tributary blood flow could be reduced by administration of a nonselective  $\beta$ -blocker was indeed ingenious. The blockade of  $\beta_1$ -adrenoceptors decreases the cardiac index and therewith the splanchnic inflow. At the same time, blockade of the  $\beta_2$ -adrenoceptors renders  $\alpha_1$ -adrenergic reaction unopposed within the splanchnic vasculature, which results in vasoconstriction and a further drop in splanchnic perfusion [108]. The decreased splanchnic perfusion and consequently the reduced portal venous inflow achieve—on average—a reduction of portal pressure by 12 % [109, 110]. It is believed that it is mainly this long-term reduction of portal pressure under continuous intake of

propranolol that reduces the bleeding risk, as shown consistently in randomized controlled trials [111]. It was suggested early on that propranolol should be dosed up to a reduction of the heart rate by 25 % or the maximal tolerated dose. Once this hemodynamic reaction is achieved, 20–40 % of patients [109, 110] show a decrease of HVPG by  $\geq 20$  %, which is believed to be the best prognostic sign for prophylaxis success. An analysis of the data of 589 individual patients from four randomized trials [111] showed that the percentage of patients without upper gastrointestinal bleeding increased from 65 % (controls) to 78 % (verum groups) within 2 years. The percentage of patients without fatal bleeding increased from 82 % (controls) to 90 % ( $\beta$ -blocker). There was a trend in favor of prolonged survival, but this was far from being significant (71 % vs. 68 %,  $p=0.34$ ).

The previously mentioned results are robust and established the role of non-selective  $\beta$ -blockers as treatment of choice for prophylaxis of first bleeding in patients with liver cirrhosis and large esophageal varices [95]. One trial [29] showed that patients with small varices might also profit. However, pharmacological approach using nonselective  $\beta$ -blockers presents some problems. Five to ten percent of patients were non-compliant or non-adherent to treatment [112], 5% of patients exhibited contraindications such as hypotension, bradycardia, impotence, or dyspnea and in 10–25 % of patients [112], adverse events occurred that required interruption of treatment. Finally,  $\beta$ -blockers must be applied on a lifelong basis since the risk of variceal hemorrhage returns to the untreated situation after withdrawal of treatment [113].

Thus, in a rather high percentage of these patients, other approaches have to be considered, such as ligation, nitrates, or carvedilol, a nonselective  $\beta$ -blocker, which also blocks  $\alpha$ -adrenergic receptors [114, 115]. The following paragraphs will address the controlled trials, which have been carried out with these different approaches to prevent first variceal bleeding in patients with liver cirrhosis and large varices.

### **Nitrates for Prevention of First Bleeding vs. Placebo**

Vasodilators, especially long acting nitrovasodilators (e.g., isosorbide dinitrate or isosorbide mononitrate) have been shown to reduce HVPG [115, 116] and esophageal variceal pressure by reduction of vascular resistance to portal collateral blood flow and possibly also intrahepatic resistance [117]. One trial [118] with 133 patients compared isosorbide-5-mononitrate in a double blind randomized trial with placebo in patients with contraindications or intolerance to  $\beta$ -blockers. No difference was found in the 1 and 2 year actuarial probability of first variceal bleeding. In further studies, nitrates were inferior to propranolol [119–121] and ligation [119]. Accordingly, nitrates are not an alternative for propranolol to prevent first bleeding. Combining nitrates with a nonselective  $\beta$ -blocker for prophylaxis of first bleeding may have a small additional beneficial effect [122, 123].

## Ligation vs. a Nonselective $\beta$ -Blocker

To date, at least 19 randomized controlled trials (eight available only as abstracts) have been published. The conclusions of two recent meta-analyses [106, 124] are quite similar in that within a time period ranging between 10 and 55 months, all-cause mortality was nearly identical (23 % vs. 24 % out of approximately 1,500 patients in total) and that variceal ligation significantly reduced the bleeding risk when all trials are analyzed (11 % vs. 20 % nonselective  $\beta$ -blockers). This effect was rather robust but it is no longer significant when only high quality trials were included [106]. Adverse events occurred more often in the  $\beta$ -blocker groups, but fatal adverse events—caused by induction of bleeding—were only reported for the ligation groups (3 %) and not in the  $\beta$ -blocker groups.

Bleeding-related complications may be lower when the interval between banding sessions surpasses 2 weeks [106]. Compliance was inconsistently reported. In our own trial [2], 5 % of patients presented contraindications, 9 % did not adhere to  $\beta$ -blockers and in 16 %,  $\beta$ -blocker treatment had to be stopped mostly due to symptomatic arterial hypotension, which may cause “rebound bleeding” [113]. Higher doses of propranolol (>75 mg/day) were somewhat more efficient than lower doses, but only in the initial period of treatment [106].

Both meta-analyses concluded that it might be appropriate to start with a nonselective  $\beta$ -blocker and to restrict ligation to patients who have contraindications or do not tolerate  $\beta$ -blockers. However, if patients prefer ligation it appears appropriate to accept their wish. Beta-blockers may be particularly suitable for patients prior to liver transplantation [125].

While prophylaxis with nonselective  $\beta$ -blockers is less cost-intensive [2], this may change in favor of ligation once life quality is additionally considered [126].

## Ligation Plus a Nonselective $\beta$ -Blocker

Several singular trials addressed the question of combining different therapeutic principles for prophylaxis of first bleeding. Ligation was more effective than nadolol plus isosorbide-5-mononitrate for prevention of first bleeding [127], while adding propranolol to ligation did not improve the effect of ligation in the setting of primary prophylaxis [128]. Thus, contrary to prevention of rebleeding [95], combination therapy is obviously not superior when first variceal bleeding is to be prevented.

## Carvedilol Instead of Propranolol

Carvedilol is a nonselective  $\beta$ -blocker with intrinsic anti- $\alpha$ 1-adrenergic activity. Hemodynamic studies [109, 110, 129] showed that a daily dose of carvedilol of 12.5–25 mg reduces the average HVPG to a higher relative degree than propranolol (around 19 % vs. approximately 10 %). Accordingly, more patients are responders

(drop of HVPG >20 % or to <12 mmHg) with carvedilol when compared to propranolol (54 % and 23 %, respectively) [110], while somewhat more than 50 % of patients, who did not respond to propranolol, still showed an adequate response to carvedilol [109]. This renders carvedilol a potential treatment of choice for bleeding prophylaxis [130]. Yet, no controlled trial on the direct comparison to propranolol for primary prophylaxis has been published to date. Regarding head to head comparison with ligation in the setting of primary prophylaxis, one trial showed a significantly lower first bleeding rate [131] in the carvedilol group (10 %) compared to ligation (23 %), while another trial found no difference [132]. Survival was not different in either trial.

Although not found in all trials, a more pronounced reduction of the mean arterial pressure under carvedilol, especially in patients with decompensated cirrhosis, remains a concern [114], especially with respect to kidney function and treatment of ascites.

Thus, more trials must be published before carvedilol can be regarded as treatment of choice for the prevention of first bleeding from varices. Nevertheless, individual patients may already be candidates.

## Fundic Varices

Coexisting gastric varices do not preclude prophylactic ligation of large esophageal varices [133]. Only one randomized trial evaluated primary prophylaxis for bleeding from large isolated gastric varices [134]. Nearly half of the untreated patients bled within 2 years. Cyanoacrylate injection significantly reduced this risk and was more successful than  $\beta$ -blockers.

## Further Alternatives in the Pipeline

Drugs that are antifibrogenic [135] and—at the same time—reduce portal pressure would be ideal (see previous discussion). Here, blunting the activated RAS in liver cirrhosis could be an option as mentioned earlier. One study found a dramatic short-term effect of the AT-1-receptor blocker losartan (25 mg daily), which reduced HVPG by nearly 50 % [136]. Unfortunately, this finding could not be confirmed by further trials [81, 82]. Furthermore, dramatic hypotensive effects in patients with highly activated RAS and kidney failure may be a problem [81, 137]. However, in patients with well-compensated cirrhosis, this approach could be an option for long-term treatment if the dose is carefully titrated. This has been suggested by preclinical studies. In rat models of cirrhosis, low-dose administration of losartan could reduce portal pressure and improve vascular hypocontractility, and finally, renal function [45, 89]. While we found no additional effect when adding irbesartan to low-dose propranolol for reduction of HVPG, sodium excretion increased when we added the AT1-antagonist [138]. Spironolactone has also shown no additive effect

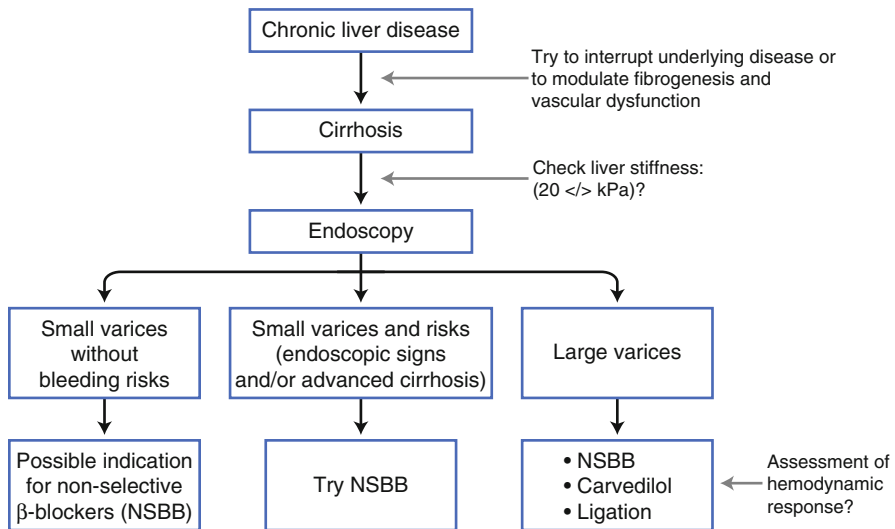
in bleeding prevention [139]. Long-term trials with relevant clinical endpoints, such as liver function/histology, bleeding, and survival, are certainly called for.

Somatostatin analogues, shown to reduce portal pressure in very early studies, are not an option for prevention of first variceal bleeding since their portal pressure lowering effect is minor or even absent [140, 141].

Other new drugs and strategies addressing fibrosis, angiogenesis, and intrahepatic resistance might be appropriate to prevent the development of varices and first bleeding as mentioned previously.

## Conclusion

Although variceal bleeding is not the main complication of liver cirrhosis, it remains a dramatic and life-threatening event for the patient. Propranolol, ligation, and carvedilol are good options to prevent first bleeding. Their prophylactic use should be tailored according to the individual situation of the patient (Fig. 7.3). The best pre-primary prophylaxis is interruption of the underlying disease.



**Fig. 7.3** An algorithm for prevention of variceal bleeding in patients with chronic liver disease. (Dosages: 40–160 mg/day propranolol, 6.25–25 mg carvedilol/day; Ligation: till obliteration (usually 2–3 sessions with 2–3 weeks interval)

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