Prevention of Variceal Bleeding and Rebleeding by Nonselective Beta-Blockers

A Tailored Approach

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KEYWORDS

• Portal hypertension • Variceal bleeding • Adrenergic beta blockers

KEY POINTS

- Nonselective beta-blockers are the cornerstone of medical therapy for the prevention of variceal bleeding and rebleeding.
- Recent studies have shown that nonselective beta-blockers not only decrease bleeding rates, but also prolong decompensation-free survival in compensated cirrhosis.
- Hepatic venous pressure gradient-guided therapy is the gold standard for the prophylaxis of variceal bleeding. Endoscopy represents a widely available alternative for prestratification and prognostication of patients.
- A tailored, individualized approach to nonselective beta-blocker therapy in the prevention of first variceal bleeding and rebleeding based on hepatic venous pressure gradient availability or varix status is proposed.

BACKGROUND

Two major pathophysiologic factors contribute to elevated levels of portal pressure in patients with cirrhosis: increased intrahepatic (sinusoidal) vascular resistance and increased portal blood inflow. Over the natural course of advanced chronic liver disease (ACLD), portal pressure rises, eventually surpassing the threshold of 10 mmHg or greater that defines clinically significant portal hypertension (CSPH).[1] In the setting of CSPH, progressive peripheral and splanchnic vasodilation ultimately lead to increases in both heart rate and cardiac output, defining the hyperdynamic circulatory portal-hypertensive syndrome.[2] Endoscopic screening for gastroesophageal varices

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(GEV) is traditionally most commonly used in clinical practice to assess the presence of CSPH; however, the presence of other portosystemic collaterals on cross-sectional imaging[3] and measurement of hepatic venous pressure gradient (HVPG)[4] allow an early diagnosis of CSPH when GEVs may not yet be present. Importantly, portal pressure, that is, the HVPG, is the main determinant for the risk of GEVs to rupture and to cause acute variceal bleeding, which is still associated with considerable mortality of up to 20%.[5]

Hemodynamic changes in patients with portal hypertension are predominantly mediated through activation of the sympathetic nervous system, and in turn, beta-adrenergic blockade through nonselective beta-blockers (NSBBs) decreases the portal pressure, thereby decreasing the risk of variceal bleeding. Thus, NSBBs represent the medical treatment of choice both for primary[6–8] and secondary[9,10] prophylaxis of acute variceal bleeding. The therapeutic effect of carvedilol as an NSBB with additional anti-α1-adrenergic activity that has a stronger effect on portal pressure as well as on systemic vasodilation has been established in the setting of primary prophylaxis,[11–13] but the evidence for its role in secondary prophylaxis[12,14] and in the setting of advanced disease with ascites[15–17] is still limited. Despite the strong body of evidence for the efficacy of NSBBs in the prevention of bleeding and potential other complications of CSPH, clinicians sometimes face difficult decisions regarding NSBB therapy in individual patients owing to side effects and tolerability issues, as well as concerns about safety in certain patient cohorts. Therefore, this article aims to provide a comprehensive review of NSBB therapy in different stages of portal hypertension, arguing for a tailored and individualized approach for the use of NSBBs for the prevention of first variceal bleeding and rebleeding.

DIAGNOSIS OF CLINICALLY SIGNIFICANT PORTAL HYPERTENSION AND ASSESSING HEMODYNAMIC RESPONSE TO NONSELECTIVE BETA-BLOCKER THERAPY BY MEASUREMENT OF THE HEPATIC VENOUS PRESSURE GRADIENT

The measurement of the HVPG represents the current gold standard for the diagnosis and monitoring of portal hypertension.[4,18] Although the procedure is invasive and requires considerable expertise and specialized infrastructure, in trained hands the measurement of the HVPG is a safe and reproducible way to evaluate portal pressure and has indisputable advantages.[4] Importantly, compensated patients might have already developed CSPH, which is associated with an important prognostic implication,[19] whereas the clinical signs of CSPH such as varices, portosystemic collaterals, and ascites occur only subsequently after CSPH has devleoped.[20] Not all patients with ACLD will show a decrease in portal pressure with NSBB treatment[21] and the efficacy of NSBB is mostly evident after CSPH has developed, that is, when HVPG is 10 mmHg or greater and splanchnic vasodilation is present, as elegantly shown by Villanueva and colleagues[22] in a mechanistical study: In their study, the authors compared the effects of NSBBs in patients with subclinical portal hypertension, that is, an HVPG of 6 to 9 mmHg, versus patients with CSPH (HVPG $\geq$10 mmHg). It was found that mean relative decreases were significantly higher ($-$16%) in patients with CSPH, as compared with patients with subclinical portal hypertension ($-$8%). This result explains why NSBBs were shown to be generally ineffective in the setting of preprimary prophylaxis, that is, in patients subclinical portal hypertension who have not yet developed varices.[23]

Sequential HVPG measurements before and after NSBB treatment initiation represent the only validated means to monitor the chronic hemodynamic effects of NSBBs, that is, to assess the hemodynamic HVPG response. The HVPG response is defined

as a decrease to absolute values of 12 mmHg or less or a relative decrease of 10% or more (primary prophylaxis)[13] or of 20% or more (secondary prophylaxis).[20] The achievement of an HVPG response is an excellent predictor of a negligible risk of variceal bleeding and a low risk for mortality in the setting of secondary prophylaxis.[24] However, the evaluation of chronic HVPG response by sequential HVPG measurements is resource intensive and, thus, is mostly performed only in specialized centers and/or within an academic or trial setting. Additionally, the predictive value of sequential HVPG measurements is limited by the potential loss of the HVPG response during follow-up that can be related to modifications of the NSBB dose, alcohol intake,[25] and worsening of liver function as by natural history of the underlying etiology of ACLD.[26] However, as of this writing, no other biomarker has shown comparable predictive quality in comparison with the invasive assessment of HVPG response. Although the achievement of an acute hemodynamic response to intravenous propranolol yielded prognostic value, it may not essentially correlate with a chronic HVPG response,[27] especially when oral carvedilol is used later,[11] however, only a single procedure of liver vein catheterization is required.[24,27]

NONINVASIVE DIAGNOSIS OF CLINICALLY SIGNIFICANT PORTAL HYPERTENSION AND DYNAMIC SURROGATES OF HEMODYNAMIC RESPONSE TO NONSELECTIVE BETA-BLOCKERS

Among potential noninvasive markers for CSPH, the measurement of liver[28] and spleen stiffness[29] by different ultrasound-based elastography methods, spleen diameter,[30,31] platelet count and von Willebrand factor[32] have been widely assessed and have been integrated into composite scores for prediction of CSPH or ruling out varices needing treatment.[30,33] Numerous other noninvasive and largely imaging-based methods have been assessed as dynamic surrogates for an HVPG response; changes in liver stiffness correlated well with changes in HVPG in a small cohort (n = 23) of patients, but have not yet been validated in a larger prospective study.[34] In contrast, changes in spleen stiffness—which at least in theory better reflects the portal venous inflow component—as estimated by transient elastography[29] and shear wave elastography[35] showed promising results. Last, it was shown that MRI-based estimated liver perfusion showed a strong positive correlation with HVPG; however, it remains to be explored in future prospective trials whether MRI perfusion studies are able to predict clinical outcomes.[36]

Further studies on non–imaging-based HVPG response surrogates have demonstrated that Ras homolog family member A (RhoA) and RhoA-kinase 2 transcription in the antrum mucosa[37] as well as serum levels of a phosphatidylcholine and a free fatty acid[38] correlated well with acute HVPG-response to intravenous propranolol and, thus, these surrogates warrant further investigation. Importantly, potential predictors that might support clinicians in the evaluation of benefits of NSBB therapy do not solely comprise hemodynamic markers, because beneficial nonhemodynamic effects of NSBB treatment have been reported in previous studies. These include a decrease in markers of bacterial translocation mediated by an amelioration of intestinal permeability.[39] Additionally, NSBB-related effects on markers of systemic inflammation were demonstrated in patients with acute-on-chronic liver failure.[40] Therefore, it should be investigated whether these novel biomarkers are able to reflect changes in HVPG and/or dynamic NSBB-related benefits in patients with CSPH. Ultimately, noninvasive biomarkers of CSPH should be tested for their prognostic value in patients with ACLD and if they are suited to be included in comprehensive risk scores for refined prognostication in personalized medicine.

STATE OF THE ART IN PRIMARY PROPHYLAXIS OF VARICEAL BLEEDING

Since the first reports on their beneficial effects in the 1980s, NSBBs have been the cornerstone of medical treatment in portal hypertension owing to their mitigating effects on portal pressure that are paralleled by lower risks of variceal bleeding and rebleeding. Thus, the European Association for the Study of the Liver (EASL), the American Association for the Study of the Liver (AASLD), and the Baveno VI guidelines have recommended the use of NSBBs for primary and secondary (in combination with endoscopic band ligation [EBL]) prophylaxis of variceal bleeding in cirrhotic patients with GEVs.[20,41,42] Still, concerns about the safety profile of NSBBs and potential deleterious effects in advanced cirrhosis have been raised in recent years, and the evidence for the benefits of NSBB treatment is weaker in certain patient cohorts, for example, in patients with refractory ascites.[15]

As outlined elsewhere in this article, HVPG-guided NSBB therapy is preferably used in all patients with CSPH to precisely predict and monitor the benefits of NSBB treatment and optimize the patient's clinical outcome.[43] However, we also acknowledge the limited availability of HVPG measurement, as well as its cost and invasive nature. Therefore, endoscopic screening for the presence of GEVs and, thus, evaluation for the risk of variceal bleeding, is currently used most widely. The subsequent overview on the evidence for best clinical practice for primary and secondary prophylaxis of variceal bleeding is, therefore, based on the prestratification of patients by the presence or absence of GEVs. This strategy provides a clinically relevant and widely feasible approach for a tailored NSBB treatment for the primary and secondary prophylaxis of variceal hemorrhage, which is complemented by data on the choice of NSBB type and doses in distinct clinical scenarios.

Primary Prophylaxis: Patients with No or Small Varices

The benefit of NSBB treatment in patients without varices was thoroughly investigated in a study by Groszmann and colleagues,[23] in which patients with cirrhosis and portal hypertension as defined by an HVPG of 6 mmHg or greater were randomly assigned to timolol or placebo. Patients were followed for a median of almost 5 years, and about 40% in both treatment groups reached the primary end point that comprised development of varices or variceal bleeding. Importantly, decreases in HVPG of 10% or greater were more frequent in the timolol group, as compared with placebo (53% vs 38%); however, the authors also reported a significantly higher rate of serious adverse events in the timolol group (18% vs 6%). Thus, there is no evidence for NSBB treatment for (pre-)primary prophylaxis in patients without CSPH and without varices as of today.

Recently, the PREDESCI study that was conducted by Villanueva and colleagues[44] demonstrated that patients with compensated cirrhosis with CSPH without high-risk varices show lower rates of first decompensation under ongoing NSBB therapy. In a cohort of 201 patients (propranolol: n = 67; carvedilol: n = 33; inactive treatment: n = 101), the primary end point that was defined as ascites development, bleeding, or hepatic encephalopathy occurred in 16 patients (16%) in the active treatment cohort, as compared with 27 patients (27%) in the placebo cohort (hazard ratio, 0.51 [95% confidence interval, 0.26–0.97], P = .041). Serious adverse events were comparable between the 2 cohorts. This study demonstrated that NSBBs not only decrease the risk for variceal bleeding, but also modify the risk of first decompensation in compensated cirrhosis in general. The ultimate conclusion of this study is, thus, to consider initiation of NSBB therapy upon diagnosis of CSPH because NSBB seem to increase decompensation-free survival, regardless of varix status. Of note, this recommendation has not yet been implemented into international guidelines.

However, there are controversial results on preprimary prophylaxis of variceal bleeding and on prevention of varix size progression from randomized controlled trials (RCTs) and a subsequent meta-analysis available.[45–47] These conflicting results were likely obtained owing to the fact that different proportions of patients without varices and, importantly, also without CSPH were enrolled. Consequently, our research group repeated the meta-analysis, including only studies on patients with small varices (CSPH) at baseline,[48] also considering the results of the RCT by Bhardwaj and colleagues[49] observing a lower risk for progression from small to large varices with carvedilol therapy. Our updated meta-analysis revealed a trend toward a lower risk of large varix development under NSBB therapy in the fixed effect model. Of note, NSBB treatment is not recommended by recent guidelines for preprimary prophylaxis or for the prevention of varix progression. However, we argue for further research on the beneficial effects of NSBB as soon as the diagnosis of CSPH has been established, regardless of the presence or absence of varices.

Primary Prophylaxis: Patients with Medium to Large or High-Risk Small Varices

The current guidelines recommend the use of NSSBs to prevent variceal bleeding in patients with medium to large varices or high-risk small varices.[20,41,42] NSBB treatment in primary prophylaxis is associated with an absolute risk reduction of −10% (25% vs 15%, as compared with inactive treatment) during 2-year follow-up, which translates into a number needed to treat (NNT) of 10 (10 patients need to be treated with NSBBs to prevent one episode of variceal hemorrhage within 2 years of follow-up).[50] When only treating patients with medium to large varices, the absolute risk reduction is −16% (NNT = 6).[50] Slightly different criteria for the definition of high-risk small varices have been proposed: Although the AASLD definition encompasses small varices in Child-Turcotte-Pugh score (Child) stage B/C or the presence of red wale marks,[42] the EASL definition is restricted to small varices in Child C patients or the presence of red wale marks.[41]

Concern about NSBB treatment owing to small varices without red wale marks in Child B/C was raised by Kalambokis and colleagues.[51,52] In their cohort study, they demonstrated an increased risk of the hepatorenal syndrome and of overall mortality related to propranolol treatment in patients with Child B/C disease. Accordingly, it may be wise to base the decision of NSBB treatment initiation both on endoscopic findings of red wale marks and the severity of liver dysfunction, that is, Child stage. Still, no adequately powered prospective study specifically addressed the effects of NSBB treatment in patients with small varices and advanced liver dysfunction as of this writing, and we encourage future studies on this field of primary prophylaxis.

In patients who have already developed medium to large varices, NSBB treatment or EBL are recommended for the primary prophylaxis of variceal bleeding.[20,41,42] The choice between NSBB treatment or EBL should consider patient preference, availability of proficient endoscopy personnel and infrastructure, and patient intolerance or adverse events under treatment. A meta-analysis including 19 studies showed no difference in overall mortality or bleeding-related mortality between primary prophylaxis with NSBB versus EBL.[53] However, a more recent meta-analysis including 32 RCTs with a total of 3362 patients with large varices and no prior history of bleeding showed that NSBB monotherapy was associated with a better safety profile and an improvement in overall mortality, as compared with EBL.[54] Importantly, although EBL is associated with a lower rate of adverse events overall, it may cause more severe and potentially life-threatening complications, such as EBL-associated ulcer bleeding. Moreover, in contrast with medical therapy with NSBBs, EBL does not impact the underlying levels of portal pressure and has no hemodynamic or disease-modifying

effects. Last, EBL is associated with significantly lower time and cost efficiency as compared with NSBB treatment. However, EBL treatment is prone to achieve variceal obliteration that could lead to long anxiety-free intervals in high-risk patients and does not rely as much on treatment adherence, which is why EBL might be preferable in some scenarios.[55] In contrast, it may be hypothesized that the results of the PREDESCI study—although excluding patients with high-risk varices—extend to all compensated patients under NSBB treatment for primary bleeding prophylaxis. Thus, patients might benefit more from NSBB treatment because it may lead to longer decompensation-free survival, as compared with endoscopic therapy.[44] Ultimately, both treatment options are validated for use in primary prophylaxis in patients with medium to large varices, and clinicians should always consider the individual patient's opinion in the process of shared decision-making.

Carvedilol Versus Propranolol and Other Conventional Nonselective Beta-Blockers

Carvedilol, in contrast with conventional NSBBs, has additional anti-α-1-adrenergic activity, which makes the compound more potent in decreasing portal pressure.[56] It was shown in a meta-analysis that carvedilol leads to stronger decreases in portal pressure levels, as compared with propranolol (-22% vs -16%).[57] Importantly, carvedilol may lead to stronger decreases in mean arterial pressure owing to its anti-α-1-adrenergic activity in comparison with conventional NSBBs. In a meta-analysis by Sinagra and associates,[57] carvedilol showed a tendency toward a stronger decrease of mean arterial pressure levels, as compared with propranolol treatment (weighed mean difference, -10.40% vs 6.35%). Moreover, it seems that higher doses of carvedilol (>12.5 mg/d) do not lead to further reductions of HVPG, although they are associated with lower mean arterial pressure levels.[11] Therefore, carvedilol should not be used in doses higher than 12.5 mg/d, with the exception of patients who show increased levels of arterial blood pressure and would need higher doses of carvedilol for antihypertensive treatment anyway.

In the setting of primary prophylaxis, an RCT comparing carvedilol versus EBL found lower rates of bleeding in the carvedilol cohort (10% vs EBL, 23%), although no differences regarding bleeding-related and overall mortality were found.[12] A second RCT by Shah and colleagues[58] also showed a trend toward lower bleeding rates with carvedilol (6.9% vs EBL, 8.5%). Of note, serious adverse events were more common in the EBL group.

Although there is no head-to-head RCT that investigated the effects of carvedilol versus propranolol in primary prophylaxis, in a study that was conducted by our group, we found that carvedilol treatment led to HVPG response, that is, a 20% or greater decrease in the HVPG or a decrease to an absolute HVPG value of less than 12 mmHg, in a high proportion (58%) of patients who did not respond to propranolol treatment.[11] Hemodynamic nonresponders to carvedilol were treated with EBL. Lower rates of variceal bleeding (carvedilol, 5%; propranolol, 11%; EBL, 25%) and mortality (carvedilol, 11%; propranolol, 14%; EBL, 31%) were observed among hemodynamic responders to NSBB treatment, as compared with EBL treatment. In conclusion, we recommend carvedilol for the primary prophylaxis of variceal bleeding in patients with compensated cirrhosis owing to its higher potency to reduce portal pressure as compared with propranolol.

Two RCTs compared carvedilol versus nadolol with or without isosorbidmononitrate in the setting of secondary prophylaxis.[59,60] In the study conducted by Lo and colleagues,[59] comparable rebleeding rates (61% and 62%) were found, the survival was similar, and serious adverse events were more common in the nadolol with or without isosorbidmononitrate group. Stanley and colleagues,[60] who conducted the

second RCT, found a rebleeding rate of 36%, irrespective of treatment. Notably, there was a trend toward an increased survival in the carvedilol group, whereas serious adverse event rates were similar between the 2 groups. Despite the promising results of these 2 RCTs, standalone carvedilol treatment has never been compared with the current state-of-the-art therapy for secondary prophylaxis, that is, combined NSBB and EBL treatment; thus, the Baveno VI faculty did not recommend its use for secondary prophylaxis.[20] In summary, carvedilol is a potent compound for the reduction of portal pressure both in primary and secondary prophylaxis. However, we do not recommend the use of carvedilol in patients with severe ascites, because carvedilol seems to impair circulatory homeostasis and this setting.[15]

STATE OF THE ART IN SECONDARY PROPHYLAXIS OF VARICEAL BLEEDING

The current guidelines recommend a combination of NSBB treatment and EBL for the secondary prophylaxis of recurrent variceal bleeding.[20,41,42] These recommendations are based on 2 meta-analyses that confirmed the protective benefits of combined medical (NSBBs with or without isosorbidmononitrate) and endoscopic therapy, that is, EBL.[61,62] Importantly, both meta-analyses showed a trend toward a lower risk of overall mortality in the combined treatment group, as compared with the EBL monotherapy group, whereas the addition of EBL to NSBB treatment was not associated with decreases in mortality. Thus, NSBBs are the cornerstone of treatment in the prophylaxis of recurrent bleeding. Interestingly, the impact of NSBB treatment on mortality seems to be restricted to secondary prophylaxis,[14] and it may be hypothesized that nonhemodynamic effects, such as a decrease in bacterial translocation,[39] but possibly also anti-inflammatory effects related to NSBBs[40] might contribute to this finding.

Patients for whom NSSBs are contraindicated or who do not tolerate medical therapy, should be evaluated for alternative treatment, for example, transjugular intrahepatic portosystemic shunt implantation.[41]

DOSE TITRATION AND NONSELECTIVE BETA-BLOCKER TREATMENT IN PATIENTS WITH ASCITES

The limited availability of HVPG measurement forces many clinicians to rely on the aforementioned noninvasive signs and biomarkers for the diagnosis of portal hypertension and, thus, the initiation and monitoring of prophylactic NSBB therapy. The absence of HVPG measurement availability often necessitates empiric treatment and titration of NSBB doses, usually to a certain target heart rate at 60 bpm[63] or even 50 to 55 bpm.[41] However, this concept is challenged by the fact that, in decompensated patients, worsening of liver function is paralleled by more pronounced sympathetic nervous system activation, leading to higher heart rates and a progressive hyperdynamic state, which implies that those patients would need higher NSBB doses to achieve those target heart rates. However, cardiac reserve is limited in end-stage cirrhotic patients, for example, in patients with refractory ascites, and Sersté and colleagues[15] were the first to report deleterious effects of NSBB treatment in patients with refractory ascites. Of note, one-half of the patients (46.7%) received high-dose propranolol treatment (160 mg/d) in their prospective cohort study. Recently, it has been demonstrated in an elegant quasi-experimental, prospective proof-of-concept study by Téllez and colleagues[64] that, in patients with refractory ascites, high-dose treatment with propranolol might indeed be detrimental to patients' circulatory homeostasis and kidney function, which could potentially worsen their prognosis. Importantly, a Danish nationwide study showed a differential impact of NSBB treatment in

81 patients with spontaneous bacterial peritonitis.[65] Although high-dose propranolol treatment, that is, 160 mg/d, was associated with increased mortality after spontaneous bacterial peritonitis (hazard ratio, 2.27, unadjusted analysis), doses of 80 mg or less per day were associated with decreased mortality after spontaneous bacterial peritonitis (hazard ratio, 0.56).

Although the potential harmful effects of (high-dose) NSBB treatment in patients with advanced disease warrant further investigation, there is evidence that carefully titrated and closely monitored NSBB treatment is not harmful to patients with ascites in general.[66–69] This finding was corroborated by the results of 2 meta-analyses. The first one concluded that NSBB treatment was not associated with an increased risk of mortality in patients with ascites or refractory ascites,[16] and the second one found that the achievement of an HVPG response was associated with a significantly lower odds of decompensation, liver transplantation, and death, regardless of the presence of ascites.[17]

The results of these studies indicate that, in patients with advanced disease, NSBB treatment seems to be a valid option for the prophylaxis of variceal bleeding, although hemodynamic treatment targets and maximum doses may have to be reconsidered. However, no RCT has thoroughly investigated the titration schemes of NSBB treatment, and the need for international recommendations remains unmet. In the absence of evidence-based guidelines on NSBB dose regimens in advanced decompensated cirrhosis, clinicians should make decisions based on individual risk/benefit considerations.[20] Signs of systemic circulatory dysfunction, severe hyponatremia,[70] a low mean arterial pressure,[71] low cardiac output,[72] and increasing levels of serum creatinine[73] allow for the identification of vulnerable patients, in which dose reduction or transient or permanent treatment discontinuation might be warranted.

Therefore, the Baveno VI consensus proposed that, in patients with refractory ascites and (i) a systolic arterial blood pressure of less than 90 mmHg, or (ii) a serum creatinine of greater than 1.5 mg/dL, or (iii) hyponatremia of less than 130 mmol/L, dose reduction or treatment discontinuation should be considered.[20]

SUMMARY: A TAILORED APPROACH TO NONSELECTIVE BETA-BLOCKER TREATMENT

NSBB treatment markedly reduces the risk of variceal bleeding in primary (absolute risk reduction, 25%–15%; NNT = 10) and secondary prophylaxis (absolute risk reduction, 63%–42%; NNT = 5), as compared with inactive treatment.[50] Accordingly, NSBBs are recommended both in primary and secondary prophylaxis by current guidelines. Although NSBBs are the first choice of medical therapy for the prevention of variceal bleeding, a considerable number of patients have to be treated to prevent a single episode of variceal hemorrhage. In addition, a large proportion of patients do not achieve the HVPG response that is associated with considerably lower bleeding rates and a lower risk of mortality.[21,50] Therefore, clinicians need to be endowed with reliable, feasible methods to accurately predict the benefit of NSBB treatment in their individual patients.

A summary of our proposed treatment algorithm is given in **Fig. 1**. Sequential HVPG measurements before and under ongoing NSBB remain the most reliable but invasive tool to assess the individual patient's response to treatment: Achieving a chronic HVPG response, that is, a reduction of 10% or more (primary prophylaxis) or 20% or more (secondary prophylaxis), or to an absolute value 12 mmHg or less is associated with a strong decrease in bleeding rates and increase in survival in secondary prophylaxis.[7,74] The evaluation of an acute response to NSBB can predict

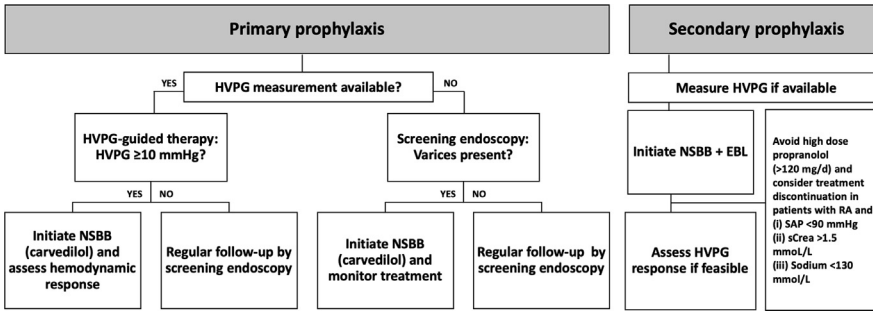

Fig. 1. A tailored approach to NSBB therapy for the prevention of first and recurrent variceal bleeding in patients with portal hypertension. The treatment algorithm for the use of NSBBs for the prevention of variceal bleeding in primary and secondary prophylaxis is shown. In primary prophylaxis, we recommend carvedilol/NSBB as the treatment of choice, whereas EBL is an alternative to NSBB therapy in case of safety or tolerability concerns or patient preference. The doses of carvedilol/NSBB should be slowly titrated and may not exceed 12.5 mg/d for carvedilol or 120 mg/d for propranolol. Close monitoring is warranted in patients with advanced liver disease considering Baveno VI recommendations for the use of NSBB therapy in patients with refractory ascites. EBL, endoscopic banding ligature; RA, refractory ascites; SAP, systolic arterial pressure; sCrea, serum creatinine.

decompensating events accurately, but still requires 1 invasive HVPG measurement.[27,75] Despite its obvious limitations in the daily clinical routine, we argue for HVPG-guided therapy in all stages of portal hypertension, because its implementation can improve clinical outcomes in patients with portal hypertension.[43] Nonetheless, the field of noninvasive surrogates for the monitoring of NSBB treatment effects remains highly relevant, and promising results were demonstrated for sequential ultrasound-based elastography assessment of the spleen.[35]

If endoscopic evaluation for GEVs is the only means of assessing portal hypertension, the initiation of NSBB treatment is recommended in all patients with medium to large varices or with high-risk varices.[20,41,42] Although patients without varices should undergo regular follow-up endoscopy for early detection of varix development, we recommend NSBB therapy also for patients with small varices even without additional risk factors such as red spot signs or advanced liver dysfunction, that is, Child stages B or C. Recent data also suggest that NSBBs prolong decompensation-free survival in compensated patients with CSPH without high-risk varices, potentially owing to nonhemodynamic effects, and thus, we recommend NSBB treatment in all of these patients.[44] In primary prophylaxis, we prefer carvedilol over propranolol owing to its greater potency to decrease portal pressure that is accompanied by a similar safety profile, as compared with propranolol.[11,12,57,58] In patients with low arterial pressure or slow heart rate, cautious dose titration under close monitoring of side effects is warranted.[20]

NSBBs combined with EBL for variceal obliteration remains the standard of care for secondary prophylaxis of variceal bleeding.[20,41,42] In patients with end-stage liver disease, for example, patients with refractory ascites, we tend to avoid carvedilol given the current lack of prospective studies that specifically addressed its use in this setting. In patient with ascites, the NSBB dose should be carefully titrated, and changing to EBL treatment in patients with refractory ascites who show a systolic arterial pressure of less than 90 mmHg, hyponatremia of less than 130 mmol/L, or a serum creatinine of more than 1.5 mg/dL should be considered.[20] We want

to emphasize, however, that in contrast with EBL monotherapy, NSBB treatment does not only decrease the risk of bleeding and even mortality in secondary prophylaxis, but it is also associated with potential nonhemodynamic benefits as compared with EBL.[39,40]

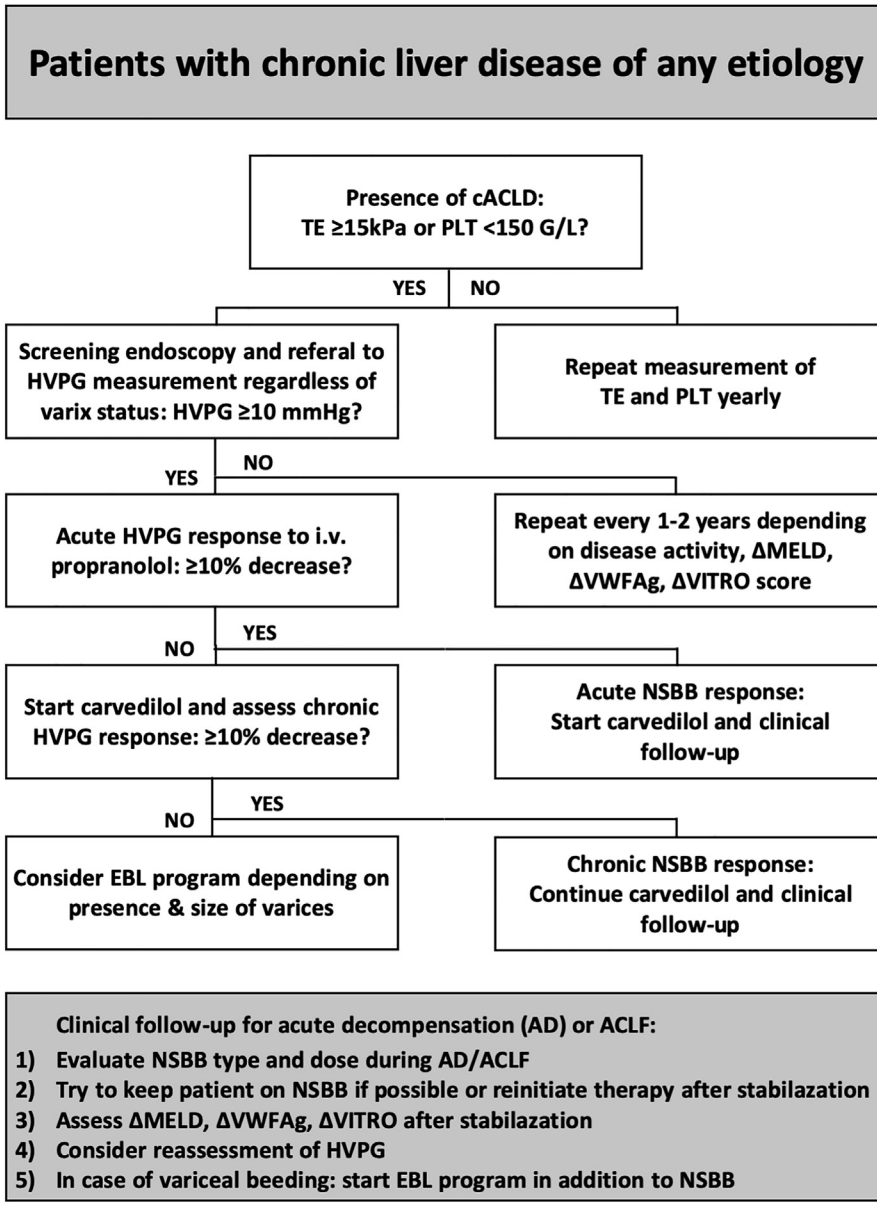

Fig. 2. The Viennese HVPG-based NSBB treatment algorithm in patients with cACLD. A summary of the Viennese algorithm on HVPG-guided NSBB therapy in patients with cACLD. ACLF, acute-on-chronic liver failure; AD, acute decompensation; cACLD, compensated advanced chronic liver disease; EBL, endoscopic banding ligature; MELD, Model for End-stage Liver Disease; PLT, platelet count; TE, transient elastography; VITRO, von Willebrand factor/PLT ratio; VWFAg, von Willebrand factor antigen activity.

We propose a patient-centered, tailored approach for the prevention of bleeding in patients with portal hypertension that considers the distinct stage of CSPH and preferably the individual patient's HVPG levels, or endoscopic varix stage for stratification.

OUTLOOK: THE VIENNESE APPROACH TO HEPATIC VENOUS PRESSURE GRADIENT-GUIDED NONSELECTIVE BETA-BLOCKER THERAPY IN PATIENTS WITH COMPENSATED ADVANCED CHRONIC LIVER DISEASE

Considering recent evidence[44,48,76] on top of international (Baveno VI,[20] AASLD,[42] EASL[41]) and national recommendations (Billroth III consensus),[77] we propose an individualized NSBB treatment algorithm for patients with compensated ACLD (**Fig. 2**). Our algorithm is based on 2 principles: (i) noninvasive risk stratification and (ii) HVPG-guided diagnosis and treatment of CSPH. In patients with suspected compensated ACLD as evident by significantly elevated liver stiffness ($\geq$15 kPa) or thrombocytopenia (platelet count of <150 g/L) we conduct screening endoscopy for the early detection of varices, but always also recommend HVPG measurement for the early detection of CSPH. If CSPH is present and the patient shows an acute 10% or greater HVPG response to intravenously applied propranolol, carvedilol (titrated to 12.5 mg/d) therapy is initiated. In case of nonresponse to intravenous propranolol, we initiate carvedilol nonetheless and assess chronic hemodynamic response after 4 to 5 weeks. In patients who achieve a chronic HVPG response to carvedilol, we keep the patient on carvedilol. However, in patients who do not achieve a chronic HVPG response to carvedilol, EBL is recommended for primary prophylaxis in case of large varices and/or red spot signs.

When patients progress from compensated to decompensated disease, we recommend reevaluating the type and dose of NSBB (eg, switch to propranolol or decrease the dose of NSBB in patients with refractory ascites and low arterial blood pressure). Importantly, NSBB treatment should not be discontinued in acute decompensation as long as the patient is hemodynamically stable, and therapy should be reinitiated as soon as possible in patients in whom transient treatment discontinuation cannot be avoided. In case of significant increases in Model for End-stage Liver Disease score or other noninvasive biomarkers for disease severity (such as von Willebrand factor antigen activity or the VITRO score), we aim for a reassessment of HVPG after stabilization of the patient. Last, if acute variceal bleeding occurs, we add EBL to NSBB-based therapy for secondary prophylaxis of variceal bleeding. A summary of our Viennese approach to HVPG-guided therapy in patients with compensated ACLD is given in **Fig. 2**.

CLINICS CARE POINTS

- The measurement of the hepatic venous pressure gradient (HVPG) is the gold standard for assessing the severity of portal hypertension and enables the detection of clinically significant portal hypertension (CSPH, i.e. HVPG $\geq$10 mmHg) before varices or other CSPH-related complications develop.
- NSBB treatment should be initated in all patients with CSPH, and HVPG-guided therapy should be applied whenever available. In settings where the measurement of the HVPG is not available, screening endoscopy should be performed. NSBB therapy should be initiated upon detection of varices.
- In patients with compensated liver cirrhosis, carvedilol is the treatment of choice for primary prophylaxis of variceal bleeding – dosed at 12.5 mg once daily.

- In patients with advanced disease, i.e. refractory ascites, propranolol should be preferred over carvedilol treatment but high doses of propranolol (>120 mg daily) should be avoided due to potential deleterious effects on circulatory homestasis by blunting critical sympathetic compensatory mechanisms.
- In case of intolerance or contraindications to NSBB treatment, endoscopic band ligation (EBL) should be considered for primary prophylaxis. Combined NSBB and EBL is the treatment of choice in secondary prophylaxis.

DISCLOSURE

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