Small Esophageal Varices in Patients with Cirrhosis—Should We Treat Them?

Thomas Reiberger1,2 · Theresa Bucsics1,2 · Rafael Paternostro1,2 · Nikolaus Pfisterer1,2,3 · Florian Riedl1,2,4 · Mattias Mandorfer1,2

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Abstract

Purpose of Review The natural history and classification systems of small varices (≤ 5 mm in diameter) in cirrhotic patients with portal hypertension are summarized. Studies that assessed the course of and therapeutic intervention for small varices are discussed.

Recent Findings Current non-invasive methods show suboptimal sensitivity to detect small varices in patients with cirrhosis. Next to etiological therapy, hepatic venous pressure gradient (HVPG)-guided non-selective betablocker or carvedilol treatment has shown to impact on natural history of small varices.

Summary The main therapeutic focus in cirrhotic patients with small varices is the cure of the underlying etiology. The optimal management of small varices should include measurement of HVPG. A pharmacological decrease in HVPG by non-selective betablocker therapy of ≥ 10% reduces the risk of progression to large varices, first variceal bleeding, and hepatic decompensation. If HVPG is not available, we would recommend carvedilol 12.5 mg q.d. for treatment of small varices in compensated patients without severe ascites. Only if small esophageal varices (EV) are not treated or in hemodynamic non-responders, follow-up endoscopies should be performed in 1–2 years of intervals considering the activity of liver disease or if hepatic decompensation occurs.

Keywords Small varices · Portal hypertension · Cirrhosis · Variceal bleeding · Low-risk varices

Introduction

Patients with cirrhosis (i.e., advanced chronic liver disease, ACLD) might develop clinically significant portal hypertension (CSPH) with hepatic venous pressure gradient (HVPG) ≥ 10 mmHg. With increasing severity of portal hypertension, patients are more likely to suffer from first variceal bleeding and recurrent variceal bleeding from esophageal varices (EV). The beneficial role of non-selective betablockers (NSBB) in combination with endoscopic band ligation (EBL) in preventing recurrent variceal bleeding (secondary prophylaxis) has been clearly demonstrated in several trials [1] and meta-analyses [2]. In the setting of primary prophylaxis, there is strong evidence for a beneficial role of NSBB if EV are medium-large sized [3* · 4*], but the impact of NSBB is less clear in patients with small EV. While there is no conclusive evidence that NSBB treatment reduces the risk of variceal bleeding or mortality in patients with small low-risk varices who have not bled [5], the absence of evidence should not be mistaken for evidence of absence. Most trials in patients with no/small varices were not sufficiently powered to detect favorable effects of NSBB on hard endpoints such as variceal bleeding or hepatic decompensation, which occur less commonly in this group of patients [6]. This is the reason why well-designed studies on clinically meaningful surrogate endpoints (e.g., variceal growth) are particularly relevant in this
setting. Previously, there were two important trials with somewhat contradictory results: While a randomized controlled trial (RCT) by Merkel et al. [7] demonstrated that conventional NSBB (nadolol) therapy is effective in preventing the progression from small to large varices in patients who have not bled, another RCT by Sarin and co-workers [8] using propranolol reported no effect. In this review on small EV, we aim to summarize important non-invasive and invasive diagnostic aspects, pathophysiological considerations, and available evidence for pharmacological therapy to guide treatment decisions in daily clinical practice.

Classification of EV: Size, Location, Presence of Red Spots, Low Versus High Risk

In CSPH, sub-epithelial longitudinal veins might enlarge to form varices in the esophagus. With increasing size and with rising intravascular pressure, they are more likely to rupture. Screening endoscopy is traditionally recommended to be performed in all patients after the diagnosis of cirrhosis. To timely initiate prophylaxis for variceal bleeding, early detection and specific classification of EV are major goals in the management of patients with ACLD [9]. Reports of gastroduodenoscopy performed in patients with cirrhosis must include information about the absence/presence of varices, their size, their location, and presence of red spot signs. The latter indicates sites where the variceal wall is thinning, and thus represents a sign for increased risk of EV rupture and bleeding.

Historically, the first endoscopic classification was developed by Brick and Palmer in 1964 [10]. Over time, other classifications were presented, with several ways to describe the size/grade of varices [11–13]. Based on these classifications, varices were described as grades I to IV, or more intuitively, as small, medium, or large. The presence of risk factors for variceal rupture was described as red wale signs, cherry spots, red spots, or by similar terminology. The recently updated Austrian Billroth III consensus simplified the grading of EV size just into small (<5 mm) and large (≥5 mm) in diameter [14].

For risk stratification, additionally to EV size, identification of red spot signs and calculation of Child-Pugh score are crucial, since these endoscopic findings and the Child-Pugh score influence the risk of bleeding and bleeding-related mortality [14, 15]. Importantly, EV can be classified as low-risk (<5 mm without endoscopic risk factors in patients with Child-Pugh A/B) or high-risk (all EV of ≥5 mm in diameter or small EV showing red spot signs or small EV in patients with Child-Pugh C) varices regarding the respective risk for variceal bleeding [14, 16]. Additionally, number of varices and localization should be thoroughly described. Due to the lack of sufficient endoscopic measurement systems, size assessment and endoscopic treatment of EV demand high level of experience and should therefore be performed in specialized centers.

Non-invasive Screening for Any Esophageal Varices and “Varices Needing Treatment” (Table 1)

Liver stiffness measured by transient elastography (TE) is a well-validated tool for the assessment of liver fibrosis [39]. Recently, the term “compensated advanced chronic liver disease” (cACLD) has been introduced by the Baveno VI consortium [3*] with liver stiffness measurement (LSM) values >15 kPa being highly suggestive of cACLD. In clinical practice, a qualitative assessment of EV (size as well as presence or absence of red spot signs) is helpful to determine the optimal treatment strategy. Therefore, the term “varices needing treatment (VNT)” has been defined as follows: Varices of medium/large size (>5-mm diameter), or small varices with red spot signs [3*]. According to the Baveno VI criteria, patients with TE values <20 kPa and a platelet count ≥150 G/L have a very low probability for the presence of VNT. Thus, the combined TE <20 kPa and platelet count >150 G/L can be used to avoid futile screening endoscopies in patients with cACLD [3*].

Multiple studies have evaluated the diagnostic performance of TE alone and/or in combination with other markers (most commonly platelet count or spleen size) to predict the presence/absence of EV and VNT (see Table 1). Regarding the detection of the presence of varices of any size using TE alone, the proposed cutoffs vary between 13.9 kPa [18] and 29.7 kPa [40]. The corresponding positive predictive values (PPV) ranged from 26% [37] to 100% [32] while the negative predictive values (NPV) varied between 31% [24] and 94% [36], depending on whether ruling in or ruling out EV was the main aim of the study. TE cutoffs for predicting VNT were usually higher, ranging from 19.0 kPa [18] to 64.5 kPa [41] with corresponding PPV of 25–90% [19, 41] and NPV of 55–100% [19, 26, 42] respectively.

By applying the Baveno VI criteria to rule in or rule out the presence of small varices or the “extended Baveno VI criteria” by Augustin et al. [43], small varices would be missed in a considerable number of patients. Only few studies assessed the performance of the Baveno VI criteria to screen for any EV and found a considerably low specificity of 38% and PPV of 21–43%, but reasonable sensitivity of 88% and NPV of 86% [34, 36] which is still inferior to the NPV of 97–100% reported for VNT [36, 44, 45].

Using LSM, low cutoffs, such as the one proposed by Kazemi et al. [18] at 13.9 kPa and validated by Castera et al. in 2009 [21], appear to be more suitable for ruling out small varices with a sensitivity of 92–96% and a NPV of 85–94% for varices of all sizes. In a small study including 60 cirrhotic patients with viral hepatitis and/or alcoholic liver disease, Bintintan et al. [32] reported a sensitivity of 95%, a specificity of 100%, a PPV of 100%, and a NPV of 86% using a LSM cutoff at 15 kPa for screening for varices of any size. The only other study reaching similar values with regard to accuracy
| Author, journal, year | Design and etiology | N patients overall | TE-cutoffs and AUC any EV/VNT | Main conclusions (specificity/sensitivity, PPV/NPV) | Additional parameters used in the study and comments |
|-----------------------|----------------------|-------------------|-----------------------------|-----------------------------------------------|--------------------------------------------------|
| Foucher, Gut, 2006 [17] | Prospective Mixed etiology | n = 144 patients with F3/F4 fibrosis | LSM: Any: n/a VNT 27.5 kPa, AUC 0.73 | LSM: Any: n/a VNT: Sens. 88%, Spec. 53%, PPV 45%, NPV 90% | The main focus was diagnosis of fibrosis stages using TE |
| Kazemi, J Hepatol, 2006 [18] | Prospective Mixed etiology | n = 165 patients analyzed | LSM: Any 13.9 kPa, AUC 0.84 VNT 19.0 kPa, AUC 0.83, | LSM: Any Sens. 92%, Spec. 39%, PPV 55%, NPV 85% VNT Sens. 89%, Spec. 59%, PPV 47%, NPV 93% | Parameters: PLT, spleen diameter, PLT, LSM/spleen size |
| Vizzutti, Hepatology, 2007 [19] | Prospective Etiology: HCV | n = 61 patients analyzed n = 30 (49.2%) with esophageal EV n = 18 (38.2%) with large EV/VNT | LSM: Any 17.6 kPa, AUC 0.76 VNT 27.4 kPa, AUC 0.76 | LSM: Any Sens. 90%, Spec. 43%, PPV 77%, NPV 66% VNT Sens. 70%, spec. 78%, PPV 90%, NPV 55% | Parameters: Prothrombin index VNT: large EV |
| Bureau, Aliment Pharmacol Ther, 2008 [20] | Prospective Mixed etiology | n = 150 patients analyzed | LSM: Any 21.1 kPa, AUC 0.85 VNT large 29.3 kPa AUC 0.76 | LSM: Any Sens. 84%, Spec. 71% VNT Sens. 81%, Spec. 61% | Parameters: PLT, FibroTest, prothrombin index, AST/ALT ratio, APRI, Lok index |
| Castéra, J Hepatol, 2009 [21] | Prospective Etiology: HCV | n = 70 patients with cirrhosis analyzed | * Any 13.9 kPa (Kazemi 2006) 17.6 kPa (Vizzutti 2007) 21.5 kPa, AUC 0.96 * VNT 19 kPa (Kazemi 2006) 21.5 kPa, AUC 0.87 30 kPa, AUC 0.87 | LSM: *Any: Cutoff 13.9 kPa: Sens. 96%, Spec. 39%, PPV 49%, NPV 94% Cutoff 17.6 kPa: Sens. 84%, Spec. 61%, PPV 57%, NPV 86% Cutoff 21.5 kPa: Sens. 76%, Spec. 78%, PPV 68%, NPV 84% *VNT: Cutoff 19.0 kPa: Sens. 85%, Spec. 62%, PPV 35%, NPV 94% Cutoff 21.5 kPa: Sens. 85%, Spec. 68%, PPV 39%, NPV 95% Cutoff 30.5 kPa: Sens. 77%, Spec. 5%, PPV 56%, NPV 94% | Diagnostic accuracy varies with severity of cirrhosis: LPS: AUC 0.94 (Child-Pugh A), AUC 0.88 (Child-Pugh B/C). |
| Author, journal, year | Design and etiology | N patients overall | N patients with any EV (%) | N patients with VNT (%) | TE-cutoffs and AUC | Main conclusions (specificity/sensitivity, PPV/NPV) | Additional parameters used in the study and comments |
|-----------------------|---------------------|-------------------|---------------------------|------------------------|-------------------|-------------------------------------------------|--------------------------------------------------|
| Kim, Am J Gastroenterol, 2010 [22] | n = 133 (34%) with VNT | Any: n/a | VNT 3.5, AUC 0.95 | VNT: Cutoff 3.5: Sens. 88%, Spec. 91%, PPV 82%, NPV 94% | VNT: Cutoff 5.5: Sens. 72%, Spec. 98% PPV 94%, NPV 88% | • Included cirrhosis Child-Pugh A-C, training cohort and validation cohort |
| Nguyen-Khac, Alcohol Clin Exp Res, 2010 [23] | n = 183 patients analyzed | LSM: VNT 48 kPa; AUC 0.75 | VNT (ALD) 47.2 kPa, AUC 0.77 | VNT (viral) 19.8 kPa, AUC 0.73 | LSM: VNT: Sens. 73%, Spec. 73%, PPV 44%, NPV 90% | • Parameters: PLT/spleen size ratio; LSM × SSM |
| Stefanescu, J Gastroenterol Hepatol, 2011 [24] | n = 137 with cirrhosis analyzed | Any 28 kPa, AUC 0.75 | SSM: Any 46.4 kPa, AUC 0.78 | LSM + SSM: Any: LSM 19 kPa, SSM 55 kPa | LSM: Any: Sens. 74%, Spec. 64%, PPV 92%, NPV 31% | • VNT: cutoffs n/a |
| Stefanescu, J Gastrointest Liver Dis, 2011 [25] | n = 231 patients analyzed | Any 19 kPa, AUC 0.66 | VNT 38 kPa, AUC 0.69 | LSM: Any: Sens. 84%, Spec. 32%, PPV 72%, NPV 49% | VNT: Sens. 56%, Spec. 75%, PPV 47%, NPV 81% | • Included cirrhosis |
| Chen, J Gastroenterol Hepatol, 2012 [26] | n = 222 patients analyzed | LSM: VNT 17.1 kPa, AUC 0.73 (all) | VNT 36.1 kPa, AUC 0.92 (ALT > 5×ULN) | LSM: VNT: Cutoff 17.1 kPa: Sens. 90%, Spec. 44%, PPV 47%, NPV 88% | VNT: Cutoff 36.1 kPa: PPV 73%, NPV 100% | • Included cirrhosis |
| | | VNT 7.9 kPa, AUC 0.79 (Child-Pugh A, rule out EV) | VNT 34.6 kPa (Child-Pugh A, rule in EV) | VNT: Cutoff 34.6 kPa: Spec. 94%, PPV 73% | VNT: Cutoff 7.9 kPa: Sens. 97%, NPV 95% | • Excluded decompensated cirrhosis, co-infection with viral hepatitis |
| | | LSPS: VNT 3.5: Sens. 78%, NPV 86% (exclusion) | LSPS: VNT: Cutoff 3.5: Sens. 78%, NPV 86% | | • Parameters: APRI, Forns Index, Lok Score, FIB4 |
| | | | | | | • VNT: grades 2–3 EV |
| | | | | | | • Included cirrhosis |
| | | | | | | • Excluded history of variceal bleeding, NSBB therapy, TIPS |
| | | | | | | • VNT: medium or large EV, or small with RSS, or decompensated cirrhosis |
| | | | | | | • Parameters: USLS; LSM × ALT, LSM × Child-Pugh, LSPS, age-PLT-AST/ALT ratio, PLT/spleen diameter ratio |
| Author, journal, year | Design and etiology | N patients overall | TE-cutoffs and AUC | Main conclusions (specificity/sensitivity, PPV/NPV) | Additional parameters used in the study and comments |
|----------------------|---------------------|-------------------|-------------------|---------------------------------------------------|---------------------------------------------------|
|                      |                     | N patients with any EV (%) |                  |                                                   |                                                   |
|                      |                     | N patients with VNT (%)   |                  |                                                   |                                                   |
| Wang, J, Gastroenterol Hepatol, 2012 [27] | Prospective Etiology: HBV | n = 126 patients analyzed | VNT Cutoff 3.5, cutoff 5.5; AUC 0.81 | VNT: Cutoff 5.5: Spec. 90%, PPV 76% (inclusion) | • Parameters: APRI, PLT, AST/ALT ratio |
|                      |                     | n = 48 (38%) with EV | | | |
|                      |                     | n = 13 (10%) with VNT | | | |
| Colechca, Gastroenterology, 2012 [28] | Prospective Etiology: HCV | n = 100 patients analyzed | LSM (AUC 0.90): | LSM: Any cutoff 16.4 kPa; Sens. 96%, Spec. 60% (rule out) | | • LSM and SSM for detection of HVPG > 12 mmHg and EV |
|                      |                     | n = 53 (53%) with EV | Any: cutoff 16.4 kPa | Any: cutoff 25.0 kPa Sens. 57%, Spec. 98% (rule in) | |
|                      |                     | n = 26 (26%) with VNT | Any: cutoff 25.0 kPa | Any: cutoff 55.0 kPa | |
| Calvanusso, J Viral Hepat, 2013 [29] | Prospective Etiology: HCV | n = 96 patients analyzed | LSM: Any 17.0 kPa, AUC 0.71 | LSM: Any: cutoff 1.32: Sens. 98%, Spec. 64% (rule out) | • Parameters: Gender, age, AST, ALT, PLT, AST/ALT ratio, APRI spleen diameter |
|                      |                     | n = 54 (56.3%) with EV | VNT 19.0 kPa, AUC 0.71 | Any: cutoff 3.83: Sens. 60%, Spec. 98% (rule in) | |
|                      |                     | n = 26 (27.1%) with VNT | Modified SSM (0-150 kPa): | Modified SSM: Any: cutoff 55.0 kPa, Sens. 72%, Spec. 96% (rule in) | |
| Shi, Liver Int, 2013 [30] | Meta-analysis All etiologies, with sub-analyses for viral etiology (HCV + HBV) | n = 3644 patients analyzed | LSM (pooled): Any: Cutoffs 15.1–28.0 kPa; AUC 0.84 | LSM (pooled): Any: Cutoffs 15.1–28.0 kPa Sens. 87%, Spec. 53%, PPV 79%, NPV 64% | • Only LS und SS independently associated with presence of EV; |
|                      |                     | n = 1786? (49.0%) with EV | VNT: Cutoffs 15.1–28.0 kPa; AUC 0.84 | VNT: Cutoffs: 17.8-48.0 kPa; Sens. 86%, Spec. 59%, PPV 79%, NPV 66% | |
|                      |                     | n = 1166? (32.0%) with VNT | | | |
| Author, journal, year | Design and etiology | N patients overall | N patients with any EV (%) | N patients with VNT (%) | TE-cutoffs and AUC any EV/VNT | Main conclusions (specificity/sensitivity, PPV/NPV) | Additional parameters used in the study and comments |
|-----------------------|---------------------|-------------------|---------------------------|------------------------|-------------------------------|-----------------------------------------------|--------------------------------------------------|
| Sharma, *Am J Gastroenterol*, 2013 [31] | n = 78 with large EV/VNT | Any 27.3 kPa, AUC 0.91 | Any: Sens. 91%, Spec. 72%, PPV 89%, NPV 76% | SSM: Any: Sens. 94%, Spec. 76%, PPV 91%, NPV 84% | • SSM: can differentiate between large and small EV | |
| Binjin, *Med Ultrason*, 2015 [32] | n = 60 patients with cirrhosis | Any 40.8 kPa, AUC 0.90 | LSMS: Any 3.09, AUC 0.87 | VNT: n/a | • Excluded decompensated cirrhosis, ACLF, active alcohol abuse | |
| Hu, *Ultrasound Med Biol*, 2015 [33] | n = 200 patients analyzed | Any 15 kPa, AUC 0.96 | VNT 28.8 kPa, AUC 0.90 | • Parameters: hemodynamic liver index, portal vascular resistance, spleno-portal index | |
| Marot, *Liver Int*, 2017 [34] | n = 3364 | Any 20.3 kPa, AUC 0.84 | VNT 25.6 kPa, AUC 0.86 | • VNT: grade 2 or 3 EV | Parameters: LSM x PLT (no detailed description available) | |
| Pu, *J Gastroenterol*, 2017 [35] | n = 2697 patients analyzed | Any 20 kPa* | VNT 20 kPa x PLT 150 G/L* | • VNT: large EV | Parameters: LSPS, PLT/spleen diameter ratio | |
| Llop, *J Gastroenterol Hepatol*, 2017 [36] | n = 161 patients analyzed | Any 20.0 kPa* | VNT 30 kPa, AUC 0.83 | • TE is the best single method to predict EV; LSPS had high and Baveno VI criteria low risk of misclassifying patients with EV | Included LSM >10 kPa |
### Table 1 (continued)

| Author, journal, year | Design and etiology | Patients overall | Patients with any EV (%) | Patients with VNT (%) | TE-cutoffs and AUC | Main conclusions (specificity/sensitivity, PPV/NPV) | Additional parameters used in the study and comments |
|-----------------------|----------------------|------------------|--------------------------|-----------------------|-------------------|---------------------------------------------------|-----------------------------------------------------|
| Wong, Liver Int, 2018 [37] | Prospective | LSM: Total n = 274/548  
\(n = 51\) (18.6%) with EV  
\(n = 11\) (4.0%) with VNT | LSM:  
\(\text{Any: AUC}_{90%}^{90\%}\, 12.5\, \text{kPa} \times \text{PLT}_{150\, \text{G/L}} \times \text{SSM}_{41.3\, \text{kPa}}\) | LSPS:  
\(\text{Any: Sens. 36\%, Spec. 84\%, PPV 30\%, NPV 88\%}\) |  |
| Manatsathit, J Gastroenterol Hepatol, 2018 [38] | Meta-analysis, Mixed etiologies | Any EV:  
\(n = 1681/3001\) (56% of LSM)  
\(n = 968/1911\) (51% of SSM) with EV  
\(n = 1466/4337\) (34% of LSM)  
\(n = 383/1119\) (34% of SSM) with VNT | LSM (pooled):  
\(\text{Any: AUC}_{90%}^{90\%}\, 84\%\, 64\%\)  
\(\text{VNT: AUC}_{90%}^{90\%}\, 83\%\, 63\%\)  
\(\text{SSM (pooled):}\)  
\(\text{Any: Sens. 91\%, Spec. 66\%}\)  
\(\text{VNT: Sens. 90\%, Spec. 73\%}\)  
\(\text{LSPS (pooled):}\)  
\(\text{Any: Sens. 91\%, Spec. 67\%}\)  
\(\text{VNT: Sens. 82\%, Spec. 87\%}\) |  |

ALD, alcoholic liver disease; ACLF, acute on chronic liver failure; APRI, AST to PLT ratio index; ARFI, acoustic radiation force impulse; AUC, area under the (receiver operating) curve; cACLD, compensated advanced chronic liver disease; EV, esophageal varices; F, fibrosis stage; FIB4, fibrosis 4 (score); kPa, kilopascal (unit); LSM, liver stiffness (measurement); LSPS, liver-stiffness-to-spleen-diameter-to-platelet-ratio score; NPV, negative predictive value; PLT, platelet count; PPV, positive predictive value; RSS, red spot sign; SSM, spleen stiffness (measurement); TE, transient elastography; TIPS, transjugular intrahepatic portosystemic shunt; ULN, upper limit of normal; USLS, ultrasound and liver stiffness score; VNT, varices in need of treatment.

The asterisk * refers to validation data for the cutoff recommend by the Baveno VI consensus conference.
was performed by Stefanescu et al., who used a combination of LSM (cutoff 19 kPa) and spleen stiffness (SSM, cutoff 55 kPa) to rule in varices of any size with a sensibility of 93% and a PPV of 95% [24].

In summary, LSM using TE in combination with platelet count (i.e., Baveno VI criteria) and/or other non-invasive markers of portal hypertension can be used for ruling out VNT, and thus, avoid unnecessary screening endoscopies in settings where low-risk varices are left untreated. Whether yearly re-evaluation of TE and platelet count is feasible for clinical surveillance and which changes of LSM or SSM or platelet count should call for endoscopic screening must be answered in future studies. As of now, we advise performing endoscopy at any given relevant increase in LSM/SSM or decrease in platelet count as advised by the Baveno VI consensus conference in 2015 [3•]. Importantly, the Baveno VI criteria are not sufficient to rule out small varices/any EV, in clinical practice. Thus, at present, endoscopy is essential if our recommendation to implement medical treatment in all patients with low-risk varices is preferred.

Natural History of Small Varices and Incidence of Bleeding

An important prospective “natural history” study evaluated the incidence of small varices in 113 patients with cirrhosis of different etiologies without varices at baseline endoscopy and found an incidence rate of 5% (0.8–8.2%) and 28% (21.0–35.0%) at 1 and 3 years, respectively [9]. Interestingly, only 2% (0.1–4.1%) of patients without varices at first endoscopy bled within 2 years. Among 93 with small EV at baseline, the rate of progression to large EV was 12% (5.6–18.4%) and 31% (21.2–40.8%) at 1 and 3 years, respectively. Alcoholic etiology of liver disease, advanced liver dysfunction (Child-Pugh B/C), and red spots signs were all risk factors for progression from small to large varices [9]. Bleeding at 2 years occurred in 12% (5.2–18.8%) and the presence of red spot signs at first endoscopy was identified as independent risk factors for variceal bleeding in patients with small varices at baseline [9].

Pathophysiological Considerations Supporting Current Recommendations for the Management of Portal Hypertension/Patients with Small Varices

Liver fibrosis/cirrhosis increases intrahepatic vascular resistance, and thus, portal pressure [46]. Increases in portal pressure, that is indirectly assessed by the measurement of HVPG, to values of ≥10 mmHg denote CSPH [47, 48•]. CSPH is associated with a substantially increased risk for developing EV and/or decompensating events, such as variceal bleeding as well as ascites and its complications. The diagnosis of CSPH is established by HVPG measurement; however, the presence of collaterals such as EV also indicates CSPH. Thus, in clinical practice, CSPH is most commonly diagnosed by endoscopy (e.g., the finding of small varices), as HVPG measurement is mostly restricted to academic centers.

Since portal hypertension drives the development of EV and hepatic decompensation, lowering HVPG by NSBB treatment provides a clinically relevant benefit [47, 48•]. However, a landmark study by Groszmann and Garcia-Tsao et al. [49], in which patients with cirrhosis and portal hypertension (defined by a hepatic venous pressure gradient [HVPG] ≥6 mmHg) but without varices were randomized to timolol or placebo, demonstrated that NSBB therapy is not generally effective to prevent the occurrence of EV [49]. Although this might seem contradictory, the increasing knowledge on the pathophysiology of portal hypertension and EV development facilitates the interpretation of the findings of this study [50]. CSPH usually develops prior to the occurrence of small EV, in turn, almost every patient with EV has already developed CSPH. While the initial trigger for CSPH development is an increase in intrahepatic vascular resistance, further increases in portal pressure/HVPG are driven by splanchnic vasodilation and hyperdynamic circulation. Since the latter two mechanisms are the targets of conventional NSBB (propranolol, nadolol, or timolol), it becomes evident that most patients without EV, who have a low likelihood of CSPH, do not benefit from NSBB [51••]. These pathophysiological considerations are also reflected by the “window hypothesis” by Krag et al. [52]. In turn, patients with CSPH who have not yet developed EV might also benefit from NSBB therapy if HVPG can be decreased by >10% or to absolute values <10 mmHg [49].

Impact of Etiological Treatment on Small Varices

The importance of curing the underlying liver disease was most evident from studies assessing the clinical course of compensated cirrhotic patients with viral hepatitis B and C after successful antiviral treatment in comparison to patients with virological treatment failure.

Lee et al. have reported two cases of patients with HCV-related cirrhosis, who showed complete regression of their esophageal varices (and splenomegaly) 3 and 8 years after sustained virological response [53]. A prospective observational study assessed the course of EV in patients with versus without sustained virological response (SVR) to interferon/ribavirin treatment in patients with compensated HCV-related cirrhosis [54]. Sixty-two patients with SVR and 65 patients without SVR were endoscopically followed for a median of about 5 years (68 months vs. 57 months, respectively). Significantly less patients with SVR developed de novo EV (3.5% vs. 15.1% without SVR), but SVR only non-significantly decreased the progression from small to large EV. Since some patients with SVR developed de novo EV or had progression to large EV, the authors concluded that
continued endoscopic surveillance for EV is still necessary in patients with HCV cirrhosis despite SVR [9].

Another case of complete regression of EV after suppression of hepatitis B virus (HBV) replication with entecavir has been reported by Jwa et al. [55]. The beneficial impact of long-term nucleos(t)ide analogues (NA) treatment on patients with small EV has been elegantly demonstrated in a prospective, 12-year multicenter study [56••]. Among the 107 HBeAg(−) patients with compensated cirrhosis, 27 patients had small EV at baseline. Long-term suppression of HBV replication by NA resulted in regression of small EV in most cases (83% cumulative incidence of regression over 12 years, 18/27) and no single patient experienced variceal bleeding. The risk of progression from small to large EV was negligible and occurred almost exclusively in patients with virological breakthrough under NA treatment [56••].

In contrast to patients with viral hepatitis, there are currently no specific therapies approved for alcoholic liver disease (ALD) or non-alcoholic steatohepatitis (NASH). In ALD, strict alcohol abstinence and supervised lifestyle modifications represent critical elements of patient management [57, 58]. Up to date, there are no studies that specifically focus on the impact of alcohol consumption/cessation on the progression of small varices. However, it is well-established that even moderate alcohol consumption worsens portal hypertension and thereby most likely affects the formation and growth of varices. After alcohol cessation, an immediate decrease of HVPG can be observed, which might induce regression of varices [59]. Moreover, Villanueva et al. showed that alcohol cessation improves the hemodynamic response in secondary prophylaxis [60]. In addition, durable alcohol abstinence results in lower re-bleeding rates [61] and decreased long-term mortality after acute variceal bleeding [62]. Negative effects of ongoing alcohol consumption seem to result from increased intrahepatic resistance, due to hepatic inflammation, characterized by parenchymal lesions (hepatocellular ballooning) that are frequently found in active drinkers [63]. In conclusion, alcohol abstinence reduces portal pressure and improves the clinical course of cirrhotic patients and should therefore be advised to all patients with small varices.

While NASH has become a highly prevalent liver disease [64], there are currently no approved pharmacological therapies for patients with NASH. The “Million Women Study,” performed in the UK, suggested that up to 17% of incident cases of cirrhosis can be directly linked to obesity [65]. Obesity in combination with cirrhosis increases risk of hepatic decompensation and negatively impacts portal hypertension [66]. The pathophysiological mechanisms are still unknown and certainly multifactorial. However, it seems that a persistent proinflammatory state triggers a fibrogenic and angiogenic response in the liver, thereby increasing intrahepatic resistance. In NASH, an increase in portal pressure has been reported in the absence of significant fibrosis [67] with hepatocellular ballooning due to lipotoxicity and/or only mild perisinusoidal fibrosis [9]. Lifestyle interventions remain the key determinants of NASH progression/regression: Weight loss is associated with decreases in HVPG irrespectively of etiology [68••]. Importantly, beneficial effects of weight loss may be observed even in the absence of changes in Child-Pugh or MELD score [66, 68••]. In selected cases, bariatric surgery might be beneficial in NASH patients [69].

### Treatment of Small Varices with Non-selective Betablockers (Table 2)

Based on a broad body of evidence, current guidelines recommend either NSBB or EBL for primary prophylaxis of variceal bleeding in patients with medium to large varices. Moreover, NSBB are considered as the mainstay of the combination therapy with EBL therapy in secondary prophylaxis [5, 79]. However, in patients with small varices who have not bled, the situation is less clear [3•, 6, 80].

In general, there is no conclusive evidence that NSBB treatment reduces the risk of variceal bleeding or mortality in patients with low-risk varices who have not bled [5]. However, most trials were not sufficiently powered to detect favorable effects on these endpoints, which occur less commonly in this group of patients [6]. This is the reason why well-designed studies on clinically meaningful surrogate endpoints (e.g., variceal growth) are particularly relevant in this setting.

While a randomized controlled trial (RCT) by Merkel et al. [7] demonstrated that conventional NSBB (nadolol) therapy is effective in preventing the progression from small to large varices in patients who have not bled, another RCT by Sarin and co-workers [8] using propranolol reported no effect. In a recently published randomized RCT by Bhardwaj and colleagues [77], a lower proportion of patients assigned to the carvedilol group progressed from small to large varices as compared to the placebo group. Carvedilol has been shown to be more potent in decreasing portal pressure due to its additional anti-α-1-adrenergic activity [81]. In a recent meta-analysis [82], the mean relative HVPG reduction was 22% for carvedilol and 16% for propranolol, resulting in a weighed mean difference of 7% in favor of carvedilol. However, owing to its anti-α-1-adrenergic activity [81], carvedilol might also lead to more pronounced decreases in systemic arterial pressure, when compared to conventional NSBB, which limits its use in patients with severe or refractory ascites [5, 79•].

We recently conducted a meta-analysis of RCT on NSBB treatment restricted to patients with small varices, also including the new study by Bhardwaj and co-workers [77]. Interestingly, in our meta-analysis [83], there was a trend towards an amelioration of the progression from small to large varices among NSBB-treated patients in the fixed effects model (odds ratio [OR] [95% confidence interval (95% CI)] 0.73 [0.5–1.06]; risk ratio [RR] [95% CI] 0.78 [0.58–1.05]).
| Author, journal, year          | Design     | N patients overall with small EV (%) | NSBB (dose)                     | HVPG measurement | Main conclusions                                                                 |
|-------------------------------|------------|--------------------------------------|---------------------------------|------------------|-----------------------------------------------------------------------------------|
| The PROVA Study Group, Hepatology, 1991 [70] | RCT        | 286/166 (58%)                        | Propranolol (160–400 mg/day)    | No               | • Small EV had a considerable risk of bleeding<br>• The incidence of variceal hemorrhage and overall mortality was not significantly different between patients receiving NSBB, sclerotherapy or combination therapy |
| Calès, Eur J Gastroenterol Hepatol, 1999(Cales, 1999 #1480) | RCT        | 206/127 (62%)                        | Propranolol (160 mg)            | No               | • NSBB therapy did neither prevent occurrence/growth of EV or variceal bleeding and did not reduce mortality in patients without/with small EV |
| Merkel, Hepatology, 2000 [71] | RCT        | 146/6 (4.1%)                         | Nadolol (40–160 mg/day)         | No               | • NSBB plus ISMN was more effective than NSBB alone in the long-term prophylaxis of first variceal bleeding |
| Merkel, Hepatology, 2000 [72] | RCT        | 49/2 (4.1%)                          | Nadolol (40–80 mg/day)          | Yes (all)        | • HVPG response was the best predictor of efficacy in patients receiving NSBB or NSBB plus ISMN for primary prophylaxis |
| Abraczinskas, Hepatology, 2001 [73] | RCT        | 49/2 (65.3%)                         | Propranolol (dose not specified) | No               | • NSBB therapy in small and large EV is effective in preventing first variceal bleeding<br>• After discontinuation of NSBB therapy, the risk of variceal bleeding persisted |
| Merkel, Gastroenterology, 2004 [74] | RCT        | 161/100 (100%)                       | Nadolol (mean dose 62 ± 25 mg/day) | Yes (11.8%)      | • Primary prophylaxis with NSBB should be considered in patients with small EV<br>• NSBB delay the growth of small EV |
| Turnes, Am J Gastroenterol, 2006 [74] | RCT        | 71/4 (6.6%)                          | Propranolol (54 ± 14 to 79 ± 12 mg/day) | Yes (all)        | • Positive impact of HVPG response in the setting of primary prophylaxis<br>• Insufficient data on patients with small EV |
| Reiberger, Gut, 2013 [75]     | Non-randomized clinical trial | 104/41 (39.4%)                      | Propranolol (80–160 mg/day)     | Yes (all)        | • Carvedilol induces HVPG response in a considerable proportion of patients with propranolol non-response<br>• Patients with small EV were included and also benefited from hemodynamic response to carvedilol |
| Sarin, Hepatol Int, 2013 [8]  | RCT        | 150 (100%)                           | Propranolol (40 mg/day followed by dose titration) | Yes (66%)        | • NSBB therapy did neither prevent growth of EV or variceal bleeding and did not reduce mortality in patients with small EV |
| Je, Clin Mol Hepatol, 2014 [76] | Retrospective study | 504/92 (18.3%)                       | Propranolol (20 mg/day followed by dose titration) | No               | • NSBB plus EBL was more effective than NSBB alone in primary prophylaxis<br>• However, EBL was performed only in patients with large EV |
| Bhardwaj, Gut, 2016 [77]     | RCT        | 70 (100%)                            | Carvedilol (mean dose 12 ± 1.67 mg/day) | Yes (all)        | • Reduction of progression to large EV |
| Kim, Dig Dis Sci, 2016 [78]   | Retrospective study | 898/775 (86.3%)                      | Carvedilol (48.6% of 898 patients were on NSBB therapy) | No               | • Variceal bleeding was a risk factor for mortality in patients with hepatocellular carcinoma |
| Pfisterer, Aliment Pharmacol Ther, 2018 [1] | Retrospective study | Primary prophylaxis: 281/48 (17.1%) | Propranolol (median dose 40 mg/day) | No               | • Addition of EBL to NSBB therapy did not further reduce the risk of first variceal bleeding or mortality<br>• Patients receiving HVPG-guided primary prophylaxis (including patients with small EV) tended to have a better prognosis than patients receiving non-HVPG-guided NSBB therapy or combination therapy |

**EBL**, endoscopic band ligation; **EV**, esophageal varices; **HVPG**, hepatic venous pressure gradient; **NSBB**, non-selective betablocker; **RCT**, randomized controlled trial
However, the random effects model might have been more accurate due to study heterogeneity. In this model, the 95% CI was substantially wider (OR [95% CI] 0.76 [0.25 to 2.29]; RR [95% CI] 0.82 [0.36 to 1.87]). Thus, the findings of our meta-analysis [83] plead for further studies to confirm the effectiveness of NSBB therapy (especially carvedilol) for preventing variceal growth.

The Role of Hepatic Venous Pressure Gradient in Guiding Treatment Decisions in Patients with Small Varices

Considering varices of all size (i.e., also medium to large varices), NSBB treatment reduces the 2-year risk of first variceal bleeding from 25% to 15%, resulting in a number needed to treat [NNT] of 10 [84]. In the group of patients with small varices, however, the NNT for preventing variceal bleeding might be considerably higher (about 20), underlining the importance of identifying patients who are most likely to benefit. To date, HVPG response is the only established surrogate for the effectiveness of NSBB therapy. Due to the need for two separate HVPG measurements, the evaluation of “chronic” HVPG response to NSBB treatment is very resource-intensive. In contrast, the assessment of “acute” HVPG response to i.v. propranolol is performed in a single session, and thus, provides a valuable alternative [85, 86]. For primary prophylaxis, the Baveno VI faculty recently unified the definition of HVPG response by using the same criteria (HVPG decrease ≥ 10% or to a value of ≤ 12 mmHg) for “acute” and “chronic” assessments [3•]. Although most of the evidence for the impact of a decrease in HVPG on hepatic decompensation [87] and mortality [88] is derived from studies comprising patients with medium-large varices, there are also some studies focusing on patients with less advanced disease. In a landmark study [49] assigning patients with portal hypertension who had not developed varices (pre-primary prophylaxis) to timolol or placebo, patients who had a relative HVPG decrease of > 10% after 1 year showed a reduced incidence of the composite primary endpoint (development of varices or variceal bleeding) [49]. Moreover, a recent RCT evaluated the impact of HVPG-guided therapy on hepatic decompensation in patients with clinically significant portal hypertension (CSPH; pre-primary prophylaxis [44%] or small varices without red spot signs [56%]). Two hundred one patients were randomized to NSBB therapy (propranolol or carvedilol in patients with and without “acute” HVPG response to i.v. propranolol, respectively) or placebo. Interestingly, the rates of hepatic decompensation were 16% and 27% in the NSBB and placebo group, respectively. Thus, HVPG-guided therapy with propranolol/carvedilol substantially reduced the risk of hepatic decompensation (hazard ratio [95% CI] 0.51 [0.58 to 1.05]), primarily by decreasing the incidence of ascites [89••], which is the most frequent first decompensating event [90].

Since nearly all patients with cirrhosis and small varices have CSPH, the findings of the aforementioned study [89••], as well as the potential effect of NSBB treatment on the progression of varices, provide a good rationale for HVPG-guided NSBB therapy in patients with small varices. This approach allows to identify patients who are likely to benefit from propranolol, while hemodynamic non-responders can be treated with carvedilol, which still achieves HVPG response in a significant proportion of these patients [69]. Moreover, information on HVPG response might facilitate treatment individualization in situations in which NSBB might have a less favorable safety profile [5, 79•], e.g., patients with refractory ascites [91], spontaneous bacterial peritonitis [92], or severe alcoholic hepatitis [93]. If HVPG measurement is not available, carvedilol 12.5 mg q.d. might be the NSBB of choice in patients without severe ascites.

Our Personal Recommendations for Screening and Management of Small Varices (Fig. 1)

Here, we want to provide the reader with recommendations for daily clinical practice, that—in absence of RCT on some specific aspects—may not always be based on high-quality evidence. First, TE cutoffs < 20 kPa applied to patients with cACLD even combined with platelet count > 150 G/L cannot sufficiently rule out the presence of small varices. Accordingly, endoscopy is essential if low-risk varices are intended to be treated with pharmacological therapy. If liver stiffness is measured at ≥ 20 kPa and/or platelet count is < 150 G/L, screening endoscopy must be performed regardless of the treatment strategy. Moreover, the occurrence of hepatic decompensation should prompt endoscopy.

Varices should then be classified as absent, small (< 5 mm), or large (≥ 5 mm). Further, presence of red spot signs and Child-Pugh score needs to be evaluated for risk stratification.

If small varices are detected, in addition to etiological therapy, we initiate NSBB therapy due to its potential beneficial effects on variceal growth and the reduced risk of hepatic decompensation. Importantly, NSBB seem to be effective even in patients with small (and large) varices who remain strictly abstinent from alcohol [9, 68••, 69, 73] and in patients who receive effective antiviral therapy [68••]. This would support the treatment of small varices both in patients with ongoing hepatic injury and in patients with effective treatment of the underlying etiology. Thus, we use NSBB in all patients with small varices, independently if the etiological factor is eliminated or not.

Acute HVPG response can be evaluated by administration of i.v. propranolol within a single session, while chronic assessment of HVPG response requires a second HVPG measurement around 3–5 weeks after initiation of conventional NSBB/carvedilol therapy. This HVPG-guided approach...
allows to identify patients who are likely to benefit from propranolol, while hemodynamic non-responders can be treated with carvedilol, which still achieves chronic HVPG response in a significant proportion of these patients. A decrease in HVPG ≥ 10% or to a value of ≤ 12 mmHg defines NSBB response. If HVPG measurement is not available, we recommend the use of carvedilol 12.5 mg once daily for treatment of small varices in patients without severe ascites.

In general, we would also recommend NSBB treatment for patients with CSPH but without EV, since HVPG response may prevent the development of varices as well as decompensating events in compensated patients.

In patients with severe/refractory ascites, arterial blood pressure should be monitored since NSBB might compromise the circulatory reserve. The risk-benefit ratio/dosing of NSBB treatment should be re-evaluated in patients with arterial hypotension, spontaneous bacterial peritonitis, and/or acute kidney injury. In some patients, NSBB therapy might need to be discontinued if arterial hypotension is severe or shock/AKI requiring vasopressors occurs; however, this might be indicative of worse prognosis and these patients should then be evaluated for more aggressive treatment strategies such as TIPS or liver transplantation.

Fig. 1 Suggested algorithm for the diagnosis and management of small varices. The green elements summarize the recommended strategy as supported by previous international guidelines that recommend screening endoscopy in all patients diagnosed with cirrhosis (i.e., ACLD). If small varices are detected, treatment with conventional NSBB or carvedilol may be started as primary prophylaxis of variceal bleeding. If no varices are detected, screening endoscopy should be repeated every 1–2 years. The orange elements summarize the Baveno VI recommendations for non-invasive diagnosis of varices in patients with cirrhosis that were designed to avoid screening endoscopies in patients with low liver stiffness (TE < 20 kPa) and normal platelet counts (PLT ≥ 150 G/L). However, since this strategy will miss a considerable number of patients with small varices (that must not be treated—but should be treated in our opinion), we would still recommend to perform screening endoscopies even in patients with TE ≥ 20 kPa or PLT < 150 G/L if cirrhosis (ACLD) is suspected. Finally, the black elements indicate advanced diagnostic/therapeutic options that we recommend for optimal management of patients with small varices: In patients with small varices and even in patients with ACLD without varices (especially in those with TE ≥ 20 kPa or PLT < 150 G/L), HVPG should be measured. If HVPG is measured at ≥ 10 mmHg, the hemodynamic response to NSBB (ideally intravenous testing) or carvedilol should be assessed and hemodynamic responders should be kept on NSBB or carvedilol if a decrease of at least ≥ 10% in HVPG is observed. In hemodynamic non-responders, follow-up endoscopy should be performed every 1–2 years in order to assess the progression to large varices. ACLD, advanced chronic liver disease; cACLD compensated advanced chronic liver disease; HVPG, hepatic venous pressure gradient; LSM, liver stiffness measurement; NSBB, non-selective beta blocker; PLT, platelet count; Y, year(s)

Conclusions

The main therapeutic focus in cirrhotic patients with small varices (≤ 5 mm in diameter) is the cure of the underlying etiology. The optimal management of small varices should include measurement of HVPG. A pharmacological decrease in HVPG by NSBB therapy ≥ 10% reduces the risk of progression to large varices, first variceal bleeding, and hepatic decompensation. If HVPG is not available, we would recommend carvedilol 12.5 mg once daily for treatment of small varices in patients without severe ascites. Only if small EV
are not treated or in hemodynamic non-responders, follow-up endoscopies should be performed in 1–2 yearly intervals considering the activity of liver disease or if hepatic decompensation occurs.

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Compliance with Ethical Standards

Conflict of Interest Thomas Reiberger, Theresa Bucsics, Rafael Paternostro, Nikolaus Pfisterer, Florian Riedl, and Mattias Mandorfer each declare no potential conflict of interest.

Human and Animal Rights and Informed Consent All reported studies/experiments with human or animal subjects performed by the authors have been previously published and complied with all applicable ethical standards (including the Helsinki declaration and its amendments, institutional/national research committee standards, and international/national/institutional guidelines).

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