REVISTA ESPAÑOLA DE
ENFERMEDADES DIGESTIVAS
The Spanish Journal of Gastroenterology

Title:
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Authors:
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DOI: 10.17235/reed.2022.8868/2022
Link: PubMed (Epub ahead of print)

Please cite this article as:
Téllez Luis, Guerrero Antonio, Albillos Agustín. Update on the diagnosis and management of portal hypertension in cirrhosis according to the Baveno VII Consensus Conference recommendations. Rev Esp Enferm Dig 2022. doi: 10.17235/reed.2022.8868/2022.

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RV 8868

Update on the diagnosis and management of portal hypertension in cirrhosis according to the Baveno VII Consensus Conference recommendations

Luis Téllez[1,2,3,4], Antonio Guerrero[1,2], Agustín Albillos[1,2,3,4]

[1]Gastroenterology and Hepatology Department. Hospital Universitario Ramón y Cajal; [2]Instituto Ramón y Cajal de Investigación Sanitaria (IRYCIS); [3]Centro de Investigación Biomédica en Red (CIBERehd); [4]Universidad de Alcalá. Madrid, Spain

Received: 19/04/2022
Accepted: 19/04/2022

Correspondence: Agustín Albillos. Servicio de Gastroenterología y Hepatología. Hospital Universitario Ramón y Cajal. Ctra. Colmenar, Km 9,100. 28034 Madrid, Spain
e-mail: agustin.albillos@uah.es

Conflicts of interest: LT has provided consultancy services to W.L. Gore y Asociados S.L., Janssen, and Bayer. AA has provided consultancy services to W.L. Gore y Asociados S.L. and Grifols.

ABSTRACT

Development of portal hypertension is the most critical hallmark in the natural history of advanced chronic liver disease, as it is responsible for most liver decompensations. Correct risk stratification allows the design of personalized treatment strategies. In addition, the dynamic nature of chronic liver disease requires a refinement of both invasive and non-invasive diagnostic methods at every stage. Treatment with non-selective beta blockers and suppression of the etiologic factor improve portal hypertension and decrease the probability of decompensation in high-risk patients. Patients admitted for variceal hemorrhage also benefit from personalized

management, where insertion of a preventive TIPS plays a relevant role.

Keywords: Portal hypertension. Variceal bleeding. Non-selective beta blockers. Cirrhosis. TIPS. HVPG.

INTRODUCTION

Increased portal pressure is a critical milestone in the natural history of chronic liver disease as it places patients at risk of developing portal hypertension complications and, as a consequence, of progressing from compensated to decompensated cirrhosis (1). Following initial decompensation a progressive increase in portal pressure rises the risk for further decompensations, for treatment refractoriness in extant ones, and for death or need of liver transplantation. Furthermore, there is increasing evidence that lowering portal pressure by treating the etiology of cirrhosis or by using drug therapies or endovascular procedures is associated with a lower risk for complications and improved overall prognosis.

The Baveno VI consensus workshop, held in 2015, validated the cirrhosis paradigm shift that was already ongoing as the condition had gone from being considered a static, irreversible disease with a single stage to being understood as a dynamic, potentially reversible disorder where several stages may be identified. As a consequence, the Baveno VI workshop acknowledged using “advanced chronic liver disease” as a term equivalent to cirrhosis to designate chronic liver disease cases at risk of complications (2). Since the concept of cirrhosis is purely histological, the adoption of this novel terminology has widened the spectrum of the condition, allowing diagnosis and staging to potentially depend on non-invasive methods. Thus, the condition can be stratified by complications risk, and therapeutic goals can be individualized. Figure 1 summarizes the stages of advanced chronic liver disease, and the therapeutic goals for each stage.

In October 2021, the Baveno VII consensus workshop, under the heading “Personalized care in portal hypertension,” has cemented and developed the concepts outlined in

Baveno VI, and incorporated the latest advances in the field in order to establish a set of practical recommendations. Major topics for discussion included the relevance of measuring hepatic venous pressure gradient (HVPG) as gold standard for diagnosing and grading portal hypertension, use of non-invasive diagnostic modalities, impact of both etiological and non-etiological treatment on cirrhosis outcome, prevention of liver decompensation, management of acute variceal bleeding events, prevention of subsequent decompensations, and new developments in the diagnosis and management of liver vascular disease (3). This review will critically summarize the most novel aspects addressed in relation to decompensation risk stratification, appropriate use of non-selective beta blockers, and management of acute variceal bleeding.

INVASIVE AND NON-INVASIVE RISK STRATIFICATION FOR LIVER DECOMPENSATION

The primary factor determining the prognosis of compensated advanced chronic liver disease (or cirrhosis) is the development of clinically significant portal hypertension (CSPH), which is defined as any increase in portal pressure estimated by a measurement of HVPG ≥ 10 mmHg (4,5). This value identifies a population at high risk of initial decompensation (ascites/hepatic hydrothorax, hepatic encephalopathy, and/or variceal bleeding) where prevention represents the therapeutic goal. Risk is greater among patients who already developed gastroesophageal varices. While the cutoff at 10 mmHg is useful for most etiologies, patients with primary biliary cholangitis, where an additional component of presinusoidal portal hypertension may be present, or with fat-related metabolic liver disease (MLD) may be at risk for decompensation even with slightly lower HVPG levels (6,7).

The gold standard for identifying the presence of CSPH is measurement of HVPG as the difference between wedge and free venous pressure by hepatic vein catheterization. This is a straightforward procedure that, in order to be reliable and reproducible, must be performed by trained personnel using balloon-tipped catheters and continuous tracings; also, the technique is unavailable in most hospitals (8). Endoscopic ultrasound with portal vein puncture may increase availability for HVPG measurement in the future but must first be validated in prospective studies (9).

Limited HVPG availability has led to develop non-invasive methods, particularly liver stiffness measurement using transient elastography (FibroScan®), to estimate the progression of chronic liver disease (10,11). As regards the diagnosis of cirrhosis (advanced chronic liver disease), liver stiffness < 10 kPa in the absence of typical imaging findings rules out cirrhosis of any etiology, whereas values between 10 and 15 kPa suggest cirrhosis, and values > 15 kPa are highly consistent with cirrhosis (3,10). The primary advance in this field resulting from the Baveno VII workshop is the definition of simple criteria to identify CSPH using liver stiffness measurement. The so-called "rule of five" establishes different liver stiffness values that, combined with platelet count, allow to estimate the presence or absence of CSPH with considerable accuracy (Fig. 2) (3). The likelihood of CSPH is high when liver stiffness > 25 kPa, and low when < 15 kPa and platelet count is normal, with both specificity and positive predictive value above 90 % for both scenarios (12-16). The gray area encompasses those patients where liver stiffness measurements range from 15 to 25 kPa, where a positive diagnosis with CSPH requires resorting to other portal hypertension signs such as platelet count. Thus, patients withliver stiffness values between 20 and 25 kPa or between 15 and 20 kPa plus a platelet count < 150 x 10^9/L or < 110 x 10^9/L, respectively, have at least a 60 % likelihood of having CSPH (17), so in them it is advisable to look for other CSPH signs such as gastroesophageal varices or abdominal collaterals. The above-mentioned liver stiffness cutoffs, as measured by transient elastography, have been validated for the positive diagnosis of CSPH in chronic liver disease of any etiology except MLD in obese patients (body mass index > 30 kg/m^2), where their use cannot be recommended as yet (16). Nor is it possible to extrapolate values obtained with other elastography techniques, including pSWE or 2-SWE, with further studies being needed to establish equivalences. Spleen transient elastography (splenic stiffness) may be used for diagnosing CSPH (values < 21 kPa rule it out, > 50 kPa confirm it), although evidence is less robust than for liver stiffness, and is limited to untreated patients with viral etiologies (10,18-20). Introducing probes specifically designed for the spleen will likely allow future advances in this setting (10,18).

Suppressing the etiological factor of cirrhosis significantly reduces the risk of liver decompensation and hepatic death. This fact, well known in patients with alcoholic

cirrhosis on withdrawal (21,22), has been more strongly confirmed in viral cirrhosis with antiviral treatment (23-26). As a consequence, eliminating the cause of liver damage involves a reassessment of decompensation risk in patients with compensated cirrhosis, and introduces a novel concept, that is, "recompensation," in those with previously decompensated cirrhosis. As a general rule, patients where HVPG is reduced to below 10 mmHg after etiological treatment for cirrhosis are protected against decompensation but retain the risk for hepatocellular carcinoma (27). Available information is sparse on the behavior of liver stiffness to allow an estimation of these changes in HVPG, and most derives from patients with HCV cirrhosis in sustained viral response. Preliminary results from a meta-analysis of individual data suggest that CSPH may be excluded for HCV cirrhotic patients with sustained viral response where liver stiffness is < 12 kPa and platelet count > 150,000/µL (14,26). In contrast, for those with stiffness ≥ 20 kPa and/or platelets < 150,000 the presence of esophageal varices must be investigated as an unequivocal marker of CSPH (23,28), and in patients with ≥ 25 kPa CSPH persistence may be assumed (3).

PROPER USE OF NON-CARDIOSELECTIVE BETA BLOCKERS IN ADVANCED CHRONIC LIVER DISEASE

Preventing decompensation

Primary NSBB indications included prevention of first variceal bleeding event in patients at high risk or Child-Pugh C, and avoidance of bleeding recurrence (2,29,30). To date, however, a benefit of NSBB therapy to prevent first variceal bleeding events in patients with smaller varices, where bleeding episodes are scarce, had not been shown (31). Nor had it been shown the benefit of NSBBs to prevent variceal bleeding or development in patients with compensated cirrhosis without varices as this is a heterogeneous population encompassing patients with and without CSPH (4) (Fig. 1). Today we know that for NSBBs to be effective, hyperdynamic circulation must have developed, leading to significantly increased splanchnic blood flow that worsen portal hypertension, which only occurs when HVPG > 10 mmHg, that is, when there is CSPH (32). The therapeutic goal for patients with compensated cirrhosis and CSPH, identified

for instance by the presence of smaller varices, is not to reduce the risk of a first bleeding event but rather of decompensation, which most commonly manifests as ascites (5). The panish multicenter study PREDESCI showed than NSBBs (propranolol and carvedilol) reduce decompensation risk in patients with compensated cirrhosis and CSPH, with benefits being greater in those with smaller varices (33). Furthermore, NSBBs have other effects that transcend purely hemodynamic action, as they reduce systemic inflammation, spontaneous bacterial peritonitis (SBP) risk, and even the risk for hepatocellular carcinoma (34-36). Therefore, the Baveno VII workshop established the indication of NSBBs for patients with compensated cirrhosis and CSPH, particularly those who developed varices whatever their size (3).

Also, in agreement with prior evidence, the PREDESCI study demonstrated that HVPG reduction is greater in patients treated with carvedilol versus propranolol (33). Furthermore, a close relationship is known to exist between HVPG reduction extent and NSBB effectiveness to prevent variceal bleeding and ascites (37,38). Besides its greater hypotensive effect, carvedilol has shown greater efficacy to prevent variceal bleeding and seems to be better tolerated than propranolol (39-41). In addition, carvedilol increases survival when compared to non-active treatment in patients with compensated cirrhosis and CSPH (42). As a consequence, the Baveno VII workshop recommended carvedilol as drug of choice for the prevention of decompensation in patients with compensated cirrhosis and CSPH (3).

In compensated cases, once NSBB therapy is initiated, there is no need for monitoring the presence and course of varices during follow-up, since endoscopy findings will not modify management. An exception may occur when a potential discontinuation of NSBB medication is considered after cirrhosis improvement because of etiological treatment. Specifically, NSBBs may be discontinued in patients where, 1-2 years after etiological factor suppression, no esophageal varices are identified by endoscopy and no evidence of CSPH is present, including liver stiffness < 25 kPa or HVPG < 10 mmHg (28). Figure 3 summarizes a diagnostic-therapeutic algorithm intended to prevent liver decompensation in patients with advanced chronic liver disease.

Use of non-cardioselective beta blockers in patients with decompensated cirrhosis (primary and secondary prevention of variceal bleeding)

A combination of NSBBs and endoscopic band ligation (EBL) is the therapy of choice for prevention of variceal bleeding (3,43,44). NSBBs represent the key component in this combination therapy since, in contrast with EBL, they may prevent the development of cirrhosis complications other than bleeding, and prolong survival (34-36,45). For this same reason, NSBBs are preferred over EBL for preventing a first bleeding event in patients with high-risk varices. While no clinical trials are available comparing the effectiveness of combined therapy using carvedilol versus propranolol, the results of a meta-analysis endorse also using carvedilol for secondary bleeding prophylaxis (46). NSBBs also prevent relapsing bleeding associated with portal hypertensive gastropathy, where they represent the first treatment step (47).

Over the past decade NSBB effectiveness and tolerability were questioned in patients with ascites, particularly when ascites control was challenging (48-50). It has been shown that in patients with severe circulatory impairment and significant systemic vasodilation, sympathetic nervous system activation, and maximal cardiac stimulation, the cardiopressor effect of NSBBs may compromise renal perfusion, trigger hepatorenal syndrome, and even reduce survival (51-53). Hence, treatment with NSBBs should be temporarily discontinued in patients with severe circulatory impairment, identified by systolic blood pressure < 90 mmHg and/or mean arterial blood pressure < 65 mmHg, acute renal failure or a breakthrough event such as SBP, sepsis or bleeding (3,51). Once the compromised hemodynamics condition is overcome, NSBBs are carefully reinstated, initially at a dose lower than at discontinuation (3). Carvedilol, because of its alpha-1 adrenergic blocker effect, may enhance systemic vasodilation in patients with severe ascites, thus making control more challenging, and therefore propranolol is rather used in this population at a dose not exceeding 160 mg daily (54-56). Figure 4 summarizes the opportunity window of NSBB use in cirrhosis.

TIPS is the treatment of choice for the prevention of relapsing bleeding in patients where the NSBB and EBL combination fails (3). TIPS is also of choice in patients with refractory ascites, and has been seen to improve survival in patients with recurrent

ascites (57-59). As a consequence the Baveno VII workshop established several recommendations for using TIPS early in patients with decompensated cirrhosis and recurrent ascites. It is recommended for patients who bleed from varices while on primary prophylaxis with NSBBs if severe or recurrent ascites is also present (at least 3 paracenteses within the past year). TIPS may also be considered over the NSBB and EBL combination for recurrence prevention in bleeding patients who already had severe or recurrent ascites (3). This recommendation is based on the preliminary results of a meta-analysis, which show that TIPS increases survival in said population (observations not reported).

MANAGEMENT OF ACUTE VARICEAL BLEEDING

Initial assessment, resuscitation, and general management

The Baveno VII workshop confirmed the most relevant recommendations issued from prior consensus statements on the general approach to patients with acute variceal bleeding (2,3), including: management in critical or intermediate care units, at least during the first few hours; compliance with a conservative transfusional strategy, aiming at hemoglobin at 7-8 g/dL; and avoidance of systematic transfusion of fresh frozen plasma or platelets to correct any coagulopathy or thrombopenia, as well as recombinant factor VII or tranexamic acid (60-67) (Fig. 5). Specifically, systematic use of a nasogastric tube or orotracheal intubation is discouraged before endoscopy, the latter option being set aside for patients impaired consciousness level or active hematemesis (68,69). This is so because of the association observed in these patients between airway manipulation, including nasogastric tube placement, and bacterial infection risk (69).

Prevention of bacterial infection remains a priority goal, and intravenous ceftriaxone (1 g/24 h) still is the most pragmatic option to that end (3). The Baveno VII workshop establishes a specific recommendation to discontinue proton-pump inhibitors onse endoscopy has confirmed the variceal origin of bleeding, since their use is known to increase bacterial infection risks in patients with cirrhosis (70,71). Furthermore, specific recommendations were included for the prevention and treatment of other

complications with potential to aggravate the prognosis of patients with acute variceal bleeding. Systematic use of lactulose (oral or enema) is advised to facilitate blood removal from the gut and to prevent or treat encephalopathy. It should also be mentioned that malnutrition is a poor prognosis factor in this scenario, hance oral diet must be initiated as soon as possible (72).

Specific drug therapy and endoscopic treatment

Specific hemostatic therapy for acute variceal bleeding involves the early administration of vasoactive drugs (terlipressin, somatostatin or octreotide), to be maintained for 2-5 days, plus endoscopic treatment (2,3). The latter consists of EBL for esophageal varices; tissue glue (cyanoacrylate, thrombin) injection for isolated fundal or gastric varices (GOV2 and IGV); or either EBL or tissue adhesives for gastroesophageal varices (GOV1) (2,3,30,73-76). As of today the evidence available is not enough to support the use of endoscopic treatment with hemostatic powder for variceal bleeding (77). The efficacy of combined treatment is conditioned by the earliest possible administration of vasoactive drugs, and endoscopy not being delayed beyond 12 hours after patient stabilization (or as soon as safe should instability persist) (78,79). Because of the above, it is key that hospitals caring for patients with acute variceal bleeding have a gastroenterologist experienced in endoscopy available for 24 hours a day, 365 days a year (3).

Management of refractory/recurrent variceal bleeding

TIPS represents the rescue therapy for patients with acute variceal bleeding refractory to standard treatment or early post-treatment recurrence (3). In these cases esophageal tamponade with a balloon or self-expandable metal stent allows temporary hemostasis until TIPS implantation. Metallic stents are currently the most appropriate option for tamponade since they are as effective as balloons, allow for improved definitive endovascular treatment planning because of their ability to longer remain in place, and are associated with fewer adverse events, particularly aspiration pneumonia (80,81). Rescue TIPS futility criteria (Child-Pugh ≥ 14, MELD > 30, lactate > 12 mmol/L) have been retrospectively analyzed, but the decision of placement or of

limiting therapeutic efforts must be individualized, especially in patients eligible or on the waitlist for liver transplantation (82).

Preventive TIPS

While TIPS emerged as a rescue treatment for patients with acute variceal bleeding, it has recently established itself as a preventive approach to cases at high risk for standard treatment failure: Child-Pugh C or Child-Pugh B with active bleeding during endoscopy (83,84). Several observational studies and a meta-analysis of individual data endorse that, in the aforementioned population at risk, preventive TIPS reduces recurrent bleeding and increases survival (85-89). More recent data extend the benefits of TIPS to patients with variceal bleeding and acute on chronic liver failure, including those with hepatic encephalopathy or severe hyperbilirubinemia (89). Should staff trained in TIPS placement be unavailable, patient transfer is advisable to a center where the procedure may be safely performed, ideally within 72 hours.

CONCLUSIONS AND FUTURE LINES OF RESEARCH

The latest advances in the management of portal hypertension in patients with advanced chronic liver disease are oriented towards a tailored approach to preventive and therapeutic measures. The dynamic perspective on cirrhosis has favored the development of non-invasive diagnostic modalities for the stratification of complications risk and effective targeting of treatment. However, the etiology-related epidemiological changes that occurred over the last few years prompt the need to explore the validity of current knowledge in novel clinical scenarios of portal hypertension.

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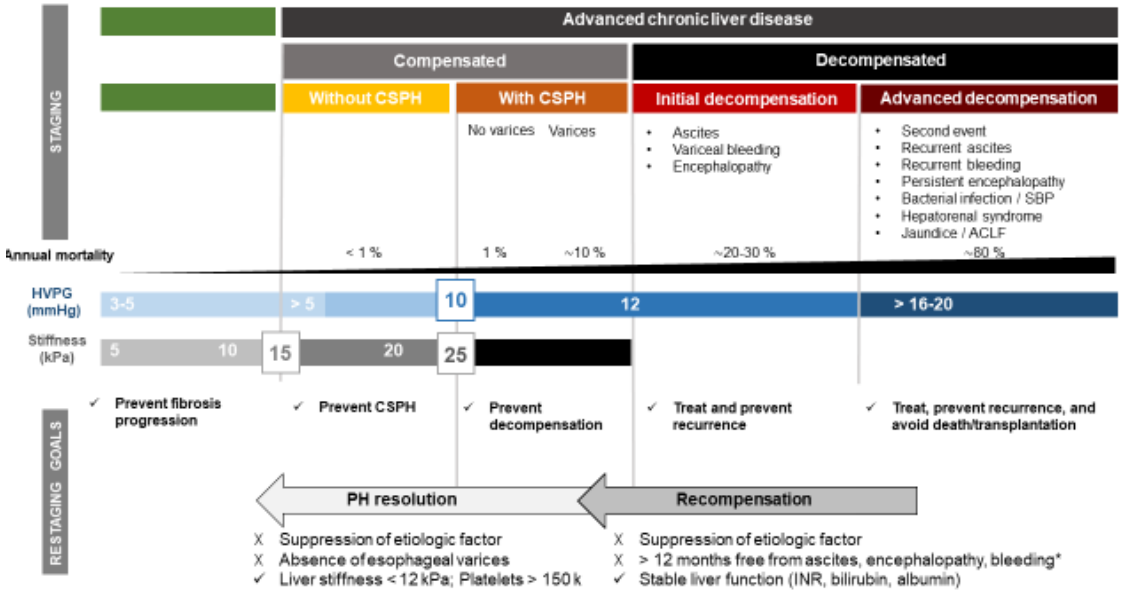

Fig. 1. The natural history of advanced chronic liver disease (ACLF: acute on chronic liver failure; CSPH: clinically significant portal hypertension; SBP: spontaneous bacterial peritonitis; HVPG: hepatic venous pressure gradient. Considered to be free from ascites when no free fluid is present and no diuretics are required; free from encephalopathy in the absence of overt hepatic encephalopathy and no lactulose +/- rifaximin is required; and free from bleeding when no portal hypertension-related bleeding occurred even under treatment with non-cardioselective beta blockers).

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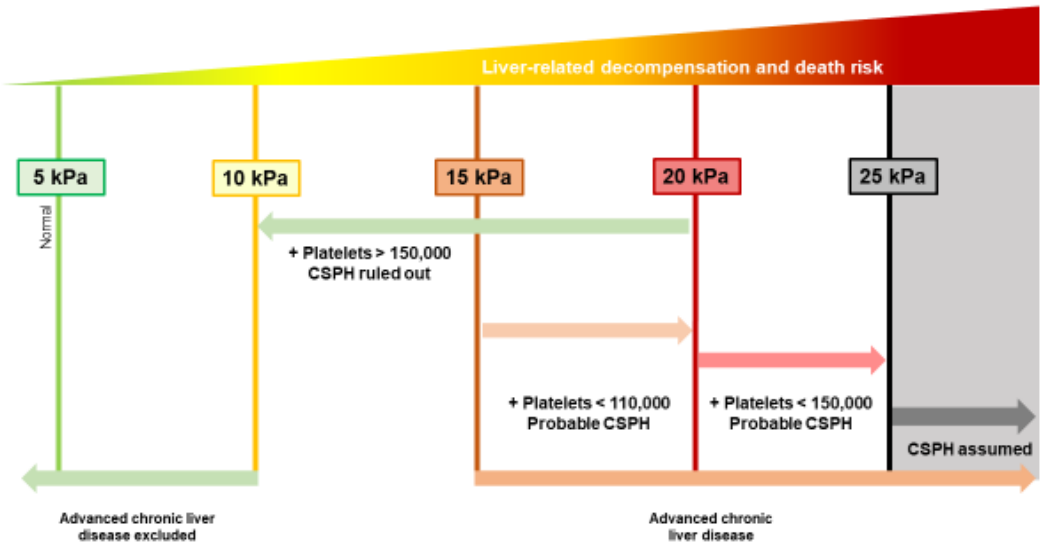

Fig. 2. Risk stratification for liver decompensation and clinically significant portal hypertension in patients with chronic liver disease. Adapted from Baveno VII. Not applicable to obese patients with NAFLD.

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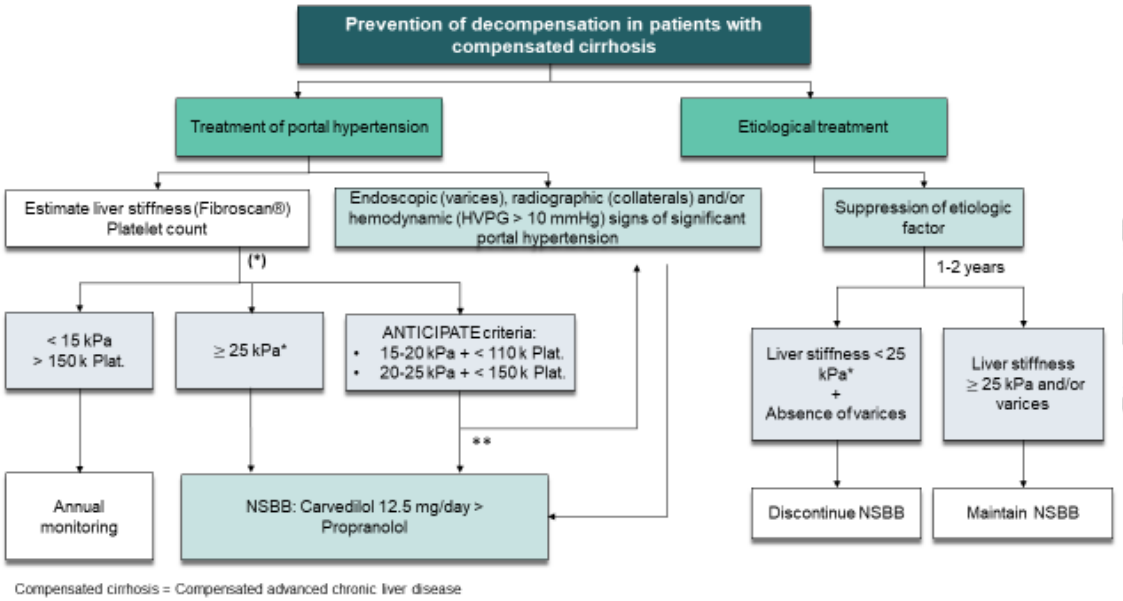

Fig. 3. Algorithm for preventing decompensation in patients with compensated cirrhosis (*Not applicable in patients with metabolic liver disease and with obesity. **In patients meeting ANTICIPATE criteria clinically significant portal hypertension may be assumed with a positive predictive value > 60 %, or upper gastrointestinal endoscopy or any other test allowing to positively diagnose clinically significant portal hypertension may be used. NSBB: non-cardioselective beta blockers; HVPG: hepatic venous pressure gradient).

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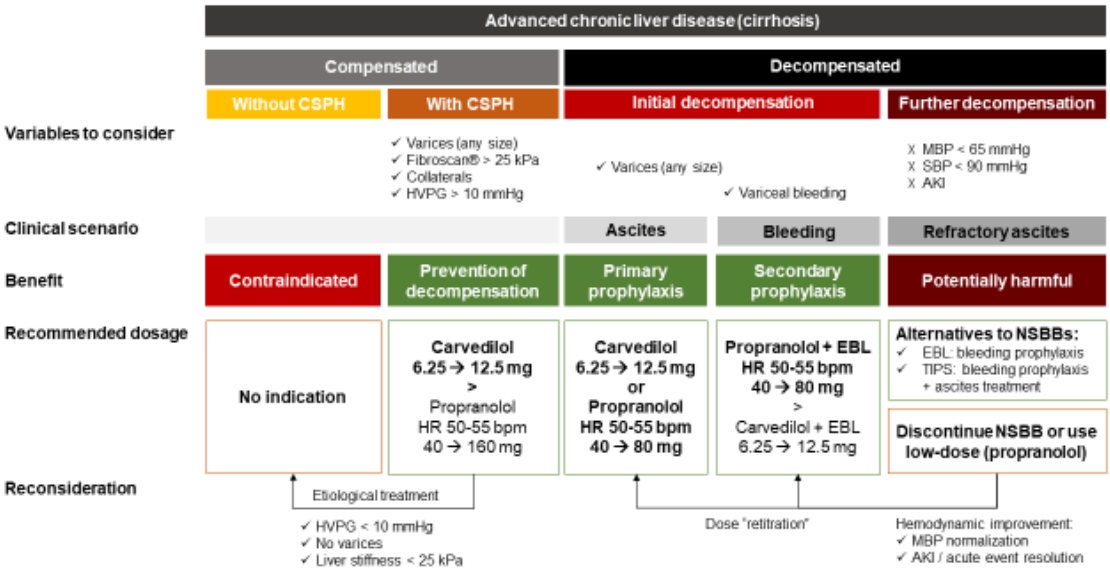

Fig. 4. Therapeutic window of non-cardioselective beta blockers in patients with cirrhosis (HVPG: hepatic venous pressure gradient; MBP: mean arterial blood pressure; SBP: systolic blood pressure; TIPS: transjugular intrahepatic portosystemic shunt; EBL: endoscopic band ligation; AKI: acute kidney injury).

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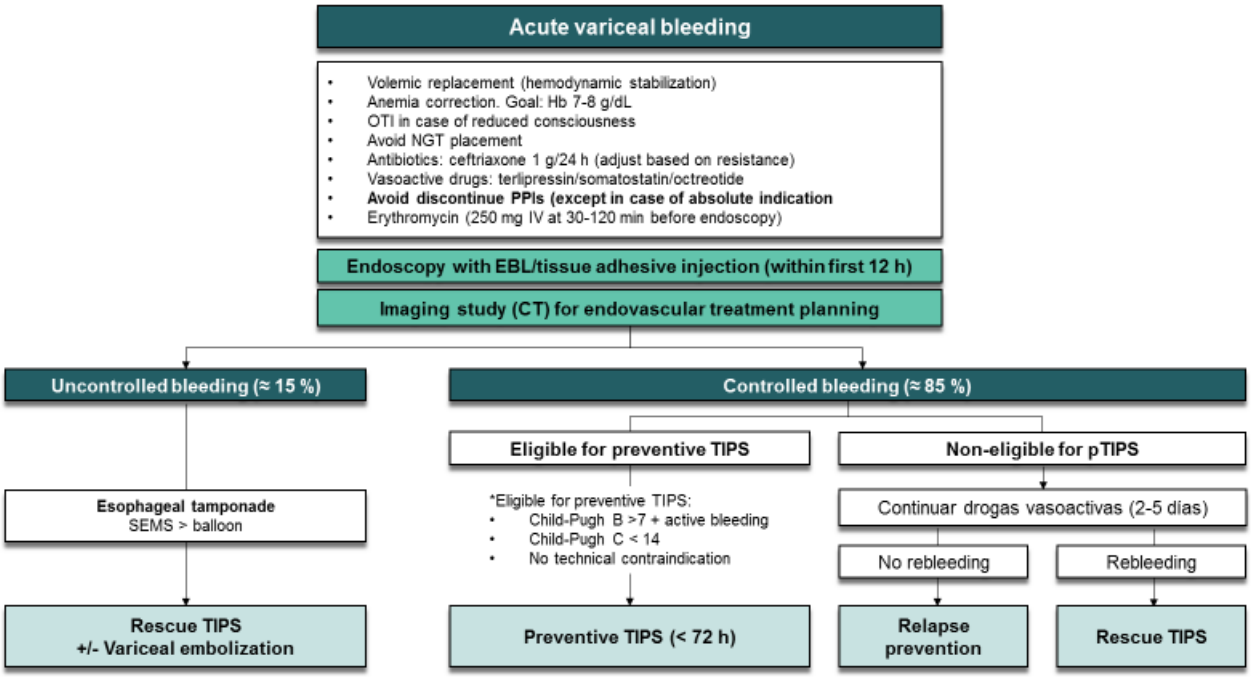

Fig. 5. Treatment algorithm for acute variceal bleeding (OTI: orotracheal intubation; NGT: nasogastric tube; PPI: proton-pump inhibitor; EBL: endoscopic band ligation; SEMS: self-expandable metallic stent).