Prevention of First Decompensation in Advanced Chronic Liver Disease

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KEYWORDS

• ACLD • Cirrhosis • Ascites • Variceal bleeding • Hepatic encephalopathy • Fibrosis • Portal hypertension • Inflammation

KEY POINTS

- The first occurrence of decompensation constitutes a watershed moment in the natural history of advanced chronic liver disease; it denotes a point of no return in a relevant proportion of patients.
- Cirrhosis-related morbidity and mortality are profoundly decreased by delaying or even preventing first decompensation.
- The magnitude of the effect of etiologic therapies is particularly high if a single causative factor is entirely removed.
- In patients who have progressed to clinically significant portal hypertension, etiologic therapies are far from being universally effective in inducing regression and preventing decompensation.
- Besides the removal of cofactors, etiology-unspecific treatments that target decisive pathomechanisms driving decompensation are already applied in clinical practice or being evaluated in randomized clinical trials.

IMPORTANCE OF PREVENTING FIRST DECOMPENSATION

The progression of chronic liver disease (CLD) to compensated advanced CLD (cACLD; a term that subsumes bridging fibrosis and cirrhosis, which can also be diagnosed noninvasively) is paralleled by an increase in the hepatic venous pressure gradient (HVPG). At values of 10 mmHg or more, which define clinically significant portal hypertension (CSPH),[1] patients may develop gastroesophageal varices or/and other portosystemic collaterals, but even more important, decompensation.[2] First decompensation (see **Fig. 1**; most commonly, the development of ascites, and less

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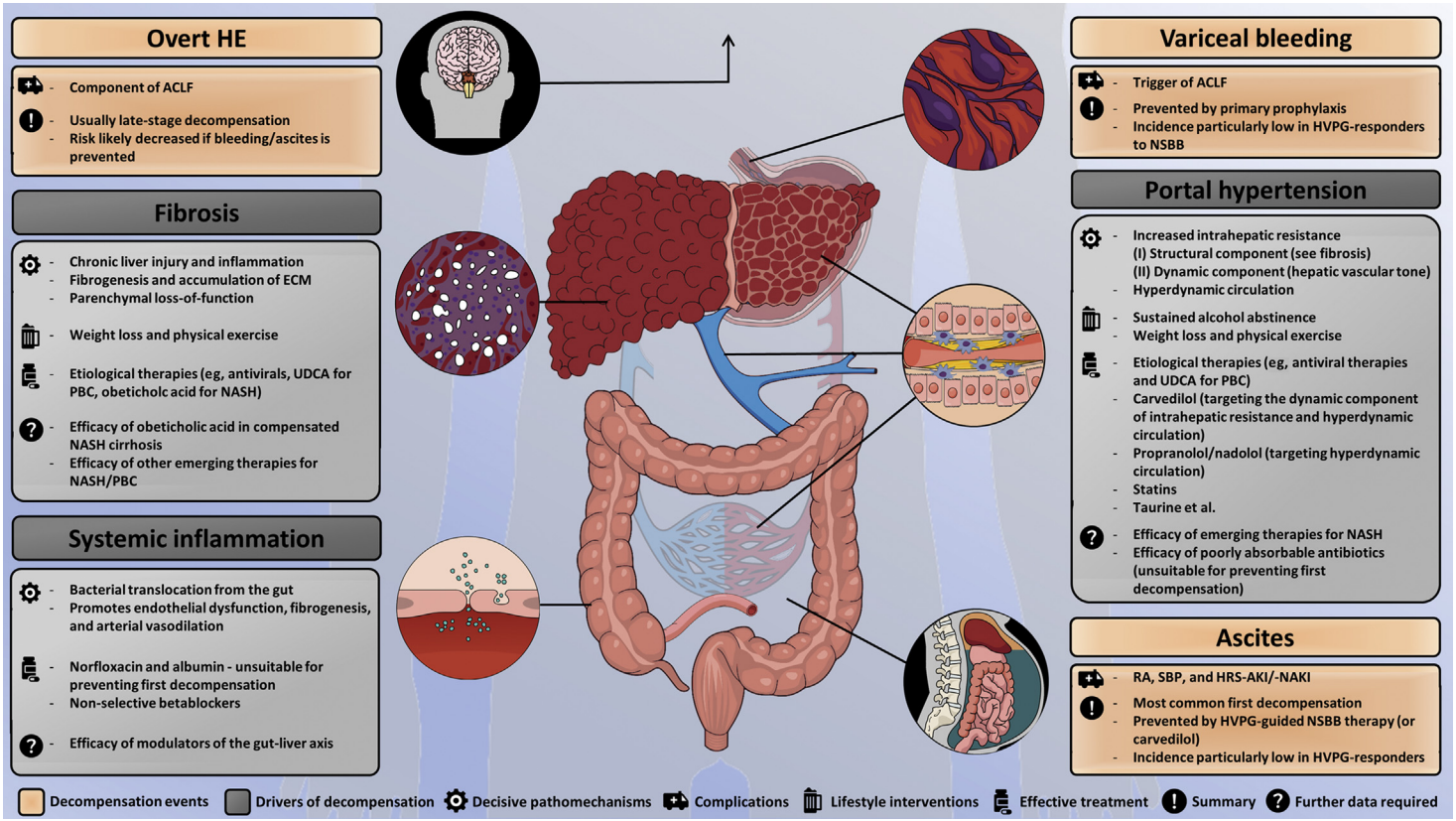

Fig. 1. Forms of first decompensation (decompensation events) are depicted in orange, and pathophysiological mechanisms promoting decompensation (drivers of decompensation) are depicted in gray. For each form of first decompensation, complications (ie, forms of further decompensation that may be direct sequalae of the initial decompensation event) and a summary of the clinical context are provided. Important drivers of decompensation are reported together with their decisive pathomechanisms, lifestyle interventions, as well as medical treatments that effectively target this pathomechanism. Finally, in relationship to all pathomechanisms, important areas of uncertainty (further data required are highlighted). ACLF, acute-on-chronic liver failure; ECM, extracellular matrix; HE, hepatic encephalopathy; HRS-AKI, hepatorenal syndrome type of acute kidney injury (formerly HRS type 1); HRS-NAKI, hepatorenal syndrome type of non-acute kidney injury (formerly HRS type 2); HVPG, hepatic venous pressure gradient; NASH, nonalcoholic steatohepatitis; NSBB, nonselective beta-blockers; PBC, primary biliary cholangitis; RA, refractory ascites; SBP, spontaneous bacterial peritonitis; UDCA, ursodeoxycholic acid.

commonly acute variceal bleeding [AVB] and overt hepatic encephalopathy [HE][3]) denotes the transition from the compensated ACLD to decompensated cirrhosis, which confers a dramatic increase in mortality risk, in particular when the concept of competing risks is considered (incidence increasing from 14% to 93% at 20 years[4]). The latter concept is particularly important in this context, because it acknowledges that decompensation usually precedes death in a patient with compensated ACLD, a fact that has largely been neglected by previous studies. Thus, although the risk of death at 20 years of follow-up was 63% in a cohort of patients with compensated cirrhosis at baseline,[4] the mortality risk of a patients who remain compensated is dramatically lower.

Once decompensation has occurred, treatments aim at decreasing the risk of mortality by preventing further decompensation and acute-on-chronic liver failure,[5] however, all currently investigated disease-modifying treatments (eg, nonselective beta-blockers [NSBB],[6,7] statins,[8] anticoagulation,[9] interventions targeting the gut–liver axis,[10,11] including poorly absorbable antibiotics[12] and microbiota transplantation,[13] long-term albumin administration,[14] and transjugular intrahepatic portosystemic shunt[15]) were—if at all—of limited effectiveness. Thus, despite the important advances regarding disease-modifying treatments for decompensated cirrhosis in recent years, which are summarized and discussed in a dedicated article of this issue, no one-size-fits-all treatment that prevents further decompensation is on the horizon, likely owing to the even higher complexity of decompensated (as compared with compensated) disease. Finally, although etiologic cure (ie, removal of the primary etiologic factor) may lead to hepatic recompensation in previously decompensated patients, a considerable proportion remains decompensated despite effective intervention (eg, cure of hepatitis C [HCV] infection), because the mechanisms that initially triggered decompensation commonly perpetuate liver injury, thereby hindering liver disease regression. Accordingly, the first occurrence of decompensation constitutes a watershed moment in the natural history of ACLD as it denotes a point of no return in the natural history of CLD in a relevant proportion of patients.

Conclusively, cirrhosis-related morbidity and mortality can be profoundly decreased by delaying or even preventing a first decompensation.

ETIOLOGIC THERAPIES

Hepatitis B

In the seminal randomized controlled trial (RCT) by Liaw and colleagues,[16] viral suppression with lamivudine decreased the incidence of a composite end point of an $\geq$ 2-point increase in the Child–Turcotte–Pugh (CTP) score, spontaneous bacterial peritonitis with proven sepsis, renal insufficiency, AVB, the development of hepatocellular carcinoma, or liver-related death in cACLD patients with chronic hepatitis B with a hazard ratio of 0.45. Increases in the CTP score and the development of hepatocellular carcinoma were the most common events. The use of current antiviral therapies with a high barrier to resistance may even lead to a more profound effect, because the emergence of the YMDD-motif variants was linked to worse outcomes. Since the RCT by Liaw and coworkers,[16] several studies of varying quality have reported similar results; these and other studies are summarized in a systematic review with meta-analysis by the Baveno VII faculty.

The findings of studies on direct clinical outcomes are complemented by short-term hemodynamic data[17] and studies with protocol biopsies after long-term treatment.[18] After 12 months of lamivudine treatment, the HVPG decreased from 14.4 to 12.4 mmHg in 19 patients with chronic hepatitis B who underwent paired HVPG

measurements; of note, an increase in the HVPG was observed only in a single patient.[17] Moreover, 74% of patients with chronic hepatitis B with pretreatment compensated cirrhosis showed a regression to noncirrhotic stages after a treatment duration of more than 5 years, whereas only 1% of patients without cirrhosis at treatment initiation progressed to cirrhosis. Importantly, the patients with cirrhosis at the end of long-term treatment had a considerably higher body mass index and a 4-fold increased prevalence of obesity, highlighting the importance of cofactors in this context.

Hepatitis C

Since highly effective interferon (IFN)-free direct-acting antiviral–based combination therapies for chronic HCV became available in 2014 (ie, approval of simeprevir and daclatasvir as combination partner for sofosbuvir), most long-term follow-up studies in patients with cACLD still used IFN-based regimens. Prominent examples include an Italian multicenter retrospective analysis by Bruno and colleagues,[19] which included 920 patients with biopsy-proven cirrhosis of whom—owing to the poor efficacy of IFN monotherapy—only 124 (13.5%) achieved a sustained virologic response (SVR). In this highly selected subgroup of patients, no patient developed decompensation (of note, patients were censored at the time of the development of hepatocellular carcinoma) during a mean follow-up of 8.6 years. In contrast, in the non-SVR group, 107 patients had a decompensation event, which resulted in 1.88 events per 100 person-years. Other retrospective cohort studies with a shorter duration of follow-up confirmed the beneficial effects of SVR on decompensation in patients with bridging fibrosis or cirrhosis; however, they also observed decompensation events despite achieving SVR.[20,21] In addition, the prospective HALT-C trial,[22] which included patients with cACLD found a decreased risk of decompensation at year 7.5 after enrollment in patients who achieved a SVR (0.9% vs breakthrough/relapse, 4.7% vs nonresponse, 11.7%; adjusted hazard ratio for SVR vs nonresponse, 0.13), even after adjusting for differences in baseline characteristics (platelet count and serum albumin). However, IFN-based regimens displayed limited virologic efficacy in patients with cACLD, in particular in patients with CSPH, who were found to be at the highest risk for treatment failure.[23] Accordingly, the probability of achieving SVR was directly dependent on the severity of underlying (baseline) liver disease and portal hypertension, which is also a central determinant of post-treatment decompensation.[24] Thus, these studies were at substantial risk of bias, because patients were usually poorly characterized in regard to the severity of their underlying portal hypertension. More recently, Di Marco and colleagues[25] prospectively investigated long-term outcomes in a cohort of patients with biopsy-proven compensated cirrhosis or small varices treated with pegylated IFN and ribavirin, who were further stratified by the presence (ruling-in CSPH) or absence (ie, patients with CSPH, or without) of small varices. SVR was protective of developing decompensation in both strata; however, although patients without varices seemed to be at negligible risk (0/67 patients), decompensation events occurred at a rate of 1.7 per 100 person-years in patients with small varices (ie, patients with CSPH) who achieved a SVR. In conclusion, findings of studies using IFN-based regimens suggested that achieving SVR decrease the risk of decompensation in patients with or without pretreatment varices and that the risk of decompensation is negligible in patients who are successfully treated before CSPH becomes evident. The latter conclusion is also supported by studies performing paired HVPG measurements that indicated that the resolution of subclinical PH is common and that progression to CSPH did not occur,[26] an observation that was also confirmed recently in a study using IFN-free regimens.[27,28]

IFN-free regimens combining several direct-acting antivirals uncoupled the severity of underlying liver disease/portal hypertension and the likelihood of SVR[29] in patients with cACLD, thereby raising the opportunity of comparing SVR and non-SVR patients in a less biased way. McDonald and colleagues[30] linked patients with chronic HCV and compensated cirrhosis who were included in a Scottish registry to hospital admissions and confirmed that achieving SVR by IFN-free treatments drastically decreased the risk of decompensation (0.188/100 patient-years vs 1.215/100 patient-years).[30] However, in another study based on the Veterans Affairs health care data, the impact of SVR on AVB analyzed as an individual end point seemed to be less pronounced in adjusted analysis (adjusted hazard ratio, 0.68) and did not attain statistical significance in the subgroups of patients with prior varices. This finding may be explained by hemodynamic studies, which indicate that the severity of portal hypertension at baseline determines the probability of (persisting) CSPH despite HCV cure, as well as the development of clinical events during follow-up.[31] CSPH—and thus, the risk of decompensation—persisted in 76% to 78% of patients during short-term follow-up (ie, at a median of 4.15 and 6.00 months after the end of treatment). The initial 2 studies also providing information on long-term changes of HVPG drew a very promising picture,[28,32] because they reported substantial HVPG decreases on the long term; however, the proportions of patients undergoing another HVPG measurement at later time points were very small, introducing the possibility of selection bias. In the 2 more recently published prospective studies reassessing HVPG during long-term follow-up (48 weeks[33] and 96 weeks[31]), persistence of CSPH was observed in 78%[33] and 53 to 65%,[31] respectively—that is, in the majority of patients. However, these studies included a variable proportion of patients with decompensated cirrhosis, in whom CSPH regression was found to be less likely. Accordingly, late decreases of HVPG could be less common than previously expected because the rates of CSPH resolution at this late timepoint were quite similar to those observed in short-term studies.

Of note, even in the IFN-free era, the comparability of treated and untreated patients or responders or nonresponders may be limited by factors that are hard to account for, for example, linkage to care, patient compliance, and concomitant alcohol use. Nevertheless, despite concerns about the appropriateness of comparing SVR and non-SVR patients, in patients with cACLD achieving SVR, the rates of decompensation are low (0.34/100 patient-years).[34]

Nevertheless, it is evident that a considerable proportion of patients with cACLD will develop decompensation despite HCV cure, underlining the need for further etiology-independent treatment strategies in this patient population.

Alcoholic Liver Disease

Although alcoholic liver disease (ALD) is the most common etiology of cirrhosis in Europe[35] and other parts of the world, robust data regarding the impact of abstinence on the development of decompensation in patients with cACLD are limited. This lack may be explained by patients with ALD presenting about 14 times more often with decompensated disease (ie, after the development of first decompensation), as compared with patients with HCV.[36] Accordingly, most studies focused on the outcome of alcoholic hepatitis, which commonly overlaps with ACLD, or decompensated cirrhosis owing to ALD. For instance, a meta-analyses confirming the impact of abstinence from alcohol on survival in patients with ALD with cirrhosis published in 2014 included only 68 patients with cACLD.[37] Masson and colleagues[38] demonstrated that, in a cohort of mostly compensated patients with biopsy-proven ACLD owing to ALD, persistent drinking is the key factor determining long-term mortality (odds ratio, 5.56), whereas the presence of alcoholic hepatitis or cirrhosis at the time of the index

biopsy was not predictive. Recently, Lackner and colleagues[39] provided information on the composite end point of decompensation or liver-related death in 60 patients with biopsy-proven ALD (also including patients without ACLD). In addition to alcoholic steatohepatitis and grade F3/F4 fibrosis, abstinence was associated with a nearly 90% decreased risk of developing the composite end point in univariate analysis. However, it was not predictive in the multivariate analysis, in which grade F3/F4 fibrosis (ie, having ACLD) was the only factor determining the outcome—possibly owing to the limited duration of follow-up (a median of 4.1 years throughout all investigated subgroups) and low sample size. Additional evidence comes from long-term outcome data of survivors in the STOPAH trial[40,41] and another series of patients with severe alcoholic hepatitis treated with corticosteroids.[42] However, these studies have to be interpreted with caution because they included both compensated and decompensated cirrhosis, as well as also noncirrhotic patients. Both studies reported a dose-dependent association between alcohol consumption and long-term mortality; however, information on decompensation was not provided.[40–42]

These findings are supported by the impact of alcohol intake versus alcohol abstinence on portal hypertension. Alcohol intake acutely aggravates portal hypertension in patients with cirrhosis owing to ALD[43] and portal hypertension is most severe in patients who have alcohol-related acute decompensation or acute-on-chronic liver failure.[44] Moreover, comparatively high HVPG values were reported in patients with alcoholic hepatitis.[45] Patients with alcoholic hepatitis or active drinkers with cirrhosis owing to ALD who did not return to harmful drinking had a 45% probability of achieving an HVPG decrease of 20% or more after a median of 100 days, whereas such decreases did not occur in patients who returned to harmful drinking. In line with these observations, in a study by Vorobioff and colleagues[46] investigating patients with cirrhosis owing ALD, a baseline of 12 mm Hg or higher, and varices, the HVPG decreased by 15.9% in abstinent patients, whereas it increased by 18.4% in nonabstinent patients after 1 year of follow-up. Interestingly, both having achieved an HVPG decrease of 15% or more and alcohol abstinence at 1 year of follow-up were independently linked to a decreased risk of AVB, suggesting that the impact of alcohol abstinence reaches even beyond what is captured by a single follow-up HVPG measurement.[46] Additional evidence for the close link between alcohol intake and hemodynamic changes is provided by studies investigating HVPG response to NSBB treatment,[47] which observed higher rates of (maintained) HVPG response in patients with alcoholic etiology,[48] particularly in those who continued to abstain from alcohol.[49,50]

Nonalcoholic Fatty Liver Disease

Only a limited number of studies investigated the impact of etiologic therapies in patients with nonalcoholic steatohepatitis (NASH), who have already progressed to ACLD. Although weight loss via lifestyle modification improves fibrosis—the main histologic determinant for decompensation in NASH—in noncirrhotic patients,[51] its impact in F4 patients has yet to be systematically investigated. Two phase 2 RCT[52] investigated 2 different dosing regimens of simtuzumab (anti-lysyl oxidase homolog 2) in compensated patients with F3 (GS-US-321–0105; n = 219)/F4 (GS-US-321–0106; n = 258) fibrosis, obtaining liver biopsies, and in F4 patients, also HVPG-measurements at weeks 48 and 96. The primary efficacy end points were changes in morphometrically quantified hepatic collagen in the F3 and HVPG-changes in the F4 study. However, both studies also investigated primary clinical efficacy end points, that is, progression to cirrhosis (histologically or decompensation) and event-free survival (the absence of decompensation, newly diagnosed varices, or worsening of CTP or model of end-stage liver disease scores) in the F3 and F4 studies, respectively.

There was no evidence of treatment efficacy in regard to liver histology, HVPG, or composite outcomes, indicating that simtuzumab is ineffective.

Another compound that has been intensively studied in cACLD is the apoptosis signal-regulating kinase 1 (ASK1)-inhibitor selonsertib. The STELLAR-3 (F3; n = 802) and −4 (F4; n = 877) RCT[53] assigned patients to different doses of selonsertib and assessed ≥1-stage improvement in fibrosis without worsening of NASH as the main histologic outcome; the investigated composite end points for F3 and F4 patients were similar to those of the above-described phase 2 studies on simtuzumab. Importantly, selonsertib had no impact on the end points assessed after/during a 48-week period.

Moreover, 24 weeks of emricasan (a pan-caspase inhibitor targeting apoptosis) failed to reduce HVPG as compared with placebo in a study comprising 263 mostly compensated patients with a baseline HVPG ≥12 mm Hg. In accordance with this observation, emricasan did not improve clinical outcomes over a 48-week period. However, there were some signs of efficacy, particularly in compensated patients with HVPG ≥16 mm Hg,[54] which is in line with the findings of a small short-term observation in patients with portal hypertension of diverse etiologies.[55] Since emricasan failed to improve liver fibrosis in noncirrhotic patients and even worsened some histologic features,[56] emricasan—if at all—could be of value for treating severe portal hypertension to prevent decompensation, but not as an etiologic treatment for NASH.

Another compound with some evidence of efficacy in regard to lowering HVPG is belapectin (a galectin-3 inhibitor). Belapectin has been evaluated in an RCT comprising 162 patients with portal hypertension owing to NASH.[57] While being ineffective in improving HVPG, histology, and clinical outcomes in the overall study population, among patients without varices, treatment with the lower dose of 2 mg was associated with a statistically significantly more pronounced absolute decrease in HVPG, which was also accompanied by a lower probability of developing varices.

These mostly negative findings regarding monotherapies in compensated F3/F4patients—despite some of them showing signs of efficacy at earlier stages of the disease—indicate that this is a particularly difficult-to-treat population. This has led to studies investigating regimens combining different modes of action such as the phase 2 ATLAS study,[58] which evaluated different combinations of selonsertib (ie, a presumably ineffective agent), cilofexor (a selective nonsteroidal farnesoid X receptor FXR-agonist), and firsocostat (an acetyl coenzyme A carboxylase-inhibitor). Based on a press release,[59] none of the tested combinations statistically significantly increased the rate of a ≥1-stage improvement in fibrosis without worsening of NASH. However, cilofexor/firsocostat combination therapy led to improvements in some histologic components as well as surrogate markers of liver fibrosis. Of note, this study was not designed to evaluate, and thus, did not provide information on clinical end points.

Finally, the results of phase 3 studies on other compounds (eg, RESOLVE-IT and AURORA) that also include patients with F3 fibrosis, as well as the REVERSE study, focusing on obeticholic acid—a steroidal FXR-agonist which has proven effective in a phase 3 study in noncirrhotic patients[60]—in F4[61] have yet to become available.

Despite several major setbacks in the clinical development of effective treatments for patients with cACLD owing to NASH, these clinical trials have undoubtedly provided important insights in the natural history of NASH which will guide the design of future studies.

Cholestatic and Autoimmune Liver Disease

Ursodeoxycholic acid (UCDA) ameliorates the progression of portal hypertension in primary biliary cholangitis (PBC), as evaluated by measurement of the portal pressure gradient (PPG, ie, direct measurement of the portohepatic gradient),[62] thereby

avoiding the underestimation of the severity of portal hypertension owing to the prehepatic component of increased intrahepatic resistance in cholestatic liver disease.[63] In the 30 compensated PBC patients randomized 1:1 to UDCA or placebo for 2 years, PPG increased in untreated patients during the first 2 years, while it did not change significantly in treated patients. Following the initiation of UDCA treatment, PPG decreased to baseline values in patients who were initially treated with placebo. In the 101 PBC patients with paired PPG measurements in the overall study population, stable (as defined by no change or an PPG-increase $\leq$20%) or decreasing PPG-values after 2 years of UDCA treatment translated into a survival benefit (hazard ratio, 4.64). However, this study included a considerable proportion of patients who only had subclinical portal hypertension at study inclusion (ie, patients who were unlikely to have had ACLD at baseline and therefore had a low risk of liver-related events) and decompensation was not evaluated as an end point. Nevertheless, the study provides important insights into the impact of UDCA treatment on the evolution of PBC, suggesting that UDCA treatment may halt disease progression but is less effective in promoting liver disease regression than other etiologic therapies, which is possibly related to inadequate responses to UDCA. In line with the observations on PPG, UDCA treatment prevents/delays disease progression to CSPH as evidenced by the decreased risk of developing varices[64] and ultimately improves transplant-free survival.[65] In addition, the prognosis of PBC may further improve with emerging treatment options such as obeticholic acid[66–69] and fibrates,[70,71] owing to further improvements in biochemical response. However, based on the available evidence, it is difficult to assess the impact of current and emerging therapies on the development of first decompensation in patients who have already progressed to ACLD.

The efficacy of UDCA treatment for PSC is controversial[72] and novel therapeutic options are currently under evaluation[73–76]; however, long-term results on direct clinical end points have yet to become available.

Although response to immunosuppressive therapy is linked to long-term outcomes in autoimmune hepatitis,[77] there are insufficient data to draw firm conclusions on its impact decompensation in patients with ACLD owing to autoimmune hepatitis.

Summary of the Impact of Etiologic Therapies and Outlook

In conclusion, there is a body of evidence indicating that etiologic therapies decrease the risk of first decompensation (see **Fig. 1**). The magnitude of the effect seemed to be particularly high in etiologies in which a (theoretically) single causative factor (ie, HBV replication, HCV infection, or alcohol consumption) is entirely removed. However, in patients who have already progressed to CSPH, even 'perfect' etiologic therapies are far from being universally effective in inducing CSPH regression and preventing decompensation. Although the underlying pathophysiological mechanisms have yet to be fully elucidated, the gut-liver-axis[10] could be of great relevance for the long-term evolution of liver disease in these patients, as bacterial translocation-induced hepatic[78] and systemic inflammation may perpetuate liver injury despite the cure of the primary etiologic factor or even directly trigger decompensation. Interestingly, markers of bacterial translocation (ie, lipopolysaccharide binding protein[28,33]) as well as associated endothelial dysfunction[79] (ie, von Willebrand factor [VWF][80]) decreased in patients achieving SVR and the observed changes were unrelated to the dynamics of HVPG.[28]

Patients who underwent etiologic therapies are less likely to require liver transplantation or die from liver-related causes, indicating that they will remain in the same disease state/need to be followed for a longer time period, as compared with patients with progressive disease. Considering that current surveillance/

treatment strategies have primarily been developed based on/extrapolated from patients with progressive disease, their application may result in unnecessary interventions in patients who underwent etiologic treatment, and thus, have a more favorable prognosis. The high interindividual variability in the impact of etiologic therapies on the course of ACLD is a major challenge in this context, which highlights the need for surrogate markers that reflect the risk of decompensation after etiologic therapies to monitor the evolution of liver disease after etiologic treatments in an individual patient. We have recently demonstrated that post-treatment HVPG/relative changes in HVPG (ie, HVPG-response, as defined by a decrease $\geq$10%) predict decompensation after HCV-cure,[28] in particular first decompensation patients with compensated CSPH. In contrast, in another study by Lens and coworkers[34] that included a considerably higher proportion of patients with decompensated cirrhosis, there was only an association between post-treatment HVPG and decompensation during follow-up in univariate analysis, which did not attain statistical significance in multivariate analysis. In addition, changes in HVPG have also been linked to outcomes in patients with ALD with HVPG $\geq$12 mm Hg who were advised to abstain from alcohol (HVPG-decrease cut-off: $\geq$15%),[46] or patients with compensated cirrhosis owing to nonalcoholic steatohepatitis (NASH) treated with simtuzumab or placebo (HVPG-decrease cut-off: $\geq$20%).[81] However, it is clear that HVPG-measurement—although being highly informative—cannot be applied for risk stratification on a broad scale, as it is not available at most centers. This indicates the need for development and validation of noninvasive methods for this specific clinical scenario.[82] In the post-SVR setting, Baveno VI criteria[83] as well as combinations of liver stiffness measurement (LSM) by vibration-controlled elastography (VCTE) and albumin[80] or VWF to platelet count ratio[80] have shown a high prognostic ability for decompensation, thereby facilitating risk stratification, individualization of surveillance, and possibly, selection of patients who may benefit from additional strategies to prevent first decompensation.

REMOVAL OF COFACTORS

Concomitant alcohol consumption modulates the impact of the removal of the primary etiologic factor on outcomes. For instance, in (mostly compensated) ACLD patients who achieved HCV-cure, alcohol consumption above the sex-specific thresholds for NAFLD (ie, >30 g/d and >20 g/d for males and females, respectively[84]) was substantially more prevalent (50% vs 9.1%) in patients who developed post-treatment decompensation and was also independently predictive of the outcome of interest.

In addition, the impact of obesity and associated metabolic disturbances on portal hypertension owing to etiologies other than NAFLD is increasingly recognized. For instance, a 16-week lifestyle intervention comprising diet and physical exercise has been shown to lead to 'clinically meaningful' HVPG-decreases $\geq$10% in 42% of obese patients with portal hypertension, with particularly profound decreases in those who achieve $\geq$10% of weight loss.[85]

Accordingly, cessation of alcohol consumption and weight loss (in obese patients) should be strongly advised to prevent decompensation.

PATHOPHYSIOLOGY-ORIENTED THERAPIES

Drivers of Decompensation

As outlined in the introduction section, sinusoidal portal hypertension (as defined by portal pressure gradient (PPG)/HVPG $\geq$6 mm Hg) is initiated by intrahepatic

microcirculatory disturbances manifesting as increases in intrahepatic resistance, which comprises tightly interrelated structural (fibrosis, microvascular occlusion, and sinusoidal capillarization) and functional (hepatic vascular tone; regulated mainly by liver sinusoidal endothelial cells and hepatic stellate cells) components.[86] The functional component (ie, hepatic vascular tone) is directly impacted by bacterial translocation from the gut which leads to hepatic and systemic inflammation—highlighting the central role of the 'gut-liver axis'[10,11] for disease progression. Systemic inflammation also promotes arterial vasodilation leading to compensatory increases in cardiac output, and thus, hyperdynamic circulation.[87] Hyperdynamic circulation further aggravates portal hypertension, which, at this point, exceeds the threshold defining CSPH.[1] At the same time, vasodilation results in effective hypovolemia which induces compensatory responses leading to sodium and fluid retention and ascites formation.[88]

These mechanisms that are summarized in **Fig. 1** are targeted by several medical therapies, of which NSBB and statins are supported by a broad body of clinical evidence.

Nonselective Beta-Blockers

Current guidelines[89,90] recommend NSBB treatment in patients with (medium to) large varices as well as high-risk small varices to prevent AVB. According to Baveno VI[89] and American Association for the Study of the Liver recommendations, CTP stage C (usually conferring to decompensated cirrhosis) or the presence of red wale marks define high-risk varices. Alternatively, endoscopic variceal ligation (EVL) may be used for primary prophylaxis in patients with (medium to) large varices. Although a meta-analysis[91] showed that EVL decreased AVB when compared with NSBB treatment (relative risk, 0.69), the beneficial effect of EVL was not confirmed in a subsequent analysis restricted to high-quality trials. Moreover, EVL—in contrast to NSBB—acts exclusively downstream of the pathophysiologic cascade of portal hypertension.

Although primary prophylaxis with NSBB therapy is well-established for these indications, early studies did not find a benefit in patients with cACLD who did not meet those criteria. In a study by Groszmann and colleagues,[92] patients with cirrhosis, with an HVPG of 6 mmHg or higher, but without varices were randomly assigned to the NSBB timolol or placebo. After a median follow-up of nearly 5 years, about 40% of patients in both groups met the composite primary end point of the development of varices or AVB. Importantly, patients who had a relative HVPG decrease of more than 10% after 1 year showed a lower incidence of the primary end point, but such decreases were only slightly more common in timolol-treated patients (53% vs 38%), which may be explained by the inclusion of a high proportion of patients with only subclinical portal hypertension (59%). Conventional NSBB such as timolol or propranolol/nadolol decrease the HVPG by decreasing cardiac output (anti-β1) and ameliorating splanchnic vasodilation (anti-β2). Accordingly, the absence of or less pronounced hyperdynamic circulation in patients with subclinical portal hypertension attenuates their antiportal hypertensive effect. This hypothesis is supported by the findings of a study by Villanueva and colleagues,[1] in which patients with subclinical portal hypertension—who had lower cardiac index and higher systemic vascular resistance—achieved a relative HVPG decrease of only 8% to intravenous (IV) propranolol, whereas the relative HVPG decrease was 16% in patients with CSPH.

Moving to patients with low-risk small varices, there is no conclusive evidence for a decrease in AVB with NSBB treatment.[6] Of note, an absence of evidence is not evidence of absence, particularly because the trials were not sufficiently powered to detect favorable treatment effects—as discussed elsewhere in this article, sample

size requirements for studies evaluating preventive strategies in low-risk patients are tremendously high.[5] To overcome this limitation, several trials investigated the efficacy of NSBB treatment to prevent the more common surrogate end point variceal growth; however, the findings were mixed.[93] Finally, it is unclear whether a decrease in variceal growth translates into a clinically meaningful benefit.

In contrast, the benefit of preventing decompensation is well-established, and findings in patients with HVPG response to NSBB treatment indicated, that NSBB-induced decreases in HVPG decrease the risk of decompensation, in particular the incidence of AVB (the decompensation event that is most directly driven by portal hypertension) and ascites.[47] Some studies also suggested a decrease in overt HE; however, it may be argued that the decreased incidence in overt HE could also be secondary to decreases in the latter 2 forms of decompensation, because AVB and the use of diuretics may precipitate overt HE. Findings of studies investigating the predictive values of acute changes in HVPG to IV propranolol provided the most convincing evidence for the preventive effect of HVPG-response to NSBB treatment, because chronic changes in HVPG are also affected by the evolution of underlying liver disease.[47] Of note, in addition to the effects that are directly related to HVPG decreases, NSBBs decrease bacterial translocation and systemic inflammation in an HVPG response-independent manner,[94] which may further add to its disease-modifying properties (see **Fig. 1**).

In their seminal PREDESCI trial, Villanueva and colleagues[95] assigned 201 compensated patients with CSPH with no or small low-risk varices to propranolol (in case of HVPG decrease of $\geq$10% to IV propranolol)/carvedilol (hemodynamic nonresponders to IV propranolol) treatment or placebo. Propranolol/carvedilol decreased the risks of decompensation or liver-related death, mostly by decreasing the incidence of ascites.[95] Although improvements in patients selection such as the exclusion of patients without CSPH and the use of HVPG-guided therapy may have been instrumental for demonstrating the ability of NSBB treatment to prevent decompensation in patients with no or only low-risk small varices, this HVPG-centric approach hampers the applicability of these findings in clinical practice. Until more evidence becomes available, this limitation could be overcome by a more pragmatic approach using noninvasive methods for ruling-in CSPH[82] and a target dose of 12.5 mg of carvedilol per day[96] in all patients, because—owing to its additional anti–alpha-adrenergic activity—carvedilol reduces HVPG more potently as compared to propranolol[97] and achieves an HVPG response in a relevant proportion of nonresponders to propranolol.[98]

Importantly, another RCT (the BOPPP trial[99]) that is adequately powered (1200 patients) to detect a potential benefit in direct clinical end points (ie, AVB; other forms of decompensation are assessed as secondary end points) in patients with small low-risk varices who have not bled (the subpopulation that benefited the most in the PREDESCI trial[95]) is currently on the way and will provide further evidence regarding the use of carvedilol in this context.

Statins

Until recently, CLD—in particular if advanced—was considered a relative contraindication for statin prescription, mainly driven by concerns regarding hepatotoxicity.[100] However, an increasing number of studies reported potential beneficial effects of statins in patients with CLD[101] (see **Fig. 1**), although the risk of severe hepatic injury seems to be comparable with that in the general population (only high-dose atorvastatin was associated with hepatotoxicity).[102] Importantly, the pharmacokinetics of statins display alterations that depend on disease stage,[8] as underlined by the observation of dose-dependent toxicity (rhabdomyolysis) upon treatment with

40 mg/d in CTP C, whereas a rescue dose of 20 mg/d seemed to yield an acceptable safety profile.[103]

By now, experimental studies demonstrated that statins exert beneficial effects on ACLD, which may be explained by an amelioration of hepatic inflammation as well as endothelial dysfunction, thus improving liver function and portal hypertension, and preventing acute-on-chronic liver failure.[8] To this end, an RCT in 59 patients with portal hypertension (HVPG of $\geq$12 mm Hg; n = 55 eligible for efficacy analysis; 38% compensated cirrhosis) reported a significant decrease in the HVPG after 1 month of therapy in both compensated and decompensated patients with or without concomitant NSBB therapy who were treated with simvastatin 40 mg/d.[104] Similarly, patients receiving simvastatin 40 mg/d for 3 months displayed a trend toward an HVPG reduction in an RCT including 34 patients, of whom only 24 patients were eligible for per-protocol analysis.[105] Finally, another RCT including 23 patients displayed that atorvastatin 20 mg/d plus propranolol led to a more pronounced HVPG decrease after 30 days of treatment, as compared with propranolol alone,[106] confirming that the effects of statins add to those of propranolol therapy.

Although these studies support the use of statins for the treatment of portal hypertension, it has yet to be demonstrated that statins prevent first decompensation. A systematic review and meta-analysis of available studies indicated a decrease in the incidence of decompensation and mortality by statin treatment, however, also highlighted the need for an RCT to draw firm conclusions.[101] Of note, the BLEPS trial including 158 patients requiring secondary prophylaxis for variceal bleeding investigated whether simvastatin 40 mg/d decreases the risk of rebleeding or death.[103] Although simvastatin displayed no benefit toward the primary (composite) end point, it was associated with a substantial decrease in the risk of death (hazard ratio, 0.39)[103] in the context of decompensated cirrhosis; however, it is unclear whether these findings can be extrapolated to patients with cACLD. The SACRED trial[107] randomly assigns patients with cACLD and (evidence of) CSPH (among other criteria, liver stiffness of $\geq$25 kPa, platelet counts of <70 G/L, or the presence of varices) to investigate to the efficacy of simvastatin 40 mg/d toward the prevention of decompensation as a primary outcome; liver-related death is assessed as a secondary outcome. Of note, this study is complemented by the LIVERHOPE efficacy trial[108] investigating whether the combination of simvastatin 20 to 40 mg/d and rifaximin (which, similarly to norfloxacin, ameliorates bacterial translocation-induced systemic inflammation[109]) prevents acute-on-chronic liver failure in patients with decompensated cirrhosis—a combination that could also be suitable to prevent first decompensation based on pathophysiologic considerations. The results of these trials will provide further important evidence regarding the use of simvastatin in ACLD.

Other Potential Therapeutic Targets

In addition to all the previously discussed measures, several additional medical therapies have the potential to prevent first decompensation (see **Fig. 1**), mostly by ameliorating portal hypertension and/or systemic inflammation. However, we abstained from discussing them in detail because they have recently been reviewed elsewhere[5,10] and only proof-of-concept clinical studies are available.

DESIGN OF TRIALS ON THE PREVENTION OF FIRST DECOMPENSATION

Future trials should analyze a composite of all forms of decompensation—rather than an individual complication such as AVB—as a primary end point. This approach

decreases the sample size requirements by increasing the number of events and ensures clinically meaningful results. Moreover, selection of patients at risk is key to obtain a sufficient number of events; in this regard, only patients with CSPH (which may be diagnosed noninvasively) should be considered, because the risk in patients with subclinical portal hypertension patients is negligible. Still, the required sample size is high: When assuming a hazard ratio of 0.7 and a 2-year rate of first decompensation of 20% (corresponding with a median HVPG of about 14 mm Hg) in the control group, 700 patients would be required.[5] Another approach to decrease sample size is to restrict the inclusion to patients who are most likely to benefit from the treatment (thereby decreasing the hazard ratio) because the pathomechanism that is, targeted by the study intervention is highly active in the individual patient. In this regard, pathophysiologically oriented biomarkers could be instrumental for study design and may facilitate personalized therapy. Such an approach may considerably decrease resource utilization; a decrease in the hazard ratio from 0.7 to 0.6 would nearly halve the required sample size (380 instead of 700).[5]

CLINICS CARE POINTS

- In patients with compensated advanced chronic liver disease, prevention of decompensation is the primary treatment goal to avoid the downward spiral of further decompensation and acute-on-chronic liver failure.
- Etiological therapies may improve liver function and fibrosis, as well as portal hypertension, thereby decreasing the risk of decompensation.
- Moreover, the effective management co-factors – in particular alcohol and overweight/obesity – is crucial.
- Hepatic venous pressure gradient (HVPG)-guided non-selective beta-blocker therapy prevents decompensation in those at risk, i.e., patients with clinically significant portal hypertension (CSPH; as defined by an HVPG $\geq$10 mmHg).
- Comparable effects may be achieved by ruling-in CSPH using non-invasive methods (e.g., liver stiffness measurement $\geq$20-25 kPa) and administering carvedilol (12.5 mg/d).

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