EXAMINING THE THERAPEUTIC LANDSCAPE OF BETA-BLOCKERS IN PORTAL HYPERTENSION

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Abbreviations: CI: confidence interval, CSPH: clinically significant portal hypertension, FU: follow-up, HVPG: hepatic venous pressure gradient, INR: international normalized ratio, MELD: model for end stage liver disease, NSBBs: non-selective β-blockers, OLT: orthotopic liver transplantation, PH: portal hypertension, RCT: randomized controlled trial, SD: standard deviation, SHR: subdistribution hazard ratio.

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Advanced chronic liver disease (ACLD) progress over time, from a compensated stage (cACLD) to development of decompensation (dACLD), with markedly declined life expectancy.(1,2) Portal hypertension (PH), usually estimated by the hepatic-venous pressure gradient (HVPG), is the main determinant leading to decompensation.(2-4) Variceal bleeding, overt ascites (or pleural effusion) and/or overt encephalopathy, define decompensation.(2) An HVPG ≥10mmHg defines clinically significant PH (CSPH), the main substage of cACLD, since varices and decompensating events develops above this threshold.(2) The presence of varices identifies a substage of cACLD with CSPH, since patients with varices have increased risk of decompensation.(5,6)

Increased hepatic vascular-resistance is the primary factor leading to PH in early cACLD, and is related to liver fibrosis with architectural distortion, endothelial dysfunction and vascular occlusion.(7,8) At this stage, mild increases in portal-pressure activates vasodilatory and angiogenic signals, developing portosystemic collaterals and progressive splanchnic vasodilatation. The ensuing increase in portal blood flow leads to hyperdynamic circulation, exacerbating PH.(6-8) The persistence of etiological/co-etiological factors, such as obesity, diabetes or alcohol consumption, by facilitating systemic delivery of PAMPs and DAMPs, may favor the release of pro-inflammatory cytokines.(9) This may further increase intrahepatic vascular-resistance and exacerbate splanchnic vasodilatation and hyperdynamic circulation, worsening PH and eventually leading to decompensation.(8-10) Cardiac-output progressively increase until advanced stages of dACLD, when cardiac compensatory reserve may be reduced, mainly in stress situations such as infections or acute on chronic liver failure, which may negatively impact on survival.(11,12)

Among patients with cACLD, hyperdynamic circulation is more developed in those with CSPH than in those with mild-PH (HVPG between 5&10 mmHg),(6) and among patients with CSPH is more accentuated in those with varices.(6,12) Non-selective beta-blockers (NSBBs) decrease PH, by β1-adrenergic-blockade (reducing heart-rate and cardiac-output) and by β2-adrenergic-blockade, causing splanchnic vasoconstriction due to unopposed adrenergic tone.(13-15) NSBBs have portal-pressure decreasing effect once CSPH has developed, but have minimal effect in patients with mild-PH, when hyperdynamic-circulation is poorly developed.(6) The HVPG-lowering effect of NSBBs is also smaller in decompensated vs compensated patients.(11) This may be related to vascular dysfunction in dACLD, with hypo-contractility induced by dysregulation of vasoactive proteins.(16) Altogether suggest that patients with cACLD and CSPH may benefit the most from NSBBs.

Preventing complications of PH is the goal of therapy in cACLD. This is particularly relevant in patients with CSPH and mainly in those with varices, due to their higher risk of decompensation.(2) A strong evidence support the efficacy of NSBBs to prevent bleeding in cirrhosis with high-risk varices.(13-18)
Furthermore, the PREDESCI study, demonstrated that NSBBs can also prevent decompensation in cACLD with CSPH, with a risk reduction by half. This was mainly achieved by preventing ascites, the most frequent and severe decompensation in cACLD. (19) Subsequent studies reinforce the value of NSBBs to prevent decompensation. (20,21) At present, CSPH can be confirmed non-invasively, mainly relying on liver stiffness measurement (LSM) by transient elastography. (18,22) LSM ≤15 KPa plus platelets ≥150x10^9/L rule-out CSPH, and LSM of ≥25 KPa rule it in quite accurately. (18,22) Detecting varices by endoscopy or collateral circulation by imaging also identifies patients with CSPH. (2) In the PREDESCI study, the benefit of NSBBs in cACLD was consistent in patients either with or without small-varices, but was more apparent with small-varices, probably due to higher risk of decompensation. (19)

In patients with high-risk varices, both NSBBs and endoscopic variceal ligation (EVL) have similar efficacy to prevent a first-bleeding in RCTs. (13,14,17) A recent individual patient data (IPD) meta-analysis (MA) of RCTs comparing NSBBs vs EVL for primary prophylaxis, stratified risk according to cirrhosis decompensation. (23) IPD-MA by optimizing the assessment of cirrhosis as multistate disease and that of outcomes as time-dependent events, demonstrated a significant reduction of mortality risk by half in cACLD favoring NSBBs over EVL. (23) This was mainly due to a decreased ascites risk, while risk of bleeding was similar. The benefit did not improve by adding EVL to NSBBs. (23) These results strongly support that, in cACLD with high-risk varices, NSBBs are preferable over EVL, as on top of similar bleeding risk, NSBBs additionally decrease the ascites risk improving survival.

Carvedilol is the preferred NSBB in cACLD. It has anti-α-adrenergic activity and also enhance intrahepatic NO release, inducing a decrease in intra-hepatic vascular-resistance, (24) a key factor leading inducing PH in cACLD. (6,8) Carvedilol has greater portal-pressure decreasing effect than classical-NSBBs, such as propranolol or nadolol, and may achieve hemodynamic response in previous non-responders to classical-NSBBs. (24,25) Furthermore, carvedilol has additional antioxidant, anti-inflammatory and antifibrotic effects. (26,27) A recent IPD-MA investigated the efficacy of carvedilol in cACLD with CSPH, including RCTs comparing carvedilol with a control-group receiving no active therapy (in patients with small varices or without varices) or EVL (if high-risk varices). (28) This IPD-MA demonstrated that carvedilol can effectively prevent decompensation and improve survival in cACLD with CSPH. (28) This supports the strategy of screening patients with cACLD for CSPH to start therapy with carvedilol, suggested in the last Baveno meeting.

The goal of treatment in dACLD consists in preventing liver transplantation and death. This implies preventing further decompensation, which is closely related to death. Whether NSBBs may be effective in dACLD without varices has not been clarified. In patients with dACLD and high-risk varices, NSBBs are no better
than EVL to prevent first bleeding, according to a previously commented IPD-MA.(23) After variceal bleeding, current guidelines advise combining NSBBs and EVL to prevent rebleeding.(2,3) According to another IPD-MA, adding NSBBs to EVL significantly decreases rebleeding risk and improves survival, compared with EVL-monotherapy, particularly in Child-Pugh B/C.(29) In this IPD-MA, NSBBs-monotherapy performed as well as combined therapy,(29) suggesting that NSBBs are cornerstone of treatment also in patients with previous bleeding. Benefit from NSBBs is particularly relevant in patients with a marked HVPG-decrease,(30,31) and it has been suggested by guiding therapy according to HVPG-response may improve efficacy.(32) Nevertheless, the limited availability and invasiveness limit such strategy.(33) Identifying non-responders using non-invasive tools is an unmet clinical need, since this is a promising strategy to guide therapy, particularly in the high risk setting of dACLD.(18,22)

In patients with advanced ascites, NSBBs should be dose-reduced or discontinued with persistently low arterial pressure (systolic <90 mmHg), or with renal impairment.(2) This is also the case in patients intercurrent conditions determining hemodynamic instability, such as bleeding, SBP or other severe infections.(13,14) After recovery, NSBBs should be re-started at lower doses and under close monitoring. Carvedilol, given its non-selective vasodilatory effect may increase sodium and water retention in patients with advanced ascites, when classical-NSBBs may be preferable.(24) Patients with dACLD and contraindication/intolerance to NSBBs, should be considered for trans-jugular intrahepatic porto-systemic shunt,(34-36) particularly those with uncontrolled ascites or recurrent decompensation.
REFERENCES


FIGURE LEGEND

Indication and clinical effects of NSBBs across the stages of compensated and decompensated ACLD.

Abbreviations: ACLD: advanced chronic liver disease; cACLD: compensated ACLD; CO: cardiac output; CSPH: clinically significant portal hypertension; dACLD: decompensated ACLD; MAP: mean arterial pressure; NSBBs: non-selective β-blockers; PH: portal hypertension