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Snapshot

Examining the therapeutic landscape of beta-blockers in portal hypertension

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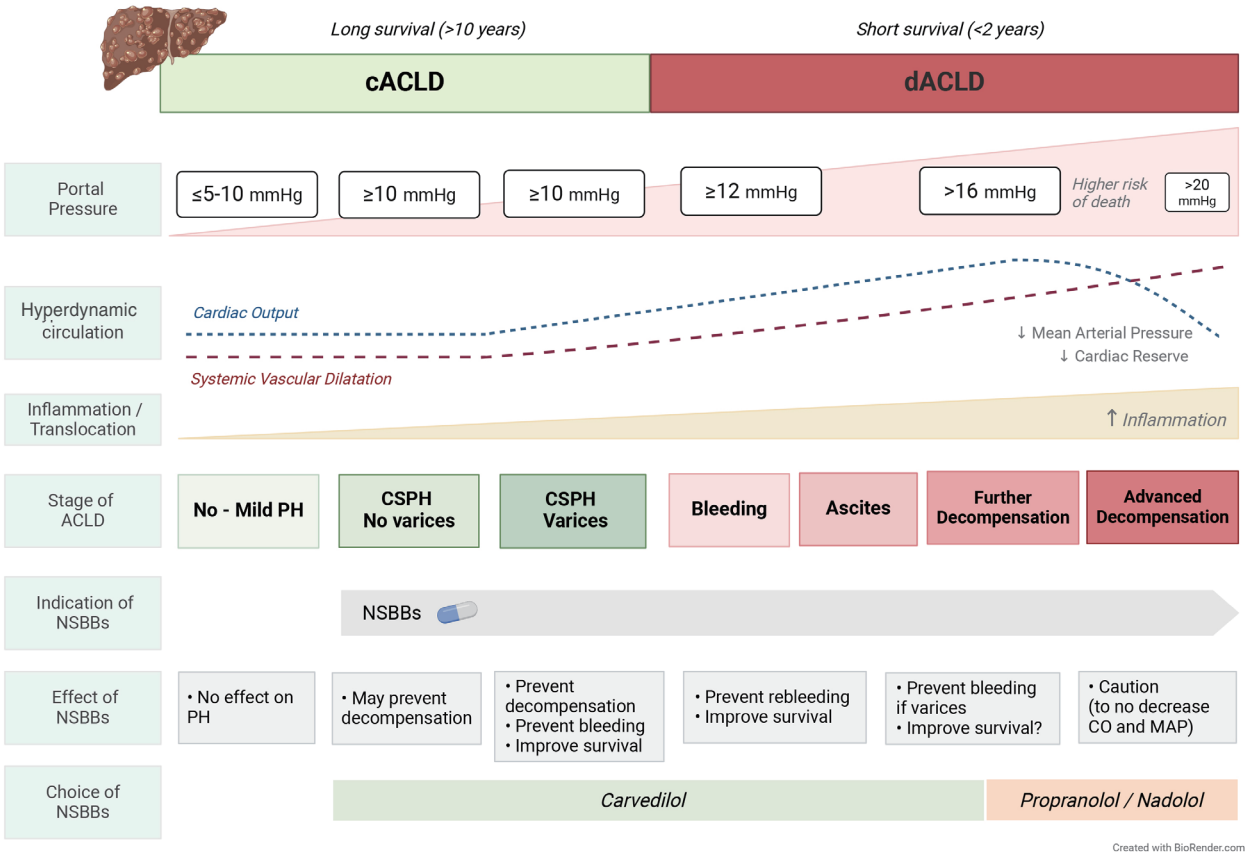

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Advanced chronic liver disease (ACLD) progresses over time, from a compensated stage (cACLD) to development of decompensation (dACLD), markedly declining life expectancy.[1,2] Portal hypertension (PH), usually estimated by the hepatic-venous pressure 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 ≥10 mmHg defines clinically significant PH (CSPH), the main substage of cACLD, since varices and decompensating events develop above this threshold.[2] The presence of varices identifies a substage of cACLD with CSPH, since patients with varices have an 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 activate 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, as well as bacterial translocation induced by PH, 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 increases until the advanced stages of dACLD, when cardiac compensatory reserve may be reduced, mainly in stressful situations such as severe bacterial infections or acute-on-chronicl iver failure, which may negatively impact 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 and 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 a portal-pressure-decreasing effect once CSPH has developed, but have a 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, indicates 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] Strong evidence supports 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 50% risk reduction. 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

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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

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 the 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] This IPD-MA, by optimizing the assessment of cirrhosis as a 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 risk of ascites, while the risk of bleeding was similar. The benefit did not improve by adding EVL to NSBBs.[23] These results strongly support for the preference of NSBBs over EVL in cACLD with high-risk varices, because NSBBs further reduce the risk of ascites and improve survival, in addition to a similar bleeding risk.

Carvedilol is the preferred NSBB in cACLD. It has anti-α-adrenergic activity and also enhances intrahepatic NO release, inducing a decrease in intra-hepatic vascular-resistance,[24] a key factor leading to inducing PH in cACLD.[6,8] Carvedilol has a greater portal-pressure-decreasing effect than classical-NSBBs, such as propranolol or nadolol, and may achieve a 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 has 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 has demonstrated that carvedilol can effectively prevent decompensation and significantly improves survival in cACLD with CSPH.[28] This supports the strategy of screening patients with cACLD for CSPH to start therapy with carvedilol, as suggested in the last Baveno meeting.

The goal of treatment in dACLD is to prevent 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 the cornerstone of treatment in patients with previous bleeding. The benefit of NSBBs is particularly relevant in patients with a marked decrease in HVPG,[30,31] and guiding therapy based on HVPG response has been suggested to potentially 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 if persistently low arterial pressure (systolic <90 mmHg), or if renal impairment.[2] This is also the case in patients with 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.

Authors' contribution

A.B. manuscript writing and approval.

C.V. concept of the work, manuscript writing and approval.

Conflicts of Interest

The authors have no conflicts to disclose.

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