Prevention of decompensation in cirrhosis: a new youth for β blockers

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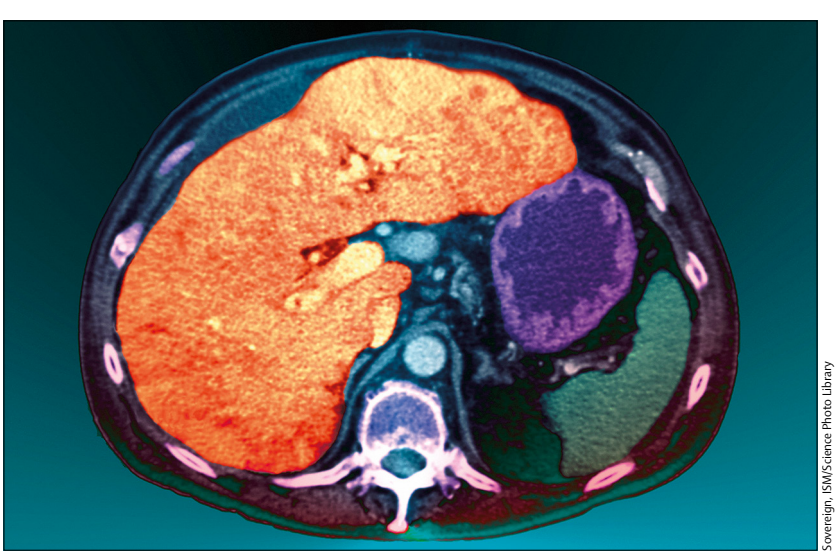
The natural history of cirrhosis can be described as a continuum from a compensated phase to decompensation and liver failure, marked by the development of ascites, overt hepatic encephalopathy, or variceal haemorrhage, occurring at a rate of 5–7% per year. This decompensation results in an increased mortality, and a median survival of 2 years versus 12 years in the compensated phase.[1] Hepatic fibrosis and the development of portal hypertension are the major pathophysiological processes of this clinical course. Hepatic venous pressure gradient (HVPG) has been shown as the strongest predictor of decompensation with a 90% negative predictive value for HVPG less than 10 mm Hg.[2] It has already been shown that non-selective β blockers are effective in reducing portal hypertension and their role in prevention of variceal haemorrhage, once high-risk varices or rupture develop, has been well established.[3,4] A trial of timolol[5] did not find any difference in the occurrence of varices or variceal haemorrhage between patients with compensated cirrhosis and HVPG greater than 6 mm Hg who were treated with timolol versus placebo. In addition, there was no significant difference in the subgroup of patients with HVPG greater than 10 mm Hg, defined as clinically significant portal hypertension (CSPH), or in those with a greater than 10% decrease in HVPG.[5]

The PREDESCI trial by Càndid Villanueva and colleagues[6] in *The Lancet* evaluated 631 male and female patients aged between 18 years and 80 years inclusive with compensated cirrhosis. Of these, 293 met inclusion or exclusion criteria (ie, provided consent and were without history or evidence of impeding liver decompensation as manifested by elevated bilirubin, high-risk varices, or at high risk for angiography) and underwent haemodynamic study with HPVG measurement, which showed CSPH in 210 patients (approximately 71%). 201 of these patients were randomly assigned to β blockers (propranolol 40–160 mg twice a day or carvedilol 6·25–25 mg/day) or placebo. The primary outcome evaluated was an event of decompensation (defined as ascites, gastrointestinal bleeding related to portal hypertension, or overt hepatic encephalopathy) or death. In both groups, cirrhosis was mostly due to hepatitis C virus infections, mean Child-Pugh score was 5·8, and mean Model for end-stage liver disease (MELD) score was 6·8. Patients were followed up by annual upper endoscopy and HVPG measurements. After a median follow-up of 37 months, the use of β blockers was associated with a nearly 50% decrease in the incidence of hepatic decompensation or death (27% placebo *vs* 16% β blocker, p<0·05). The most significant effect was decreased incidence of ascites (20% placebo *vs* 9% β blocker). Benefit was mainly noted for patients with at least a 10% decrease in HVPG or to less than 10 mm Hg (decompensation or death 9% *vs* 29%), particularly in patients with small varices and non-alcoholic cirrhosis, and was mostly noted after 24 months of treatment. There was no difference in the incidence of notable side-effects between the two groups. Furthermore, compliance was high at 83%. This emphasises the prognostic power of HVPG and its value as a biomarker for the effectiveness of therapy and shows the pathophysiological logic for target therapy to lower HVPG with β blockers.

Should all patients with compensated cirrhosis be treated with β blockers? This trial challenges conventional practice and expands the boundaries of the existing indication for β blocker treatment by introducing it in a subgroup of patients who were compensated.

The study was limited to patients with compensated cirrhosis and HVPG greater than 10 mm Hg, measured



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by transjugular catheterisation. As it is not feasible to subject all patients with cirrhosis to an invasive procedure, the question arises as to whether we can accurately identify CSPH by other modalities. Liver stiffness measured by transient elastography,[7,8] collaterals on imaging,[4] magnetic resonance elastography,[9] or combinations of several non-invasive tests might be alternatives,[10] but have thus far not proved accurate. Of note, most of the study patients had active hepatitis C virus infection and follow-up terminated once antiviral treatment was issued. Such treatment is highly effective, accessible, and can reduce HVPG and decompensation prevalence.[11,12] The benefit of β blockade in this population of treated patients is yet to be proven. It is important to note that β blockade should be intended as chronic pharmacotherapy, which can be compromised by fatigue, dizziness, reduced libido, and physical capacity. Furthermore, the long-term assessment of efficacy, safety, and cost-effectiveness of such treatment is limited by the follow-up period of this study. Nonetheless, this trial provides evidence for the benefit of early β blocker treatment and thus might represent a change in treatment paradigm for patients with compensated cirrhosis. This treatment strategy provides the physician, for the first time, with a possible therapeutic tool, in conjunction with the control of the cause of liver disease, during the early phases of cirrhosis. Further trials are needed to better characterise and select the patients who will most probably benefit from long-term β blockade.

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We declare no competing interests.

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