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HEPATOLOGY

In Case You Missed It

Can We Prevent Hepatic Decompensation? Most Likely, With Nonselective Beta Blockers

Sonali Paul, MD, MS

[1]*Assistant Professor of Medicine, Division of Gastroenterology, Hepatology & Nutrition, Pritzker School of Medicine, the University of Chicago, Chicago, IL*

Dr Sonali Paul
Associate Editor

This summary reviews Villanueva C, Albillos A, Genescà J, et al. β blockers to prevent decompensation of cirrhosis in patients with clinically significant portal hypertension (PREDESCI): a randomized, double-blind, placebo-controlled, multicenter trial. Lancet. 2019 Apr 20;393(10181):1597-1608. doi: 10.1016/S0140-6736(18)31875-0.

Correspondence to Sonali Paul, MD, MS. Associate Editor. Email: EBGI@gi.org

STRUCTURED ABSTRACT

Question: Can nonselective beta blockers decrease the risk of decompensation or death in compensated cirrhosis with clinically significant portal hypertension (defined as hepatic venous pressure gradient [HVPG] ≥10 mm Hg)?

Design: Double-blind, randomized controlled trial (RCT).

Setting: Eight hospitals in Spain from January 2010 through July 2013. Patients were followed until June 2015.

Patients: Included 201 patients with compensated cirrhosis and clinically significant portal hypertension without high-risk varices (i.e., no esophageal varices or small esophageal varices without red spots).

Interventions/Exposure: During measurement of HVPG, study patients were

given intravenous (IV) propranolol with active measurement of HVPG. If HVPG-decreased ≥10%, the patients were randomly assigned to propranolol (40mg twice a day up to 160mg twice a day) vs placebo. If HVPG did not decrease ≥ 10%, the patients were labelled non-responders and were assigned to carvedilol (6.25 mg/day up to 25 mg/day) vs placebo. Doses were titrated to tolerance—ideally a heart rate of 55 beats per min and systolic blood pressure greater than 90 mm Hg. The median length of follow-up was 37 months. Surveillance upper endoscopy was performed annually. If patients developed high-risk varices, prophylactic banding was performed and the study drug continued. No preventive therapy for ascites or encephalopathy was allowed.

Outcome: The primary endpoint was incidence of cirrhosis decompensation (development of ascites, gastrointestinal (GI) bleeding related to portal hypertension, or overt encephalopathy) or death. Secondary outcomes included development of each decompensating event separately, spontaneous bacterial peritonitis, development of high-risk varices, and liver cancer development.

Data Analysis: Intention-to-treat analysis. Fisher's exact test was used to compare categorical variables and student's t test (for paired data within each group) was used for continuous variables. The primary and secondary outcomes were assessed as time-to-event variables. Data were censored at time of death, liver transplantation, last visit, or end of follow-up period, whichever came earliest. Patients lost to follow-up, who withdrew consent, or who started direct antiviral agents for hepatitis C virus (HCV) were censored after the last documented visit.

Funding: Spanish Ministries of Health and Economy.

Results: From January 2010 through July 2013, 631 patients were screened, 320 were excluded, and 110 declined to participate/withdrew, leaving 201 patients to be randomized. Study patients' mean age: 59-60; male: 59-63%; Child's Pugh A: 80%; etiology of cirrhosis: HCV (54-58%), alcohol (14-19%), HCV plus alcohol (8-9%), and nonalcoholic steatohepatitis (NASH; 5-8%). One hundred and thirty-five patients had HVPG-decrease ≥10% in response to IV propranolol during HVPG measurement and were randomized to propranolol (n=67) or placebo (n=67). An additional 66 patients were non-responders to IV propranolol and were randomized to carvedilol (n=33) or placebo (n=33).

Patients receiving nonselective beta blockers had less decompensation or death: 27% vs 16%; hazard ratio (HR) 0.51, (95% confidence interval [CI] 0.26–0.97, *P*=0.041) (**Figure 1**). Specifically, the incidence of ascites was reduced in those taking beta blockers compared to placebo: 20% vs 9%; HR = 0.42, (95% CI 0.19–

0.92, *P*=0·03). Additionally, the benefit of nonselective beta blockers for ascites was slightly higher in the carvedilol group compared to those receiving propranolol. Similar results were also found for death from any case. However, these were not statistically significant. GI bleeding due to portal hypertension was low in groups treated with beta blockers and placebo: 4% vs 3%, respectively. Development of high-risk esophageal varices was numerically less common in the beta blocker group during study follow-up: 16% vs 25%, respectively, although approximately 70% of these patients received prophylactic esophageal band ligation of varices which would reduce the risk of GI bleeding.

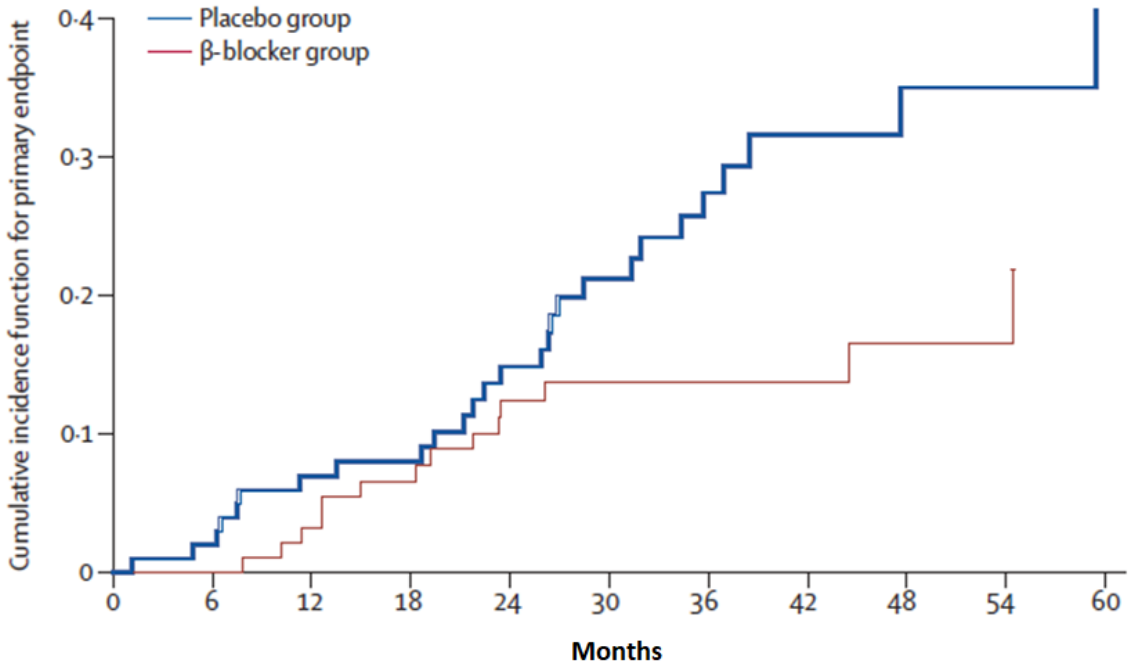

Figure 1. Time to hepatic decompensation or death.

COMMENTARY

Why Is This Important?

Decompensated cirrhosis, as defined by ascites, variceal bleeding, and hepatic encephalopathy is associated with high mortality and poor prognosis. Clinically significant portal hypertension (HVPG ≥10 mm Hg) has been found to be the main determinant of decompensation. Beta blockers decrease portal venous inflow thereby reducing portal pressures, especially in those who have clinically significant portal hypertension. Methods to reduce this gradient are needed. Nonselective beta blockers decrease portal flow through a decrease in cardiac output and through splanchnic vasoconstriction. It is common practice to start nonselective beta blockers in those with compensated cirrhosis and varices that are at high risk of bleeding (medium/large, small varices with red wale signs) as primary prophylaxis.[1] Ascites prevention is also important as this event is associated with transplant-free mortality rates ranging from 15%-20% in 1 year to nearly 50%-60% in 5 years.[2,3]

Key Study Findings

Patients receiving nonselective beta blockers had less decompensation or death: 27% vs 16%; HR 0.51, 95% CI 0.26–0.97, *P*=0.041. Specifically, the incidence of ascites was reduced in those taking beta blockers compared to placebo: 20% vs 9%; HR 0.42, 95% CI 0.19–0.92, *P*=0.03.

Caution

Patients with compensated cirrhosis should be screened for clinically significant portal hypertension. However, the methods used in this paper are unrealistic in real practice. Not every patient with cirrhosis has their HVPG measured. Certainly, even if they have clinically significant portal hypertension, IV propranolol is not routinely used to assess response. The applicability of these results to real world practice is difficult. However, the role of beta blockers is still important, especially since there are now non-invasive methods of assessing this[4] (see *My Practice* below). Additionally, the majority of patients studied had HCV since this study was done before routine use of direct acting anti-viral therapies. It is unclear if this will translate to other causes of liver disease, importantly alcohol and nonalcoholic/metabolic-associated fatty liver disease. Specifically, based on the new Baveno VII Consensus guidelines released in 2022, a small percentage of patients with NASH-related cirrhosis may have signs of clinically significant portal hypertension with HVPG values < 10mmHg.[4]

My Practice

In those patients with compensated cirrhosis who have had formal HVPG testing at diagnosis, I routinely administer nonselective beta blockers. My preference is carvedilol as it is more effective in reducing HVPG (as it not only decreases portal flow, but has vasodilatory effects), preventing decompensation, and improved tolerance compared to other nonselective beta blockers.[4] However, I am often limited by blood pressure in these patients. Propranolol or nadolol are alternatives as they affect blood pressure less. Each is titrated to goal heart rate 55-60 beats/minute as tolerated.

For those without direct HVPG measurements, I use the Baveno guidelines to determine who should initiate nonselective beta blockers.[4] Liver stiffness measurements (LSM) by transient elastography can help differentiate the presence of clinically significant portal hypertension in patients with compensated cirrhosis. The previous Baveno VI criteria (and current AASLD guidelines[1]) use LSM > 20kPa and platelets count $<150x10^9$/L to diagnose clinically significant portal hypertension and determine the need for variceal screening. The updated Baveno VII guidelines are more nuanced:

- LSM $\leq$15 kpa and platelet count $\geq 150x10^9$/L rules out clinically significant portal hypertension with a sensitivity and negative predictive value of >90%.
- In those with viral or alcohol related cirrhosis and non-obese NASH related cirrhosis, LSM $\geq$25 rules in

clinically significant portal hypertension. I routinely start these patients on non-selective beta blockers.

- For those that cannot tolerate non-selective beta blockers (low baseline heart rate, low blood pressures, or other reasons), I determine the need for endoscopy if the LSM $\geq$ 20 or platelet count $\leq 150 \times 10^9$/L. However, using this strategy requires annual LSM and platelet counts to assess changes and endoscopy needs overtime.

Of note, the above only applies to those with compensated cirrhosis. I do not routinely prescribe nonselective beta blockers in those with decompensated cirrhosis and perform variceal screening on every patient with any form of decompensation.

For Future Research

While transient elastography is a fantastic tool to screen for fibrosis and clinically significant portal hypertension, in some patients it is inaccurate because of body habitus and/or the interquartile range is high. In these situations, magnetic resonance elastography is used. However, we do not yet have magnetic resonance elastography measurements to define clinically significant portal hypertension and administration of nonselective beta blockers.

Conflict of Interest

Dr. Paul has no relevant conflicts of interest.

The authors of this article are active on social media. Tag them to discuss their work and this EBGI summary.

@jaumebosch9 (Jaume Bosch)
@jcgarciapagan (JC Garcia-Pagan)

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