

## $\beta$ Blockers Failed in Primary Prevention of Gastroesophageal Varices

Groszmann RJ, Garcia-Tsao G, Bosch J, et al. Beta-blockers to prevent gastroesophageal varices in patients with cirrhosis. *N Engl J Med* 2005;353:2254–61.

### Study Overview

**Objective.** To assess the efficacy of nonselective  $\beta$  blockers in preventing gastroesophageal varices.

**Design.** Randomized, double-blind, placebo-controlled trial.

**Setting and participants.** 213 patients aged 18 to 75 years in 4 medical centers in Europe and the United States who had cirrhosis and portal hypertension (defined as having hepatic venous pressure gradient [HVPG] > 6 mm Hg without gastroesophageal varices on initial endoscopy) were enrolled between August 1993 and March 1999 and were randomized to either timolol ( $n = 108$ ) or placebo ( $n = 105$ ). Participants were followed until September 2002 or until the occurrence of 1 of the study endpoints.

**Main outcome measures.** Primary endpoints were the development of varices or variceal hemorrhage identified by endoscopy. Secondary endpoints were the development of ascites or encephalopathy, liver transplantation, or death.

**Main results.** 84 patients reached the primary endpoints (42 in the timolol group and 42 in the placebo group;  $P = 0.89$ ). 44 patients reached the secondary endpoints (22 of 66 patients in the timolol group and 22 of 63 patients in the placebo group;  $P = 1.0$ ). Serious nonfatal adverse events were significantly associated with the timolol group versus the placebo group (48% versus 32%;  $P = 0.02$ ). Compared with baseline values, the HVPG of timolol-treated patients decreased by a median of 1.45 mm Hg as compared with 0.5 mm Hg in placebo group ( $P = 0.07$ ).

**Conclusion.** Using nonselective  $\beta$  blockers in patients with cirrhosis and portal hypertension does not prevent gastroesophageal varices and likely causes adverse events.

### Commentary

Variceal bleeding is a complication of cirrhosis and portal hypertension, and depending on the severity of liver disease, in-hospital mortality can reach 30% to 50% for the initial episode and increases to 78% with recurrence [1]. Once varices

develop in patients with portal hypertension, the average annual bleeding risk ranges from 5% to 15%, depending on the size of varices. Nonselective  $\beta$  blockers are routinely used for primary prophylaxis of variceal bleeding in cirrhotic patients with known varices and work by reducing portal hypertension and decreasing development of collaterals, which are thought to be variceal precursors [2,3]. In select populations, variceal banding, usually reserved for treatment of actively bleeding varices, can prevent bleeding but does not improve mortality [4]. Thus, preventing variceal formation in cirrhotic patients can potentially minimize morbidity and mortality.

Two prior studies that evaluated the ability of nonselective  $\beta$  blockers to slow or prevent the growth of varices have had mixed results [5,6]. Groszmann et al sought to test if  $\beta$  blockers can prevent variceal development altogether. Careful selection of patients with either biopsy-proven cirrhosis or measurement of mildly elevated HVPG to document portal hypertension and endoscopy ensured that patients were at the earliest stage of compensated cirrhosis. In doing so, the authors likely selected patients that were at such low risk for variceal development that many more patients needed to be treated for a much longer duration before any potential benefit could be realized. However, even the relatively small number of patients treated with timolol demonstrated a high adverse event rate such that a larger study is probably not feasible. Perhaps a future study that includes patients with higher risk of variceal development can demonstrate a more favorable risk-benefit ratio for treatment with  $\beta$  blockers. Such a study cohort may be selected by measuring baseline HVPG, which Groszmann et al found to be the strongest independent predictor of variceal development.

### Applications for Clinical Practice

For patients with cirrhosis and portal hypertension, nonselective  $\beta$  blockers should not be used to prevent variceal development. In those who have varices,  $\beta$  blockade to prevent bleeding is still warranted.

—Review by Mark S. Horng, MD

### References

1. de Franchis R, Primignani M. Natural history of portal hypertension in patients with cirrhosis. *Clin Liver Dis* 2001;5:645–63.
2. Bosch J, Albrades JG. Variceal bleeding: pharmacological therapy. *Dig Dis* 2005;23:18–29.
3. Talwalkar JA, Kamath PS. An evidence-based medicine approach to beta-blocker therapy in patients with cirrhosis. *Am J Med* 2004;116:759–66.
4. Sarin SK, Lamba GS, Kumar M, et al. Comparison of endoscopic ligation and propranolol for the primary prevention of variceal bleeding. *N Engl J Med* 1999;340:988–93.
5. Cales P, Oberti F, Payen JL, et al. Lack of effect of propranolol in the prevention of large esophageal varices in patients with cirrhosis: a randomized trial. French-Speaking Club for the Study of Portal Hypertension. *Eur J Gastroenterol Hepatol* 1999;11:741–5.
6. Merkel C, Marin R, Angeli P, et al. A placebo-controlled clinical trial of nadolol in the prophylaxis of growth of small esophageal varices in cirrhosis. *Gastroenterology* 2004;127:476–84.

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