Carvedilol—NSBB of Choice in All Cirrhotics? Short Title: Carvedilol for Portal Hypertension

Portal hypertension is the main cause of morbidity and mortality in patients with cirrhosis. A portal pressure gradient (estimated by the hepatic venous pressure gradient or HVPG) of 10 mmHg or more defines the presence of clinically significant portal hypertension (CSPH) and puts a patient at risk of clinical decompensation.[1,2] The HVPG threshold required for variceal bleeding is 12 mmHg.[3] Several longitudinal studies have demonstrated that if the HVPG decreases below 12 mmHg by means of pharmacological treatment[4] or spontaneously due to an improvement in liver disease,[5] variceal bleeding is totally prevented. Even if this target is not achieved, a substantial decrease in portal pressure from baseline levels (>20%) offers almost complete protection from variceal bleeding and decreases the risk of developing ascites, spontaneous bacterial peritonitis, hepatorenal syndrome, and death.[4] Current guidelines recommend using either a nonselective beta-adrenergic blocker (NSBB) or endoscopic band ligation (EBL) as firstline therapy for the prevention of first bleeding and a combination of NSBB and EBL as firstline therapy for the prevention of recurrent bleeding.[6]

Traditional NSBBs (nadolol, propranolol) reduce portal pressure by decreasing portal venous inflow, portocollateral blood flow,[7] and variceal pressure.[8] The decrease in splanchnic blood flow is the result of a decrease in cardiac output due to the blockade of cardiac beta-1 adrenoceptors, and of splanchnic vasoconstriction due to the beta-2 receptor blockade, that in turn leads to unopposed alpha-adrenergic activity.[9]

Carvedilol further enhances the NSBB mechanism of action by adding in a mild intrinsic alpha-1-adrenergic blocker effect. This alpha-blockade leads to a reduction in hepatic vascular tone and hepatic resistance. In keeping with this multifaceted blockade, several studies have confirmed that there is a greater decrease in portal pressure with carvedilol than propranolol, both acutely and chronically.[10,11] In addition, a recent study from Austria demonstrated that 56% of the patients not achieving a sufficient hemodynamic response to propranolol responded to carvedilol.[11]

As described in the current issue of this journal, Wani *et al*. evaluated 102 cirrhotic patients with a HVPG of >12 mmHg in order to evaluate the effect of carvedilol on the portal pressure measured 3 months after "dose optimization." At study baseline, 42% of the patients had Child–Pugh A disease, 31% Child–Pugh B, and 27% Child–Pugh C. Thirty-eight percent had at least some degree of ascites and the mean systolic blood pressure was 118 mmHg. Dose optimization was carried out by titrating up carvedilol by 6.25 mg per week to target a systolic blood pressure of 90 mmHg and heart rate of 55 bpm. By the 3-month follow-up HVPG reading, the authors reported a significant reduction in all hemodynamic parameters including the HVPG (from 16.8 to 12.6 mmHg) and the systolic blood pressure (from 118 to 90 mmHg). Consistent with previous studies[12,13] approximately 60% of the patients demonstrated a chronic HVPG response with carvedilol. There was no statistically significant difference in the response across Child–Pugh classes. Drug withdrawal due to side effects occurred only in two patients. Clinical outcomes were not reported as part of this study. The authors concluded that a dose of >18.5 mg of carvedilol (presumably determined from the mean dose used in hemodynamic responders) should be utilized, particularly in patients with Child–Pugh A disease.

The authors should be commended for carrying out a large HVPG-based trial evaluating carvedilol. The study conclusions regarding the optimal dose of carvedilol and the use of this agent as the beta-blocker of choice, however, need to be interpreted with caution in light of existing evidence.

First, there is insufficient data to state that carvedilol is the NSBB of choice in cirrhosis. The most recent guidelines from the Baveno VI consensus support that either the traditional NSBB (nadolol, propranolol) or carvedilol could be a valid firstline treatment option in the primary prophylaxis of variceal bleeding. Although the guidelines recognize that carvedilol is more effective than traditional NSBBs in reducing HVPG, there are insufficient head-to-head trials comparing traditional NSBBs to carvedilol to support the use of one over the other. In the setting of secondary prophylaxis, the guidelines do not recommend the use of carvedilol as it has not been compared with the current standard of care. Moreover, the guideline appropriately warns against the use of any NSBB agent (including carvedilol) in patients with cirrhosis, refractory ascites any one of a systolic blood pressure of <90 mmHg, hyponatremia with a serum sodium <130 meq/L or acute kidney injury.[6] It is surprising that there were so few adverse effects seen in the study by Wani *et al*. Although the dose optimization was titrated to a systolic blood pressure of 90 mmHg, as the mean systolic pressure at the end of the trial was 90 mmHg, this would

suggest that approximately 50% of the patients had a pressure of less than this value.

Secondly, the optimal dose of carvedilol remains unclear and needs to be balanced by considering both efficacy and safety. The best available evidence would support a dose of 12.5 mg daily. There is evidence to suggest that the vasodilating effects of carvedilol are dose dependent, with increasing rates of adverse effects, mainly hypotension and sodium and water retention at higher doses.[12] This finding was confirmed by a more recent study by Reiberger *et al*., where a dose of 12.5 mg daily was found to be associated with less adverse effects and yet be hemodynamically and clinically as effective as higher doses (25–50 mg daily). Moreover, of the four randomized trials in the area with clinical outcomes, all utilized a fixed dosage of 12.5 mg daily.[14-17]

In summary, carvedilol is undoubtedly a promising addition to the portal hypertension armamentarium. There is building evidence for its efficacy and safety. Future randomized controlled trials will help to clarify whether carvedilol is the superior NSBB in portal hypertension and whether there is an "optimal dose" for all patients that can balance potential adverse effects with portal pressure reduction.

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