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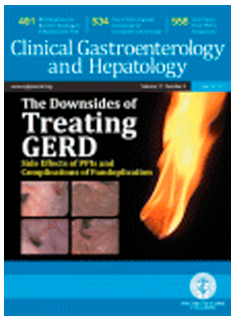

Carvedilol as best beta-blocker for secondary prophylaxis of variceal bleeding: Are we there, or not yet?

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PII: S1542-3565(22)00809-6
DOI: https://doi.org/10.1016/j.cgh.2022.08.026
Reference: YJCGH 58638

To appear in: *Clinical Gastroenterology and Hepatology*
Accepted Date: 12 August 2022

Please cite this article as: Bosch J, Carvedilol as best beta-blocker for secondary prophylaxis of variceal bleeding: Are we there, or not yet?, *Clinical Gastroenterology and Hepatology* (2022), doi: https://doi.org/10.1016/j.cgh.2022.08.026.

Title page

Editorial for Clinical Gastroenterology and Hepatology

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Carvedilol as best beta-blocker for secondary prophylaxis of variceal bleeding: Are we there, or not yet?

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Acknowledgements:

Supported in part by the Swiss Liver Foundation

Conflicts of Interest

None regarding this manuscript.

Dr JBosch is a Consultant for Boehringer Ingelheim and Astra-Zenecha. In the previous two years (2020 and 2021) he has been a Consultant for Surrozen and has given lectures sponsored by Actelion and Gore.

Editorial for Clinical Gastroenterology and Hepatology

Carvedilol as best beta-blocker for secondary prophylaxis of variceal bleeding: Are we there, or not yet?

Carvedilol has emerged as the non-selective beta-blocker (NSBB) of choice for treating portal hypertension in compensated cirrhosis (1) (2),(3)(4); (5). This is due to strong evidence demonstrating that it has a more pronounced effect than propranolol to reduce the hepatic vein pressure gradient (HVPG, equivalent to portal pressure gradient in cirrhosis) (5); (6); (7); (8), together with good patient acceptability and safety profile(1); (3). More importantly, high-quality evidence from phase II and phase III prospective randomized clinical trials (RCT) and meta-analyses has shown that this hemodynamic advantage translates into a better clinical efficacy in terms of preventing decompensation, ascites, and bleeding, as well as in improving survival compared to other treatments (placebo, propranolol, endoscopic variceal ligation -EVL- or no therapy) (3); (9). Because of this, the very recent Baveno VII recommendations declare carvedilol as the preferred NSBB, and support its use in all compensated patients with direct (HVPG ≥ 10 mmHg) or indirect signs of clinically significant portal hypertension (presence of varices on endoscopy or of collaterals in imaging, presence of clinical or subclinical ascites or hydrothorax, fulfillment of Baveno VI criteria for need of endoscopy due to suspicion of varices needing treatment) (1). The only recommended precaution is to use low doses (6.25 to 12.5 mg per day) to avoid hypotension (systolic blood pressure <90 mmHg). A special case is the patient with high blood pressure (present in 2/3 of patients with compensated cirrhosis nowadays (9), in which carvedilol can be used as primary antihypertensive agent at doses of up to 25-50 mg/day to control both arterial hypertension and portal hypertension (rather than associating with other anti-hypertensive drugs with uncertain effects on HVPG).

Why is carvedilol then not yet recommended in secondary prophylaxis, which is the scenario where propranolol was first used? The main reason is that a previous study (at a time when carvedilol was titrated up to 50 mg/day) showed that it might worsen sodium retention in one third of patients with ascites, as suggested by a mild increase in body weight, plasma volume, and in the dose of diuretics, which was ascribed to a significant decline in arterial blood pressure (7). Of note, there was no drop in glomerular filtration rate (GFR), no increase in plasma creatinine, and plasma renin activity decreased significantly after carvedilol. In any case, to be on the safe side, it was suggested at that time that initial RCTs testing clinically the use of carvedilol should be restricted to compensated patients. While this advice was followed in the PREDESCI trial (aimed at testing whether NSBBs might prevent decompensation and ascites, which was indeed demonstrated) (10), other RCTs on carvedilol focused on its use in primary prophylaxis of variceal bleeding in patients with high-risk varices, a situation in which about 40-50% of the patients also have ascites (11);(9). These studies also showed high efficacy in preventing bleeding and raised no alarms on adverse effects in patients with ascites.

Based on the aforementioned data, there should be no concerns using carvedilol in secondary prophylaxis in patients without ascites (about 50% of the cases in this scenario), while in patients with ascites the concerns should probably be limited to those with refractory ascites where changes in blood pressure and renal function should be closely monitored. Why are there no large secondary prophylaxis RCTs that have been performed or are ongoing? The answer is probably related to the increasing cost of clinical trials and lack of interest from the pharmaceutical industry since carvedilol already has extensive label indications, such as arterial hypertension and heart failure. Despite several governments' funding RCTs of no industrial interest, there are usually restrictions for international cooperation, diminishing the chances these will be ever conducted.

In this context, one understands initiatives aimed at providing more information on the effects of carvedilol Vs propranolol based on retrospective comparisons of series of patients treated with either

drug associated with EVL. This is specifically what Jachs et al have done in the carefully conducted study presented in this issue of CGH (12). The study confirms several important advantages of carvedilol in secondary prophylaxis, namely, its greater reduction of HVPG, which translates into a greater proportion of patients with good hemodynamic response (a fall in HVPG to values below 12 mmHg or at least of 20% of baseline) (13); (14); (15), together with positive data confirming that such a good hemodynamic response is indeed associated with better clinical efficacy in terms of decreasing the risk of bleeding and enhancing survival. Unfortunately, the retrospective nature of the study and the fact that the pattern of choosing one drug or the other changed over time, that it encompassed a very prolonged period, and was not analyzed strictly on an intent-to-treat basis (among other limitations) precludes drawing definite conclusions on safety, and limits clinical efficacy comparisons. Nevertheless, the study is clinically valuable because it certainly does not point against the use of carvedilol for this indication. Moreover, even if carvedilol caused a mild decrease in arterial pressure, no instances of AKI-HRS or signs of impending renal impairment were observed. Therefore, despite not being an RCT, the study still strongly suggests that carvedilol is at least as safe as propranolol. In addition, the study indicates that the more favorable hemodynamic effect contributes to a greater efficacy. As an expert in the field, I am in complete agreement with the authors in suggesting that carvedilol is likely to represent the best NSBB in the treatment of portal hypertension regardless of the clinical scenario, including prevention of decompensation, ascites, first bleeding, or recurrent bleeding. Admittedly, I am somewhat frustrated by experiencing increasing difficulties in performing high quality investigator initiated RCTs after being educated on the value of “evidence-based medicine” over “eminence” based opinions! I remember the advice I got in the past from Tom Chalmers, the father of RCTs in liver disease: “Randomize from the first patient!”, and another giant such as Jean-Pierre Benhamou saying: “When I don’t know which treatment is best, I randomize”. Let’s hope the time will come when new international initiatives such as the Baveno Cooperation – an EASL consortium- and changes in priorities from funding agencies may facilitate progress in the treatment of portal hypertension. This is an area where most advances that

have led to a dramatic reduction in the incidence and mortality from bleeding and from decompensation

have been made possible by investigator-initiated studies and public funding.

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