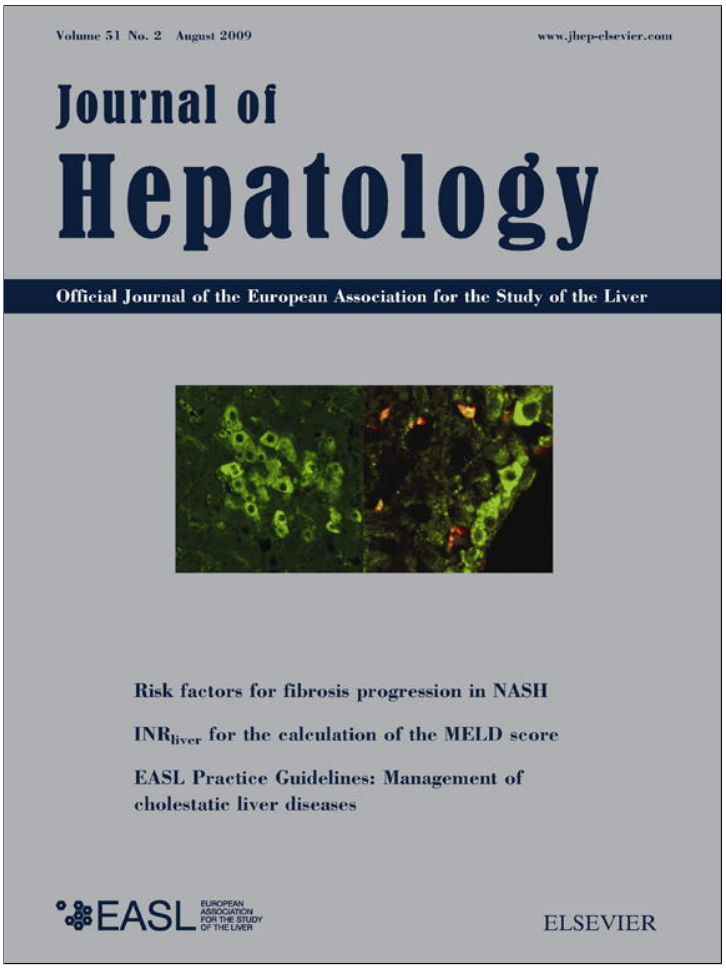

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Editorial

A short cut to predict the clinical response to beta-blocker therapy in cirrhosis? ☆

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See Article, pages 279–287

It is clearly established that patients with cirrhosis who respond to 1–3 month beta-blocker treatment with a decrease in their hepatic venous pressure gradient (HVPG) to $\leqslant$12 mmHg or of $\geqslant$20% of the baseline values are protected from the risk of variceal bleeding, while such risk pertains almost exclusively to patients who do not meet these hemodynamic response criteria [1,2]. This holds true both in the setting of primary prophylaxis and that of prevention of rebleeding. In addition, hemodynamic criteria represent the only validated prognostic indicator of clinical effectiveness of treatment with beta-blockers. A recent meta-analysis showed that the risk of bleeding in hemodynamic "good responders" is markedly lower than that of "poor responders" [3]. However, concerns have been raised in relation to the feasibility, the clinical appropriateness, the risks and the costs of repeat HVPG measurement [4], which is an invasive procedure and needs to be performed twice within a 1–3 month period in order to define response. These problems have long been known to investigators involved in the study of portal hypertension, and efforts were devoted to try to overcome them. For instance, the potential predictive role of the response to the first dose of beta-blockers, administered under HVPG measurement, was explored but subsequently discarded, since the acute hemodynamic changes appeared markedly different from the chronic ones in many patients [5–7], possibly in relation to the hypotensive effect of the first dose, and the absence of those systemic and regional hemodynamic adjustments which only occur during long-term treatment [7].

In this issue of the Journal, La Mura and colleagues [8] challenge these consolidated general lines, reporting a cohort study of patients with cirrhosis and portal hypertension, in whom the hemodynamic response to the first dose of beta-blocker, administered under HVPG measurement, was highly predictive of the clinical efficacy of long-term treatment, and was even more predictive than the response to chronic beta-blocker administration. Furthermore, they observed that the best threshold discriminating good from poor responders on the basis of the acute beta-blocker challenge was a 12% decrease in HVPG instead of the widely accepted 20% value emerging from studies of chronic response. The predictive value of the acute challenge was particularly evident in the scenario of the prevention of rebleeding, where the number of "events" was higher. The effect could be detected also in the setting of primary prophylaxis, although it did not reach statistical significance.

Based on these data, should we reconsider our previously accepted guidelines, and modify our clinical practices to introduce the response to the first dose of beta-blockers as an indicator of clinical efficacy?

Before jumping to conclusions, it is probably appropriate to consider these data and their implications in further detail. Firstly, the choice of a 12% threshold value was a data-driven, post-hoc choice, as the authors

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Abbreviation: HPVG, hepatic venous pressure gradient.

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themselves clearly state in the discussion. A 12% cut-off point had been already proposed in 1991 [9], but was subsequently replaced by the 20% threshold, which gained strength from several reports [3], and became an almost "magic number". It is uncertain whether the newly proposed 12% threshold will prove valid once utilized as a predefined criterion.

In addition, the prognostic value of the response to the acute challenge in this series was much weaker than that reported in previous chronic studies. Indeed, the risk of bleeding in poor responders to acute challenge was approximately double compared to that of good responders both in the context of the prevention of rebleeding, and in that of primary prophylaxis. These values are very different from those reported in a meta-analysis, based on all available literature, produced by D'Amico and colleagues [3], who reported an approximately 6-fold higher risk for poor responders in prevention of rebleeding, and a 7-fold higher risk in primary prophylaxis, compared to the good responders, as expressed by the pooled Odds Ratios. Since in the present series the discriminating ability of the chronic effect was reported to be lower than that of the acute challenge, as inferred from the larger misclassification rate, we have to conclude that this series is quite different from those already published, especially in relation to the poor discriminatory ability of the chronic effect. It is, therefore, conceivable that the higher predictive value of the acute challenge compared to the chronic effect may be due to some peculiar features of the patient population, who turned out to be unfit for the prediction of the clinical outcome based on the chronic effect.

Furthermore, the clinical relevance of a classification error varies according to the occurrence of a false-positive or false-negative result. Indeed, it is expected that only a limited number of the poor responders will undergo a variceal bleeding, and, at least within the context of primary prophylaxis, the majority will not bleed during follow-up; conversely, it is very important from a clinical point of view to minimize the number of the patients classified as good responders who actually bleed. In the latter situation, the classification error bears relevant clinical consequences, as the use of an ineffective treatment, which is believed to be effective, prevents us from using an alternative treatment which may be more effective [10,11]. From the present report it appears that most classification errors are of the first type (poor responders who do not bleed during follow-up), even though exact values are not provided. If the difference in the misclassification rate between acute challenge and chronic treatment is due, at least to an extent, to the occurrence of bleeding in individuals classified as good responders to chronic treatment, this difference would be of importance.

Finally the pathophysiology of the issue needs to be considered. While it follows from the available knowledge that a stable decrease in portal pressure is important in lowering the risk of bleeding in these patients, together with all the other complications of portal hypertension [12], and that keeping a good hemodynamic response during the course of treatment is also a positive prognostic factor [13], the mechanisms underlying the relationship between the response to the first dose, which also in this series was shown to be very frequently different from that during chronic treatment, and the long-term clinical outcome are only partially understood.

For all these reasons, the data presented in the study by La Mura and colleagues need external validation, and many researchers involved in this area of research may consider the appropriateness of performing such a validation study. Meanwhile, I have re-analyzed a small series from our study group, in which patients were evaluated both after acute challenge and after chronic treatment with beta-blockers [7]. In this study, patients classified as poor responders to chronic treatment were switched to a combined treatment with beta-blockers plus nitrates, while good responders were kept on beta-blockers. In the 11 patients good responders to chronic treatment six of whom were also good responders to the acute challenge (the remaining five were poor responders to the acute challenge) the clinical outcome in terms of variceal bleeding was evaluated [7]. Having reclassified these patients on the basis of the 12% threshold for a good response to the acute challenge, six were qualified as acute good responders and five as acute poor responders. Overall, there was a single patients who bled during follow-up in the group of the 11 patients, and this individual was an acute good responders. In contrast, none of the patients belonging to the group of the acute poor responders underwent variceal bleeding. Thus this small series would not support the hypothesis that the response to the acute challenge is a better predictor of variceal bleeding. It would have also been interesting to assess the clinical outcome of patients classified as poor responders to chronic treatment, but these were switched to combined treatment, and we do not know what their outcome would have been had they been treated with beta-blockers only.

In conclusion, while it seems early days for the implementation of the acute challenge as a predictor of outcome, the very fact that these new data do not fully fit the currently accepted model for the relationship between hemodynamic effects and clinical outcome may open new lines of research.

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