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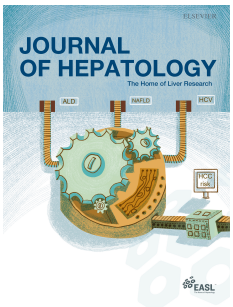

Enhance the picture by improving the focus

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ENHANCE THE PICTURE BY IMPROVING THE FOCUS

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We thank the interest of McPhail et al in our recent individual patient data meta-analysis (IPD-MA) assessing the value of carvedilol in compensated cirrhosis.(1) However, we would like to highlight relevant methodological issues with several points raised in their letter,(2) just to enhance the picture by improving the focus.

Our colleagues reanalyze the effect of carvedilol on decompensation and on survival using raw odds ratios based on aggregated data of RCTs comparing carvedilol vs each control therapy. This does not help to improve what shown our previous study, since our analysis undoubtedly used a much more appropriate approach. We performed an IPD-MA relying on the individual-level data of patients included in RCTs, thus allowing the assessment of decompensating events and of survival using a time-to-event and competing-risk approach, with IPTW adjustment for baseline covariates. This permitted approaching cirrhosis as a multistage disease and outcomes as time-dependent events, which is a much more appropriate strategy when investigating the long-term efficacy of medications.(3) Through the collaborative involvement of multiple studies and centers providing IPD, we succeeded in gathering a large amount of data, which allowed an optimized statistical strategy. It is hard to understand how reanalysis of the data using a less robust and sound approach may help to enhance the picture achieved.

Our colleagues express caveats regarding the use of a control group involving different therapies (i.e. placebo and variceal ligation). Rather, they preferred to draw conclusions by splitting the data of what they qualify as a small-MA and assumed differences when the point estimates of one assessment are completely included in the 95%CI of the other one. However, the data shown by McPhail et al is a bit confusing since it is uncertain what are they referring to when showing decompensation and death using the same data (plots A and C in their Figure). Of note, in our study both the carvedilol and the control groups were very homogenous, since they included only patients with compensated cirrhosis with CSPH and thus at high risk of developing a first decompensating event. CSPH was confirmed by the presence of varices in the majority of the patients included (up to 94% of those included had varices) and by an HVPG ≥10mmHg in the small proportion without varices. Patients in the control group received no active therapy. Actually, we considered the use of EVL in patients with high-risk varices as non-active therapy, since EVL may prevent bleeding but hardly impacts the risk of developing the other decompensating events investigated, in particular ascites. This allowed the inclusion of compensated patients with varices, who according to the PREDESCI study are at highest risk of developing any decompensating event (including ascites) and, consequently, those who may benefit the most from preventive treatment.(4) In addition, it should be noted that the subgroup analyses of our study showed a similar effect regardless of the control therapy used (placebo or EVL) and no heterogeneity was detected regarding the primary end-points.

Regarding publication bias, tests to estimate the risk of this sort of bias, such as the Egger's test, have limitations and caveats in terms of interpretation. Instead

of this, we performed a thorough and rigorous systematic review including an extensive search strategy which involved a comprehensive search of the main medical databases and a manual search of conference abstracts. This search strategy is detailed in the article and the supplementary appendix, as well as the reasons and methods for the individual patient data acquisition. With such a careful approach, we are confident that all available data was included in our IPD meta-analysis.

Finally, we completely agree with our colleagues that a large RCT will certainly be of great value to further define the role of carvedilol in compensated cirrhosis. In the meanwhile, a recent survey has shown data further supporting the value of carvedilol to prevent decompensation and death in cirrhosis.(5) So, we believe our recent study clearly shows that in patients with compensated cirrhosis and CSPH, long-term therapy with carvedilol may prevent the progression of compensated cirrhosis to decompensation, significantly improving survival and reducing the healthcare burden and cost of managing these patients.

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