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## Uncertain benefits of simvastatin in the treatment of patients with variceal haemorrhage

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Dear Sir, we read with interest the recent study describing reduced mortality in patients with recent variceal haemorrhage treated with simvastatin.<sup>1</sup> This important study is the first that aims to prospectively evaluate a role for statin therapy in improving outcomes for patients with advanced cirrhosis. The study is supported by pre-clinical work showing an approximately 10% reduction in hepatic venous pressure gradient in simvastatin treated patients with cirrhosis<sup>2</sup> and a number of retrospective analyses.<sup>3, 4</sup> The study reports no effect of simvastatin treatment on the composite primary endpoint of rebleeding or death but in a prespecified secondary endpoint analysis there was a significant reduction in overall mortality. There are however several aspects of the report that would benefit from clarification.

The authors use data regarding the number of expected events from a previous randomised trial of a similar patient cohort. In the description of the power calculation they use the number of events required to accrue and a precise reduction in the composite primary endpoint of 21%. It is not clear how this estimate is derived given the modest effect of simvastatin on portal pressure reduction previously described.<sup>2</sup> In addition, it is unclear whether the study was powered using a time to event calculation. This is particularly important since the duration of follow-up was extended after the trial was initially designed. Whilst this is described as a technicality the publicly available information regarding trial registration still lists the primary endpoint analysis at 12 months after randomisation.<sup>5</sup> In the analysis of the dataset the duration of follow-up is also worthy of comment since many patients did not reach 12 months after randomisation. Indeed, 25% of patients included had follow-up duration of less than 6 months. Of these patients the majority were censored and the reasons for this are not presented. It may be that this relates to treatment discontinuation and understanding this important parameter would be helpful in determining the real world effectiveness of statin therapy in patient with advanced cirrhosis. In addition, these patients should be considered in any intention to treat analysis if treatment discontinuation was indeed the cause of censoring rather than short follow-up duration *per se*.

Finally, the selection of a composite endpoint for the primary endpoint was done recognising the importance of competing risks in patients with variceal haemorrhage. It is critical that this same observation is carried forward to analysis of the mortality endpoint where transplantation is a recognised competing event. The inclusion of patients undergoing transplantation (two patients in the simvastatin group vs. zero in the placebo group) in a composite endpoint diminished the effect of simvastatin such that statistical significance is lost according to the stratified analysis presented. Whilst this effect is described in the results insufficient weight is given to this in the conclusion, particularly when overall mortality is a secondary endpoint that the trial has not been adequately powered to address.

Agreement from the authors to publish the trial protocols and subsequent amendments would provide important information that could be used to inform future studies and allow readers to better understand the trial design and the reliability of results. Based on the published methods and data it is our view that the benefit of improved survival of patients with variceal haemorrhage treated with simvastatin is overstated. Whilst a further randomised study is warranted there is a striking pattern in the published literature where positive effects of statins reported in preclinical models and large retrospective observational studies are then followed by large negative randomised controlled trials.<sup>6</sup>

<sup>7</sup> For patients with advanced liver disease and few therapeutic options one hopes that treatment of portal hypertension will be the exception.

## References

1. Abraldes JG, et al. Gastroenterology 2016;150:1160-1170 e3.
2. Abraldes JG, et al. Gastroenterology 2009;136:1651-8.
3. Mohanty A, et al. Gastroenterology 2016;150:430-40 e1.
4. Simon TG, et al. Hepatology 2016 epub ahead of print.
5. Efficacy of statin association with standard treatment in prevention of recurrent haemorrhage in patients with cirrhosis and variceal bleeding.  
<http://www.clinicaltrials.gov/ct2/show/NCT01095185>, accessed May 2016.
6. Criner GJ, et al. N Engl J Med 2014;370:2201-10.
7. Papazian L, et al. JAMA 2013;310:1692-700.