Reviewer's report

**Title:** Simvastatin decreases the level of heparin-binding protein in patients with acute lung injury

**Version:** 3  **Date:** 15 April 2013

**Reviewer:** Jeffrey R Jacobson

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This work by McAuley et al investigates the effect of oral simvastatin administration on plasma levels of heparin-binding protein (HPB) in patients with ALI. This is an extension of an earlier study published by the authors (HARP) which included 60 ALI patients and reported an improvement in non-pulmonary organ dysfunction associated with simvastatin treatment but, notably, did not identify effects on several clinically important outcomes including mortality. The authors now report increased HPB levels in ALI patients compared to controls and a significant effect of simvastatin on reduced plasma HPB levels in ALI patients at day 7. Moreover, ICU survival from ALI was also associated with decreased HPB levels at day 7. This is a brief report but represents important and novel findings that may ultimately have significant clinical impact. There are only a few minor concerns detailed below.

**Minor Revisions**

1. The report would be strengthened by a more detailed discussion of potential mechanisms by which simvastatin decreases HPB levels. Fortunately, a plausible mechanism can be found in the existing literature. Specifically, statin effects on various integrins have been reported, including in the context of ALI. Most notably, however, Weitz-Schmidt et al have reported effects of statins on the inhibition of integrin b2 family proteins (Nature Med, June 2001). This obviously fits very nicely with the idea that simvastatin may inhibit HPB release from neutrophils via the inhibition of integrin b2-dependent adhesion. At the very least, a few lines on this in the discussion are warranted.

2. The authors should address the fact that although (1) simvastatin decreased HPB levels in ALI patients over time and (2) the fold change in HPB levels over time was associated with survival, simvastatin treatment did not effect ALI survival. While this may simply be a matter of sample size, this should be clearly stated and discussed. Along these same lines, the last sentence in the results should be rewritten as, in its current form, it suggests that simvastatin treatment was in fact associated with ICU survival.

**Level of interest:** An article whose findings are important to those with closely related research interests

**Quality of written English:** Acceptable
**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**

I declare that I have no competing interests.