Reviewer's report

Title: The effect of homocysteine-lowering with B-vitamins on osteoporotic fractures in patients with cerebrovascular disease: substudy of VITATOPS, a randomised placebo-controlled trial

Version: 2 Date: 2 June 2013

Reviewer: Nathalie van der Velde

Reviewer's report:

The article is well written and given the limited publications/trials on this matter, the data add to the insight of the earlier reported association between homocysteine/B-vitamins and fractures. However, as the authors state themselves, the low fracture rate seriously limits any conclusion that may be drawn, but in agreement with the authors, publishing the data may be of value for future meta-analyses on this issue.

Furthermore, changes in gathering of events over the study period may have hampered the results, e.g. dilute any potential effect, although it is not likely that this was differential between the groups.

Major comments:

1. Methods page 8/9: Although VITATOPS main outcomes have been published elsewhere; readability would improve if assessment/statistical handling of baseline characteristics is presented in the methods section. Furthermore, please add information regarding handling of potential differences between the intervention group and control group and handling of potential interaction e.g. which potential stratifications where considered.

2. Methods & results: please add information regarding potential different effects for gender, age-groups, and baseline levels; and potential other variables with positive interaction-terms.

3. Methods: please shortly state the duration of intervention and explain differences in follow-up period.

4. Methods/results: was per protocol analysis performed/considered? If results were comparable, please mention briefly; if they differed, please elucidate.

5. Results page 9/10: please add information regarding adverse events

6. Results page 10: the overall fracture rate appears to be caused for +/- 50% by the hip fracture rate. From an epidemiological point of view this is quite unlikely, and underlines the selective gathering of results during the first part of the study (as is mentioned by the authors). Since any osteoporosis-treatment/preventive measure may potentially have different effects on different bone structures (E.g. fracture sites) this may have biased the results. Please state this clearly in the limitation-section.

7. Discussion page 11, first paragraph: Please rewrite first sentence, because of
the lack of power, the conclusion needs to be written down less firm.

8. Discussion page 12 second paragraph: please rewrite limitation regarding change in gathering of the primary outcome for this study as mentioned above (comment 7)

Discretionary comments:

1. Because of altering insights, osteoporoses/fracture research is more and more changing towards addressing not only ‘osteoporotic fracture’ but ‘any fracture’. If possible, it would be interesting to add ‘any fracture’ as secondary outcome measure’.

2. In my opinion, adding an overall analyses of predictors of osteoporotic fracture for this particular population does not add to the insight of homocysteine-related fracture risk.

**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