Reviewer's report

Title: Incident venous thrombotic events in the Prospective Study of Pravastatin in the Elderly at Risk (PROSPER).

Version: 1 Date: 12 August 2010

Reviewer: Caroline Sirois

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Major compulsory revisions

1) The rationale for using a case-control analysis should be stated. It is not clear why such analysis was used since Cox regressions were also performed. If the case-control analysis was used because some variables were available for a portion of the population only (as suggested in the statistical analysis portion), there are questions that have to be answered: Why not use sensitivity analyses for missing variables in the whole cohort instead? If the variables were available only for a portion of the population, it is unclear why they were available for all cases, but not for the whole cohort. Could this be problematic?

Also, it is not clear why patients on warfarin at baseline were not excluded before the matching process was performed (especially since they were excluded in the analyses involving the whole cohort). It is odd to exclude cases and controls afterwards. It means there are cases that are not matched to two controls and controls that are not matched to cases.

More details should be given on how the matching process was performed (eg, could controls be chosen more than once?)

Minor essential revisions

ABSTRACT

2) It would be informative for the reader to know that hazard ratios were used to evaluate the risk of VTE.

3) Since Cox regressions were used for the identification of the majority of factors associated with VTE, it should be clearly stated in the methods. The multivariate analysis should be announced in the methods (it appeared only at the end of the results section).

4) It is not clear why a case-control analysis was performed. In fact, from the abstract, the reader may think case-control analysis was used for identification of all factors. (Are the results of the case-control analysis essential for the abstract? Would it be easier for the reader if only the results from the cohort analysis are presented?)

BACKGROUND
5) At the end of the second paragraph, please give more details why “it was not certain that elderly people benefit”. Was it because there were too few of them included in the trials? Because of heterogeneity of the results?...

6) In the third paragraph, a sentence should be added after the first sentence to explain that the data from PROSPER was used for the present study. (The authors may refer to the way it is formulated in the abstract.)

METHODS

7) In general, the distinction between the analyses performed in the whole cohort and those performed within the case-control analysis should be made clearer. For example, on lines 16-17 of the paragraph under subject, it is stated, “For the nested case-control study non-cases were all individuals not identified as either a definite or probable case”. However, this also applies to the Cox regression. The term “cases” may lead to confusion, because it usually relates to case-control analyses, but is also used in the cohort. Also, instead of saying “where date were available only for the cases and controls…”, it may be more informative to state which plasma risk markers were available only for the case-control analysis (page 8, statistical analysis).

8) At the end of the paragraph under subjects on page 6, it is not clear why VTE cases were separated into those who had and those who did not develop cancer during the study.

9) When were blood analyses performed? At baseline? Please add the information on page 7.

10) In the statistical analysis, please give more information on multivariate analyses (eg, on page 9 in the results section, it is described that all variables significant at the 5% level on univariate analysis where allowed to enter the model. This information should be found in the method section instead).

11) Were only univariate analyses planned for the case-control analysis? Please add the information about multivariate analysis if appropriate.

RESULTS

12) The cancer diagnosis has not been well explained in the method section (it only appeared on page 6, where it was said that cases were separated according to cancer status.) To be adequate, the variable has obviously to be obtained for all cohort members. Please add the information.

13) Please give the adjusted HR for BMI and country (page 9).

14) The rationale for the risk factor profile (page 10) is not clear. Since cancer was a variable in the multivariate analysis, it is not clear what this analysis adds and where it stands relative to the study objectives. Was the risk factor profile also studied for the “non-cases”??
**DISCUSSION**

15) First sentence: the following could be deleted, “with a point estimate for risk above one”. The result is not statistically significant. It doesn’t make any difference whether it is above or below 1.

16) Second sentence, please specify again what was the population studied in JUPITER.

17) Third sentence. There is a need to explain in more details what the authors meant by comparing the confidence intervals and the point estimate. It could be hazardous to compare two different studies this way.

18) Fourth sentence. How many person-years of follow-up were there in each study?

19) The second paragraph of discussion would be more efficient if it followed the fourth sentence of the first paragraph.

20) First paragraph, last sentence: please specify that the similar lack of effect of statins was on VTE.

21) It may be informative to discuss the limits of having results from blood analyses only at baseline.

**REFERENCES**

22) Reference number 7 has been published (2010;31(10):1248-56)

**TABLES**

23) Table 1. It may be useful to use other terms than cases and non-cases to ensure there is no confusion with the case-control analysis.

24) Table 2. Specify they are unadjusted Odds Ratios

**Discretionary revisions**

**BACKGROUND**

25) The first sentence commences with “Venous thrombosis” whereas in the second, the term “Venous thromboembolism” is used. Do they refer to the same condition? If so, please use only one term.

26) In the first sentence, instead of defining the “old” in parentheses, the actual number could be used: (...) but is close to 1% per annum among those aged over 70 years.

27) In the fifth line of the first paragraph, please use the abbreviation VTE as it was already defined (see line #3). Please use it thereafter (eg, second paragraph, line 4).
METHODS

28) Editing: anticoagulant is written as “anti-coagulant” on line 11, and “anticoagulant” on line 14.

29) It would have been interesting to have more information on papers that are cited in the statistical analysis. Why were they not included as part of the introduction or discussed later in the article?

DISCUSSION

30) In the first sentence, please add, “the study showed “with data from” a randomized trial … “.

31) Second paragraph, third sentence. We find the same sentence in the introduction. It could be deleted in this paragraph.

32) Second paragraph, line 6-7. Please user one or the other (greater or #)

Level of interest: An article of importance in its field

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