Author's response to reviews

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

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Author's response to reviews: see over
Response to Editors’ Comments

In the nested-case control analysis, the cohort should be defined. For example `a nested case-control analysis was performed, where the cohort was those patients for whom the `variable¿ was available (n= `provide the number of patients in the cohort`).

This information has now been added to the Abstract Pg3.

Also, the rationale for not excluding patients on warfarin from the cohort in the nested case-control study is still not clear. You have 76 cases in total and 72 who did not use warfarin, why match the 76 cases and then exclude the 4 after the match? Since the exclusion of warfarin users at the time of case and control selection would not change the results, I suggest adding a rationale along the following lines (if this was the real reason): It would seem more reasonable to exclude exposed cases before matching, however this was not done because exposure was defined at the time of VTE occurrence for the case and its matched control; time that was not known for the control before the match. To assess exposure to warfarin at the time of matching and exclude ineligible controls complicates the selection procedure substantially. Since the cohort analyses revealed a very small number of cases exposed to warfarin, we decided to exclude exposed cases and controls at the time of analyses; this decision would not affect the results and the matching procedure would be simplified extensively.

Our presentation of the case control analysis is clearly confusing. Therefore we have reanalysed the data on a more straightforward basis as suggested by Reviewer 2 where each individual case is analysed with their respective matched controls rather than using bins. For the majority of cases, 2 controls were available, but for 3 cases, 1 of their matched controls was on warfarin and eliminated from the analysis giving a 1 to 1 matching. These data are now presented in the manuscript (Table 2) and show almost identical results to the previous analysis. The abstract, methods and results sections have been changed accordingly. We have also redrawn Figure 1 to indicate the new analysis. We hope this is a more comprehensible analysis but we are happy to present either this or the original analysis, whichever the editors prefer.
Response to Reviewers’ comments

Reviewer 1.

Minor Comments

1. Page 3, first and second line: correct spelling is “deep vein thrombosis and pulmonary embolism”
The text has been corrected Pg 3.

2. Page 15, third line say “may not be able to detect a small benefit of pravastatin treatment.” Considering that the risk estimate for pravastatin is 1.42, which indicates increased risk rather than benefit of pravastatin treatment, I suggest to replace the word “small benefit” with “small effect”.
The text has been changed as suggested Pg 15.

3. Table 1: To me, 0.2L/L increase in hematocrit seems a bit high considering clinical relevance. Since the standard deviation is approximately 0.03, I would suggest calculating the HR for 1SD increase (or alternatively 0.05L/L) increase in hematocrit.

HR have now been calculated for a 1SD increase (0.04L/L) (Table 1).

Reviewer 2

Major compulsory revisions

1. The way case-control analyses were performed is still not clear. How were the conditional logistic regression performed, if there was no matching of specific individual cases with specific controls? In fact, it still feels awkward that patients on warfarin at baseline were not excluded before the selection of cases and controls, especially when those patients were excluded in the Cox regression.

The matching was carried out by selecting two controls for each case within the same two year age band, by gender and by country. For the analysis the age, gender and country combinations were analysed as separate groupings (bins). It may have been the case that 2 cases had the same age, gender and country combination and therefore the analysis was carried out for 2 cases vs 4 controls for that grouping (and so on for greater numbers). When we removed the warfarin cases and controls the numbers of cases and controls in each bin may only have been reduced by 1 (e.g. 1 case vs 4 controls) having little impact on the overall results.

However, we accept that this may be complicated for readers to understand and have therefore reanalysed the data on a more straightforward basis where each individual case is analysed with their respective matched controls. For the majority, 2 controls were available, but for 3 cases 1 of their matched controls was on warfarin and eliminated from the analysis giving a 1 to 1 matching. These data are now presented in the manuscript and show almost identical results (Table 2). The abstract, methods and results sections have been changed accordingly.
It would be interesting to indicate in Figure 1 (flow diagram), that the right-hand side refers to the cohort analysis (cox regressions) and the left-hand side to the case control analysis.

The appropriate annotation has been made to Figure 1 and we have updated this figure to illustrate the new matching process.

Minor compulsory revisions

2. In results, please indicate whether it is an increased/decreased BMI that is associated with an increase in risk for VTE. Also specify the change (increased/decreased) for systolic blood pressure.

The direction of the association has been indicated in the text for BMI and BP Pg 11.

3. In discussion, the authors state that there were fewer events in PROSPER than in JUPITER, however, the incidence rates are very similar (0.26% per annum vs 0.28%). Person years of follow-up should be reported for JUPITER, or the incidence rates be compared at this point.

The incidence rates are compared as suggested by the reviewer Pg 13.

Discretionary revisions

Abstract

4. It would be informative to know if it is an increased or decreased BMI that is associated with VTE.

This has now been indicated in the abstract Pg 3.

5. For consistency, please state the p value for Scotland vs Netherlands even though not statistically significant.

Individual P values are now stated in the abstract Pg 3.

6. The results of the case-control analysis are stated, but this analysis was not presented in the methods section.

The case control analysis is now mentioned in the methods section of the abstract Pg3.

Discussion

7. The last paragraph of the discussion would be more efficient if it followed the fourth sentence of the first paragraph since it involved a comparison between PROSPER and JUPITER.

As suggested the last paragraph of the discussion has been moved to follow the first paragraph of the discussion Pg 13.

Reviewer 3

No comments to address