PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	The association of statin use with a reduced incidence of venous thromboembolism – A population-based cohort study
AUTHORS	Lassila, Riitta; Jula, Antti; Pitkäniemi, Janne; Haukka, Jari

VERSION 1 - REVIEW

REVIEWER	Alessandro Squizzato University of Insubria Varese Italy Intellectual conflict of interest: topic of this paper is one of my main research lines
REVIEW RETURNED	18-Jun-2014

GENERAL COMMENTS	The manuscript may be improved before publication. - it is not clear if ICD codes 180.0-180.9 are the right ones for deep venous thrombosis, as this codes are for 'phlebitis and thrombophlebitis of SUPERFICIAL vein'. The authors should provide reasons for this choice. - I do not understand the reason for including in the outcomes also cerebral vein thrombosis. Why not to include other rare vein thrombosis, such as splancnich vein thrombosis, retinal vein occlusion, etc. The authors should provide the rationale - The authors should provide the reason for missing data on 2007 and 2009-2011. It is a very wide range of period, and a major limitation of the study that the authors should discuss - Female are nearly 55% of total population. Is this the gender distribution in Finland? Provide reasons for this difference between man and women. Is it real? Why ? Is it a selection bias ? Why? - Increased risk associated with antithrombotic drugs has been explained as 'confounding by indication'. Therefore, also the positive effect of statin on thrombotic events by be an 'healthy-users effect'. please, discuss this issue. - Discussion: the JUPITER study is a randomized controlled trial and not a meta-analysis as reported.

REVIEWER	Willem Lijfering LUMC The Netherlands
REVIEW RETURNED	02-Jul-2014

GENERAL COMMENTS	In this study, authors observed a reduced risk of venous thrombosis in individuals who received statin as compared with non-statin after

	adjustment for potential confounding with standard statistical techniques plus IPW. Comments 1) As explained in observational statin studies on all-cause mortality (Danaei et al, Am J Epidemiol, 2012), including prevalent statin use as an exposure can lead to survivor bias; i.e. a biased and lower (below HR=1.0) relative risk. Bias can occur because statin users have by definition survived under statin treatment until enrollment (i.e. they are alive at time of enrollment and are still willing to take statins). Danaei et al suggests a way to overcome this bias by including incident statin users in the exposure group only. I would like to urge the authors to perform a similar analysis as Danaei et al did with incident statin users vs non-statin users, at least as a sensitivity analysis to see if this changes their results. 2) Although the cohort is quite large and community based (all advantages of the study) a drawback is that the total number of statin users with an event (n=18) is quite small. This may be problematic in terms of (over)adjustments. Because the adjustment makes such a difference to the relative risk of a venous thrombosis in statin vs non-statin users, the authors should at least discuss the potential limitation of small numbers possibly leading to over-fit statistical models. The authors may be inclined to believe that their results are valid though, as they are in line with other (larger) studies on this issue. 3) Do authors know the validity of ICD diagnosed venous thrombosis in Finland, i.e. how many venous thrombosis are accurately diagnosed as venous thrombosis with ICD codes? 4) Can authors make a distinction between PE and DVT as endpoint. Most studies thus far (e.g. the study from Glynn in NEJM 2009) suggest that statins are more able to reduce the risk of DVT than of PE. I am not sure if this analysis is possible due to small numbers though. 5) Similar to comment 4, can authors distinguish type of statin to the risk of venous thrombosis? This would be interesting as most studies (especially the Rahimi study in Plos Med) suggests that rosuvastatin is the most potent statin to reduce venous thrombosis risk.

VERSION 1 – AUTHOR RESPONSE

Reviewer 1.

We thank for the constructive expert comments (bolded underlined) and respond to them as follows:

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1 " - it is not clear if ICD codes 180.0-180.9 are the right ones for deep venous thrombosis, as this codes are for 'phlebitis and thrombophlebitis of SUPERFICIAL vein'. The authors should provide reasons for this choice. - I do not understand the reason for including in the outcomes also cerebral vein thrombosis. Why not to include other rare vein thrombosis, such as splancnich vein thrombosis, retinal vein occlusion, etc. The authors should provide the rationale" Reply: 2. ICD codes. The ICD code used has been I80-180.9, which includes all the listed forms of deep vein thrombosis, including

thrombophlebitis. The rare forms of thrombosis, such as splancnic and cerebral sinus thrombosis represents just individual cases, as expected from the previous knowledge. We chose the reporting of venous thromboembolism partially basing on the experience of our previous publication of coeliac disease and VTE (Ludvigsson et al. Brit J Hematol, 2007139:121-7).

2 "---- - The authors should provide the reason for missing data on 2007 and 2009-2011. It is a very wide range of period, and a major limitation of the study that the authors should discuss" Reply: Missing data. The reason for missing data during 2007 and 2009-11 is that data provider was not able to deliver data because of technical reasons.

3 "- Female are nearly 55% of total population. Is this the gender distribution in Finland? Provide reasons for this difference between man and women. Is it real? Why ? Is it a selection bias ? Why?" Reply: The sample of Health 2000 Study gave larger weight to old age classes. Because of this, and fact that life expectancy of women is considerably longer (81 years in 2000) than men (74 years), proportion of women is higher in our sample. Participation characteristics of sample are described in report http://www.terveys2000.fi/julkaisut/baseline.pdf, pages 14-15. p.

4 "- Increased risk associated with antithrombotic drugs has been explained as 'confounding by indication'. Therefore, also the positive effect of statin on thrombotic events by be an 'healthy-users effect'. please, discuss this issue."
Reply: We have discussed the healthy users effect.

5 "- Discussion: the JUPITER study is a randomized controlled trial and not a meta-analysis as reported."
Reply: JUPITER trial is cited correctly as a randomized trial (ref 3) in the introduction. In Discussion, however, we have errorneously cited JUPITER trial later analysis (16) as an meta-analysis and corrected this (1 para, lines 5-6).

Reviewer 2.
We thank the reviewer for the constructive expert comments and respond to them as follows:

1- "1)As explained in observational statin studies on all-cause mortality (Danaei et al, Am J Epidemiol, 2012), including prevalent statin use as an exposure can lead to survivor bias; i.e. a biased and lower (below HR=1.0) relative risk. Bias can occur because statin users have by definition survived under statin treatment until enrollment (i.e. they are alive at time of enrollment and are still willing to take statins). Danaei et al suggests a way to overcome this bias by including incident statin users in the exposure group only. I would like to urge the authors to perform a similar analysis as Danaei et al did with incident statin users vs non-statin users, at least as a sensitivity analysis to see if this changes their report. "
Reply: We acknowledge the suggestion of trying to exclude the bias by using the method of Danaei.. In order to check survivor bias we carried out modeling without subjects with prevalent statin use in start of follow-up (N=460 excluded)

2- "2) Although the cohort is quite large and community based (all advantages of the study) a drawback is that the total number of statin users with an event (n=18) is quite small. This may be problematic in terms of (over)adjustments. Because the adjustment makes such a difference to the relative risk of a venous thrombosis in statin vs non-statin users, the authors should at least discuss the potential limitation of small numbers possibly leading to over-fit statistical models. The authors may be inclined to believe that their results are valid though, as they are in line with other (larger) studies on this issue."
Reply: We acknowledge this notion. Obviously these low numbers have to do with the relatively low

annual incidence of VTE, 1-2/1000. We have taken up this issue now in the second last paragraph of Discussion, as suggested.

3- "3) Do authors know the validity of ICD diagnosed venous thrombosis in Finland, i.e. how many venous thrombosis are accurately diagnosed as venous thrombosis with ICD codes?"
Reply: In the same paragraph we have taken up the issue of overall validity of diagnosis of VTE (ref 23). The validity of ICD diagnosed venous thrombosis in Finland is not known. Overall, this diagnosis of an acute potentially life threatening disease is taken seriously and the ICD codes are uniformly used when discharging the patient from hospitals.
4- "4) Can authors make a distinction between PE and DVT as endpoint. Most studies thus far (e.g. the study from Glynn in NEJM 2009) suggest that statins are more able to reduce the risk of DVT than of PE. I am not sure if this analysis is possible due to small numbers though."
Reply: We agree that this would be nice to know. However, as discussed above the incidences are low and as venous thromboembolism is overlapping in 50% of the patients, this will not allow us to interpret the findings further.
5- "5) Similar to comment 4, can authors distinguish type of statin to the risk of venous thrombosis? This would be interesting as most studies (especially the Rahimi study in Plos Med) suggests that rosuvastatin is the most potent statin to reduce venous thrombosis risk."
Reply: The statin type data would be interesting as well, but as above the low numbers hamper the validity of the analysis and we would hesitate to use that analysis.

VERSION 2 – REVIEW

REVIEWER	Alessandro Squizzato Research Center on Thromboembolic Disorders and Antithrombotic Therapies Department of Clinical and Experimental Medicine School of Medicine University of Insubria Varese Italy Intellectual conflict of interest
REVIEW RETURNED	06-Sep-2014

- The reviewer completed the checklist but made no further comments.

REVIEWER	Willem Lijfering LUMC, the Netherlands
REVIEW RETURNED	15-Sep-2014

- The reviewer completed the checklist but made no further comments.