PEER REVIEW HISTORY

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ARTICLE DETAILS

| TITLE (PROVISIONAL) | Are statin trials in diabetes representative for real world diabetes care: a population-based study on statin initiators in Finland |
|---------------------|--------------------------------------------------------------------------------------------------------------------------|
| AUTHORS             | Ruokoniemi, Päivi; Sund, Reijo; Arffman, Martti; Helin-Salmivaara, Arja; Huupponen, Risto; Keskimaki, Ilmo; Vehko, Tuulikki; Korhonen, Maarit |

VERSION 1 - REVIEW

| REVIEWER            | Muhammad Mamdani  
|---------------------| Li Ka Shing Knowledge Institute of St. Michael's Hospital and University of Toronto, Canada |
|                     | I have been on advisory boards and received honoraria from AstraZeneca, Bristol-Myers Squibb, Eli Lilly and Company, GlaxoSmithKline, Hoffman La Roche, Novartis, Novo Nordisk, and Pfizer. |
| REVIEW RETURNED     | 10-Apr-2014 |

| GENERAL COMMENTS    | In this study the authors address a very important issues in clinical research: the generalizability of clinical trials to ‘real world’ populations. The authors conclude that over 40% of ‘real world’ patients in Finland would not be eligible for inclusion into two large, relatively pragmatic pivotal clinical trial assessing the efficacy and safety of statin therapies. The authors also examined the ‘real world’ cardiovascular outcomes among statin users meeting trial eligibility criteria relative to those not meeting eligibility criteria. Adherence to statin therapy was assessed using the mean possession ratio approach. Several comments for consideration are outlined below. |
|                     | 1. The definition of diabetes using the Diabetes in Finland (FinDM) database is outlined on page 5 with a reference to a technical report. It would be helpful to provide information on the validity of the approach to identifying patients with diabetes (i.e. sensitivity, specificity, positive predictive value, etc). Further, the validity of the approach identifying Type I and Type 2 diabetes would also be helpful. |
|                     | 2. The statistical analysis section outlined on page 7-8 is somewhat vague – more detail here would be helpful. For example, it appears a Cox proportional hazards model was the survival model used in the analysis. This should be specified and if so, other details should be provided (e.g. how was the proportionality assumption tested?). |
|                     | 3. The definitions of exclusion can be quite tricky using large healthcare databases without a sense of the validity of each of the approaches used in the exclusion criteria. For example, if some |
codes underestimate the prevalence of a particular exclusion criteria, the authors may overestimate eligibility. On the other hand, if some codes of a particular exclusion criteria are ‘overcoded’ they may overestimate ineligibility. The validity of the estimates outlined in this study is largely driven by the quality of the coding of the exclusion criteria variables. A better sense of coding validity for each of these exclusion criteria would be very helpful.

4. While the survival analyses presented on pages 26-27 were interesting, much more detail needs to be provided in his regard in both the methods and results sections. ‘Real world’ patients ineligible for the trial are likely quite different from those eligible for the trial, so there may be considerable confounding present. At the very least, a table outlining the demographic and clinical differences between these two populations of patients, the presentation of unadjusted and adjusted HRs, and a more fulsome description of the covariates included in the survival model in the methods section would be extremely helpful.

**REVIEWER**
Peter M Nilsson
Lund University
Dept. Clinical Sciences
Skåne University Hospital

**REVIEW RETURNED** 06-May-2014

**GENERAL COMMENTS**
I think that the paper s a fair description of the situation in Finland, a Nordic country, a few years ago, but the situation is changing over the years, why the aspect of "recent history" in prescription patterns of statins to patient with diabetes should be acknowledged.

I have no specific methodological concerns. The STOBE criteria have been applied.

This is an observational study on the discrepancy between results obtained in RCT for statin treatment of patients with diabetes (HPS, CARDS) and the real life situation in Finland. I think that the results are trustworthy, but also expected, i.e. that the real life situation does not match the rigorous standards of RCTs. The authors also state that the situation is changing based on data from the last year of observation (2010). This means that observations 2005 are not relevant any more (mean dosage of statins for example) and therefore the contextual background should be kept in mind. The situation is expected t change even more following the recent ESC-EASD document on risk factor control in diabetes (Eur Heart J 2013) that could be referred to.

**VERSION 1 – AUTHOR RESPONSE**

Responses to comments received from Reviewer Muhammad Mamdani.

1. Response: In FinDM the patients with diabetes have been simultaneously identified from several administrative registers with data covering both prescription information and clinical data. Especially, the entitlement for special reimbursement for diabetes medication is based on predefined criteria including measured glucose values, a written certificate by the patient’s treating physician, and a review process conducted by the Social insurance Institution. Therefore, we state in the discussion
section of the manuscript: “the validity of our data for capturing real-world patients with pharmacologically treated diabetes in clinical practice in Finland is good” (please see Discussion, Strengths and limitations, lines 2-3). We have also evaluated the completeness of the nationwide FinDM data by comparing the numbers of patients with diabetes to a local diabetes database (Reference No. 51, Sund et al. 2010). Validity of the data has turned out to be good in comparison to similar data in other countries (Kiivet et al. 2013; PMID: 23769506) and when young patients with Type I diabetes were manually checked for inclusion (Harjutsalo et al. 2013; PMID: 23917294). In the present study, we categorized the diabetes subtypes similarly as was done previously (Vehko et al. 2010; PMID:20228159). The classification is based on patterns of antidiabetic medication use and age (and data on gestational diabetes from the Medical Birth Register), and gives a good face validity to separate patients with obvious Type I diabetes as well as patients having gestational diabetes only from the patient population with Type II diabetes. However, the sensitivity, specificity and positive predictive value of the diabetes subtype have not yet been studied. Hence, we have revised the discussion as follows (Please see below and the revised manuscript, Discussion, Strengths and limitations – section, lines 4-11):

“We have missed some patients with diabetes, especially among persons aged 65 years or more who either had undiagnosed diabetes or who were on diet therapy only and had not received any hospital care [51]. We had no data on liver function tests, cholesterol levels, or smoking habits and the actual date of diabetes onset was estimated using the first diabetes related record in any of the registers. In addition, some complications, such as retinopathy, microalbuminuria, and nephropathy, are likely to have been under-ascertained. Furthermore, the validity of our data on capturing clinically determined diabetes subtype has not been studied. Therefore, we were not able to define the eligibility criteria exact in the same way that the reviewed trials had done and we may have slightly under- or overestimated the proportions of eligible patients.”

2. Response: We did not use Cox proportional hazards models. We apologize that the wording may have been unclear and have revised it as follows in the Statistical Analyses of the Methods section (Please see below and the revised manuscript, Methods, Statistical analyses section, lines 2-5):

“We calculated the proportions of real-world patients meeting the eligibility criteria applied in the HPS(DM) trial and of those meeting any single criteria for exclusion (Figure 1A). For both groups of patients deemed either eligible or ineligible, we estimated the cumulative hazard function for the composite endpoint using a Nelson-Aalen estimator (Figure 2A) in a stratified survival analysis from the date of the first statin purchase until the date of the composite endpoint or censoring.”

We have slightly modified the figures 2a and 2b and re-submit them with the revised manuscript.

3. Response: We agree with the referee on the relevance of this issue, which concerns a limitation common to all epidemiological studies using administrative register data. As outlined in the discussion section (Strengths and limitations), and the bullet point section in the beginning of the manuscript, we acknowledge the possibility for having under- or overestimated the proportion of those eligible for the trials. For most of the variables applied as exclusion criteria, however, we believe our register data to have reasonable coverage and validity. As stated in the methods section, the validity of the Hospital Discharge Register and the Causes of Death Register for capturing CVD events is good: Since the 1980s the coverage has been 88-98%, sensitivity 50-97% and positive predictive value 85-95%, as reported in various validation studies (Sund R. Quality of the Finnish Hospital Discharge Register: a systematic review. Scand J Public Health. 2012; 40(6):505-15). Additionally, the variables were captured from several registers simultaneously: The Hospital Discharge Register, The Special Reimbursement Register and the Prescription Register. The demographic characteristics were captured in the aforementioned administrative databases, as Finland assigns a personal identification code to all Finnish inhabitants. However, the validity of our data on capturing the proportion of those
with recently diagnosed diabetes or with history of retinopathy/micro/macroalbuminuria has not been studied. Following the referee’s comment, we have further highlighted this issue in the discussion section (Please see Discussion, Strengths and limitations –section, lines 7-11 and our response no. 1) and revised the terminology in the bullet point section as follows (please see third bullet point in the beginning of the manuscript):

"All trial eligibility criteria could not be assessed by registry data and we may have slightly under- or overestimated the proportion of those eligible for the trials."

4. Response: We agree with the referee that patients deemed eligible and ineligible for the trials are likely quite different. Our estimates of the cumulative hazard for CVD events are unadjusted and descriptive only. The overall differences in the baseline risk of CVD events between the two groups is supposedly reflected in these unadjusted survival curves in Figures 2a and 2b. Figures 1a and 1b show the numbers and proportions of patients excluded due to each exclusion criterion; the differences in these characteristics are presumably the main reasons for difference in the cumulative hazard of CVD events between those eligible and ineligible to the HPS shown in Figure 1a.

Response to the comments received from Reviewer Peter M Nilsson:

We thank the referee for highlighting this issue on the time-dependent nature of our findings and have taken the opportunity to amend our manuscript (Please see the revised manuscript, Discussion, Strengths and limitations –section, lines 21-23.):

"In addition, there was a shift towards higher statin doses: only one fifth of the patients in 2010 initiated their statin use with a dose corresponding to <20 mg of simvastatin. Finally, diabetes care, including treatment of dyslipidemia, is constantly evolving [53] and our assessment represents a case study in Finland. Although the prevalence of statin use in diabetes in Finland seems to be at an average level [54], the treatment practices vary between countries [55]. Thus, similar evaluations of the representativeness of RCTs with respect to the care of diabetic patients in other countries are needed."