Reviewer’s report

Title: Investigating the Risk of Bone Fractures in Elderly Patients with Type 2 Diabetes Mellitus: a retrospective study

Version: 0 Date: 09 Jun 2019

Reviewer: Baqiyah Conway

Reviewer's report:

Horii et al used repurposed EHR data to investigate factors associated with fracture risk in elderly patients with diabetes. They found that being female and the use of thiazolidine were associated with increased risk while chronic kidney disease was associated with decreased risk. While the manuscript is of interest, I have some comments and concerns presented below.

Abstract:

In the abstract, the authors state that there is a lack of clinical data on fracture risk. Is this true? Please see for example, Conway et al "Glycemic Control and Fracture Risk in Elderly Patients with Diabetes". Diabetes Research and Clinical Practice 2016; 115: 47-53.

Please provide some description of the EHR the study uses. A hospital in Japan? A clinic? A conglomerate of clinics? A university medical center?

In the conclusion something needs to be said about the protective relationship of an eGFR less than 60 since it is very strong, effectively cutting risk in half, and not what one would have expected. (in the limitations section, this also needs to be discussed in issues related to repurposing operational data for research since the data were not collected for research purposes- is data for calculating eGFR routinely collected in the patients, particularly as consistently as mediation use and glycemic control or is it disproportionately collected in select patients for reasons indicating a need to measure kidney function?)

Introduction:

The one paragraph introduction is much too long. Please split it into multiple paragraphs. For example, the sentence beginning with "In Japan, the frequency..." can be the start of a new paragraph. Likewise, the sentence starting with "Elderly patients with T2DM can be the start of a third paragraph."
The sentence, "Moreover, patients with type 1 and T2DM..." can be removed since it is immaterial to the manuscript.

Methods:

Page 4, line 85. Greater clarity on what is meant by cutoff should be provided so that it is clear immediately. Cut off in which way? Good vs. poor (or not good) glucose control?

Results:

Lines 150 to 155

Perhaps the authors should simply state that risk associated with TZDs did not differ by sex and then provide the ORs and 95% CIs.

Discussion

The opening paragraph of the Discussion started off as an overall summary of the study and should remain so.

Lines 163-164. This information is already stated in the first sentence of the discussion

Lines 164-169 provide explanations for very specific findings and is not usually provided in the opening paragraph of the discussion.

Page 8,line 183. Again, please specify what is meant by HbA1c cutoff. As written, it sounds as if no patients with an HbA1c less than 7 were included in the study.

Page 8, lines 186-191. Perhaps further stratification by HbA1c level in your study would reveal a difference. Is it possible that an HbA1c of 6.5 to <7 is optimal in terms of fracture risk and that an HbA1c below or above this range increases risk?

Page 8, line 190. What is meant by only previous HbA1c levels were used? Was there only one HbA1c level that was used?

Page 9, 200 to 202. I disagree with the authors statement here since all patients were 65 years and older unless TZD users were substantially more likely to be older than nonusers.

Lines 208 on. Please provide other limitations to using EHR data for research. For example, the problems with missing data since the data were not originally collected for research; the
problems with validation of fracture cases since it was based on ICD codes; the problem with renal data in the EHR.

Tables.

Table 1, lines 36-40. This row should be removed from the table.

Table 1, line 46. What is meant by agent? Perhaps removed this word since it is distracting.

Table 3 has serious problems. In the second column, under "All patients" the label "Univariate Analysis" is missing. There seems to be a serious formatting problem, with data in many columns often missing. For example, for the final multivariate column in women is very often missing.

**Are the methods appropriate and well described?**
If not, please specify what is required in your comments to the authors.

Yes

**Does the work include the necessary controls?**
If not, please specify which controls are required in your comments to the authors.

Yes

**Are the conclusions drawn adequately supported by the data shown?**
If not, please explain in your comments to the authors.

Yes

**Are you able to assess any statistics in the manuscript or would you recommend an additional statistical review?**
If an additional statistical review is recommended, please specify what aspects require further assessment in your comments to the editors.

I am able to assess the statistics.

**Quality of written English**
Please indicate the quality of language in the manuscript:

Acceptable
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