Reviewer's report

Title: Association between age and initiation of antihyperglycaemic treatment in UK patients with newly diagnosed type 2 diabetes

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Reviewer: Mark Peyrot

Reviewer's report:

This paper addresses an important clinical topic – initiation of antihyperglycemic therapy. The authors have a good database but need to perform some additional/alternative analyses. It is also necessary to further clarify some of the methods.

Major Compulsory Revisions

1. A general comment is that the authors should refer to their outcome as initiation of antihyperglycemic medication (AHM), since they do not consider diet or exercise as antihyperglycemic therapy.

2. Another general comment is that the authors should change the title of their paper to include the other factors investigated in this study, perhaps “Factors associated with initiation of antihyperglycemic medication in UK patients with newly diagnosed type 2 diabetes.” Relatedly, the abstract should report the other factors associated with initiation of AHM (not just age and A1c).

3. The major problem with the paper is that the present approach does not allow us to determine whether initiation of AHM is appropriate. For example, while only about half of patients were on AHM at end of study, it may be that all those not on AHM have adequate glucose control without AHM. Thus more attention is needed to this problem. The analysis could be revised to address this problem. First, the main analysis would classify patients into one of three baseline A1c categories: not available, below a cut-off for AHM initiation, above a cut-off for AHM initiation (8.0 might be a good cutoff because it is roughly the sample median, but the authors might want to set it lower based on guideline recommendations, or might want to have multiple A1c levels). This strategy would allow the main analysis to include the full study population (as opposed to eliminating 45% of patients), and would allow us to see what happens to those who do not have A1c readings. Most importantly, it would allow us to evaluate the current state of treatment in terms of adequacy of treatment.

4. The authors create age categories rather than using age as a continuous covariate. Creating categories generates measurement error and should not be used unless there is a rationale for doing so. I do not see the rationale for age categorizations and would recommend that the analysis treat age as a continuous covariate. The authors might want to test for a nonlinear association with age (e.g., quadratic and cubic terms). The age categories could still be used
for descriptive analyses (e.g., types of medication used for different age groups). Relatedly, it would be useful to know the HR (and CI) for age before and after adjustment for all other factors.

5. In testing for the interaction between age and A1c, I suggest that there the authors create two interactions: continuous age with A1c not available and continuous age with A1c above cut-off. The authors might also want to do a supplementary analysis looking only at those with A1c available and using an interaction term of continuous age and continuous A1c; this would be the most powerful and accurate test for the interaction of age with A1c level.

6. Ideally, the authors would investigate the impact of follow-up A1c levels on initiation of AHM. The authors specifically note that guidelines recommend obtaining follow-up A1c and basing initiation of AHM on those results. Yet we do not know whether those who are not on AHM at end of study are above the recommended A1c levels for AHM initiation. Again, this might be a subset of the study population, but this would be very useful information for interpreting the implications of the study results. If this is not done, the authors should indicate this as a limitation of the study.

7. On page 6 the authors describe the “baseline” A1c as “collected for the 6-month window centered on the index date…” Presumably this means 3 months before and after diagnosis – if so, please indicate. Using an A1c from after diagnosis seems a problem unless the authors are using this as part of the time-varying regression models. In fact, it the authors do not use A1c levels over time as one of the covariates in these models. This seems a serious omission and represents a major limitation of the paper’s findings. Much of what is attributed to other factors in the model may be due to unmeasured/unanalyzed A1c variability (i.e., the model is mis-specified).

8. Results, page 8: The authors report that HR for AHM in the different age groups depends on the cut-offs for A1c in the different age groups. It is not clear how this result was achieved. If this is clinically and/or statistically significant, the authors need to explain in the Analysis section how this analysis was performed, and why.

Minor Essential Revisions

9. Study Design and Patient Selection: Provide rational for why observation was terminated at two years post-diagnosis.

10. Sentence 1 of Analysis subsection: “The primary outcome was whether the patient initiated antihyperglycemic medication during the…”

11. Results, page 7: I would like to see a significance test for the relationship between age and medications prescribed. The simplest, most powerful and most accurate test would use the correlation between age and each type of medication.

12. Results, page 8: The authors indicate that one correlate of AHM initiation is
“hospitalizations (within 60 days preceding initiation)…” How was the time period selected, or was it? This should be explained in the methods. Also, in the same sentence the HR and CI are not reported for the new prescriptions other than AHM.

**Level of interest:** An article of importance in its field

**Quality of written English:** Acceptable

**Statistical review:** Yes, and I have assessed the statistics in my report.

**Declaration of competing interests:**

I consult with and have research funding from numerous pharmaceutical companies that market antihyperglycemic medications. The paper does not deal with specific medications per se, so the specific pharma do not seem relevant.