Author's response to reviews

Title: Factors associated with initiation of antihyperglycaemic medication in UK patients with newly diagnosed type 2 diabetes

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Version: 2 Date: 13 December 2011

Author's response to reviews: see over
December 13, 2011

Timothy Shipley, PhD
In-house Editor
BMC Endocrine Disorder

Dear Dr. Shipley:

On behalf of my co-authors, I am submitting our revised manuscript now entitled "Factors associated with initiation of antihyperglycaemic medication in UK patients with newly diagnosed type 2 diabetes" to be considered for publication. We appreciate the efforts of the reviewers have addressed their comments in our response document and within the manuscript. We feel that the comments have been fully addressed and hopefully the manuscript is now ready for acceptance.

I look forward to your decision on this manuscript.

Sincerely,

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Reviewer 1:

1) Missing values for HbA1c seem to be evenly distributed across age groups; a formal comparison should be reported.

Authors' response: Using a Chi-square analysis, no significant association was found between age and missing HbA1c values (p = 0.3876). This information was added to the Results section (p. 8). Furthermore, in the regression model, an interaction term for age and missing HbA1c values was also not significant; thus supporting the Chi-square analysis.

2) HbA1c at initiation of therapy could be a more interesting point than the first available HbA1c after diagnosis; many patients could have reached the target within a few months with nonpharmacological treatments only. I would suggest to verify the number of patients reaching HbA1c<7, <7.5, and <8% six months after diagnosis, and to evaluate the proportion who were prescribed a pharmacological treatments among those not reaching each target in different age groups. LOCF could be used for missing HbA1c values at 6 months.

Authors' response: Reviewer 2 had a similar comment (#6) but suggested looking at the HbA1c value and proportion of patients untreated after the 2-year follow-up period. Therefore, we addressed both reviewers' comments by stratifying the proportion of untreated patients by age and by last available HbA1c value. The analysis revealed that patients in the older age groups were more likely to remain untreated regardless of their last available HbA1c value. We added these new results (p. 10) in a figure (Figure 2; p. 21) to the manuscript.

3) I wonder if the database allows the calculation of a comorbidity score, e.g. the Charlson’s index; in that case, the index could be used as a confounder in multivariate analysis.

Authors' response: Instead of using a combined score as suggested, we put in all the related comorbidity conditions as individual terms within the model. The rationale is that a single score would not give you an accurate picture of which specific condition might be a main driver on the time to initiating antihyperglycemic treatment. Although we would lose some degree of freedom, we gain some insights on the most related conditions by including individual comorbidity conditions.
Reviewer 2:

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.

Authors' response: We appreciate the reviewer's comment and have referred to antihyperglycemic medication as the primary outcome. We also clarify that medication is synonymous with treatment and therapy in our discussion of the findings (p. 6).

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).

Authors' response: We revised the title and updated that abstract as suggested (pp. 1-2).

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.

Authors' response: Based on comments 3-5, we revised the model to include the following variables (stratified HbA1c as missing, <7.5%, and ≥7.5%; age as a continuous variable; and the proposed interaction terms between age and HbA1c cut off or missing). We selected 7.5% as this is the top of the HbA1c range for medical intervention per the UK NICE recommendations (p. 8).

The new results are consistent with the previous model that suggested older age is associated with longer time to treatment and a baseline HbA1c at least 7.5% was associated with shorter time to treatment. The interaction for age and HbA1c at least 7.5% was significant, suggesting that the influence of age on non-treatment was reduced as HbA1c increased above 7.5%. The interaction for age and HbA1c missing was not significant, suggesting the age and missing HbA1c values were not associated. This is similar to the Chi-square results reported in the response to question 1 from Reviewer 1. Table 2 was updated with the new results and the text was revised accordingly.
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.

Authors' response: See response to #3 above.

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.

Authors' response: See response to #3 above.

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.

Authors' response: In a new analysis, we addressed the reviewer's comments by stratifying the proportion of untreated patients by age and by last available HbA1c value. The analysis revealed that patients in the older age groups were more likely to remain untreated regardless of their last available HbA1c value. We added the analysis information to the Methods (p. 7) and the new results in a figure (p. 10 and Figure 2). Furthermore, among the untreated patients, the proportion with an HbA1c ≥7.5% was not statistically different across age groups (p>0.05). This information was added to the Results section (p. 10).
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).

Authors' response: The reviewer is correct in his assessment of the window. This window was selected to reduce the number a patients with missing HbA1c values near the index date. Further, the potential 3-month period beyond the index date was chosen because the full effect of any diet or exercise intervention was not likely attained within this short time period. This information has been added to the Methods section (p. 7).

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.

Authors' response: Since the updated model is using age a continuous variable, we deleted the "turn-around HbA1c values" and text from the manuscript.

Minor Essential Revisions

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

Authors' response: The 2-year follow-up period was selected to allow for sufficient time to initiate medication following guideline treatment recommendations, while also ensuring the largest cohort possible relative to using longer follow-up periods. The text was added to the Methods section (p. 7). Further, for example, if we added one more year of follow up the patient count would be reduced by 15-30% (p. 13).

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

Authors' response: The text was modified as suggested (p. 6).

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.

Authors' response: We performed a Chi-square test on the trend in selected treatments across age groups. The p-values for these tests have been added to the Results section (p. 9).
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.

Authors' response: This was an error in the previous version. The variable should have been any hospitalization during follow up and not within 60 days preceding initiation. Furthermore, we removed all HR and CI values in the text and refer the reader to the results in Table 2.