Reviewer's report

Title: What to do with diabetes therapies when HbA1c lowering is inadequate: add, switch, or continue? A MASTERMIND study

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Reviewer: Rohini Mathur

Reviewer's report:

This is a cohort study utilizing the CPRD to investigate treatment response following the continuation, addition, or switching of glucose lowering treatment in individuals with no or poor response to initial treatment. The authors found that 21.9% of individuals commencing a 2nd or 3rd line non-insulin therapy experienced treatment non-response and that addition of a new therapy was associated with the largest HbA1c reduction as compared to continuing or switching treatment.

The authors have addressed a very important issue facing practitioners today - this question is of interest to both general practitioners, commissioners, and policy makers. The language is clear and the methods are appropriate. The subgroup and sensitivity analyses using propensity score matched analysis and matching by medication class/line add useful weight to the conclusions.

My questions, comments, and suggestions are mainly around the reporting of the study - particularly around the clarity of the methods.

1. In the aims and methods - you state the cohort is drawn from individuals who had either worsening or limited improvement in HbA1c 6 months after starting an additional glucose therapy- does this mean that individuals initiating first line glucose lowering therapy for the first time following initial diagnosis were not part of the study cohort? The wording is unclear as to whether this cohort of initiators is eligible (I think that they are, but this needs to be expressed more clearly if this is the case).

2. The methods section does not clearly state the study design at any point, not the time period from which the participant were drawn from the CPRD (Were people with incident diabetes drawn from the whole dataset from 1989 onwards?) The methods later state that the drug data was drawn from the time period 2004-2017 - I think it would be clearer to state the time period up front, or just be clear about the cohort derivation period vs. treatment period of interest.
3. The authors state the an algorithm was used to identify incident diabetes diagnoses- did the authors do anything to reduce the likelihood of individuals with prevalent diabetes (with unknown diagnosis date) being included? for example - requiring 12 months continuous registration in CPRD prior to diabetes first diabetes diagnosis date.

3. The wording of the methods section makes it difficult to discern the order of events - I think a diagram, or some re-ordering would help with this. Some but not all aspects of this are captured in the flowchart - so this could be expanded, or an additional figure created for the appendix.

As I understand it:

a) People start a new glucose lowering therapy - The latest HbA1c in the 6 months prior to that is the baseline HbA1c

b) Response to the initial new treatment is measured 6 months after treatment start (initial treatment response/six-month outcome HbA1c? Keeping the terminology consistent would help here)

c) those with limited/no treatment response then form the cohort of interest

d) Treatment continuation/switch/add status is determined 12 months after the initial treatment response HbA1c

e) Outcome HbA1c is measured 12 months after continuation or 6 months after addition/switch

d) The main study outcome of interest is the difference between the outcome hbA1c and the initial treatment response HbA1c

4. The study was limited to individuals with complete HbA1c data - though you cannot extrapolate the findings to these groups of people - is there some data on the characteristics of the excluded groups (perhaps at baseline) to better understand the limits of generalizability of the findings.

5. The finding that adding treatment was associated with the largest improvement in hbA1c, is perhaps unsurprising. The discussion section may benefit from a bit more discussion about the clinical implications of the findings for general practitioners and diabetes care specialists. The point made about clinical inertia is useful - but how do these data support potential changes to clinical management of diabetes - given that large variability of HbA1c can lead practitioners
potentially to continue ineffective therapy. What is the key takehome message for the target audience of this work?

6. I think the figures reporting the change in HbA1c would benefit from reporting the actual numbers and confidence intervals, perhaps in a table below the figure, or in-line with the image somewhere.

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

No

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?
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