Author’s response to reviews

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

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Reviewer reports:

Reviewer #1: 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.
Author responses >> We thank the reviewer for their kind comments and detailed review of our paper. We have attempted to address all their points below.

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).

>> We thank the reviewer for highlighting this point. This group (people stating first line diabetes treatment) was not included as the majority of people initiating first line therapy start metformin. UK guidelines (and international guidelines) recommend dose up titration rather than adding or switching when there is a limited initial response. This can often take many months. In addition metformin is also often started close to diagnosis and the rapid changes in glucose around this time (including the influence of dietary and lifestyle changes) may make it difficult to interpret HbA1c response. We therefore limited our analysis to the response to second and third glucose lowering medications. We have clarified this point in the manuscript (Research design and methods section, paragraph 1; pg 3) and explained the rationale (Research design and methods section, Setting and participants subsection, Paragraph 2; pg 4).

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.

>> Thank you. We have moved the last line of the introduction to the start of the methods to clearly state the study design and added the study dates:

“We conducted a retrospective cohort analysis of 55,530 people with type 2 diabetes starting a second or third ever glucose lowering medication between 2004 and 2017 inclusive. We analysed those who had either a worsening or a limited improvement in HbA1c (HbA1c fall <5.5mmol/mol [0.5%]) six months after this additional glucose lowering therapy. We compared the subsequent glycemic outcomes in those who continued therapy unchanged, switched to an
alternative therapy, or added an additional agent.” (Research design and methods section, paragraph 1; pg 3).

In addition we have also expanded on the explanation of the cohort derivation period: We included all people with T2D from CPRD regardless of the date of diagnosis. But, as previously stated, only included those initiating a second or third medication between 2004-2017. We hope that the updated text adds clarity here (Research design and methods, Setting and participants, paragraph 1; pg 4).

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.

>> Yes. We required no measured HbA1c values within the diabetes range, no diabetes medication prescriptions, and no diabetes diagnosis codes recorded, within three months of the current registration date. This is described in the cited cohort profile paper but now also added to this manuscript for completeness (Research design and methods, Setting and participants, paragraph 1; pg 4).

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

>> Thank you. The reviewer has described the order of events is correctly. We agree that making this element of the study design as clear as possible is very important.

In order to clarify this we have updated Figure 1 and made some modifications to the text in the methods under a new subsection title “Identification of participants with limited initial HbA1c response to second and third line glucose lowering therapy” (Research design and methods, Identification of participants with limited initial HbA1c response to second and third line glucose lowering therapy; pg 4). We have also ensured that we refer to the HbA1c described in (b) above as “initial treatment response HbA1c” consistently throughout the paper.

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.

>> We agree that this is an important consideration. We have therefore added an additional supplementary table (Supplementary Table 10) to compare the characteristics of those eligible for inclusion with those excluded.

We also describe this in the methods (Results, Subgroup and sensitivity analyses, Paragraph 4; pg 6) results (Results, Subgroup and sensitivity analyses, Paragraph 4; pg 8) and discussion (Discussion, Paragraph 3; pg 9)

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 takeaway message for the target audience of this work?
Thank you.

Our results show that drugs should not be stopped on this basis of apparent poor initial response. The take home message is that a single HbA1c measure cannot be used to judge if treatment is effective, this strategy should not be included in clinical guidelines: glucose lowering medication should be continued (where tolerated) even if initial HbA1c does not appear to improve. We have modified the paper to clarify and emphasise these messages: (Discussion, Paragraphs 1 and 5; pgs 9 and 10). We have also updated the conclusion in the abstract and end of the paper to highlight the take-home message:

“Where a glucose lowering therapy does not appear to be effective on initial HbA1c testing, changing agents does not improve glycemic control. The initial agent should therefore be continued (where that agent is tolerated) and additional therapy added.”

We have also removed some material from the discussion which may have been detracting from the message.

While this result is perhaps not unsurprising if you are aware of the intrinsic high variability of HbA1c in those on stable glucose lowering therapy, it is contrary to many clinicians’ (and guideline writers’) assumptions. If those who initially get worse on a treatment (as selected in our study) really were ‘non responders’ then this treatment could be stopped without diminishing glycaemic control. Therefore adding a therapy and continuing the previous ‘ineffective’ medicine would not be substantially more effective than adding therapy and stopping the previous ’ineffective’ medication. A major question is whether any therapies really are ‘ineffective’ in some individuals – ie are there truly biological ‘non responders’ to a therapy. While our analysis suggests that this is not the case (or at least if non responders do exist they cannot be identified from a single on treatment measurement), we cannot robustly answer this from this dataset: HbA1c testing is performed infrequently in routine clinical care, it is not possible to know if patients are truly taking therapy (we can only assess medication possession), and extra treatment will in most cases be added where HbA1c remains high on repeated measurements. To fully address this question we would, in our opinion, need a cohort with frequently measured HbA1c, robustly assessed adherence, and a lack of up titration of therapy in those with poor glycaemic control on repeated HbA1c measurements. This would allow assessment of whether multiple HbA1c measures might be used to robustly identify individuals with poor response.
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.

>> We have added the patient numbers to each group to all figures and ensured that all figures have appropriate confidence intervals.

Reviewer #2: This study attempts to answer the important clinical question - what to do if a patient with T2DM shows an inadequate response to addition of a new therapy to existing treatment? The data suggest that the best strategy is probably to add additional therapy rather than to switch treatment, as this policy does not seem to result in a greater improvement in HbA1c, compared to simply continuing the apparently ineffective treatment.

The study also confirms previous data showing that treatment escalation is often significantly delayed in UK primary care (clinical inertia).

Have the authors considered looking at HbA1c trajectory in the period prior to starting new therapy in this analysis? It is possible that those patients who showed an inadequate response to therapy were in fact on a steeper upward trajectory of HbA1c at the time of addition of the new treatment compared to those who showed an improvement.

>> We thank the reviewer for their detailed review of our paper. The limitation of this additional suggested analysis would be that requiring multiple HbA1c measures (on stable therapy) prior to the initial response episode which would potentially create substantial selection bias. Our results suggest that rapid progression is unlikely – if this was the case these participants would have deteriorated further if no additional treatment was added, however our results are contrary to this with a small improvement in HbA1c on repeat therapy in those who continued exiting glucose lowering therapy without changes. This is consistent with random (non-treatment related) variation in HbA1c being a major contributor to initial ‘poor response’, with subsequent regression to the mean explaining the subsequent improvement in HbA1c despite glucose lowering therapy remaining unchanged.

The policy of switching therapy with inadequate response could be related to the patient experiencing an adverse event or not tolerating a particular medication rather than an inadequate biological response. Although this information cannot easily be extracted from CPRD data, it
would be worth mentioning this in the discussion and if possible investigating if coding consistent with side effects was the reason for switch in some patients?

>> Thank you. This is an interesting and important point. In our understanding from the point of view of our analysis and primary question the reason for stopping or continuing a therapy is not necessarily important, except in relation to underlying treatment adherence. For example our analysis would be equally valid if the clinician stopped the therapy because of a safety warning, or because HbA1c did not improve, it is the effect of this treatment decision that is important to our research question. However a potential bias could result if those stopping had higher rates of non-adherence (e.g. because of side effects) that those continuing or adding: non-adherence would be a stronger contributor to observed poor response in the ‘switch’ than add and continue groups. We have attempted to address this though including only those adherent using medication possession ratio, however we accept this measure has clear limitations (picking up prescriptions does not necessarily equate to taking the medication). We have therefore added this limitation to the discussion section of the paper as well as describing the lack of data available on the rationale for the treatment choice (continue, switch, or add) (Discussion, Paragraph 3; pg 9).

CPRD data was included from a 2004 to 2017. There have been substantial changes in practice over that time with reduction in use of TZDs (and withdrawal of rosiglitazone), and introduction of several new classes (DPP4i, GLP1RA and SGLT2i). Is there any evidence that the proportion of patients who show inadequate response has changed over time? Could a large number of people switching from rosiglitazone when it was withdrawn have influenced the results?

>> We agree that this is a very interesting area. Especially with regards to the change in response over time. We included year of treatment, a priori, as a covariate in our models to account for a possible change in response by year. We found that increasing year of treatment was associated with a very modest although clinically insignificant, worsening of response to treatment choice (add switch, or continue); 0.12 (0.03, 0.21; p=0.011) mmol/mol/year) [Supplementary table 2]. However, we have limited our analysis to this at the moment, as we have carried out substantial further work addressing this question separately as part of another project. This is being reported in another paper under peer review elsewhere, which we hope will become available soon.
With regards to the withdrawal of pioglitazone: in our understanding the main implication of discontinuations due to rosiglitazone withdrawal would be possible over-reporting of discontinuation rates. All participants included in this analysis had poor initial response to glucose lowering therapy at six months. As discussed above in our understanding whether a clinician changed treatment because of safety concern or poor response would not be expected to effect the glycaemic impact of that treatment change, and therefore would not influence our key analysis.