Author's response to reviews

Title: Severe hypoglycemia symptoms, antecedent behaviors, immediate consequences and association with glycemia medication usage: secondary analysis of the ACCORD Clinical Trial data

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Author's response to reviews: see over
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Editor (s), BMC Endocrine Disorders

Dear Sirs and Madams,

We respectfully submit the revised manuscript “Severe hypoglycemia symptoms, antecedent behaviors, immediate consequences and association with glycemia medication usage: secondary analysis of the ACCORD Clinical Trial data”. We have carefully read and addressed all of the reviewers’ concerns on the attached pages and believe the paper is improved because of their thoughtful comments.

Please do not hesitate to contact me if I can be of any assistance. My telephone number is 301-435-0379 and my email is bondsde@nhlbi.nih.gov.

Sincerely,

Denise E. Bonds, MD, MPH

Medical Officer
Response to reviewers:

Reviewer 1:

1. Did the authors use a validated method for classification of hypoglycemic symptoms as being autonomic or neuroglycopenic - e.g. The Edinburgh method?

   When notified of a severe hypoglycemic episode, the study staff asked the participant if they had experienced any of 11 symptoms (shaky, fast heart beat, sweating, weakness/fatigue, dizzy, anxious, hungry, confused/disoriented, blurry vision, headache, irritable). More than one symptom could be checked. Classification into autonomic or neuroglycopenic was done post hoc at the time of writing. Symptoms that are classified in our discussion section (page 11, paragraph 2) do correspond with the Edinburgh system of classification as described by Deary et al in their 1993 paper published in Diabetologia.

2. The fraction of episodes with possible contribution from alcohol is quite low. How was alcohol involvement assessed?

   At the time of reporting of the hypoglycemic episode, the study staff were asked to determine the circumstances surrounding an event and to indicate which activities and circumstances from a checklist were antecedent. Ingestion of alcohol was included as a possible antecedent. Since the study staff relied on participant self-report for determination of antecedents, it is possible that the low reporting of alcohol ingesting represents under-reporting by participants. We have added this to the discussion section as a possible limitation (page 13, paragraph 2):

   Symptoms, antecedents and consequences of the hypoglycemic events rely to some degree on patient self-report and thus may be subject to under or over-reporting.

3. I suppose that co-medications were recorded. Were there any influence of use of psychoactive drugs? By classes of antihypertensives or by women's use of P-pills?

   Classes of concurrent medications were collected at the annual visit for all participants. Participants were instructed to report severe hypoglycemic events to their study site immediately. At the time of reporting, an updated list of concurrent medications was not entered into the ACCORD database. The list of potential antecedents and circumstances on the data collection form for severe hypoglycemia did include
   
   “started on or increased dose of:
   
   beta blocker,
   ACE inhibitor,
   angiotensin receptor blocker,
   other drug reported to cause hypoglycemia (e.g. quinine, pentamidine)”

   As described in table 2, only 2% of participants in the intensive glycemia group and 8% of the participants in the standard group had this listed as a possible antecedent. While this was different by study intervention group, in comparison to other antecedents, it was a relatively infrequently reported activity. We have added a statement describing this to the discussion section (page 11, paragraph 1):
At the time of reporting severe hypoglycemic events, participants and staff were also asked about changes in medications that were not used to treat diabetes but known to lower blood glucose. While there was differential reporting of these as antecedents between the intensive interventional study group and the standard interventional study group, overall, this was infrequently listed as an antecedent.

4. Use of TZDs was associated with severe hypoglycemia in both treatment groups with HRs comparable to those of the insulins. This is very intriguing and deserves further attention in the discussion, particularly as the opposite was observed for biguanides. Confounders or potential mechanistic explanations?

_We agree this is an intriguing finding and have added to the discussion (page 12, paragraph 2):_

Although the mechanism for this finding is not clear, it is possible that the insulin sensitizing action of the TZD accentuates the risk of hypoglycemia of insulin when these two are used in combination. Alternatively, rosiglitizone has been shown to preserve and possibly improve pancreatic beta cells function. This preservation/improvement in the responsiveness of the beta cells in combination with exogenous insulin and improved insulin sensitivity could lead to increased risk of hypoglycemia.

_Reviewer 2:_

The only revision I would recommend it to clarify language both in the abstract and body of the document where the term INT and STD are used without a clear explanation that they mean INTERVENTION Group and STANDARD treatment.

_We thank the reviewer for this suggestion and have clarified the abstract to make it clearer for the reader (page XX):_

_Background:_ Hypoglycemia is a common complication of diabetes treatment. This paper describes symptoms, predecessors, consequences and medications associated with the first episode of severe hypoglycemia among ACCORD participants with type 2 diabetes, and compares these between intensive (Int: goal A1C <6.0%) and standard (Std, goal A1C 7-7.9%) glycemia intervention groups.