EDITORIAL (SEE RIDDLE ET AL., P. 983)

ACCORD Glycemia Results Continue to Puzzle

"If I had a world of my own, everything would be nonsense. Nothing would be what it is, because everything would be what it isn't. And contrary wise, what is, it wouldn't be. And what it wouldn't be, it would."

This quote by Alice from the Disney film version of *Alice in Wonderland* by Lewis Carroll may make sense in the world she experiences. In our world, Alice's wish is usually not fulfilled, but some findings of the Action to Control Cardiovascular Disease in Diabetes (ACCORD) glycemic control study may be an exception.

The report by Riddle et al. (1) in this issue of *Diabetes Care* attempts to explain in an observational post hoc analysis of the ACCORD trial whether features of glucose control explain the higher observed death rate in the intensive compared with the standard glycemic control treatment arms (2). All the provisos associated with observational research must be kept in mind when interpreting this analysis, which does not have the same high standard of evidence as testing prespecified hypotheses of a randomized controlled trial. The ACCORD trial assessed the effects of several interventions directed at blood pressure, dysipidemia, and hyperglycemia on diabetes outcomes. The results of the glucose control aspect of the trial defied expectations when it was announced that the intensive glucose control arm was prematurely terminated due to higher mortality associated with assignment to this treatment. Because the target A1C in this arm was normoglycemia, i.e., an A1C <6.0%, the number one suspect has been that hypoglycemia explains the greater event rate noted with intensive therapy. The result reported by Riddle et al. in this article, though, is not what was expected and would please Alice. Overall, they found no evidence to suggest that lower average A1C was associated with higher mortality, as would have been expected if hypoglycemia had been the cause of death. In fact, a higher mortality rate was observed in both the intensive and standard therapy arms for individuals with a higher average and last recorded A1C. This result was statistically significant in the intensive treatment arm only, and the authors also observed a significant interaction such that the magnitude of this effect in the intensive treatment arm exceeded that seen in the standard arm beyond what would be expected by chance. The fitted plot of mortality hazard ratio by study average A1C in Fig. 1 supports the presence of a linear association between these measures in the intensive treatment arm (1).

The ACCORD trial attempted to quickly achieve the target A1C in the intensive treatment arm, as demonstrated by the precipitous decline in this measure occurring during the first year of the trial (supplemental Fig. A1, available in an online appendix at http://care.diabetesjournals.org/cgi/content/full/dc09-1278/DC1) (1). Hence a too rapid drop in A1C became another suspect for the higher mortality rate and led to an examination of change during the first year and even the first 4 months of the trial as predictors of mortality. In all these comparisons, a decline in A1C was associated with a lower risk of mortality, which was statistically significant for the 1-year difference only, as opposed to the higher risk that would have been expected if an early rapid reduction in A1C had been responsible for excess mortality. An examination of event rate versus study time (supplemental Fig. A2) also argues against an early excess mortality with intensive treatment (1). The excess mortality in the intensive arm does not appear until after year 2. Figure 2 provides general support for the finding of lower mortality associated with a decline in A1C, but also portrays in the intensive arm only a higher risk of mortality among individuals whose A1C did not change or increased somewhat (1). This finding suggests that lack of response to an intensive glucose control strategy may lead to a higher event rate in this population, or, alternatively, that the lack of response identifies individuals at higher risk for mortality for reasons unrelated to the treatment strategy.

The analysis of Riddle et al. confirmed the results that we all would have expected regarding lower mortality associated with better glycemic control, except for the main outcome of interest, which went in the opposite direction. Of course, there are other questions that quickly come to mind regarding hypoglycemia in this trial. Was hypoglycemia directly implicated in the deaths of subjects? Does the lower A1C expected in the intensive treatment arm predict a higher risk of hypoglycemia? The ACCORD investigators have already examined these issues in publications that will have appeared by the time this editorial is published. The results of these analyses continue to run counter to what we would have expected and fail to support hypoglycemia as the cause of the excess number of deaths in the intensive treatment arm. Of the 10,194 subjects in the ACCORD study who had at least one assessment for hypoglycemia, 451 deaths occurred to the time that the study was terminated, but only 1 was adjudicated as being directly related to hypoglycemia (3). More hypoglycemic events occurred in the intensive treatment arm, and a higher risk of mortality was seen in individuals who experienced one or more of such events. Yet the proportion of deaths that could be attributed to hypoglycemia was low and of similar magnitude in the intensive (5.9%) compared with the standard (5.1%) treatment arms. Regarding the prediction of hypoglycemic events, the ACCORD data demonstrated that these events increased in frequency with poorer glucose control as reflected by greater average A1C over the course of the study in both treatment groups, not lower values as one might have expected (4).

So, to reiterate, a clinical trial of intensive glucose control resulted in higher mortality due to the intervention. Reasonable assumptions to explain this finding include *1*) better glucose control results in hypoglycemia, 2) hypoglycemia results in an excess of deaths, and 3) better glucose control is related to higher mortality. None of these is what it is. A clue, if there is one to be found, may be the higher mortality associated with resistance to glucose control seen in Fig. 2. Whether continuing to pursue intensive treatment in patients in whom no im-

provement in glucose control leads to more harm than good should be pursued as a possible explanation for the puzzling findings of ACCORD and an exit for us all out of Wonderland.

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