Journal of Diabetes Science and Technology
Volume 2, Issue 3, May 2008

LETTER TO THE EDITOR

Regarding the Announcement to Halt the Intensive Glucose Lowering Arm of the Action to Control Cardiovascular Risk in Diabetes

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An announcement to halt the intensive glucose lowering arm of the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial has received tremendous press recently. The basis for stopping the trial was that more deaths from cardiovascular events were noted in the treatment group.[1] No specific cause has been identified as yet. Past studies that aimed for "tight" control such as the Diabetes Control and Complications Trial (DCCT)[2] have concluded that lower hemoglobin A1c levels were associated with improved cardiovascular health. The new findings appear to contradict this conclusion. One important difference in the ACCORD trial is the study population. In the DCCT trial, exclusion criteria eliminated concurrent hypertension and hyperlipidemia, whereas in the ACCORD study, one of the objectives was to examine the effect of intensive glycemic lowering in subjects who had concurrent hyperlipidemia and hypertension. A known mathematically described principle in control engineering (conservation of uncertainty) states that every connected system has a conserved or constant amount of uncertainty and that attempts to rein in more certainty in one area automatically create uncertainty in another area. When applying this principle to physiology, and in particular the ACCORD study, it is conceivable that attempts to constrain or increase certainty in glycemic control, blood pressure, and hyperlipidemia all at the same time, may be inducing uncertainty or vulnerability in other physiological functions, potentially resulting in a catastrophic event. For a review of this principle, refer to the Journal of Diabetes Science and Technology commentary article.[3]

In light of recent ACCORD findings, it will be important to consider a range of potential mechanisms and explanations that may be at play. The conservation of the uncertainty principle, in fact, predicts the consequences resulting from restricting the system's range of physiological responses. These consequences might include increased fragility in the microvasculature, leading to myocardial infarction, stroke, or unwanted adverse effects, such as increased risk of hypoglycemia or other neuroendocrine problems. A precise event cannot be specified without a detailed model of the system's complete physiology. Moving forward, when dealing with the complexity of several interconnected physiological functions, careful consideration should be given to studying the system biology along with the specific molecular and cellular mechanisms.

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Keywords: ACCORD, DCCT, glycemic control, hyperlipidemia, hypertension

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