

# Counterpoint: Intensive Glucose Control and Mortality in ACCORD—Still Looking for Clues

Early cessation of the intensive glyce-mic treatment arm of the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial because of a 22% excess of all-cause mortality compared with the standard arm (1) came as an unpleasant surprise to many observers. Since then, considerable discussion of the significance of this result has ensued along with various theories as to why it occurred. In the companion article, a respected statistician, John Lachin, proposes yet another hypothesis: that the finding was due to the play of chance (2). In response, this article will address three related issues: 1) Dr. Lachin's hypothesis; 2) a review of findings of post hoc analyses of the ACCORD data seeking support or lack of support for the other main theories; and 3) my own opinions on why continued study of the ACCORD data are needed, including a reformulation of one of the original theories regarding the cause of excess mortality.

## The play-of-chance hypothesis

"How often have I said to you that when you have eliminated the impossible, whatever remains, however improbable, must be the truth?" asked Sherlock Holmes of Dr. Watson in *The Sign of the Four* (1890).

Dr. Lachin's exposition of the theory that the apparent excess of mortality in ACCORD was due to the play of chance is very welcome. This possibility has not previously been given enough attention. The excess of deaths with the intensive glyce-mic treatment strategy was indeed not large, a 22% relative increase from 1.1 to 1.4% of participants affected per year (1). In absolute terms, it was 257 versus 203 deaths or an excess of 54 among 10,251 study participants. Had this been the primary end point, a direct comparison would have shown the level of statistical significance generally regarded as conclusive. But it was not the primary end point and repeated measurements were made, increasing the likelihood of drawing an erroneous conclusion. However, this proposal cannot be evaluated without

context. The quotation above from Sherlock Holmes (alter ego of the author Dr. Arthur Conan Doyle) describes this dilemma. If other explanations are proven extremely unlikely, then the play-of-chance hypothesis looks good. The main hypotheses to explain excess mortality with intensive glyce-mic treatment in ACCORD have concerned: 1) an overly rapid reduction and maintenance of low A1C levels; 2) effects of severe hypoglycemia; 3) high doses of potentially harmful individual drugs or drug combinations; or 4) weight gain with its own harmful consequences. Because we have not eliminated some of these plausible mechanisms, it seems premature to put play-of-chance at the top of the list. But surely it belongs on the list, so we'll add: 5) a play of chance.

Considering the above, is there reason to think the Data and Safety Monitoring Board (DSMB) was in error in advising that intensive glyce-mic treatment be halted? I think clearly not. The DSMB's charge was to protect the participants' collective safety by reviewing data currently available, identifying trends, and assessing future possibilities. Its members had no way to know whether or not a specific cause for excess mortality would be found, and no statistical formula could perform the task required. As Dr. Lachin correctly points out, their recommendation to halt the study on the basis of the information then available cannot be criticized.

## What we have learned so far from post hoc analyses in ACCORD

"I have devised seven separate explanations, each of which would cover the facts as far as we know them. But which of these is correct can only be determined by the fresh information which we shall no doubt find waiting for us," said Sherlock Holmes to Dr. Watson in *The Adventure of the Copper Beeches* (1892).

Of the four original hypotheses regarding causes of excess mortality, two have not yet been adequately studied. These are the potential effects of specific

drugs or drug combinations and the effects of weight gain. The hypothesis that has been most helpfully addressed by post hoc analyses is that rapid reduction and maintenance of low A1C levels was harmful. The rationale for ACCORD came from prior epidemiologic findings that greater degrees of hyperglycemia in type 2 diabetes subjects, reflected by higher A1C, correlated with higher risk of both cardiovascular death and nonfatal cardiovascular events (3). Epidemiologic analysis of data from the truncated period of randomized treatment has confirmed this relationship (4). This presents a paradox: higher A1C is associated with higher risk, yet a treatment strategy that maintained median A1C at 6.4% led to higher risk compared with one keeping median A1C at 7.5%. The paradox is partly resolved by the further finding that the intensive strategy significantly changed the relationship between A1C and risk of death (interaction  $P < 0.0007$ ). The association of higher A1C with higher risk was stronger with the intensive strategy (hazard ratio for 1% higher updated average A1C 1.66,  $P < 0.0001$ ) than with the standard strategy (1.14,  $P = 0.17$ ) (4). The participants seeking near-normal glyce-mic control who had average A1C below 7% were not the ones with increased risk, but rather it was those with higher values. Further analyses showed that individuals who failed to reduce A1C from baseline values when attempting the intensive strategy seemed at greater risk (4). These findings reject the rapid-A1C-reduction hypothesis.

Examination of the association between severe hypoglycemia and mortality has not supported the view that hypoglycemia is a likely mediator of harm with intensive treatment (5,6). Severe hypoglycemia was infrequently associated with death in either arm in ACCORD. Having had a severe hypoglycemic event did increase risk of later death with both intensive and standard treatments, but participants using the intensive strategy who had at least one severe event were less likely to die at a later time than those

using the standard treatment who had experienced a severe event. This observation fails to confirm the hypoglycemia hypothesis but may not exclude it entirely.

### Why keep trying to find a cause?

If the 22% increased risk of death accompanying the intensive treatment strategy is potentially due to chance alone, why continue looking for other possible causes? A short answer to the question is that there are other plausible explanations. A longer answer must include the entire rationale for performing clinical trials. A well designed trial is intended to answer one primary question but can further contribute by posing additional hypotheses. In the case of the UK Prospective Diabetes Study (UKPDS), the question was whether intensified treatment with single-agent pharmacotherapy shortly after diagnosis of type 2 diabetes would reduce microvascular or cardiovascular complications of the disease. The randomized treatment period confirmed microvascular but not cardiovascular benefit (7). However, other analyses made major contributions: defining the progressive course of type 2 diabetes (8), confirming longer-term cardiovascular benefit (9), demonstrating persistence of microvascular benefit long after cessation of intensified treatment (the legacy effect) (9), and suggesting unique cardio-protective effects of metformin (10). These insights were the products of secondary, post hoc, or epidemiologic analyses, but they have guided subsequent studies and clinical decisions. In the case of ACCORD, all three parts of the trial (glucose, blood pressure, and lipid interventions) tested whether very intensive regimens could limit rates of cardiovascular events more than standard therapies in a population of patients with high cardiovascular risk and long-duration type 2 diabetes. None of the intensive interventions had a significant effect on the primary end point, a composite of all-cause mortality, nonfatal myocardial infarction, and nonfatal stroke (2,11,12). One logical interpretation of these findings is that established cardiovascular disease in diabetes is not easily reversed. In this way overt cardiovascular disease may be similar to established diabetic nephropathy, the effects of which can be mitigated by various means but the condition itself cannot be reversed by treatment of hyperglycemia or hypertension. However, like UKPDS, ACCORD

is likely to advance our understanding and treatment of type 2 diabetes in other ways. For example, drawing on the insights of both UKPDS and ACCORD (and also the Diabetes Control and Complications Trial [DCCT]), we now have reason to ask whether very early intervention in type 2 diabetes can establish a positive legacy effect by preventing the earliest injury to tissue by glycation or oxidative stress, thereby delaying or minimizing later cardiovascular risks that may prove irreversible.

In the shorter term, two additional hypotheses may be refined by further analyses of data from ACCORD. The first concerns the apparently vulnerable subgroup of patients who, when attempting the intensive glycemic treatment strategy, were unable to reduce A1C and maintain it below 7%. Defining that subgroup and identifying what features contributed to higher risk of death would be a significant contribution, perhaps leading to new tactics in managing type 2 diabetes. If different therapeutic targets are appropriate for different groups of patients, finding ways to assign individuals to the right category would also permit new forms of treatment to be tested.

A second hypothesis concerns the role of hypoglycemia, which cannot be entirely dismissed as a contributor to risk in such patients. Beside the main observations regarding severe hypoglycemia reviewed above, there were other notable findings. The risk of severe hypoglycemic events was epidemiologically associated with higher rather than lower A1C values in both arms of the study (6). This surprising pattern has been reported in other studies (13,14) and draws further attention to those individuals attempting intensive treatment whose A1C levels remained above 7% and who appeared at greater risk of death. Also, study of reports of nonsevere hypoglycemia from a subset of participants who also reported at least one severe hypoglycemic event suggested that prior minor hypoglycemia might be protective against later death (5). A potential mechanism for such an effect is known. Repeated mild or moderate hypoglycemia can suppress the usual response of catecholamines, which causes the most apparent symptoms of hypoglycemia and also contributes to the return of plasma glucose toward normal levels (15). Usually this syndrome of "hypoglycemia unawareness" is considered harmful in predisposing to severe events that can lead to automobile accidents or other

serious injuries. However, blunting of catecholamine responses may have a protective effect as well by limiting the risk of potentially fatal arrhythmias during a later more serious hypoglycemic event. Minor hypoglycemia was very common during intensive glycemic treatment in ACCORD. Is it possible that isolated severe hypoglycemia, not preceded by minor hypoglycemia, could be a mediator of excess mortality in the individuals attempting intensive treatment but continuing to have elevated A1C? The hypoglycemia hypothesis for excess mortality in ACCORD may need to be modified to include the phenomenon of "hypoglycemic preconditioning." Clarification of such physiologic mechanisms may lead to improved tactics, in addition to graded targets, for the treatment of high risk individuals with type 2 diabetes.

In summary, the possibility that the excess mortality accompanying intensive glycemic treatment in ACCORD was due to chance cannot be excluded. However, other candidate mechanisms have not yet been convincingly excluded either. Further study of the large and excellent database from ACCORD may provide further clues on this point and, more generally, is likely to guide important changes in the therapy of type 2 diabetes. Among these are earlier intervention to preclude cumulative tissue damage from hyperglycemia, identification of lower versus higher risk subgroups that require specific glycemic treatment targets and tactics, and perhaps a broader understanding of the role of hypoglycemia in cardiovascular risk.

MATTHEW C. RIDDLE, MD

From the Oregon Health & Science University, Portland, Oregon.

Corresponding author: Matthew C. Riddle, riddlem@ohsu.edu.

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