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Editorial

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ACCORD: More data, more debate

The intensive blood glucose-lowering arm of the ACCORD (Action to Control Cardiovascular Risk in Diabetes) trial was discontinued at 3.5 years of study duration due to an unexpected increase in mortality in the standard therapy arm (hazard ratio [HR], 1.22; 95% confidence interval [CI], 1.01–1.46; *P*=0.04; ACCORD Study Group et al, 2008). In the intensively treated participants, within 4 months of randomisation, the median HbA_{1c} level had decreased from a mean of 8.1% (65 mmol/mol) at baseline to 6.7% (50 mmol/mol) in the intensive-control group and to 7.5% (58 mmol/mol) in the standard group. Median HbA_{1c} levels were stable at 6.4% (46 mmol/mol) and 7.5% (58 mmol/mol) in the respective groups over the next year and remained so until the termination of the intensive-treatment arm. At the termination of the intensively treated arm, participants in that arm were transferred to the standard therapy protocol. Consequently, mean HbA_{1c} increased from 6.3% (45 mmol/mol) to 7.2% (55 mmol/mol) in that group.

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Prior to the intensive therapy arm being terminated, both groups were similar in their rates of the primary outcome (a composite of non-fatal myocardial infarction, non-fatal stroke, or death from cardiovascular causes), but with more deaths of any cause (albeit predominantly cardiovascular causes; HR, 1.22; 95% CI, 1.02–1.44), and fewer non-fatal myocardial infarctions (HR, 0.79; 95% CI, 0.66–0.95), in the intensively treated arm. While there were significant differences in the mortality between the intensive and standard groups, it is also pertinent to remember that people in the intensive-treatment arm also had higher rates of hypoglycaemia (3- to 4-fold), increased weight gain (>10 kg in 25% of the group) and greater fluid retention.

A recent study documents the 5-year follow-up of the ACCORD cohort (ACCORD Study Group et al, 2011). This study demonstrates that the 2008 report's trends in mortality persisted during the whole follow-up period, with the HR for death remaining higher – and the HR for non-fatal myocardial infarction remaining lower – in the previously intensively treated participants when compared with the standard therapy group. This was despite the increase in HbA_{1c} experienced by the group following their transfer to standard therapy at 3.5 years post-randomisation. The authors concluded that intensive blood glucose-lowering therapy for 3.7 years to a target HbA_{1c} of <6% (<42 mmol/mol) reduced 5-year non-fatal myocardial infarction rates, but increased 5-year mortality. Consequently, such a strategy has not been recommended for people with advanced type 2 diabetes at high cardiovascular risk, as those recruited into the ACCORD study were.

The reasons behind these findings in the ACCORD cohort – particularly the higher mortality in the intensive-therapy group after reassignment to standard therapy – remain unclear and considerable effort has been made to explain them. A range of hypotheses to explain the excess mortality in the intensive glycaemic control arm have been suggested.

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These include:

- That a rapid reduction in HbA_{1c} levels – in some participants very low glycaemia was achieved within 4 months of intensive therapy commencement – confers increased cardiovascular risk.
- That severe hypoglycaemia associated with intensive blood glucose-lowering increases cardiovascular risk.
- That individual antidiabetes agents, or combinations of them, may be harmful.
- That the increased mortality is attributable to weight gain per se.
- That a significant increase in mortality in this cohort was the result of chance.

While the effects of specific therapies or therapeutic combinations and the effects of weight gain per se have not yet been adequately evaluated, some of the other hypotheses listed above have received significant post hoc analysis. These analyses have demonstrated an association between higher HbA_{1c} levels and higher cardiovascular risk in both the intensively and standard treated arms, but the relationship seems considerably stronger in the former that the latter. Indeed, these analyses have also demonstrated that individuals who failed to achieve HbA_{1c} targets during intensive blood glucose-lowering therapy were at the greatest risk of death. These findings appear to reject the hypothesis that the increased mortality resulted from a too rapid reduction in HbA_{1c} (Calles-Escandón et al, 2010; Bonds et al, 2010; Miller et al, 2010; Riddle et al, 2010).

Severe hypoglycaemia in the ACCORD cohort has been examined and does not appear to be the cause of increased mortality. While an episode of severe hypoglycaemia did increase risk of death during follow-up in both the intensive- and standard-treatment groups, participants in the intensively treated arm who had at least one severe event were less likely to die during follow-up than participants in the standard treatment group who had experienced the same. Furthermore, the risk of severe hypoglycaemic events was epidemiologically associated with higher, rather than lower, HbA_{1c} levels in both arms of the study (Bonds et al, 2010; Miller et al, 2010).

On the final hypothesis in my list, statistician John M Lachin's (2010) excellent article in *Diabetes Care* presents a cogent argument for the increased mortality in the intensively treated arm of ACCORD being simply a chance finding.

The initial and longer-term findings of the ACCORD study demonstrate an increased mortality with intensive glycaemic control in people with advance type 2 diabetes who were at high cardiovascular risk. The causes for this increased mortality remain to be elucidated.

ACCORD Study Group, Gerstein HC, Miller ME (2008) Effects of intensive glucose lowering in type 2 diabetes. *N Engl J Med* **358**: 2545–59

ACCORD Study Group, Gerstein HC, Miller ME et al (2011) Long-term effects of intensive glucose lowering on cardiovascular outcomes. *N Engl J Med* **364**: 818–28

Bonds DE, Miller ME, Bergenstal RM et al (2010) The association between symptomatic, severe hypoglycaemia and mortality in type 2 diabetes: retrospective epidemiological analysis of the ACCORD study. *BMJ* **340**: b4909

Calles-Escandón J, Lovato LC, Simons-Morton DG et al (2010) Effect of intensive compared with standard glycemia treatment strategies on mortality by baseline subgroup characteristics: the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial. *Diabetes Care* **33**: 721–7

Lachin JM (2010) Point: Intensive glycemic control and mortality in ACCORD – a chance finding? *Diabetes Care* **33**: 2719–21

Miller ME, Bonds DE, Gerstein HC et al (2010) The effects of baseline characteristics, glycaemia treatment approach, and glycated haemoglobin concentration on the risk of severe hypoglycaemia: post hoc epidemiological analysis of the ACCORD study. *BMJ* **340**: b5444

Riddle MC, Ambrosius WT, Brillon DJ et al (2010) Epidemiologic relationships between A1C and all-cause mortality during a median 3.4-year follow-up of glycemic treatment in the ACCORD trial. *Diabetes Care* **33**: 983–90