# ACCORD: Action to Control Cardiovascular Risk in Diabetes

**The ACCORD (Action to Control Cardiovascular Risk in Diabetes) study was a large clinical trial of adults with established type 2 diabetes who were at especially high risk of cardiovascular disease. The study tested treatment approaches to determine the best ways to decrease the high rate of major cardiovascular events, and delivered surprising results which cast doubt on the benefits of intensive glycaemic control in high-risk patients. With many *post hoc* and long-term analyses conducted since, what are the key messages from ACCORD, and how should it influence our practice?**

## ACCORD blood glucose trial

- 3.5 years into the ACCORD study, analysis showed that, in the intensive glycaemic target group, death from cardiovascular (CV) causes was increased significantly by 35% and all-cause mortality was increased by 22% compared with standard treatment (ACCORD Study Group, 2008). Non-fatal myocardial infarction (MI) was reduced by 24% in the intensive target group compared to the standard group.
- As a result, the intensive group were transitioned to the standard group over 0.2 years and followed for an additional mean 1.2 years to the planned end of the glucose trial, while continuing to participate in one of the other sub-trials (*Figure 1*).
- The increase in the primary outcome was unexplained and caused confusion over what glycaemic targets were appropriate in those with longer-duration diabetes, as tight, intensive treatment was known to reduce the risk of microvascular complications (Dahl, 2008).

## Post-trial analyses

- After the trial finished, *post hoc* analyses compared ACCORD data with other glucose-lowering trials to try and explain the increase in the primary outcome.
  - Severe hypoglycaemia, weight gain and use of specific antidiabetes agents (including insulin) have been ruled out as explanations for the increased mortality (ACCORD Study Group, 2016).
  - Gerstein et al (2014) analysed the 3.7 years of active intensive therapy plus the additional mean 1.2 years of standard therapy and concluded that active treatment in fact lowered the risk of cardiac events. Fatal MI risk appeared to increase, but the number of events was small and the increase was not statistically significant. During the total 5-year follow-up, non-fatal MI was reduced by 19%, coronary revascularisation by 16% and unstable angina by 19%.
  - Riddle et al (2010) concluded that persisting higher $HbA_{1c}$ levels, rather than low $HbA_{1c}$ at the most recent follow-up, were the likely contributors to the increased mortality risk observed in the intensive target group. People who failed to achieve tight glycaemic control despite multiple treatments were at greatest risk.

### ACCORD study design

- Multicentre, randomised, placebo-controlled trial.
- 77 clinical sites across the US and Canada.
- Participant criteria: long-standing type 2 diabetes (median duration, 10 years) and high risk of cardiovascular events.
- 10 251 participants randomised to intensive or standard glycaemic control. Participants were also randomised to either the lipid or blood pressure sub-trials (*Figure 1*).
- Primary outcome: a composite of major adverse cardiac events, including non-fatal MI, non-fatal stroke and death from cardiovascular causes.

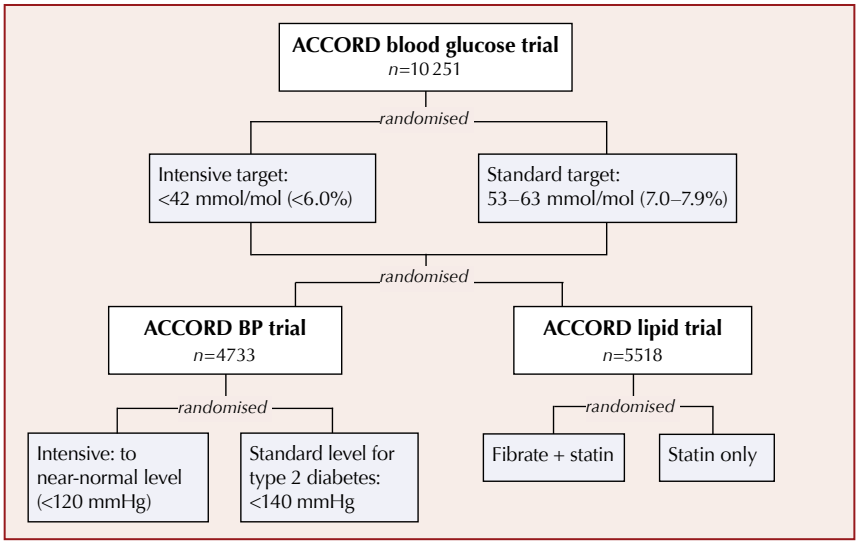


*Figure 1. Patient randomisation diagram for the blood glucose trial and two sub-trials of the ACCORD (Action to Control Cardiovascular Risk in Diabetes) study. BP=blood pressure.*

## Long-term follow-up

- All surviving participants were invited to participate in the observational ACCORDION follow-on study. Nine years after study closure, previous intensive control had a neutral effect on overall mortality and non-fatal CV events. The increased risk of CV-related death persisted but was smaller (ACCORD Study Group, 2016).
- The one clear benefit was in retinal outcomes, with a 58% reduction in the odds of diabetic retinopathy progression with intensive control (ACCORDION Eye Study Group, 2016).

## ACCORD blood pressure (BP) sub-trial

- There was no significant difference between the two treatment groups in the primary composite outcome of MI, stroke and death (ACCORD Study Group, 2010a). There was also a higher risk of severe adverse events in the intensive treatment group.
- However, there was a lower rate of stroke (41%), which is consistent with other BP treatment trials.
- Thus, the data suggest that a systolic BP (SBP) target of <120 mmHg may reduce stroke risk in people with diabetes (Allen et al, 2013).
- The American Diabetes Association (2016) recommends an SBP target of <140 mmHg, and a target of <130 mmHg may be appropriate in younger people, those with microvascular complications and those with hypertension.

## ACCORD lipid sub-trial

- The lipid sub-trial did not provide evidence supporting the use of combination fenofibrate and simvastatin therapy in reducing CV events in the majority of people with type 2 diabetes who had HDL-cholesterol and triglyceride levels within the normal range compared to statin monotherapy (ACCORD Study Group, 2010b).

## Take-home messages

- The death rates in all ACCORD participants were lower than those for comparable diabetes groups in other studies (Dahl, 2008). It should be a priority to control blood pressure and lipids to prevent CV events in people with type 2 diabetes.
- Early intensive glucose-lowering – to a target of <53 mmol/mol (7.0%) – in people with diabetes, combined with aggressive treatment of other risk factors, is likely to result in a long-term reduction in CV risk (Chiasson and Le Lorier, 2014).
- In those above the age of 65 years with comorbidities, it may be suitable to relax the $HbA_{1c}$ target to <64 mmol/mol (8.0%).
- For people with high CV risk, intensive glucose-lowering may still improve retinal outcomes. ■

### Clinical perspective – ACCORD results

**Colin Kenny, GP, Dromore, and Editor, *Diabetes Distilled***

The ACCORD study was designed to answer a very important question: does intensive blood glucose control reduce the risk of major cardiovascular events in a high-risk group of people who have been living with type 2 diabetes for some time? The participants had been living with "indifferent" glycaemic control for a median of 10 years. They all had high cardiovascular risk to increase the power of the study. Those in the intervention arm went rapidly from loose glycaemic control to tight control, achieving a median $HbA_{1c}$ of 46 mmol/mol (6.4%).

The answer we got from this study was to proceed with caution in such patients, as more people in the intensive treatment group died compared with the standard treatment group.

Whilst this important study has been much discussed, re-analysed and compared with other contemporary studies, part of the frustration about commentating on it is the fact that not all data, particularly about how different agents were used, are in the public domain.

This study partially introduced the concept of a "J-shaped" curve into blood glucose reduction, whereby optimum $HbA_{1c}$ levels in high-risk patients might be 58 mmol/mol (7.5%) but further reductions might be hazardous. Patients with high cardiovascular risk need a careful, multifactorial intervention and, as with any J-shaped curve, persisting with poor glycaemic control is also unsafe. Clinicians should avoid interpreting ACCORD as demonstrating that everyone with long-standing disease should have lax glycaemic control.

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