ACCORD 5-year follow-up results: *Primum non nocere*

Anyone who knows me will confirm that when it comes to diabetes, I am, well, something of an anorak! However, despite my appetite for the subject I suspect I was not the only one who read with eager excitement the article recently published in the *New England Journal of Medicine* by the ACCORD (Action to Control Cardiovascular Risk in Diabetes) Study Group et al (2011) reviewing further data on the long-term effects of intensive blood glucose lowering on cardiovascular outcomes.

Considerable evidence exists to support a progressive relationship between hyperglycaemia and adverse cardiovascular outcomes (Huxley et al, 2005). The ACCORD trial was designed to study whether striving to achieve healthy HbA_{1c} levels would reduce the risk of serious cardiovascular events in middle-aged and older people with type 2 diabetes compared with a target HbA_{1c} level of 7.5% (58 mmol/mol). The rest, as they say, is history. There were fewer non-fatal myocardial infarctions in the intensive treatment group and the two groups did not differ significantly in the primary outcome (a composite of non-fatal myocardial infarction, non-fatal stroke or death from cardiovascular causes). However, and most importantly, the study was terminated early after a mean treatment period of 3.7 years due to the observation of a higher mortality rate (primarily cardiovascular) in the intensive treatment group.

The most recent publication analyses the data from a further 1.3 years of follow-up (5-year outcomes of a mean of 3.7 years of intensive blood glucose lowering) on mortality and cardiovascular outcomes. This subsequent data is no less exciting. After intensive intervention was terminated, as expected the mean HbA_{1c} level rose, from 6.4% (46 mmol/mol) to 7.2% (55 mmol/mol) in the intensive treatment group. However, the same trends in outcomes persisted: there was a continued increased risk of death in people who had previously received intensive treatment.

Prior to the trial being terminated, the original data had shown higher rates of hypoglycaemia in the intensive treatment group as well as showing higher rates of mortality in people who experienced significant hypoglycaemia. These new data have been eagerly awaited and, I would suggest, many of us expected them to provide confirmation of the fact that hypoglycaemia underpinned the increased mortality rate – it is well known that hypoglycaemia is a precipitant of adverse cardiovascular events and death (Zoungas et al, 2010). After intense intervention ceased (again as one would expect) there were similar rates of hypoglycaemia in both groups.

The ACCORD group, however, remain unclear about the reasons for the higher mortality rate in the pretransition period and, most interestingly of all, they rule out severe hypoglycaemia as a cause. One of the reasons given is that both groups in the posttransition period have similar rates of hypoglycaemia. As such, hypoglycaemia alone cannot explain the continued higher mortality rate in intensively treated people after the trial was terminated.

I remain a touch sceptical about the role hypoglycaemia has to play and probably need more convincing. Clearly further analysis is needed to explore possible adverse risks of drug combinations, weight gain and the speed at which HbA_{1c} level is lowered.

The real question, however, is whether ACCORD has led to any change in practice for us at the coal face in primary care. For me it is a resounding yes and ACCORD should be regarded as a seminal study. It was a "real

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life" study in that it recruited exactly the type of person we see day-in and day-out in our surgeries and clinics. Before ACCORD, intuition suggested that the lower the HbA_{1c} level, the better. ACCORD made us strongly question this philosophy. It was also published at a time of increasingly stringent QOF indicators, sometimes, therefore, leading to a tension between achieving indicators and doing the right thing for our patients.

Overall I believe ACCORD was a force for good. It resulted in many of us taking a step back and looking again at the individual in front of us. For me, ACCORD heralded an age of pragmatism in terms of managing people with diabetes. In younger people early on in their diabetes journey, we must be aggressive in managing dysglycaemia (being equally aggressive with blood pressure and lipids). Data in these circumstances does show long-term

benefits – the so-called "metabolic memory" (Holman et al, 2008). However, such a strategy cannot be recommended for older, more high-risk people. ACCORD reminds us very clearly of the first rule of medicine: first do no harm, *primum non nocere*. ■

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

Holman RR, Paul SK, Bethel MA et al (2008) 10-year follow-up of intensive glucose control in type 2 diabetes. *N Engl J Med* **359**: 1577–89

Huxley R, Barzi F, Woodward M (2005) Excess risk of fatal coronary heart disease associated with diabetes in men and women: meta-analysis of 37 prospective cohort studies. *BMJ* **332**: 73–8

Zoungas S, Patel A, Chalmers J et al (2010) Severe hypoglycemia and risks of vascular events and death. *N Engl J Med* **363**: 1410–18

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