Going too low: HbA_{1c} targets for people at risk of cardiovascular disease

In this section, a panel of multidisciplinary team members give their opinions on a recently published paper. In this issue, we focus on the 5-year outcomes of the ACCORD (Action to Control Cardiovascular Risk in Diabetes) Trial.

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The ACCORD trial (ACCORD Study Group et al, 2008) attempted to ascertain whether strict glycaemic control with intensive treatment might prevent major cardiovascular (CV) events and influence mortality in people with type 2 diabetes who have macrovascular disease. The absence of a significant CV benefit was accompanied by a higher number of deaths from any cause in the intensive-therapy group, which led to early termination of the trial and much subsequent angst about what had caused this excess mortality.

The latest article (ACCORD Study Group et al, 2011; summarised alongside) presents the 5-year outcome data on mortality and CV events, following a mean period of 3.7 years of intensive blood glucose lowering. Although glycaemic control after transition from intensive to standard therapy was similar in both groups, the previously observed trends in mortality continued with a greater number of deaths occurring in those originally randomised to the intensive-therapy group.

The negative outcome of ACCORD has been widely debated. In particular, potential causes of the excess mortality have been scrutinised by the investigators and have aroused much speculation. Attention has been directed to the possible roles of weight gain, the use of specific medications and increased exposure to hypoglycaemia, which many clinicians still regard as being the most likely protagonist. Although hypoglycaemia has profound CV effects and can certainly cause cardiac ischaemia and arrhythmias (Wright and Frier, 2008), when attempts are made to assess the role of hypoglycaemia in the adverse outcome of ACCORD, Churchill's observation about Russia comes to mind: that it is "a riddle wrapped in a mystery inside an enigma".

The evidence implicating hypoglycaemia as the underlying cause of CV events and excess mortality appears to be contradictory and confusing and is difficult to interpret. The 2008 ACCORD data revealed that participants in either group – intensive or standard-therapy – were more likely to die if they had experienced a severe hypoglycaemic event (ACCORD Study Group et al, 2008), but in those with no history of severe hypoglycaemia, mortality was greater in the intensive-therapy group while in those having at least one severe hypoglycaemic event, mortality was greater in the standard-therapy group (Bonds et al, 2010; Miller et al, 2010). These apparently counter-intuitive findings have been used by the ACCORD investigators to dismiss hypoglycaemia as the cause of the excess mortality.

In the post-transition period, rates of severe hypoglycaemia were similar in the intensive and standard-therapy groups, suggesting that hypoglycaemia could be discounted as a cause of the continuing higher mortality observed in the intensive-therapy group. Many clinicians remain unconvinced by this assertion, but unfortunately, the putative role of hypoglycaemia in precipitating CV events cannot be confirmed as simultaneous continuous-glucose monitoring and electrocardiography Holter monitoring were not performed during the study.

Whatever the cause of the excess mortality, ACCORD has clearly demonstrated the dangers of striving for very strict glycaemic control in a high CV risk population with type 2 diabetes. In a commentary on the use of intensive therapies for people with type 2 diabetes, Montori and Fernandez-Balsells (2010) stressed the practical difficulties inherent in adopting such a therapeutic strategy and commented that "clinicians should avoid glycaemic control interventions that overwhelm the patients' capacity to cope clinically, psychologically, and financially". This is an important consideration because of the profound impact that intensive treatment may have on the quality of life of a person with diabetes, and does not solely concern safety aspects of blood glucose-lowering regimens. This should not prevent strict glycaemic control being pursued in people newly-diagnosed with type 2 diabetes with no evidence of macrovascular disease, in whom future CV benefits may be substantial.

ACCORD has emerged as a landmark study because it has focused debate on what glycaemic targets are appropriate in people with type 2 diabetes at high risk of CV morbidity, how therapy should be instigated and which blood glucose-lowering agents should be used.

ACCORD Study Group et al (2008) *N Engl J Med* **358**: 2545–59
ACCORD Study Group et al (2011) *N Engl J Med* **364**: 818–28
Bonds DE et al (2010) *BMJ* **340**: b4909
Miller ME et al (2010) *BMJ* **340**: b5444
Montori VM, Fernandez-Balsells M (2009) *Ann Intern Med* **150**: 803–8
Wright RJ, Frier BM (2008) *Diabetes Metab Res Rev* **24**: 353–63

Long-term effects of intensive glucose lowering on cardiovascular outcomes

ACCORD Study Group, Gerstein HC, Miller ME et al (2011) *N Engl J Med* **364**: 818–28

NEJM

Increased risk of death persists following a period of intensive blood glucose lowering

1 Elsewhere, intensive blood glucose lowering has been shown to increase mortality among people with T2D who are at risk of cardiovascular disease.

2 In the present study, the ACCORD (Action to Control Cardiovascular Risk in Diabetes) Study Group describe long-term outcomes on mortality and key cardiovascular events following a period of intensive blood glucose lowering.

3 Participants were male and female volunteers from 77 USA and Canadian clinical centres aged 40–79 years who had T2D and an HbA_{1c} level of ≥7.5% (≥58 mmol/mol) and had previous evidence of cardiovascular disease or risk factors for cardiovascular disease.

4 Participants (n=4733) were randomly assigned to receive either intensive blood glucose-

lowering therapy (target HbA_{1c} level <6.0% [<42 mmol/mol]) or standard blood glucose-lowering therapy (target HbA_{1c} level 7.0–7.9% [53–63 mmol/mol]). Primary outcome was a composite of nonfatal myocardial infarction, nonfatal stroke, or death from cardiovascular causes.

5 Intensive therapy was terminated early (mean 3.7 years); at this time the intensive-therapy group did not differ significantly from the standard-therapy group in the rate of the primary outcome (P=0.13) but had more deaths from any cause (primarily cardiovascular; hazard ratio [HR], 1.21; 95% confidence interval [CI], 1.02–1.44) and fewer nonfatal myocardial infarctions (HR, 0.79; 95% CI, 0.66–0.95).

6 Those initially randomised to receive intensive therapy were reassigned to standard therapy.

7 After the intensive intervention was terminated, the median HbA_{1c} level in the intensive-therapy group rose from 6.4% (46 mmol/mol) to 7.2% (55 mmol/mol), and the use of blood glucose-lowering medications and rates of severe hypoglycemia and other adverse events were similar in the two groups.

8 The trends of reduced 5-year nonfatal myocardial infarctions (HR, 0.82; 95% CI, 0.70–0.96) but increased 5-year mortality (HR, 1.19; 95% CI, 1.03–1.38) persisted during the entire follow-up period among the participants originally receiving intensive blood glucose-lowering therapy.

9 The authors concluded that, in persons who have a high risk of cardiovascular disease and suboptimally controlled, long-standing T2D, an intensive therapeutic approach targeting normal HbA_{1c} levels with the use of multiple medications is associated with higher mortality than is a standard approach. HbA_{1c} levels below 6.0% (42 mmol/mol) cannot be generally recommended in this population.

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The summary results of the four recent trials examining benefits of intensive blood glucose control have surely given us an unmistakable clinical steer (Control Group et al, 2009).

We know that the benefits of intensive blood glucose control in type 2 diabetes are minor in terms of macrovascular event prevention, especially when compared with the much larger benefits stemming from lipid-lowering and antihypertensive therapies (Preiss and Sattar, 2010). In addition, aiming for very low glycaemic targets in some subgroups – including those with longer duration of diabetes or evidence of existing micro- or macrovascular complications – appears to increase mortality. These findings have led some to question the value of – and motives behind – intensive blood glucose lowering (Yudkin et al, 2011).

The Scottish Intercollegiate Guidelines Network (SIGN, 2010) have responded by recommending less strict HbA_{1c} targets, saying: "an HbA_{1c} target of 7.0% (53 mmol/mol) among people with type 2 diabetes is reasonable to reduce risk of microvascular disease and macrovascular disease. A target of 6.5% (48 mmol/mol) may be appropriate at diagnosis". These suggestions seem entirely sensible given the current evidence.

Against this background, what was it hoped that the relatively short (about 17 months) follow-up of the ACCORD trial (ACCORD Study Group et al, 2011; summarised alongside) would achieve? In one respect, the authors were obliged to report these data simply because the trial was terminated early due to more deaths with intensive therapy. But this update tells us little that is new.

The follow-up period was too short to have detected a "legacy" effect (i.e. where the benefits of the intervention are only fully realised many years later). Although glycaemia was more comparable between the two groups following the whole cohort transition to the standard targets, there was little difference in the number of people experiencing one of the primary outcomes (intensive 123 vs standard 129) and only a few more deaths from any cause in the formerly intensively-treated group (108 vs 95). Overall – and wholly unsurprisingly– this updated ACCORD report concludes that a "strategy of intensive therapy to target HbA_{1c} to below 6% (42 mmol/mol) cannot be recommended for high-risk patients with advanced diabetes".

Despite its limitations, there are some points of interest in this article. The authors' discussion reminds us that, to date, the mechanisms behind the excess deaths in the intensive arm of ACCORD (ACCORD Study Group et al, 2008) are still far from certain. Complex statistical analyses reported elsewhere go against – but do not completely exclude – severe hypoglycaemia as the main culprit (Bonds et al, 2010). Nor does too rapid a reduction in HbA_{1c} appear to be a key factor (Riddle et al, 2010). Rather, excess deaths appeared to be linked to a failure to reduce HbA_{1c} in high-risk individuals (Riddle et al 2010), an observation that merits further exploration. Future studies will examine other potential causes for excess deaths in this population (e.g. weight gain, drug interactions) and may lead to evidence for specific subgroups being at greater or lesser risk from intensive blood glucose lowering.

Ultimately, clinical common sense must prevail and here, in my opinion, the SIGN guidance (i.e. an HbA_{1c} target of 7.0% [53 mmol/mol] in the majority of people) appears reasonable, as does the need to prioritise lipid-lowering and antihypertensive therapies for the prevention of cardiovascular disease in type 2 diabetes. In those people with advanced diabetes, specific complications or in the elderly, even less stringent glycaemic targets may be sensible and this is an area where, in time, specific clinical guidance will be helpful.

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

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

Control Group, Turnbull FM, Abraira C et al (2009) Intensive glucose control and macrovascular outcomes in type 2 diabetes. *Diabetologia* **52**: 2288–98

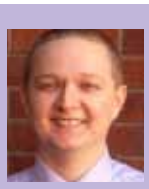
Preiss D, Sattar N (2010) Reducing cardiovascular risk in type 2 diabetes mellitus. *Medicine* **38**: 632–7

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

Scottish Intercollegiate Guidelines Network (2010) *Management of Diabetes: A National Clinical Guideline.* SIGN, Edinburgh

Yudkin JS, Richter B, Gale EA (2011) Intensified glucose control in type 2 diabetes--whose agenda? *Lancet* **377**: 1220–2

"We should be no less complacent with regard to hypoglycaemia simply because it does not appear to be the direct cause of the higher mortality rate seen in ACCORD. Hypoglycaemia is a real fear for people with diabetes."



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The original ACCORD trial (ACCORD Study Group et al) published in 2008 was a landmark study and probably changed the approach to the medical management of people with type 2 diabetes. It was designed to study whether targeting normal HbA_{1c} levels would reduce the risk of serious cardiovascular events in middle aged and elderly people with type 2 diabetes compared with an HbA_{1c} target of 7.5% (58 mmol/mol). As we know, there was no difference in the primary outcome (a composite of non-fatal myocardial infarction, non-fatal cardiovascular attack or death). However, the intensive intervention was terminated early due to the observation of a significantly higher mortality rate in that group. This effect was evident from the first year of the trial and led to the reassignment of all participants to the 7.5% (58 mmol/mol) target group after a mean of 3.7 years.

The more recently published follow-up study (ACCORD Study Group et al, 2011; summarised on pages 104–5) analyses data from a further 1.3 years of follow-up (i.e. 5-year outcomes) on mortality and cardiovascular outcomes. Fascinatingly, a continued increase in mortality in those originally randomised to the intense group was seen, despite their reassignment to the standard group.

The original ACCORD data (ACCORD Study Group, 2008) showed a significantly higher mortality among those participants exposed to significant hypoglycaemia – this was true for both the intervention and control groups. Quite early, therefore, hypoglycaemia became the front runner as the likely culprit of the higher mortality rate. However, despite rates of hypoglycaemia after cessation of intensive therapy being similar across the groups, a higher mortality rate in the intensive group persisted. Therefore, the authors argue, hypoglycaemia alone is not enough to explain the higher mortality in the intensive group in the original study. Further work is needed to elucidate the aetiologies underpinning this effect, including evaluation of particular therapeutic combinations as well as the rapidity at which HbA_{1c} is lowered.

What I really want to know is what are the take-home messages from these two studies? What lessons from ACCORD should be translated into clinical practice? Can the data from ACCORD, and similar studies such as ADVANCE (Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified-Release Controlled Evaluation; ADVANCE Collaborative Group et al, 2008), be translated into clinical practice especially when there are mixed benefits in terms of micro- and macrovascular outcomes?

What is clear from the ACCORD trials is that one must exercise caution and pragmatism before taking an aggressive approach to blood glucose lowering in a person with type 2 diabetes who has, or is at high risk of, cardiovascular disease. As GPs, we are continually balancing risks and benefits. First, we must do no harm, and I feel ACCORD helps signpost the approach we should adopt in managing many of the people we see on a day-to-day basis in our surgeries and clinics. In younger people with type 2 diabetes, or in those in whom there is not as high a cardiovascular risk, more stringent HbA_{1c} targets can and should be adopted (Holman et al, 2008).

We should be no less complacent with regard to hypoglycaemia simply because it does not appear to be the direct cause of the higher mortality rate seen in ACCORD. Hypoglycaemia is a real fear for people with diabetes. We should try, as much as we can, to use medications from the therapeutic armamentarium that do not expose people to a significant risk of hypoglycaemia. Yet, given the pressures facing us in primary care to adhere to increasingly stringent prescribing budgets, this will not be a straightforward task.

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

ADVANCE Collaborative Group, Patel A, MacMahon S et al (2008) Intensive blood glucose control and vascular outcomes in patients with Type 2 Diabetes. ADVANCE Collaborative Group. *N Engl J Med* **358**: 2560–72

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

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The original "interim" analysis of the 3.5-year ACCORD study (ACCORD Study Group et al, 2008) demonstrated that targeting treatment for people with type 2 diabetes and a high risk of cardiovascular disease to an HbA_{1c} level <6% (<42 mmol/mol) increased mortality and did not reduce major cardiovascular events. The authors concluded that the findings "identify a previously unrecognised harm of intensive glucose lowering in high-risk patients with type 2 diabetes", and seeds of doubt were sown as to whether tight glycaemic control is beneficial in type 2 diabetes. *Post hoc* analyses have ruled out any cause from baseline characteristics (Calles-Escandón et al, 2010), the achieved HbA_{1c} level and the speed at which it was reduced (Riddle et al, 2010), or hypoglycaemic events (Bonds et al, 2010; Miller et al, 2010).

The ACCORD study may have already had a significant impact on the clinical management of people with type 2 diabetes; despite speculation that QOF targets for HbA_{1c} would be lowered in 2008/9 they remained at 7.0% (53 mmol/mol) and this year have been increased to 7.5% (58 mmol/mol; NHS Employers, 2011). The question is now, with the follow-up data (ACCORD Study Group et al, 2011; summarised on pages 104–5), can we identify the cause of the adverse risk profile in the ACCORD cohort?

Despite treatment targets being relaxed and the intensive therapy group reaching a median HbA_{1c} level of 7.2% (55 mmol/mol) post-transition, compared with 7.6% (60 mmol/mol) in the standard therapy group, the authors report a sustained increased risk of all-cause mortality in those participants originally assigned to the intensive blood glucose-lowering arm; the cardiovascular mortality risk increased from 27% at transition to 29% by study end and achieved statistical significance. However, the follow-up period was short and the number of events small, making statistical analysis weak and giving little evidence on which to draw additional or new conclusions.

The ACCORD follow-up study and its online supplementary appendix reveal that the baseline characteristics of the two treatment groups were similar, and that weight gain in the intensive therapy group between baseline and pre-transition was maintained at study end – on average the intensive therapy group gained 3 kg, increased waist circumference by 3 cm and had a 1 kg/m^2 greater BMI both prior to transition to the standard arm and at study end, compared with baseline.

At the transition date, the authors note that therapy was "relaxed at least as often in the intensive therapy group as in the standard therapy group", which suggests that a difference in therapies used may have been maintained. At the first post-transition visit, relaxation of therapy was reported for 94% of the intensive therapy group and 69% of the standard therapy group. Drug data reveal that all medication use was reduced, but of particular note are the changes in thiazolidinedione (TZD) use. In the original article (ACCORD Study Group et al, 2008) it was reported that 92% of the intensive therapy group and 58% of the standard therapy group used any TZD before intensive therapy was discontinued. In the follow-up study, use of any TZD by the intensive therapy group reduced from 54% at transition to 27% at study end, and from 29% to 25% in the standard treatment arm.

Further analysis of weight gain and specific drug use should be conducted to see if interactions between treatment and cardiovascular risk can be found. The authors acknowledge the potential for these analyses in the article.

My fear is that the conclusions drawn from this study may be having a much wider impact than we realise. Namely, that we are leaving people with diabetes at an unnecessarily high risk of diabetes-related complications by allowing HbA_{1c} levels to run high. Furthermore, the shadow of ACCORD may now make it unethical to conduct future studies of tight glycaemic control in diabetes. Clinicians need evidence on which to base their practice, but that evidence must be robust. The authors should be encouraged to address these concerns and to substantiate their conclusions with further detailed analysis.

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

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

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

NHS Employers (2011) *Changes to QOF 2011/12.* NHS Employers, Leeds. Available at: http://bit.ly/hiit7Q (accessed 31.05.11)

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

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