How low should you go? New data on intensive glucose lowering in type 2 diabetes

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In the pages of this journal, Colin Kenny discussed the disappointing outcome of three long-term trials of intensive glucose-lowering in type 2 diabetes with regard to cardiovascular disease events (Kenny, 2008). These trials (Veterans Affairs Diabetes Trial, ADVANCE [Action in Diabetes and Vascular disease: preterAx and diamicroN mr Controlled Evaluation] and ACCORD [Action to Control CardiOvascular Risk in Diabetes]) were presented and discussed at the *American Diabetes Association's 68th Scientific Sessions* in June 2008. This article summarises the new information and seeks answers to the practical dilemmas arising from their confounding results.

Ever since the UKPDS (UK Prospective Diabetes Study) hinted at a possible reduction in cardiovascular risk, at least among overweight people on metformin (UKPDS Study Group, 1983), the search for how to limit the excess cardiovascular disease (CVD) morbidity and mortality associated with type 2 diabetes has been on. The multifactorial approach has become standard care for type 2 diabetes with treatment targets tightening considerably over time; and recently attention has returned to glycaemic control as a factor. Perhaps driven by the growing understanding of diabetes' pathophysiology and the increasing range of oral agents and insulin preparations which make tighter glycaemic control achievable, studies have sought to clarify whether normalizing HbA_{1c} levels below those achieved in the UKPDS might have a greater impact on the remaining excess CVD risk. The results of these trials are now emerging, and are not only disappointing but also raise new concerns about intensive blood glucose control. This article summarizes what we now know, and what it might mean day-to-day for people with diabetes and clinicians.

The Veterans Affairs Diabetes Trial

The Veterans Affairs Diabetes Trial was a long-term (7.5 years) trial among older veterans, most of whom were male (see American Diabetes Association [2008] for more information). The aim was to assess the impact on cardiovascular disease (CVD) events related to intensive blood glucose control in addition to optimal control of associated CVD risk factors; the control group were provided standard blood glucose control. Participants had a mean HbA_{1c} of 9.5% at randomisation, half had abnormal lipids, 80% had hypertension and over 40% had prior CV events.

The first aim of achieving and maintaining CVD risk factor control was achieved in both groups. Blood pressure (BP) and low-density lipoprotein cholesterol levels fell to a mean of 127/70mmHg and 2.0mmol/L, respectively. Percentage of participants smoking also fell from 16% to 10% across both groups. Target HbA_{1c} was between 8% and 9% in the control group (a median of 8.4% achieved), and as near

Article points

1. Three recent long-term trials have investigated intensive glucose-lowering in patients with type 2 diabetes.
2. The results reveal a higher mortality rate among those patients subject to intense glucose control than in those with more relaxed glucose targets and less medical attention.
3. In this article, we try to come to grips with the clinical implications of these unexpected results.

Key words

- Intensive glucose lowering
- Hypoglycaemia
- Cardiovascular disease

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normal as possible in the intervention group (a median of 6.9% achieved). Insulin was used in 90% of the intensive group after the first year, and 74% of the control group. Severe hypoglycaemia was much higher in the intensive group (21% of participants versus 10% of controls).

Over a mean 6.25 years' follow up, CV events were 30% lower than expected in both groups. There were 231 events in the intensive group, and 263 in the control group, representing around a quarter of each group. The difference did not reach significance. The microvascular outcomes will be presented at the *European Association for the Study of Diabetes Annual Meeting* in September 2008.

The ADVANCE trial

The ADVANCE (Action in Diabetes and Vascular disease: preterAx and diamicroN mr Controlled Evaluation) trial was a factorial randomised controlled trial with BP and blood glucose lowering arms. The BP arm was reported on in 2007 (ADVANCE Collaborative Group, 2007). The glycaemia arm randomised approximately 11 000 people with type 2 diabetes to intensive or routine blood glucose lowering (ADVANCE Collaborative Group, 2008). Participants were on average 66 years of age, with a mean diabetes duration of 8 years. While not selected for added CV risk factors, around one third had experienced a previous CV event. Mean HbA_{1c} at randomisation was 7.5%.

The intensive blood glucose lowering arm involved the use of gliclazide modified release 30–120mg daily, otherwise glucose-lowering therapy was at the clinician's discretion. Over the trial period, each patient in the intensively treated group visited their health professional an average of 31 times (compared with 11 times each for those in the standard group). By the end of the study 40% were using insulin compared with 24% of the control group.

The ADVANCE trial was powered to detect a 16% difference in primary outcomes over 3.5 years, but the actual rates were low; so, in order to increase the power of the study, the glucose arm was extended to 5 years. Key results are as shown in *Table 1*. The primary end points were composites of major macro- and microvascular events, assessed both together and separately.

Achieving a reduction in HbA_{1c} of 0.7 percentage points over a median of 5 years reduced nephropathy by 21% and microvascular events by 14%. The absolute risk reduction for microvascular events was 1.5%, giving a number needed to treat (NNT) of 67. A little marginal perhaps, but at least this clarifies the benefit that can be achieved among typical patients with type 2 diabetes at this HbA_{1c} range.

In this author's opinion this trial firmly establishes the lack of benefit from intensifying glucose control when it comes to CV reduction. While those participants with pre-existing CVD had

Table 1. Summary of results from the ADVANCE (Action in Diabetes and Vascular disease: preterAx and diamicroN mr Controlled Evaluation) trial. Baseline HbA_{1c} was 7.5% in the intensive and standard treatment arms (ADVANCE Collaborative Group, 2008).

Outcome	Intensive control	Standard control	RR	*P*-value
Final HbA_{1c} (%)	6.5	7.3	–	–
Combined micro and macrovascular events (%)	18.1*	20*	0.9	0.01
Microvascular events (%)	9.4	10.9	0.86	0.006
New or worsening nephropathy (%)	4.1	5.2	0.79	0.006
New or worsening retinopathy (%)	6.0	6.3	0.95	0.5**
Macrovascular events (%)	10.0	10.6	0.94	0.32**
Cardiovascular death (%)	4.5	5.2	0.88	0.12**
All-cause mortality (%)	8.9	9.6	0.93	0.28**

**Percentage of participants; **not statistically significant. RR, relative risk.*

Page points

1. The ACCORD study set out to address the advantages or otherwise of tight glycaemic and blood pressure control in a range lower than those currently recommended, with HbA1c targeted below 6%.
2. The glucose-lowering arm of the ACCORD study was halted in February 2008, due to 22% more patients in the intensive-glucose control arm having died than those with more relaxed blood.
3. Twice as many patients in the intensive group as in the standard group gained >10kg of weight during the ACCORD study period, which might have led to a divergence in risk.
4. ACCORD participants who experienced a serious hypoglycaemica were much more likely to die, regardless of which treatment group they were in.
5. Analysis of different glucose-lowering medications is difficult as ACCORD patients were randomised to strategies, not to individual drugs.

a higher rate of events, they were even less likely to benefit from intensive glucose control than primary prevention patients. However, among those with no prior CVD, intensive treatment reduced the rate of events from 18% to 15.6%, giving a significant absolute risk reduction of 2.4% (NNT 40), while among those with pre-existing disease the absolute risk reduction was a non-significant 1.1%. These results may suggest that tight glycaemic control influences the development of atherosclerosis but not its consequences.

The ACCORD Study

The ACCORD (Action to Control Cardiovascular Risk in Diabetes) Study Group set out to address the advantages or otherwise of tight glycaemic and blood pressure control (assessed separately) in a range lower than that currently recommended, with HbA_{1c} targeted below 6% (ACCORD Study Group, 2008). The ACCORD study randomised over 10 000 people with well-established diabetes (median duration 10 years) and either established CVD, or two risk factors for CVD. As in the ADVANCE trial, intensively treated participants had more visits to their health professional (every 1–2 months, with telephone contact between visits). Target HbA_{1c} was <6.0% in the intensive group, 7–7.9% for the control group.

The glucose-lowering arm of the ACCORD study was halted in February 2008 (National Heart Lung and Blood Institute, 2008), due to a significant excess of all-cause mortality among intensively treated patients. Participants had spent between 3 and 5 years in the study, and the overall mortality was 1.41% in the intensive group and 1.14% among the standard treatment group. The absolute risk reduction was 2.7%, relative risk increase was 22% (P=0.04). That is, as an apparent result of intensive blood glucose control, 22% more patients in the intensive arm died than those with more relaxed glucose targets and less medical attention.

Following the study being halted, sub-analysis of the ACCORD data is being undertaken, and aims to answer a number of questions.

- Were certain groups of patients more or less likely to benefit or be harmed by intensive glycaemic control?
- Were any of the medications used responsible?
- Have we really reached the bottom in our efforts to remove the residual CV risk carried by people with type 2 diabetes?

It is important to be cautious when looking at sub-analyses as they can give a false sense of association. For example, if lower HbA_{1c} was found to be directly harmful in the ACCORD study, most glucose-lowering treatments would be implicated by association because they were being used more often in patients who are achieving lower HbA_{1c} levels.

Prior CV risk is not a major concern because all relevant risk factors were very uniform between the intensive and control groups in this large randomised study. However, twice as many participants in the intensive group as in the control group (28% versus 14%) gained more than 10kg of weight during the study, which might have led to a divergence in risk.

Hypoglycaemia in this study is a source of strong interest, especially in light of some evidence that severe hypoglycaemia is associated with adverse outcomes in other studies (Amiel et al, 2008; Shorr et al 1997; Campbell, 1985). *Table 2* compares mortality rates among those who did and did not experience one or more severe hypoglycaemic events during the study.

These fascinating data tells us two things: Firstly, people experiencing severe hypoglycaemia were much more likely to die regardless of which treatment group they were in; and, secondly, among those who had experienced one or more serious event(s) post-randomisation, the intensive group fared significantly better. This seems to suggest that hypoglycaemia was not the mechanism by which intensively treated patients were carried to an early demise, but mortality in this group was in fact associated with some other causal factor.

What about social, educational and behavioural factors? In fact, insulin was used in 77% of intensively treated patients (55% of control), and bolus insulin in 40% (versus 20% of control). Self-monitoring of blood glucose was prescribed 3–8 times daily among the intensive group, including post-prandial monitoring. The

Table 2. Comparison of mortality rates among patients who did and did not experience one or more severe hypoglycaemic events during the ACCORD study.

Group	No hypoglycaemic events (%)	Hypoglycaemic events (%)
Overall mortality	1.2	3.3
Intensive group	1.3	2.8
Control group	1.1	4.9

study authors do not indicate whether insulin self-adjustment was encouraged, but certainly the potential for erratic self-medication existed among the intensively treated patients.

Analysis of different glucose-lowering medications is difficult as patients were randomised to strategies, not to individual drugs. When duration of follow up on each drug was accounted for, there was a significant association with excess mortality only for patients on premixed and bolus insulins; a non-significant association existed for patients on glyburide, metformin, rosiglitazone and basal insulin; a non-significant improvement in survival was associated with use of pioglitazone; and a significant improvement was associated with the use of exenatide (although use of this drug occurred later in the study and was of generally short duration). Rosiglitazone use was associated with slightly lower mortality in intensively treated patients with pre-existing CVD and longer duration of diabetes.

Discussion

What are the implications of these trails' outcomes for the primary care practitioner and the person with diabetes?

While intensive glucose-lowering does significantly reduce the risk of microvascular complications, and slows the progression of early complications, it does not significantly reduce CV events. On its own, this finding would continue to support intensive glucose-lowering for all patients, but the unexplained excess mortality among intensively treated patients in the ACCORD study suggests that an HbA_{1c} target greater than 6% is more appropriate. Selecting an intermediate HbA_{1c} target is difficult, and the results of the studies discussed above suggest that individual target-setting is more relevant than ever. We need to consider factors that include the relative burden of micro- and macrovascular risks, age and duration of diabetes. We face a growing population of younger people with type 2 diabetes who will live with the condition for even longer periods of time (30 years–). For these patients end-stage microvascular complications are a real long-term risk. In contrast, older patients who are unlikely to survive diabetes for more than 20 years, are much less likely to reach that stage of microvascular deterioration, and less stringent HbA_{1c} targets alongside aggressive CV risk reduction will be more sustaining.

The latest NICE guidelines published in May 2008 (National Collaborating Centre for Chronic Conditions, 2008) suggest a phased approach, with lower HbA_{1c} targets around 6.5% in diabetes' early years when glucose control is achievable with diet and moderate doses of a single oral medication, moving to a less stringent HbA_{1c} target of around 7.5% as treatment becomes more complex. Primary care teams will likely consider this strategy more practical, more achievable and less stressful for all concerned than the 'as low as possible' approach with all the guilt that limited achievement usually entails.

Two other conclusions jump out from a close reading of these large studies. Firstly, HbA_{1c} levels tend to remain quite horizontal in these studies, in contrast to the inexorable rise throughout the UK Prospective Diabetes Study (UKPDS; 1998), demonstrating the effectiveness of regular review and stepwise intensification of glucose-lowering therapy. Secondly, the risk of a CV event is falling short of that predicted when these studies were being designed, which is an important marker of the success of multi-factorial targeted risk reduction for CV events in diabetes from the time of diagnosis; success not only in design, but in execution.

As a GP, this author finds it undesirable to burden people with diabetes with a large number of drugs, but the evidence continues to support this line of action.

Type 2 diabetes continues to impose an excess risk of CVD aside from changes in CV risk factors – a state of affairs for which we currently have no solution. ■

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Page points

1. The unexplained excess mortality among intensively treated patients in ACCORD study suggests that a HbA_{1c} target >6% is more appropriate.
2. These new studies indicate that while intensive glucose-lowering does significantly reduce the risk of microvascular complications, it does not significantly reduce CVD events.
3. Selecting an intermediate HbA_{1c} target is difficult, and the results of these studies suggest that individual target-setting is more relevant than ever.
4. The latest NICE guidelines suggest a phased approach to HbA_{1c} targets. Primary care teams will likely consider this strategy more practical and achievable.
5. The HbA_{1c} levels in these studies tend to remain quite horizontal, demonstrating the effectiveness of regular review and stepwise intensification of glucose therapy.