Does intensive blood glucose control confer long-term risk reduction?

In this section, a panel of multidisciplinary team members give their opinions on a recently published diabetes paper. In this issue, the panel focus on the 10-year follow-up of the United Kingdom Prospective Diabetes Study.

Anthony Barnett, Professor of Medicine at the University of Birmingham and Clinical Director for Heart of England NHS Foundation Trust

Recently, there has been much interest concerning the possible dangers of "overly intensive" glycaemic control in type 2 diabetes, given the increased mortality reported in the ACCORD (Action to Control Cardiovascular Risk in Diabetes Study Group, 2008) trial in the intensively treated group, and the lack of demonstration of cardiovascular benefit in the VADT (Veterans Affairs Diabetes Trial; Abraira, 2008) and the ADVANCE (Action in Diabetes and Vascular disease: Preterax and Diamicron Modified Release Controlled Evaluation; ADVANCE Collaborative Group, 2008). However, these trials were of long duration, and the participants were individuals at high risk of cardiovascular disease. Perhaps in the ACCORD trial it was not too surprising that "if you hit patients with everything, including the kitchen sink" they may not respond too well!

This new paper puts things into better perspective; for example, we should be trying to achieve tight glycaemic control in people with type 2 diabetes from diagnosis. The benefits achieved will be long-term: not just regarding reduced risk of microvascular complications, (which is what the original UKPDS [UKPDS Group, 1998] data demonstrated), but, additionally, that there is a "legacy effect", such that these benefits can still be seen 10 years after the end of the study. Importantly, the benefits obtained relate not only to continued reduction in microvascular risk, but also to risk reductions for myocardial infarction and death from any cause. Continued benefit with metformin therapy was also confirmed for overweight individuals.

The message is very clear – good glycaemic control in the early years after diagnosis of type 2 diabetes is particularly important. I believe that NICE has got it right in its updated guidelines for type 2 diabetes (National Collaborating Centre for Chronic Conditions, 2008): recommending an HbA_{1c} target of 6.5% early in the treatment algorithm, with a "call for action" at slightly more relaxed levels of HbA_{1c} at a later stage of progression of the condition. Control matters, particularly in the first few years after diagnosis.

"Control matters, particularly in the first few years after diagnosis."

Colin Dayan, Consultant Senior Lecturer in Medicine and Head of Clinical Research, University of Bristol

The 10-year follow-up of the UKPDS participants, following the conclusion of the randomised trial, provides fascinating new insight into the different effects of glycaemic control and blood pressure control on the long-term complications of diabetes. Subjects were, on average, in the randomised trial for 8 years and then followed post-trial for 8 years, by which time 44% of the participants had died.

Despite the loss of any difference in HbA_{1c} between the conventionally and intensively treated groups within 1 year of the end of the trial period, people who initially were intensively treated went on to develop impressive late reductions in myocardial infarction (of 15% for sulphonylurea or insulin treatment, and 33% for metformin) and overall mortality rates (of 13% for sulphonylurea or insulin, and 27% for metformin). This finding is particularly reassuring as at the end of the original UKPDS study (UKPDS Group, 1998) there was concern over a possible increase in mortality with the combination of metformin and sulphonylurea. In addition, benefits in microvascular outcomes were maintained during the whole follow-up period for the intensively treated group (24% reduction). No benefit of early tight glucose control was seen for stroke or peripheral vascular disease.

The late macro- and microvascular benefits appear to be a true "legacy effect", as the companion paper on blood pressure control shows that the relative advantages of good blood pressure control for the first 8 years were lost within 4 years for microvascular disease (Holman, 2008). Early blood pressure control had reduced stroke rates (but not overall mortality or myocardial infarction rates) at the end of the trial, but even this effect was lost after a further 8 years of follow-up.

The key message is that the benefits of tight glycaemic control are long-lasting. Blood pressure control is also beneficial, but if control is relaxed, the benefits are lost within 4 years.

10-year follow-up of intensive glucose control in type 2 diabetes

Holman RR, Paul SK, Bethel MA et al (2008) *NEJM* **359**: 1577–89

NEJM

Intensive blood glucose control provides long-term macrovascular benefits in type 2 diabetes

1 This paper reports the findings from the 10-year follow-up of the United Kingdom Prospective Diabetes Study (UKPDS), which originally reported in 1998.

2 The original UKPDS study showed that intensive therapy to control blood glucose levels conferred reductions in micro- and macrovascular complications. It was planned that this 10-year follow up would coincide with the mortality of 50% of the study cohort.

3 Out of the original 5102 study participants newly diagnosed with type 2 diabetes, 4209 were randomised into two groups: either conventional therapy (dietary restriction) or intensive therapy (either sulphonylurea or insulin, or metformin in the overweight).

4 Post-trial monitoring was conducted in order to determine whether improved glucose control would continue, and whether the therapy would have a long-term effect on macrovascular outcomes.

5 A total of 3277 participants were asked to attend UKPDS clinics annually, for 5 years. Staff made no attempt to maintain any participant's previously assigned regimen.

6 Annual questionnaires were sent to participants who were unable to attend the clinic. Due to a lack of funding, all participants were followed up by questionnaire in years 6–10 of the post-trial period.

7 Seven prespecified aggregate clinical outcomes were assessed on an intention-to-treat basis. These were any diabetes endpoint, diabetes-related death, death from any cause, myocardial infarction, stroke, peripheral vascular disease and microvascular disease.

8 Differences in HbA_{1c} between the groups were lost after the first year. Significant reductions in relative risk in the sulphonylurea–insulin group compared with the conventional therapy group, which were observed during the original intervention, for any diabetes-related endpoint and microvascular disease, were maintained.

9 The risk reductions in the sulphonylurea–insulin group at 10 years were: 9% for any diabetes-related endpoint (P=0.04); 24% for microvascular disease (P=0.001). The following risk reductions emerged over time as more events occurred: 17% for diabetes-related death (P=0.01); 15% for myocardial infarction (P=0.01) and 13% for death from any cause (P=0.007).

10 Significant risk reductions in the metformin group persisted at 10 years for any diabetes-related endpoint (21%; P=0.01), myocardial infarction (33%; P=0.005), and death from any cause (27%; P=0.002).

11 After 10 years, the risk of developing microvascular complications, and the emergent risk of myocardial infarction and death from any cause, was reduced in the intensively treated group, despite the early loss of the between-group difference in HbA_{1c}.

12 These results highlight the importance of maintaining good glycaemic control to reduce the risk of coronary events and death from any cause, and indicate emergent long-term benefits on cardiovascular risk.

Brian Karet, GPwSI in diabetes, Bradford

In the list of things that don't happen much, attending a diabetes talk where the UKPDS isn't mentioned must come fairly near the top. It's been 10 years since the trial that has shaped our approach to treating people with type 2 diabetes was published, telling us conclusively that tighter diabetes control (by reducing HbA_{1c} by less than 1 percentage point) reduced the risk of microvascular disease by a quarter (UKPDS Group, 1998). It also supported, but couldn't prove, our intuitive idea that better glycaemic control also reduced the risk of cardiovascular disease – which most people with diabetes die from.

Tantalisingly, the DCCT/EDIC (Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications) 12-year follow-on study in people with type 1 diabetes (Nathan et al, 2005) did demonstrate a reduction in macrovascular events, so the recent publication of the 10-year follow-up data from the UKPDS was awaited with baited breath – and it has not disappointed.

The big news is that, despite the convergence of the HbA_{1c} levels of those in the intensively treated group and the conventionally treated group, there was a significant 15% reduction in myocardial infarction and the microvascular benefits were also sustained. Those in the intensive therapy group were treated with sulphonylurea or insulin (and don't forget they used chlorpropamide, glibenclamide and glipizide). This message got a bit swamped by the ACCORD versus ADVANCE debate, where the main theme seems to be that too big a reduction in HbA_{1c} might not be a good idea.

Back in real life we don't often strive to get people's HbA_{1c} levels under 6.5%, but we must get the message across not only that any reduction in HbA_{1c} is a good thing, but also that sustaining good glycaemic control for as long as possible leads to long-term benefits, and is as important as good control of lipid levels and blood pressure. The body seems to remember that it used to have less sugar about to damage its endothelium, and is grateful. *We* should be grateful for the UKPDS.

Partha Kar, Consultant Diabetologist, Queen Alexandra Hospital, Portsmouth

My recent trip to Rome to attend the 44th Annual Meeting of the European Association for the Study of Diabetes was, admittedly, quite a fruitful one! Apart from enjoyment of the Roman heritage, one big facet of this year's conference was the 10-year post-trial data presentation from the UKPDS by Professors Holman and Matthews. As a trainee, over the course of the years, one has been indoctrinated about the findings of the UKPDS, which was correctly hailed as one of the landmark trials in type 2 diabetes. Thus, it was a pleasure to be in the heavily packed auditorium listening to the 10-year post-trial data.

The original UKPDS data (UKPDS Group, 1998) had shown improvement in microvascular outcomes with the changes in macrovascular outcomes lacking statistical significance. What was interesting from the 10-year post-trial data was that, despite the lack of an enduring difference in glycaemic control between the intensive and standard therapy groups, participants in the intensive therapy group had experienced significant reductions in any diabetes-related end-point, microvascular disease, myocardial infarction, and all-cause mortality, as compared with the conventional group.

In contrast to the ACCORD (ACCORD Study Group, 2008), ADVANCE (ADVANCE Collaborative Group, 2008) and VADT trials (Abraira, 2008), these data did show an effect of glycaemic control on cardiovascular outcomes, which reflects the need to correct this parameter at the earliest possible opportunity. One plausible explanation that has been suggested is the inability to play "catch-up" with diabetes control. As Professor Holman suggested: "we can't afford to wait until people have problems; we'll have to treat [high] glucose [levels] from day one and treat [them] properly".

The results suggest that clinicians should continue to address cardiovascular risk factors in the treatment of type 2 diabetes, while being aware of the need for early intervention in glycaemic control.

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Action to Control Cardiovascular Risk in Diabetes Study Group (2008) Effects of intensive glucose lowering in type 2 diabetes. *NEJM* **358**: 2545–59

ADVANCE Collaborative Group (2008) Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. *NEJM* **358**: 2560–72

Holman RR, Paul SK, Bethel MA (2008) Long-term follow-up after tight control of blood pressure in type 2 diabetes. *NEJM* **359**: 1565–76

National Collaborating Centre for Chronic Conditions (2008) *Type 2 diabetes: national clinical guideline for management in primary and secondary care (update).* Royal College of Physicians, London

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