

Editorial

Glycaemic control and macrovascular complications of type 2 diabetes

Several large prospective trials have shown that an improvement in glycaemic control results in a significant reduction in the microvascular complications of both type 1 and type 2 diabetes, and such complications are thus established as being the consequence of hyperglycaemia.^{1,2} While these complications constitute the most important causes of blindness, end-stage renal failure and peripheral neuropathy, the most important cause of mortality in diabetes is macrovascular disease, which leads to a marked increase in cardiovascular events.³ Approximately 70% of patients with diabetes are likely to die of a cardiovascular event, compared with 45% of those without diabetes. Clearly, therefore, macrovascular disease or atherosclerosis is an important challenge in this context, more so since the incidence and prevalence of type 2 diabetes are increasing relentlessly.

In any condition associated with diabetes, one has to consider the possibility that hyperglycaemia may play a role. Do atherosclerosis and its complications increase with increasing levels of glycaemia and is the control or reversal of hyperglycaemia associated with a reduction in atherosclerosis and cardiovascular events? These are important questions to which answers are necessary in order to appropriately manage and prevent cardiovascular events, and to reduce cardiovascular morbidity and mortality.

The data from the UK Prospective Diabetes Study (UKPDS) show that increasing glycaemia is associated with a significant increase in the incidence of cardiovascular events, and that this trend starts at relatively low HbA1c levels.¹ In this study, the lowering of HbA1c by 0.9% did not result in a significant reduction in macrovascular events in the intensively treated group, but there was a statistical trend towards a reduction during the study period. However, a further follow up of these patients has now been shown to be associated with a significant reduction in cardiovascular events in spite of the convergence of HbA1c values in the control and the intensively treated groups.⁴

The recent results from the UKPDS are reminiscent of those from the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT-EDIC) study, which covered people with type 1 diabetes.⁵ The DCCT study was published in 1993; after a follow up of nearly a decade, the results showed that among the intensively treated patients, whose HbA1c values fell by 2% in comparison with the control group of patients, there was a marked reduction (60%) in the incidence of micro-angiopathic complications of diabetes.² Somewhat similar to the UKPDS, there was a trend towards a reduction in cardiovascular events, but this was not statistically significant. However, after a decade's further follow up, it was found that there was a reduction not only in the progression of carotid intimal-medial thickness, but also in cardiovascular events.^{5,6} Interestingly, the HbA1c levels were similar in both arms of the study during the follow up period and yet, as in the UKPDS, there was a reduction in macrovascular events in the previously intensively treated group. Clearly, therefore, glycaemic control has an effect, which takes a long

period to manifest itself. Furthermore, this effect outlasts the actual period of good glycaemic control.

While these two studies provide consistent observations in relation to glycaemic control and appear to clarify the question posed at the beginning of this article, three other recently reported studies have given rise to confusion again. The Action to Control Cardiovascular Risk in Diabetes (ACCORD) study aimed to answer whether a reduction of HbA1c to 6% or less in those with type 2 diabetes and established cardiovascular risk would reduce cardiovascular events.⁷ Patients started with a median HbA1c of 8.1% and the median HbA1c in the intensively treated patients was 6.4%. Although the rate of non-fatal acute myocardial infarction was significantly reduced (by 24%), total mortality and cardiovascular mortality increased significantly in the intensively treated group and the glycaemic arm of the trial was stopped prematurely. Since the rapid and profound reductions in the HbA1c values in these patients were achieved primarily through intensive insulin therapy, the rate of hypoglycaemia was markedly increased. In view of the association between cardiac dysrhythmias and hypoglycaemia, it is possible that the increased mortality may have been related to the use of rapid and progressive intensive insulin therapy in the absence of an adequate tradition/culture/learning of aggressive insulin therapy previously. However, it should be noted that hypoglycaemia, weight gain or the use of any specific agent for the management of diabetes in the intensive group was not found to be responsible for the increase in mortality by the investigators.

The second report to appear recently is the Action in Diabetes and Vascular Disease: Preterax and Diamicon MR Controlled Evaluation (ADVANCE) study, which investigated the effect of lowering HbA1c to <6.5% from a median of 7.2% on the combined end-point of microvascular and cardiovascular events.⁸ At the end of the study, the intensively treated group achieved a median HbA1c of 6.3%, while the group given standard therapy achieved a median HbA1c of 7%. There was a significant improvement in the combined primary end-point, but this was largely attributable to a reduction in renal events, namely, both micro- and macro-albuminuria, rather than that in macrovascular events. Gliclazide was the major agent used to improve glycaemia and the occurrence of hypoglycaemia was not a major issue. Thus, the study confirmed that intensive glycaemic control reduces micro-angiopathic complications, but did not provide evidence of any benefit or harm in terms of macrovascular disease.

The third recent report, presented at the meeting of the American Diabetes Association in 2008, was on the Veterans Affairs Diabetes Trial (VADT).⁹ This study aimed to investigate the effect of intensive glycaemic control (reducing the HbA1c value to <6%, compared with a target of 8%–9% for those given conventional therapy) on cardiovascular events. In the intensively treated group, the HbA1c values were reduced from 9.4% to 6.9%, while in the group receiving conventional therapy, the value achieved was 8.4%. The majority of the patients in the intensively treated group were on insulin and oral agents. There was a trend towards a reduction in cardiovascular events, but this was not statistically significant. However, this study brought out some important points, which are valuable in terms of clinical management and the planning of future trials. First, future trials will have to involve much larger cohorts of patients and be of longer duration. Second, aggressive control of diabetes appeared to be of greater benefit to younger patients who have had diabetes for a shorter duration of time and who do not have established cardiovascular disease. Third, in patients who had severe hypoglycaemic episodes, there was a marked increase in mortality, often within 3 months of the hypoglycaemic episode.

While some confusion has arisen about the glycaemic targets that should be achieved in people with diabetes, the Steno study, which instituted intensive control of glucose (HbA1c <6.5%), lipids (cholesterol <175 mg/dl, triglycerides <150 mg/dl) and blood pressure (systolic <130 mmHg, diastolic <80 mmHg) in people with type 2 diabetes at high risk of cardiovascular disease, clearly showed that multifactorial intervention leads to a significant reduction (of 46%) in total mortality, a reduction of 57% in cardiovascular mortality and a reduction of 59% in cardiovascular

events.^{10,11} The results of the Steno study have been confirmed by our own clinical experience of multifactorial intervention in people with type 2 diabetes at our centre over the past 11 years (unpublished observation). With the achievement of a mean HbA1c of 6.8%, low-density lipoprotein (LDL) cholesterol of 75 mg/dl, high-density lipoprotein (HDL) cholesterol of 38 mg/dl in men and 45 mg/dl in women, systolic blood pressure (BP) of 125 mmHg and diastolic BP of 78 mmHg, we have been able to totally eliminate foot ulcers, gangrene and amputations for 11 years. There has been a significant reduction in micro-albuminuria and no end-stage renal failure, dialysis or transplantation in this population for 7 years. Patients with proliferative retinopathy have been able to stop further laser treatment within 2 years of attending our clinic. The glycaemic goals have been achieved with the use of insulin in 65% of the patients, while 85% are on statins and aspirin, and 90% are taking angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs).

What do we conclude from the above apparently conflicting data? The UKPDS and DCCT-EDIC studies have generated clear data showing the benefit of improved glycaemic control on cardiovascular events and atherosclerosis. The ACCORD study shows that acute myocardial infarction is reduced by intensive glycaemic control but somehow, mortality increases among patients who have high cardiovascular risk and are treated intensively. The VADT shows that intensive glycaemic control induces a trend towards reduced cardiovascular events, which may have become significant if the trial had lasted for a longer period. Both the ACCORD study and VADT show that younger patients who have had diabetes for a shorter duration of time and who do not have established cardiovascular disease are more likely to benefit from intensive treatment than are others. Finally, the VADT demonstrates that severe hypoglycaemia is a major determinant of mortality. Both mild and severe hypoglycaemic episodes occurred with greater frequency in the ACCORD study and the VADT.

While we await further data from the continuation of these studies and new studies get instituted, the lessons for a clinician are: improved glycaemic control improves macrovascular disease and reduces cardiovascular events, even if it takes a long time; and the outcomes are likely to be better if we achieve glycaemic control in patients early in the course of their disease and who do not have established cardiovascular disease. Furthermore, we must not ignore the fact that aggressive control of hypertension and hyperlipidaemia with ACE inhibitors, ARBs, thiazides and statins is likely to deliver clinical benefits in conjunction with glycaemic control in the very short term, as has been demonstrated by several studies over the past decade and a half. Therefore, we need to be committed and aggressive, and to curb not just hyperglycaemia but every possible risk factor in people with diabetes right from the time of diagnosis.

REFERENCES

- 1 UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet* 1998;**352**:837–53.
- 2 The Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med* 1993;**329**:977–86.
- 3 CDC. *National Diabetes Fact Sheet*. United States, 2005.
- 4 Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HA. 10-year follow-up of intensive glucose control in type 2 diabetes. *N Engl J Med* 2008;**359**:1577–89.
- 5 Nathan DM, Cleary PA, Backlund JY, Genuth SM, Lachin JM, Orchard TJ, *et al.*; Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Study Research Group. Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes. *N Engl J Med* 2005;**353**:2643–53.
- 6 Nathan DM, Lachin J, Cleary P, Orchard T, Brillon DJ, Backlund JY, *et al.*; Diabetes Control and Complications Trial; Epidemiology of Diabetes Interventions and Complications Research Group. Intensive diabetes therapy and carotid intima-media thickness in type 1 diabetes mellitus. *N Engl J Med* 2003;**348**:2294–303.
- 7 Action to Control Cardiovascular Risk in Diabetes Study Group, Gerstein HC, Miller ME, Byington RP, Goff DC Jr, Bigger JT, Buse JB, *et al.* Effects of intensive glucose lowering in type 2 diabetes. *N Engl J Med* 2008;**358**:2545–59.
- 8 ADVANCE Collaborative Group, Patel A, MacMahon S, Chalmers J, Neal B, Billot L, Woodward M, *et al.* Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. *N Engl J Med* 2008;**358**:2560–72.
- 9 Duckworth W, Abraira C, Moritz T, Reda D, Emanuele N, Reaven PD, *et al.* Glucose control and vascular complications in veterans with type 2 diabetes. *N Engl J Med* 2009;**360**:129–39.

- 10 Gæde P, Vedel P, Larsen N, Jensen GVH, Parving HH, Pedersen O. Multifactorial intervention and cardiovascular disease in patients with type 2 diabetes. *N Engl J Med* 2003;**348**:383–93.
- 11 Gaede P, Lund-Andersen H, Parving HH, Pedersen O. Effect of a multifactorial intervention on mortality in type 2 diabetes. *N Engl J Med* 2008;**358**:580–91.

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