Intensive insulin therapy and CVD

In this section, a panel of multidisciplinary team members give their opinions on a recently published diabetes paper. In this issue, the focus is on the results of the long-term follow-up study to the Diabetes Complications and Control Trial, Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC).

Mark Kearney, Cardiologist, King's College Hospital, London

This long-term study confirms the suspicions of many doctors that reducing hyperglycaemia reduces the incidence of cardiovascular events and hence that hyperglycaemia affects both small and large vessels.

A recently published follow-up study to the Diabetes Control and Complications Trial demonstrated a reduction of 42 % of any cardiovascular disease event in people with type 1 diabetes who are undergoing intensive therapy. Furthermore, the risk of non-fatal myocardial infarction, stroke or death from cardiovascular disease was reduced by 57 %. These findings suggest that hyperglycaemia in some way affects the natural history of cardiovascular atherosclerosis. The earlier findings that there is a reduction in the progression of atherosclerosis, assessed by measurements of carotid artery intima–media thickness and coronary calcium scores, support this notion.

It is also interesting that there was a beneficial effect on heart rate, suggesting an improvement in cardiac autonomic function, which itself may contribute to improved cardiovascular electrical stability.

Moreover, there was a significant improvement in microalbuminuria, which supports a beneficial effect on endothelial function/permeability.

This study has important implications for cardiologists by demonstrating that reducing blood sugar influences multiple pathways, which may have favourable effects on not only the blood vessel wall but also cardiovascular stability.

'This study has important implications […] by demonstrating that reducing blood sugar influences multiple pathways, which may have favourable effects on not only the blood vessel wall but also cardiovascular stability.'

Janet Sumner, Senior Diabetes Specialist Nurse, Oxford Centre for Diabetes Endocrinology and Metabolism, Churchill Hospital, Oxford

This study continues to add to the body of evidence relating to the long-term benefits of intensive diabetes management leading to normoglycaemia. It demonstrates that the lower HbA_{1c} levels achieved by the participants during the years they were involved in the 'intensive arm' of the Diabetes Control and Complications Trial (DCCT) have continued to have beneficial effects. In the follow-up period a significant reduction of the participants' risk of developing cardiovascular disease has been observed (mean follow-up was 17 years) despite the fact that the differences have narrowed between the intensive group and the conventional treatment groups over this period.

The medical implications for the future are to promote normoglycaemia as soon as possible and to consider the cardiovascular risk at an early stage of treatment.

The challenges for me as a diabetes specialist nurse have not changed since the initial DCCT publication in 1993: the giving and receiving of information does not necessarily equate to a response to the information. Therefore, more problem-solving based education programmes using goals that are set by the individual are necessary. This will include facilitating patients to:

- identify the approach they will use to respond to the information
- develop their own strategies
- become an active problem solver.

The education and empowerment process of helping patients through the decision-making about their own diabetes management, including cardiovascular risk, will remain my goal.

Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes

Nathan DM, Cleary PA, Backlund JY et al; Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Study Research Group (2005) *New England Journal of Medicine* **353**(25): 2643–53

NEW ENGLAND JOURNAL OF MEDICINE

Intensive insulin therapy significantly lowers risk of CVD in people with type 1 diabetes

1 Compared with an age-matched population without diabetes, people with type 1 diabetes have at least a ten-fold higher risk of developing cardiovascular disease (CVD).

2 Intensive therapy, for people with type 1 diabetes, aimed at achieving normal glycaemic levels has been shown to lower the risk of developing microvascular and neurological complications.

3 This paper describes a study which compared intensive with conventional therapy, during the Diabetes Control and Complications Trial (DCCT) and its long-term follow-up study, Epidemiology of Diabetes Interventions and Complications (EDIC), with respect to their effect on the long-term incidence of CVD (defined as non-fatal myocardial infarction, →

→ stroke, death from CVD, confirmed angina or the need for coronary artery revascularisation).

4 Intensive therapy consisted of three or more daily injections of insulin or treatment with an external pump based on at least four self-monitored glucose measurements; the goal for HbA_{1c} was <6.05%. Conventional therapy consisted of one or two daily injections of insulin and did not go beyond the goals of preventing the symptoms of hypoglycaemia and hyperglycaemia.

5 The DCCT had randomly assigned 1441 participants with type 1 diabetes to intensive or conventional therapy between 1983 and 1993; treatment lasted for a mean of 6.5 years. Ninety-three per cent of this group were followed up, for a mean of 17 years, in the DCCT/EDIC study.

6 Participants were examined annually. HbA_{1c} levels were noted quarterly, and fasting lipid levels and serum creatinine levels (among other CVD risk factors) were measured annually.

7 During the 17-year follow-up period, 46 CVD events occurred in 31 participants from the intensive therapy group compared with 98 events in 52 participants from the conventional therapy group. At study end mean HbA_{1c} levels were 7.9% and 7.8% for the intensive and conventional treatment groups, respectively.

8 The authors claim that their data demonstrate that intensive therapy reduces the risk of any CVD event occurring by 42% (95% confidence interval [CI], 9–63%; P=0.02) and of non-fatal myocardial infarction, stroke and death from CVD by 57% (95% CI, 12–79%; P=0.02).

9 Microalbuminuria and albuminuria were significantly associated with an increase in the number of CVD events; however, differences between the intensive and conventional therapy groups remained significant after adjusting for these factors (P≤0.05).

10 The study concludes that intensive therapy aimed at achieving normal glycaemic levels in people with type 1 diabetes, which in turn lowers CVD risk, will prove to have long-term health and economical benefits.

This study is a very valuable addition to the body of evidence which states that achieving near normoglycaemic control in patients with type 1 diabetes reduces the risk of developing related microvascular and macrovascular complications. It stresses the importance of optimising glycaemic control as early as possible in those with type 1 diabetes.

'[The study] stresses the importance of optimising glycaemic control as early as possible.'

Traditionally, paediatricians have been satisfied with the diabetes management of their young patients if they have good growth parameters and are asymptomatic of hypoglycaemia. However, over the last 2–3 years interest has turned to intensifying diabetes control much earlier in the course of the condition with many children being placed on intensive or flexible regimens that utilise basal–bolus or insulin pump therapy as early as the point of diagnosis. This approach is to be greatly encouraged as it is well known that duration of diabetes is one of the major contributory factors in the development of microvascular and macrovascular disease and it is our young patients who will suffer from diabetes for the longest.

Fiona Campbell, Consultant Paediatric Diabetologist, Leeds Teaching Hospitals Trust, St James's University Hospital, Leeds

'The message ought to be that improving glycaemia at any HbA_{1c} as early, as much and for as long as possible will limit all vascular risks. Achieving this in paediatric, adolescent and young adult populations remains a challenge.'

John Reckless, Honorary Reader in Medicine, University of Bath; Consultant Endocrinologist, Royal United Hospital, Bath

Heart attack and stroke risk in diabetes is long-established; so is diabetic hyperglycaemia with multiplicative-risk independent of tobacco use, cholesterol and blood pressure. Cholesterol lowering with statins successfully reduces heart attacks – matching the epidemiology – and reduces stroke in excess of expectation, while smoking cessation and hypertension control limit macrovascular risks. Elusive has been glycaemic control evidence, although hyperglycaemia is a diabetes hallmark.

That long-term poor control increases macrovascular and microvascular risk was well demonstrated by Pirart, and before, but reducing atheromatous risk with improved glycaemia remained largely an act of faith. The UKPDS produced suggestive but disappointing evidence for type 2 diabetes. An HbA_{1c} drop of 0.9% gave a 16% myocardial infarct reduction (P=0.052), half the epidemiological relationship.

In type 1 diabetes, DCCT intensive control reduced microvascular events over 6 years compared with conventional treatment (HbA_{1c} 7.4% versus 9.1%, respectively), but at 11 years the EDIC follow-up mean HbA_{1c} was 7.9% versus 7.8% and intensively treated patients had a 42% reduced risk of any cardiovascular event. A 'metabolic memory' is suggested where the latter EDIC events reflect earlier DCCT glucose levels, with effects persisting after microalbuminuria adjustment. At DCCT baseline EDIC patients with events were older (31 years versus 27 years for those with no cardiovascular disease), had longer diabetes duration (7 years versus 6 years), were plumper (body mass index, 24.0 kg/m^2 versus 23.3 kg/m^2), smoked more and had higher LDL-cholesterol (3.3 mmol/l versus 2.8 mmol/l).

The message ought to be that improving glycaemia at any HbA_{1c} as early, as much and for as long as possible will limit all vascular risks. Achieving this in paediatric, adolescent and young adult populations remains a challenge. On this additional evidence-base (but limited to 144 events over 17 years) hyperglycaemia joins but does not displace the classical macrovascular risk factors for therapy.