ADVANCE-ON: further support for intensive glucose control in type 2 diabetes

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We are familiar with the use of multi-risk factor interventions in diabetes to reduce microvascular and macrovascular complications.1,2 Local, national and international guidelines recommend targets for the management of lipids, blood pressure and glycaemia, based on the results of large, randomised controlled trials. Most of these trials had a relatively simple trial design: usually double-blind and comparisons of active drugs versus placebo, one drug versus another drug, or low dose versus high dose of a drug. Targets for blood pressure and cholesterol have been derived from the blood pressure and cholesterol levels achieved in these studies, and relatively few studies set out a target blood pressure or a target cholesterol to be reached as part of the study.3,4 The primary endpoints in these studies were a combination of cardiovascular endpoints such as myocardial infarction, stroke and cardiovascular death, and these endpoints are easy to define. Double-blind, randomised, controlled trials can also be used to test the cardiovascular safety of new antidiabetic drugs, and recently published trials on alogliptin5 and saxagliptin6 are examples of these.

By contrast, studies that compare intensive glycaemic control versus conventional glycaemic control have a much more complex study design. Intensive glycaemic control in people with type 1 or type 2 diabetes requires a package of interventions, which includes advice on lifestyle, education and motivation of the patient, and the use of antidiabetic drugs.7,8 By the nature of the study design it is an open study, as the target is known to the investigator and the patient. Furthermore, in addition to macrovascular outcomes we are interested in specific diabetes complications, but these are harder to measure in a study setting and changes in retinal photography, changes in proteinuria and changes in nerve function have been used as surrogate markers for the important outcomes of blindness, renal failure and amputation.

**ADVANCE**

The Action in Diabetes and Vascular disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) trial was a large, multicentre, randomised controlled trial in 11 140 people with type 2 diabetes which combined the different approaches described above. It included an intervention that looked at blood pressure control and an intervention that looked at intensive glycaemic control. For the blood pressure study all patients were blindly allocated to a fixed dose of an ACE inhibitor (perindopril) and a diuretic (indapamide) or to placebo in addition to current blood pressure lowering therapy.9 It was planned to run the blood pressure study for five years but it was halted prematurely when it was identified that there was a significant reduction in all-cause mortality in the intervention group. Cardiovascular death and total coronary events were also reduced. Of the microvascular outcomes total renal events were reduced, new microalbuminuria was reduced, and there were numerical reductions in eye events that were not statistically significant.

For the ADVANCE blood glucose control study patients were randomly allocated to intensive blood glucose control, with a target HbA1c of 6.5% or less, or standard blood glucose control.10 A mean HbA1c of 6.5% was reached three years into the study in the intensive control group, which compared to an HbA1c of 7.3% in the standard control group, and the study ran for the full five years as planned. At the end of five years there was a significant reduction in a composite outcome that combined macrovascular and microvascular outcomes. When these were examined in detail the decrease was mostly in new or worsening renal events. There was no significant reduction in macrovascular events during the five years of the study, and importantly there was no evidence of an increase in macrovascular events or mortality. This contrasted with the ACCORD study, published at the same time, which demonstrated an increase in total mortality with intensive glucose lowering.11

**ADVANCE-ON**

Much important clinical scientific information has been obtained from epidemiological follow up of intensive glycaemia control studies. In people with type 1 diabetes follow up of the DCCT subjects in the EDIC observational study demonstrated that previous intensive therapy significantly reduced the development of an impaired GFR12 and had long-term beneficial effects on cardiovascular outcomes.13 In people with type 2 diabetes post-trial monitoring of the UKPDS (UKPDS PTM) demonstrated significant reductions in myocardial infarctions in people who had previously been allocated to intensive therapy based on sulphonylureas or insulin,14 reductions that had not reached statistical significance during the study itself.9

ADVANCE-ON was an epidemiological follow up of subjects who had been in the ADVANCE trial, and was particularly focused on possible long-term benefits on all-cause mortality and macrovascular events.15 Not all of the investigational centres that were involved in the original study took part in the follow up, so there were 8494 of the original 11 140 patients who participated in post-trial follow up for a further six years. Macrovascular endpoints were defined according to conventional criteria, but it was not possible to examine the same microvascular surrogate outcomes that were outcomes in ADVANCE as serum creatinine and urinary albumin were not routinely collected in all subjects as part of the follow up. It was possible, however, to collect the important patient-related microvascular outcome measures of end-stage renal disease, death from renal disease, requirement for retinal photocoagulation and diabetes-related blindness.
As in the UKPDS PTM, between-group differences in blood pressure and HbA1c disappeared soon into follow up. When patients were analysed according to previous blood pressure treatments there were still differences in total mortality and cardiovascular deaths in patients who were previously on the active fixed-dose combination, but these had been attenuated. There was no difference in major clinical microvascular events, and end-stage renal disease, death from renal causes, and visual outcomes were all similar. When patients were analysed according to previous glucose control no macrovascular benefit had developed, and death from any cause and major macrovascular events (cardiovascular death, myocardial infarction, stroke) remained similar in the previous intensive control and standard control groups. The composite of major clinical microvascular events was non-significantly reduced. A statistically significant reduction in end-stage renal disease was observed, however, but the number of events was small and end-stage renal disease developed in 29 patients in the group that had been intensively treated and 53 patients in the standard glucose control group.

**Discussion**

At first look, the results of ADVANCE-ON may seem disappointing as no macrovascular benefit accrued during epidemiological follow up and there was no macrovascular ‘legacy’ of previous intensive blood glucose control. The ADVANCE-ON results, however, are compatible with the results from EDIC and UKPDS PTM. The difference in HbA1c during the DCCT was around 2% for the mean of 6.5 years in the study, and the cardiovascular analysis in EDIC was performed after nine years, totalling 17 years of follow up. The difference in HbA1c during UKPDS was around 1% for the 10 years of the study, and post-trial monitoring was completed 10 years later, totalling 20 years of follow up. By contrast, the within trial HbA1c separation in ADVANCE was 0.7% for the five years of the study and ADVANCE-ON follow up was at six years, totalling 11 years of follow up. It should also be remembered that patients in ADVANCE had a longer duration of diabetes. Collectively, the results of UKPDS PTM and ADVANCE-ON suggest that as wide a separation of HbA1c for as is safely possible for as long as possible may be required for the maximum cardiovascular legacy of intensive glucose control.

The ACCORD blood glucose study was halted early at 3.5 years because of harm from the intensive therapy intervention. Total mortality was increased as were cardiovascular deaths. Severe hypoglycaemia and weight gain of more than 10kg were more common in the intensive therapy group. Despite multiple post-hoc analyses and publications of the data, no clear explanation for the increased mortality has emerged. Because of the evidence of harm in the treatment approach that was adopted, it is often overlooked that a significant reduction in non-fatal myocardial infarctions was observed at 3.5 years. A further analysis was performed at five years and the results were very similar; total mortality was increased in patients who had previously received intensive therapy, and non-fatal myocardial infarctions were reduced. Subjects from the ACCORD trial are being followed in the ACCORDION observational study which follows participants through until 2014, so providing 6.5 years of follow up on top of the 3.5 years in the study. The primary aim of the follow up is to see if prior intensive therapy reduces cardiovascular events. The investigators also hope that further follow up may provide some further insights into the harm that was caused by the particular treatment package that was used during the trial.

There has been much debate about the relative importance of treating hyperglycaemia, lipids and blood pressure in reducing cardiovascular risk in people with diabetes. At the most extreme of opinion is the suggestion that if blood pressure and lipids are aggressively treated then there is no benefit to be obtained from treating blood glucose. This is false dichotomy that would only be true if blood glucose was being managed to reduce cardiovascular events. Diabetes is a common cause for end-stage renal disease so the reduction in end-stage renal disease in ADVANCE-ON is a clinically meaningful benefit from prior intensive glucose control. Together the results of UKPDS post-trial monitoring and ADVANCE-ON indicate a substantial microvascular legacy from intensive blood glucose control in type 2 diabetes.

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**Declaration of interests**

Glasgow Royal Infirmary was a centre in the ADVANCE study and ADVANCE-ON follow up. Prof Fisher was the principal investigator for the centre and a member of the ADVANCE and ADVANCE-ON collaborative groups.

**References**