Does intensive blood glucose control improve vascular outcomes in T2DM?

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 an international randomised controlled trial looking at the effects of intensive blood glucose control on vascular outcomes in people with type 2 diabetes.

Marc Evans, Consultant Physician, Llandough Hosital, Cardiff

Data from the ADVANCE trial demonstrated that intensive blood glucose lowering to an HbA_{1c} value of 6.5% reduces the incidence of a combined composite outcome of major macrovascular or microvascular events. The main contributor to the 10% relative risk reduction observed in association with intensive blood glucose control was a 21% relative risk reduction in new or worsening nephropathy. No effects on new or worsening retinopathy, or major macrovascular events, were seen in the ADVANCE study. The results of ADVANCE, thus, suggest that blood glucose control well below the current Quality and Outcomes Framework target of 7.5% is rewarded by nephropathy outcome benefits; however there was a 1.6mmHg reduction in blood pressure noted in the intensive blood glucose lowering group, which may contribute to the observed effects on nephropathic outcomes. The absence of a significant reduction in macrovascular events, in association difference in HbA_{1c} of 0.7 percentage points between the standard and intensive blood glucose lowering groups in the ADVANCE study, may reflect the fact that this study lacked the adequate statistical power to reliably detect any effect: with the annual observed macrovascular event rates of 2.2% being lower than the anticipated 3%. Consequently, in the context of greater statin, anti-platelet and antihypertensive therapy, a longer observation period may be required to demonstrate any beneficial effect of the HbA_{1c} difference observed by the ADVANCE study on macrovascular outcomes.

The ADVANCE study, thus, reiterates the need for a multifactorial risk-intervention approach in order to optimise macrovascular risk reduction in people with type 2 diabetes.

'Lowering glycaemia to near-normal levels does not seem to further reduce CV risk.'

Roger Gadsby, GP and Associate Professor, Warwick Diabetes Care

This was a large, well-conducted multicentre study, in a population of people with type 2 diabetes with similar characteristics to those we see in UK practice. The glycaemic control of people in the intensive arm of the study improved over a period of around 2 years to a near-normal HbA_{1c} of 6.5% using therapy initially based on gliclazide modified-release. About one-third of individuals had pre-existing macrovascular disease, so the trials assessed the benefit of glycaemic control in those with and without pre-existing CVD. Primary endpoints were composites of major macrovascular and microvascular events assessed both jointly and separately.

Intensive control reduced the combined macrovascular and microvascular endpoint by 10%, primarily as a consequence of a 21% relative reduction in nephropathy. There was no effect on macrovascular events.

The weight gain of the participants was negligible and although the rates of hypoglycaemia in the intensive group were greater than those in the control group, they were generally quite low. There was no increase in deaths in the intensive arm in comparison with the ACCORD study.

The most important message from the study is that near-normal blood glucose control (HbA_{1c} of 6.5%) for 5 years does not reduce CV events. In the study, non-glycaemic CVD risk factors were not optimally controlled, as only about half were on statin therapy at the end of follow-up. The use of statin therapy and good blood pressure control, therefore, remains the mainstay of CV risk reduction in type 2 diabetes. Lowering glycaemia to near-normal levels does not seem to further reduce CV risk.

The results support the new NICE HbA_{1c} recommendations of 6.5% for people on simple glucose-lowering regimens, or a target of 7.5% for people needing more complex regimens.

Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes.

ADVANCE Collaborative Group (2008) *NEJM* **358**: 2560–72

NEJM

Intensive blood glucose control reduces vascular risk due to reduced nephropathy

1 This paper presents the results of the comparison of blood glucose lowering strategies from the factorial randomised controlled trial, ADVANCE (Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation).

2 This trial was carried out across 20 countries that assessed the effects on vascular outcomes of lowering HbA_{1c} to a target of ≤6.5%.

3 Participants in the trial were aged 55 years or older at study entry, diagnosed with type 2 diabetes at 30 years of age or later; and had a history of micro- or macrovascular disease, or had at least one further risk factor for vascular disease.

4 Exclusion criteria were: an indication for long-term insulin therapy;a definite indication for any of the agents used in the trial; a definite contraindication for any of the agents used in the trial.

5 Those who met the inclusion criteria (n=12877) entered a 6-week run-in period. During the run-in, individuals continued their usual methods of blood glucose control with the addition of a fixed combination of perindopril and indapamide.

6 Individuals who completed the run-in period (n=11140) were randomised to receive placebo or continue with the perindopril and indapamide. They were also randomised to either intensive blood glucose control (target HbA_{1c}≥6.5%; n=5571) or standard blood glucose control with HbA_{1c} targets based on local protocols (n=5569).

7 Those in the intensive treatment arm were required to discontinue any sulphonylurea and received gliclazide modified-release 30–120mg daily. Other treatments were added at the clinician's discretion to reach the target.

8 People in the intensive arm were seen at week 2 after randomisation and then at months 1, 2, 3, 4 and 6, then every 3 months following. Those in the standard arm were seen at 3, 4 and 6 months following randomisation and then every 6 months. The study ran for a median of 5 years.

9 HbA_{1c}, blood glucose levels, blood pressure and lipids were measured at each visit as well as adherence and tolerability. At the 2-year, 4-year and final follow-up visits albumin:creatinine ratio was measured and a retinal examination performed.

10 At the end of the follow-up period average HbA_{1c} in the intensive arm was 6.5%, and 7.3% in the standard arm. Incidence of combined major vascular events was significantly lower in the intensive arm than the standard arm (P<0.01).

11 The reduction in vascular events in the intensive arm was as a consequence of a significant reduction in incidence of nephropathy in this group (21%; P=0.006).

12 Intensive blood glucose control to an HbA_{1c} of 6.5% reduced the risk of major vascular events by 10%, mostly due to the 21% reduction in nephropathy.

Vinod Patel, Consultant Physician at the George Eliot Hospital, Nuneaton, and Associate Professor at the University of Warwick

Over 11 000 individuals studied for 5 years in a randomised controlled trial have given us results that will be critical to defining the role of future therapies in diabetes care. Although the end result of only an absolute risk reduction of 1.9% (relative risk reduction 10%) with respect to combined major macrovascular and microvascular events is purportedly disappointing, I find the overall results tremendously exciting for several reasons.

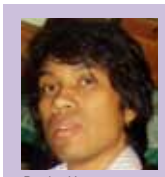
Firstly, this trial demonstrates that HbA_{1c} can be reduced to an average of 6.5% in an intensively treated group relatively safely, with a rate of severe hypoglycaemia of 7 events per 1000 patients per year versus 4 per 1000 patients per year in the standard group, whose average HbA_{1c} was 7.3%. The main significant outcome achieved with intensive control, a 21% reduction in nephropathy (mainly development of macroalbuminuria) is well worth striving for. There was also a trend towards reducing renal death and end-stage renal disease by 33%, which was not significant (P=0.09).

The annual predicted macrovascular event rate at the start of the study was 3.0%. During the study, however, the event rate was only 2.2% – a significantly lower rate by 27%. This is likely to be due to the greater use of aspirin (44% at baseline versus 56% at study end), statins (28% at baseline versus 47% at study end) and antihypertensive drugs (blood pressure reduced from 145/80mmHg to 136/74mmHg). This is, therefore, my first learning point from the study: multi-factorial intervention with statins, aspirin, antihypertensives and glycaemic control is safe and, almost certainly, reduces macrovascular event rates.

The second point is that the main tools to do this effectively (aspirin, statin, and angiotensin-converting-enzyme inhibitors) are now extremely cost-effective and should be considered in most individuals with diabetes. This message is also clear from the new NICE guidelines on the management of type 2 diabetes.

Finally, I await the results of the effects of perindopril/indapamide and intensive glycaemic control together versus neither of the above or either alone. This will add further data to the slowly emerging evidence based for multi-factorial intervention that still remains sparse being based on STENO 2, UKPDS and the Anglo-Scandinavian Cardiac Outcomes Trial only, to date.

'The main significant outcome achieved with intensive control, a 21% reduction in nephropathy [...] is well worth striving for.'



Partha Kar, Consultant Diabetologist, Queen Alexandra Hospital, Portsmouth

The ADVANCE study findings reiterate a commonly held belief among diabetes health professionals that treatment for diabetes should be individualised and not target-based. The finding that lowering HbA_{1c} to near-normal levels does not improve macrovascular outcomes, but has an effect on microvascular outcomes is not surprising – keeping in mind conclusions from the UKPDS. In the ADVANCE study, the non-glycaemic CV factors were not optimally controlled; possibly explaining the lack of macrovascular outcomes, and highlighting their importance in type 2 diabetes.

The effect on nephropathy is, however, interesting and needs further long-term studies to assess the "real-time benefits" of this outcome in people with type 2 diabetes, keeping in mind the association of nephropathy with CV outcomes.

The drive towards lower HbA_{1c} targets comes with expected complications of increased rates of severe hypoglycaemia and hospitalisation, which, once again, emphasises the point of having individualised approaches towards diabetes management.

Importantly, this study did not show any increased risk of death in the intensive treatment arm – in contrast with the ACCORD study. What is reassuring is that the results of the ADVANCE study have been based on more than twice as much data and similar levels of blood glucose control as in ACCORD.

The strategy of using gliclazide (modified release), along with other drugs as necessary, in the intensive treatment arm highlights the safety and effectiveness in lowering glycaemic targets in type 2 diabetes, with this class of agents.

The results of this trial should be considered in light of the fact that established targets for hypertension and hyperlipidaemia were achieved in a minority of individuals. The take home message continues to be to target established risk factors and have an individualised approach to glycaemic control.