Cardio DIGEST
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Editorial

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Does intensive glycaemic control provide cardiovascular benefit?

Type 2 diabetes significantly increases the risk of cardiovascular (CV) events. There is limited evidence for the benefits of blood glucose lowering with respect to CV risk in people with type 2 diabetes.

The ACCORD and ADVANCE trials sought to determine the effects of lowering blood glucose to near-normal levels on CV risk (Action to Control Cardiovascular Risk in Diabetes [ACCORD Study Group, 2008], Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation [ADVANCE Collaborative Group, 2008], respectively). Most participants in both studies received a variety of different blood glucose lowering agents. In the ACCORD trial there were no restrictions on blood glucose-lowering therapies, whereas all those in the intensive treatment arm of the ADVANCE trial were mandated to receive glicalazide modified-release. Glitazone use was infrequent in the ADVANCE trial, whereas rosiglitazone was used in 90% of those in the intensive and 58% of those in the standard arms of the ACCORD trial. Baseline characteristics of both study populations were typical for adults with type 2 diabetes (duration of diabetes 8–10 years, median HbA_{1c} 7.2–8.1%). Approximately one-third of individuals in each study had had a previous CV event, hence both studies assessed the effect of intensive glycaemic control in people with and without macrovascular disease.

In the ADVANCE trial the intensive-control group met the treatment target of a mean HbA_{1c} of 6.5%, whereas few in the ACCORD trial met the HbA_{1c} goal of <6%, with the mean achieved HbA_{1c} in the intensive group being 6.4%. The most compelling message from both studies is that intensive glycaemic control to these levels for a median of 3.5–5 years does not reduce CV events within that time frame. The primary outcome in ADVANCE was a composite of macro- and micro-vascular events. Intensive treatment resulted in a 10% relative reduction in this composite endpoint, primarily as a consequence of reduction in nephropathy. When macrovascular events were considered separately, there was no observed significant reduction.

An unexpected and troubling finding from the ACCORD study was that of an increased rate of all-cause mortality in association with intensive glycaemic control (causing the intensive control arm of the study to be stopped in February this year). A closer examination revealed that for the composite primary outcome (major fatal or non-fatal CV events) there was no statistical difference between both groups. Paradoxically, there were fewer CV events in the intensive-therapy group, with the event rates beginning to separate after 3 years in favour of intensive therapy – although this difference did not reach statistical significance. There were also inconsistencies in the direction of association between intensive glycaemic control and the various reported outcomes. For example, death from any cause and from CV causes were higher in the intensive therapy group, but the rate of non-fatal myocardial infarction was significantly lower, while the rates of non-fatal stroke and congestive heart failure were similar in both groups.

How can we explain the reported differences in outcomes seen in these two studies? Firstly, although the absolute levels of glycaemia in the intensive therapy groups of both studies were similar, the rate of reduction in HbA_{1c} was markedly greater in the ACCORD trial, with a decrease in HbA_{1c} of 1.4% occurring within 4 months. In the ADVANCE trial, the decrease in HbA_{1c} was 0.5% at 6 months and 0.6% at 12 months. Neither study was designed to address the relationship between rate of decline in HbA_{1c} and outcome. It may, however, be hypothesised that the rapid decline in HbA_{1c} observed in ACCORD may be associated with greater hypoglycaemia and glucose variability – contributing to detrimental effects on vascular physiology. Secondly, the differences in drug use between the two studies, in particular the higher use of insulin and glitazones in ACCORD, could be relevant. However, analysis of outcome by treatment class demonstrated that drug use in the ACCORD trial did not provide an explanation for the excess observed mortality.

What are the implications of these studies for the management of people with type 2 diabetes? Data from both trials demonstrate that reducing HbA_{1c} to levels below current targets does not have a beneficial effect on CV outcomes. Current guidelines advocate an individualised target for HbA_{1c}, noting that less intensive goals may be indicated for those with frequent hypoglycaemia. On the basis of these data, special consideration may need to be given to high-risk individuals with multiple risk-factors for heart disease.

These studies did not address the issue of blood glucose lowering and CV outcomes in lower-risk patients who do not have CVD or additional risk factors. In the ACCORD trial, the sub-group of participants at the lowest baseline risk seemed to gain outcome benefit from intensive blood-glucose control. The absence of any significant CV benefit for intensive glucose control in these studies may be related to their duration, and if these studies were to extend to 7, or even 10, years then outcome benefits for intensive blood-glucose control may become apparent.

Thus, while outcomes from both the ADVANCE and ACCORD trials are important contributions to our understanding of the treatment paradigm for blood glucose lowering in type 2 diabetes, we still do not have a definitive answer to the problem of glycaemic control and CVD.

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ACCORD Study Group (2008) Effects of intensive glucose lowering in type 2 diabetes. *NEJM* **358**: 2545–59
ADVANCE Collaborative Group et al (2008) Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. *NEJM* **358**: 2560–72