

## **NZSSD EXPERT OPINION**

### **Comment on the ACCORD and ADVANCE studies**

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The majority of our patients with type 2 diabetes will suffer from the adverse effects of cardiovascular disease during the course of their diabetes, often with fatal consequences. Major studies that look at strategies aimed at reducing the cardiovascular burden associated with diabetes are therefore of great interest. Two such studies were reported earlier this year. They are the ACCORD (Action to Control Cardiovascular Risk in Diabetes)<sup>1</sup> and ADVANCE (Action in Diabetes and Vascular Disease)<sup>2</sup> studies. Several New Zealand sites contributed patients to the ADVANCE study. There were many similarities between these studies. Both were large randomised controlled trials aimed at reducing composite endpoints through intensive glucose lowering strategies in patients at moderately high risk of cardiovascular disease, study duration was similar (3.4 years for ACCORD, 5 years for ADVANCE), but the strategies used to lower glucose were different.

The rationale for undertaking these studies was based on epidemiological evidence which shows an association between glucose or glycated haemoglobin levels and cardiovascular risk. This association has been seen in multiple studies and has recently been demonstrated to be present in the New Zealand setting.<sup>3</sup> In microvascular disease, randomised controlled trials, including the DCCT and UKPDS, have shown that the impact of glucose lowering strategies on complications delivers a level of risk reduction that mirrors the epidemiological association between glucose control and microvascular disease. In contrast, both ACCORD and ADVANCE showed that aggressive pharmaceutical based glucose lowering strategies had no impact on cardiovascular mortality, thus they were essentially negative studies. One of the reasons why there has been so much focus on the exact strategy used in the ACCORD study in particular, is that the ACCORD study was terminated early because of the increased number of subjects in the intensively treated group who died during the study (257 versus 203 in the standard treatment arm, out of a total of 10,251 subjects). This suggests that the intensive treatment strategy did more harm than usual treatment. This finding should however be placed in context; the number of events in both ACCORD and ADVANCE was lower than anticipated, probably reflecting the widespread use of agents such as statins, antihypertensives and aspirin. Post hoc analysis, which has its inevitable limitations, did not discern a single clear reason for, or therapeutic association with the increased mortality in the intensive study arm, so we do not know if there was a particular component of the ACCORD treatment strategy that should be avoided.

What were the strategies used in ACCORD and ADVANCE and what is their relevance to the New Zealand setting? ACCORD aimed to achieve a target HbA1c of <6.0% (median baseline HbA1c was 8.1%), using any registered agent or combination of agents, individualised at the discretion of the investigator. This ambitious glycaemic target proved difficult to achieve and the intensively treated group only managed a median HbA1c of 6.4%. Rosiglitazone was widely used, also towards the end of the study some subjects were started on incretin mimetics. In contrast, ADVANCE patients started with a median HbA1c of 7.2% and has the less ambitious target of ≤6.5%, achieving a median HbA1c of 6.4%. The primary treatment strategy was sustained release gliclazide, using other therapies as required, but use of thiazolidinediones was much less than in ACCORD and use of insulin was also lower. It could therefore be argued that of the two studies, the ADVANCE strategy looked most like the type of strategy we would use in our clinics in New Zealand.

In summary, intensive glucose lowering in moderate to high risk patients, using an aggressive approach based on multiple pharmaceutical interventions, does not confer any cardiovascular advantage over a 3.4 to 5 year period. It would seem reasonable to keep the New Zealand glycaemic target for type 2 patients at <7.0%.<sup>4</sup> This does not of course mean that we can ignore glycaemic control in low risk patients in whom it is easy to achieve an HbA1c <7.0%. For example, no one is suggesting that diet controlled patients should 'eat up' to get their HbA1c above 6.4%! Also there is no threshold value of HbA1c below which microvascular complications are avoided, so patients at high risk of significant microvascular disease should continue to aim to keep glucose levels as close to physiological levels as possible, whilst avoiding significant hypoglycaemia. The low overall mortality in these studies emphasises the benefits of adequate non glycaemic based cardiovascular risk reduction therapies. At one level, publication of ACCORD and ADVANCE implies that we can continue with a 'business as usual' approach towards diabetes management in New Zealand, but these studies also highlight the fact that much work needs to be done with our routine patients and clinics, to achieve the level of (non glycaemic) cardiovascular risk factor reduction experienced by patients taking part in these clinical trials.

## References

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