Editorial

How low to go with glucose control

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Key words: cardiovascular risk, hypoglycaemia.

(Aust Prescr 2009;32:30–1)

The Diabetes Control and Complications Trial[1] in type 1 diabetes and the UK Prospective Diabetes Study (UKPDS)[2] in type 2 diabetes showed that a strategy aimed at intensified control of blood glucose reduced the risk of microvascular complications of diabetes. These results advanced the management of hyperglycaemia and led to the current recommendation that all patients with diabetes aim for a glycated haemoglobin (HbA1c) target below 7%.

There has been a general acceptance that tight glycaemic control will reduce cardiovascular disease, but there is a lack of definitive evidence that outcomes will improve. The studies involved relatively young patients who were therefore at lower cardiovascular risk. In particular, the UKPDS recruited people with type 2 diabetes at the time of diagnosis and the study may have been too short for a cardiovascular benefit to emerge. The failure to show a benefit may also relate to the fact that the initial reductions in HbA1c were not sustained.

Post-study follow-up (observational) of the UKPDS cohort[3] over 10 years did, however, show continued reduction in not only microvascular (24%, p = 0.001) but also cardiovascular outcomes (15% in myocardial infarction, p = 0.01) and in death from any cause (13%, p = 0.007). This benefit – a so-called 'legacy effect' – persisted despite early loss (within a year) of within-study differences in glycaemic control between the intensive and standard groups.

In 2008, two major cardiovascular-outcome trials reported their results.[4,5] These trials involved people with long-standing type 2 diabetes with high vascular risk.

The Action to Control Cardiovascular Risk in Diabetes (ACCORD)[4] study randomised 10 251 people with poorly controlled type 2 diabetes (mean age 62 years, mean duration 10 years, median HbA1c 8.1%). There was an intensive glucose lowering arm aiming for normoglycaemia (HbA1c less than 6%) and an arm with a standard glucose target (HbA1c of 7–7.9%). The primary outcomes were cardiovascular events including cardiovascular death, stroke or non-fatal myocardial infarct. Both groups used almost all of the available drug therapies in different combinations and doses.

The Action in Diabetes and Vascular Disease (ADVANCE)[5] study involved 11 140 patients with similar age and diabetes duration (mean age 66 years, mean duration 8 years). However, these patients had significantly better glycaemic control at baseline (median HbA1c of 7.2%) compared to the ACCORD groups. They were randomised to either an intensive glucose lowering arm (aiming for HbA1c under 6.5%) or to a standard glucose lowering arm. Multiple drug therapies were used, but the oral hypoglycaemic drug taken by everyone in the intensive arm was modified-release gliclazide. The primary outcomes for the ADVANCE study also differed in that they included not only cardiovascular events, but also major microvascular events.

The intensive glucose lowering arms in both ACCORD and ADVANCE achieved a median HbA1c of 6.4%. This was, respectively, 1.1% and 0.6% lower than the HbA1c in the standard treatment arms. During the ADVANCE study, intensive glucose lowering yielded a 21% (p = 0.006) relative reduction in microvascular events (in nephropathy), but no significant effect on major cardiovascular events. Unexpectedly, the ACCORD

In this issue…

Many drugs are metabolised by the liver, so their clearance will be affected by liver disease. Andrew Sloss and Paul Kubler tell us what should be considered when prescribing for a patient with reduced liver function.

An increased concentration of a single hepatic enzyme does not mean that the patient has liver disease. Pat Phillips explains how healthy people may have abnormal test results, and suggests how errors can be reduced.

Laboratory measurements are sometimes used as an indication of the patient's prognosis. Scott Twaddell cautions us that such surrogate markers may not always be directly linked to clinical outcomes. It is important to manage the patient and not just the surrogate marker.

Glycated haemoglobin (HbA1c) is a surrogate marker in diabetes. Kris Park warns us that intensive treatment to reduce HbA1c may not improve cardiovascular outcomes in patients with diabetes.

The outcomes of an injection of botulinum toxin are usually quick to appear. Although there is great interest in the cosmetic use of this drug, Adam Scheinberg describes some of its clinical applications.

study showed a 22% (p = 0.04) relative increase in total mortality in the intensive glucose lowering arm. Although non-fatal myocardial infarctions reduced, there were more deaths from cardiovascular causes. As a result of safety concerns, the intensive treatment arm of the ACCORD study was stopped 18 months early, at three and a half years into the study.

Neither study has shown that intensive glucose lowering (HbA1c less than 6.5%) reduces macrovascular events when compared to standard glucose lowering (HbA1c of 7–7.5%) in older individuals with a long history of diabetes. Rapid and intensive glucose lowering could be harmful in this high-risk group. To date, there is no clear explanation for the higher mortality in ACCORD. No specific drugs (including thiazolidinediones) have been implicated, however drug therapy was not randomised in the trials. In ACCORD, severe hypoglycaemia requiring medical assistance was three times more common in the intensive group (10.5% and 3.5% respectively). It is plausible that severe hypoglycaemia may possibly have triggered fatal cardiac events such as ventricular arrhythmias particularly in those with compromised cardiac function and established autonomic neuropathy. An adverse cardiovascular outcome was not seen in the ADVANCE group who had generally better glycaemic control at the start of the study and who had a more gradual lowering of glucose during the study. Severe hypoglycaemia was less frequent than in ACCORD.

Given the rather unexpected and conflicting findings in these studies, how aggressive should we be in managing hyperglycaemia in people with type 2 diabetes? The findings from ACCORD and ADVANCE are important and should not be dismissed, however they do not change the treatment goal for most patients with type 2 diabetes. The HbA1c target should remain at or less than 7% because there is clear and consistent evidence of considerable benefit in microvascular outcomes.[1,2,3,5] In younger patients with a recent diagnosis of type 2 diabetes and no history of cardiovascular disease, a lower HbA1c target, even below 6.5%, should be considered if it can be reached with relative ease without the need for multiple drugs and with a low risk of severe hypoglycaemia. The 'legacy effect' seen in the UKPDS post-trial period certainly supports this strategy. However, in patients with a long duration of diabetes and established vascular disease, tight glycaemic control may not improve the cardiovascular outcomes. Rapid correction of hyperglycaemia and excessively tight glycaemic control appears harmful and should be avoided. In these high-risk individuals, an HbA1c target of 7–7.5% would be appropriate. The target can be adjusted for each patient with regular assessment for severe hypoglycaemic episodes and hypoglycaemia unawareness. Finally, optimal therapy for people with diabetes includes addressing not only glycaemic control, but also other coexisting vascular risk factors such as hypertension, lipid abnormalities and platelet dysfunction.

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Dr Park was a principal investigator for the ADVANCE Study.

Letters

Letters, which may not necessarily be published in full, should be restricted to not more than 250 words. When relevant, comment on the letter is sought from the author. Due to production schedules, it is normally not possible to publish letters received in response to material appearing in a particular issue earlier than the second or third subsequent issue.

Sulfur allergy

Regarding my previous correspondence (Aust Prescr 2008;31:88–9), I suppose one has to accept the Americanism 'sulfur', but this applies to chemical 'sulphur' as used in dandruff preparations. When sulphonamide preparations first came on the market they were conveniently referred to as 'sulfa' drugs and therefore allergy to these drugs is 'sulfa' allergy and not 'sulfur allergy' as your article stated.

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