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.

References

1. The Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med 1993;329:977-86.
2. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet 1998;352:837-53.
3. Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HA. 10-year follow-up of intensive glucose control in type 2 diabetes. N Engl J Med 2008;359:1577-89.
4. The Action to Control Cardiovascular Risk in Diabetes Study Group. Effects of intensive glucose lowering in type 2 diabetes. N Engl J Med 2008;358:2545-59.
5. The ADVANCE Collaborative Group. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. N Engl J Med 2008;358:2560-72.

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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