DIABETES

Meta-analysis suggests intensive glucose control could cut coronary events

A meta-analysis of five large, randomized, controlled trials reveals that intensive approaches to glycemic control might limit the risk of coronary heart disease in patients with type 2 diabetes mellitus.

Epidemiologists have previously demonstrated an association between blood glucose levels and the risk of cardiovascular disease. Nonetheless, clinical trials that aimed to assess the effect of intensive glycemic control on individual cardiovascular disease outcomes produced conflicting results. Indeed, some studies found that intensive glycemic control might actually cause harm. To overcome the inherent limitations of single studies (such as a lack of adequate statistical power), to quantify potential associations with precision, and to address concerns about the safety of intensive glucose-lowering regimens,

a team led by Kausik Ray (University of Cambridge, UK) set out to combine the evidence from previously published, large-scale, clinical trials of intensive versus standard glycemic control.

The researchers performed a literature search to identify randomized, controlled trials that enrolled patients with pre-existing type 2 diabetes mellitus. The main outcomes assessed were HbA_{1c} level, nonfatal myocardial infarction, coronary heart disease (nonfatal and fatal myocardial infarction), stroke and all-cause mortality. Five studies fulfilled their inclusion criteria: the United Kingdom Prospective Diabetes Study (UKPDS), the Prospective Pioglitazone Clinical Trial in Macrovascular Events (PROactive), the Action in Diabetes and Vascular Disease: Preterax and Diamicon Modified Release Controlled Evaluation (ADVANCE) trial, the Veterans' Affairs Diabetes Trial (VADT) and the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial.

Ray and co-workers abstracted relevant data from these studies (for example, the number of individuals with cardiovascular events in the intensive versus conventional treatment arms) and calculated the odds ratios across different studies for various end points to ensure consistency. The odds ratios from individual studies were then combined to generate a pooled odds ratio for individual cardiovascular disease outcomes and total mortality; the effects of intensive versus standard glucose-lowering therapies on these outcomes were subjected to meta-analysis using a random-effects model. This method allows for variation in the true treatment effect across individual clinical trials, and so provides a fairly conservative estimate of effects.

The meta-analysis included data from 33,040 individuals aged 53–66 years with ~163,000 person-years of follow-up. Participants who received intensive treatment had a lower mean HbA_{1c} level

at follow-up than that recorded in the standard-treatment group (difference 0.9%). Overall, 1,497 events of nonfatal myocardial infarction, 2,318 of coronary heart disease, 1,127 of stroke and 2,892 of all-cause mortality were reported during around 5 years of treatment. The key finding of the meta-analysis was that intensive glycemic control reduced the risk of nonfatal myocardial infarction and coronary heart disease by 17% and 15%, respectively, but did not provide any appreciable benefit in terms of prevention of stroke or reductions of mortality from any cause. As a consequence, the researchers suggest that intensive glycemic control has beneficial effects on coronary heart disease end points, but without increased risk of harm. When compared with standard glycemic control, however, the implementation of intensive glucose control was associated with increased weight gain at follow-up (a 2.5 kg difference between groups) and almost twice the number of severe hypoglycemic episodes.

The meta-analysis presented by Ray and colleagues is clearly of interest but some potential limitations must be considered. First, the individual studies differed widely with respect to treatment regimen, duration of follow-up and demographics of the study population. Second, insufficient data were available to enable subgroup analyses to be performed.

The researchers plan to take their work forward by combining data on individual participants from different trials to create a database. This approach will allow detailed study of subgroups to determine whether the effects of intensive glycemic control vary by parameters such as age and sex.

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Original article Ray, K. K. *et al.* Effect of intensive control of glucose on cardiovascular outcomes and death in patients with diabetes mellitus: a meta-analysis of randomised controlled trials. *Lancet* **373**, 1765–1772 (2009).