Controlling hyperglycaemia and cardiovascular benefit: The story continues

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The impact of the diabetes state on cardiovascular risk is well established. There has been an ongoing debate as to whether lowering hyperglycaemia alone has a clear cardiovascular benefit. We now have a handful of randomised controlled trials, assessing different drug classes and intensive versus usual-care regimens, to guide clinical practice.

The original UGDP (University Group Diabetes Programme) trial was one of the first to assess the effects of different glucose lowering therapies but the results were obscured due to clear trial design issues (Salsburg, 1971). Several decades on, there are only a handful of trials evaluating glucose lowering as a single risk factor treatment in reducing cardiovascular events.

The recent meta-analysis by Ray et al (2009) has attempted to integrate the results of five trials (UKPDS [UK Prospective Diabetes Study], PROactive [Prospective Pioglitazone Clinical Trial in Macrovascular Events], ADVANCE [Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation], VADT [Veterans Affairs Diabetes Trial] and ACCORD [Action to Control Cardiovascular Risk in Diabetes]) with a headline observation that a reduction in HbA_{1c} by 0.9 percentage points (9.8 mmol/mol) translates into a significant reduction in cardiovascular events (with a 17% reduction in non-fatal myocardial infarctions and a 15% reduction for all coronary heart disease [CHD]) without an increase in overall mortality (Ray et al, 2009).

In clinical practice, individuals with type 2 diabetes are characterised by heterogeneous features – age of onset and length of disease, influence of ethnicity, metabolic predisposition, associated risk factors for cardiovascular disease (CVD) and occult vascular disease as well as specific diabetes-associated microvascular complications. One of the challenges of this meta-analysis is that the patient pool is, itself, heterogeneous. This fact alone may dilute the true results and thus the relevance to clinical practice.

There are several issues that contribute to this "dilutional effect". In age terms, the mean age difference in the trials (a mean 7–13 year gap) may be an important confounding factor in the assessment of mortality. The range in mean duration of known diabetes (<1 year to 12 years) would also add to the observed effect. Variations in baseline HbA_{1c} level (7.1–9.4% [54–79 mmol/mol]) need to be taken into account. Trial participants were recruited in the USA and in Europe. The percentage of ethnic group representation varied (for example, Hispanic in the USA, and Asian in the UK) and is well recognised as important when assessing impact on CVD and mortality. Adding socioeconomic factors into the mix would inform a "reality view" of treatment effects and outcome. Duration of diabetes, degree of obesity (BMI in the range 28–32 kg/m^2) and smoking (prevalence varied by over 15% in the trials) are all key factors in cardiovascular and non-CHD mortality.

Despite methodological shortcomings in this meta-analysis, the take-home message is positive and does indicate to clinicians that lowering blood glucose levels is beneficial (despite the difficulties in doing so). This information adds to the data on cardiovascular benefit observed in trials of lowering single risk factors, such as cholesterol or blood pressure, in individuals with type 2 diabetes. Important results from the multifactorial intervention, Steno 2 study (Gaede et al, 2008) underscore that, in clinical practice, single risk factor intervention is a thing of the past.

A final comment with regard to glucose lowering: we should not become unduly distracted by current reflections on macrovascular impact but remind ourselves that lowering glucose in type 2 diabetes is important in reducing diabetes-specific microvascular complications. ■

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Ray KK, Seshasai SR, Wijesuriya S et al (2009) 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**: 1765–72

Salsburg DS (1971) The UGDP study. *JAMA* **218**: 1704–5