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Editorial

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Hyperglycaemia and coronary heart disease: The meta picture

The major cause of morbidity and mortality in people with type 2 diabetes continues to be cardiovascular (CV) disease and, in particular, coronary heart disease (CHD). Recent improvements in blood pressure control and cholesterol lowering have substantially reduced CHD events and overall mortality in type 2 diabetes, as exemplified by event rates observed in recent large-scale trials. However, residual risk in CHD does continue (Mazzone, 2007; Mazzone et al, 2008).

Epidemiological data clearly demonstrate that measures of glycaemic control are related to coronary artery disease events in individuals with type 2 diabetes (UK Prospective Diabetes Study [UKPDS] Group, 1998a; 1998b). In addition, there are numerous *in vivo* and *in vitro* studies examining surrogate endpoints, demonstrating the pathophysiological negative effects of hyperglycaemia on the development of atherosclerosis, including endothelial dysfunction, local inflammatory response, oxidative stress, altered matrix composition, altered lipoprotein composition and concentration, and the presence of accelerative factors, such as abnormal renal function. Furthermore, in type 1 diabetes, long-term follow-up of the DCCT/EDIC (Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications) study has revealed long-term beneficial effects on CHD, with a 57% reduction during the extended follow-up period of the study (Duckworth et al, 2009). Similarly, extended follow-up of those who have had type 2 diabetes for up to 10 years has demonstrated a "memory" effect of improved glycaemic control, resulting in a reduction in CHD events during a period when no significant changes were noted between the intensively and conventionally treated group. Clearly, improved glycaemic control has long-term benefits on CV events.

Why is it that large, well controlled trials have failed to demonstrate a beneficial effect of improved glycaemic control on CV events (Dormandy et al, 2005; ACCORD [Action to Control Cardiovascular Risk in Diabetes] Study Group, 2008; ADVANCE [Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified-Release Controlled Evaluation] Collaborative Group, 2008; Duckworth et al, 2009)? While many of these trials provide details of the populations enrolled, therapeutic interventions used to specific targets, endpoints evaluated and observation periods, the lower than expected event rates would, by the nature of these studies, be responsible for negative results. Also, the differences in glycaemic control, albeit statistically significant, were not large enough to demonstrate clinical benefit during the observation period.

A meta-analysis of these studies examining the effect of glucose control on CHD has, however, revealed a significant reduction of 17% and 15% in events of non-fatal myocardial infarction and CHD, respectively, due to improved glycaemic control (Ray et al, 2009). Indeed, intensive glycaemic control compared with conventional glycaemic control significantly reduced coronary events in the meta-analysis without an increased risk of death. The authors of the meta-analysis were clear, however, in recognising the limitations of this report in that the mechanism, speed and extent of HbA_{1c} reduction may have had different effects in different populations. It is also clear that the meta-analysis did not demonstrate a significant impact of improved glycaemia on overall mortality.

In view of the recent meta-analysis (Ray et al, 2009), which provides appropriate information given the lower than expected event rates in the individual trials and the results available in the long-term studies of type 1 diabetes, together with the enormous database on the pathophysiology of atherosclerosis in the presence of hyperglycaemia, it would appear prudent to strive for improved glycaemic control. This is particularly the case, as the impact on macrovascular disease would of course be in parallel to the enormous benefit in microvascular disease. While HbA_{1c} goals need to be individualised, it would appear that a value of somewhere around 7% (53 mmol/mol) for most people with type 2 diabetes would be appropriate, so long as hypoglycaemia is avoided. With the legacy effect examined in the UKPDS (Holman et al, 2008), intensive glucose control efforts might need to be initiated sooner after the onset of diabetes. Perhaps other studies would also be initiated to examine the value of improved glycaemic control to the levels currently being discussed, but such that the improvement is initiated as soon after the diagnosis of diabetes as possible as opposed to many of the recent studies that have, by nature of their inclusion criteria, examined people who have a duration of diabetes of approximately 10 years or so. Most importantly, it would be cavalier to ignore the effects of glycaemia on CV disease, though the effects may be smaller than those witnessed with blood pressure and lipid control.

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