Does normalization of blood glucose reduce the rate of cardiovascular events?

"Healthcare professionals must keep in mind the established benefits of intensive glycemic control in preventing debilitating microvascular complications."

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Diabetes is the leading cause of kidney failure, adult blindness and nontraumatic lower-limb amputations in the USA [1]. Diabetes is also a significant cause of cardiovascular morbidity and mortality. In patients with Type 2 diabetes, the prevalence of heart attacks and strokes is two- to four-times more frequent than in those without diabetes [2]. A large body of prospective randomized, controlled trials consistently indicated that intensive treatment regimens in patients with Type 1 and 2 diabetes significantly reduced the risk of development and progression of microvascular complications by between 25 and 75% when compared with conventional treatment regimens [3–6]. However, the relation of hyperglycemia to macrovascular complications in subjects with diabetes is controversial [3,4]. While many epidemiologic studies and meta-analyses have shown a direct relationship between hemoglobin A1C levels (A1C) and cardiovascular disease (CVD) [7–9], the impact of intensive glycemic control in reducing CVD events has not been clearly defined in the literature. In the Diabetes Control and Complications Trial (DCCT) [5], there was an approximately 60% reduction in the development or progression of diabetic retinopathy, nephropathy and neuropathy in the intensively treated group (mean achieved A1C of ~7%) versus the standard group (mean achieved A1C of ~9%) over an average of 6.5 years. No significant reduction in CVD events was noted during the active intervention trial in the intensive control group, although there was a trend toward lower risk of CVD events. It was only during the 9-year post-DCCT follow-up that participants previously randomized to the intensive arm were noted to have a 42% reduction ($p < 0.02$) in CVD outcomes and a 57% reduction ($p < 0.02$) in the risk of nonfatal myocardial infarction, stroke or CVD death compared with those previously in the standard arm [10]. Similarly, in the UK Prospective Diabetes Study (UKPDS) of individuals with newly diagnosed Type 2 diabetes mellitus followed for 10 years, a 25% overall reduction in the rate of microvascular complications in the intensive glycemic control arm (mean achieved A1C: 7.0%) compared with the conventional arm (mean achieved A1C: 7.9%) was reported. A 16% reduction in cardiovascular complications in the intensive glycemic control arm was also observed, although this difference was not statistically significant ($p = 0.052$). Interestingly epidemiologic analysis of the study cohort demonstrated that for every percentage point decrease in the A1C, there was an 18% decrease in CVD events, which was statistically significant.

Three recent clinical trials, Action to Control Cardiovascular Risk in Diabetes (ACCORD) [11], Diabetes and Vascular Disease Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) [12], and the Veterans Affairs Diabetes Trial (VADT) [13] aimed to assess the impact of intensive glucose control on CVD, and reported no significant reduction in CVD outcome with intensive glycemic control in Type 2 diabetes mellitus. The ACCORD study randomized 10,251 participants with either history of a CVD event or significant CVD risk factors to an intensive glycemic control group (target A1C < 6.0%) or to a control treatment group (target A1C: 7.0–7.9%). The intensive treatment group reached a median A1C of 6.4% within 12 months of randomization, and the standard group reached a median A1C of 7.5%. Cardiovascular risk factors were equally and aggressively treated in both groups. The intensive control group had more use of insulin in combination with multiple oral agents, significantly more weight gain and more episodes of hypoglycemia. There was an increased rate of mortality in the intensive arm compared with the standard arm (257 vs 203 deaths) over 3.5 years, with a similar increase in cardiovascular deaths. This led to early termination of the glycemic control study of ACCORD. The ADVANCE study was

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an international trial that recruited 11,140 participants with Type 2 diabetes mellitus randomized to an intensive glycemic control arm (targeted A1C <6.5%) with the use of sulfonylurea and additional medications or insulin, and a standard group with glycemic target determined by local standards. ADVANCE participants were at least 55 years of age with either known CVD or with multiple cardiovascular risk factors. They had lower baseline A1C (median 7.2%) compared with the ACCORD group. There was almost no use of insulin at enrollment. It took several years to achieve maximal separation in the two groups. Despite differences in A1C levels in the intensive control (6.3%) and standard groups (7.0%), no significant reduction was noted in the macrovascular events (0.94 [0.84–1.06]; p = 0.32), including myocardial infarction, stroke and cardiovascular death. The VADT randomized 1791 patients with uncontrolled Type 2 diabetes on insulin or maximal-dose oral agents with known cardiovascular events or with multiple risk factors into an intensive arm (target A1C < 6.0%) or into a standard arm (target A1C of at least 1.5% more than the intensive group), aiming to use similar medications in both groups. The mean A1C achieved was 6.9 and 8.5%, respectively, in the two arms. The CVD risk factors were treated aggressively and equally in both groups. During the median follow-up of 5.6 years, there were more cardiovascular deaths noted in the intensive arm as compared with the standard arm; however, this difference was not statistically significant. *Post hoc* subgroup analyses suggested that a duration of diabetes of less than 12 years appeared to have a CVD benefit of intensive glycemic control, and that the development of severe hypoglycemia (<40 mg/dl) was a strong predictor of CVD mortality.

The principal learning point from these three major trials is that intensive glycemic control failed to demonstrate a significant reduction in cardiovascular events in individuals with Type 2 diabetes mellitus. Several potential explanations for the lack of CV benefit with intensive glycemic control have been proposed in the literature, including a rapid and aggressive correction of hyperglycemia, more frequent use of insulin therapy, use of multiple oral agents, multiple drug combinations/interactions, weight gain and the development of severe hypoglycemic events. The trials were conducted in individuals with established diabetes (duration of diabetes mellitus: 8–11 years) with known CVD or with multiple CVD risk factors and established atherosclerosis. Subset analysis of the three trials suggested a benefit of intensive glycemic control on CVD in participants with shorter duration of diabetes, lower A1C at entry and absence of known CVD. No benefits were seen in older individual subjects with longer duration of diabetes, established CVD, and in those who experienced severe hypoglycemia during the intervention period, suggesting that intensive glycemic control may be beneficial in patients with Type 2 diabetes when initiated early in the disease process, prior to the establishment of atherosclerosis.

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We should not disregard the lower-than-predicted CVD rates in the ACCORD, ADVANCE and VADT studies, as well as in the STENO-2 multiple risk factor intervention [6], which strongly support the concept that comprehensive care for diabetes involves treatment of all risk factors and not just hyperglycemia. Healthcare professionals must keep in mind the established benefits of intensive glycemic control in preventing debilitating microvascular complications. The lack of a significant reduction in CVD should not lead us to abandon the American Diabetes Association recommended target A1C of less than 7%. The American Diabetes Association and American Heart Association have emphasized the importance of primary and secondary CVD risk reduction in patients with diabetes. In addition to glucose control, current guidelines aim to control cardiovascular risk factors, including blood pressure lowering, lipid lowering with statins, aspirin prophylaxis, smoking cessation and healthy lifestyle behaviors, in order to reduced CVD events and mortality.

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