Glucose Control and Cardiovascular Disease

Is it important? No

IGNACIO CONGET, MD, PHD
MARGA GIMÉNEZ, MD

There is a substantial amount of clinical data showing the relationship between diabetes and atherosclerosis and its clinical complications (1,2). Cardiovascular disease (CVD) is more common in people with diabetes than in subjects without the disease, and when it is present, it also has a more aggressive course and a worse prognosis (3). The bulk of epidemiological data has firmly established that type 2 diabetes is associated with more than a twofold increased risk for cardiovascular (CV) death. In the case of subjects with type 1 diabetes, in spite of the fact that the CVD rate is significantly lower compared with the population with type 2 diabetes, their relative risk for coronary heart mortality is sevenfold higher than in matched counterparts without the disease (4). Despite all of these data concerning the association of diabetes and CVD, the exact mechanism by which diabetes, and its alterations, is linked to atherosclerosis remains incompletely elucidated. This is especially true in the case of hyperglycemia. The role of nonglycemic factors that accompany the vast majority of patients with type 2 diabetes, such as high blood pressure, dyslipidemia, and hemorreological abnormalities, among others, is much better understood and seems to be independent of glycemia. In addition to this, there have been studies demonstrating that interventions addressed to control these other factors in patients with diabetes effectively reduce CV risk. There also have been data including the use of statins, aspirin, the aggressive management of hypertension, and the use of ACE inhibitors (5,6). Therefore, the positive effects that the control of other factors beyond hyperglycemia exert on CVD are, nowadays, unquestionable. In contrast, to date, the positive effect of intensive glucose management in comparison to nonintensive glucose control on CVD outcomes is still far from proven and seems unlikely to change in the near future (7). As an example, the American Diabetes Association/American Heart Association in their last joint scientific statement on primary prevention of CVD in people with diabetes declared that, "No clinical trials of a glycemic intervention have provided clear-cut evidence that glucose lowering reduces the risk of CVD in subjects with diabetes" (8). Furthermore, one of the latest U.S. Food and Drug Administration announcements on antidiabetic agents clearly concluded that, "There is insufficient information available to determine whether any oral antidiabetic medicine reduces cardiovascular risk" in people affected by diabetes.

AVAILABLE DATA ASSESSING THE CARDIOVASCULAR EFFECTS OF GLUCOSE CONTROL ONLY PROMISES FOR THE REDUCTION OF RISK — Hypertension and dyslipidemia, among other risk factors for CVD, are common in subjects with diabetes. Together, they can explain most, but not all, of the excess of risk of CVD in patients affected by the disease. High blood glucose has long been considered a risk factor for developing atherosclerosis, but data directly relating this alteration to the development and progression of CVD *are* conflicting. In this context, several glucose-lowering trials in both type 1 and type 2 diabetes showing significant reductions in microvascular complications have systematically failed to achieve significant reductions in macrovascular events (5). Nevertheless, it should also be mentioned that some systematic reviews and metanalysis performed in type 1 and type 2 diabetes (in the case of type 1 diabetes including some studies with few subjects and none or very small number of CV events) have suggested that attempts to improve glycemia reduce the incidence of CVD (9,10).

Before going through "proper" trials evaluating the effects of glycemic control and CVD, the results of the diabetes Insulin-Glucose Infusion in Acute Myocardial Infarction (DIGAMI) trial require some comments (11,12). The DIGAMI trial demonstrated that a high-dose insulin infusion followed by 3 months of intensive subcutaneous insulin therapy was associated with a statistically significant reduction in mortality after a 12-month follow-up in patients with diabetes and an acute myocardial infarction (no significant differences in the primary end point at 3 months of follow-up). In the study, high doses of insulin infusion and high blood glucose targets were used during the acute phase of the protocol. Moreover, during the subcutaneous insulin treatment period and conventional clinical targets of glucose control, there were no differences in glucose values as expressed by A1C. Thus, DIGAMI strictly could not be considered a glucose-lowering trial supporting the beneficial effects of glucose control. In addition to this, the results of the unsuccessful DIGAMI-2 trial failed to find significant differences in A1C using different strategies on glucose management in type 2 diabetic subjects and acute myocardial infarction, as well as in mortality and CV outcomes (13). In conclusion, DIGAMI-2 did not provide additional information confirming or denying the beneficial effects of glucose control.

The University Group Diabetes

From the Endocrinology and Diabetes Unit, IDIBAPS (Institut d'Investigacions Biomèdiques August Pi i Sunyer), Hospital Clínic i Universitari, Barcelona, Spain.
Corresponding author: Ignacio Conget, iconget@clinic.ub.es.
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Project (409 participants) may be considered the first glucose-lowering trial evaluating the CV effects of different strategies aimed at glucose control in type 2 diabetes (insulin addressed/not addressed to intensive control, phenformin, tolbutamide, and placebo) (14,15). After 12.5 years of follow-up, there were no differences in CVD events between the intensive control group with insulin, the nonintensive control insulin group, or the placebo. Phenformin and tolbutamide were discontinued because of the development of lactic acidosis and an excess of CV mortality, respectively.

In the Veterans Affairs Cooperative Study of Diabetes Mellitus (VACSDM), 153 subjects with type 2 diabetes were followed up for a mean of 2.25 years (16,17). This was a pilot feasibility trial in which patients under intensive glucose control (either with insulin or sulfonylureas) achieved a significant reduction in A1C (−2.1% absolute reduction). In spite of this, there was a nonsignificant trend toward an increase in CV events in the group under intensive control.

The Kumamoto study was designed to elucidate whether intensive glucose control (multiple injections of insulin) was associated with a decrease in the frequency (primary prevention) or severity (secondary prevention) of microvascular complications in 110 patients with type 2 diabetes (18). After 8 years and a 2.2% reduction in A1C, in the group receiving intensive control, there were positive results in both primary and secondary prevention of microvascular disease. After evaluating the effect of intensive treatment on CV events (cardiac, cerebrovascular, and peripheral), this was not significant, and this negative result was attributed to the small number of subjects included in the study by the authors.

Undoubtedly, the U.K. Prospective Diabetes Study (UKPDS) is still the landmark study evaluating the effects of glucose control on type 2 diabetes complications (19). Including more than 3,800 subjects, the study demonstrated a 12% significant reduction in a composite of micro- and macrovascular type 2 diabetes–related end points. However, it should be mentioned that UKPDS was underpowered to specifically assess the effect of improving glucose control on CVD. There was a nonsignificant reduction (16%) in the risk of MI and a statistically nonsignificant increase in the risk of stroke (Table 1). The positive effects of using metformin to improve glycemic control is a large claim because it was statistically associated with beneficial effects preventing any diabetes-related end point, diabetes-related mortality, and the frequency of MI (20). However, these results derived from a substudy of UKPDS were limited to overweight type 2 diabetic subjects.

Table 1—*Effect of glycemic control on CVD in the UKPDS and DCCT studies*

	Intensive (rate/100 patient-years)	Conventional (rate/100 patient-years)	Risk reduction (%)	*P*
End points				
UKPDS				
Any diabetes related*	4.09	4.60	12	0.029
Myocardial infarction	1.47	1.74	16	0.052
Stroke	0.56	0.50	—	0.52
Peripheral vascular disease	0.11	0.16	—	0.15
DCCT				
Cardiac	0.06	0.29	78	0.065
Peripheral vascular disease	0.43	0.55	22	0.16
Combined	0.49	0.84	42	0.082

From Refs. 19 and 24. *Combined microvascular and macrovascular events.

The use of pioglitazone in type 2 diabetes (secondary prevention) has been evaluated in the PROspective pioglitAzone Clinical Trial In Macrovascular Events (PROactive) (21). It was claimed that the use of the drug was associated with a positive and significant reduction in a secondary composite end point of the study (death, stroke, and MI). Considering that the use of pioglitazone was associated not only with a reduction in A1C, but also triglycerides, the ratio of LDL to HDL, and blood pressure, whether the beneficial effects of pioglitazone were due to the improvement of glucose, to the amelioration of the other CVD risk factors, or to both remains to be elucidated (22).

The milestone study evaluating glucose control improvement and diabetes complications in type 1 diabetes is the Diabetes Control and Complications Trial (DCCT) (23). As a result of this study, intensive management of glycemia with multiple insulin doses is the gold-standard therapy in subjects with the disease to reduce the burden of microvascular complications (primary and secondary prevention). Because of the low rate of macrovascular events during the follow-up, the study lacked enough power to evaluate the effect of glucose control on CVD (24) (Table 1). The DCCT/Epidemiology of Diabetes Interventions and Complications (EDIC) study followed up 1,341 initial participants evaluating CV events (17 years in total after entry in the DCCT). There was a 42% reduction for any CV event and a 57% reduction for CV death, MI, or stroke in the group originally assigned to intensive management (25). In spite of the fact that the authors attributed this positive finding to the DCCT period of intensive glucose control, this piece of data from the DCCT/EDIC study was derived from an epidemiological and observational investigation. While exciting, these results are far from definitive.

CONCLUSIONS — The lack of positive effects of glycemic control on CVD complications in diabetes in the abovementioned trials that, up to now have assessed this topic, could be due to different factors: low number of subjects included, low number of CV events, not lengthy enough follow-up, low efficacy of therapies that have been used, the degree to which glucose reduction might reduce CVD events has not been achieved, or just because the effect of glycemic control on CVD is superfluous in comparison with the effect of controlling other risk factors in diabetes. Under this context, the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study, which was designed to determine whether intensively lowering blood glucose (below current recommendations) would reduce the risk of CV events or death from CVD, specifically in people with type 2 diabetes who were at a particularly high risk, recently has shown that this strategy is associated with an increased risk of death. Therefore,

the degree to which glucose reduction may safely reduce CVD remains unclear.

In conclusion, currently, the relationship (if there is any) between glucose control and CVD in diabetes is still a matter of controversy. The results of the effect of intensive glucose control in comparison with usual management of major CV events are still inconclusive. In the meantime, an overall strategy toward risk management for our patients with type 1 and type 2 diabetes should place appropriate emphasis on blood pressure and lipid control to reduce the leading complications of diabetes.

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