Providing cardiovascular benefits with safe diabetes therapy

"We should aim to treat diabetic patients to the best glycemic control we can, and try to prevent CVD in these individuals."

Jacob Ilany
Institute of Endocrinology, Sheba Medical Center, Tel-Hashomer, 52621 Israel
Tel.: +972 3530 5382
or +972 523 852 461
Fax: +972 3635 7018
jacob.ilani@sheba.health.gov.il

It is amazing to find how little we know regarding the basics of diabetes after so many years of treatment and research. Recently, the targets for the treatment of diabetes and hyperglycemia were re-evaluated because of the results of several large studies [1]. These studies show that intensive treatment of hyperglycemia may not prevent macrovascular complications related to dysglycemia, and may even increase mortality [2–4]. Should the prevention of cardiovascular disease (CVD) be one of the aims of diabetes treatment?

Diabetes is closely related to CVD. This relation is well established in many studies in different populations. Diabetic patients have a higher prevalence of CVD. In addition, CVD is premature, more extensive and with worse prognosis in diabetic patients. Prediabetic conditions, especially impaired glucose tolerance (IGT), are also related to an increased risk of CVD [5]. In many studies, postprandial glucose levels, both in diabetic and prediabetic patients, are more related to CVD than fasting glucose levels [6]. However, the causality relation is less clear. For example, one large study showed that patients have an increased risk for CVD 15 years or more before developing diabetes [7]. Another study found that diabetic patients lacking other characteristics of the metabolic syndrome do not posses an increased risk for CVD [8]. These results may imply that hyperglycemia *per se* is not the cause of atherosclerosis, but rather a coexisting phenomenon. On the other hand, in other studies such as the United Kingdom Prospective Diabetes Study (UKPDS) [9], a correlation between the level of glycated hemoglobin and the prevalence of CVD was demonstrated, so that one might expect that improving the hemoglobin A1c levels prevents coronary artery disease. However, improving glycemic control, while preventing diabetic microvascular complications, does not efficiently prevent macrovascular complications [10]. As a result, approximately a third of the cardiac intensive care unit (ICU) patients have diabetes, and dysglycemia is probably the most prevalent risk factor in cardiac ICU patients [11]. This led to more intensive treatment regimens aiming to approach near-normal glycemia. As mentioned above, these studies failed to demonstrate CVD prevention, and in one case even found a harmful effect [2–4]. Interestingly, similar findings were found in non-diabetic hyperglycemic patients in the setting of ICUs. Hyperglycemia in this situation is also related to worse outcomes [12]. Studies conducted to correct the hyperglycemia in the ICU showed improved outcome [13,14]. When the glucose target was lowered to a 'normal' level, however, increased mortality was recently reported [15].

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All these studies should be carefully examined before jumping to the conclusion that we should refrain from near-normal glycemia as a target for diabetic patients. Many questions need to be answered, for example:

- What is the reason for the failure to prevent CVD and for the increased mortality in these studies?
- What kinds of treatment were used?
- Is there evidence that any treatment for hyperglycemia can prevent CVD?

In my opinion, several factors can explain, at least partially, the results of these studies. First, in most of the studies of the treatment of Type 2 diabetes, including the recent intensive treatment studies, the target was reducing hemoglobin A1c. Usually, the fasting plasma glucose level was also measured. Unfortunately, despite its importance, postprandial glucose levels are not specifically targeted. It is easier, more convenient and cheaper

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for both the patient and the physician to follow fasting plasma glucose and hemoglobin A1c levels. This is probably the main reason for using these parameters as targets of treatment. Studies with acarbose, a medication that reduces the postprandial glucose level, provided some evidence that macrovascular complications can be prevented by treating hyperglycemia *per se* even in prediabetic patients with normal or near-normal hemoglobin A1c levels [16,17]. The Diabetes Control and Complications Trial (DCCT)/Epidemiology of Diabetes Interventions and Complications (EDIC) study demonstrated that more intensive insulin treatment can prevent CVD in Type 1 diabetic patients [18]. Although in this study the hemoglobin A1c level was higher, treatment with more insulin injections, especially short-acting insulin, probably improves the postprandial glucose control.

Second, many of the recent studies were underpowered because the rate of events was much lower than what was hypothesized in the prestudy sample size calculations. These estimations are based on historical data. It is probably due to the improved treatment of other cardiovascular risk factors (especially hypertension and hyperlipidemia), as well as the hyperglycemic control, that the actual rate of events was lower than expected. This was one of the problems in the Hyperglycemia and Its Effect After Acute Myocardial Infarction on Cardiovascular Outcomes in Patients With Type 2 Diabetes Mellitus (HEART2D) trial, in which treatment of postprandial versus fasting glycemia was compared in post acute myocardial infaction patients [19,20]. Due to this phenomenon, much larger and longer studies will be needed to prove the effect on CVD outcome.

Furthermore, in some of the recently published studies, an important component of the treatment was rosiglitazone. For example, in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study, 91.2% of the intensive therapy group were prescribed rosiglitazone, compared with 57.5% in the standard therapy group [2]. In the Veterans Affairs Diabetes Trial (VADT), most of the patients were treated with rosiglitazone [4]. Rosiglitazone was suspected to be connected with increased CVD incidence and mortality in some recent studies [21,22]. Therefore, it may not be the right medication to prevent CVD.

Regarding the cause of increased mortality in intensive diabetes treatment studies, hypoglycemia is the natural suspect. Patients in the intensive groups have more hypoglycemic events, but the relationship between hypoglycemia and mortality is not clear. In the DCCT study, where CVD was uncommon (young Type 1 diabetes patients), the increased frequency of hypoglycemic events was not associated with mortality [23]. In Type 2 older patients, it is much harder to differentiate cases of suspected cardiac mortality or sudden death from hypoglycemia, and to rule out the possibility that the hypoglycemic event triggered the cardiac event. A recent article shows that even in ICU post acute myocardial infaction patients, insulin treatment-related hypoglycemic events do not cause an excess of mortality [24].

> "*Studies that utilize 'good' medications, while targeting postprandial glucose and preventing cardiovascular disease, are urgently needed.*"

Taking all the above into account, I think that we should aim to treat diabetic patients to the best glycemic control we can, and try to prevent CVD in these individuals. However, we should achieve this by trying:

- First, to target post prandial glucose level specifically and not just normalized A1c;
- Second, to use medications that were shown to prevent CVD like metformin [25], acarbose [16,17] and insulin [18];
- Third, to test and treat patients at risk for occult CVD before further reducing their glucose levels;
- Fourth, to aggressively treat other risk factors (dyslipidemia and hypertension) where treatment proved to prevent coronary events;
- Fifth, to avoid hypoglycemia as much as possible.

New medications that treat post-prandial glucose with minimal risk of hypoglycemia (i.e., glucagon-like peptide-1 analogs and dipeptidyl peptidase-4 inhibitors) may help us to achieve these goals. Some ongoing studies may provide us with some more answers to these questions. For example, the Outcome Reduction With Initial Glargine Intervention (ORIGIN) trial compared intensive and conservative hyperglycemia treatment in high-risk CVD patients. However, it shares some of the above-mentioned problems, which may limit its contribution. Studies that utilize 'good' medications, while targeting postprandial glucose and preventing CVD, are urgently needed.

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