

# Is Hyperglycemia a Cardiovascular Risk Factor?

FRANK PISTROSCH, MD<sup>1,2</sup>  
ANDREA NATALI, MD<sup>3</sup>  
MARKOLF HANEFELD, MD<sup>1</sup>

Patients with diabetes show an increased vascular morbidity and mortality that reduces their life expectancy by ~5–15 years (depending on the age at diagnosis) (1). There is convincing evidence from epidemiological and pathophysiological studies that hyperglycemia per se is largely responsible for the harmful effects of the disease. As recently shown by clinical trials, treatment of this condition may reduce cardiovascular events and mortality, and several therapies should be considered: initiating early and individualized treatment and avoiding hyperglycemia.

## HYPERGLYCEMIA AS A CARDIOVASCULAR RISK FACTOR IN EPIDEMIOLOGICAL STUDIES

As shown in the Multiple Risk Factor Intervention Trial, at any given level of major cardiovascular risk factors, diabetes is associated with an odds ratio of 2–4 for cardiovascular mortality compared with nondiabetic subjects (2). These results were confirmed by the European Prospective Investigation of Cancer and Nutrition (EPIC Norfolk) study (3) and a recent analysis of the Atherosclerosis Risk in Communities (ARIC) study (4).

Furthermore, a recently published 18-year follow-up study from Finland demonstrated a similar impact of type 1 and type 2 diabetes on cardiovascular mortality. The adjusted hazard ratios

compared with age-matched subjects without diabetes were 5.2 and 4.9 for type 1 and type 2 diabetes, respectively (5).

Thus, today evidence exists on long-term follow-up population-based studies in patients with type 1 and type 2 diabetes. This evidence clearly suggests that hyperglycemia is a key risk factor not only for diabetes-related disease, but also for cardiovascular and all-cause mortality. On the basis of these long-term observations, one can assume an increment of cardiovascular disease per increase of 1 unit (%) A1C of ~18% (6).

## PATHOPHYSIOLOGICAL ASPECTS OF ACUTE AND CHRONIC HYPERGLYCEMIA

As shown in numerous prospective studies, the deleterious effects of dysglycemia (fasting and postprandial hyperglycemia) develop before diabetes is diagnosed. In the Glucose Tolerance in Acute Myocardial Infarction study of patients with acute coronary syndrome, abnormal glucose tolerance was the strongest independent predictor of subsequent cardiovascular complications and death (7). In the Asian Pacific Study, fasting plasma glucose was shown to be an independent predictor of cardiovascular events up to a level of ~5.2 mmol/L (8). A fresh look at old facts (the importance of peaks and valleys, or in scientific terms, of quality of glucose homeostasis) was possible when reliable

and precise continuous glucose measurement systems became available for clinical use. As shown by Monnier et al. (9), glucose fluctuations measured as mean average glycemic excursions were closely associated with oxidative stress generation, whereas average glycemic level was not. Already in 1999, our group could show in the Risk Factors in IGT for Atherosclerosis and Diabetes study that parameters of glycemic variability instead of A1C were significantly related to carotid intima-media thickness (10).

Today, we have consistent data from pathophysiological investigations that glucose fluctuations may be a vascular risk factor in its own right. Glucose fluctuations and hyperglycemia are triggers for inflammatory responses via increased mitochondrial superoxide production (11) and endoplasmic reticulum stress (12). The inflammatory responses induced by one transient short-term episode of hyperglycemia might last for several days (13). Inflammation leads to insulin resistance (14) and  $\beta$ -cell dysfunction, which further aggravates hyperglycemia. The molecular pathways that integrate hyperglycemia, oxidative stress, and diabetic vascular complications have been most clearly described in the pathogenesis of endothelial dysfunction (15). According to the response to injury hypothesis, endothelial dysfunction represents the first step of atherogenesis (16).

The results of these molecular investigations were confirmed by studies in patients. Acute hyperglycemia rapidly attenuated endothelium-dependent vasodilation (17,18) and reduced myocardial perfusion (19). Thus, direct effects of glucotoxicity, oxidative stress, and low-grade inflammation act in a vicious circle that impairs insulin sensitivity, accelerates and escalates loss of  $\beta$ -cells, impairs endothelial function, and leads to microvascular and macrovascular disease.

## EFFECTS OF BLOOD GLUCOSE LOWERING ON CARDIOVASCULAR EVENTS IN ADVANCED DIABETES

Because pathophysiological and epidemiological evidence demonstrated a direct link between hyperglycemia and cardiovascular

From the <sup>1</sup>Center for Clinical Studies, Endocrinology and Metabolic Research, GWT (Gesellschaft für Wissenschaft und Technologietransfer), Technical University Dresden, Dresden, Germany; the <sup>2</sup>University Hospital "Carl Gustav Carus," Department of Internal Medicine III, Technical University Dresden, Dresden, Germany; and the <sup>3</sup>Department of Internal Medicine, University of Pisa, Pisa, Italy.

Corresponding author: Markolf Hanefeld, hanefeld@gwtonline-zks.de.

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or all-cause mortality in type 2 diabetic patients, one could expect a risk reduction by glucose-lowering treatment strategies. However, the results of large clinical trials investigating the potential of improved glycemic control to reduce cardiovascular events are not fully convincing. Three mega-trials in patients with type 2 diabetes—the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study (20), the Action in Diabetes and Vascular Disease: Preterax and Diamicon Modified Release Controlled Evaluation (ADVANCE) (21), and the Veterans Affairs Diabetes Trial (VADT) (22)—were recently conducted to clarify whether lowering blood glucose to near-normal levels will reduce cardiovascular risk. All of these trials included older patients with a diabetes duration of 8–11.5 years. One-third of the patients have had a history of cardiovascular disease. Despite an acceptable glycemic control in the intensified treatment arm (ACCORD: A1C 6.4 vs. 7.5%; ADVANCE: A1C 6.4 vs. 7.0%; VADT: A1C 6.9 vs. 8.5% for the intensified treatment vs. standard treatment, respectively), none of these trials showed a significant difference of cardiovascular events between the patients receiving intensified treatment and those receiving standard treatments.

Speculation about the reasons for these disappointing results has been published; however, there is not yet a convincing explanation. A common hypothesis attributed the excess mortality to the higher rate of hypoglycemia in the intensified treatment group. However, as demonstrated by our group using continuous glucose monitoring, the rate of hypoglycemia is not inevitably related to A1C (23). Interestingly, some new post

hoc analyses of the ACCORD study, which has been terminated early because of excess mortality in the intensified treatment arm, indicated a decrease of cardiovascular mortality in patients who indeed reached the target A1C value of 6.0% under intensified treatment (24). In other words, a low A1C itself did not necessarily mean a higher mortality rate.

Some baseline conditions of patients participating in the ACCORD trial might have contributed to cardiovascular mortality, e.g., congestive heart failure and albuminuria/renal impairment or neuropathy (25). These conditions clearly increase the risk for hypoglycemia or hypoglycemia unawareness and hypoglycemia-induced myocardial damage.

Another aspect to consider is the low rate of mortality, especially in the standard treated patients (Table 1) compared with the Steno-2 study (26), another landmark trial, despite the similar age of patients at the end of the trials. This finding reflects the high grade of care for concomitant disorders (e.g., hypertension and hyperlipidemia) in ACCORD, ADVANCE, and VADT and indeed suggests only a partial influence of glycemic control for cardiovascular mortality. However, based on epidemiological data, the mortality rate of standard care patients in these trials was still twice as high as in healthy people (5). A recent meta-analysis of large intervention trials in type 2 diabetes could at least demonstrate a significant improvement of cardiovascular events—a calculated 15% reduction per 1% unit A1C over 5 years of treatment—without a reduction of mortality (27). However, a significant benefit of intensified glucose-lowering treatment for all-cause mortality could be shown in patients with newly diagnosed type

2 diabetes during long-term follow-up of the Diabetes Intervention Study, as shown in Fig. 1 (28).

### EARLY TREATMENT OF HYPERGLYCEMIA AND CARDIOVASCULAR EVENTS—

The Diabetes Control and Complications Trial (DCCT) showed a trend toward a 41% risk reduction of cardiovascular events in type 1 diabetic subjects (29). The post-trial 9-year follow-up observational period demonstrated a cardiovascular benefit for patients previously randomized to the intensive treatment arm—a significant 42% reduction of cardiovascular disease (30).

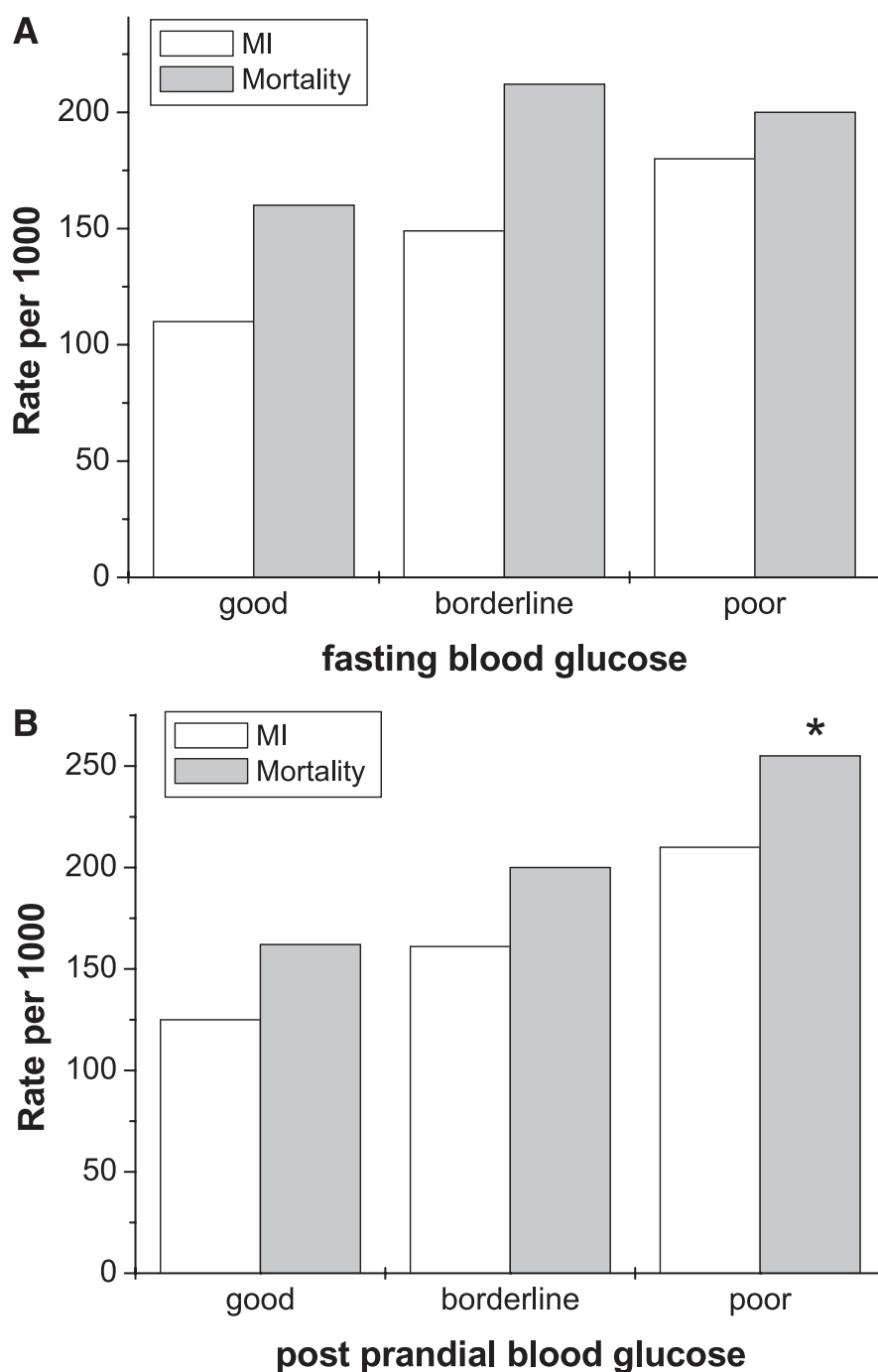
The UK Prospective Diabetes Study, which researched newly diagnosed type 2 diabetes, also failed to demonstrate a significant reduction of cardiovascular events during the core study in the intensive treatment arm compared with the standard treatment (risk reduction 16%,  $P = 0.052$ ) (31). Only a subpopulation of obese patients who were intensively treated with metformin had a cardiovascular benefit (32). However, a 10-year post-trial observational period of the UK Prospective Diabetes Study showed a significant 15% reduction of myocardial infarction and a 17% reduction of diabetes-related deaths in patients who were initially randomized to the intensive treatment arm (33). These results suggest a legacy effect of good glycemic control if initiated during the early stages of type 1 as well as type 2 diabetes.

**CONCLUSIONS**—We conclude that hyperglycemia is still a key cardiovascular

**Table 1—Selected baseline characteristic of patients (age, A1C, blood pressure, and LDL cholesterol), cardiovascular end point, and yearly mortality rate of recent large prospective intervention studies with regard to glycemic control**

	ACCORD (20)	ADVANCE (21)	VADT (22)	Steno-2 (26)
<i>n</i>	10,251	11,140	1,791	160
Follow-up (years)	3.5	5.0	5.6	13.3
Age (years)	62.2 ± 6.8	66 ± 6	60.5 ± 9.0	55.1 ± 7.2
BMI (kg/m <sup>2</sup> )	32.2 ± 5.5	28 ± 5	31.2 ± 4.0	30.7 ± 5.2
Diabetes duration (years)	10	7.9 ± 6.3	11.5 ± 7.0	5.8
A1C (%)	8.3 ± 1.1	7.5 ± 1.6	9.4 ± 2.0	8.6 ± 1.6
Blood pressure systolic/diastolic (mmHg)	136/75 ± 17/11	145/81 ± 22/11	132/76 ± 17/10	147/85 ± 20/10
LDL cholesterol (mmol/L)	2.71 ± 0.88	3.12 ± 1.04	2.79 ± 0.88	3.4 ± 0.93
Hazard ratio of intensified treatment for primary end point (MACE, 95% CI)	0.90 (0.78–1.04)	0.90 (0.82–0.98)	0.88 (0.74–1.05)	0.41 (0.25–0.67)
Yearly mortality rate (%) of the entire study population (intensified/standard therapy)	1.28 (1.41/1.14)	1.85 (1.78/1.92)	1.96 (2.03/1.81)	3.0 (2.25/3.75)

MACE, major adverse cardiovascular event.



**Figure 1**—Diabetes Intervention Study 11-year follow-up: incidence of myocardial infarction (MI) and all-cause mortality by quality of glycemic control. Fasting blood glucose values (A) and postprandial blood glucose values (B) (28). \*P < 0.05 vs. good control.

risk factor for patients with type 2 diabetes, and treatment of hyperglycemia to near-normal levels might reduce cardiovascular events and mortality of these patients if we consider several aspects: 1) an early initiation of treatment seems to be necessary, 2) hypoglycemia should be avoided, and 3) an individualized therapeutic regimen should be developed,

taking into account concomitant diseases and the individual risk profile.

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