Is glycemic control relevant to cardiovascular clinical outcomes?

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Abstract

In patients with diabetes mellitus (DM), cardiovascular disease (CVD) and the onset of acute coronary syndromes are more prevalent than in the nondiabetic population: the mere presence of DM can be considered an equivalent of CVD. Furthermore, in diabetic patients, the classic risk factors for CVD are present in a much more severe form. However, an important—probably the most important—risk factor for CVD is the presence of microangiopathy. The question of whether glycemic control influences cardiovascular outcomes is multifaceted and requires more than a simple "yes or no" answer. Recent data have shown that treatment regimens to decrease blood glucose levels are often unnecessarily aggressive. To overcome the issue of increased incidence of hypoglycemia, especially in elderly patients with CVD, it is essential not only to seek a glycemic target more in line with the life expectancy of the patient and the real needs of prevention, but also to use drugs that do not induce hypoglycemia. In this context, incretin hormones have been an important therapeutic innovation in the field of diabetes treatment; nonetheless, of the sulfonylureas (SUs), gliclazide modified release (gliclazide MR) has robust evidence showing it to be the one that induces less hypoglycemia and cardiovascular events. ADVANCE (Action in Diabetes and Vascular disease: PreterAx and Diamicron MR Controlled Evaluation) is the only megatrial that has shown a benefit in terms of microvascular disease progression. That finding is important, as not only are micro- and macrovascular disease tightly intertwined, but the former frequently predicts the latter. ■ *Heart Metab*. 2015;68:20-26

Keywords: cardiovascular disease; diabetes mellitus; microvascular complications; risk factors

The mechanisms leading to atherosclerosis in patients with type 2 diabetes mellitus (DM) are complex (*Figure 1*), and they can be both metabolic and inflammatory. Hyperglycemia is firstly associated with endothelial activation and then later with dysfunction. In the presence of the latter, endothelial cells lose vasodilatory properties, vascular smooth muscle cells constrict and proliferate, procoagulant factors increase, and proteolytic enzymes, such as matrix metalloproteinase, become more active.[1] The regeneration of endothelial cells after de-endothelialization is slower, due to reduced numbers and activity of endothelial progenitor cells derived from bone marrow.[2] Furthermore, the end products of advanced glycation (AGE), with their specific receptors, disrupt the barrier function of the endothelium. These changes may explain the increase in vascular permeability and transport of macromolecules across the endothelium. Increased oxidative stress is among the possible mechanisms by which DM can induce

Abbreviations

ACCORD: Action to Control Cardiovascular Risk in Diabetes; **ADVANCE:** Action in Diabetes and Vascular disease: PreterAx and Diamicron MR Controlled Evaluation; **ADVANCE-ON:** ADVANCE posttrial ObservatioNal study; **CHD:** coronary heart disease; **CVD:** cardiovascular disease; **DM:** diabetes mellitus; **DPP-4:** dipeptidyl peptidase-4; **EMPA-REG OUTCOME:** Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients; **EPIC-Norfolk:** European Prospective Investigation into Cancer and Nutrition-Norfolk [cohort study]; **EXAMINE:** EXamination of cArdiovascular outcoMes with alogliptIN versus standard carE in patients with type 2 diabetes mellitus and acute coronary syndrome; **FAST-MI:** French registry of Actue ST-elevation and non–ST-elevation Myocardial Infarction; **GLP-1:** glucagon-like peptide-1; **HbA$_{1c}$:** glycated hemoglobin A$_{1c}$; **MR:** modified release; **ORIGIN:** Outcome Reduction with Initial Glargine INtervention; **PROactive:** PROspective pioglitAzone Clinical Trial In macroVascular Events; **RECORD:** Rosiglitazone Evaluated for Cardiovascular Outcomes in and Regulation of glycemia in Diabetes; **SAVOR:** Saxagliptin Assessment of Vascular Outcomes Recorded in patients with diabetes mellitus; **SU:** sulfonylurea; **TECOS:** Trial Evaluating Cardiovascular Outcomes with Sitagliptin; **UKPDS:** United Kingdom Prospective Diabetes Study; **VADT:** Veterans Affairs Diabetes Trial

endothelial dysfunction.[3] DM, in addition to the traditional dysmetabolic framework, is characterized by the presence of a chronic subclinical inflammatory process, which at the later stage of the disease may account for plaque vulnerability, and the onset of acute coronary syndromes.

The relationships between HbA$_{1c}$ and cardiovascular disease

Cardiovascular disease (CVD) is detectable even when levels of glycated hemoglobin A$_{1c}$ (HbA$_{1c}$) are well below the diagnostic threshold for DM, 6.5% (48 mmol/mol). In the EPIC-Norfolk cohort study (European Prospective Investigation into Cancer and Nutrition-Norfolk), the relative risk of CVD mortality increased continuously, in both genders, according to HbA$_{1c}$.[4] Compared with a concentration of HbA$_{1c}$

equal to 5%, each 1% increase in HbA$_{1c}$ was associated with a 20% increase in CVD events. A recent analysis involving participants with no previous history of CVD and DM has shown an association between CVD and HbA$_{1c}$: HbA$_{1c}$ was better at predicting cardiovascular risk than were fasting plasma glucose and postprandial glucose levels.[5] In patients with DM, for every percentage point increase in HbA$_{1c}$, the relative risk of CVD was equal to 1.18 for patients with type 2 DM and 1.15 for patients with type 1. Significant coronary lesions are found post mortem in 50% to 80% of diabetics without a diagnosis of coronary heart disease (CHD) in life. An analysis by the Emerging Risk Factors Collaboration considered data extracted from 698 782 persons evaluated in 102 prospective studies: in patients with DM, the risk associated with ischemic heart disease was equal to 2.00; with ischemic stroke, 2.27; with hemorrhagic stroke, 1.56; and with death from CVD, 1.73.[6] In a recent cohort study including nearly 2 million people with type 2 DM, it was determined that 17.9% of patients had a first episode of CVD where symptoms of peripheral artery disease were commonly the first clinical sign.[7] Due to the high prevalence of CVD in patients with type 2 DM, the mere presence of DM can be considered an equivalent of CVD.

Microangiopathy is the most important risk factor for macroangiopathy

Microvascular complications independently predict CHD; this is true both for nephropathy and retinopa-
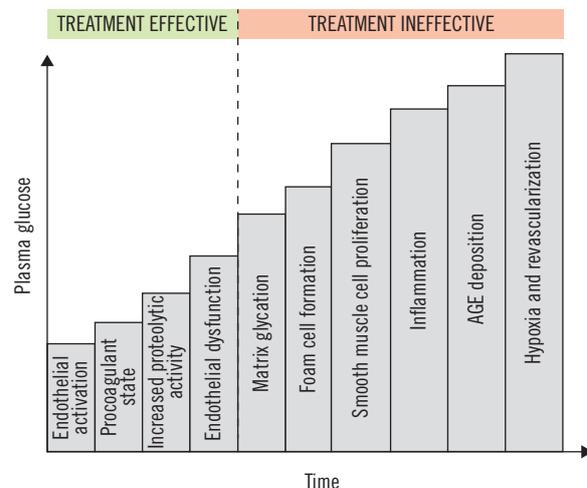

Fig. 1 *Hypothetical time course of different pathogenetic mechanisms induced by hyperglycemia on the vascular wall, and their possible responses to antidiabetic treatment.*
Abbreviations: *AGE, advanced glycation end product.*

thy. A reduction in renal function and the presence of microalbuminuria independently associate with and predict CVD.[8] High blood pressure is a major risk factor for microalbuminuria, which itself is a predictor of macroproteinuria and overt nephropathy. The relationship between urinary albumin excretion and cardiovascular events is positive and begins at levels of albuminuria that are lower than those considered normal.[9] Microalbuminuria not only predicts CHD, but also cerebrovascular and peripheral artery disease. Equally important is the presence of retinopathy: the diameter of the retinal vessels is a predictor of mortality from stroke and CHD in middle-aged people.[10] The presence of proliferative retinopathy, compared with its absence, confers a 25-fold greater risk of nontraumatic amputation of the lower limbs.[11] The presence of some form of microangiopathy is associated with an increased incidence of a first coronary event both in men and in women.[12] Similarly, neuropathy is a powerful predictor of events and CVD mortality. It is still debatable whether microvascular complications are mere markers or whether they can be considered an early stage of CVD. It is commonly considered that microangiopathy is a late event in the natural history of DM; however, this assumption is not entirely correct as it can be detected in the heart even in the absence of overt CHD.[13] In light of these observations, one can hypothesize that micro- and macroangiopathy represent a continuum of what we consider diabetic angiopathy (*Figure 2*).

Does glycemic control reduce cardiovascular disease?

The question of whether glycemic control influences cardiovascular outcomes is multifaceted and cannot be answered by a simple "yes" or "no." While there is much evidence that the risk of cardiovascular mortality increases with an increase in HbA_{1c}, the intervention trials aimed to determine whether a reduction in HbA_{1c} is associated with a reduction in CVD have offered controversial results at best.

The UKPDS trial (United Kingdom Prospective Diabetes Study) was designed to investigate whether, in new-onset type 2 DM patients, tight glycemic control can reduce both micro- and macrovascular complications.[14] In that study, treatments with sulfonylurea (SU), metformin, or insulin reduced microvascular complications; this positive effect was noticed after the trial's end. The UKPDS trial did not demonstrate a clear-cut positive effect on macrovascular complications from intensified glycemic control: metformin treatment reduced the risk of macrovascular disease only in a small subset of obese diabetics. However, a significant reduction in events has been shown during posttrial monitoring, thus suggesting a protective effect on macrovascular disease from intensified glycemic control when implemented immediately after clinical diagnosis.[15]

Regrettably, the results of other large studies, such as ACCORD (Action to Control Cardiovascular Risk in Diabetes), PROactive (PROspective pioglitAzone Clinical Trial In macroVascular Events), RECORD (Rosiglitazone Evaluated for Cardiovascular Outcomes in and Regulation of glycemia in Diabetes), and VADT (Veterans Affairs Diabetes Trial) seem to deny the notion that tight glycemic control might provide protection against CVD in DM patients.[16] A recent meta-analysis reported that meticulous control of blood sugar produces a limited benefit in terms of mortality from all causes and cardiovascular mortality.[17] The same authors argue that the benefits of an intensive treatment to control blood glucose can be offset by an increase in hypoglycemia. This has led some authors to conclude that, even today, we find ourselves in a "dark age" in terms of the treatment of diabetes.[18] The reasons for this failure are several: the drugs used in these trials induced an increased incidence of hypoglycemia and weight gain, and the patients enrolled already had advanced CVD, a stage of the disease in which the glucose-induced damage is probably minor when compared with that due to other risk factors.
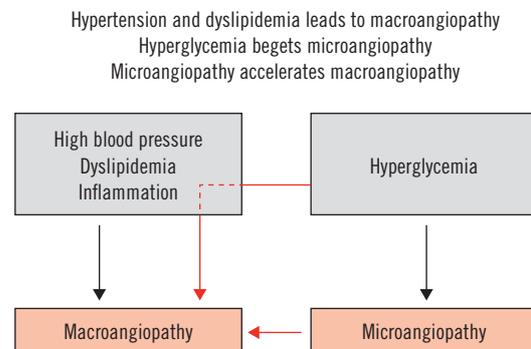
Hypertension and dyslipidemia leads to macroangiopathy
Hyperglycemia begets microangiopathy
Microangiopathy accelerates macroangiopathy

Fig. 2 *High blood pressure, dyslipidemia, and inflammation are the most important risk factors for macroangiopathy. Hyperglycemia, which is the single most important risk factor for microangiopathy, potentiates the effect of the other risk factors on macroangiopathy. Moreover microangiopathy is, itself, a powerful risk factor for macroangiopathy.*

In that context, numerous studies have shown that the pharmacological treatment of dyslipidemia and hypertension significantly reduce major cardiovascular events regardless of the presence or absence of CVD, both in patients with or without DM.[19] In the STENO-2 study, a 70% risk reduction in patients with type 2 DM at high cardiovascular risk was attributed to statin treatment.[20] Another possible reason for the poor outcome in some of the megatrials is that the HbA$_{1c}$ target was too ambitious for patients with comorbidities and advanced age.

Having said that, there are several demonstrations highlighting the importance of blood glucose control in DM patients. The STENO trial showed approximately a 50% reduction in cardiovascular mortality in patients with type 2 diabetes at high risk when all the major cardiovascular risks, together with antiplatelet treatment, approached targets. In the VADT trial, intensive glycemic control reduced cardiovascular events in those with a lower extent of calcification in the coronary tree and in patients with disease duration of less than 15 years.[21] The recently published follow-up of that trial shows that DM patients who were randomly assigned to intensive glycemic control for 5.6 years had 8.6 fewer major cardiovascular events per 1000 person-years than those assigned to standard therapy[22]; however, no improvement was seen in the rate of overall survival. In support of this

finding, further meta-analysis showed that randomization to intensive glycemic control reduced the risk of major cardiovascular events by 9%, mainly attributed to a reduction in the risk of myocardial infarction by 15%. The benefit was observed mainly in patients without apparent CVD. A recent analysis of the ACCORD study showed that myocardial infarction, coronary revascularization, and unstable angina were less frequent in patients randomized to intensive treatment compared with standard treatment; this advantage was lost for the lowest values of HbA$_{1c}$.[23]

Four meta-analyses conducted on several studies—UKPDS, ACCORD, VADT, and ADVANCE (Action in Diabetes and Vascular disease: PreterAx and Diamicron MR Controlled Evaluation)—showed, in spite of an average increase in the risk of hypoglycemia equal to 2.59, a 14% reduction in the risk of myocardial infarction, with no increase in mortality.[24] The increased hypoglycemia observed in the trials is not necessarily linked to the glycemic targets achieved; it also depends on the type of treatment used. For example, the ORIGIN study (Outcome Reduction with Initial Glargine INtervention), which demonstrated a neutral cardiovascular effect on treatment with basal insulin (*Figure 3*), showed that the incidence of hypoglycemia was significantly lower, with the same glycemic control, in those who were randomized to insulin glargine.[25] The PROactive study demonstrated that
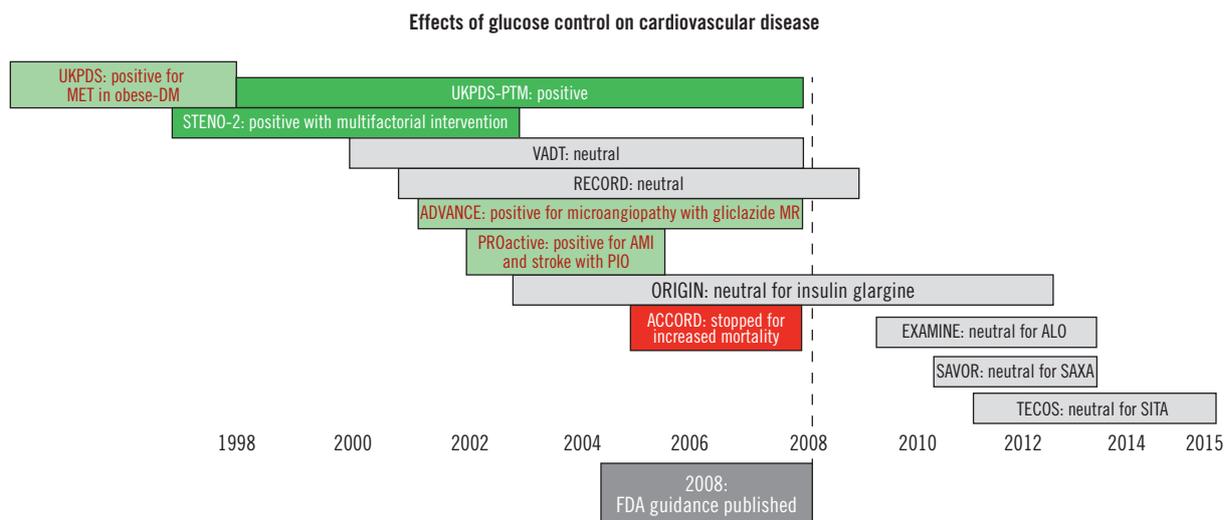

Fig. 3 *Time line for efficacy and safety megatrials in type 2 diabetic patients, and their results (positive/neutral) in regards to cardiovascular disease.*

Abbreviations: *ACCORD, Action to Control Cardiovascular Risk in Diabetes; ADVANCE, Action in Diabetes and Vascular disease: PreterAx and Diamicron MR Controlled Evaluation; ALO, alogliptin; AMI, acute myocardial infarction; DM, diabetes mellitus; EXAMINE, EXamination of cArdiovascular outcoMes with alogliptIN versus standard carE in patients with type 2 diabetes mellitus and acute coronary syndrome; FDA, US Food and Drug Administration; gliclazide MR, gliclazide modified release; MET, metformin; ORIGIN, Outcome Reduction with Initial Glargine Intervention; PIO, pioglitazone; PROactive, PROspective pioglitAzone Clinical Trial In macroVascular Events; PTM, posttrial monitoring; RECORD, Rosiglitazone Evaluated for Cardiovascular Outcomes in and Regulation of glycemia in Diabetes; SAXA, saxagliptin; SAVOR, Saxagliptin Assessment of Vascular Outcomes Recorded in patients with diabetes mellitus; SITA, sitagliptin; TECOS, Trial Evaluating Cardiovascular Outcomes with Sitagliptin; UKPDS, United Kingdom Prospective Diabetes Study; VADT, Veterans Affairs Diabetes Trial.*

treatment with pioglitazone reduced acute coronary syndrome by 37% in those who had been randomized to the drug and reduced fatal and nonfatal stroke by 47% in patients with a previous stroke.[26] The landmark study ADVANCE showed that intensive glycemic control significantly reduced the primary end point owing to a significant reduction in microvascular outcome, with no significant reduction in macrovascular outcome.[27] Indeed, that study demonstrated a significant reduction in the risk of new or worsening albuminuria when median HbA_{1c} was lowered to 6.3% compared with standard glycemic control. There was no increase in overall or cardiovascular mortality in the intensive compared with the standard glycemic control arm; furthermore, patients had no significant weight gain. Most importantly, patients experienced less severe hypoglycemia: <3% of intensively treated ADVANCE participants, approximately 16% of intensively treated ACCORD patients, and 21% of intensively treated VADT patients. These differences may be related to differences in therapeutic approach; in the ADVANCE trial, the number of patients on insulin treatment was significantly smaller than that in the ACCORD and VADT trials. Second, weight change in the intensively treated patients was smaller than in other trials. Third, the reduction in HbA_{1c} levels was less aggressive in the ADVANCE trial than in AC-CORD and VADT. Fourth, in both arms of the VADT and ACCORD trials, multiple drugs were employed; in ADVANCE, treatment with multiple drugs added to gliclazide modified release (gliclazide MR, a sulfonylurea) was compared with treatment with multiple drugs with no gliclazide.

The effects of gliclazide on cardiovascular safety may be explained by some particular mechanisms of action, eg, it may decrease the ongoing oxidative stress both in the vessel wall and in the kidney.[28] Given the importance of protecting the kidney in order to avoid future cardiovascular events, that drug effect is important from a pathophysiological perspective. Gliclazide has been shown to be superior to other SUs, not only by the ADVANCE study, but also by FAST-MI (the French registry of Acute ST-elevation and non–ST-elevation Myocardial Infarction). FAST-MI collects comprehensive data on the management and outcome of consecutive patients admitted to intensive care units for definite acute myocardial infarction over a 1-month period in France, irrespective of the type of institution to which the patients were admitted.[29]

Of the 374 centers that treated patients with acute myocardial infarction at that time, 223 participated in the study (60%). Mortality was significantly lower in patients previously treated with SUs (3.9%) vs those on other oral medications (6.4%), insulin (9.4%), or no medication (8.4%) (*P*=0.014). Among SU-treated patients, in-hospital mortality was lower in patients receiving pancreatic cell–specific SUs (gliclazide or glimepiride) (2.7%), compared with glibenclamide (7.5%) (*P*=0.019). Monami and colleagues, in a retrospective observational cohort study performed on a consecutive series of 568 outpatients with type 2 DM treated with either glibenclamide or gliclazide, observed 33 and 11 deaths in the glibenclamide and gliclazide groups, respectively, with a yearly mortality rate of 4.3% and 2.2% (*P*<0.05).[30] On Cox regression analysis, after adjustment for potential confounders, including comorbidity, glibenclamide treatment was associated with a significant increase in all-cause mortality (*P*<0.05). In the Danish Registry, a total of 107 806 subjects were included, of whom 9607 had previous myocardial infarction. Compared with metformin, in patients with previous myocardial infarction, gliclazide treatment was not associated with increased mortality, which was observed for glimepiride, glibenclamide, glipizide, and tolbutamide.[31]

Recently, Simpson and colleagues investigated whether mortality and the risk of CVD events varies according to the type of SU prescribed.[32] The relative risk of death compared with glibenclamide was 0.65 (95% confidence interval [CI], 0.53-0.79) for gliclazide, 0.83 (95% CI, 0.68-1.00) for glimepiride, 0.98 (95% CI, 0.80-1.19) for glipizide, 1.13 (95% CI, 0.90-1.42) for tolbutamide, and 1.34 (95% CI, 0.98-1.86) for chlorpropamide. Similar associations were noted for cardiovascular-related mortality. These data confirm that gliclazide is associated with a lower risk of all-cause and cardiovascular-related mortality compared with glibenclamide.

The recent results from the ADVANCE-ON (ADVANCE posttrial ObservatioNal study) monitoring data have confirmed the cardiovascular safety of gliclazide MR.[33] The implications of these studies are that clinicians should consider possible differences in risk of mortality when selecting a SU. In 2008, the US Food and Drug Administration (FDA) issued guidance on the assessment of cardiovascular risk for new drugs to treat type 2 DM. The first three safety studies published to date are SAVOR (Saxagliptin Assess-

ment of Vascular Outcomes Recorded in patients with diabetes mellitus), EXAMINE (EXamination of cArdiovascular outcoMes with alogliptIN versus standard carE in patients with type 2 diabetes mellitus and acute coronary syndrome), and TECOS (Trial Evaluating Cardiovascular Outcomes with Sitagliptin).[34-36] These three trials, conducted in DM patients at high and very high risk, demonstrated good safety profiles for saxagliptin, alogliptin, and sitagliptin, respectively. However, in the SAVOR study, increased hypoglycemia and hospitalization for heart failure was observed in patients randomized to saxagliptin treatment. Very recently, the study EMPA-REG OUTCOME (Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients) was published: in this trial, the type 2 sodium-glucose transporter inhibitor (SGLT2) empagliflozin significantly reduced the 3-point (cardiovascular death, nonfatal acute myocardial infarction, and nonfatal stroke) major adverse cardiac event rate by 14%. This study, along with a previous study on dipeptidyl peptidase-4 (DPP-4) inhibitors, offers an additional and reassuring therapeutic approach for those with type 2 diabetes.[37] We are currently awaiting a number of other trials that will evaluate the safety of DPP-4 inhibitors and glucagon-like peptide-1 (GLP-1) receptor agonists.

Conclusions

It is clear that unnecessarily aggressive treatment to decrease blood glucose is often implemented in patients with comorbidities. To avoid the increased incidence of hypoglycemia, especially in elderly patients with CVD, it is necessary not only to seek a glycemic target more in line with the life expectancy of the patient and the real needs of prevention, but also to use drugs that do not induce hypoglycemia. The advent of incretin hormones in this context has been an important therapeutic innovation in the field of diabetes treatment; nonetheless, among SUs, there is robust evidence that gliclazide MR induces less hypoglycemia and cardiovascular events. Of the megatrials, ADVANCE is the only study that has shown a benefit in terms of microvascular disease progression. This is of importance as not only are micro- and macrovascular disease tightly intertwined, but the former frequently predicts the latter. Acknowledging glycemic control to be a weak strategy for improving the cardiovascular prognosis of DM patients is necessary, not only to

promote the design of innovative strategies, but also to better understand the mechanisms underlying cardiovascular events. So, to the question Is glycemic control relevant to cardiovascular clinical outcomes? the answer is yes, depending on the therapeutic approach to be used. ■

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