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ST. MICHAEL'S HOSPITAL, UNIVERSITY OF TORONTO, ONTARIO

Scientific Update™

Glycemic control in diabetes: Does it matter?

Originally presented by: Lawrence A. Leiter, MD, FRCPC, with an introduction by Bernard Zinman, MD, FRCPC

An educational report from a Satellite Symposium presentation at the 2008 Canadian Cardiovascular Congress

October 25-29, 2008 Toronto, Ontario

By KAMRAN AHMAD, MD, FRCPC

Diabetes mellitus is a state of premature cardiovascular death associated with chronic hyperglycemia and may also be associated with blindness and renal failure. – Miles Fisher

Although cardiovascular disease (CVD) eclipses many of the disabling and fatal complications of diabetes and diabetes management leads to a reduction in microvascular as well as macrovascular complications, it may be incorrect to assume that effective management of diabetes will lead to a reduction in CV events in the same time frame as management of other modifiable CV risk factors, such as hypertension, lipids, and smoking. Evidence of a reduction in macrovascular complications may not be detected until years after reductions in microvascular complications. This issue of *Cardiology Scientific Update* reviews the literature surrounding the relationship between glucose control and the risk of CVD.

Traditional markers of effective diabetes management (eg, adequately low fasting blood sugars, glycated hemoglobin [HbA_{1c}]) are correlated with a reduction in microvascular events, but may not be as strongly correlated with a reduction in macrovascular events. Other aspects of glycemic control (such as glucose "excursions" beyond the normal range and glucose variability) are not well reflected in fasting blood glucose (FBG) and HbA_{1c} measurements. These other aspects may remain suboptimally controlled in the face of adequate HbA_{1c} measurements and FBG, and have a strong correlation with increased macrovascular disease in diabetes. Current Canadian Diabetes Association (CDA) guidelines continue to emphasize the importance of glucose control, but elements of diabetes management that have a stronger impact on macrovascular disease may be addressed by long-term follow-up of clinical trials to find better predictors of macrovascular disease, as well as by glucose management other than "tight" glucose control (eg, HbA_{1c} and FBG measures) and, potentially, by new device technologies such as continuous subcutaneous insulin infusion (CSII, or "insulin pump") and continuous glucose monitoring.

The Impact of Diabetes

Currently, 171 million people worldwide have diabetes and this number is projected to reach 366 million by 2030. The current population burden of diabetes is expected to result in 3 million deaths, 1 million amputations, and 500,000 new cases of renal failure. The costs of treatment are estimated to be US$ 150 billion.[1] Diabetes has long been known as a risk factor for coronary artery disease (CAD), but estimates for the magnitude of CV morbidity and mortality resulting from diabetes have varied between studies. In 1998, the concept of diabetes as a "coronary equivalent" was suggested;[2] when data indicated that adjusted mortality in diabetic patients was equivalent to mortality in non-diabetic patients with a previous myocardial infarction (MI). More recent data, however, suggests that the associated risk for CAD in diabetic patients is not that high, but is still clearly higher than patients without diabetes.[3]

Reasons to Improve Glucose Control

Improved glucose control undoubtedly reduces the incidence of blindness, nephropathy, and diabetic neuropathy; therefore, even without considering a reduction in CVD, there are compelling reasons to maintain normoglycemia. To reduce these complications, the HbA_{1c} targets suggested by various guidelines range between 6.5% and 7.0%;[4-10] however, only 37%-68% of patients achieve those targets.[11-15] Suboptimal glycemic control is associated with an increase in all the complications of diabetes, CV events included. A borderline elevated FBG of 6.1 mmol/L has been associated with a relative risk (RR) of 1.33 for CV events (eg, amputations and MIs).[16] In the Epic-Norfolk population study,[17] a 1% increase in HbA_{1c} was associated with a 22% increase in CVD events and a 20% increase in mortality. This relationship was observed for values of HbA_{1c} <6%; yet, while most diabetes trials have shown a clear reduction in

St. Michael's Hospital, 30 Bond St., Suite 7049, Queen Wing, Toronto, Ontario M5B 1W8 Fax: (416) 864-5941

Table 1: Does intensive glycemic control reduce macrovascular complications in T2DM?

	UKPDS[19] (N=3867)	ADVANCE[20] (N=11 140)	ACCORD[21] (N=10 251)	VADT[22] (N=1791)
HbA_{1C} (%)	7.0 vs 7.9	6.5 vs 7.3	6.4 vs 7.5	6.9 vs 8.4
Macrovascular events	MI	CV death, MI stroke	CV death, MI stroke	Any major CV event
Relative risk reduction (%)	16	6	10	13
P value	0.052	0.32	0.16	0.12

In recent trials of intensive vs. conventional insulin therapy, statistically significant differences in cardiovascular (CV) event rates were not observed in the initial follow up period. Lower CV event rates were observed in longer follow up of earlier trials of intensive vs conventional insulin therapy. T2DM = type 2 diabetes mellitus; MI = myocardial infarction

microvascular events with increased glycemic control, a reduction in CV events has not been as strongly demonstrated.

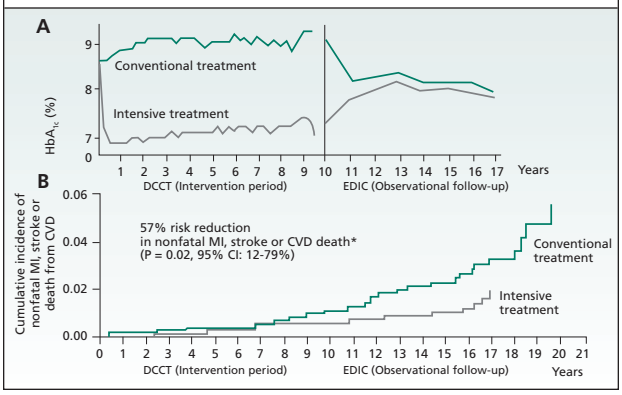
CV Event Reduction in Trials of Glucose Lowering

The two landmark trials comparing conventional versus intensified glucose control are the Diabetes Control and Complications Trial (DCCT)[18] and the United Kingdom Prospective Diabetes Study (UKPDS).[19] The DCCT randomized 1441 type 1 diabetics (T1DM) to conventional vs intensified glycemic control with an average of 6.5 years of follow-up. While there was significant reduction in microvascular complications, no lowering of CV events was observed with intensified therapy.[18] The UKPDS randomized 4209 patients with a new diagnosis of type 2 diabetes (T2DM) to conventional vs intensified glycemic control. After an average follow-up of 10 years, intensified control resulted in significantly fewer microvascular complications; CV events were reduced by 16%, but this did not meet statistical significance.[19]

Three more recent trials examined the effect of conventional vs intensified glucose control on the reduction of CV events in T2DM patients, who were older than the subjects in the UKPDS, had a longer duration of diabetes, and a higher risk for CV events. In the Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) trial,[20] a reduction of HbA_{1c} to 6.5% vs 7.3% in the control group was achieved, but this only resulted in a nonsignificant 6% RR reduction for MI. The Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial[21] achieved an HbA_{1c} of 6.4% (intensified control) vs 7.5% (conventional control) with a nonsignificant 10% reduction in CV endpoints. The sponsoring National Heart, Lung, and Blood Institute (NHLBI) terminated the intensified vs conventional control arm 18 months early because of excess mortality in the intensified arm (257 vs 203 deaths). The Veterans' Administration Diabetes Trial (VADT)[22] achieved an HbA_{1c} of 6.9% (intensified) vs 8.4% (control) and a nonsignificant 13% RR reduction in CV events (Table 1).

Should these results make clinicians pessimistic about the likelihood of a reduction in CV events achieved by tighter glycemic control in diabetic patients? Initially, the results appear incongruous with epidemiologic observations indicating fewer CV events corresponding with lower HbA_{1c} levels. When these

Figure 1: DCCT/EDIC: glycemic control reduces the risk of nonfatal MI, stroke or death from CVD in T1DM[23-25]



* Intensive vs conventional treatment

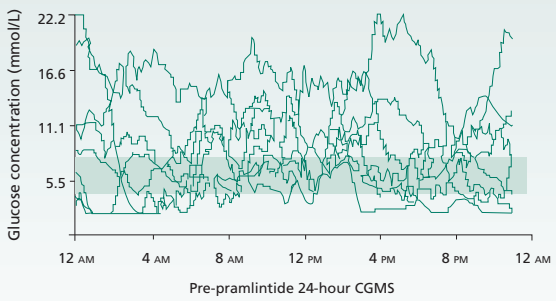
Even after cessation of trial-directed intensive insulin therapy, a late benefit of fewer CV complications was observed in long-term follow-up of the intensive insulin therapy group. A. Adapted from DCCT. *N Engl J Med.* 1993;329(14):977-986,[23] and DCCT/EDIC. *JAMA.* 2002; 287(19):2563-2569.[24] B. Copyright © 2005, Massachusetts Medical Society. All rights reserved. DCCT = Diabetes Control and Complications Trial; EDIC = Epidemiology of Diabetes Interventions and Complications (study); CVD = cardiovascular disease; Hb = hemoglobin

trial results are reconsidered in terms of treatment duration, follow-up, and time of treatment initiation, these elements may explain why CV event reductions are not as high as anticipated. Furthermore, many aspects of glycemic control are manifest beyond just the achieved HbA_{1c} value.

Long-term follow-ups of the DCCT and UKPDS trials have revealed important data about the expected time frame and reasons for CV-event reduction in diabetes. In 2005, long-term follow-up study of DCCT patients demonstrated that in all subjects, HbA_{1c} values were observed to drift towards a value between the values of the intensified vs conventional control after the initial study ended. There was a divergence in CV-event risk in long-term follow-up (Figure 1);[23-25] those patients who had been under intensified control had fewer CV events. A similar phenomenon was observed in the UKPDS;[26] there was a "legacy" effect of earlier, intensified glycemic control early in the course of disease observed in a 2008 long-term follow-up study. In fact, a 16% RR reduction in MI was observed that was statistically significant at the 14-year follow-up (*P*=0.014), whereas the same magnitude of risk reduction fell just outside of significance at the 6-year follow-up (*P*=0.05).[26] These differing results when compared with ADVANCE, ACCORD, and VADT suggest that at least 10 years of follow up are needed to detect a reduction in CV events with intensified vs conventional control in diabetes. They also suggest that intensive control is more effective in reducing CV events, if it is applied at an earlier stage of diabetes, perhaps even before macrovascular disease is immediately apparent.

A recent joint statement of the American Diabetes Association (ADA) and the American Heart Association (AHA) acknowledges the results of the ACCORD, ADVANCE, and VADT trials.[27] It emphasizes that adequate glycemic control (HbA_{1c} <7%) unequivocally reduces the incidence of microvascular disease and in general this benchmark should be adhered to. Primary and secondary prevention of CVD by nonglycemic risk reduction (blood pressure, lipids, smoking cessation, acetyl-

Figure 2: HbA_{1c} alone may not tell the full story of glycemic control[28]



- N=9, treated with continuous subcutaneous insulin infusion (insulin lispro)
- Mean HbA_{1c} = 6.7% (range 5.8%-7.1%)
- 24-hour continuous glucose monitoring sensor data
- Desired glycemic range in nondiabetic subjects: 4.4-7.7 mmol/L

For the same HbA_{1c} values in different patients, there was a wide daily variation in glucose concentration between patients with some exhibiting a great deal of glycemic variability while others had much less variability.
CGMS = continous glucose monitoring system

salicylic acid [ASA], and statins when appropriate) should also continue to be aggressively pursued in diabetics. The AHA and ADA maintain that the <7% goal is appropriate for the prevention of macrovascular disease based on long-term follow-up of the DCCT and UKPDS, particularly in the years soon after diabetes diagnosis. A less stringent target is suggested to be appropriate for patients with a history of severe hypoglycemia, limited life expectancy, advanced microvascular or macrovascular complications, or extensive comorbid conditions or those with longstanding diabetes in whom the general goal is difficult to attain despite all reasonable therapeutic efforts.

Glycemic Control – HbA_{1c} May Not be the Full Story

The weak early reduction in mortality and CV event rates may be due (as previously noted) to a delayed effect of intensive glycemic control. The ACCORD study demonstrated a worrisome finding of increased mortality with intensive control in patients with high CV risk, which also diminishes any potential beneficial effect of intensive glycemic control on CV events. There are other measures of glycemic control that can vary considerably in diabetic patients with the same HbA_{1c}. Indeed, two patients can have either stable random blood glucose values with little variation or wide "excursions" or variations in blood glucose and still have the same HbA_{1c} measurement after 3 months (Figure 2).[28] Postprandial glucose as well as FBG are 2 frequently used clinical measures that reflect variability in blood glucose. Newer technologies, such as continuous glucose measurement as provided by glucose monitoring devices and some subcutaneous insulin infusion systems, can demonstrate these variations as well as the frequency of hypoglycemic events. These measures can predict mortality, morbidity, and CV events and interventions targeting these measures may also reduce events.

The Diabetes Epidemiology: Collaborative analysis Of Diagnostic criteria in Europe (DECODE) study[29] analyzed the results from a number of prospective European studies of morbidity and mortality in diabetes with reference to FBG and 2-hour postprandial glucose. The study demonstrated that the 2-hour postprandial glucose and not the FBG predicted all-cause mortality. Increased glycemic variability is a risk factor for both microvascular and macrovascular complications. In a retrospective analysis of the DCCT trial, for all patients with an HbA_{1c} of 9%, the risk of retinopathy was 22-times higher than nondiabetic patients in the conventional-treatment arm as opposed to 8-times higher in the intensive-treatment arm.[30] The higher event rate was likely due to increased glycemic variability in the conventional-treatment arm. The mechanisms for increased glycemic variability on CV morbidity and mortality may be several-fold. In the VADT study, hypoglycemia occurring in the previous 3 months of follow-up conferred a 2.06-fold RR of an adverse event. In these cases, patient apprehensiveness regarding another hypoglycemic event prompted a reduction in insulin doses.[31] Hypoglycemia can also lengthen the QT interval on the 12-lead electrocardiogram (ECG).[32] A prolonged QT interval is a marker of increased CV risk and sudden cardiac death (SCD) is indeed increased in diabetic patients.[33] Predictors of SCD in diabetic patients include hypoglycemic episodes, autonomic neuropathy, and increased QT dispersion on the ECG.[34]

Evidence is emerging that management reducing glycemic variability can reduce adverse CV events in diabetic patients. In the Study to Prevent NonInsulin-Dependent Diabetes Mellitus (STOP-NIDDM),[35] which randomized patients with impaired glucose tolerance to treatment with acarbose (a short-acting, oral hypoglycemic meant to be taken preprandially) vs placebo, there was a significant reduction in CV events. Postprandial glucose was significantly reduced in the treatment arm. In a 2004 meta-analysis of trials using acarbose in diabetic patients, there was a 34% RR reduction in CV events.[36] The atherosclerosis burden may also be reduced. In a study of glyburide vs repaglanide, treatment with repaglanide lowered postprandial blood sugar significantly more than glyburide and was also associated with a decrease in carotid intimal medial thickness.[37]

Conclusions

The evidence presented suggests that there is a "care gap" in the treatment of some diabetic patients; this is apparent from a lower than expected reduction in CV events as compared with the strength of the association epidemiologically between better glycemic control and a lower incidence of CV endpoints. Reasons for this include the duration of intensive glucose management in most trials that were not long enough to allow for a realization of CV endpoint benefit. Starting therapy to improve glycemic control late in the course of diabetes has less impact on CV events than starting it much earlier on. In many cases, the first presentation of CAD is also the time of diagnosis of T2DM. Two-thirds of patients with CAD also have some degree of impaired glucose tolerance, and improved glycemic control in these patients may more effectively lower the subsequent risk of CV events. On the other hand, it may be even more beneficial to determine how to identify these patients in the first place with population screening long before they develop CAD because the impact on CV risk is likely to be greater with earlier treatment of diabetes or glucose intolerance.

Increased glycemic variability, even when it does not raise HbA_{1c} levels, is associated with adverse CV outcomes via atherosclerotic mechanisms and also through hypoglycemia. In turn, this can cause patients to become averse to intensive glycemic control strategies, as well as increase CV mortality through SCD. Improvements in pharmacotherapy (eg, shorter-acting oral hypoglycemic agents), as well as in insulin therapy (ultra-rapid insulins, subcutaneous insulin infusion pumps) may be helpful in reducing glycemic variability, hypoglycemic episodes, and ultimately CV events. Thus far, stronger evidence comes from pharmacologic agents, since insulin infusion pumps have not been shown to be effective in T2DM over shorter follow-up periods.[37] It is conceivable that with improvements in the technologies involved, and with longer follow-up periods, a benefit on CV endpoints may be realized.

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Dr. Ahmad has no disclosures to announce in association with the contents of this issue.

SNELL Medical Communication acknowledges that it has received an unrestricted educational grant from Medtronic to support the distribution of this issue of *Cardiology Scientific Update*. Acceptance of this grant was conditional upon the sponsors' acceptance of the policy established by the Division of Cardiology, St. Michael's Hospital, and SNELL Medical Communication guaranteeing the educational integrity of the publication. This policy ensures that the author and editor will at all times exercise unrestricted, rigorous, scientific independence free of interference from any other party.