# Intensive glycemic control

## *Implications of the ACCORD, ADVANCE, and VADT trials for family physicians*

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### Research question

How does intensive glycemic control affect cardiovascular (CV) outcomes in patients with type 2 diabetes?

### Relevance to family physicians

Type 2 diabetes is an important health problem all over the world. The incidence of CV events is 2 to 4 times higher in patients with diabetes than in those without diabetes. Approximately 80% to 90% of people with diabetes are primarily managed by family physicians, in Canada and around the world. Owing to results of recent trials, family physicians should make sure their knowledge is up-to-date to ensure better glycemic management.

We have long known that intensive glycemic control reduces diabetes-related complications, including CV events. Some studies, like the DCCT (Diabetes Control and Complications Trial)[1] and the UKPDS (United Kingdom Prospective Diabetes Study),[2] have clearly shown a direct relationship between glycosylated hemoglobin $A_{1c}$ ($HbA_{1c}$) levels and incidence of CV disease, and that intensive glycemic control might lead to reduction in risk of all CV events, including nonfatal myocardial infarction, stroke, and sudden death. On the basis of these and other trials, both the Canadian Diabetes Association and the American Diabetes Association recommend $HbA_{1c}$ levels below 7%.

In 3 recently published trials—ACCORD (Action to Control Cardiovascular Risk in Diabetes),[3] ADVANCE (Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation),[4] and VADT (Veterans Affairs Diabetes Trial)[5]—intensive glycemic control did not have any favourable effect on CV risk reduction in patients with type 2 diabetes, which has led to physicians modifying control of hyperglycemia in this population.

### ACCORD trial

The ACCORD trial began in 2001 and included 3 different approaches, 1 of which was to determine how intensive glucose-lowering strategies act on CV outcomes in patients with type 2 diabetes by assessment of $HbA_{1c}$ levels. There were 10251 participants, with an average age of 62 years. Average duration of diabetes was 10 years, and the average baseline $HbA_{1c}$ level was 8.1%. Participants were divided into 2 groups. One group received intensive glucose control with $HbA_{1c}$ target levels below 6%; the other group followed a standard regimen with $HbA_{1c}$ target levels of 7% to 7.9%.

The study was halted in February 2008 owing to the increased fatality rate in the intensive-control group. The data analyses showed that in an average of 3.5 years of treatment (range 2 to 7 years), a total of 257 participants in the intensive-control group and 203 in the standard-control group died; this suggests that intensive glucose control increased death by 22%. Among the 460 total deaths, 229 were due to CV causes—135 in the intensive-control group and 94 in the standard-control group; that is a 35% higher rate of death due to CV causes in the intensive-control group. More episodes of serious hypoglycemia were found among patients following the intensive regimen (10%) than among those following the standard regimen (3.5%). Deaths due to CV disease in this trial were related to severe hypoglycemia.

### ADVANCE trial

The ADVANCE trial was started in June 2001 and completed in March 2008. The objective was to identify the relationship between intensive glycemic control and microvascular and macrovascular outcomes. There were 11140 participants with type 2 diabetes. The average duration of disease was 8 years, and the average baseline $HbA_{1c}$ level was 7.2%. Average age was 66 years. Patients were divided into intensive-control and standard-control groups, with $HbA_{1c}$ goals of 6.3% and 7.0%, respectively.

There was no significant difference in all-cause mortality, including CV mortality, between groups. Major microvascular complications were reduced significantly in the intensive-control group ($P = .01$); however, no macrovascular risk reductions were found. Significantly more episodes of severe hypoglycemia were found in the intensive-control group: 2.7% compared with 1.5% in the standard-control group ($P < .001$).

### VADT trial

During a 5.6-year follow-up in the VADT trial, 1791 participants (average age 60 years, average duration of diabetes of 11.5 years, mean baseline $HbA_{1c}$ level 9.4%) were divided into intensive- and standard-control groups.

There were more deaths due to CV causes in the intensive-control group than there were in the standard-control group (38 vs 29, respectively; sudden deaths 11 vs 4, respectively). More episodes of hypoglycemia were found in the intensive-control group than in the standard-control group (21% vs 10%, respectively).

### Analysis of methodologies

These trials were large, rigorous, well-conducted randomized trials with meaningful clinical outcomes;

however, they were of shorter duration and enrolled generally older patients than previous studies such as the DCCT and the UKPDS. Patients had had diabetes for longer and were at higher risk of CV events than patients in earlier studies. Further, the strategies used to achieve intensive glycemic control in these studies varied and often included multiple medications and interventions. The way in which risk factors are modified is important; the type and number of treatments used to modify risk factors shape the strategy's effect on patient outcomes.[6] The treatments might have had effects other than the intended effects on CV risk factors.

## Hypoglycemia and major vascular events

Patients with type 2 diabetes are always prone to elevated CV risk. Subgroup analyses of ACCORD, ADVANCE, and VADT, with a total of 23 182 participants, failed to establish that intensive glucose-lowering strategies reduce CV events. Study results showed very intensive glucose control might be associated with frequent episodes of severe hypoglycemia and deaths from CV events.

In healthy individuals acute hypoglycemia provokes sympathoadrenal activation and counter regulatory hormonal secretion. This mechanism plays an important role in protecting the brain from neuroglycopenia through altering blood flow in the brain and other metabolic changes to restore blood glucose to normal. In healthy individuals this does not cause any detrimental effects. In patients with diabetes who have already developed endothelial dysfunction, acute hypoglycemia leads to acute hemodynamic and hematologic changes, which ultimately lead to increased risk of tissue ischemia and major vascular events, including myocardial infarction and stroke. The possible mechanisms include release of inflammatory cytokines, white cell activation, and vasoconstriction.

## Application to clinical practice

The benefits of intensive glycemic control on microvascular and macrovascular complications are well established in patients with type 2 diabetes and in those with type 1 diabetes. Physicians should note the following conclusions drawn as a result of ACCORD, ADVANCE, VADT, and other observational studies. The general target of $HbA_{1c}$ levels below 7% should remain the same. Patients who have not had type 2 diabetes for long and who do not have established atherosclerotic disease might derive CV benefit from intensive glycemic control. Patients with very long duration of type 2 diabetes, known history of severe hypoglycemia, advanced atherosclerosis, and advanced age might not get CV benefit from intensive glycemic control. Physicians should be vigilant about this contingent of patients with diabetes to avoid hypoglycemia and should not attempt stringent glycemic control to achieve near-normal $HbA_{1c}$ levels, which cannot be safely achieved. For some high-risk patients, glycemic targets should be individualized. For primary and secondary CV risk reduction, clinicians should give special attention to smoking cessation, dietary, and physical activity counseling; following evidence-based recommendations for blood pressure control with angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers and lipid-lowering therapy with statin and aspirin prophylaxis; and recommending other healthy lifestyle and behavioural changes.

### BOTTOM LINE

- The general target of $HbA_{1c}$ levels <7% should remain the same. Targets should be individualized for patients with additional cardiovascular risk factors.
- Patients who have not had type 2 diabetes for long and who do not have established atherosclerotic diseases might derive cardiovascular benefit from intensive glycemic control.
- Physicians should encourage cardiovascular risk reduction through smoking cessation, dietary, and physical activity counseling; following evidence-based recommendation for blood pressure control with angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers and lipid-lowering therapy with statin and aspirin prophylaxis; and recommending other healthy lifestyle and behavioural changes.

### POINTS SAILLANTS

- L'objectif général de maintenir le taux de $HbA_{1c}$ à <7 % devrait rester le même. Les seuils à viser devraient être individualisés pour les patients qui ont des facteurs de risques cardiovasculaires additionnels.
- Les patients qui n'ont pas le diabète de type 2 depuis longtemps et qui n'ont pas de maladie athéroscléreuse établie pourraient bénéficier sur le plan cardiovasculaire d'un strict contrôle glycémique.
- Les médecins devraient encourager la réduction des risques cardiovasculaires en donnant des conseils pour cesser de fumer, bien s'alimenter et faire de l'activité physique; en suivant les recommandations fondées sur des données probantes pour contrôler l'hypertension au moyen d'inhibiteurs de l'enzyme de conversion de l'angiotensine ou d'antagonistes des récepteurs de l'angiotensine II, et d'une thérapie hypolipidémiante et de l'aspine par prévention; et en recommandant d'autres changements pour un mode de vie et des comportements sains.

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**Competing interests**
None declared

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