

The New Diabetes Standard of Care: More Than Just Glycemic Control

Advancement in Diabetes Management: A Canadian Diabetes Steering Committee Report

Purpose

Clinical practice guidelines can be useful in the management of diabetes. However, implementation of guidelines in clinical practice is an ongoing challenge for primary care physicians (PCPs) who manage the majority of type 2 diabetes patients in Canada. Evidence suggests that there is a care gap between the Canadian Diabetes Association (CDA) clinical practice guidelines and the standard of care in family practice.¹

The CDA guidelines review current standards in diabetes care and make practical recommendations to help optimize diabetes management in family practice. The first two reports in this series will review the updated recommendations of the CDA 2008 clinical practice guidelines, including cardiovascular (CV) protection and pharmacotherapy options to optimize

glycemic control. Later reports will discuss emerging therapeutic options for the management of diabetes and explain how these agents may be utilized in family practice.

Report 1 Objectives

After reading this report, physicians will:

1. Be informed of the updates to the CDA 2008 clinical practice guidelines;
2. Understand key findings from pivotal trials and their relevance to clinical practice;
3. Realize the importance of vascular protection, blood pressure (BP) and glucose control in type 2 diabetes; and
4. Recognize the value of implementing an individualized approach to diabetes management, with a focus on customized self-management education (SME).

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In this Report

This report explores updates to the latest CDA clinical practice guidelines, with a focus on the prevention of vascular complications. It will also address the benefits and potential risks associated with intensive glycemic control strategies. Achievement of targets may be improved by patient involvement; thus patient SME and individualization of treatment are addressed in this report as well.

Updated: CDA 2008 Clinical Practice Guidelines

In 2008, the CDA published the latest version of their clinical practice guidelines—an update that represents an international survey of the most current peer-

TABLE 1

Interventions for Vascular Protection⁶

Population	Interventions
All people with diabetes	<ul style="list-style-type: none"> • Lifestyle modifications <ul style="list-style-type: none"> – achievement and maintenance of a healthy body weight – healthy diet – regular physical activity – smoking cessation • Optimize BP control • Optimize glycemic targets
All people with diabetes considered at a high risk of CV event	<ul style="list-style-type: none"> • ACE inhibitor or ARB therapy • Antiplatelet therapy (as recommended) • Lipid-lowering medication (primarily statins; target LDL-C < 2 mmol/l)

ACE = angiotensin converting enzyme.

ARB = angiotensin II receptor agonist.

Adapted from the CDA 2008 Clinical Practice Guidelines.⁶

reviewed literature. The updates were carried out by a newly expanded expert committee whose constituents stem from a diverse range of expertise. Thus, the guidelines represent a comprehensive, evidence-based guide to the prevention and management of diabetes with an emphasis on individualized decision-making to address the multifaceted nature of this progressive disease.

In addition to including an updated treatment algorithm and recommendations that reflect the current state of clinical practice, the guidelines contain newly added chapters. The additions serve to more completely address the increased risk of macrovascular complications and issues associated with the delivery of diabetes care—issues which have more recently been brought to the forefront of diabetes management.

Vascular Complications: A Challenge of Diabetes

Diabetes is associated with an increased risk of macrovascular and microvascular complications. These complications can have a significant impact on morbidity and mortality in individuals with diabetes, and place a significant burden on the healthcare system. Of particular concern is the elevated risk of CV

disease associated with diabetes.² Data from the Framingham Heart Study indicate that the risk of CV disease attributable to diabetes has increased over the past 50 years.³ Diabetes confers an equivalent degree of CV risk as aging 10 to 15 years, with men being more at risk than women.⁴ Furthermore, those who do suffer from acute coronary events have worse short- and long-term outcomes compared to non-diabetics.^{5,6}

The CDA recommends that the first priority in the prevention of macrovascular complications should be the reduction of CV risk through a multifaceted approach, integrating lifestyle and pharmacologic measures.⁶

To this extent, the guidelines make recommendations for the prevention of macrovascular disease that should be instituted in all individuals with diabetes. These are followed by recommendations for vascular protection which target individuals at a higher risk for CV disease (Table 1).

Considerations for All Individuals with Diabetes

The association between elevated BMI and waist circumference, diabetes and CV risk has long been recognized as an important issue in the management of diabetes. Clinically significant weight loss is defined by as little as a 10% reduction from baseline body weight and may be associated with improvements in lipid and BP parameters, and reduced CV risk.⁷

People with diabetes and elevated BP should be aggressively treated to achieve a target BP of < 130/80 mmHg to reduce the risk of micro- and macrovascular complications. For persons with diabetes without nephropathy, first-line agents include ACE inhibitors or ARBs (with special consideration given their additional renal benefits), as well as dihydropyridine calcium channel blockers (CCBs) and thiazide-like diuretics. Add-on drugs should be chosen from the first-line choices listed above, although evidence would not suggest any additional benefit from combining an ACE inhibitor and an ARB. For people with diabetes and albuminuria, an ACE inhibitor or ARB is recommended as initial therapy.⁶

Optimal glycemic control is critical in all individuals with diabetes and the CDA guidelines devote several chapters to targets, strategies and therapeutic options. The guidelines may be consulted for further recommendations and discussion surrounding the aforementioned topics.

Considerations for Individuals at High Risk for CV Events

The CDA guidelines set clear parameters in 2008, for defining individuals with diabetes that should be considered at high risk for CV events:

- Men aged ≥ 45 years;
- Women aged ≥ 50 years; and
- Men aged < 45 years and women aged < 50 years with ≥ 1 of the following:
 - macrovascular disease;
 - microvascular disease;
 - multiple additional risk factors;
 - extreme level of a single risk factor (*i.e.*, LDL > 5.0 or systolic BP > 180 mmHg);
 - duration of diabetes > 15 years with age > 30 years.

In addition to lifestyle modifications, BP control and glycemic control, all high-risk individuals with diabetes should be considered for the following:⁶

- ACE inhibitor or ARB at doses that have demonstrated vascular protection
 - *i.e.*, ramipril (10 mg) or telmisartan (80 mg)
 - these agents should be considered even if BP is $< 130/80$ mmHg;
- Antiplatelet therapy in people with stable CV disease
 - low-dose (81 to 325 mg) acetylsalicylic acid (ASA). Clopidogrel (75 mg) should be used if the individual is unable to tolerate ASA;
 - antiplatelet therapy for primary prevention of CV events should be based on individual clinical judgment;
- Lipid-lowering therapy (primarily statins)
 - primary target: low-density-lipoprotein cholesterol (LDL-C) ≤ 2 mmol/L;
 - secondary target: total cholesterol to high-density-lipoprotein cholesterol (TC:HDL-C) ratio < 4 .

Intensive Glycemic Control and Long-term Vascular Outcomes

Glycemic control has been extensively studied in type 2 diabetes. Recent research has addressed the issue of whether or not intensive glycemic control has the potential to reduce the risk of vascular complications over time. Intensive glycemic control involves targeting near-normal glucose levels in the hopes that this will reduce diabetes complications.

In 2008, results of three large randomized trials contributed to our understanding about the effect of intensive glycemic control on diabetes complications.

The first priority in the prevention of diabetes complications should be the reduction of CV risk by vascular protection, through a comprehensive, multifaceted approach, including lifestyle modification, BP control and glycemic control for all people with diabetes.

In addition, for all high-risk people with diabetes, treat with ACE inhibitor or ARB, antiplatelet therapy as recommended, and lipid-lowering medication.

Key Action Messages:

- People with diabetes should be encouraged to adopt a healthy lifestyle including weight loss. A modest weight loss of 5% to 10% of initial body weight can substantially improve insulin sensitivity and glycemic, BP and lipid control
- People with diabetes and elevated BP should be aggressively treated to achieve a target BP of $< 130/80$ mmHg to reduce the risk of micro- and macrovascular complications
- All individuals with diabetes should be counseled on smoking cessation
- **High-risk people** should receive an ACE inhibitor or an ARB (even if BP is $< 130/80$ mmHg)
- **High-risk people** should receive lipid-lowering medication (primarily statins) to target an LDL-C ≤ 2 mmol/L and a TC:HDL-C ratio < 4

I. Veteran Affairs Diabetes Trial (VADT). The VADT demonstrated that intensive glycemic control (targeting an A1C $< 6\%$) had no effect on any macrovascular or death outcome among individuals with advanced diabetes over 5.6 years.⁸

II. Action to Control Cardiovascular Risk in Diabetes (ACCORD). The ACCORD trial set out to determine the effects of intensive glucose lowering (targeting an A1C $< 6\%$) on macrovascular outcomes.

Key Action Messages:

- Intensive glycemic control involving lowering A1C to < 6% to < 6.5% has the potential to lower microvascular risk, with no demonstrated benefit on macrovascular risk reduction
- The decision to lower the glycemic target must be balanced by the risk of hypoglycemia and increased risk of mortality in those at elevated risk for CV events
- Target A1C for most individuals with diabetes remains $\leq 7\%$

The glucose-control arm of ACCORD was prematurely terminated due to excessive mortality in the intensively treated cohort, with a mean follow-up of 3.5 years. It was concluded that in this very high-risk population, intensive glycemic control had no significant effect on the combined endpoint of CV-related death, myocardial infarction (MI), and stroke. However, intensive therapy was associated with a significant increase in severe hypoglycemia, perhaps due to the extensive use of sulfonylureas, intensive insulin therapy and a target A1C of < 6.0%.⁹ The cause of increased mortality in the intensive arm of ACCORD has not yet been elucidated.

III. Action in Diabetes and Vascular Disease: Preterax and Diamicon MR Controlled Evaluation (ADVANCE). The ADVANCE trial targeted an A1C of < 6.5%. It was able to demonstrate a 10% reduction in the combined outcome of macrovascular and microvascular events with intensive glycemic control, and no significant difference in death rates between study groups. There was no evidence of reduction in macrovascular events in ADVANCE, and the risk reduction of the primary endpoint was due to a 21% reduction in nephropathy.¹⁰

In contrast to the three recent randomized trials, a nine-year observational follow-up of the United Kingdom Prospective Diabetes Study (UKPDS) 33, which used a study population of newly diagnosed patients, demonstrated that previous intensive glycemic control does impart a significant risk reduction on microvascular outcomes, MI and death.¹¹

Together, these data (Table 2) suggest that intensive glycemic control has the potential to reduce the risk of microvascular complications, with an inconclusive effect on macrovascular outcomes. The effects may be

CDA 2008 clinical practice guidelines currently recommend an A1C target of $\leq 7\%$, which may be lowered to $\leq 6.5\%$ to reduce the risk of nephropathy in select patient types.⁶

influenced by—and be dependent on—when in the course of the disease aggressive therapy is initiated, the underlying risk of CV events, and the risk:benefit profile of the treatment regimen used. Based on the cumulative study findings, the guidelines currently recommend an A1C target of $\leq 7\%$ for most individuals, which may be lowered to $\leq 6.5\%$ to reduce the risk of nephropathy in select patient types. The decision to lower the glycemic target must be balanced by the risk of hypoglycemia and increased risk of mortality in those at elevated risk for CV events.

Emphasis on a “Patient-centric” Approach to Diabetes Management

In addition to a significant focus on CV risk management, the 2008 clinical practice guidelines boast an expanded discussion addressing the value of an individualized approach to diabetes management as well as the importance of patient involvement in decision-making. The emphasis on individualized decision-making reflects the burden of diabetes on the daily lives of patients and the resultant need for patient involvement in preventing disease progression and complications.

Overview of Guideline Modifications

Over time, clinical data have reiterated the importance of maintaining a healthy body weight, BP and adequate glycemic control in diabetic individuals. For this reason, they are targeted within the guidelines as mainstays in the preventive approach to the management of diabetes and its complications. This is reflected by the expansion of the “Macrovascular and

Key Action Messages:

- SME is a fundamental component of diabetes care and is most effective when ongoing diabetes education and comprehensive healthcare occur together

TABLE 2

Summary of Pivotal Clinical Trials Evaluating the CV Effects of Intensive vs. Standard Anti-hyperglycemic Therapy

Study	Patient Population	Study Aim	Treatment	Results
VADT ⁸	Veterans with advanced diabetes (mean of 11.5 years since diagnosis) with mean A1C 9.4%.	To compare the effects of intensive vs. standard glucose control on CV events in type 2 diabetics.	Intensive therapy: maximal therapy dosing; insulin added if A1C 6% not achieved. Standard therapy: half-maximal therapy dosing; insulin added if A1C 9% not achieved.	After a median of 5.6 years, A1C levels were 1.5% lower in the intensive group as compared to the standard group; no significant between both groups in the rates of macro- or microvascular events were observed; increased hypoglycemia was observed in the intensive group compared to the standard-therapy group.
ACCORD ⁹	Diabetics with advanced disease, high CV risk (mean of 10 years since diagnosis) with mean A1C 8.3%.	To compare the effects of intensive vs. standard glucose control on micro- and macrovascular events in type 2 diabetic patients with established CV disease or additional CV risk factors.	Intensive therapy: target A1C < 6.0%; varied combination therapy. Standard therapy: target A1C 7.0 to 7.9%; varied combination therapy.	The trial was discontinued after 3.5 years; no significant reductions in major CV events were observed; intensive therapy resulted in increased mortality (greater mortality was observed as a result of CV events in the intensive-therapy group).
ADVANCE ¹⁰	Patients with advanced diabetes (mean of 7.9 to 8.0 years since diagnosis) with mean A1C 6.53 to 7.52%.	To compare the effects of intensive vs. standard glucose control on a combined micro- and macrovascular outcome in type 2 diabetics.	Intensive therapy: target A1C ≤ 6.5%; varied combination therapy. Standard therapy: target A1C ≤ 7.0%; sulfonylurea therapy only.	After a median of 5 years of follow-up, intensive glucose control resulted in a reduced combined micro- and macrovascular outcome. No significant reduction was observed in macrovascular outcomes alone (21% relative reduction in nephropathy explained the reduction in the combined outcome).
UKPDS 33 ¹¹	Newly diagnosed diabetics with mean A1C 7.9 to 8.9%.	To compare the effects of intensive vs. standard glucose control on micro- and macrovascular events in type 2 diabetics.	Intensive therapy: target FPG < 6 mmol/L; therapy involved a sulfonylurea or insulin (in some overweight cases, metformin was added). Standard therapy: target FPG < 15 mmol/L; therapy involved diet modification.	After 10 years, significant reductions in microvascular events but not macrovascular events were observed. Overweight patients taking metformin experienced significant reductions in MI and death. After 10 years of further follow-up, continued reductions in microvascular events were observed with emerging emerging risk reductions in MI and death. Overweight patients continued to reap the benefits of metformin therapy.

Microvascular Complications” section in the 2008 clinical practice guidelines, which now includes individual chapters addressing the identification of individuals at high risk of coronary artery disease, the screening and management of coronary artery disease and the treatment of people with heart failure. The emphasis on CV health extends to individual chapters addressing vascular protection, hypertension, and dyslipidemia—the hallmarks of CV disease. Moreover, it should not go unnoticed that the discussion and recommendations formerly addressing diabetic nephropathy are extended to a broader discussion of chronic kidney disease, which also has negative implications for CV health if not managed.

Implementation of the aforementioned recommendations should be carried out in a manner that encourages patient involvement in decision-making to ensure that the patient is adequately equipped to take on an active role in the progression toward improved health. The described updates to the clinical practice guidelines warrant a more cognizant and detail-oriented

“The objectives of SME are to increase the individual’s involvement in, confidence with and motivation for control of their diabetes, its treatment and its effect on their lives.”

- Newman S et al.¹²

approach to diabetes management guided by the findings of clinical research and experiential learning, and serve to address the role of poor CV health in the progression of diabetes.

In the Next Report

The next report will provide an overview of the incretin agents in the management of type 2 diabetes.

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