RATES OF DIABETES ARE INCREASING IN CANADA,¹ AND FAMILY PHYSICIANS REMAIN THE MAIN POINT OF PRIMARY CARE FOR PEOPLE WITH DIABETES.² THE CHALLENGE FOR PHYSICIANS IN THIS CONTEXT IS TO DESIGN REALISTIC TREATMENT PLANS AND NEGOTIATE PRIORITIES TO MAXIMIZE HEALTH BENEFITS FOR THESE PATIENTS. THIS ARTICLE SUMMARIZES RECOMMENDATIONS FROM THE CANADIAN DIABETES ASSOCIATION (CDA) 2008 CLINICAL PRACTICE GUIDELINES (CPGS). THE GUIDELINES ARE AVAILABLE ON-LINE AT WWW.DIABETES.CA/FOR-PROFESSIONALS/RESOURCES/2008-CPG/. THIS REVIEW COVERS THE CARE OF ADULTS WITH TYPE 2 DIABETES AND GIVES PARTICULAR ATTENTION TO NEW RECOMMENDATIONS. TO ASSIST WITH READABILITY, GRADING AND EVIDENCE LEVELS HAVE BEEN SIMPLIFIED TO SINGLE LETTERS (EG, GRADE A RECOMMENDATION = [A]). TABLE 1 SUMMARIZES THE GRADING SYSTEM USED BY THE CDA.

<table>
<thead>
<tr>
<th>GRADE OR LEVEL</th>
<th>CRITERIA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade A Level 1A</td>
<td>The best evidence is level 1</td>
</tr>
<tr>
<td>Level 1B</td>
<td>Systematic overview or meta-analysis of high-quality randomized controlled trials or appropriately designed randomized controlled trial with adequate power to answer the question posed by the investigators</td>
</tr>
<tr>
<td>Level 2</td>
<td>Randomized controlled trial or systematic overview that does not meet level-1 criteria</td>
</tr>
<tr>
<td>Grade C Level 3</td>
<td>The best evidence is level 3</td>
</tr>
<tr>
<td>Level 4</td>
<td>Nonrandomized clinical trial or cohort study</td>
</tr>
<tr>
<td>Grade D</td>
<td>The best evidence is level 4 or consensus</td>
</tr>
</tbody>
</table>

**Glycemic control and diabetes**

**Targets for glycemic control.** The new guidelines recommend a target hemoglobin A₁c (HbA₁c) level of ≤ 7% for all patients with diabetes (A). A more aggressive target of ≤ 6.5% can be considered for some patients to help prevent microvascular complications, but this benefit must be weighed against an increase in mortality in patients at very high risk of cardiovascular (CV) events (A).

The benefit of achieving the target HbA₁c level of ≤ 7% for microvascular risk reduction is well established.³ The 2003 CPGS also suggested a more aggressive target of ≤ 6%, but 2 recent randomized controlled trials showed no macrovascular benefit to this target. The ACCORD trial demonstrated that a therapeutic strategy to lower the level of HbA₁c to < 6% in high-risk patients did not reduce the risk of macrovascular disease and, in fact, was associated with a small increase in mortality.³ The ADVANCE trial did not show this increased mortality, but it also did not demonstrate macrovascular benefit of lowering the HbA₁c level below 6.5%; it did, however, show a reduction in nephropathy in the intensive-control group.⁶ In contrast, the posttrial monitoring of the United Kingdom Prospective Diabetes Study (UKPDS-PTM) demonstrated a reduction in myocardial infarction and all-cause mortality in the subgroup with intensive glycemic control after a 10-year posttrial follow-up.⁶ The key differences between the UKPDS-PTM and the ACCORD and ADVANCE trials are UKPDS-PTM’s early intervention and longer follow-up. This suggests that earlier intervention has lasting benefit but that a target HbA₁c level of ≤ 7% is more appropriate in patients at high risk of vascular events who have had diabetes for a long time.

**Recommended targets for glycemic control**

1. Patients should be treated to achieve a target HbA₁c level of ≤ 7% to reduce microvascular complications in all (A) and macrovascular complications in type 1 diabetes (C).  

2. To reach an HbA₁c level of ≤ 7%, people with diabetes should aim for the following:  
   - fasting plasma glucose or preprandial plasma glucose target of 4.0-7.0 mmol/L (B) and  
   - 2-hr postprandial plasma glucose target of 5.0-10.0 mmol/L (B).  

3. Further postprandial blood glucose lowering to 5.0-8.0 mmol/L might be considered if HbA₁c targets are not reached with the postprandial target of 5.0-10.0 mmol/L (D).  

**Monitoring glycemic control.** Patients with type 2 diabetes taking once-daily insulin and oral antihyperglycemic agents should monitor their blood glucose at least once a day at different times (D), or more often if they are on multiple doses of insulin (C). Because there is contradictory evidence about the benefit of self-monitoring of blood glucose for patients who are not taking insulin, self-monitoring should be individualized according to the type of treatment and level of control (D).
**Pharmacologic management of type 2 diabetes.** As more antihyperglycemic agents become available, careful consideration should be given to their advantages and disadvantages. Figure 1 summarizes the key points from the guidelines. Metformin remains the initial drug for type 2 diabetes, but the guidelines now support its use in all people with diabetes, irrespective of body weight (D). When glycemic targets are not met with metformin alone, 1 or more agents from a different class should be added to metformin. The choice of second-line agents depends on the desired (and undesired) characteristics of the treatment. The incretin agent, dipeptidyl peptidase-4 inhibitor, is a new option. In the presence of marked hyperglycemia (HbA1c ≥9%), the 2008 CPGs recommend starting combination pharmacologic therapy immediately, concurrent with lifestyle changes (D). When basal insulin is added to antihyperglycemic agents, the guidelines recommend considering insulin analogues (eg, insulin detemir or insulin glargine) instead of neutral protamine Hagedorn (NPH) to reduce risk of nocturnal or symptomatic hypoglycemia (A).

**Cardiovascular risk and diabetes**

Cardiovascular disease (CVD) is the number 1 cause of death among those with diabetes. Thus, a thorough assessment of CV risk and implementation of a treatment plan (if necessary) is essential for all patients with diabetes (D).

**Cardiovascular risk assessment.** The degree of benefit of medical intervention is based on patients’ absolute risk of CV events, with higher-risk patients deriving greater benefit. Thus, identifying those at high risk can ensure that those who are most likely to benefit will receive treatment. Age is among the strongest predictors of risk, so the CDA recommends that men 45 years and older and women 50 years and older should be considered high risk. Patients below these age cutoffs, but meeting any 1 of the other important CV risk factors, should also be considered high risk.

**Vascular protection.** People with diabetes develop vascular disease approximately 15 years earlier than people without diabetes. The concept of vascular protection was introduced in the 2003 CPGs, but it has been further stratified in the 2008 version, owing to evidence that shows a comprehensive multifactorial approach to vascular protection substantially reduces complications. All patients with diabetes should receive interventions to reach target blood pressure (BP) of <130/80 mm Hg and HbA1c levels of ≤7%, to stop smoking, and to maintain healthy diets, physical activity, and healthy body weight.

![Figure 1. Pharmacologic management of type 2 diabetes](image-url)

- **Symptomatic hyperglycemia with metabolic decompensation:**
  - HbA1c < 9.0%: Initiate lifestyle interventions (eg, nutrition therapy, physical activity) if no change in 3 months.
  - HbA1c ≥ 9.0%: Initiate metformin and lifestyle interventions concurrently.

Add an agent best suited to your patient (see advantages and disadvantages below):

<table>
<thead>
<tr>
<th>Agent</th>
<th>HbA1c*</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sulfonylurea</td>
<td>I</td>
<td>• improved postprandial control</td>
<td>• associated hypoglycemia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• newer sulfonylureas are associated with less hypoglycemia</td>
<td>• requires 3-4 doses daily</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• weight neutral</td>
<td>• weight gain</td>
</tr>
<tr>
<td>TZD</td>
<td>I</td>
<td>• durable monotherapy</td>
<td>• 6-12 wk for maximal effect</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• rare hypoglycemia</td>
<td>• weight gain</td>
</tr>
<tr>
<td>α-Glucosidase inhibitor (acarbose)</td>
<td>J</td>
<td>• improved postprandial control</td>
<td>• GI side effects</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• weight neutral</td>
<td></td>
</tr>
<tr>
<td>Insulin</td>
<td>I</td>
<td>• no dose ceiling</td>
<td>• weight gain</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• many types, flexible regimes</td>
<td>• associated hypoglycemia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• in HbA1c</td>
<td></td>
</tr>
<tr>
<td>DPP-4 inhibitor</td>
<td>J to J</td>
<td>• improved postprandial control</td>
<td>• new agent (long-term safety not known)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• weight neutral</td>
<td></td>
</tr>
<tr>
<td>Weight-loss agent</td>
<td>J</td>
<td>• weight loss</td>
<td>• GI side effects (orlistat)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• no hypoglycemia</td>
<td>• increased heart rate, BP (sibutramine)</td>
</tr>
</tbody>
</table>

If still NOT at target:

- Add another agent
- Add bedtime basal insulin to other agent(s)
- Intensify insulin regimen

Timely adjustments or additions of antihyperglycemic agents should be made to attain target HbA1c within 6-12 mo

BP—blood pressure, CHF—congestive heart failure, DPP-4—dipeptidyl peptidase-4, GI—gastrointestinal, TZD—thiazolidinedione.

* J = <1.0% decrease, JJ = 1.0%-2.0% decrease, JJJ = >2.0% decrease.
weight. On top of these interventions, those found to be at high risk should be prescribed angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARBs), lipoprotein-lowering medications (particularly statins), and possibly acetylsalicylic acid (ASA). It is important to note that ARBs are now included in the CPGs as an alternative to ACE inhibitors. Specific reference to statins is also new and reflects the growing literature on the benefits of these medications for high-risk groups. Recommendations regarding ASA have also been modified, because ASA therapy has been shown to have less of a cardioprotective effect in patients with diabetes than in those without diabetes, and to have no benefit in primary prevention. Thus, the 2008 CPGs state that low-dose ASA therapy (81 to 325 mg) could be considered in people with stable CVD (D) but clinical judgement should be exercised regarding its use in primary prevention (D).

**Cardiovascular risk assessment recommendations**

1. All patients with diabetes should be assessed for cardiovascular risk annually (D).

2. Patients with diabetes are considered high risk if they are
   - male ≥ 45 y or female ≥ 50 y (B) or
   - male < 45 y or female < 50 y with any of the following (D):
     - macrovascular or microvascular disease,
     - 2 or more cardiac risk factors (eg, first-degree relative with premature coronary or cerebrovascular disease, smoking, hypertension, dyslipidemia),
     - an extreme single risk factor (eg, systolic blood pressure > 180 mm Hg or low-density lipoprotein level > 5.0 mmol/L), or
     - diabetes for longer than 15 y and age > 30 y.

**Recommendations for vascular protection**

1. For vascular protection for all individuals with diabetes (A) for patients older than 40 y with type 2 diabetes and microalbuminuria; (D) for all others, aim for the following:
   - HbA1c level ≤ 7.0% (see glycemic control),
   - blood pressure < 130/80 mm Hg,
   - smoking cessation,
   - physical activity,
   - healthy diet, and
   - healthy body weight.

2. For high-risk patients, prescribe 1 or more of the following:
   - angiotensin-converting enzyme inhibitor or angiotensin receptor blocker (A) for those with vascular disease; (B) for other high-risk groups),
   - a lipid-lowering medication, particularly statins (see Treatment of dyslipidemia), or
   - acetylsalicylic acid (for secondary prevention).
Treatment of hypertension. Strict control of BP improves morbidity and mortality in patients with diabetes. The CDA recommends that BP be measured at every visit and hypertension be diagnosed according to the national hypertension guidelines (www.hypertension.ca/chep). Treatment targets remain systolic BP < 130 mm Hg (C) and diastolic BP < 80 mm Hg (B). Clinical trials have shown that multiple medications and titrations are required to achieve these targets. A summary of recommended first-line and combination medications is provided in Table 2, but it is important to note that ACE inhibitors and ARBs are given special consideration as first-line treatment agents because of their renal benefits (D) and that α-blockers are not recommended as first-line agents for patients with diabetes (A).

Table 2. Hypertension medication for patients with diabetes

<table>
<thead>
<tr>
<th>DIABETIC POPULATION</th>
<th>INITIAL MEDICATIONS</th>
<th>ADDITIONAL MEDICATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>BP ≥ 130/80 mm Hg or albuminuria</td>
<td>ACE inhibitor (A)</td>
<td>Cardioselective β-blocker (B)</td>
</tr>
<tr>
<td></td>
<td>ARB (A/B)*</td>
<td>Non-DHP CCB (B)</td>
</tr>
<tr>
<td>Isolated systolic hypertension</td>
<td>ACE inhibitor (B)</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td>ARB (B)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Thiazide-like diuretic (B)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Long-lasting DHP CCB (C)</td>
<td></td>
</tr>
</tbody>
</table>

ACE—angiotensin-converting enzyme, ARB—angiotensin receptor blocker; DHP CCB—dihydropyridine calcium channel blocker.

* (B) for patients with non–left ventricular hypertrophy; (A) for all others.

Recommendations for treatment of hypertension

1. Blood pressure (BP) should be measured at every diabetes clinic visit and hypertension should be diagnosed according to the national hypertension guidelines (D).
2. Treatment should target BP < 130/80 mm Hg ([C] for systolic BP; [B] for diastolic BP).
3. Most people require multiple BP-lowering medications to reach BP targets. Pharmacologic recommendations are summarized in Table 2.
4. Lifestyle interventions to reduce BP (eg, healthy weight, low sodium intake) should be encouraged alongside pharmaceutical interventions (D).

Screening for coronary artery disease. Asymptomatic cardiac ischemia is common among those with diabetes. Many patients who present with myocardial infarction have no preceding symptoms. To identify those with established coronary artery disease in the absence of symptoms, the 2008 CPGs recommend that baseline electrocardiograms be conducted in all individuals older than 40 years of age (D).

Lifestyle modification and diabetes

Lifestyle modifications are important for treatment and prevention of diabetes. Many of the 2008 recommendations on nutrition and exercise are the same as or similar to those in the 2003 guidelines. One new recommendation is that patients be referred to and supported by exercise specialists. Structured physical activity counseling by health care providers increases physical activity and produces modest, sustained weight loss; the effects of simply recommending that patients exercise more, which most clinicians do, are less certain.

Conclusion

Clinical practice guidelines are designed to enable health care providers to engage with the evidence and better apply it in their practices. For conditions like type 2 diabetes, which are complex and multidimensional, treatment plans should be developed and discussed with patients. This might require stepwise introduction of various treatments and tests, and continued patient
education, so that patients understand the value that each intervention has for optimizing their health.

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Competing interests

Dr Bhattacharya is on the executive committee of the clinical and scientific section of the CDA and on the Guideline Dissemination and Implementation Committee of the CDA. Dr Cheng served on the expert and steering committees for the CDA 2008 guidelines.

References