FOCUS ON DIABETES

RESEARCH
Glucose-responsive insulin and glucagon delivery improves short-term glucose control and reduces the risk of hypoglycemia in type 1 diabetes

REVIEW
Risks and benefits of intensive blood lowering in patients with type 2 diabetes

PRACTICE
A purulent foot ulcer in a man with diabetes

COMMENTARY
Choosing the right angiotensin-receptor blocker: still controversial
Q: Why should patients get only a number when they can also get helpful information?

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3 Study conducted in 2012 in the UK and the U.S. with 102 diabetes patients. LifeScan, data on file.

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† Supérieur à l’objectif

Dans l’objectif

Inférieur à l’objectif

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Diabetes: diagnosis and treatment in evolution

Kirsten Patrick MBBCh DA

As Steenkamp and colleagues highlight in their review of atypical diabetes (p. 51), we now understand that the term diabetes mellitus refers not to one or two conditions, but to a heterogeneous group of conditions. Because it is important to get the diagnosis right to optimize treatment, the authors outline the approach that primary care practitioners might take when their patient’s diabetes doesn’t quite fit the mould. A guideline on screening for type 2 diabetes in adults, from the Canadian Task Force on Preventive Health Care (p. 58), points out that between 1% and 2% of Canadian adults have diabetes but don’t know it and that the greatest increase in prevalence has been seen in younger groups. The guideline discusses the importance of establishing a patient’s risk of diabetes using a validated risk calculator as a first step before screening.

Lipscombe and Detcky remind us not to assume that diabetes is a progressive and irreversible condition that will require lifelong treatment once the fasting glucose threshold has been breached (p. 76). We need to consider the risk of future complications in the context of what we know about the patient’s overall health and lifestyle and to consider potential benefits, and adverse effects, of pharmacologic treatment. Considerations of frailty and comorbidity are also important when deciding if intensive treatment, particularly in older people, is burdensome and should be abandoned (p. 72).

When treatment is necessary, it is important to get it right. Why? Because macro- and microvascular complications of poorly controlled diabetes underpin the disease’s high associated rates of morbidity and death, such as those associated with renal disease. End-stage renal disease disproportionately affects indigenous populations in Canada, with the risk being 2.7 times higher among First Nations than among non–First Nations adults with diabetes. The risk is even higher among those with onset of diabetes at a younger age (p. 25).

So which pharmacologic treatment is best for the prevention of macrovascular complications of diabetes? Not so fast. First, it is important to address the multiple risk factors implicated alongside hyperglycemia in the pathogenesis of vascular complications of diabetes. Hypertension requires aggressive management in people with diabetes. The findings of a large cohort study comparing the relative effectiveness of angiotensin-receptor blockers in preventing macrovascular disease in patients with type 2 diabetes (p. 9) suggest that telmisartan and valsartan have the advantage over other angiotensin-receptor blockers. However, a linked commentary urges caution in interpreting the results, especially because it is difficult to explain why these two drugs should be more cardioprotective than others in their class (p. 42). Substantial debate rages about the most appropriate blood pressure targets for diabetes patients with hypertension. A review article by Rabi and colleagues (p. 46) discusses the wisdom of a lower blood pressure target in the face of accumulating evidence that lower systolic pressures in patients with diabetes may be associated with an increased risk of adverse events, such as stroke.

In patients with type 1 diabetes, scrupulous glycemic control is known to be the best defence against micro- and macrovascular complications. Although intensive insulin therapy can achieve good glycemic control, it comes with a high risk of hypoglycemia, a potentially fatal condition of which some patients develop an impaired awareness (p. 68). An elegant, small randomized crossover trial (p. 16) compared insulin and glucagon closed-loop delivery (dual-hormone artificial pancreas) with standard insulin-pump therapy. The dual-hormone delivery system, guided by a predictive dosing algorithm informed by glucose sensor readings, reduced short-term glucose control and episodes of hypoglycemia. Although the system has potential problems that need to be ironed out, the authors of a linked commentary (p. 44) call it the “future of care for type 1 diabetes.”

If complications associated with diabetes do occur, they can be difficult to treat and require a multidisciplinary approach, as seen with diabetic foot ulcers (p. 70) and gastroparesis (p. 75). The Canadian Diabetes Association (CDA) 2013 clinical practice guidelines (http://guidelines.diabetes.ca/fullguidelines) emphasize the importance of a multidisciplinary approach organized around the person with diabetes to provide optimal care and to lower the risk of complications developing or progressing.

What about patient involvement in care? Do group medical visits for patients with diabetes in a primary care setting improve self-management and disease outcomes? The findings of a meta-analysis of 26 studies (13 randomized trials) showed that group medical visits had a positive effect on clinical and patient-reported outcomes, with significant reductions in glycated hemoglobin (p. 32). It is always worth remembering, and sharing with the patient, that drug treatment isn’t everything when it comes to diabetes. The CDA guidelines recommend lifestyle modifications for all adults and children with diabetes. A healthy diet and regular exercise can, in some cases, turn a patient with diabetes into one without.

Competing interests: See www.cmaj.ca/site/misc/cmaj_staff.xhtml
Affiliation: Kirsten Patrick is Deputy Editor, CMAJ
Correspondence to: CMAJ editor, pubs@cmaj.ca
Q : Pourquoi les patients devraient-ils se contenter d’un chiffre, alors qu’ils pourraient aussi obtenir de l’information utile ?

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6 Les seuils d’objectif inférieur (Hypo) et supérieur (Hyper) que vous avez définis s’appliquent à tous les résultats de glycémie, notamment aux tests effectués avant et après les repas ou lors de la prise des médicaments ou à toute autre activité pouvant influencer votre glycémie. Assurez-vous d’indiquer à vos patients les seuils Hypo et Hyper qui correspondent à leurs propres besoins.

* Plus qu’un simple chiffre.

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Comparative effectiveness of angiotensin-receptor blockers for preventing macrovascular disease in patients with diabetes: a population-based cohort study

Tony Antoniou PhD, Ximena Camacho MMath, Zhan Yao MSc, Tara Gomes MHSc, David N. Juurlink MD PhD, Muhammad M. Mamdani MPH PharmD

See related commentary by Cooper on page 42

**Abstract**

**Background:** Telmisartan, unlike other angiotensin-receptor blockers, is a partial agonist of peroxisome proliferator–activated receptor-γ, a property that has been associated with improvements in surrogate markers of cardiovascular health in small trials involving patients with diabetes. However, whether this property translates into a reduced risk of cardiovascular events and death in these patients is unknown. We sought to explore the risk of myocardial infarction, stroke and heart failure in patients with diabetes who were taking telmisartan relative to the risk of these events occurring in patients taking other angiotensin-receptor blockers.

**Methods:** We conducted a population-based, retrospective cohort study of Ontario residents with diabetes aged 66 years and older who started treatment with candesartan, irbesartan, losartan, telmisartan or valsartan between Apr. 1, 2001, and Mar. 31, 2011. Our primary outcome was a composite of admission to hospital for acute myocardial infarction, stroke or heart failure. We examined each outcome individually in secondary analyses, in addition to all-cause mortality.

**Results:** We identified 54,186 patients with diabetes who started taking an angiotensin-receptor blocker during the study period. After multivariable adjustment, patients who took either telmisartan (adjusted hazard ratio [HR] 0.85, 95% confidence interval [CI] 0.74–0.97) or valsartan (adjusted HR 0.86, 95% CI 0.77–0.95) had a lower risk of the composite outcome compared with patients who took irbesartan. In contrast, no significant difference in risk was seen between other angiotensin-receptor blockers and irbesartan. In secondary analyses, we found a reduced risk of admission to hospital for heart failure with telmisartan compared with irbesartan (adjusted HR 0.79, 95% CI 0.66–0.96), but no significant differences in risk were seen between angiotensin-receptor blockers in our other secondary analyses.

**Interpretation:** Compared with other angiotensin-receptor blockers, telmisartan and valsartan were both associated with a lower risk of admission to hospital for acute myocardial infarction, stroke or heart failure among older adults with diabetes and hypertension. Telmisartan and valsartan may therefore be the preferred angiotensin-receptor blockers for use in these patients.

A bout 366 million people worldwide live with diabetes, a number that is projected to increase to 552 million by 2030. Because disease-attributable macrovascular complications are the principal causes of death for people with type 2 diabetes, many therapies have the goal of reducing vascular events among these patients. Blockade of the renin–angiotensin–aldosterone system with angiotensin-receptor blockers is a commonly used and particularly appealing strategy in this regard, given the multiple mechanisms through which angiotensin II contributes to a heightened risk of diabetes-related macrovascular disease and the superior tolerability profile of these drugs relative to angiotensin-converting enzyme (ACE) inhibitors.

Although angiotensin-receptor blockers are considered largely interchangeable in clinical practice, evidence from experimental studies and small comparative trials suggest that telmisartan exhibits several pleiotropic properties that distinguish it from other members of this drug class. Most notably, telmisartan is a partial agonist of peroxisome proliferator–activated receptor-γ (PPARγ), a property associated with improvements in surrogate markers of cardiovascular health in small trials involving patients with type 2 diabetes. However, whether...
Research

Continued Medications used in previous 1 yr

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Angiotensin-receptor blocker, no. (%)*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Telmisartan (n = 8 182)</td>
</tr>
<tr>
<td>Age, yr, median (IQR)</td>
<td>73 (69–78)</td>
</tr>
<tr>
<td>Age group, yr</td>
<td>66–74</td>
</tr>
<tr>
<td></td>
<td>75–84</td>
</tr>
<tr>
<td></td>
<td>≥ 85</td>
</tr>
<tr>
<td>Female sex</td>
<td>4 782 (58.4)</td>
</tr>
<tr>
<td>Duration of diabetes, yr, median (IQR)</td>
<td>6.0 (2.3–10.8)</td>
</tr>
<tr>
<td>No admission to hospital</td>
<td>6 272 (76.7)</td>
</tr>
<tr>
<td>Charlson comorbidity index</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>567 (6.9)</td>
</tr>
<tr>
<td>1</td>
<td>595 (7.3)</td>
</tr>
<tr>
<td>≥ 2</td>
<td>748 (9.1)</td>
</tr>
<tr>
<td>Reason for admission to hospital in previous 5 yr</td>
<td></td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>519 (6.3)</td>
</tr>
<tr>
<td>Angina</td>
<td>163 (2.0)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>347 (4.2)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>2 867 (35.0)</td>
</tr>
<tr>
<td>Stroke or transient ischemic attack</td>
<td>261 (3.2)</td>
</tr>
<tr>
<td>Hypertrophic cardiomyopathy</td>
<td>11 (0.1)</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>186 (2.3)</td>
</tr>
<tr>
<td>Ventricular dysrhythm</td>
<td>194 (2.4)</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>58 (0.7)</td>
</tr>
<tr>
<td>Percutaneous coronary intervention</td>
<td>907 (11.1)</td>
</tr>
<tr>
<td>Coronary artery bypass grafting</td>
<td>10 (0.1)</td>
</tr>
<tr>
<td>History of chronic liver disease in 1 yr</td>
<td>92 (1.1)</td>
</tr>
<tr>
<td>History of chronic kidney disease in 1 yr</td>
<td>713 (8.7)</td>
</tr>
<tr>
<td>Residence in a long-term care facility</td>
<td>148 (1.8)</td>
</tr>
<tr>
<td>No. of prescription drugs in previous 1 yr, median (IQR)</td>
<td>8 (5–12)</td>
</tr>
<tr>
<td>Medications used in previous 1 yr</td>
<td></td>
</tr>
<tr>
<td>Angiotensin-converting enzyme inhibitors</td>
<td>4 740 (57.9)</td>
</tr>
<tr>
<td>Acetylsalicylic acid</td>
<td>868 (10.6)</td>
</tr>
<tr>
<td>Other antiplatelet drugs</td>
<td>209 (2.6)</td>
</tr>
<tr>
<td>ß-adrenergic receptor antagonists</td>
<td>1 953 (23.9)</td>
</tr>
<tr>
<td>Calcium-channel blockers</td>
<td>2 740 (33.5)</td>
</tr>
</tbody>
</table>

that, owing to its pleiotropic effects, telmisartan would be associated with a lower risk of macrovascular events in these patients relative to other angiotensin-receptor blockers.

Methods

Study design
We conducted a population-based retrospective cohort study involving Ontario residents with...
diabetes aged 66 years and older who started treatment with either candesartan, irbesartan, telmisartan, losartan or valsartan between Apr. 1, 2001, and Mar. 31, 2010.

Data sources
We determined medication exposure using data from the Ontario Drug Benefit database, which contains comprehensive records of prescription drugs dispensed to Ontario residents aged 65 years and older. We excluded the first year of eligibility for prescription drug coverage (age 65 yr) to avoid having incomplete medication records. We obtained data on hospital admissions from the Canadian Institute for Health Information’s Discharge Abstract Database, which contains detailed clinical information regarding all hospital admissions in Ontario. The abstraction of patient charts is undertaken by trained health information professionals using standard diagno-

Table 1 (part 2 of 2): Baseline characteristics of patients

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Angiotensin-receptor blocker, no. (%)*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Telmisartan (n = 8 182)</td>
</tr>
<tr>
<td>Medications used in previous 1 yr</td>
<td></td>
</tr>
<tr>
<td>Thiazide diuretics</td>
<td>1 842 (22.5)</td>
</tr>
<tr>
<td>Aldosterone antagonists</td>
<td>162 (2.0)</td>
</tr>
<tr>
<td>Other diuretic agents</td>
<td>1 533 (18.7)</td>
</tr>
<tr>
<td>Other antihypertensive agents</td>
<td>66 (0.8)</td>
</tr>
<tr>
<td>Nitrates</td>
<td>409 (5.0)</td>
</tr>
<tr>
<td>Statins</td>
<td>4 411 (53.9)</td>
</tr>
<tr>
<td>Digoxin</td>
<td>196 (2.4)</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>46 (0.6)</td>
</tr>
<tr>
<td>Warfarin</td>
<td>349 (4.3)</td>
</tr>
<tr>
<td>Nonsteroidal anti-inflammatory drugs</td>
<td>2 257 (27.6)</td>
</tr>
<tr>
<td>Diabetes treatments used in previous 1 yr</td>
<td></td>
</tr>
<tr>
<td>Insulin</td>
<td>709 (8.7)</td>
</tr>
<tr>
<td>Metformin</td>
<td>3 683 (45.0)</td>
</tr>
<tr>
<td>Acarbose</td>
<td>83 (1.0)</td>
</tr>
<tr>
<td>Pioglitazone</td>
<td>263 (3.2)</td>
</tr>
<tr>
<td>Rosiglitazone</td>
<td>213 (2.6)</td>
</tr>
<tr>
<td>Sulfonylureas</td>
<td>2 237 (27.3)</td>
</tr>
<tr>
<td>Repaglinide</td>
<td>30 (0.4)</td>
</tr>
<tr>
<td>Income quintile</td>
<td></td>
</tr>
<tr>
<td>1 (lowest)</td>
<td>1 815 (22.2)</td>
</tr>
<tr>
<td>2</td>
<td>1 798 (22.0)</td>
</tr>
<tr>
<td>3</td>
<td>1 691 (20.7)</td>
</tr>
<tr>
<td>4</td>
<td>1 473 (18.0)</td>
</tr>
<tr>
<td>5 (highest)</td>
<td>1 374 (16.8)</td>
</tr>
<tr>
<td>Missing</td>
<td>31 (0.4)</td>
</tr>
<tr>
<td>Specialty of prescribing physician</td>
<td></td>
</tr>
<tr>
<td>Family physician/general practitioner</td>
<td>6 376 (77.9)</td>
</tr>
<tr>
<td>Endocrinology</td>
<td>206 (2.5)</td>
</tr>
<tr>
<td>Nephrology</td>
<td>82 (1.0)</td>
</tr>
<tr>
<td>Other</td>
<td>632 (7.7)</td>
</tr>
<tr>
<td>Unknown</td>
<td>886 (10.8)</td>
</tr>
</tbody>
</table>

Note: IQR = interquartile range.
*Unless otherwise indicated.
†Standardized difference > 0.1 between losartan and telmisartan groups.
‡Standardized difference > 0.1 between candesartan and telmisartan groups.
sis and procedure codes. We used the Ontario Health Insurance Plan database to identify claims for physician services, and the Ontario Diabetes Database to obtain information regarding diabetes diagnoses. This database is a validated administrative data registry of Ontario residents with diagnosed diabetes, which was generated from hospital records and physician services claims. The definition of at least 1 hospital admission or 2 physicians’ claims with a diabetes diagnosis within a 2-year period has sensitivity of 86% and specificity of 97% for identifying people with diabetes (excluding gestational diabetes) in primary care records. 14 Finally, we used the Institute for Clinical Evaluative Sciences Physician Database to determine physician specialties and the Registered Persons Database to obtain patient demographic data. These databases were linked in an anonymous fashion using encrypted health card numbers; they are regularly used for population-based drug research. 15–18

Identification of cohort
We defined the index date as the date on which the first prescription for a study drug was dispensed. To restrict our analysis to patients taking these drugs for the first time, we excluded people who had received a prescription for any angiotensin-receptor blocker in the year preceding the index date. We also excluded patients who received their diagnosis of diabetes after they were given a prescription for an angiotensin-receptor blocker, patients who had a myocardial infarction in the 5 years preceding the start of treatment and patients who received an ACE inhibitor in conjunction with an angiotensin-receptor blocker.

We considered the use of an angiotensin-receptor blocker to be continuous if a prescription was refilled within 1.5-times the number of days of the preceding prescription’s supply.

We included patients who switched between formulations of the same drug, but we censored those who either switched to a different angiotensin-receptor blocker during follow-up or who stopped treatment. We considered treatment to have stopped if a prescription was not refilled within 1.5-times the number of days of the preceding prescription’s supply. In addition, we censored patients after 5 years of total observation time, at death or at the end of follow-up (Mar. 31, 2011), whichever occurred first.

Outcome measures
Our primary outcome was a composite of admission to hospital for acute myocardial infarction, heart failure or stroke. In secondary analyses, we determined the time to each outcome separately, as well as the time to death from any cause. For patients with multiple admissions to hospital during the study period, we considered only the first admission as an outcome. We determined dates of death using the Registered Persons Database and identified diagnoses during hospital admissions using the relevant codes from the 9th and 10th editions of the International Classification of Diseases (Appendix 1, available at www.cmaj.ca/lookup/suppl/doi:10.1503/cmaj.121771/-/DC1).

Statistical analysis
We calculated descriptive statistics for patients’ baseline demographic and clinical characteristics and used standardized differences to test for intergroup differences. Standardized differences of less than 0.1 suggest good balance between groups for a given covariable. 19

We conducted time-to-event analyses for the primary outcome using multivariable Cox proportional hazards regression to adjust for baseline demographic and clinical variables (Appendix 2, available at www.cmaj.ca/lookup/suppl/doi:10.1503/cmaj.121771/-/DC1). We used patients taking irbesartan as the reference group. We selected irbesartan as the referent drug a priori because, like telmisartan, it has a long elimination half-life and has shown superior antihypertensive efficacy relative to comparative angiotensin-receptor blockers. 20–24 Finally, we conducted a dose-response assessment in which we considered low, medium and high doses of angiotensin-receptor

<table>
<thead>
<tr>
<th>Drug</th>
<th>n/N</th>
<th>Unadjusted HR (95% CI)</th>
<th>Adjusted HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Irbesartan</td>
<td>685/12 691</td>
<td>1.00 (ref)</td>
<td>1.00 (ref)</td>
</tr>
<tr>
<td>Telmisartan</td>
<td>306/8 182</td>
<td>0.78 (0.68–0.89)</td>
<td>0.85 (0.74–0.97)</td>
</tr>
<tr>
<td>Candesartan</td>
<td>603/10 940</td>
<td>1.04 (0.93–1.16)</td>
<td>0.99 (0.89–1.11)</td>
</tr>
<tr>
<td>Losartan</td>
<td>467/8 411</td>
<td>1.00 (0.89–1.13)</td>
<td>0.93 (0.83–1.05)</td>
</tr>
<tr>
<td>Valsartan</td>
<td>651/13 962</td>
<td>0.84 (0.75–0.93)</td>
<td>0.86 (0.77–0.96)</td>
</tr>
</tbody>
</table>

Figure 1: Risk of the composite outcome (admission to hospital for heart failure, acute myocardial infarction or stroke), by angiotensin-receptor blocker used among older adult patients with diabetes. Ratios were adjusted for all variables listed in Appendix 2 (available at www.cmaj.ca/lookup/suppl/doi:10.1503/cmaj.121771/-/DC1). CI = confidence interval, HR = hazard ratio, ref = reference.
blockers to be time-dependent covariables, using low-dose treatment as the reference. We verified the proportional hazards assumption by testing the statistical significance of a time-dependent treatment variable and by visually inspecting the estimated log(−log) survival curves. All analyses were performed using SAS version 9.2.

This study was approved by the Research Ethics Board of the Sunnybrook Health Sciences Centre, Toronto, Ontario.

Results

We identified 54,186 patients with diabetes who started treatment with an angiotensin-receptor blocker during the study period. Of these patients, 10,940 (20.2%) took candesartan, 12,691 (23.4%) took irbesartan, 8,411 (15.5%) took losartan, 8,182 (15.1%) took telmisartan and 13,962 (25.8%) took valsartan (Table 1). For the primary outcome, patients were collectively followed for a total of 107,315 person-years of treatment. Overall, patients were highly similar with respect to demographic characteristics, the specialties of the prescribing physicians, comorbid illnesses and concomitant medications (Table 1).

In the main analysis, the primary outcome (admission to hospital for either acute myocardial infarction, heart failure or stroke) occurred in 2712 (5.0%) patients taking an angiotensin-receptor blocker. After multivariable adjustment (Appendix 2), we found that telmisartan (adjusted hazard ratio [HR] 0.85, 95% confidence interval [CI] 0.74−0.97) and valsartan (adjusted HR 0.86, 95% CI 0.77−0.96) were associated with a significantly lower risk of the primary outcome when compared with irbesartan (Figure 1). In contrast, we found no difference in the risk of the primary outcome between irbesartan and either losartan (adjusted HR 0.93, 95% CI 0.83−1.05) or candesartan (adjusted HR 0.99, 95% CI 0.89−1.11) (Figure 1).

In the secondary analyses, we identified 2708 deaths, 1505 admissions to hospital for heart failure, 806 admissions for acute myocardial infarction and 804 admissions for stroke. We found a lower risk of heart failure with telmisartan versus irbesartan (adjusted HR 0.80, 95% CI 0.66−0.96), but we saw no significant differences between angiotensin-receptor blockers in all other comparisons (Figure 2).

In the dose−response analysis, we found no differences in the risk of the primary outcome with either moderate (adjusted HR 1.04, 95% CI 0.95−1.14) or high (adjusted HR 1.05, 95% CI 0.90−1.23) doses of angiotensin-receptor blockers relative to low doses of these drugs. Our main findings did not change appreciably after adjusting for dose (Appendix 3, available at www.cmaj.ca/lookup/suppl/doi:10.1503/cmaj.121771/-/DC1), although the effectiveness of valsartan was somewhat attenuated (adjusted HR 0.88, 95% CI 0.77−1.0).

Interpretation

In this population-based study of more than 50,000 older adult patients with diabetes starting treatment with an angiotensin-receptor blocker, we found that valsartan and telmisartan were associated with a reduced risk of admission to hospital for either stroke, myocardial infarction or heart failure relative to irbesartan. Furthermore, telmisartan was associated with a lower risk of admission to hospital for heart failure when compared with irbesartan. Our findings suggest that statistically important differences exist in the effectiveness of angiotensin-receptor blockers when used for the prevention of diabetes-related macrovascular disease, and that a class effect for these agents may not be assumed when used for this purpose in clinical practice.

Although angiotensin-receptor blockers share...
common structural features, important pharmacologic differences exist between the drugs that may explain our results. Specifically, at clinically attainable serum concentrations, telmisartan is unique among these drugs in its ability to structurally interact with and activate the PPARγ receptor, a ligand-activated transcription factor that regulates lipid metabolism and insulin sensitivity.8,21 Because telmisartan is a partial agonist of PPARγ, it is not associated with the adverse effects typically seen with full agonists (e.g., thiazolidinediones), such as sodium and water retention, edema and heart failure.26,27

Randomized controlled trials and observational studies comparing cardiovascular outcomes and mortality among patients with diabetes taking individual angiotensin-receptor blockers are lacking. A previous observational study comparing 5 angiotensin-receptor blockers in patients with congestive heart failure found no difference in all-cause mortality between people using telmisartan and those using losartan, but the conclusions were limited by a small sample size (only 143 patients received telmisartan).28 Our study builds upon the results of smaller trials involving patients with diabetes in which telmisartan was associated with significantly greater reductions in serum lipid levels, plasma glucose concentration, glycated hemoglobin levels and markers of insulin resistance relative to other angiotensin-receptor blockers.9-13

In addition, we saw a reduced risk of our primary outcome among patients receiving valsartan. Although this effect was attenuated after adjusting for dose, some evidence suggests that valsartan may impart cardioprotective effects in patients with diabetes unrelated to dose or to the drug’s efficacy as an antihypertensive agent. Val-
sartan has inhibited platelet aggregation in a manner that was neither dose- nor time-dependent, an effect that was more pronounced among patients with diabetes relative to those without the disease.29

Limitations
As with all observational studies, it is possible that our results are biased by intergroup differences in the baseline risk of macrovascular disease and death. However, this seems unlikely, because all groups were highly similar with respect to baseline characteristics, such that any residual differences were negligible and unlikely to account for our results. Furthermore, we adjusted our analyses for an array of important clinical and sociodemographic predictors of angiotensin-receptor blocker use and macrovascular disease.

Although we had no access to clinical information such as smoking history or body mass index, these limitations apply equally to each of the angiotensin-receptor blockers we investigated. Thus, it is difficult to conceive of an unmeasured variable that would be strongly associated with our outcomes but distributed differentially among the various groups to an extent that could sufficiently compromise our findings. A large randomized controlled trial could conclusively show differences in efficacy among individual angiotensin-receptor blockers in patients with diabetes; however, conducting a trial comparing the efficacy of 5 distinct agents would be expensive and time consuming.

Although miscoding is another possible source of bias in observational studies, we used validated codes for identifying stroke, acute myocardial infarction and heart failure in our databases, and differential miscoding among patients using angiotensin-receptor blockers is unlikely.10-32

Finally, our study involved patients with diabetes aged 66 years and older. Thus, our findings may not be applicable to younger patients or to patients with hypertension who do not have diabetes.

Conclusion
Our results suggest that telmisartan and valsartan are associated with a lower risk of admission to hospital for heart failure, stroke or acute myocardial infarction in older patients with diabetes. Pending confirmatory data from additional observational studies or randomized controlled trials, we suggest that a class effect may not be assumed when using angiotensin-receptor blockers for the prevention of diabetes-related macrovascular complications or heart failure, and that telmisartan and valsartan may be the preferred drugs for this indication.

References


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Contributors: Tony Antoniou, Ximena Camacho, Tara Gomes, David Juurlink and Muhammad Mamdani conceived and designed the study. Tony Antoniou, Ximena Camacho, Tara Gomes, David Juurlink, Muhammad Mamdani and Zhan Yao analyzed and interpreted the data. Ximena Camacho and Zhan Yao acquired the data. Tony Antoniou drafted the manuscript. Tony Antoniou, Ximena Camacho, Tara Gomes, David Juurlink, Muhammad Mamdani and Zhan Yao critically revised the manuscript for important intellectual content. All authors approved the final version of the manuscript submitted for publication. Tony Antoniou is the guarantor of this work and, as such, had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of its analysis.

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The Diabetes Control and Complications Trial has shown that intensive insulin therapy in type 1 diabetes with the aim of good glycemic control substantially reduces microvascular and macrovascular complications.1,2 However, despite advances in insulin analogs, insulin pumps and continuous glucose-monitoring systems, glucose control remains problematic, and most patients with type 1 diabetes do not achieve their glycemic targets.3

Hypoglycemia remains the major barrier to the intensification of insulin therapy.4 Intensive insulin therapy and lower levels of glycated hemoglobin are unfortunately associated with an increased risk of hypoglycemia.5 The frequency of patient-reported nonsevere hypoglycemia (blood glucose ≤ 3.5 mmol/L, with or without symptoms) is about 2.7 episodes/patient per week,6 with episodes commonly occurring during the night. In a recent continuous glucose-monitoring trial conducted by the Juvenile Diabetes Research Foundation,7 hypoglycemia (glucose sensor reading < 3.3 mmol/L) occurred during 8.5% of the nights included in the study.
period, with 47% of those nights involving at least 1 hour of hypoglycemia, 23% involving at least 2 hours, and 11% involving at least 3 hours.

Advances in insulin infusion pumps and continuous glucose-monitoring systems could improve glycemic control; however, we still lack the ability to combine these devices in an automated manner. Closed-loop insulin delivery systems (i.e., the artificial pancreas) combine the 2 devices using a mathematical algorithm. These systems might improve glycemic control and reduce the risk of hypoglycemia compared with conventional insulin-pump therapy (i.e., continuous subcutaneous insulin infusion). However, a clinically significant number of hypoglycemic events (blood glucose < 3.0 mmol/L) were still reported during tests of closed-loop delivery systems. Dual-hormone closed-loop delivery systems have also been proposed to regulate glucose levels. These systems combine insulin delivery with subcutaneous glucagon delivery to further reduce the risk of hypoglycemia. However, their potential benefits to improve glycemic control are currently unknown. We sought to determine whether dual-hormone closed-loop delivery, compared with conventional insulin pump therapy, can improve glycemic control and reduce the risk of hypoglycemia in adults with type 1 diabetes.

Methods

Study design
We used an open-label, randomized, crossover design to compare dual-hormone closed-loop delivery with continuous subcutaneous insulin infusion (the control) in adults with type 1 diabetes. Each study visit included an evening exercise session, followed by a meal, a bedtime snack and an overnight stay. The 2 interventions were separated by 7 (interquartile range [IQR] 3–14) days.

Participants
From February 2011 to January 2012, we enrolled participants from the diabetes clinic at the Institut de Recherches Cliniques de Montréal (Montréal, Quebec). Participants were required to be more than 18 years of age and to have been using an insulin pump for at least 3 months. Patients whose diabetes was poorly controlled (glycated hemoglobin > 10%) were excluded. Other exclusion criteria were detailed in Appendix 1 (available at www.cmaj.ca/lookup/suppl/doi:10.1503/cmaj.121265/-/DC1). All participants provided their written informed consent. The study was approved by the research ethics committee at the Institut de Recherches Cliniques de Montréal.

Sample size and randomization
We anticipated that dual-hormone closed-loop delivery would increase the percentage of time for which plasma glucose concentrations are in the target range by 22% (standard deviation [SD] = 22%). We calculated that 10 participants would provide 80% power at the 5% level of significance to detect such a difference between the 2 interventions. The study included, by its design, an interim assessment to evaluate the appropriateness of the sample size after 6 participants had completed both arms (i.e., a total of 12 completed visits). Subsequently, we adjusted the number needed to enrol to 16 participants, one of whom did not complete the study (Figure 1).

We used blocked randomization with an equal allocation ratio to generate allocation sequences. Patients were not blinded to the allocation. Blinding was practically challenging, because patients had to control their glucose levels during control visits, but not during dual-hormone closed-loop delivery.

Study protocol
Participants arrived at the research facility at about 1500 and received treatment from 1600 until 0700 the next day.

The exercise session consisted of a 30-minute workout on a stationary bicycle at 60% \( V_{O_2} \)max (each patient’s \( V_{O_2} \)max had been determined before randomization). At 1730, participants’ capillary glucose levels were checked using a glucose meter. The exercise session began at 1750 if the glucose level was above 6.0 mmol/L. If the glucose level was below 6.0 mmol/L, 15 g carbohydrate was given orally, and the exercise session began once the glucose level was above 6.0 mmol/L.

Each participant received a standardized meal (60 g carbohydrate for females, 80 g carbohydrate for males) at 1920 and a bedtime snack (15 g carbohydrate) at 2200 (for a description of the meal and snack, see Appendix 2, available at www.cmaj.ca/lookup/suppl/doi:10.1503/cmaj.121265/-/DC1). Participants were blinded to their plasma and sensor glucose data during both visits and to the hormonal infusions during closed-loop visits.

We drew venous blood samples every 10–30 minutes to determine plasma glucose and insulin levels, and every 10–60 minutes to determine plasma glucagon levels. Plasma glucose levels were measured using a YSI2300 STAT Plus Analyzer (Yellow Springs, Ohio). Plasma insulin and glucagon were measured using an immunoassay (Millipore, Billerica, Massachusetts).
During visits involving dual-hormone closed-loop delivery, glucose levels were regulated using variable subcutaneous insulin delivery combined with subcutaneous miniboluses of glucagon. Insulin aspart and recombinant glucagon were delivered by 2 infusion pumps (MiniMed Paradigm Veo, Medtronic, Northridge, California), according to recommendations, at 10-minute intervals and as determined by our dosing algorithm (Appendix 2). At the time of the evening meal, we entered the meal’s carbohydrate content into the algorithm to calculate the prandial bolus. Insulin and glucagon delivery was otherwise based only on readings from a continuous glucose sensor measuring interstitial glucose (Sof-sensor, Medtronic).

Every 10 minutes, we manually entered the real-time readings from the continuous glucose sensor into a computer that calculated insulin and glucagon delivery. We then manually gave the insulin and glucagon through the infusion pumps. We used a single sensor that we calibrated using finger-stick capillary glucose measurements. We did not recalibrate or replace the sensor in the event of suboptimal accuracy, and we always adhered to the dosing algorithm.

![Flowchart](image-url)

Figure 1: Flow of participants through the crossover study, showing the crossover in therapies between visits 1 and 2. The crossed-over streams are shown in parallel on each side of the flow chart. IQR = interquartile range, $VO_{max}$ = maximum oxygen uptake.
Figure 2: Profiles (medians and interquartile ranges) of (A) plasma glucose concentration and (B) basal insulin infusion with dual-hormone closed-loop delivery and continuous subcutaneous insulin infusion. (C) The histogram of glucagon delivery during closed-loop delivery.
During control visits, participants received continuous subcutaneous insulin infusion. Participants had access to their finger-stick glucose measurements, knew the carbohydrate content of their meal and snack, and consequently adjusted their insulin delivery (including temporary basal and correction boluses) as per their standard practice.

**Outcomes measures**

Our primary outcome was the percentage of time for which plasma glucose concentrations were in the target range during each 15-hour visit (4.00–10.00 mmol/L between the hours of 1600 and 2300, and 4.00–8.00 mmol/L between the hours of 2300 and 0700).

Our secondary outcomes were the percentage of time spent below the target range, the percentage of time spent above the target range, the total amount of insulin delivered, the standard deviation of plasma glucose concentrations and the number of participants with hypoglycemic events (blood glucose < 3.0 mmol/L).

**Statistical analysis**

For each continuous outcome, we used a repeated-measures regression model based on the ranked normal transformation (with the exception of mean glucose, which was not transformed) to compare the 2 treatments, adjusting for the starting glucose level and the period effect. We used the McNemar test to compare rates of hypoglycemia.

**Results**

Fifteen participants completed the study and were included in our analysis (Figure 1). The

<table>
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<tr>
<th>Table 1: Comparison of outcomes among 15 adults with type 1 diabetes receiving both interventions</th>
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<tr>
<td><strong>Intervention, median (IQR)</strong>†‡</td>
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<tr>
<td><strong>Outcome</strong></td>
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<tr>
<td><strong>Overall (duration of visit, from 1600 to 0700)</strong></td>
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<tr>
<td>Plasma glucose level at start of visit, mmol/L</td>
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<td>Time spent at specific glucose level, %</td>
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<td>Target range‡</td>
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<td>&lt; 4.0 mmol/L</td>
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<td>&lt; 3.3 mmol/L</td>
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<td>Above target range</td>
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<tr>
<td>Plasma glucose level, mmol/L, mean ± SD</td>
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<td>Plasma glucose level, mmol/L, SD</td>
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<td>Insulin delivery, U</td>
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<td>Insulin concentration, mU/L</td>
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<td>Glucagon concentration, pg/mL</td>
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<tr>
<td><strong>Overnight (from 2300 to 0700)</strong></td>
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<tr>
<td>Time spent at specific glucose level, %</td>
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<td>Target range</td>
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<td>Glucagon concentration, pg/mL</td>
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Note: IQR = interquartile range, SD = standard deviation.
* Unless stated otherwise.
† Repeated measures analysis.
‡ Primary study outcome.

Dual-hormone closed-loop delivery generally reduced interpatient variability in plasma glucose concentrations (Figure 2). The median and IQRs of participants’ glucose levels during control visits suggest that, during the night, 25% of the participants had glucose levels below 4.0 mmol/L at about 0100, and 25% of the participants had glucose levels above 10.0 mmol/L at about 0530 (Figure 2). During visits involving closed-loop delivery, participants’ plasma glucose levels were in the target range a median of 70.7% of the time (IQR 46.4%–88.4%), compared with 57.3% of the time (IQR 25.2%–71.8%) during control visits (p = 0.003; Table 1). Compared with conventional treatment, closed-loop delivery significantly decreased the percentage of time spent in hypoglycemia (0.0% v. 10.2% for plasma glucose levels < 4.0 mmol/L, and 0.0% v. 2.8% for plasma glucose levels < 3.3 mmol/L; Table 1).

The percentage of time spent in the target range for plasma glucose levels during the night was higher for closed-loop delivery than for conventional treatment (72.0% v. 45.8%, repeated measures analysis p = 0.07, Table 1). Closed-loop delivery also reduced nocturnal hypoglycemia. When samples collected during the night were combined (Table 2), 45 (12.3%) of the measurements of plasma glucose concentration were below 4.0 mmol/L during control visits, compared with only 2 measurements (0.5%) during closed-loop delivery, a more than 20-fold reduction. The total amounts of insulin delivered did not differ between the 2 interventions (Table 1). Prandial boluses, as determined using our algorithm, were lower by 0.9 (IQR 0.6–2.2) units during visits involving closed-loop delivery, compared with patient-determined boluses during control visits (repeated measures analysis p = 0.004). Prandial boluses were given at the start of meal ingestion on both visits.

**Hypoglycemic events**

We saw no adverse events other than hypoglycemia. Eight participants (53%) had at least 1 hypoglycemic event (plasma glucose concentration < 3.0 mmol/L) during a control visit, whereas only 1 participant (7%) had at least 1 hypoglycemic event during dual-hormone closed-loop delivery (McNemar test p = 0.02), an 8-fold difference. For 7 participants (47%), hypoglycemic events occurred only during the control visit; no participants had hypoglycemic events only during closed-loop delivery. 1 participant (7%) had hypoglycemic events during both visits, and 7 participants (47%) had no hyperglycemic events during either visit (data not shown). For the participant with hypoglycemia during both visits, 3 episodes occurred during the control visit and 2 episodes occurred during closed-loop delivery (data not shown). We saw a total of 12 hypoglycemic events during control visits and 2 events during closed-loop delivery (data not shown). We treated each event with 15 g oral carbohydrate. A second treatment was necessary for 4 events (all during control visits), 1 of which required a third treatment.

**Characteristics of glucagon delivery**

Total glucagon delivery during closed-loop delivery was 0.076 (IQR 0.016–0.170) mg per visit (Appendix 3), resulting in a modest increase in mean plasma glucagon level (66 v. 56 pg/mL, repeated measures analysis p = 0.01; Table 1). Glucagon was delivered intermittently (average of 1 minibolus every 3.6 h) and in small amounts (0.014 [IQR 0.013–0.036] mg/bolus). Insulin delivery was suspended for 40 (± 35) minutes before delivering glucagon but was not enough to prevent falling glucose levels (Figure 3). Glucagon delivery was used to prevent impending hypoglycemia rather than to treat it. The median plasma glucose level was 4.9 mmol/L and descending at a rate of 0.8 mmol/L per hour

<table>
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<tr>
<th>Table 2: Rates of hypoglycemia and nocturnal plasma glucose concentrations among 15 patients with type 1 diabetes during each intervention</th>
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<td><strong>Outcome</strong></td>
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<td>Patrons with at least 1 hypoglycemic event†</td>
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<td>Patrons with at least 1 exercise-induced hypoglycemic event§</td>
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<td>Nocturnal† plasma glucose measurements¶</td>
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*McNemar test. †Defined as at least 1 measurement of plasma glucose concentration < 3.0 mmol/L, which was treated by oral carbohydrate. ‡Between the hours of 2300 and 0700. §From start of exercise to 2300. ¶Measurements were taken at 20-min intervals.
at the time of glucagon delivery, and 5.3 mmol/L and ascending at a rate of 1.5 mmol/L per hour 20 minutes after glucagon delivery (Figure 3). None of the participants reported any gastrointestinal symptoms after receiving glucagon boluses. Of the 61 glucagon miniboluses delivered, 24 (40%) were given nocturnally. Insulin delivery before a glucagon minibolus was suspended for a longer time during the night compared with during the overall study period (57 min v. 40 min). This was because, in case of impending hypoglycemia, glucose levels fell less rapidly during the night than during exercise or the late postprandial period.

Sensor performance

Sensor performance was adequate for closed-loop delivery (relative absolute error 12.9% [IQR 6.5%–21.6%]). However, sensor readings often showed concentrations in the target range when plasma glucose was actually in the hyperglycemic range (sensor under-read by 1.07 [IQR 0.25–1.88] mmol/L in the hyperglycemic range [plasma glucose > 8.0 mmol/L]; n = 555). This may explain why the percentage of time spent above the target range was not reduced with closed-loop delivery. During closed-loop delivery, sensing errors possibly increased time spent above the target range by 10%–15% (the median percentage of time spent above the target range was 16% [data not shown] when calculated using sensor data, compared with 29% when calculated using plasma glucose measurements [Table 1]). We did not see sensor under-reading in the nonhyperglycemic range (0.18 [IQR −0.70 to 0.85] mmol/L [plasma glucose ≤ 8.0 mmol/L]; n = 828). Improvements in sensor performance will likely further improve closed-loop delivery.

Interpretation

Dual-hormone closed-loop delivery improved glucose control and reduced the risk of hypoglycemia in our 15 participants, as compared with continuous subcutaneous insulin infusion. Rates of hypoglycemia (plasma glucose concentration < 3.0 mmol/L) were reduced, with no increased risk of hyperglycemia.

Hypoglycemia is common in type 1 diabetes, and its management is difficult because patients might not show symptoms. Hypoglycemia remains underestimated, with up to 60% of events going unrecognized. Recurrent hypoglycemia leading to hypoglycemia unawareness emphasizes the need for improved prevention and mitigation strategies. Hypoglycemia alarms are now an essential part of continuous glucose sensors, but they are of limited benefit during the night. Hypoglycemia is feared by most patients and remains the most common adverse effect of insulin therapy. Dual-hormone closed-loop delivery appears to have the potential to reduce the risk of hypoglycemia. Patients with hypoglycemia unawareness might benefit the most from this technology. However, this potential should be confirmed with larger and longer studies in an outpatient setting.

![Figure 3: Profiles (medians and interquartile ranges) of plasma glucose concentration and basal insulin infusion before and after receipt of glucagon bolus (n = 61 boluses).](image-url)
Mean plasma glucose levels did not differ between the 2 treatments. However, between-patient variability in mean plasma glucose level was 50% higher during control visits than during closed-loop delivery, suggesting higher dispersion of individual mean plasma glucose levels. Hypoglycemia was common during control visits and therefore reduced mean glucose levels, whereas closed-loop delivery eliminated most hypoglycemia without increasing mean glucose levels. This trend is also seen in the glucose profiles shown in Figure 1.

Comparison with other studies
Recent randomized trials involving adults with type 1 diabetes have shown that overnight closed-loop insulin delivery increases the percentage of time for which plasma glucose levels are in the target range and decreases the time spent in the hypoglycemic range compared with conventional treatment. However, the reductions in time spent in the hypoglycemic range and numbers of patients with hypoglycemic events were not as remarkable as those in our study.

Although there have been previous studies of closed-loop insulin delivery and closed-loop insulin and glucagon delivery involving adults with type 1 diabetes, they did not have a randomized study design to make comparisons with conventional therapy. Furthermore, most of these studies have assessed the performance of the dosing algorithm rather than the clinical application of the whole system. Instead of a single glucose sensor, infusions were based on venous glucose or multiple sensors, and were sometimes overridden by an attending physician. Moreover, the glucose sensor was calibrated using reference-quality venous plasma glucose instead of capillary finger-stick measurements, potentially overestimating the benefits of closed-loop delivery. These issues may limit the application of the results of such studies in clinical practice. Our study avoided these shortcomings.

Limitations
Our study was powered using data from other studies of closed-loop delivery; despite having statistical significance in most outcomes, our study was limited by its small sample size. An additional limitation to our study was the absence of allocation blinding, but blinding participants to the interventions was practically challenging. Finally, current glucagon formulations are unlikely to be suitable for extended pump use, because they are unstable at room temperature after reconstitution. Research is underway to develop more stable formulations of the hormone.

Conclusion
Compared with conventional therapy, dual-hormone closed-loop delivery improved short-term glycemic control and reduced the risk of hypoglycemia among 15 adults with type 1 diabetes. Closed-loop delivery systems have the potential to substantially improve the management of diabetes and the safety of patients. These systems will probably be introduced gradually to clinical practice, with early generations focusing on overnight glucose control and using insulin alone. Their limitations and benefits will be elucidated, and their performance will be perfected over time.

References

**Affiliations:** From the Institut de Recherches Cliniques de Montréal (Haidar, Dallaire, Alkhateeb, Coriati, Messier, Rabasa-Lhoret); the Centre for Intelligent Machines, McGill University (Haidar, Boulet); the Montréal Children’s Hospital (Haidar, Boulet); the Nutrition Department (Rabasa-Lhoret), Université de Montréal; and the Endocrinology Division (Rabasa-Lhoret), Montreal University Hospital, Montréal, Que.; and the Jaeb Center for Health Research (Cheng), Tampa, Fla.

**Contributors:** Ahmad Haidar and Rémi Rabasa-Lhoret coordinated the study. Ahmad Haider, Rémi Rabasa-Lhoret, Laurent Legault, Benoît Boulet and Ammar Alkhateeb designed the study. Ahmad Haider, Maryse Dallaire, Rémi Rabasa-Lhoret, Laurent Legault, Adèle Coriati and Ammar Alkhateeb conducted the study. Ahmad Haidar designed and implemented the dosing algorithm. Ahmad Haider, Ammar Alkhateeb, Virginie Messier, Peiyao Cheng and Maude Millette analyzed the data. All of the authors contributed to the interpretation of the results, the writing and critical review of the manuscript, and the approval of final version submitted for publication.

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Differential mortality and the excess burden of end-stage renal disease among First Nations people with diabetes mellitus: a competing-risks analysis

Ying Jiang MSc, Nathaniel Osgood PhD, Hyun-Ja Lim PhD, Mary Rose Stang PhD, Roland Dyck MD

BACKGROUND: Diabetes-related end-stage renal disease disproportionately affects indigenous peoples. We explored the role of differential mortality in this disparity.

METHODS: In this retrospective cohort study, we examined the competing risks of end-stage renal disease and death without end-stage renal disease among Saskatchewan adults with diabetes mellitus, both First Nations and non–First Nations, from 1980 to 2005. Using administrative databases of the Saskatchewan Ministry of Health, we developed Fine and Gray subdistribution hazards models and cumulative incidence functions.

RESULTS: Of the 90,429 incident cases of diabetes, 8254 (8.9%) occurred among First Nations adults and 82,175 (90.9%) among non–First Nations adults. Mean age at the time that diabetes was diagnosed was 47.2 and 61.6 years, respectively (p < 0.001). After adjustment for sex and age at the time of diabetes diagnosis, the risk of end-stage renal disease was 2.66 times higher for First Nations than non–First Nations adults (95% confidence interval [CI] 2.24–3.16). Multivariable analysis with adjustment for sex showed a higher risk of death among First Nations adults, which declined with increasing age at the time of diabetes diagnosis. Cumulative incidence function curves stratified by age at the time of diabetes diagnosis showed greatest risk for end-stage renal disease among those with onset of diabetes at younger ages and greatest risk of death among those with onset of diabetes at older ages.

INTERPRETATION: Because they are typically younger when diabetes is diagnosed, First Nations adults with this condition are more likely than their non–First Nations counterparts to survive long enough for end-stage renal disease to develop. Differential mortality contributes substantially to ethnicity-based disparities in diabetes-related end-stage renal disease and possibly to chronic diabetes complications. Understanding the mechanisms underlying these disparities is vital in developing more effective prevention and management initiatives.

Indigenous peoples experience an excess burden of diabetes-related end-stage renal disease, but the reasons for this disparity are incompletely understood. Although the increase in end-stage renal disease among indigenous peoples has paralleled the global emergence of type 2 diabetes mellitus, disparities in end-stage renal disease among Canada’s First Nations adults persist after adjustment for elevated prevalence of diabetes. In an earlier study, we suggested that First Nations adults might be more prone to diabetic nephropathy and might experience more rapid progression to end-stage renal disease. However, although albuminuria is more prevalent in this population, affected individuals unexpectedly have a longer average time from diagnosis of diabetes to end-stage renal disease than people from non–First Nations populations. These findings could be explained by a younger age at the time of diabetes diagnosis and lower mortality among those with chronic kidney disease. An age-related survival benefit among First Nations adults with diabetes could lead to longer exposure to the metabolic consequences of diabetes and greater likelihood of end-stage renal disease.

Our objective was to examine the contribution of differential mortality to disparities in diabetes-related end-stage renal disease within large populations of indigenous and non-indigenous North Americans. Accordingly, we used competing-risks survival analysis to compare the simultaneous risks of diabetes-related end-stage renal disease and death without end-stage renal disease among First Nations and non–First Nations adults.
Methods

Study populations

In this retrospective, population-based cohort study, we examined the competing risks of end-stage renal disease and death without end-stage renal disease among Saskatchewan adults in whom diabetes was diagnosed from 1980 to 2005, using data from the province’s physicians’ services, hospital separation and person registry databases. The study was approved by the University of Saskatchewan Research Ethics Board, and its populations have been previously described.²,6 Briefly, the Canadian province of Saskatchewan has a population of about 1 million. About 99% of its citizens are beneficiaries of a universal health care system that generates administrative data for the Ministry of Health. Beneficiaries were subdivided into self-identified First Nations registered under section 6 of the Indian Act of Canada and non–First Nations. The latter are predominantly white, but this group also includes nonregistered First Nations (< 0.5%) and Métis (of mixed First Nations and non–First Nations heritage; about 5%).⁶

We identified cases of diabetes using a validated algorithm.⁶,10 For each participant, the diabetes incident year was the first calendar year in which the case definition was met. We excluded persons whose diabetes occurred before age 20 years and women with gestational diabetes.⁶ We identified end-stage renal disease using an algorithm based on physicians’ fee-for-service codes for long-term dialysis and renal transplantation.² The incident year for end-stage renal disease was the calendar year in which the person started dialysis or underwent a pre-emptive transplant.²

Although we could not identify the underlying cause, cases of end-stage renal disease that occurred in the same year as the case definition for diabetes was met (or thereafter) were designated as diabetes-related end-stage renal disease. Time from diagnosis of diabetes to diagnosis of end-stage renal disease was designated as 0.5 years when the 2 diagnoses occurred in the same calendar year. We excluded people whose end-stage renal disease occurred before diabetes. Finally, we obtained sex, birth year, death year and loss of health care coverage for all study participants.

Statistical analysis

We compared the distributions of individual-level variables between ethnic groups using t tests and χ² tests. The significance level for all descriptive, univariable and multivariable analyses (including interactions) was 0.05.

We used competing-risks survival analysis to compare the simultaneous risks of end-stage renal disease or death without end-stage renal disease in the 2 populations.² Survival time was the number of years from the age of diabetes diagnosis until either diagnosis of end-stage renal disease or death without end-stage renal disease. We previously compared different statistical modelling approaches to optimize the analysis of competing-risks data.¹¹ Accordingly, for the current study, we used the Fine and Gray model,¹²,¹³ a semipropotional subhazards model that provides the cumulative incidence (or sub-distribution) of each event of interest (diagnosis of end-stage renal disease or death before end-stage renal disease) while simultaneously considering the competing risk of the other outcome. Thus, people who die before end-stage renal disease occurs are not censored in a way that might bias the estimates, as is possible in a Cox cause-specific analysis. First, we used univariable analysis to test whether there was a significant effect of ethnicity, sex or age at diabetes diagnosis. For the multivariable analysis, we included

![Figure 1: Identification of study participants. ESRD = end-stage renal disease.](image-url)
predictors shown to be significant in the univariable analysis, as well as significant interactions.

We created cumulative incidence function curves to illustrate the probability of end-stage renal disease or death without end-stage renal disease by sex and ethnicity over the study period. We plotted the overall cumulative incidence of the 2 events against years since diabetes diagnosis and compared sex-specific results using Gray’s test.14 We also stratified curves by age at diabetes diagnosis (20 < 40 yr, 40–60 yr, > 60 yr).

We performed statistical analyses with SAS software, version 9.2 (SAS Institute, Cary, NC) and R-package cmprsk (www.R-project.org).

Results

Study population
From 1980 to 2005, a total of 90 429 cases of diabetes meeting our study criteria were identified in Saskatchewan (Figure 1). The mean age at diabetes diagnosis among the 8254 First Nations individuals was 47.2 years, and 3718 (45.0%) were male (Table 1). Among the 82 175 non–First Nations individuals, diabetes was most often diagnosed up to age 60 (6777 or 82.1%), whereas among non–First Nations individuals, diabetes was most often diagnosed after age 60 (46 025 or 56.0%). End-stage renal disease occurred in 200 (2.4%) of the First Nations participants, and 1482 (18.0%) of this group died without end-stage renal disease. Overall, 53 627 (59.3%) of the 82 548 participants died without end-stage renal disease. Overall, 53 627 (59.3%) of the 82 175 non–First Nations individuals, diabetes was most often diagnosed after age 60 (46 025 or 56.0%).

We performed statistical analyses with SAS software, version 9.2 (SAS Institute, Cary, NC) and R-package cmprsk (www.R-project.org).

Table 1: Key characteristics of study groups

<table>
<thead>
<tr>
<th>Variable</th>
<th>First Nations (n = 8 254)</th>
<th>Non–First Nations (n = 82 175)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, male</td>
<td>3 718 (45.0)</td>
<td>44 820 (54.5)</td>
</tr>
<tr>
<td>Age at diabetes diagnosis</td>
<td>47.2 ± 14</td>
<td>61.6 ± 15.3</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>2 685 (32.5)</td>
<td>7 290 (8.9)</td>
</tr>
<tr>
<td>&lt; 40 yr</td>
<td>4 092 (49.6)</td>
<td>28 860 (35.1)</td>
</tr>
<tr>
<td>40–60 yr</td>
<td>1 477 (17.9)</td>
<td>46 025 (56.0)</td>
</tr>
<tr>
<td>&gt; 60 yr</td>
<td></td>
<td></td>
</tr>
<tr>
<td>End-stage renal disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. (%) of participants</td>
<td>200 (2.4)</td>
<td>600 (0.7)</td>
</tr>
<tr>
<td>Age at diagnosis, yr, mean ± SD</td>
<td>56.5 ± 11.2</td>
<td>64.1 ± 13.7</td>
</tr>
<tr>
<td>Death without end-stage renal disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. (%) of participants</td>
<td>1 482 (18.0)</td>
<td>28 450 (34.6)</td>
</tr>
<tr>
<td>Age at death, yr, mean ± SD</td>
<td>66.4 ± 14.4</td>
<td>78.3 ± 11.1</td>
</tr>
<tr>
<td>SD = standard deviation.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>*All differences were statistically significant (p &lt; 0.001) by t test (continuous variables) or χ² test (categorical variables).</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Competing-risk analysis

Univariable models showed that male sex increased the risk for both events of interest (end-stage renal disease and death without end-stage renal disease) (Table 2). The risk of end-stage renal disease was 3.86 (95% confidence interval [CI] 3.29–4.53) times higher among First Nations participants than among non–First Nations participants, but the risk of death without end-stage renal disease was only 0.49 (95% CI 0.47–0.52) as high among First Nations participants. Increasing age at the time of diabetes diagnosis reduced the risk of end-stage renal disease but increased the risk of death without this condition.

The final multivariable model showed that the risk of end-stage renal disease was 2.66 times higher among First Nations participants than among non–First Nations participants (Table 3). Men experienced a 49% higher risk of end-stage renal disease than women. Increasing age at the time of diabetes diagnosis reduced the risk of end-stage renal disease by about 3% per year after adjustment for ethnicity and sex. There were no significant interactions.

The final multivariable model for death without end-stage renal disease showed interactions between sex, ethnicity and age at the time of diabetes diagnosis. Like the univariable model, the multivariable model showed that increasing age at

Table 2: Univariable Fine and Gray modelling of relations between significant variables and competing risk events

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hazard ratio (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>End-stage renal disease</strong></td>
<td></td>
</tr>
<tr>
<td>Sex, male</td>
<td>1.42 (1.23–1.64)</td>
</tr>
<tr>
<td>First Nations ethnicity</td>
<td>3.86 (3.29–4.53)</td>
</tr>
<tr>
<td>Age at diabetes diagnosis, per yr</td>
<td>0.964 (0.960–0.967)</td>
</tr>
<tr>
<td><strong>Death without end-stage renal disease</strong></td>
<td></td>
</tr>
<tr>
<td>Sex, male</td>
<td>1.21 (1.19–1.23)</td>
</tr>
<tr>
<td>First Nations ethnicity</td>
<td>0.49 (0.47–0.52)</td>
</tr>
<tr>
<td>Age at diabetes diagnosis, per yr</td>
<td>1.08 (1.08–1.08)</td>
</tr>
</tbody>
</table>

Note: CI = confidence interval.
*All differences statistically significant (p < 0.001) based on p values and 95% CIs generated by Fine and Gray modelling.
the time of diabetes diagnosis and male sex increased the risk of death without end-stage renal disease. Unlike the univariable model, however, the multivariable model showed that First Nations participants experienced a higher risk of death without end-stage renal disease than non–First Nations participants in a significant interaction with age at time of diabetes diagnosis (after adjustment for sex). Thus, the degree of elevation in the hazard ratio for death without end-stage renal disease among First Nations compared with non–First Nations individuals slowly diminished with increasing age at the time of diabetes diagnosis.

**Cumulative incidence function curves**

Cumulative incidence function curves for end-stage renal disease (Figure 2) and death without end-stage renal disease (Figure 3), both overall and stratified by age at the time of diabetes diagnosis, were generated by ethnicity and sex. Overall, there were significant differences among the 4 complete groups (First Nations men, First Nations women, non–First Nations men, non–First Nations women) in the probability of both end-stage renal disease and death without end-stage renal disease ($p < 0.001$). First Nations individuals experienced a higher probability of end-stage renal disease and a lower probability of death without end-stage renal disease over time than non–First Nations individuals. For each overall outcome, men from both ethnic groups experienced a significantly greater risk than women with increasing duration of diabetes. The ethnicity-based disparity in risk of end-stage renal disease was present regardless of age at the time of diabetes diagnosis.

### Table 3: Multivariable Fine and Gray modelling of relations between significant variables and competing risk events

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hazard ratio (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>End-stage renal disease</strong></td>
<td></td>
</tr>
<tr>
<td>Sex, male</td>
<td>1.49 (1.29–1.72)</td>
</tr>
<tr>
<td>First Nations ethnicity</td>
<td>2.66 (2.24–3.16)</td>
</tr>
<tr>
<td>Age at diabetes diagnosis, per yr</td>
<td>0.969 (0.966–0.973)</td>
</tr>
<tr>
<td><strong>Death without end-stage renal disease</strong></td>
<td></td>
</tr>
<tr>
<td>Sex, male</td>
<td>2.25 (1.96–2.58)</td>
</tr>
<tr>
<td>First Nations ethnicity</td>
<td>3.13 (2.49–3.92)</td>
</tr>
<tr>
<td>Age at diabetes diagnosis, per yr</td>
<td>1.08 (1.08–1.08)</td>
</tr>
<tr>
<td>Interaction: age at diabetes diagnosis × First Nations ethnicity</td>
<td>0.986 (0.982–0.990)</td>
</tr>
<tr>
<td>Interaction: age at diabetes diagnosis × male sex</td>
<td>0.994 (0.992–0.996)</td>
</tr>
</tbody>
</table>

Note: CI = confidence interval.

*All differences statistically significant ($p < 0.001$) based on $p$ values and 95% CIs generated by Fine and Gray modelling.

Despite the overall higher risk of death without end-stage renal disease among non–First Nations individuals over time, ethnicity-based disparities were less clear when stratified by age at the time of diabetes diagnosis. Apart from those in whom diabetes was diagnosed the earliest, the most consistent differences were observed between sexes: compared with women, men with diabetes diagnosed in all age strata (both First Nations and non–First Nations) had a greater risk of death without end-stage renal disease with increasing duration of diabetes. In contrast to end-stage renal disease, the cumulative incidence of death without end-stage renal disease over time was progressively higher with each increase in age stratum for time of diabetes diagnosis.

**Interpretation**

Differential mortality amplifies the risk of end-stage renal disease among First Nations adults with diabetes. Because they are younger than non–First Nations individuals when diabetes first develops, First Nations individuals are more likely to survive long enough for end-stage renal disease to occur, presumably because of lower cardiovascular mortality. This phenomenon occurs in the formerly perplexing context of higher age-adjusted mortality among First Nations individuals with diabetes, and it also explains our earlier observation that the time from diabetes diagnosis to end-stage renal disease is significantly longer among First Nations individuals, despite evidence for poorer quality of diabetes care and a larger proportion of patients with early diabetic nephropathy. These findings are notable because they reveal an important mechanism underlying ethnicity-based disparities in end-stage renal disease that has serious long-term implications for First Nations and other indigenous populations. They may also help to explain similar disparities in other diabetic complications.

Although differences in diabetes-related incidence of end-stage renal disease have diminished between First Nations and non–First Nations populations in Canada and between comparable populations in the United States, significant ethnicity-based disparities in end-stage renal disease persist and have remained incompletely understood. Known contributing factors include genetic and other prenatal determinants.
Environmental factors such as glycemic and blood pressure control\textsuperscript{8,24} and social determinants such as quality of and access to health care.\textsuperscript{18,19} We have now confirmed that an age-related survival advantage after diabetes diagnosis also contributes to the elevated risk for diabetes-related end-stage renal disease among First Nations individuals.

End-stage renal disease and death without end-stage renal disease are competing risks among people with diabetes, because each precludes the other.\textsuperscript{9} Because end-stage renal disease reduces quality of life and its treatment is resource intensive, death after a normal life span without end-stage renal disease is the preferred outcome. Nonetheless, few studies have considered this issue among people with diabetes. Agarwal and associates\textsuperscript{25} and Derose and colleagues\textsuperscript{26} examined the predictors of end-stage renal disease versus death among people with all-cause chronic kidney disease, as did the FinnDiane Study Group among people with type 1 diabetes.\textsuperscript{13} We are not aware of any other population-based studies that have examined the contribution of competing risks to ethnicity-based disparities in diabetes-related end-stage renal disease between indigenous and non-indigenous peoples. However, our findings are consistent with the results of a study comparing Pima Indians with onset of type 2 diabetes in youth or adulthood. In that study, a higher incidence of end-stage renal disease in the younger cohort by middle age was largely attributable to longer duration of diabetes.\textsuperscript{27}

The implications of our findings are sobering. Among First Nations adults, type 2 diabetes is increasingly occurring during younger decades of life.\textsuperscript{6} Among First Nations children, the prevalence of diabetes tripled between 1980 and 2005,\textsuperscript{28} and the offspring of these individuals are in turn experiencing an even higher risk of childhood type 2 diabetes.\textsuperscript{29} These demographic trends suggest that steadily increasing numbers of young First Nations individuals will face prolonged exposure to the metabolic consequences of type 2 diabetes. Without substantial improvements in the prevention and treatment of this disease, this pattern will likely translate into increasing numbers of First Nations people with diabetes-related end-stage renal disease and possibly other chronic diabetic complications.

What can we learn from these observations? First, they reinforce the need for an emphasis on diabetes prevention and management initiatives for First Nations children and young adults, with

![Figure 2: Cumulative incidence function curves for end-stage renal disease (ESRD) in study populations, for all ages and stratified by age at time of diabetes diagnosis. For most First Nations participants, diabetes was diagnosed when they were 60 years of age or younger, when the incidence of ESRD is higher. Conversely, for most non–First Nations participants, diabetes was diagnosed when they were older than 60 years of age, when the incidence of ESRD is lowest. Particularly among First Nations people, men consistently experienced a trend toward higher incidence of end-stage renal disease than women, regardless of age group at time of diagnosis, although the differences for comparisons with small sample sizes were not significant.](image-url)
particular attention to diabetes in pregnancy.6 Second, strategies to postpone type 2 diabetes should be considered: if the occurrence of diabetes can be delayed, it seems plausible that the risk of chronic complications and premature deaths will be reduced. Finally, addressing disparities in both accessibility and quality of diabetes care6,19 is imperative to achieve therapeutic targets for glycemic, blood pressure and lipid control.18,19 Although the reasons underlying these disparities are complicated, they are also modifiable, and substantial improvements are likely during even the early stages of resolution.

Strengths and limitations

The strengths of this analysis include long duration of the study period, consideration of total populations, use of validated algorithms for both diabetes and end-stage renal disease, and our ability to distinguish First Nations and non–First Nations populations.2,6 We previously evaluated the most appropriate competing-risks methodology for analyzing this kind of data11 and, on the basis of that evaluation, used Fine and Gray models for the current analysis, as has been proposed by others.13

The limitations of the study include our inability to control for important predictors of end-stage renal disease and death without end-stage renal disease, such as glycemic, blood pressure and lipid control, and related changes in medical practice, such as the introduction of angiotensin-converting enzyme inhibitors,10 that occurred during the course of the study period. However, these factors would not have affected the difference in age of diabetes onset between First Nations and non–First Nations people. We were unable to identify indigenous people other than First Nations, but this limitation would lead to underestimation of the real differences between First Nations and non–First Nations populations. We were also unable to distinguish between type 1 and type 2 diabetes or among various causes of end-stage renal disease (diabetes versus other causes). Finally, the Fine and Gray model assumes proportional hazards12 between groups in the risks for end-stage renal disease and death without end-stage renal disease over time. We do not know if that assumption is entirely correct, but when we used Cox cause-specific models to analyze our data, the results (not shown) were very similar to those reported here.

Figure 3: Cumulative incidence function curves for mortality in study populations, for all ages and stratified by age at time of diabetes diagnosis. For most First Nations participants, diabetes was diagnosed when they were 60 years of age or younger, when mortality rates are lower. Conversely, for most non–First Nations participants, diabetes was diagnosed when they were older than 60 years of age, when mortality rates are highest.
Conclusion
In this competing-risks analysis, First Nations adults experienced a higher risk of both end-stage renal disease and death without end-stage renal disease. However, most non–First Nations individuals are older than 60 at the time of diabetes diagnosis, when cumulative risk of end-stage renal disease is lowest, and most First Nations adults are much younger when diabetes occurs, when the cumulative risk of end-stage renal disease is highest. Therefore, First Nations adults with diabetes are more likely to survive long enough to experience end-stage renal disease and possibly other chronic diabetic complications. Further effective primary prevention initiatives are urgently needed to reduce the incidence of type 2 diabetes. Among those with diabetes, reduced rates of microalbuminuria and slowed progression of chronic kidney disease are achievable through early diagnosis, cessation of smoking and achievement of established clinical practice guideline targets for glycemic, blood pressure and lipid control. Finally, we suggest that delaying the onset of type 2 diabetes should now be considered in the overall strategy for reducing diabetes complications. Further research is required to evaluate the cost and effectiveness of screening for and treating pre-diabetes among indigenous peoples and others.

References

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Contributors: Ying Jiang helped design the study, performed the statistical analysis, interpreted the data and completed a master’s thesis based on this project. Nathaniel Osgood conceived and helped design the study, interpreted the data and supervised the analysis. Hyun-Ja Lim helped design the study, interpreted the data and supervised the statistical analysis. Mary Rose Stang helped design the study and acquired the data. Roland Dyck acquired the data, co-conceived and helped design the study, interpreted the data, oversaw the project and wrote the manuscript. All authors contributed to the discussion, reviewed and edited the manuscript, and read and approved the final manuscript submitted for publication.

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Increasing evidence shows that strengthening the foundation of primary health care will lead to improved health and provide better management for people with one or more chronic conditions. In Canada, increased attention on the primary health care system is particularly important given the growing number of people living with one or more chronic conditions. The move to renew and redesign primary care has led to a number of innovations, including group medical visits.

Group medical visits are a format for health care delivery whereby medical appointments are offered to a group of patients with the same disease instead of the traditional one-to-one patient–provider format. During the group visit, patients receive a health evaluation and educational information about their condition and about the prevention of complications and disease progression, and they may have prescriptions, referrals and laboratory tests ordered. The visit is usually facilitated by a physician or a nurse practitioner and may involve other interdisciplinary team members such as a registered nurse, nutritionist and pharmacist.

Group medical visits offer an ideal format for patients with chronic diseases because they allow health care practitioners to provide care to 12–15 patients in one appointment and enable patients to interact with people who share their condition. In Canada, group medical visits are increasingly being used to provide primary health care to patients with diabetes. Type 1 and type 2 diabetes affect about 6.8% of the Canadian population. Social support from peers with diabetes has been shown to improve some clinical outcomes.

Although health care providers have reported this care model to be an effective way to deliver care, data are limited and differ on the impact of group medical visits on patient outcomes. We conducted a systematic review and meta-analysis to measure the effect of group medical visits on biophysical, process-of-care and patient-reported outcomes among patients with type 1 and 2 diabetes.
Methods

We used the PICO (population, intervention, comparison and outcome) approach to develop the research question for our systematic review — population: patients with type 1 or 2 diabetes; intervention: group medical visits; comparison: usual care; outcomes: biophysical, patient-reported and process-of-care outcomes.

Literature search

We conducted a comprehensive search of the following electronic databases from inception through February 2012: MEDLINE (PubMed), CINAHL, Biosis, ProQuest Dissertations and Theses, Embase, Web of Science, Psych Info and the Cochrane Database of Systematic Reviews. We also searched various sources of grey literature. Bibliographies of selected articles were manually searched for additional studies. Details of our search strategies are available in Appendix 1 (available at www.cmaj.ca/lookup/suppl/doi:10.1503/cmaj.130053/-/DC1). A librarian was consulted to review the search strategy.

Study selection

A 3-step process was used to determine the eligibility of studies for our review. First, the title of relevant articles were independently screened by each of us. Second, if titles were deemed relevant, abstracts were independently reviewed by 2 of us (L.H. and either S.T.W. or M.D.). Finally, if abstracts were deemed relevant, full-text articles were independently reviewed by 2 of us (as described above). Decisions regarding inclusion and exclusion of studies were made by consensus between the 2 reviewers; disagreements were resolved by the third reviewer as required.

We included randomized controlled trials (RCTs) and observational studies published in English or translated into English that included patients aged 16–80 years with type 1 or 2 diabetes and had group medical visits as the intervention. We excluded studies in which the intervention was for educational purposes or did not include a health care provider who could diagnose, prescribe, make referrals and order laboratory tests.

Multiple articles from the same study or group of patients were classified as “kinned” articles. We grouped kinned articles together and counted them as one study.

Data synthesis

We included only RCTs in the meta-analysis. We analyzed the data from RCTs using Review Manager software (RevMan, version 5.1, Nordic Cochrane Centre). For each RCT, the effect size was calculated to determine the mean differences between the intervention and control groups at the longest reported time after the intervention.

Mean differences were first pooled into a fixed-effects model. A χ² test for heterogeneity was performed; when significant heterogeneity was found (I² > 25%), the analysis was recalculated with a random-effects model. The mean differences were weighted and pooled following Hedges’ method for calculating standardized mean differences.¹⁴

When measures of dispersion were not reported for outcome data, we used baseline SDs or calculated SDs from reported p values. When no baseline SD or p values were reported, we estimated SDs from the baseline range data. When examining these estimated SDs, we found that they were conservative estimates of the value; a sensitivity analysis in which we removed studies with uncertain SDs yielded improved HbA₁c outcomes with a decrease in effect size.

We performed a meta-regression analysis to determine (a) if the length of time patients spent attending group medical visits was related to effect size and (b) if the number of group visits a patient attended in a year was related to effect size. To examine the number of group visits attended per year, we created an “intensity”
value by dividing the number of appointments by
the number of years of the intervention. For the
meta-regression analysis, we used Stata soft-
ware, version 12.1 (StataCorp LP).

Results

We identified 92 potentially eligible articles. The
most common reasons for exclusion were that
the intervention did not involve a health care
provider who could prescribe, diagnose, assess
and refer patients; the article was a narrative or
commentary based on other research studies; the
study did not include a group medical visit as the
intervention; and the article was not in English.
A total of 26 studies met our inclusion criteria
(Figure 1).5,15−45

Study characteristics

The characteristics of the 13 RCTs included in the
meta-analysis are summarized in Table 114−33 (for
characteristics of all 26 studies, see Appendix 2,
available at www.cmaj.ca/lookup/suppl/doi:
10.1503/cmaj.130053/-/DC1). The number of
studies published after 2002 increased substan-
tially (4 studies before 2002, 12 between 2002
and 2007, and 16 between 2008 and 2012). One
document was a doctoral dissertation, completed
in 2011.43 Most of the studies (n = 20) were con-
ducted in the United States,5,15−23,25−28,33,34,36−43 with
the remainder conducted in Europe (Austria n = 1,44
France n = 1,15 Italy n = 329−32,45 Norway n = 145).
Samples ranged in size from 37 to 707 partici-
pants. Three studies included fewer than 50
patients, and 6 had more than 200; the remainder
had between 50 and 100 patients (n = 7 studies) or
between 100 and 200 patients (n = 10).

Of the total 4652 patients, 3112 received
group care or attended group medical visits as an
intervention. The mean age of participants in the
studies that reported this information was 59.3
years, and 56% of participants attending group
medical visits were men.

Study quality

A summary of the risk-of-bias assessment of the
13 RCTs can be found in Table 2. The amount of
bias varied across the trials. Only one had a low
risk of bias in most areas.22 The other RCTs
either did not report enough information for bias
to be assessed or had 2 or more areas assessed as
a high source of bias.

Clinical outcomes

Eleven of the RCTs reported HbA1c data at base-
line. The baseline values did not differ signifi-
cantly between the studies (weighted mean dif-
ference −0.09, 95% confidence interval [CI]
−0.29 to 0.11). Only 10 studies reported HbA1c
data that could be included in our meta-analysis.
Pooled analysis of HbA1c values after the inter-
vention period showed significantly lower values
among the patients attending group medical vis-
ts (weighted mean difference −0.46, 95% CI
−0.80 to −0.13) (Table 3, Figure 2).

In the meta-regression analysis, we found
that duration of treatment directly affected
patients’ HbA1c values. Patients who attended
group medical visits for longer periods had bet-
ter HbA1c outcomes. For every year increase in
the duration of treatment, there was a decrease
in effect size of 0.25, which indicated a drop in
HbA1c of one quarter of 1%. When we examined
whether the frequency of group visits had an
effect on HbA1c outcomes, it did not explain the
difference in the effect size, which indicated that
the duration of treatment had a greater effect on
HbA1c outcomes than the number of appoint-
**Table 1 (part 1 of 3):** Characteristics of 13 randomized controlled trials included in the meta-analysis

<table>
<thead>
<tr>
<th>Study</th>
<th>Study duration</th>
<th>Duration and frequency of group medical visits</th>
<th>No. of patients</th>
<th>Study population</th>
<th>% male</th>
<th>Outcomes measured</th>
<th>HbA₁c outcome</th>
<th>BP outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clancy et al., 2003&lt;sup&gt;11&lt;/sup&gt;</td>
<td>6 mo</td>
<td>2-h sessions; monthly over 6 mo</td>
<td>Intervention: 59 Control: 61</td>
<td>Age &gt; 18 yr; type 2 diabetes with HbA₁c &gt; 8.5% at most recent evaluation</td>
<td>21.7</td>
<td>Trust in physician (scale). ADA process-of-care indicators, patient care assessment tool, HbA₁c lipid profiles</td>
<td>At 6 mo: 9.513% in intervention and 9.714% in control; difference not significant</td>
<td>Not measured</td>
</tr>
<tr>
<td>Clancy et al., 2007&lt;sup&gt;10&lt;/sup&gt; and 2008&lt;sup&gt;10&lt;/sup&gt;</td>
<td>12 mo</td>
<td>2-h sessions; monthly over 12 mo</td>
<td>Intervention: 96 Control: 90</td>
<td>Age &gt; 18 yr; poorly controlled type 2 diabetes (HbA₁c &gt; 8%)</td>
<td>28</td>
<td>Emergency department visits, inpatient stays, and specialty outpatient visits, total charges, HbA₁c testing, lipid profiles, adherence to ADA guidelines, cancer screens</td>
<td>Not measured; instead study looked at no. of patients who received HbA₁c testing</td>
<td>Not measured</td>
</tr>
<tr>
<td>Cohen et al., 2011&lt;sup&gt;15&lt;/sup&gt;</td>
<td>6 mo</td>
<td>2-h sessions over 6 mo; weekly for 4 wk, then monthly for 5 mo</td>
<td>Intervention: 50 Control: 49</td>
<td>Veterans with type 2 diabetes; HbA₁c &gt; 7.0%, LDL cholesterol &gt; 100 mg/dL (or &gt; 70 mg/dL if coronary artery disease present); BP &gt; 130/80 mm Hg</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Edelman et al., 2010&lt;sup&gt;12&lt;/sup&gt;</td>
<td>12.8 mo</td>
<td>90-120 min per session; every 2 mo over 12 mo; total 7 sessions</td>
<td>Intervention: 133 Control: 106</td>
<td>Veterans with poorly controlled diabetes (HbA₁c ≥ 7.5%) and hypertension (systolic BP &gt; 140 mm Hg, diastolic BP &gt; 90 mm Hg); type of diabetes not specified</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Naik et al., 2011&lt;sup&gt;10&lt;/sup&gt;</td>
<td>12 mo</td>
<td>60-min sessions; 4 sessions every 3 wk over 3 mo</td>
<td>Intervention: 45 Control: 42</td>
<td>Veterans aged 50-90 yr with a primary care provider; type 2 diabetes mean HbA₁c 7.5% 6 mo before study</td>
<td>Unknown</td>
<td>HbA₁c diabetes self-efficacy scale, diabetes specific knowledge and understanding scale</td>
<td>At 1 yr: 8.05% ± 1.40% in intervention v. 8.64% ± 1.39% in control (p = 0.05)</td>
<td>Not measured</td>
</tr>
<tr>
<td>Rygg et al., 2012&lt;sup&gt;12&lt;/sup&gt;</td>
<td>12 mo</td>
<td>5-h sessions; every 2 wk over 6 wk, or every 3 wk over 9 wk, depending on site</td>
<td>Intervention: 73 Control: 73</td>
<td>Age &gt; 18 yr; type 2 diabetes; consultation with general practitioner in past 3 yr</td>
<td>&quot;Approximately 50%&quot;</td>
<td>HbA₁c patient activation, diabetes knowledge, BP, weight, BMI, total and HDL cholesterol, triglycerides, creatinine, oral glucose-lowering medication, visits with health care personnel in past 3 mo, satisfaction with diabetes treatment, problem areas in diabetes, EQ-VAS, SF-36 (physical and mental health domains), self-management (diet, foot care and blood glucose)</td>
<td>At 12 mo: no significant difference (p = 0.432), except in subgroup analysis of patients with highest HbA₁c (&gt; 7.7%) at baseline (8.2% ± 1.4% in intervention group v. 8.8% ± 1.4% in control group; p = 0.012)</td>
<td>Systolic BP intervention: 140.6 (17.1), control: 143.7 (20.8). diastolic BP intervention: 82.6 (10.3), control 83.3 (10.3)</td>
</tr>
</tbody>
</table>
Table 1 (part 2 of 3): Characteristics of 13 randomized controlled trials included in the meta-analysis

<table>
<thead>
<tr>
<th>Study</th>
<th>Study duration</th>
<th>Duration and frequency of group medical visits</th>
<th>No. of patients</th>
<th>Study population</th>
<th>% male</th>
<th>Outcomes measured</th>
<th>HbA1c outcome</th>
<th>BP outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sadur et al., 1999⁹</td>
<td>12 mo</td>
<td>2-h sessions; monthly over 6 mo</td>
<td>Intervention: 82 Control: 74</td>
<td>Age 16–75 yr; type 1 and 2 diabetes; HbA₁c &gt; 8.5%, or no HbA₁c test performed in previous yr</td>
<td>Intervention: 58.8</td>
<td>HbA₁c, self-reported changes in self-care practices, self-efficacy, satisfaction, utilization of inpatient and outpatient health care</td>
<td>≥ 5 mo after randomization: 8.18% in intervention and 9.33% in control (p &lt; 0.0001)</td>
<td>Not measured</td>
</tr>
<tr>
<td>Schillinger et al., 2009⁸</td>
<td>12 mo</td>
<td>90-min sessions; monthly over 9 mo</td>
<td>Intervention: 104 Control (usual care): 108 3rd arm (wkly automated telephone support with nurse follow-up): 112</td>
<td>Adult patients with type 2 diabetes; uninsured with high school education or less; ≥ 1 primary care visit in past yr; recent HbA₁c ≥ 8.0%</td>
<td>Intervention: 36.3</td>
<td>1-yr changes in structure (patient assessment of chronic illness care), communication processes (interpersonal processes of care) and outcomes (behavioural, functional and metabolic)</td>
<td>No difference between groups (9.0% ± 2.0% in both groups; p = 0.3)</td>
<td>Systolic BP 138.9 ± 20.3 mm Hg in intervention and 141.5 ± 23.9 mm Hg in usual-care group (p = 0.1); diastolic BP 75.5 ± 11.3 mm Hg in intervention and 78.5 ± 18.5 mm Hg in usual-care group (p = 0.08)</td>
</tr>
<tr>
<td>Taveira et al., 2010⁷</td>
<td>4 mo</td>
<td>2-h sessions; weekly over 4 wk</td>
<td>Intervention: 58 Control: 51</td>
<td>Veterans aged ≥ 18 yr with type 2 diabetes; HbA₁c, 7%–9% in previous 6 mo</td>
<td>Intervention: 91.4</td>
<td>HbA₁c, BP (systolic &lt; 130 mm Hg, diastolic &lt; 80 mm Hg), lipids, tobacco use</td>
<td>Target reached by 40.4% in intervention and 21.6% in control; absolute mean change −0.9 ± 1.6 in intervention and 0.0 ± −1.5 in control</td>
<td>Target systolic BP reached by 65.5% in intervention and 39.9% in control; absolute mean change −7.3 ± 20.3 mm Hg in intervention and −1.7 ± −19.6 mm Hg in control. Target diastolic BP reached by 65.5% in intervention and 68.6% in control; absolute mean change −6.5 ± 10.0 mm Hg in intervention and 1.0 ± 10.8 mm Hg in control</td>
</tr>
<tr>
<td>Taveira et al., 2011⁴</td>
<td>6 mo</td>
<td>90-min sessions; weekly for 4 wk, then monthly for 5 mo</td>
<td>Intervention: 44 Control: 44</td>
<td>Veterans with depression and type 1 or 2 diabetes; HbA₁c &gt; 6.5% in previous 6 mo</td>
<td>Intervention: 100</td>
<td>HbA₁c &lt; 7% at 6 mo, adherence to ADA guidelines (systolic BP &lt; 130 mm Hg, diastolic BP &lt; 80 mm Hg), total, LDL and HDL cholesterol, tobacco cessation, change in 10-yr coronary event risk at 6 mo, depression symptoms</td>
<td>7.4% ± 1.2% in intervention v. 8.4% ± 2.0% in control group (p &lt; 0.05)</td>
<td>Systolic BP 123.4 ± 12.3 mm Hg in intervention and 127.0 ± 17.3 mm Hg in control (p &lt; 0.05 from baseline)</td>
</tr>
</tbody>
</table>

Continued
**Table 1 (part 3 of 3):** Characteristics of 13 randomized controlled trials included in the meta-analysis

<table>
<thead>
<tr>
<th>Study</th>
<th>Study duration</th>
<th>Duration and frequency of group medical visits</th>
<th>No. of patients</th>
<th>Study population</th>
<th>% male</th>
<th>Outcomes measured</th>
<th>HbA₁c outcome</th>
<th>BP outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trento et al., 2002, 2001&lt;sup&gt;4&lt;/sup&gt; and 2004&lt;sup&gt;5&lt;/sup&gt;</td>
<td>4 yr</td>
<td>Duration of session not stated; session every 3 mo</td>
<td>Intervention: 56 Control: 56 (42 in each group at yr 5)</td>
<td>Type 2 diabetes, treated with diet alone or diet and oral hypoglycemic agents; attended diabetes clinic</td>
<td>51.1</td>
<td>Weight, fasting blood glucose level, HbA₁c, serum creatine, total and HDL cholesterol, triglycerides, microalbumin: creatinine ratio, diabetes-related quality of life, knowledge of diabetes, health behaviours, BP, BMI</td>
<td>At 5 yr after randomization: 7.3% ± 1.0% in intervention and 9.0% ± 1.6% in control (p &lt; 0.001)</td>
<td>Not measured</td>
</tr>
<tr>
<td>Trento et al., 2005&lt;sup&gt;5&lt;/sup&gt;</td>
<td>3 yr</td>
<td>Duration of session unclear; every 2–3 mo; total 15 sessions over 36 mo</td>
<td>Intervention: 30 Control: 28</td>
<td>Age &lt; 70 yr; type 1 diabetes with onset before 30 yr; insulin started within 1 yr of diagnosis ≥ 1 yr previous attendance in clinic</td>
<td>61.3</td>
<td>Diabetes-related quality of life, knowledge of type 1 diabetes, health behaviours, HbA₁c, total and HDL cholesterol, microalbumin: creatinine ratio, complications (hypoglycemic episodes retrospective), economic analysis</td>
<td>At 3 yr: 7.88% ± 0.20% in intervention and 8.79% ± 1.38% in control (p = NS)</td>
<td>Not measured</td>
</tr>
<tr>
<td>Wagner et al., 2001&lt;sup&gt;11&lt;/sup&gt;</td>
<td>2 yr</td>
<td>Half-day sessions; “periodic” (intervals of 3 mo and 6 mo)</td>
<td>Intervention: 278 Control: 429</td>
<td>Age &gt; 30 yr; patients with diabetes (type not specified) using insulin or oral hypoglycemic therapy were “preferentially selected”</td>
<td>51.8</td>
<td>Subscales of SF-36 (general health, physical function, emotional role function, social function and pain), bed disability, restricted-activity days</td>
<td>At 24 mo: no difference between groups (7.9% in both groups; p = 0.9)</td>
<td>Not measured</td>
</tr>
</tbody>
</table>

Note: ADA = American Diabetes Association, BMI = body mass index, BP = blood pressure, EQ-VAS = EuroQol 5-d measure of health outcome, HDL = high-density lipoprotein, LDL = Low-density lipoprotein, NS = not significant, SF-36 = Medical Outcomes Study 36-item Short Form.
ments attended per year. We did not analyze other attributes of group visits using meta-regression techniques because the data were not consistently reported in the RCTs.

When we excluded studies with 2 or more methodologic features assessed as a high source of bias, the overall effect of group medical visits on HbA$_{1c}$ improved (weighted mean difference $-0.62$, 95% CI $-1.23$ to $-0.01$). When we excluded studies with 3 or more features assessed as a high source of bias, the effect size did not change significantly ($-0.47$, 95% CI $-0.94$ to $0.00$). When we excluded studies that had only patients with type 1 diabetes, the effect size increased ($-0.58$, 95% CI $-1.12$ to $-0.04$).

Five of the RCTs evaluated the effects of group medical visits on systolic blood pressure, and 4 assessed the effects on diastolic pressure. No statistically significant effect on either type of blood pressure was found in the meta-analysis (Table 3; see also Appendix 3, available at www.cmaj.ca/lookup/suppl/doi:10.1503/cmaj.130053/-/DC1).

Group medical visits had a slightly positive effect on patients’ weight, but no effect on body mass index; the effect on weight was not statistically significant. A negative effect of group medical visits on total and high-density lipoprotein cholesterol levels was noted; however, the effects were minimal (Table 3, Appendix 3).

**Other outcomes**

Patients who attended group medical visits reported improvements in quality of life, as measured by the Diabetes Quality of Life Questionnaire$^{24}$ (weighted mean difference $-29.30$, 95% CI $-60.64$ to $2.05$); however, the results were limited to 2 RCTs and were not statistically significant.

Data on process-of-care outcomes in the RCTs were insufficient to include them in the meta-analysis. In our synthesis of findings from all 26 studies, we noted reports on aspects of patients’ engagement in their health care, including positive outcomes in the domain of self-care$^{21,25}$, physical activity,$^{39}$ the setting and achievement of measurable goals$^{24,34,36}$, patient knowledge$^{24,31,32,41,44}$, self-efficacy$^{23,25}$, and self-management.$^{24,26,34,36,40,44}$

**Interpretation**

Our meta-analysis showed that group medical visits for patients with diabetes led to significant reductions in HbA$_{1c}$. Small decreases have been shown to have substantial clinical impacts: a 1.0% reduction in HbA$_{1c}$ may be associated with a 37% decrease in microvascular complications, up to a 14% reduction in the incidence of myocardial infarction and a 21% decrease in the risk of death from diabetes.$^{47}$

Patients with diabetes are known to be at increased risk of cardiovascular disease and cardiovascular-related death.$^{50,52}$ Although not statistically significant, the reductions in systolic and diastolic blood pressure among patients attending group medical visits are of interest. Many lifestyle modifications such as weight reduction, dietary changes, physical activity and alcohol consumption have been found to reduce systolic blood pressure by 2–8 mm Hg.$^{50}$ A reduction of

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**Table 2: Risk-of-bias assessment of the randomized controlled trials**

<table>
<thead>
<tr>
<th>Study</th>
<th>Random sequence generation (selection bias)</th>
<th>Allocation concealment (selection bias)</th>
<th>Blinding of participants and personnel (performance bias)</th>
<th>Blinding of outcome assessment (detection bias)</th>
<th>Incomplete outcome data (attrition bias)</th>
<th>Selective reporting (reporting bias)</th>
<th>Other bias</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clancy et al.</td>
<td>High</td>
<td>Unclear</td>
<td>High</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Unclear</td>
</tr>
<tr>
<td>Clancy et al.</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Unclear</td>
</tr>
<tr>
<td>Cohen et al.</td>
<td>High</td>
<td>High</td>
<td>High</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Unclear</td>
</tr>
<tr>
<td>Edelman et al.</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Unclear</td>
</tr>
<tr>
<td>Naik et al.</td>
<td>Low</td>
<td>Low</td>
<td>Unclear</td>
<td>High</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Unclear</td>
</tr>
<tr>
<td>Rygg et al.</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Unclear</td>
<td>Low</td>
<td>Unclear</td>
<td>Unclear</td>
</tr>
<tr>
<td>Sadur et al.</td>
<td>High</td>
<td>High</td>
<td>High</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Unclear</td>
</tr>
<tr>
<td>Schllinger et al.</td>
<td>Low</td>
<td>High</td>
<td>High</td>
<td>Unclear</td>
<td>Low</td>
<td>Unclear</td>
<td>Unclear</td>
</tr>
<tr>
<td>Taveira et al.</td>
<td>High</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Unclear</td>
</tr>
<tr>
<td>Tavera et al.</td>
<td>High</td>
<td>High</td>
<td>Unclear</td>
<td>High</td>
<td>Low</td>
<td>Unclear</td>
<td>Unclear</td>
</tr>
<tr>
<td>Trento et al.</td>
<td>Low</td>
<td>Unclear</td>
<td>Low</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Unclear</td>
</tr>
<tr>
<td>Trento et al.</td>
<td>High</td>
<td>High</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Unclear</td>
</tr>
<tr>
<td>Wagner et al.</td>
<td>High</td>
<td>High</td>
<td>Unclear</td>
<td>Unclear</td>
<td>High</td>
<td>Unclear</td>
<td>Unclear</td>
</tr>
</tbody>
</table>
2 mm Hg in diastolic blood pressure has been associated with a 6% decrease in the risk of coronary heart disease and a 15% reduction in stroke and transient ischemic attacks.51

An additional factor to consider when caring for patients with diabetes is their quality of life. Although only 2 of the RCTs measured this outcome using the Diabetes Quality of Life Questionnaire, the aspects of patients’ quality of life examined in many of the other studies were similar to the domains covered in the questionnaire. Only 2 of the RCTs examined the risk of hypoglycemic events associated with group medical visits.22,32 Studies have shown that intensive glucose-lowering therapy among patients with diabetes may increase the risk of morbidity and mortality owing to hypoglycemic events.32,53

**Limitations**

There were few long-term studies examining the effectiveness of group medical visits for diabetes care. Fifteen of the 26 studies were 12 months or less in duration, and 6 studies were up to 2 years in duration. The study with the longest duration followed patients for 5 years after the intervention. Therefore, the long-term or sustainable outcomes of group medical visits are unclear, and it is difficult to know if the outcomes were maintained for a substantial length of time after the intervention.

Another limitation was that we restricted our search to include only published studies. We realize that studies showing a lack of effect may not have been published. We also included only articles written in English or translated into English, thereby excluding 2 studies not published in English.

Many of the studies involved specific populations of patients, such as those with low incomes, those with different ethnic backgrounds and veterans. Although group medical visits may work for populations with specific characteristics, the mixed results indicate that further examination of the types of populations and types of delivery models is needed.

**Conclusion**

Group medical visits for patients with diabetes were found to be effective in terms of reducing HbA1c. The results of our meta-analysis, combined with the other benefits reported by patients and providers, suggest that wider implementation of group medical visits for patients with diabetes will have a positive effect on patient outcomes.

<table>
<thead>
<tr>
<th>Study</th>
<th>Group medical visit</th>
<th>Mean difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clancy et al.17</td>
<td>9.51 ± 2.52</td>
<td>−0.20 (−1.10 to 0.70)</td>
</tr>
<tr>
<td>Edelman et al.22</td>
<td>8.3 ± 1.3</td>
<td>−0.30 (−0.66 to 0.06)</td>
</tr>
<tr>
<td>Naik et al.23</td>
<td>8.05 ± 1.4</td>
<td>−0.59 (−1.18 to −0.00)</td>
</tr>
<tr>
<td>Rygg et al.24</td>
<td>7.2 ± 1.2</td>
<td>0.00 (−0.42 to 0.42)</td>
</tr>
<tr>
<td>Sadur et al.29</td>
<td>8.5 ± 1.9</td>
<td>−0.10 (−0.78 to 0.58)</td>
</tr>
<tr>
<td>Schillinger et al.26</td>
<td>9 ± 2</td>
<td>0.00 (−0.58 to 0.58)</td>
</tr>
<tr>
<td>Taveira et al.28</td>
<td>7.4 ± 1.2</td>
<td>−1.00 (−1.69 to −0.31)</td>
</tr>
<tr>
<td>Trento et al.31</td>
<td>7.3 ± 1.6</td>
<td>−1.70 (−2.27 to −1.13)</td>
</tr>
<tr>
<td>Trento et al.32</td>
<td>7.88 ± 0.30</td>
<td>−0.91 (−1.43 to −0.39)</td>
</tr>
<tr>
<td>Wagner et al.33</td>
<td>7.9 ± 0.94</td>
<td>0.00 (−0.14 to 0.14)</td>
</tr>
</tbody>
</table>

Overall: Heterogeneity: $I^2 = 82\%$

Table 3: Pooled analysis of the effect of group medical visits on clinical outcomes reported in randomized controlled trials

<table>
<thead>
<tr>
<th>Outcome</th>
<th>No. of trials</th>
<th>Weighted mean difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA1c</td>
<td>10</td>
<td>−0.46 (−0.80 to −0.13)</td>
</tr>
<tr>
<td>Systolic BP</td>
<td>5</td>
<td>−2.81 (−6.84 to 1.21)</td>
</tr>
<tr>
<td>Diastolic BP</td>
<td>4</td>
<td>−1.02 (−2.71 to 0.67)</td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>3</td>
<td>0.04 (−0.21 to 0.30)</td>
</tr>
<tr>
<td>HDL cholesterol</td>
<td>3</td>
<td>0.01 (−0.07 to 0.10)</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>3</td>
<td>−0.01 (−0.41 to 0.38)</td>
</tr>
<tr>
<td>Weight</td>
<td>3</td>
<td>−0.50 (−3.87 to 2.88)</td>
</tr>
<tr>
<td>BMI</td>
<td>4</td>
<td>0.05 (−0.90 to 1.00)</td>
</tr>
</tbody>
</table>

Note: BMI = body mass index, BP = blood pressure, CI = confidence interval, HDL = high-density lipoprotein.

Figure 2: Pooled analysis of the effect of group medical visits versus usual care for patients with diabetes on glycaated hemoglobin (HbA1c) reported in randomized controlled trials. A weighted mean difference of less than zero indicates a positive effect of group medical visits. CI = confidence interval, SD = standard deviation.
References

1. Epping-Jordan JE, Pratt S, Bengoa R, et al. Improving the qual-
ity of health care for chronic conditions. Qual Saf Health Care


Available: www.impectbc.ca/what-we-do/projects/practice-
support-program/(accessed 2010 Apr 18).

4. Bodenheimer T, Grumbach K. Alternatives to the 15-minute
visit. Improving primary care: strategies and tools for a better prac-

5. Kirsh S, Watts S, Pascuzzi K, et al. Shared medical appoint-
ments based on the chronic care model: a quality improvement
project to address the challenges of patients with diabetes with

6. Diabetes in Canada: facts and figures from a public health per-

7. van Dam HA, van der Horst F, Knoops L, et al. Social support in
diabetes: a systematic review of controlled intervention studies.

type 2 diabetes: cluster randomised controlled trial. BMJ 2011;
342:d1715.

9. Scott JC, Robertson BJ. Kaiser Colorado’s Cooperative Health
Care Clinic: a group approach to patient care. Manag Care Q

patient visits for chronically ill older HMO members: the Cooper-

11. Bronson DL, Maxwell RA. Shared medical appointments:
increasing patient access without increasing physician hours.

12. Buley KB, Haney R. Shared medical appointments: improving
access, outcomes, and satisfaction for patients with chronic car-

13. Higgins JPT, Altman DG, editors. Cochrane handbook for sys-
tematic reviews of interventions. Version 5.0.0 (updated Febru-

14. Higgins JPT, Green S, editors. Cochrane handbook for system-
atic reviews of interventions. Version 5.1.0 (updated March

ically and economically disadvantaged patients with type 2 dia-
abetes and their relationships to clinical outcomes. Top Health Inf
Manag 2010;24:28-44.

in an uninsured or inadequately insured patient population

17. Clancy DE, Fredrickson S, Melnyk S, et al. Medical clinics ver-
sus usual care for patients with both diabetes and hypertension:

of goal setting in diabetes mellitus group clinics: randomized

based diabetes self-management education for patients with type 2
diabetes mellitus. A randomized control trial. Patient Educ

health maintenance organization. Efficacy of care management

ment support on structure, process and outcomes among vulner-
able patients with diabetes: a three-arm practical clinical trial.
Diabetes Care 2009;32:559-66.


medical appointments for the management of type 2 diabetes
with comorbid depression in older adults. Ann Pharmacother
2011;45:1346-55.

group care prevents deterioration of type II diabetes: a 4-year
randomized controlled clinical trial. Diabetologia 2002;45:
1231-9.

metabolic control in type 2 diabetes: a 2-year follow-up. Dia-
betes Care 2001;24:995-1000.

trolled study of learning, problem solving ability, and quality of
life in people with type 2 diabetes managed by group care.

27. Trento M, Passera P, Biaardi M, et al. A 3-year prospective ran-
domized controlled clinical trial of group care in type 1 diabetes.

medical appointments for the management of type 2 diabetes
with comorbid depression in older adults. Ann Pharmacother
2011;45:1346-55.

group care prevents deterioration of type II diabetes: a 4-year
randomized controlled clinical trial. Diabetologia 2002;45:
1231-9.

30. Trento M, Passera P, Biaardi M, et al. A 5-year randomized con-
trolled study of learning, problem solving ability, and quality of
life in people with type 2 diabetes managed by group care.

31. Trento M, Passera P, Biaardi M, et al. A 3-year prospective ran-
domized controlled clinical trial of group care in type 1 diabetes.

for diabetes in primary care: a system-wide randomized trial.
Diabetes Care 2001;24:695-700.

comes for fee-for-service physician practices participating in dia-

34. Clancy DE, Brown S, Magruder K, et al. Group visits in med-
ically and economically disadvantaged patients with type 2 dia-
abetes and their relationships to clinical outcomes. Top Health Inf
Manag 2010;24:28-44.

in an uninsured or inadequately insured patient population

36. Clancy DE, Fredrickson S, Melnyk S, et al. Medical clinics ver-
sus usual care for patients with both diabetes and hypertension:

37. Edelman D, Fedrickson S, Melnyk S, et al. Medical clinics ver-
sus usual care for patients with both diabetes and hypertension:

38. Edelman D, Fedrickson S, Melnyk S, et al. Medical clinics ver-
sus usual care for patients with both diabetes and hypertension:

of goal setting in diabetes mellitus group clinics: randomized

based diabetes self-management education for patients with type 2
diabetes mellitus. A randomized control trial. Patient Educ

health maintenance organization. Efficacy of care management

ment support on structure, process and outcomes among vulner-
able patients with diabetes: a three-arm practical clinical trial.
Diabetes Care 2009;32:559-66.

43. Taveira TH, Friedman P, Cohen, et al. Pharmacist-led group
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Choosing the right angiotensin-receptor blocker for patients with diabetes: still controversial

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See related research article by Antoniou and colleagues on page 9

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The rise in diabetes continues unabated, and the major burden of this condition is its macrovascular complications. Current guidelines emphasize the importance of addressing multiple risk factors implicated in the pathogenesis and progression of these complications. Treatment should thus include optimal glycemic control and aggressive management of hypertension and dyslipidemia, as was clearly shown in the Steno-2 study.1

For the last 2 decades, interruption of the renin–angiotensin system using either angiotensin-converting enzyme (ACE) inhibitors or angiotensin-receptor blockers has been the first-line choice for reducing blood pressure in patients with diabetes, particularly in those with evidence of renal disease.2 Benefits over other classes of antihypertensive agents have been reported with respect to microvascular complications including nephropathy and, more recently, retinopathy.3 However, the main focus of studying these agents has been their effects on macrovascular complications, although the superiority of targeting the renin–angiotensin system over other blood pressure–lowering strategies remains unproven. This issue remains unresolved, despite a number of theoretical reasons for a difference in the cardiovascular effects between ACE inhibitors and angiotensin-receptor blockers, including in the setting of diabetes. Indeed, the ONTARGET study failed to identify any significant differences in cardiovascular outcomes between use of the ACE inhibitor ramipril and the angiotensin-receptor blocker telmisartan in a large cohort of patients at high risk of cardiovascular disease, including a substantial number of patients with type 2 diabetes.4 This issue continues to be controversial. Indeed, a recent meta-analysis has suggested a potential superiority of ACE inhibitors over angiotensin II antagonism.5 However, because this report was a meta-analysis rather than a clinical trial, such data must be interpreted with caution.

Another controversy that remains to be resolved is whether there are differences among the various angiotensin-receptor blockers available to clinicians and widely used in this population of patients. Angiotensin-receptor blockers are often used in patients with diabetes as a result of the positive results from trials that suggested that these agents were renoprotective in type 2 diabetes.6 A recent retrospective study reported in CMAJ has provocatively suggested that 2 angiotensin-receptor blockers, valsartan and telmisartan, may afford superior cardiovascular benefits, specifically in reducing the risk of admission to hospital for acute myocardial infarction, stroke or heart failure, when compared with other widely prescribed drugs in this class such as losartan, candesartan and irbesartan.7 The authors are cautious in their interpretation of the data, which represents an analysis of more than 54 000 patients with diabetes started on an angiotensin-receptor blocker, with a composite primary outcome of admission to hospital for either acute myocardial infarction, stroke or heart failure. Secondary analyses suggested the superiority of valsartan and telmisartan over other angiotensin-receptor blockers with respect to lowering the risk of heart failure.

The importance of these results remains to be determined, and their reproducibility is unlikely to be formally tested in an appropriately designed randomized trial. The authors suggest that the potential benefits of telmisartan may be related to its reported action as a partial peroxisome proliferator-activated receptor-γ (PPARγ) agonist,8 an effect that could lead to improved macrovascular complications are the major burden of diabetes.

In addition to optimal glycemic control, diabetes treatment should include aggressive management of hypertension and dyslipidemia.

Whether angiotensin-converting enzyme inhibitors and angiotensin-receptor blockers have different cardiovascular effects remains unresolved.

Without appropriately designed randomized controlled trials, there is scant evidence to support using any particular angiotensin-receptor blocker for cardioprotection in patients with diabetes.
metabolic profile, as shown by lower glucose levels and reduced insulin resistance. Telmisartan’s role as a PPARγ agonist has been clearly shown in vitro, however, whether this action translates clinically to improved metabolic control has been difficult to confirm in appropriately designed studies in humans.

Furthermore, the assumption that PPARγ agonism would lead to improved cardiovascular outcomes may be flawed. For example, the PPARγ agonist rosiglitazone is associated with a potentially deleterious effect on cardiovascular outcomes. Not only is rosiglitazone associated with fluid retention (a well-reported adverse effect of this class of drugs) and, in some patients, overt heart failure; it has a potential association with increased cardiovascular events as a result of macrovascular disease, as shown by increased risk of myocardial infarction. In addition, pioglitazone, another PPARγ agonist, is associated with increased heart failure, although a deleterious effect on macrovascular outcomes is unlikely. The PROACTIVE study suggested a potential cardiovascular benefit for pioglitazone, although a positive outcome on the primary outcome was not reached in that trial. Thus, although Antoniou and colleagues have attributed the potential benefit of telmisartan as described in their analysis to its action as a PPARγ agonist, this conclusion is unlikely because PPARγ agonism would not be predicted to lead to a reduction in heart failure.

The putative benefits of valsartan are even more difficult to explain. This drug is not generally considered to be the most potent in its class and is not known to be a strong PPARγ agonist. Antoniou and colleagues concede that this result was unexpected and that part of the benefit of valsartan may have been related to the doses used by the study participants. Other suggested actions include inhibition of platelet aggregation and effects on the anti-inflammatory hormone adiponectin. However, there is no clear evidence that such potentially antiatherosclerotic actions are not seen with other angiotensin-receptor blockers.

The clinical situation for type 2 diabetes is continuously changing, with an ongoing reduction in the overall rate of cardiovascular events. New treatment paradigms are being considered for the condition, particularly with respect to glucose lowering, as a result of the advent of newer classes of glucose-lowering agents in wide use, such as incretin analogues and dipeptidyl peptidase 4 inhibitors, or drugs that have recently been introduced into clinical practice, such as sodium–glucose cotransporter 2 inhibitors.

For now, whether certain angiotensin-receptor blockers are more cardioprotective than others in type 2 diabetes remains to be seen. Although Antoniou and colleagues’ retrospective study has generated some intriguing results, without appropriately designed randomized controlled trials, there is scant evidence to support preferring one drug in this class over another for patients with type 2 diabetes. Thus, the results reported by Antoniou and colleagues would require further work before they could be translated into changes in the current guidelines for the management of type 2 diabetes and its complications.

References


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The future of care for type 1 diabetes

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See related research article by Haidar and colleagues on page 16

Type 1 diabetes is a chronic degenerative disease characterized by gross dysregulation of glycemia, owing to autoimmune destruction of β-cell function, and by long-term complications associated with hyperglycemia. The current approach to improve the long-term course of type 1 diabetes is to try to replace insulin physiologically, with the goal of achieving blood glucose levels as close to the nondiabetic range as possible. Near-normal glycemia has been shown to reduce the development and progression of microvascular and cardiovascular disease among patients with diabetes.1,2,3

Two approaches to achieving near-normal glycemia have dominated our efforts in the past 3 decades. “Biologic” approaches that replace missing β-cell function by transplanting whole-organ pancreas or isolated islets, although far more effective than in decades past, have been limited by the need for immunosuppression and its attendant risks, the risks of procedures necessary to transplant insulin-producing tissue, and the availability of organs. In addition, the limited survival of transplanted tissue, particularly isolated islets, necessitates adding exogenous insulin therapy within 2 to 4 years of transplantation.4 The “mechanical” approach has been to develop devices that emulate physiologic insulin levels. Subcutaneous administration of insulin by injection, the conventional means of insulin therapy since its introduction in 1922, suffers from delayed and erratic absorption from subcutaneous depots and its reliance on the patient to select doses to match insulin need, which is influenced by ambient glucose levels, meal size and composition, and level of activity. Given the inconstancy and hectic pace of modern life, compounded by the guesswork of insulin dosing and the inconsistent absorption, duration and peak effects of insulin with current methods of insulin therapy, it is remarkable that we have done as well as we have in managing this condition.

Although some patients with type 1 diabetes have been able to achieve glycated hemoglobin levels of less than 7%, with the expectation that their long-term good health will be preserved, major challenges remain for many patients. Current intensive insulin-replacement therapy is arduous for patients, requiring frequent self-monitoring or continuous glucose monitoring, frequent daily injections or the use of insulin pumps, and other lifestyle changes. Even when these interventions are successfully implemented, glycated hemoglobin levels are not truly normalized. Furthermore, patients who undergo intensive therapy have a 3-fold increased risk of hypoglycemia,5 which can be merely disruptive or can pose serious risks for injury or even death. Although rapid-acting insulins have reduced the rate of hypoglycemia among patients with diabetes, hypoglycemia remains one of the major impediments to intensive therapy.

Reducing the burden of intensive therapy and the frequency of hypoglycemia while maintaining near-normal glucose levels has been a major goal of treating type 1 diabetes. A promising approach is to replace decision-making by patients with a computer algorithm that receives frequent data from a continuous glucose monitor, calculates insulin dosing and automatically administers the insulin with no intervention by the patient. This apotheosis of the “mechanical” approach to insulin therapy has been called an artificial or bionic pancreas. It has the advantage of using data from continuous glucose monitors to adjust insulin dosing to the patient’s changing needs, including during the vulnerable period of sleep.

Until recently, artificial pancreas systems relied only on insulin to regulate blood glucose levels. However, the normally functioning pancreas uses both insulin and glucagon to maintain glucose lev-
els in the physiologic range. Glucagon opposes the effects of insulin on the liver, converting the liver from a major extractor of glucose to a net producer. Although glucagon-secreting cells are not destroyed in type 1 diabetes, the glucagon response to hypoglycemia is lost during its course, leaving patients vulnerable.

Haidar and colleagues\(^5\) add to a growing body of evidence\(^6–8\) that glucagon can be used to prevent hypoglycemia in a dual-hormone artificial pancreas that more closely mimics normal pancreatic function. Their 15-hour inpatient crossover study compared the artificial pancreas and continuous glucose monitoring with conventional pump therapy using less frequent self-monitoring.

Although their study is neither the first nor the longest investigation using a dual-hormone artificial pancreas,\(^6–8\) it is the first to compare such an apparatus to conventional intensive therapy in a randomized design. Treatment with the artificial pancreas increased the amount of time patients spent in the target range of blood glucose levels and decreased hypoglycemia. Thus, Haidar and colleagues show that low doses of glucagon administered under the control of a computer algorithm can act as a counter-regulatory hormone, preventing glucose levels from falling too low.

However, if insulin dosing algorithms were sufficiently refined, would there be any role for glucagon? Insulin sensitivity and the speed with which food is absorbed vary widely, making appropriate insulin dosing quite challenging. This problem is compounded by the slow absorption of subcutaneous insulin, even with “rapid-acting” insulin analogs, and by variable maximal effects.

Finally, unanticipated exertion may reduce insulin requirements after an insulin dose has been selected by the algorithm and delivered. Any mismatch in insulin requirement and delivery owing to these factors could lead to hypoglycemia. Even complete suspension of insulin delivery is unlikely to stave off impending hypoglycemia, because it cannot erase the delayed effect of insulin already in the subcutaneous tissue but not yet absorbed into the blood. These factors likely account for the fairly high rates of hypoglycemia in studies involving insulin-only artificial pancreases.\(^9–10\)

Given these considerations, it seems unlikely that automated, safe glucose control can be achieved without a counter-regulatory hormone such as glucagon.

There are several substantive challenges to the further development of a dual-hormone artificial pancreas. First, all studies to date have been in highly supervised settings, with the longest studies lasting fewer than 3 days.\(^7\) With greater confidence in these devices, longer-term studies in more authentic outpatient settings are necessary. Second, glucagon is commercially available in lyophylized form, which becomes unstable in solution. Although glucagon retains biological activity for a few days, new formulations that remain reliably stable in pumps are needed.

To date, insulin-only and dual-hormone artificial pancreases have been developed in parallel, with disparate trial designs that do not allow comparisons of performance between algorithms. Insulin-only and dual-hormone approaches will need to be compared in head-to-head trials under actual home-use conditions to clarify their relative merits. In the meantime, both insulin-only and dual-hormone approaches will have to prove their mettle in progressively less regimented settings.

References


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Contributors: Both of the authors contributed substantively to the writing and editing of the manuscript, and approved the final version submitted for publication.
The debate about appropriate blood pressure targets for patients with hypertension and diabetes is of substantial public health importance because the global burden of diabetes and hypertension is large and continues to increase. In Canada, nearly 1 in 10 adults has diabetes, and the prevalence is expected to double by 2030.1 As well, 1 in 4 Canadians has high blood pressure, and the age-standardized prevalence of hypertension has increased by 10% over the past decade.1 The combination of diabetes and hypertension is associated with a 57% increase in the risk of adverse cardiovascular events, including stroke and myocardial infarction.2 Studies have unequivocally shown that lowering blood pressure is the most effective single intervention to reduce cardiovascular morbidity and mortality.2–4

Until recently, international clinical practice guidelines5,6 almost universally recommended that hypertension in patients with diabetes be treated to a target blood pressure level of less than 130/80 mm Hg (in contrast to < 140/90 mm Hg recommended for patients without diabetes). However, some emerging evidence suggests that lower systolic blood pressure targets may be associated with an increased risk of adverse events, calling into question the appropriateness of this target and prompting further review of the evidence.

In this article, we review the major studies that address target blood pressure levels for patients with diabetes and hypertension. In particular, we summarize the rationale for the current Canadian Hypertension Education Program and Canadian Diabetes Association harmonized clinical practice recommendations, which continue to recommend blood pressure targets of less than 130/80 mm Hg for patients with diabetes.7 A summary of the evidence used in this review, which comes from randomized controlled trials and meta-analyses, is presented in Box 1.

What is the basis for the blood pressure target of less than 130/80 mm Hg for patients with hypertension and diabetes?

Since 2004, the Canadian Hypertension Education Program has recommended a target blood pressure of less than 130/80 mm Hg.8 The diastolic target of less than 80 mm Hg is based on 2 randomized trials: the Hypertension Optimal Treatment (HOT) trial9 and the normotensive Appropriate Blood Pressure Control in Diabetes (ABCD) trial.10 The Canadian Hypertension Education Program rates this as grade A evidence, because it is based on treat-to-target randomized controlled trial data. Published in 1998, the HOT trial randomly assigned 18 790 individuals with hypertension to 1 of 3 targets for diastolic blood pressure (< 140/90 mm Hg recommended for patients without diabetes). However, some emerging evidence suggests that lower systolic blood pressure targets may be associated with an increased risk of adverse events, calling into question the appropriateness of this target and prompting further review of the evidence.

In this article, we review the major studies that address target blood pressure levels for

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**Key points**

- The treatment of hypertension in people with diabetes is a highly effective strategy to reduce the risk of cardiovascular disease and vascular complications of diabetes.
- A blood pressure target of less than 130/80 mm Hg is recommended for patients with hypertension and diabetes.
- Intensive reduction of systolic blood pressure reduces the risk of stroke, but it increases the risk of treatment-related adverse events (e.g., syncope, hypotension and bradycardia).
- People with the highest elevations in blood pressure have the most to benefit from any intervention to reduce blood pressure, irrespective of the target.
of 90 mm Hg or lower (45 events) compared with a diastolic blood pressure of 80 mm Hg or lower (22 events).

The normotensive ABCD trial,\textsuperscript{10} published in 2002, randomly assigned 480 people with diabetes and blood pressures of less than 140/90 to either an intensive (lowering diastolic blood pressure by > 10 mm Hg) or moderate (targeting a diastolic blood pressure between 80–90 mm Hg) diastolic blood pressure control strategy over a mean 5.3 year follow-up period. The primary outcome was change in 24-hour urinary creatinine clearance. The mean blood pressure levels achieved over the last 4 years of follow-up were 128/75 mm Hg in the intensive-control arm and 137/81 mm Hg in the moderate-control arm. Although there was no significant difference in the primary outcome of creatinine clearance, the odds of stroke (a prespecified secondary outcome) were significantly higher among those in the moderate-control group than in the intensive-control group (13 v. 4 events, odds ratio [OR] 3.29, 95% CI 1.06–10.25).

The Canadian Hypertension Education Program has assigned a grade C rating to its target of less than 130 mm Hg systolic blood pressure. Grade C level evidence is based on lower-quality randomized controlled trial data and/or observational data. There is a lack of direct evidence for this target from treat-to-target randomized controlled trials.\textsuperscript{11} The systolic target was based partly on data from the ABCD trial, in which a significant reduction in the risk of stroke corresponded to an achieved mean systolic blood pressure of 128 mm Hg. Consideration was, however, also given to the post hoc epidemiologic analysis of the United Kingdom Prospective Diabetes Study (UKPDS 36, n = 3642), which found a strong and independent association between increased systolic blood pressure and the risk of clinically significant events.\textsuperscript{12} For each 10 mm Hg increase in systolic blood pressure, a 15% (95% CI 9%–16%) increase in all-cause mortality and a 17% (95% CI 13%–21%) increase in diabetes-related death was observed.

### Are there any new trials that directly evaluate the systolic blood pressure target of less than 130 mm Hg?

No new evidence is available that directly informs the 130 mm Hg target. However, additional evidence examining intensive blood pressure control for patients with diabetes is available from the Action to Control Cardiovascular Risk in Diabetes–Blood Pressure (ACCORD-BP) randomized controlled trial\textsuperscript{13} and 2 recently published meta-analyses of randomized controlled trials.\textsuperscript{14,15}

The ACCORD-BP trial, published in 2010 and involving in 4733 people, compared a standard strategy that targeted a systolic blood pressure of less than 140 mm Hg to an intensive strategy that targeted less than 120 mm Hg. After 4.7 years of follow-up, no significant difference was found between the 2 strategies in reducing the primary composite outcome of major adverse cardiovascular events (237 events [2.09%] in the standard-treatment group v. 208 events [1.87%] in the intensive-treatment group).\textsuperscript{13}

Four aspects of the ACCORD-BP trial deserve emphasis. First, the event rate in the control group for the primary outcome (a composite of nonfatal myocardial infarction, nonfatal stroke and death from cardiovascular causes) was only half of the expected event rate of 4%; therefore, the study may have been underpowered to truly detect a difference between the strategies.\textsuperscript{13}

Second, ACCORD-BP was part of the larger ACCORD trial, in which all 10 251 patients with diabetes and at high-risk of cardiovascular disease were randomly assigned to either an intensive glucose-lowering strategy (with a target glycated hemoglobin of 6.0%) or a standard glucose-lowering strategy (target glycated hemoglobin of 7%–7.5%). Using a 2 × 2 factorial design, patients were randomly assigned to 1 of 2 substudies: to either a lipid comparison (statin plus placebo v. statin plus fenofibrate) or the ACCORD-BP arm. Therefore, of the 4733 people assigned to treatment within the ACCORD-BP trial, 2371 were also receiving an intensive glycemic intervention and 2362 were receiving a standard glycemic intervention. The result of the statistical test for interaction between the glycemic and blood pressure interventions was 0.08, a p value that is significant when evaluating interactions in factorial

**Box 1: Evidence used in this review**

The studies used in this review were selected from the searches performed to develop the 2012 Canadian Hypertension Education Program recommendations.\textsuperscript{4} A Cochrane Collaboration librarian searched MEDLINE using a highly sensitive search strategy for randomized controlled trials and systematic reviews of trials published up to August 2011 that evaluated cardiovascular outcomes. To ensure that all relevant studies were included, bibliographies of the identified articles were manually searched. (The details of the search strategies and retrieved articles are available on request.) The search was repeated in August 2012 in preparation for the 2013 Canadian Hypertension Education Program’s Consensus Conference. The Canadian Hypertension Education Program’s diabetes subcommittee (including R.E.G., L.A.L., S.W.T. and D.M.R.) reviewed this evidence and felt that there were insufficient data to prompt a change in the currently recommended targets for systolic and diastolic blood pressure.
trials.\textsuperscript{16} Thus, the potential for interaction between the 2 study arms is raised. If interaction was present, analyses would need to be conducted separately within the 2 factorial subgroups, rather than by pooling all of the patients together — and this may result in further loss of power.

Third, the intensive blood pressure lowering strategy was effective in significantly reducing the risk of stroke, a prespecified secondary outcome, by \(47\%\) (2.6\% v. 1.5\%; hazard ratio [HR] 0.53, 95\% CI 0.39–0.89) but also increased the risk of serious adverse events (hypotension, bradycardia and hyperkalemia).

Fourth, our current recommendation for a target systolic blood pressure of less than 130 mm Hg was not tested in the ACCORD study. Therefore, this study, if negative, does not provide definitive evidence on the difference in risks and benefits of less than 130 mm Hg systolic blood pressure compared with less than 140 mm Hg.

Since the publication of ACCORD, Bangalore and colleagues\textsuperscript{14} and Reboldi and colleagues\textsuperscript{15} independently published meta-analyses that summarize the current literature on hypertension management for patients with diabetes. Although these authors used different methodologic approaches to reviewing and summarizing the evidence, both groups sought to document the relative benefits and risks of lower blood pressure targets.

The meta-analysis by Bangalore and colleagues\textsuperscript{14} included 13 trials that compared an achieved systolic blood pressure of less than 135 mm Hg to less than 140 mm Hg or that compared an achieved systolic blood pressure of less than 130 mm Hg to less than 140 mm Hg. Trials were eligible for inclusion if they enrolled patients with diabetes or impaired fasting glucose, and the primary outcome was major adverse cardiovascular events including mortality, cardiovascular mortality, myocardial infarction, stroke and heart failure. The authors also examined microvascular events and serious adverse events as secondary outcomes. Compared with an achieved systolic blood pressure of 140 mm Hg, an achieved blood pressure of less than 135 mm Hg was associated with a reduced odds of death (8.2\% v. 7.3\%; OR 0.87, 95\% CI 0.79–0.95). An achieved systolic blood pressure of less than 130 mm Hg also reduced the odds of stroke (1.6\% v. 0.82\%; OR 0.53, 95\% CI 0.38–0.75).\textsuperscript{14}

The meta-analysis by Reboldi and colleagues\textsuperscript{15} included 31 antihypertensive drugs trials that included patients with diabetes (excluding data for patients with impaired fasting glucose only). The authors performed series of stratified meta-analyses and meta-regression analyses to determine the effect of systolic blood pressure control on myocardial infarction and stroke.\textsuperscript{15} Similar to the results reported by Bangalore and colleagues,\textsuperscript{14} this analysis found that lower achieved systolic blood pressure was associated with a reduced risk of stroke (RR 0.61, 95\% CI 0.48–0.79) but not myocardial infarction (RR 0.87, 95\% CI 0.74–1.02). For every 5% reduction in systolic blood pressure, the risk of stroke was reduced by 13\% (95\% CI 5\%–20\%).\textsuperscript{15} Not surprisingly, they also found that patients with the highest elevations in blood pressure at entry to the trials had the greatest degree of benefit from any blood pressure–lowering interventions. Those in the highest tertiles of systolic blood pressure on entry had an 18\% pooled risk reduction for stroke (95\% CI 0.71–0.94) and a 15\% pooled risk reduction for myocardial infarction (95\% CI 0.74–0.98), irrespective of the achieved blood pressure. Thus, moving the systolic blood pressure target for people with diabetes from less than 130 mm Hg to less than 140 mm Hg may result in an increase in strokes.

What are the risks of intensive blood pressure control?

Intensive blood pressure control has been found to increase the risk of adverse events including hypotension, syncope, bradycardia or arrhythmia, hyperkalemia, angioedema, renal failure and end-stage renal disease. In the ACCORD-BP trial, participants assigned to the intensive-control arm experienced 77 of these adverse events, compared with only 30 adverse events in the standard-control arm.\textsuperscript{13} The meta-analysis by Bangalore and colleagues\textsuperscript{14} extracted and pooled data on serious adverse events across trials and similarly found that those who achieved lower systolic blood pressure levels experienced significantly more adverse events (OR 1.20, 95\% CI 1.08–1.32). When the achieved systolic blood pressure was less than 130 mm Hg, the magnitude of risk for adverse events was even greater (OR 1.40, 95\% CI 1.19–1.64).\textsuperscript{14}

How does this recent evidence affect clinical practice?

Choosing a single systolic blood pressure target that applies to all people with diabetes appears more complex than previously appreciated. Systolic blood pressure lowering appears to primarily reduce the risk of cerebrovascular disease. Additionally, it is important to remember that those with the highest blood pressure levels and...
those at highest global risk (i.e., with multiple cardiovascular risk factors) derive the most benefit from reducing blood pressure. Accordingly, a decrease from 140 mm Hg to 130 mm Hg in a person with recent-onset diabetes, no target-organ damage and no other vascular risk factors would have a comparatively lower effect in terms of cardiovascular risk reduction.

People with hypertension and diabetes who can achieve a systolic blood pressure of less than 130 mm Hg may have better outcomes than those that do not achieve this target. However, intensive blood pressure reduction represents a trade-off between stroke reduction and an increased risk of drug-related adverse effects. From a purely mathematical perspective, the risk of an adverse event appears roughly equal to the degree of benefit achieved in terms of reduction in the risk of stroke. However, stroke is generally considered to be a more debilitating and a less reversible outcome than many of the adverse effects that occurred in the ACCORD-BP trial (e.g., hypotension, syncope and bradycardia).13

The available meta-analyses14,15 are limited in that they focus on achieved systolic blood pressure levels rather than a priori protocol-specified systolic blood pressure targets. It is possible, and indeed probable, that patients who are able to achieve lower systolic blood pressure have characteristics that are associated with better vascular outcomes, independent of their blood pressure.

The ACCORD trial13 raised the potential for interaction between glycemic control and systolic blood pressure reduction, in that the efficacy of blood pressure lowering may also depend on the degree of glycemic control. Because the meta-analyses14,15 did not control for differences in the duration of diabetes or degree of glycemic control achieved, the relative contributions of glycemic control and systolic blood pressure reduction to risk reduction seen in these studies is unclear.

After considering the pre-ACCORD-BP evidence, the results of the ACCORD-BP trial13 and the 2 subsequently published meta-analyses,14,15 most (> 80%) of the Canadian Hypertension Education Program’s Recommendations Task Force, which included representatives from the Canadian Diabetes Association subcommittee on hypertension, voted to maintain the target of 130/80 mm Hg. In addition to the above factors considered in making this decision, the effect of diabetes and hypertension on a population-wide level was also considered. Achieving population-level reductions in stroke was deemed a critically important objective, and on the balance, stroke prevention was felt to outweigh the increased risk of drug-related adverse events.

As with all guideline recommendations, we recommend that care providers use their clinical judgment when applying recommendations to individual patients, particularly in the very elderly (aged > 80 yr), considering the trade-offs of risks and benefits, patient preferences and individual clinical profiles when making treatment decisions.16 This systolic blood pressure target recommendation remains a grade C recommendation, reflecting the evidence discussed above. Although the systolic blood pressure target recommended by the Canadian Hypertension Education Program differs from that of the European Society for Hypertension and the American Diabetes Association, which both recommend a target systolic blood pressure of less than 140 mm Hg, the evidence synthesis among groups has been similar. Both groups recognize that there are potential cerebrovascular benefits to be gained from lower systolic targets and acknowledge the limitations of the ACCORD-BP trial in identifying a clear systolic target. These issues were addressed differently by each group, with the European Society for Hypertension recommending a systolic target “well below 140 mm Hg,” suggesting that targets below 140 mm Hg are beneficial but that lower targets may be appropriate for certain individuals. Similarly, the American Diabetes Association provides a grade B recommendation for a systolic blood pressure target less than 140 mm Hg, but it also provides a grade C recommendation for a target of less than 130 mm Hg “if it can be achieved without undue treatment burden.”17

There is still uncertainty about optimal blood pressure targets. The Canadian Hypertension Education Program, in collaboration with the Canadian Diabetes Association, will continue to review the evidence annually and revise our recommendations as new evidence emerges.

References

7. Daskalopoulou SS, Khan N, Quinn RR, et al. The 2012 Canadian hypertension education program recommendations for the...

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Contributors: Doreen Rabi reviewed all identified studies, synthesized data and was the lead writer of the manuscript. Raj Padwal reviewed all identified studies, synthesized data and contributed substantially to the manuscript. Sheldon Tober, Richard Gilbert, Lawrence Leiter identified relevant studies for review and contributed substantially to the manuscript. Nadia Khan and Robert Quinn chaired the consensus conference and evidence review and also contributed to the manuscript. All of the authors approved the final version submitted for publication.

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Approach to the patient with atypical diabetes

Devin W. Steenkamp MD, Sara M. Alexanian MD, Elliot Sternthal MD

The overarching term “diabetes mellitus” represents a heterogeneous group of metabolic conditions characterized by hyperglycemia. All of these conditions are underpinned by a combination of various insulin secretory defects and impaired insulin action. According to the American Diabetes Association, diabetes can be broadly classified into four clinical classes: type 1 diabetes, characterized by immune-mediated destruction of the insulin-secreting β cells, which usually leads to absolute insulin deficiency and dependence on exogenous insulin; type 2 diabetes, an undefined polygenic disorder with various degrees of insulin resistance preceding progressive insulin secretory defects; gestational diabetes, diagnosed for the first time during pregnancy; and diabetes due to specific causes other than those noted above. This fourth group remains poorly defined, and atypical forms of diabetes often fall into this “catch-all” category.

Type 2 diabetes accounts for over 90% of cases seen in primary care, and type 1 diabetes accounts for the majority of the rest (between 5%-10% of all cases). However, physicians occasionally encounter individuals with impaired glucose metabolism who are lean, lack markers of insulin resistance or the typical type 2 diabetic dyslipidemic profile, are without hypertension or other typical cardiovascular risk factors, and who are not completely insulin dependent. These patients present a diagnostic challenge.

Diagnosing type 2 diabetes is not usually difficult. Progressive hyperglycemia (usually preceded by a period of glucose intolerance), obesity, insulin resistance and associated cardiovascular risk factors are its usual features. Type 1 diabetes is often thought to be a condition of lean adolescents and young adults that may be associated with other autoimmune diseases. More than 80% of patients with type 1 diabetes harbour markers of β cell autoimmunity, including antibodies to glutamic acid decarboxylase and islet antigen-2. At diagnosis, C-peptide levels, indicative of endogenous insulin production, are nearly undetectable, whereas in most individuals with type 2 diabetes, endogenous insulin production is preserved, albeit decreasing, until late in the disease course.

Some individuals are not easily classified as having either type 1 or type 2 diabetes and may have overlapping features of both. Individuals with phenotypic type 2 diabetes do sometimes present with de novo ketoacidosis. Those with phenotypic type 1 diabetes who do well on oral agents or require minimal insulin may also present potential diagnostic confusion. Molecular diagnostic capabilities have confirmed a heterogeneous spectrum of diabetes. It is important to classify these forms accurately because the diagnosis of particular molecular subtypes carries important implications for predicting disease progression, considering the prognosis, making decisions about optimal treatment and possibly counselling the affected individual and family members regarding heritability of the disease.

We review the approach to making an accurate diagnosis in patients with atypical or “intermediate” forms of diabetes that may masquerade as the common type 1 and type 2 diabetes phenotypes, with particular reference to monogenic diabetes (also referred to as maturity-onset diabetes of the young or MODY), ketosis-prone diabetes and latent autoimmune diabetes of adulthood.

Box 1 outlines the evidence used in this review.

General diagnostic considerations

Accurately recognizing individuals with atypical diabetes is not always straightforward, nor is it an exact science. Often the diagnosis is suspected on the basis of unusual clinical features and only becomes clear once the natural history

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**Key points**

- Atypical diabetes is increasingly recognized but is often poorly defined and may masquerade as type 1 or type 2 diabetes.
- Recognition of an atypical diabetes phenotype is important in facilitating timely work-up and often leads to referral for confirmation of the specific diagnosis, prognosis and treatment plans.
- Hepatocyte nuclear factor 1α (HNF1A) monogenic diabetes (also known as maturity-onset diabetes of the young [MODY] type 3) is the most common single-gene cause of diabetes.
- Ketosis-prone diabetes should be considered in individuals with phenotypic type 2 diabetes who present with insulin deficiency and ketoacidosis.
of the condition itself has become apparent. Clinicians caring for individuals with diabetes must first acknowledge that “other” forms of diabetes exist, so they can recognize the salient and sometimes subtle clinical features that define a particular phenotype. Although mutations in certain genes correlating with the clinical features of a monogenic diabetes phenotype can be considered diagnostic, in many instances the “atypical” diagnosis is suspected clinically through recognition of a characteristic phenotype that differs from typical type 1 or type 2 diabetes. Table 1 compares the clinical features of type 1 diabetes, type 2 diabetes, hepatocyte nuclear factor 1α (HNF1A) diabetes, ketosis-prone diabetes and latent autoimmune diabetes of adulthood. Box 2 provides a case-based example of how clinical and laboratory features can be used to identify a patient with atypical diabetes.

**Monogenic diabetes**

Monogenic diabetes or MODY accounts for about 1%–2% of all cases of diabetes. Before the advent of molecular genetic diagnostic testing, this form of diabetes was believed to constitute a form of maturity-onset diabetes (i.e., type 2 diabetes) occurring at an unusually young age. Affected patients lack severe manifestations of absolute insulin deficiency, which distinguishes them from patients with the classic juvenile form of diabetes, now termed type 1 diabetes. This form of diabetes is often mislabelled as “lean” type 2 diabetes.

Monogenic diabetes is a heterogeneous group of disorders involving a variety of single-gene mutations in transcription factors or glycolytic

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**Box 1: Evidence used in this review**

The goal of our review was to provide a practical clinical approach to a heterogeneous group of disorders, while paying particular attention to the more common forms of atypical diabetes that are likely to be encountered in general practice. Therefore, we were interested in articles about monogenic diabetes or maturity-onset diabetes of the young (MODY), in particular HNF1A diabetes (MODY 3), as well as ketosis-prone diabetes and latent autoimmune diabetes of adulthood. We searched MEDLINE (from 1948 to January 2013) and Google Scholar for relevant English-language articles using the following search terms: “atypical diabetes,” “monogenic diabetes,” “MODY,” “HNF1A diabetes,” “ketosis-prone diabetes,” “latent autoimmune diabetes” and “LADA.” We included both primary research articles and pertinent review articles. We also reviewed the reference lists of pertinent studies. Small case series and isolated case reports are common in this subject area, and we reviewed this literature, particularly for descriptions of novel therapeutic options. Given the emerging nature and heterogeneity of many atypical forms of diabetes, as well as the clinical overlap among them, the quality of the literature is highly variable. We included literature from major research groups that we believed to be of particular relevance to the topic. We placed particular emphasis on larger case series, cohort studies, clinical intervention trials and basic molecular pathophysiology literature, where available.

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**Table 1: Clinical comparison between type 2 diabetes mellitus, type 1 diabetes mellitus, HNF1A diabetes, ketosis-prone diabetes and latent autoimmune diabetes of adulthood**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Type 2 diabetes</th>
<th>Type 1 diabetes</th>
<th>HNF1A diabetes (monogenic)</th>
<th>Ketosis-prone diabetes</th>
<th>Latent autoimmune diabetes of adulthood</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mode of inheritance</td>
<td>Polygenic, with environmental interaction</td>
<td>Polygenic, class II HLA</td>
<td>Monogenic, autosomal dominant</td>
<td>Polygenic; increased frequency of HLA alleles associated with type 1 diabetes</td>
<td>Polygenic, with environmental interaction</td>
</tr>
<tr>
<td>Age at presentation</td>
<td>Variable (usually adulthood)</td>
<td>Young</td>
<td>Young (often &lt; 25 yr)</td>
<td>Variable (usually adulthood)</td>
<td>&gt; 30 yr (adult, by definition)</td>
</tr>
<tr>
<td>Penetration, %</td>
<td>Variable (10–40)%</td>
<td>Incomplete (&lt; 25)</td>
<td>High (80–96)%</td>
<td>Variable (&lt; 50)</td>
<td>Similar to type 1 diabetes</td>
</tr>
<tr>
<td>Body habitus</td>
<td>Obese</td>
<td>Non-obese</td>
<td>Non-obese</td>
<td>Typically obese</td>
<td>Non-obese</td>
</tr>
<tr>
<td>Ethnicity</td>
<td>High prevalence worldwide</td>
<td>White</td>
<td>White, European ancestry</td>
<td>Afro-Caribbean or Hispanic, with strong family history of phenotypic type 2 diabetes</td>
<td>Similar to type 1 diabetes</td>
</tr>
<tr>
<td>β-Cell antibodies, %</td>
<td>&lt; 10⁶</td>
<td>&gt; 85⁴</td>
<td>&lt; 1³</td>
<td>&lt; 30²</td>
<td>100 (by definition)⁶</td>
</tr>
<tr>
<td>First-line therapy</td>
<td>Metformin in most patients</td>
<td>Insulin</td>
<td>Low-dose sulfonylurea</td>
<td>Insulin during acute presentation; up to 60% of patients require insulin by 10 yr after diagnosis⁵</td>
<td>Insulin independence for at least 6 mo, progressing to insulin dependence over time⁷</td>
</tr>
</tbody>
</table>

Note: HNF1A = hepatocyte nuclear factor 1α, HLA = human leukocyte antigen.
enzymes involved in β cell glucose sensing and metabolism. To date, 11 subtypes have been described, and all are associated with a β cell defect, although the subtypes differ in terms of clinical phenotype and spectrum of associated conditions.¹⁰ The most common forms relate to mutations in the genes encoding HNF1A (also termed MODY 3) and glucokinase (also termed MODY 2). These two subtypes account for about 80% of cases. HNF1A diabetes is the most common, occurring in up to 60% of individuals of European ancestry with monogenic diabetes.¹¹ The estimated minimum prevalence for all diagnoses of MODY in a UK referral population was reportedly 108 cases per million.¹² Regional variation in prevalence for all MODY subtypes is common.¹² However, the prevalence is likely underestimated, with regional variation resulting from differences in referral rates, which in turn reflect extent of awareness, misdiagnosis or variation in access to genetic testing.¹² Further discussion here is limited to HNF1A monogenic diabetes (MODY 3).

The hallmark of monogenic diabetes is autosomal dominant transmission, with high penetrance in families leading to multiple affected generations. Whereas individuals with type 2 diabetes usually have 30%-40% of first-degree relatives similarly affected, monogenic diabetes affects 50% of children born to a mutation carrier, and penetrance is often above 90%, such that three or more generations are usually affected.¹¹ HNF1A diabetes is characterized clinically by marked postprandial hyperglycemia, with fasting glucose tolerance relatively preserved early in the disease course.¹⁰ This feature makes early diagnosis solely on the basis of fasting glucose measurements challenging, especially in adolescence or childhood, when fasting glucose values are often normal. A suggestive diagnostic feature of HNF1A diabetes is the large incremental glucose response seen after a standard oral glucose load. More specifically, a glucose increment greater than 3 mmol/L at two hours after ingestion of 75 g oral glucose suggests HNF1A diabetes, especially if the fasting plasma glucose is less than 5.5 mmol/L. This pattern contrasts with glucokinase diabetes, in which the two-hour increment is small (< 3 mmol/L), fasting glucose is invariably above 5.5 mmol/L, and diagnosis is more often based on the results of fasting glucose more often at two-hour oral glucose tolerance test.¹¹ Notably, the diagnosis would be missed in as many as 60% of individuals with HNF1A diabetes if glucose tolerance testing were omitted in favour of fasting glucose measurement alone.¹¹ However, insulin secretion is progressively reduced at all glucose concentra-

tions, and fasting hyperglycemia often develops over time. Therefore, certain suggestive features, as described in Table 2,¹³⁻¹⁸ should prompt formal genetic testing to establish the diagnosis. Increased insulin sensitivity may explain the lower-than-expected insulin requirements and proclivity to hypoglycemia with low-dose therapies.¹⁴

**Which diagnostic tests are useful?**

Potentially helpful laboratory tests in HNF1A diabetes include a lipid panel,¹⁷ oral glucose tolerance testing,¹⁵ urinalysis for glucose¹⁶ and high-sensitivity testing for C-reactive protein,¹⁸ although none of these is considered diagnostic. Islet cell antibodies (i.e., antibodies to glutamic acid decarboxylase and/or islet antigen-2) are usually absent in HNF1A diabetes (positive result in < 1% of individuals), which provides reliable discrimination from type 1 diabetes (positive result in > 85%) and latent autoimmune diabetes of adulthood. Therefore, antibody testing should be routinely performed before more
expensive genetic testing. Where available, genetic testing should be used to confirm a specific diagnosis of monogenic diabetes.

**What are the benefits and implications of diagnosis?**

HNF1A diabetes carries a risk for complications of poor glycemic control similar to that of type 1 diabetes. Despite frequent absence of associated cardiovascular risk factors, cardiovascular morbidity is higher and life expectancy lower than among matched nonaffected family members. However, the β cell defect is often managed successfully for years with insulin secretagogue therapies, such as sulfonylurea or meglitinide drugs. Because of increased insulin sensitivity, individuals may have exquisite sensitivity to the insulin secretagogue drugs. The lowest available dose of a particular sulfonylurea drug is often adequate to treat HNF1A diabetes, especially early in the disease course; however, certain individuals may continue to struggle with hypoglycemia despite careful dose titration.

The role of incretin mimetic drugs, such as glucagon-like peptide-1 agonists or the weaker dipeptidyl peptidase-4 inhibitors, has yet to be established, and very few prospective data are available to inform their use. Nateglinide, a short-acting meglitinide-class secretagogue, has been prospectively studied in a small group of patients with HNF1A diabetes; it was associated with effective postprandial glucose control, lower peak insulin concentrations and less hypoglycemia than low-dose sulfonylurea therapy. Metformin and thiazolidinediones are much less effective and do not address the underlying pathophysiologic defect of impaired insulin secretion; as such, they are rarely indicated.

Insulin may be required to achieve glycemic control during periods of reduced insulin sensitivity (e.g., pregnancy), in acute illness or when oral secretagogue agents are no longer effective because of the often progressive natural history of HNF1A diabetes. Prandial rapid-acting insulin at small doses may be all that is needed, given the heightened insulin sensitivity and often well-maintained fasting glucose values. In addition, the 50% chance of having an affected child carries implications for family planning and genetic counselling. Table 2 outlines clinical considerations and laboratory findings in HNF1A diabetes.

**Ketosis-prone diabetes**

Ketosis-prone diabetes is seen in an emerging, heterogeneous group of individuals in whom diabetic ketoacidosis develops without the typical phenotype of type 1 diabetes. However, differentiation of ketosis-prone diabetes from type 1 diabetes in older, obese, nonwhite individuals can be challenging, and the correct diagnosis may be

<table>
<thead>
<tr>
<th>Table 2: Clinical and laboratory features of HNF1A diabetes (maturity-onset diabetes of the young type 3)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical considerations</strong></td>
</tr>
<tr>
<td>Autosomal dominant inheritance; often more than three generations with diabetes</td>
</tr>
<tr>
<td>High penetrance in families</td>
</tr>
<tr>
<td>European ethnicity most common</td>
</tr>
<tr>
<td>Lean (BMI often &lt; 25)</td>
</tr>
<tr>
<td>Usually young (&lt; 25 yr)</td>
</tr>
<tr>
<td>No ketoacidosis</td>
</tr>
<tr>
<td>Increased insulin sensitivity; patients often have minimal requirement for insulin</td>
</tr>
<tr>
<td>Hypersensitivity to sulfonylurea drugs</td>
</tr>
<tr>
<td>Postprandial hyperglycemia dominates</td>
</tr>
<tr>
<td>Prevalence of microvascular and macrovascular complications similar to that of patients with type 1 diabetes</td>
</tr>
<tr>
<td>Progressive β-cell failure over time, with increased fasting glucose</td>
</tr>
</tbody>
</table>

Note: BMI = body mass index, HDL = high-density lipoprotein, HNF1A = hepatocyte nuclear factor 1α.
discerned only with careful follow-up. Ketoacidosis follows severe β cell dysfunction with marked insulin deficiency. Affected patients often present with an episode of unprovoked diabetic ketoacidosis and are discharged from hospital on insulin therapy. However, in certain individuals, this acute dysfunction is transient and is followed by robust β cell recovery, with complete resolution of exogenous insulin requirement and near normoglycemia. Over periods of months to years, these individuals may “swing” between periods of acute insulin deficiency and subsequent “remission” characterized by milder dysglycemia, with minimal to no need for anti-hyperglycemic agents.

Ketosis-prone diabetes has been variably termed “atypical,” “Flatbush,” “reversible” or “ketosis-prone type 2 diabetes,” which reflects the ongoing difficulty of classifying this heterogeneous group. A useful classification system, designated the AB classification scheme, has been proposed. In this system, individuals are categorized into one of four groups, depending on the presence or absence of islet cell autoantibodies (A+ or A–, respectively) and the presence or absence of β cell functional reserve once the period of acute metabolic decompensation has resolved (B+ or B–, respectively). A+B– and A–B– individuals are distinct subgroups with differing genetic and immunologic underpinnings, but they share the clinical characteristics of type 1 diabetes, including reduced β cell secretory function. In contrast, A+B+ and A–B+ individuals share the features of type 2 diabetes, with preservation of β cell function over time.

Patients in the largest of these four groups (A–B+) resemble people with the type 2 diabetes obese phenotype and account for 50% of all those with ketosis-prone diabetes. Unprovoked diabetic ketoacidosis, with absent islet cell antibodies and frequent evolution to insulin independence, is the hallmark of this group. About half of patients will become insulin independent after an early episode of diabetic ketoacidosis, but ultimately 60% will be insulin dependent 10 years after diagnosis. Individuals are often of Afro-Caribbean or Hispanic ancestry, but ketosis-prone diabetes has been described in many ethnic groups worldwide. Male predominance is another hallmark of the group with unprovoked diabetic ketoacidosis. The exact prevalence of ketosis-prone diabetes is unknown, given limited detailed epidemiologic data. However, this form of diabetes is being increasingly reported and recognized around the world.

Which diagnostic tests are useful?

There are no gold standard diagnostic tests defining ketosis-prone diabetes. Islet cell antibodies and C-peptide levels should be obtained for all patients with suspected atypical phenotypes to evaluate for markers of β cell autoimmunity and β cell secretory reserve. Referral to an endocrinology specialist is often appropriate to aid in establishing the specific cause and for help in formulating an approach to treatment.

What are the benefits and implications of diagnosis?

The main clinical relevance of diagnosing ketosis-prone diabetes is in distinguishing individuals with this form of diabetes from those with type 1 diabetes, who will require lifelong insulin therapy.

### Table 3: Clinical and laboratory features of ketosis-prone diabetes

<table>
<thead>
<tr>
<th>Clinical considerations</th>
<th>Laboratory features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unprovoked ketoacidosis often occurs; may be new-onset diabetes</td>
<td>β-cell antibodies present in up to 28% of patients</td>
</tr>
<tr>
<td>Afro-Caribbean or Hispanic ancestry</td>
<td>C-peptide often low or undetectable during diabetic ketoacidosis; recovery expected in &gt; 60%</td>
</tr>
<tr>
<td>Periods of insulin independence interspersed with periods of acute insulin deficiency and diabetic ketoacidosis</td>
<td>Ratio of fasting C-peptide (nmol/L) to glucose (mmol/L) &gt; 11 may be used as reliable predictor of insulin discontinuation</td>
</tr>
<tr>
<td>Type 2 diabetes phenotype common (obesity, insulin resistance, metabolic syndrome)</td>
<td>Presence of HLA alleles for type 1 diabetes associated with insulin dependence within 1–2 yr</td>
</tr>
<tr>
<td>Fluctuating glycated hemoglobin (A1C) pattern consistent with β-cell failure and recovery</td>
<td></td>
</tr>
<tr>
<td>Male predominance among patients with unprovoked diabetic ketoacidosis (male–female ratio 2.6:1)</td>
<td></td>
</tr>
<tr>
<td>Insulin should always be initial therapy, with reduction of cardiovascular risk factors</td>
<td></td>
</tr>
</tbody>
</table>

Note: HLA = human leukocyte antigen.
therapy. β cell recovery is not easy to predict, given the heterogeneity of this group. However, for individuals with new-onset, unprovoked diabetic ketoacidosis and absent islet cell autoantibodies, the rate of insulin discontinuation is favourable. Of the three specific factors that may predict β cell recovery and insulin discontinuation in this subgroup — new-onset diabetes, onset of diabetes in middle age and significant β cell functional reserve (ratio of C-peptide [nmol/L] to glucose [mmol/L] > 11) — the third is the strongest predictor.27 If insulin is successfully withdrawn, insulin sensitizers such as metformin and thiazolidinediones are often appropriate first-line agents.5 Table 3 outlines clinical considerations and laboratory findings in ketosis-prone diabetes.

**Latent autoimmune diabetes of adulthood**

Latent autoimmune diabetes of adulthood is perhaps the least well defined and most confusing form of atypical diabetes. Affected patients generally include adults with phenotypic type 2 diabetes and detectable islet cell antibodies, who present without ketoacidosis or catabolism. In simplified terms, this condition is slowly progressive autoimmune type 1 diabetes that is usually diagnosed at an older age than typical type 1 diabetes. To add further confusion, latent autoimmune diabetes of adulthood has also been called “slowly progressive type 1 diabetes,” “latent type 1 diabetes,” “double diabetes” and “type 1.5 diabetes.” Additionally, there may be significant clinical overlap with ketosis-prone diabetes, which again highlights the imperfect clinical discrimination of current diabetes classification. The American Diabetes Association does not consider this form of diabetes distinct from type 1 diabetes.1 A somewhat arbitrary and imprecise definition proposed by the Immunology of Diabetes Society (in an effort to facilitate study) lists the following criteria: onset of diabetes at older than 30 years of age, presence of at least one of the four islet cell antibodies common to type 1 diabetes and insulin independence for at least six months after diagnosis.7

These individuals are typically older and may even present with antibody-positive diabetes in the seventh or eighth decade of life. In fact, recent studies have suggested that autoimmune diabetes presenting in adulthood most commonly presents as latent autoimmune diabetes of adulthood.28 Hyperglycemia is initially controlled with oral antihyperglycemic therapy, but over months to years patients progress to insulin dependence.29 Latent autoimmune diabetes of adulthood may well be a truly “intermediate” form of diabetes, as certain genetic features common to both type 1 and type 2 diabetes are present.30 However, the clinical utility of diagnosing this form of diabetes is highly debated.31,32

<table>
<thead>
<tr>
<th>Table 4: Clinical and laboratory features of latent autoimmune diabetes of adulthood8,20,33</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical considerations</strong></td>
</tr>
<tr>
<td>Age &gt; 30 yr</td>
</tr>
<tr>
<td>Patients may be overweight, but typically leaner than those with type 2 diabetes</td>
</tr>
<tr>
<td>Patients may have mild to moderate insulin resistance27</td>
</tr>
<tr>
<td>Occurs in people of various ethnicities</td>
</tr>
<tr>
<td>Progression to insulin therapy slower than for patients with type 1 diabetes, but quicker than for those with type 2 diabetes</td>
</tr>
<tr>
<td>Avoid β-cell stressors such as secretagogues21</td>
</tr>
<tr>
<td>May be treated initially with oral antihyperglycemic agents, but insulin should be introduced early if glycemic control cannot be maintained</td>
</tr>
</tbody>
</table>

Note: GAD = glutamic acid decarboxylase, ICA = islet cell antibodies.

**Which diagnostic tests are useful?**

As with ketosis-prone diabetes, there are no gold standard diagnostic tests that define latent autoimmune diabetes of adulthood. However, positive markers of β cell autoimmunity are required, and measurement of β cell secretory reserve (i.e., C-peptide) is useful to predict insulin secretory capacity.

**What are the benefits and implications of diagnosis?**

The controversial clinical entity of latent autoimmune diabetes of adulthood constitutes the most common presentation of autoimmune diabetes in adults. The value of considering this diagnosis lies in recognizing its prevalence in the growing epidemic of type 2 diabetes. In particular, β cell autoimmunity may be found in phenotypic type 2 diabetes. Even if only 10% of cases of phenotypic type 2 diabetes are latent autoimmune diabetes of adulthood, this represents a much larger autoimmune diabetes burden than is represented by confirmed childhood type 1 diabetes. These individuals progress to insulin dependence faster than patients with antibody-negative type 2 diabetes.
Thus, insulin treatment may be introduced earlier in the disease course, for the theoretical benefit of correcting glucotoxicity and possibly prolonging β cell reserve. Drugs with potential deleterious effects on β cell function, such as sulfonylureas, are best avoided.11 Table 4 outlines clinical considerations and laboratory findings in latent autoimmune diabetes of adulthood.

Conclusion

Although the various forms of atypical diabetes are relatively uncommon, it is important that they be accurately diagnosed, as diagnosis may have a substantial impact on the prognosis and management of individual patients and their families. However, for both clinicians and patients, it is often less important to label the specific type of diabetes than it is to understand the pathophysiology of the hyperglycemia to allow effective treatment.

References

11. Fujans SS, Bell GI, MODY: history, genetics, pathophysiology, and clinical decision making. Diabetes Care 2011;34:1878-80.

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Contributors: Devin Steenkamp and Sara Alexanian conceived the article. Devin Steenkamp performed the initial literature search and reviewed and extracted relevant information from the included articles. Elliot Sternthal searched for and reviewed further relevant articles pertaining to latent autoimmune diabetes of adulthood. Devin Steenkamp drafted the article, which was revised by all authors. All of the authors approved the final version submitted for publication.
Recommendations on screening for type 2 diabetes in adults

Canadian Task Force on Preventive Health Care

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Competing interests: Neil Bell has received a research grant from Sanofi-Aventis for an economic analysis of an office-based care model for patients with type 2 diabetes. None of the other members of the guidelines writing group (listed at the end of the article) declared competing interests.

The list of current members of the Canadian Task Force on Preventive Health Care is available at www.canadiantaskforce.ca/members_eng.html.

This article has been peer reviewed.

Correspondence to: Canadian Task Force on Preventive Health Care, info@canadiantaskforce.ca

In 2008/09, an estimated 2.4 million Canadians (6.8%) had either type 1 or type 2 diabetes, and an additional 480 000 (1.4%) were unaware that they were affected. The most recent Canadian data indicate that, from 1998/99 to 2008/09, the prevalence of diagnosed diabetes increased by 70% (Figure 1). The greatest relative increase in prevalence was seen in the age groups 35–39 and 40–44 years, in which the proportion doubled. In 2008/09, almost 50% of people with newly diagnosed diabetes were 45–64 years old (Figure 2). Substantial increases in prevalence are projected over the next decade. Because type 1 diabetes is much less common than type 2 diabetes and is generally symptomatic, we focused on type 2 diabetes in these guidelines.

Laboratory values used to define the diagnosis of diabetes have become more inclusive over time2−6 (Appendix 1). In 2002, a new diagnostic category (now commonly known as prediabetes) was created to describe patients at very high risk of diabetes. More recently, glycated hemoglobin (herein referred to as A1C), which reflects an individual’s average plasma glucose level over the previous 2–3 months, has been accepted as an alternative diagnostic test for type 2 diabetes.7,8

Long-term consequences of type 2 diabetes include microvascular (retinopathy, nephropathy, neuropathy) and macrovascular (stroke, myocardial infarction) complications.9 An estimated 65%–80% of people with diabetes will die of a cardiovascular event, many without prior signs or symptoms of cardiovascular disease.10

Type 2 diabetes is a prevalent and costly chronic illness that demands lifestyle interventions, effective monitoring and pharmacologic management.11 Management of risk factors, including physical inactivity, blood pressure and blood lipid levels as well as blood glucose levels, is required to prevent long-term complications.12

Uncertainties remain about how best to prevent diabetes, the relative benefits of population screening and risk assessment, the ideal frequency of screening in high-risk populations and the potential harms of screening. This document updates the 2005 Canadian Task Force on Preventive Health Care recommendations on screening asymptomatic adults for type 2 diabetes. It does not apply to people with symptoms of diabetes or those who are at risk of type 1 diabetes.

Methods

The Canadian Task Force on Preventive Health Care is an independent panel of clinicians and methodologists that makes recommendations about clinical manoeuvres aimed at primary and secondary prevention (www.canadiantaskforce.ca). Work on each set of recommendations is led by a workgroup of 2 to 6 members of the task force. Each workgroup establishes the research questions and analytical framework for the guideline.

The current work was led by a workgroup of 6 members of the task force (listed at the end of the article). The research questions and analytical framework for this guideline are available in Appendix 2. The recommendations were revised and approved by the entire task force and underwent external review by experts in the field and by stakeholders. Details about the task force’s methods can be found elsewhere.13,14 The systematic review on which the recommendations are based was performed independently by the Evidence Review and Synthesis Centre (www.canadiantaskforce.ca/about_eng.html) and is available at http://canadiantaskforce.ca/recommendations/2012/diabetes.

Key points

- There is no evidence that screening for type 2 diabetes in adults who are at low to moderate risk of diabetes reduces the incidence, mortality or complications of diabetes.
- Low-quality evidence suggests that screening adults at high or very high risk of diabetes will reduce rates of myocardial infarction, microvascular complications and mortality.
- Use of a validated risk calculator, such as FINDRISC or CANRISK, is recommended to identify people at high or very high risk of diabetes.
- Validated risk calculators can be used to select patients for screening and may inform them about their risk factors.
- For adults who choose screening, low-quality evidence suggests that an interval of every 3–5 years is appropriate, except for people at very high risk of diabetes (determined with a validated risk calculator), for whom annual screening may maximize health benefits.
Figure 1: Age-standardized* prevalence and number of cases of diagnosed diabetes among individuals aged 1 year and older, Canada, 1998/99 to 2008/09. *Age-standardized to the 1991 Canadian population. Source: Canadian Chronic Disease Surveillance System, Public Health Agency of Canada, July 2011.

Figure 2: Prevalence of diagnosed diabetes among individuals aged 1 year and older, by age group and sex, Canada, 2008/09. Source: Canadian Chronic Disease Surveillance System, Public Health Agency of Canada, July 2011.
Recommendations

A summary of the recommendations for clinicians and policy-makers is shown in Box 1. The recommendations have been graded according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system, which is summarized in Box 2.

Box 1: Summary of recommendations for clinicians and policy-makers

Recommendations are presented for screening asymptomatic adults for type 2 diabetes. They do not apply to people with symptoms of diabetes or those at risk of type 1 diabetes.

- For adults at low to moderate risk of diabetes (determined with a validated risk calculator†), we recommend not routinely screening for type 2 diabetes. (Weak recommendation; low-quality evidence)
- For adults at high risk of diabetes (determined with a validated risk calculator†), we recommend routine screening annually with A1C.‡ (Weak recommendation; low-quality evidence)
- For adults at very high risk of diabetes (determined with a validated risk calculator†), we recommend routine screening annually using A1C.‡ (Weak recommendation; low-quality evidence)

*Risk of diabetes developing within 10 years: low risk = 1/100–1/25 (1%–4%); moderate risk = 1/6 (17%); high risk = 1/3 (33%); very high risk = 1/2 (50%). For adults ≥ 18 years of age, we suggest risk calculation at least every 3–5 years.

1FINDRISC (the Finnish Diabetes Risk Score) has been selected as the preferred validated risk calculator, but CANRISK (the Canadian Diabetes Risk Assessment Questionnaire) is an acceptable alternative. Factors considered in FINDRISC and CANRISK are age, obesity, history of elevated glucose levels, history of hypertension, family history of diabetes, limited activity levels, and diet with limited intake of fruits and vegetables.

1A1C has been selected as the preferred blood test, but fasting glucose measurement and the oral glucose tolerance test are acceptable alternatives. An A1C level of 6.5% or greater is recommended.

Box 2: Grading of recommendations

- Recommendations are graded according to the Grading of Recommendations Assessment, Development and Evaluation system (GRADE).† GRADE offers two strengths of recommendation: strong and weak. The strength of recommendation is based on the quality of supporting evidence; the degree of uncertainty about the balance between desirable and undesirable effects; the degree of uncertainty or variability in values and preferences; and the degree of uncertainty about whether the intervention represents a wise use of resources.
- Strong recommendations are those for which we are confident that the desirable effects of an intervention outweigh its undesirable effects (strong recommendation for an intervention) or that the undesirable effects of an intervention outweigh its desirable effects (strong recommendation against an intervention). A strong recommendation implies that most people will be best served by the recommended course of action.
- Weak recommendations are those for which the desirable effects probably outweigh the undesirable effects (weak recommendation for an intervention) or undesirable effects probably outweigh the desirable effects (weak recommendation against an intervention) but appreciable uncertainty exists. A weak recommendation implies that most people would want the recommended course of action but that many would not. For clinicians, this means you must recognize that different choices will be appropriate for each person, and they must help each person arrive at a management decision consistent with his or her values and preferences. Policy-making will require substantial debate and involvement of various stakeholders. Weak recommendations result when the balance between desirable and undesirable effects is small, the quality of evidence is lower, and there is more variability in the values and preferences of patients.
- Evidence is graded as high, moderate, low or very low based on how likely further research is to change our confidence in the estimate of effect.

For more details, see the GRADE Companion Document to Task Force Guidelines, available at www.canadiantaskforce.ca/docs/grade_ENG.pdf.

Adults at low to moderate risk

For adults at low to moderate risk of diabetes (determined with the use of a validated risk calculator), we recommend not routinely screening for type 2 diabetes. (Weak recommendation; low-quality evidence.)

We found no randomized trials or observational studies showing that blood test screening for type 2 diabetes improved intermediate outcomes (differences in A1C, frequency of diagnosis) or final health outcomes (mortality and diabetes complications) among adults at low to moderate risk of type 2 diabetes (Appendix 3). Evidence from 2 modeling studies⁶⁷ suggests that screening adults starting between 30 and 45 years of age is cost-effective and maximizes health benefits (e.g., reducing mortality and microvascular complications), and results from 2 randomized controlled trials (RCTs)⁶⁸⁹¹ suggest that the harms associated with screening for type 2 diabetes are minimal (Table 1, Appendix 4).

However, a large cluster-randomized controlled trial from the United Kingdom recently showed that risk calculation plus one-time blood screening did not reduce all-cause or cardiovascular-related mortality over a median follow-up of 10 years in a population with a 3% baseline prevalence of diabetes, among whom an additional 3% was detected in the screened group. “High risk” or “very high risk” as defined by the task force implies a FINDRISC score (Finnish Diabetes Risk Score) of 15 points or higher, which is associated with prevalences of type 2 diabetes detected through screening that are several times higher than in the UK RCT, depending on the population.¹²¹³ Thus, we concluded that the findings of the UK RCT are applicable to a population at low to moderate risk of diabetes, rather than to adults at high or very high risk.

In our judgment, the discrepant findings for mortality between the UK RCT and the modelling studies reduce confidence in the putative benefits for microvascular outcomes suggested by the latter. On balance, we conclude that available evidence warrants a weak recommendation against screening in adults who are at low or moderate risk of diabetes. Adults in this category who place a high value on uncertain benefits of screening and who are less concerned with the undesirable consequences of anxiety and the burden associated with a diagnosis of diabetes are likely to choose screening.

Adults at high risk

For adults at high risk of diabetes (determined with the use of a validated risk calculator), we
recommend routinely screening every 3–5 years with the use of A1C. (Weak recommendation; low-quality evidence.)

We found 1 recent population-based cohort study that examined the impact of screening for type 2 diabetes and related cardiovascular risk factors on mortality in 2 cohorts of women and men aged 40–65 who were invited to undergo screening during 1990–1992 (first cohort) and 2000–2003 (second cohort). Overall mortality did not differ significantly between the invited and noninvited cohorts when assessed after a median follow-up of 10 years (first cohort: hazard ratio 0.79, 95% confidence interval [CI] 0.63–1.00) and after a median of 8.1 years (second cohort: hazard ratio 1.18, 95% CI 0.93–1.51) (Table 2).

In our judgment, the findings of the UK RCT are not directly applicable to the screening of people at high or very high risk of diabetes. The 2 modelling studies described earlier are not generalizable to the population at large because they included insulin-treated diabetes patients.

### Table 1: Summary of evidence of harms associated with screening for type 2 diabetes

<table>
<thead>
<tr>
<th>Outcome measure</th>
<th>Mean score ± SD</th>
<th>Absolute effect (95% CI)†</th>
<th>GRADE quality of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Anxiety</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spielberger State Anxiety Inventory</td>
<td>34.1 ± 12.1 / n = 168</td>
<td>Mean score 3.5 higher (0.22 to 6.78)</td>
<td>Moderate§¶**</td>
</tr>
<tr>
<td></td>
<td>37.6 ± 12.2 / n = 77</td>
<td></td>
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</tr>
<tr>
<td></td>
<td>32.7 ± 11.5 / n = 199</td>
<td>Mean score 0.53 lower (–2.60 to 1.54)</td>
<td>Low¶**‡‡§§</td>
</tr>
<tr>
<td></td>
<td>32.7 ± 11.6 / n = 2 468</td>
<td></td>
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</tr>
<tr>
<td></td>
<td>31.8 ± 11.4 / n = 358</td>
<td>Mean score 1.51 higher (–0.17 to 3.20)</td>
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</tr>
<tr>
<td></td>
<td>33.5 ± 12.0 / n = 2 504</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>32.8 ± 11.8 / n = 304</td>
<td>Mean score 0.57 higher (–1.11 to 2.24)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>35.5 ± 12.2 / n = 2 377</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hospital Anxiety and Depression Scale: Anxiety Subscale</td>
<td>6.62 ± 3.39 / n = 255</td>
<td>Mean score 0.46 lower (–0.99 to 0.07)</td>
<td>Low§¶**‡‡§§</td>
</tr>
<tr>
<td></td>
<td>6.04 ± 3.79 / n = 3 140</td>
<td></td>
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</tr>
<tr>
<td></td>
<td>5.97 ± 3.86 / n = 442</td>
<td>Mean score 0.12 lower (–0.55 to 0.32)</td>
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<tr>
<td></td>
<td>5.91 ± 3.89 / n = 3 159</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>5.81 ± 3.87 / n = 377</td>
<td>Mean score 0.01 lower (–0.47 to 0.45)</td>
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</tr>
<tr>
<td></td>
<td>5.85 ± 3.87 / n = 3 034</td>
<td></td>
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<tr>
<td>Depression</td>
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<tr>
<td>Hospital Anxiety and Depression Scale: Depression Subscale</td>
<td>4.52 ± 3.48 / n = 256</td>
<td>Mean score 0.37 lower (–0.93 to 0.18)</td>
<td>Low¶**‡‡§§</td>
</tr>
<tr>
<td></td>
<td>4.24 ± 3.31 / n = 3 161</td>
<td></td>
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<tr>
<td></td>
<td>4.18 ± 3.38 / n = 444</td>
<td>Mean score 0.01 higher (–0.51 to 0.54)</td>
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<td></td>
<td>4.24 ± 3.40 / n = 3 177</td>
<td></td>
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</tr>
<tr>
<td></td>
<td>4.03 ± 3.35 / n = 378</td>
<td>Mean score 0.22 higher (–0.31 to 0.74)</td>
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<tr>
<td></td>
<td>4.28 ± 3.40 / n = 3 049</td>
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</tr>
</tbody>
</table>

Note: CI = confidence interval, RCT = randomized controlled trial, SD = standard deviation.

*Our systematic review of harms associated with screening for type 2 diabetes in adults of any age identified 2 RCTs.
†Eborall et al. used adjusted mean differences for age and comorbidity (use of antihypertensives) to compute absolute effect.
‡Questionnaire was sent 6 weeks after last contact (either test or invitation).
§Unclear allocation concealment.
¶No information regarding blinding.
**Quality rating is for a single study; thus, imprecision and publication bias criteria were rated as "no" and "unlikely.”
††Questionnaire was given immediately after the initial blood test for those who attended screening, or after first contact for controls; data for those who attended screening were included in the analysis only if the questionnaire was completed and returned before the results of the test were received.
‡‡A nonrandomized sample of screening practices was used.
§§Large loss to follow-up (for the follow-up periods 3–6 and 12–15 mo).
Table 2: Summary of evidence of benefits associated with screening for type 2 diabetes*

<table>
<thead>
<tr>
<th>Study Type</th>
<th>Design</th>
<th>Limitations</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Other Considerations</th>
<th>Screening, no. (%)</th>
<th>Control, no. (%)</th>
<th>Relative Effect (95% CI)</th>
<th>Absolute Effect (95% CI)</th>
<th>Evidence Quality</th>
<th>Importance</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Overall mortality</strong></td>
<td></td>
<td></td>
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<td></td>
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<td></td>
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</tr>
<tr>
<td>1 cluster RCT†*</td>
<td>Randomized trial</td>
<td>No serious risk of bias</td>
<td>No serious inconsistency**</td>
<td>No serious indirectness††</td>
<td>No serious imprecision‡‡</td>
<td>None§§</td>
<td>n = 1532</td>
<td>n = 377</td>
<td>HR 1.06 (0.90 to 1.25)</td>
<td>5196 more per million (from 8726 fewer to 21454 more)</td>
<td>High</td>
<td>Critical</td>
</tr>
<tr>
<td>1 cohort study**</td>
<td>Observational study</td>
<td>No serious limitations†††</td>
<td>No serious inconsistency**</td>
<td>No serious indirectness</td>
<td>No serious imprecision</td>
<td>None**</td>
<td>n = 1705</td>
<td>n = 3231</td>
<td>HR 0.79 (0.63 to 1)</td>
<td>14455 fewer per million (from 2519 fewer to 0 more)</td>
<td>Low</td>
<td>Critical</td>
</tr>
<tr>
<td><strong>Cardiovascular mortality</strong></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 cluster RCT†*</td>
<td>Randomized trial</td>
<td>No serious risk of bias</td>
<td>No serious inconsistency**</td>
<td>No serious indirectness††</td>
<td>No serious imprecision‡‡</td>
<td>None§§</td>
<td>n = 482</td>
<td>n = 124</td>
<td>HR 1.02 (0.75 to 1.38)</td>
<td>590 more per million (from 7408 fewer to 11513 more)</td>
<td>High</td>
<td>Critical</td>
</tr>
</tbody>
</table>

Note: CI = confidence interval, GRADE = Grading of Recommendations Assessment, Development and Evaluation, HR = hazard ratio, RCT = randomized controlled trial.

*Our systematic review of benefits associated with screening for type 2 diabetes in adults of any age identified 1 cluster RCT and 1 cohort study, which looked at the effect of screening for type 2 diabetes and related cardiovascular risk factors on overall mortality; the RCT also looked at the effect on cardiovascular mortality. Evidence from modelling studies is available in Appendices 4 and 5.

†Follow-up was from November 2001 to November 2011 (median 9.6 years, interquartile range [IQR] 8.9–9.9 years; 184 057 person-years).

‡Int cohort: follow-up was from 1991 to 1999 (median 10 years; 47 854 person-years of risk). Second cohort: follow-up was from 2000 to 2008 (median 8.1 years; 23 144 person-years of risk).

§Population-based cluster RCT. Study reported data from 32 general practices in eastern England randomized to 1 of 3 groups (screening plus intensive treatment for diagnosed diabetes [n = 14]; screening plus routine care for diabetes patients [n = 13]; no-screen control [n = 5]). Study population included 20 184 individuals 40–69 years of age (median 59 years IQR 53–65 years) at high risk of prevalent undiagnosed diabetes on the basis of previously validated risk score (minimum score of 0.17 – reflects top 25% of risk distribution in participating practices).

¶Cochrane Risk of Bias Tool was used to examine this study. The appraisal process was completed by 2 independent reviewers who agreed there was uncertainty regarding allocation concealment and that it was not possible to blind patients and their physicians to their screening status; however, this potential performance bias was unlikely to affect the outcome of interest (mortality). All other domains of bias covered in the Cochrane tool were determined to have a low risk of bias. On the basis of the overall assessment, the evidence was not downgraded for any serious concerns regarding study limitations.

**Single study.

††Study sample characteristics, risk-assessment variables and screening test were similar to the Canadian population and screening context of interest for this review.

‡‡Large sample and large event rate with narrow confidence interval around estimate of effect.

§§Single study; literature search indicated no other RCTs have been conducted or published for this particular comparison and outcome.

†††Unadjusted prevalence of diabetes in screening practices was 3.0% (standard deviation [SD] 1.0%). Characteristics of eligible participants in screening practices at baseline: mean age 58.2 (SD 7.7) years; 63.9% men (n = 10 260); mean body mass index (BMI) 30.5 (SD 4.6), median diabetes risk score 0.35 (IQR 0.24–0.52); 45.9% prescribed antihypertensive medication (n = 7372); 5.4% prescribed steroids (n = 866).

‡‡‡Unadjusted prevalence of diabetes in control practices was 3.3% (SD 0.8%). Characteristics of eligible participants in control practices at baseline: mean age 57.9 (SD 7.8) years; 63.9% men (n = 2641); mean BMI 30.6 (SD 4.6), median diabetes risk score 0.34 (IQR 0.24–0.51); 44.8% prescribed antihypertensive medication (n = 1853); 3.7% prescribed steroids (n = 154).

****The authors reported potential selection bias: “Despite random selection of participants into invitation groups, participants who were offered screening were older at baseline, lived in more deprived areas and included a smaller proportion of men.” However, we did not downgrade this criterion, because in the analysis, the authors adjusted for age, sex and deprivation.

††††52 (45%) of the deaths were recorded as cancer-related, 41 (35%) were due to cardiovascular causes, and 23 (20%) were coded as “other.”

§§§§107 (47%) of the deaths were cancer related, 74 (32%) were due to cardiovascular causes, and 48 (21%) were coded as “other.”

****p = 0.05; adjusted for age, sex and deprivation. For 22 (6%) of those who died (1991–1999), diabetes was included as the underlying cause on the death certificate.

††††††p = 0.05; adjusted for age, sex and deprivation. For 22 (8%) of those who died (2000–2008), diabetes was included as the underlying cause on the death certificate.
were extended using a new effectiveness model that was performed at our request. The new analyses simulated the screening of individuals beginning at age 30, 45 and 60 years of age, at intervals of 1, 3 and 5 years. It also simulated the screening of people with hypertension, considered at higher risk of diabetes. The results of the new model suggest that clinically relevant benefits can be expected when screening individuals at higher risk of diabetes (Appendix 5).

Individuals at higher risk of diabetes generally have other risk factors for cardiovascular disease, such as obesity, inactivity, hypertension and dyslipidemia, all of which are potentially amenable to intervention. Using a validated risk calculator to guide the use of screening with blood tests offers an opportunity to identify and address these other risk factors as well as dysglycemia. In addition, there is evidence that the harms of screening for diabetes are small. In our judgment, these considerations warrant a weak recommendation for screening for type 2 diabetes in adults who are at high risk of diabetes.

No RCTs address the optimal frequency for blood test screening. Evidence from the modelling studies suggests that the health benefits associated with a screening interval of 5 years are similar to those with an interval of 3 years. Screening more frequently than every 3–5 years does not appear to increase benefits further in the general population, yet it leads to substantially increased costs and greater inconvenience to patients.

Data from these modelling studies also suggest that screening adults at high risk (e.g., those who are obese or hypertensive) every 3–5 years leads to reduced rates of myocardial infarction, microvascular complications and death, and preserves nearly all of the benefits of annual screening, but with reduced adverse effects, inconvenience and cost (Appendix 3).

Adults in this category who place a low value on the potential benefits of screening and who are more concerned with the undesirable consequences of unnecessary diagnostic testing and potential overdiagnosis are likely to decline screening.

**Adults at very high risk**

*For adults at very high risk of diabetes (determined with the use of a validated risk calculator), we recommend routine screening annually with A1C. (Weak recommendation, low-quality evidence.)*

Data from 2 modelling studies24,25 (Appendix 4) suggest that there is value to screening patients at very high risk annually to decrease microvascular complications. The potential benefit of screening is magnified and the potential harm of false-positive results reduced among people at highest risk when screening is performed annually. Whether more frequent screening is economically attractive among people at very high risk is uncertain (Appendix 3).

Adults in this category who place a low value on the potential benefits of screening and who are more concerned with the undesirable consequences of unnecessary diagnostic testing and potential overdiagnosis are likely to decline screening.

**Selection of risk calculator**

Type 2 diabetes is caused by a combination of genetic, behavioural and environmental factors.26–27 Because the causes cannot be explained by any single risk factor and the level of risk increases with the number of risk factors, there are a variety of approaches to estimating an individual’s risk of diabetes.

A recent systematic review, rated as being of high methodologic quality, evaluated 94 risk prediction models and scores developed for estimating the risk of type 2 diabetes on the basis of multiple characteristics.28 It identified 7 as being the most promising for adaptation and use in routine clinical practice: the Atherosclerosis Risk in Communities (ARIC) risk calculator, the Australian Diabetes Risk Assessment Tool (AusDrisk), the Cambridge Risk Score, FINDRISC, the Framingham Offspring Study risk score, the San Antonio Heart Study risk score and the QDScore. Preliminary results of a study that used FINDRISC to identify high-risk people showed a reduction in the incidence of type 2 diabetes after 12 months when combining the application of the risk calculator with an educational intervention.29 Also, FINDRISC was found to have been validated in the most countries and studied in relation to patient-important outcomes.

More recently, a cross-sectional screening study30 evaluated the accuracy and discrimination of the Canadian Diabetes Risk Assessment Questionnaire (CANRISK)31,32 for detecting diabetes. CANRISK was not included in the systematic review; however, it was based on FINDRISC, and the authors state the tool may be suitable for assessing diabetes risk in Canada’s multi-ethnic population.33 Thus, we compared FINDRISC and CANRISK in terms of their accuracy and implications for patient-important outcomes (Appendix 6). For FINDRISC, there was evidence of internal and external validation,34 prospective research, test accuracy similar to that of CANRISK and evidence of improved patient-important outcomes in randomized clinical trials.27,28 Although CANRISK includes more items than FINDRISC, it has...
been validated only in a cross-sectional convenience sample of patients\textsuperscript{30,33} and has not yet been studied in clinical practice. Based on these factors, we selected FINDRISC as the preferred validated risk calculator and CANRISK as an acceptable alternative.

**Selection of blood test for screening**
Evidence from a high-quality systematic review\textsuperscript{36} suggests that A1C and glucose measurement perform similarly in predicting type 2 diabetes and related microvascular complications such as retinopathy. We placed more value on the convenience for patients and the use of A1C in addressing variability in glucose levels, and less value on the small risk of interference of severe illness and hemoglobinopathies with A1C measurement in some assays (Appendix 7). An A1C value of 6.5% or greater is recommended as the threshold for diagnosing diabetes. There is insufficient evidence to make a recommendation about management of levels below 6.5%.

**Considerations for implementation**

**Calculating risk in practice**
For the purposes of applying this guideline in practice, either FINDRISC or CANRISK may be used to assess the risk of type 2 diabetes in asymptomatic adults. There is no evidence to guide the optimal frequency of risk calculation. However, on the basis of the evidence for diabetes screening intervals, we suggest risk calculation at least every 3–5 years.

No evidence was found to suggest that recommendations on screening Aboriginal people, people in rural or remote areas, women and elderly people should differ from those for asymptomatic adults in the general population. However, practitioners should be aware that certain ethnic groups (Aboriginal, South Asian, Hispanic and black people) are at increased risk of diabetes and may be at increased risk of poor health outcomes related to diabetes.

**Screening test in practice**
Depending on the clinical context and patient preferences, clinicians may choose A1C, fasting glucose measurement or the oral glucose tolerance test for screening, recognizing that each test may detect a slightly different population of patients with diabetes.\textsuperscript{37} An abnormal A1C or fasting glucose level may warrant repeat testing to confirm diagnosis of diabetes. Approximate costs are S6–S8 for A1C,\textsuperscript{38} S6–S10 for a fasting blood glucose test\textsuperscript{39} and S30 for an oral glucose tolerance test.\textsuperscript{40}

**Patient preference**
Patients place a high value on clear communication about how screening is done, as well as the potential benefits, harms and consequences of screening, including the possibility of diabetes being diagnosed.\textsuperscript{41,42} Regardless of the messaging style, patients accepted an invitation to screen if it was important to them. This suggests that patients who accept screening programs want physicians to identify diabetes and its risk factors (if present); to provide clear information about managing risk factors (if screening is negative); and to advise on how to prevent complications of diabetes (if screening is positive).\textsuperscript{43,44} Risk calculators may provide an avenue to inform patients about risk factors and the importance of early lifestyle interventions for those at high and very high risk of diabetes.

**Patients with prediabetes**
Although the focus of this guideline is on the detection of diabetes to improve patient-important outcomes rather than on prediabetes, documented prediabetes (impaired fasting glucose or impaired glucose tolerance) is important for risk calculation. A diagnosis of prediabetes puts a patient in the category of very high risk of diabetes.

**Role of other health professionals**
The task force’s work is aimed at family physicians. However, diabetes is one area in which other health professionals, such as registered nurses, pharmacists and dietitians, play an important role. The initial stage of screening — risk calculation using FINDRISC or CANRISK — does not result in a diagnosis of diabetes; rather, it identifies people at elevated risk in whom more intensive testing is appropriate. Risk calculation may be performed by other health professionals, in a range of settings. A summary of the guidelines has been prepared for use by family physicians and other health professionals (Appendix 8).

**Management of other cardiovascular risk factors**
Any benefits of screening for type 2 diabetes likely accrue through management of other cardiovascular risk factors as well as dysglycemia. Therefore, consideration should also be given to assessing and managing other cardiovascular risk factors such as obesity, physical inactivity, tobacco use, hypertension and dyslipidemia in individuals with diabetes detected through screening.

**Potential harms of screening**
Screening may lead to overdiagnosis, inappropriate investigation and treatment, avoidable adverse effects, and unnecessary psychosocial and eco-
nomic costs. However, no studies were found that specifically examined these issues in diabetes. Physical harm associated with diabetes screening may be considered negligible, but psychological and social harm could be more substantial. Despite the absence of evidence, clinicians should remain aware of the potential harm resulting from a positive diagnosis of type 2 diabetes.

**Suggested performance measures**

We developed a set of performance measures to accompany the diabetes screening guideline for consideration by policy-makers and clinicians:

- The proportion of adults who are assessed for risk of diabetes using a risk calculator
- The proportion of adults who are screened for diabetes
- The proportion of adults who undergo blood test screening within the recommended interval (every 3–5 years for those at high risk; every year for those at very high risk).

**Other guidelines**

Differences between the current and previous task force recommendations can be attributed to new evidence and new methodology. The previous guidelines recommended screening using fasting glucose measurement among patients with hypertension or hyperlipidemia. The current

<table>
<thead>
<tr>
<th>Table 3: Summary of available recommendations on screening for type 2 diabetes in adults</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Organization</strong></td>
</tr>
</tbody>
</table>
| Canadian Task Force on Preventive Health Care (current) | Use of FINDRISC or validated risk calculator (e.g., CANRISK) to calculate risk of diabetes at least every 3–5 years | • Recommend not routinely screening adults at low to moderate risk  
  • Recommend routinely screening adults at high risk every 3–5 years  
  • Recommend routine screening annually for adults at very high risk | A1C ≥ 6.5% |
| Canadian Task Force on Preventive Health Care (2005) | No recommendation | • Evidence insufficient to recommend for or against routine screening of asymptomatic adults  
  • Recommend screening adults with hypertension and hyperlipidemia | Fasting plasma glucose |
| Canadian Diabetes Association | Annual assessment on the basis of demographic and clinical history | • Recommend routine screening every 3 years for adults starting at age 40 years  
  • Recommend earlier screening or more frequent screening, or both, among people with additional risk factors for diabetes | Fasting plasma glucose ≥ 7.0 mmol/L  
  • Casual plasma glucose ≥ 11.1 mmol/L + symptoms of diabetes  
  • 2-h plasma glucose in 75-g OGTT ≥ 11.1 mmol/L  
  • A1C ≥ 6.5% |
| American Diabetes Association | Measurement of BMI and ≥ 1 additional risk factor for diabetes | • Recommend routine screening every 3 years for adults starting at age 45 years  
  • Recommend routine screening every 3 years for adults who are overweight or obese and have 1 or more additional risk factor for diabetes | A1C ≥ 6.5%  
  • Fasting plasma glucose ≥ 7.0 mmol/L  
  • 2-h plasma glucose in 75-g OGTT ≥ 11.1 mmol/L |
| US Preventive Services Task Force | Blood pressure measurement | • Evidence insufficient to recommend screening for asymptomatic adults with blood pressure of 135/80 mm Hg or lower  
  • Recommend screening every 3 years for asymptomatic adults with sustained blood pressure (either treated or untreated) greater than 135/80 mm Hg | (Same as for American Diabetes Association) |
| UK National Institute for Health and Clinical Excellence | Use of validated risk assessment tool or self-assessment questionnaire, or both; risk reassessed at least every 5 years if at low risk, at least every 3 years if at moderate risk, and at least every year if at high risk | • For adults at moderate to high risk or with possible diabetes, recommend blood test to confirm level of risk; choose either fasting plasma glucose or A1C | Fasting plasma glucose ≥ 7.0 mmol/L  
  • A1C ≥ 6.5% |

Note: A1C = hemoglobin A₁c, BMI = body mass index, CANRISK = Canadian Diabetes Risk Assessment Questionnaire, FINDRISC = Finnish Diabetes Risk Score, OGTT = oral glucose tolerance test.
guidelines recommend starting with risk calculation to identify people at high or very high risk and screening with A1C.

The current recommendations are based on new evidence that supports the use of risk calculators and A1C; new evidence on the lack of benefit associated with screening in people at low or moderate risk; lack of evidence showing that screening reduces mortality in the general population; and new evidence suggesting that screening and treatment are likely to be most beneficial for people at high or very high risk of diabetes. The current recommendations also conclude that (except for people at very high risk) screening more frequently than every 3–5 years.

The current recommendations highlight the limited potential value for screening annual screening with a blood test appears to be screening. Our recommendations highlight the frequency and initial age for screening, the optimal laboratory test for screening in relation to patient outcomes, and the clinically relevant benefits of screening to detect type 2 diabetes in adults at moderate risk of diabetes. No trials evaluated the effect on the incidence of microvascular and macrovascular complications in any population. No data from controlled studies were identified for people at high risk or very high risk of diabetes. Limited data on the potential harms of screening were identified, but no studies were found that specifically examined the effects of overdiagnosis, inappropriate investigation and treatment, avoidable adverse effects, and unnecessary psychosocial and economic costs in diabetes. Observational studies or clinical trials are needed to refine the optimal frequency and initial age for screening, the optimal laboratory test for screening in relation to patient outcomes, and the clinically relevant benefits and harms of treating prediabetes. Researchers conducting these studies should carefully evaluate whether their conclusions are likely to be influenced by the underlying risk of diabetes or preferences of the population studied.

Conclusion

A validated risk calculator should be used to assess the risk of diabetes and guide the use of screening. Our recommendations highlight the lack of evidence to support routine screening with a blood test for type 2 diabetes in adults at low to moderate risk of diabetes. Although annual screening with a blood test appears to be beneficial in adults at very high risk of diabetes, there is limited potential value for screening adults at high risk of diabetes with a blood test more often than every 3–5 years.


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CMAJ
Decisions

Impaired awareness of hypoglycemia in a man with type 1 diabetes

Gilles Plourde MD PhD, Agnes V. Klein MD, Robert Dent MDCM

A 32-year-old man with a 22-year history of type 1 diabetes presented to the diabetes clinic following a loss of consciousness at home the previous evening. The incident, which occurred when the patient was awake, was witnessed by his wife. She administered intramuscular glucagon within minutes. After regaining consciousness, the patient drank some orange juice and then consumed a meal consisting of complex carbohydrates. His blood glucose was not checked at the time of the loss of consciousness, but it was normal after initial treatment with glucagon and orange juice. His diabetes is managed with 38 units of rapid-acting insulin glulisine with each meal and 62 units of long-acting insulin glargine at bedtime. The patient stated that he had not had any recent problems with hypoglycemia. He reported that he measures his blood glucose level at least once a day and that it is “always normal.” He drives a car as part of his job and was injured in a traffic collision within the past year, but he is unable to recall the details of the collision.

What questions should the patient be asked?
Physicians should ask about the frequency and timing of severe hypoglycemia, personal awareness of hypoglycemia, signs of hypoglycemia detected by others and hypoglycemia detected only because of monitoring. Risk factors for impaired awareness of hypoglycemia include age greater than 50 years, infrequent self-monitoring of blood glucose, duration of diabetes longer than 10 years, glycemic control with glycated hemoglobin (HbA1c) less than 7.0% (optimal control: < 7.0%; suboptimal: 7.0%–8.4%; inadequate: > 8.4%) and episodes of hypoglycemia where assistance was required or where there was a loss of consciousness (Box 1).1–6

Clarke’s hypoglycemia awareness questionnaire aims to quantify the degree of impaired awareness of hypoglycemia. Each response is rated as “R” (reduced awareness) or “A” (aware). A patient who provides four or more “R” responses is considered to have impaired awareness of hypoglycemia.

What is the most likely diagnosis?
The patient scored 5 on the Clarke questionnaire, which is consistent with a diagnosis of impaired awareness of hypoglycemia. Hypoglycemia is a risk associated with insulin therapy; impaired awareness has a physiologic basis related to the impact of hypoglycemia on the brain and an impaired response of counter-regulatory mechanisms in the setting of long-standing type 1 diabetes and insulin-treated type 2 diabetes.

In patients with impaired awareness of hypoglycemia, the ability to perceive the onset of hypoglycemia becomes diminished or absent. Symptoms are insidious and include difficulty concentrating, confusion, reduced consciousness, coma or seizures that occur before autonomic activation (tremor, sweating, palpitation and nausea). Impaired awareness is believed to affect about 20%–25% of people with type 1 diabetes and up to 10% of people with insulin-treated type 2 diabetes. The condition increases the risk of severe hypoglycemia by three- to sixfold compared with people with normal awareness. It should be differentiated from “hypoglycemia unawareness,” which suggests a rare but total loss of symptomatic response to low glucose. The differential diagnosis also includes a number of rare conditions, including all of the causes of syncope, with the two broad categories being cardiac and neurologic. The latter includes seizure disorders.

How can awareness of hypoglycemia be restored for this patient?
The key to reversing impaired awareness of hypoglycemia is relaxing glycemic control to avoid episodes of hypoglycemia (Box 1). To achieve this, experts recommend frequent self-monitoring of blood glucose, including preprandial and nocturnal measurements, avoiding blood glucose values less than 4 mmol/L, raising blood glucose targets (e.g., preprandial target 6.0–12 mmol/L and bedtime > 8 mmol/L), preventing an HbA1c level of less than 6.0%, and including regular snacks between meals and at bedtime.14
Helping patients identify subtle cues to their low blood glucose level is also recommended.1–4 Although guidelines from the Canadian Diabetes Association give some recommendations about hypoglycemia and driving,1 this patient requires special consideration for two reasons: part of his job requires that he drive a car, and he has had both a period of unconsciousness and a motor vehicle collision where impaired awareness of hypoglycemia was a plausible explanation.

Case revisited
We recommended that our patient decrease all of his insulin doses by 30% and perform regular self-monitoring of blood glucose at least four times daily (preprandial and at bedtime). Because he was injured in a motor vehicle accident for which impaired awareness of hypoglycemia played a plausible role, we notified the ministry of transportation, who then investigated his suitability for driving, according to provincial law.7

Regular self-monitoring of blood glucose showed frequent asymptomatic hypoglycemia, requiring further reductions in his insulin dose. With our recommended treatment, the patient was able to avoid hypoglycemia completely and to reduce his total daily insulin dose by another 20% over a period of two months. Simultaneously, he began to regain warning symptoms when his blood glucose fell into the hypoglycemic range. He was allowed to drive again with a noncommercial licence, provided that he self-monitor his blood glucose before driving and periodically during every driving exposure.7 He was able to organize a change in his work functions, which permitted him to keep his job.

Box 2 includes resources for both physicians and patients.

References

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Contributors: All authors participated in the planning, writing and revision of the manuscript and approved the final version submitted for publication.

Box 1: Factors in the diagnosis and management of impaired awareness of hypoglycemia1–4

Factors to address during medical history-taking
• Drugs that may increase risk: β-blockers (nonselective), hypnotics, tranquilizers and alcohol
• Social support: fear of hypoglycemia and its impact on other family members (e.g., anxiety)
• Daily routine: insulin administration, eating patterns and exercise
• Blood glucose self-monitoring diary: frequency and distribution of hypoglycemia

Principles of treatment
• Structured patient education should include discussion of the symptoms of hypoglycemia and hypoglycemia avoidance, self-monitoring of blood glucose, the adequate use of insulin and a discussion of management strategies (carbohydrate intake and insulin dose) for exercise training, alcohol intake and the appropriate selection of food for meals and snacks.2
• Strategies to increase compliance to therapy should be emphasized to restore awareness of hypoglycemia and to protect patients from severe hypoglycemia.1,4
• Patients may require psychological counselling to help them modify management of diabetes and to address problems of “low concern” or “denial” regarding hypoglycemia unawareness, which are often seen in these patients.4
• Impaired awareness of hypoglycemia poses a potential risk to safety, not only when patients are driving but also when they are exposed to heights, under water, operating machinery and other activities, and justifies the recommendation to perform self-monitoring of blood glucose in relation to such activities, even if it seems inconvenient.13
• Relatives should be taught about impaired awareness of hypoglycemia and how to administer glucagon (subcutaneous or intramuscular injection).3

Box 2: Resources for physicians and patients
A 60-year-old man with poorly controlled type 2 diabetes mellitus and associated neuropathy presents to his family doctor with a wound on the plantar aspect of his left foot. He has no history of foot ulcers. The ulcerating wound, which has been present for 6 weeks, has recently become purulent and foul smelling. The physician feels underlying bone when probing the ulcer with a sterile instrument. A superficial swab of the wound is performed, from which methicillin-susceptible Staphylococcus aureus and Pseudomonas aeruginosa are isolated. The physician considers the relevant components of the management of this patient’s condition.

Is this patient’s foot ulcer infected?

Not all foot ulcers in patients with diabetes are infected. However, this patient’s history and physical examination are suggestive of a mild to moderate diabetic foot infection (Table 1). At least 2 signs of inflammation (i.e., erythema, warmth, pain, induration or purulence) should be present to diagnose a diabetic foot infection. Factors shown to increase the risk of a diabetic foot infection include a history of diabetic neuropathy, recurrent ulcers or ulceration for more than 30 days, traumatic wound, peripheral vascular disease in the affected limb (e.g., ankle brachial index < 0.9) and renal impairment.1,2

Should another wound culture be done before starting antimicrobial therapy, and if so, how?

This patient is hemodynamically stable with a new diagnosis of a diabetic foot infection. A proper wound culture should be done before antibiotic therapy is started. Swabs of the superficial surface of the ulcer are inadequate and are generally discouraged. Such samples are prone to contamination with commensal and colonizing organisms (such as Pseudomonas species and methicillin-resistant S. aureus) and will often fail to detect the true deep-tissue pathogens. Recent clinical practice guidelines from the Infectious Diseases Society of America recommend culturing deep tissue from biopsy or curettage of the ulcer base after the cleaning and débridement of the wound.1 Clinicians uncomfortable performing débridement should consider referral to a specialist. Purulent collections can be aspirated and provide acceptable samples for culture.1

In some cases, empiric therapy may be started before obtaining culture results and should be directed at typical skin organisms such as S. aureus and streptococci.1 In such cases, careful follow-up is needed to ensure adequate response. Antibiotic agents should be changed to the narrowest spectrum of effective therapy once the culture results are available or if risk factors for other organisms are present (Table 1).1 For this patient, given the acuity of the infection and lack of recent antibiotic exposure, empiric treatment with cloxacillin given intravenously was started pending culture results.

After deep tissue cultures are obtained, what further evaluation is needed?

The duration of recommended antimicrobial therapy is determined by the extent of the infection, specifically whether there is underlying osteomyelitis. In the absence of complication (e.g., abscess or osteomyelitis), treatment for 7–10 days is usually sufficient, although longer courses may be recommended for severe infections.1 In cases of osteomyelitis, treatment is typically for 6 weeks. The ability to probe to underlying bone with a narrow, hard object is highly suggestive of infection with underlying osteomyelitis (positive likelihood ratio 6.4, 95% confidence interval [CI] 3.6–11).3 Despite their frequent use in these settings, both erythrocyte sedimentation rate and C-reactive protein level lack sufficient evidence to justify their use in diagnosing osteomyelitis.1,3 Plain radiographs, although insensitive for osteomyelitis (sensitivity 0.54, 95% CI 0.44–0.63), are appropriate first-line imaging tests and may also show underlying soft-tissue gas or foreign bodies.14 Magnetic resonance imaging (MRI) should be done if radiographs appear normal but suspicion of osteomyelitis remains high, or if there is suspicion of soft-tissue abscess. Combination radionuclide bone scan and labelled leukocyte...
Any new ulcers and prevent future infections has been shown to substantially reduce the rate of subsequent amputations, and its importance cannot be overemphasized.¹

References


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**Table 1:** Classification of severity and microbiological considerations in diabetic foot infection¹²

<table>
<thead>
<tr>
<th>Severity</th>
<th>Characteristics</th>
<th>Common causative pathogens</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mild</strong></td>
<td>Local infection involving epidermis and subcutaneous tissue</td>
<td>Aerobic gram-positive cocci</td>
</tr>
<tr>
<td></td>
<td>Local signs of inflammation in the absence of systemic signs and symptoms</td>
<td></td>
</tr>
<tr>
<td><strong>Moderate</strong></td>
<td>Infection involving tissue deeper than epidermis and subcutaneous tissue</td>
<td>Acute, less extensive: aerobic gram-positive cocci</td>
</tr>
<tr>
<td></td>
<td>Local signs of inflammation with erythema &gt; 2 cm in the absence of systemic signs</td>
<td>Chronic, more extensive: gram-positive and gram-negative organisms, anaerobes</td>
</tr>
<tr>
<td><strong>Severe</strong></td>
<td>Local infection with signs of systemic inflammatory response syndrome*</td>
<td>Gram-positive organisms (including MRSA), gram-negative organisms, anaerobes</td>
</tr>
<tr>
<td></td>
<td>Hemodynamic compromise, metabolic disturbances (severe hyperglycemia, new onset renal insufficiency)</td>
<td></td>
</tr>
</tbody>
</table>

Special considerations

- Exposure to antibiotic agents in the previous 1 mo: Gram-negative bacilli
- Previous history of MRSA infection or colonization within the last year, high local prevalence of MRSA, severe infection or prolonged wound: MRSA
- Frequent exposure to water, high local prevalence, warm climate: *Pseudomonas aeruginosa*

Note: MRSA = methicillin-resistant *Staphylococcus aureus*.

*The presence of more than 2 of the following signs and symptoms: temperature higher than 38°C or lower than 36°C; heart rate faster than 90 beats/min; respiratory rate faster than 20 breaths/min; partial pressure of carbon dioxide less than 32 mm Hg; leukocyte count greater than 12 or less than 4 cells/mL, or more than 10% bands.
Diabetes in an older woman living in a long-term care residence

Daniel M. Tessier MD, Graydon S. Meneilly MD

A 80-year-old woman is seen for a periodic health examination by her family physician. Laboratory test results in her chart show a fasting blood glucose level of 11 mmol/L and a hemoglobin A1C concentration of 9.5%. She has a body mass index of 28. She was diagnosed with type 2 diabetes 10 years earlier, but no formal treatment was started. She has been living in a long-term care residence for the last five years. The decision to move there was made because the patient did not feel secure living at home after an incidental fall. She is dependent for all of her instrumental activities of daily living (e.g., cooking and cleaning) and bathing, and she needs assistance with dressing. Her family has noted progressive cognitive problems over the last two years. The patient gets easily fatigued, walks slowly with a cane and has a low level of physical activity. She has been described as a “frail older person.”

How does the patient’s frailty affect targets for glycemic control?

Frailty is a widely used term for a multidimensional syndrome that gives rise to increased vulnerability.1 Frail older patients with diabetes have a median life expectancy of 23 months.2 Therefore, it is unlikely that these patients will live long enough to obtain the benefits of tight glycemic control. In addition, attempts at tight glucose control in these patients may be associated with hypoglycemia. Blood glucose levels in this group should be controlled well enough to prevent the effects of uncontrolled hyperglycemia, such as polyuria, infections and confusion. Recent guidelines from the Canadian Diabetes Association and other groups recommend that the target in this population should be a fasting or preprandial blood glucose level of 6–11 mmol/L and a hemoglobin A1C concentration of 7.6%−8.5%.3,4 These guidelines are based on consensus among clinicians, and further studies are needed in this patient population to determine appropriate goals. In this patient’s case, it might be reasonable to aim for a fasting blood glucose level of 6–9 mmol/L, a premeal blood glucose level of less than 12 mmol/L and a hemoglobin A1C concentration of 7.6%–8.5%.

Cognitive problems may have an effect on some aspects of diabetes management, such as learning how to measure blood glucose, how to recognize hypoglycemia and how to manage treatment with insulin (if required.) There is growing evidence of an association between type 2 diabetes in older patients and the risk of dementia (vascular and Alzheimer type).5 A longer duration of diabetes is associated with poorer cognitive performance.5 The exact mechanism underlying the association between these two entities is a matter of debate, but vascular lesions and repeated hypoglycemia may be contributing factors. Genetic factors, such as the presence of APOE4, may also be involved.5 The clock-drawing test is a good screening tool for cognitive problems that may affect therapy in patients with diabetes. Because this patient is in a long-term care residence, concerns regarding self-management of diabetes are minimized.

Is the patient a candidate for a nonpharmacologic approach?

Nutritional education programs can improve metabolic control in ambulatory older people with diabetes.3 Dietitians and physicians should

KEY POINTS

- Diabetes in older people is metabolically distinct from diabetes in younger people, and the approach to therapy should be different.
- Insulin secretagogues (e.g., sulfonylureas) should be used selectively because the risk of hypoglycemia increases exponentially with age.
- If cognitive impairment or long-lasting disease is present, clinicians should address the patient’s ability to recognize symptoms of hypoglycemia and adapt the treatment accordingly.
- Long-acting basal insulin analogues are associated with a lower frequency of hypoglycemia than conventional insulin in this age group.
- Choice and dosage of antidiabetic medication should, in most cases, take into account the estimated kidney function.
be cautious about recommending weight loss when frailty is present in patients with type 2 diabetes. A “healthy eating” attitude is more appropriate in many situations. For patients who live in long-term care residences, there is no evidence that “diabetic” diets improve control. For this patient, nutritional intake should meet the daily energy and protein requirements, and malnutrition should be avoided. The intervention of a dietician may be desirable.

Physical training programs cannot be successfully implemented for older people with diabetes, although comorbid conditions may prevent aerobic training. Exercise programs may reduce the risk of falls and improve balance, but it appears to be difficult to maintain these lifestyle changes outside of a supervised setting. For this frail patient, regular walking sessions within the residence should be encouraged.

**What pharmacologic agents could be considered?**

Initial therapy for obese older patients should involve agents that improve insulin resistance, such as metformin. In lean older patients, agents that stimulate insulin secretion may be preferable because the underlying problem is inadequate insulin secretion. However, sulfonylureas (insulin secretagogues) should be used with caution because of the risk of severe hypoglycemia. Gliclazide and glimeperide are preferred over glyburide. Meglitinides (non-sulfonylurea insulin secretagogues, e.g., repaglinide and nateglinide) are associated with a lower frequency of hypoglycemia in older patients compared with glyburide and are preferable for people with irregular eating habits.

Several newer therapies have been evaluated in older patients, although no outcome data are available. Glitazones may be contraindicated in older patients because of an increased incidence of fractures, fluid retention and bladder cancer, and an uncertain impact on cardiovascular outcomes.

Drugs acting on the effects of incretin hormones, such as dipeptidyl peptidase IV inhibitors, are at least as effective in older patients and, when used as monotherapy, are associated with a much lower frequency of hypoglycemia than insulin secretagogues. There are limited data on glucagon-like peptide analogues, such as exenatide and liraglutide. For most of the drugs administered orally to treat diabetes, adjustments to dosing should be made according to the patient’s estimated glomerular filtration rate (eGFR).

Insulin analogues glargine and detemir are associated with a lower frequency of hypoglycemia in older patients than NPH or premixed human insulin. To date, there is no information on the use of glucose absorption inhibitors in older patients.

**Is recognition of hypoglycemia a concern in this older patient?**

The risk of severe or fatal hypoglycemia in response to agents administered orally or insulin increases exponentially with age. Hypoglycemia is associated with falls, fractures, cardiovascular events and a variety of other adverse events. It is one of the most common reasons for emergency admission to hospital for adverse drug events in older patients. Continuous glucose monitoring has shown that asymptomatic hypoglycemia is common and often prolonged in these patients. Hypoglycemia is more likely to develop in patients with dementia and, conversely, severe hypoglycemia later in life can predispose people to dementia. The increased risk of hypoglycemia with increasing age is due to reduced awareness of autonomic warning symptoms, impaired glucagon secretion (the most important counterregulatory hormone) and altered psychomotor performance during hypoglycemia that prevents the patient from taking steps to return the blood glucose level to normal. As noted above, selected oral agents and insulin preparations are associated with a lower frequency of hypoglycemia than other pharmacologic treatments in older patients.

**Case revisited**

The patient had an eGFR of 40 mL/min per 1.73 m². She was given metformin (500 mg orally twice daily) and will stay on this dose. More frequent blood glucose testing was ordered for three weeks, and she will be re-evaluated in one month. After one month, depending on the level of glycemia, there is an option to start a low dose of add low-dose treatment with gliclazide (preferred to glyburide because the patient’s eGFR is less than 50 mL/min per 1.73 m² and there is a lower risk of hypoglycemia with gliclazide) or a dose of dipeptidyl peptidase IV inhibitor adjusted for the GFR. A single daily dose of basal insulin will be a future option depending on the effects of the oral treatment. With the addition of new agents, it is reasonable to increase the frequency of blood glucose testing for a period of time (e.g., daily or twice daily for 7–10 d) and to decrease the frequency when the blood glucose levels are stable.

**References**


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**Decisions** is a series that focuses on practical evidence-based approaches to common presentations in primary care. The articles address key decisions that a clinician may encounter during initial assessment. The information presented can usually be covered in a typical primary care appointment. Articles should be no longer than 650 words, may include one box, figure or table and should begin with a very brief description (75 words or less) of the clinical situation. The decisions addressed should be presented in the form of questions. A box providing helpful resources for the patient or physician is encouraged.
A 60-year-old woman with long-standing poorly controlled type 2 diabetes mellitus was admitted to hospital following 3 weeks of nausea and nocturnal vomiting, and weight loss of 4 kg. On physical examination, she had a soft abdomen and a palpable gallbladder. Abdominal radiography using water-soluble oral contrast medium (Figure 1) showed pooling in the pelvic region. Computed tomography performed immediately after radiography showed massive dilatation of the stomach and gallbladder (Figure 1). There was no radiographic or endoscopic evidence of neoplasm or stenosis. We diagnosed diabetic gastroparesis.

Major gastric dilatation can be seen in many clinical situations, including a range of dysmotility syndromes, neurologic disorders and connective tissue diseases and in association with neoplasm. The most common cause, however, is diabetic gastroparesis, which occurs in up to 50% of patients with long-standing type 1 or 2 diabetes. Diabetic gastroparesis is typically much less extreme than in our patient’s case. Gastric motility studies are the diagnostic gold standard.

Diabetic gastroparesis can be asymptomatic or it may manifest with postprandial fullness, nonspecific epigastric discomfort and weight loss. The pathophysiology is believed to involve some combination of autonomic neuropathy and dysfunction of Cajal pacemaker cells, although hyperglycemia can also delay gastric emptying.

Conservative treatment consists of dietary changes, blood glucose management and the judicious use of promotility agents. Our patient responded well to this approach, but gastrojejunostomy tubes and gastric pacing devices may be helpful in recalcitrant cases.

References
Two key assumptions that underlie clinical practice guidelines for type 2 diabetes have resulted in a vast increase in the number of patients receiving multiple lifelong therapies.

The first assumption is that type 2 diabetes is a progressive, irreversible condition that is diagnosed on the basis of blood glucose level exceeding a single threshold on one of three tests. One of the thresholds is based on observational studies that show that at a fasting glucose level of 7.0 mmol/L the prevalence of retinopathy **begins** to increase. This diagnostic definition does not recognize the continuous relationship between glucose and the risk of complications or the contribution of other factors such as duration of dysglycemia, age, comorbidity, genetics and etiology. For instance, a 57-year-old obese man with hypertension and a fasting glucose level of 15 mmol/L does not recognize the continuous relationship between glucose and the risk of complications or the contribution of other factors such as duration of dysglycemia, age, comorbidity, genetics and etiology.

The second assumption is that therapies that lower glucose levels will benefit all people who receive a diagnosis of type 2 diabetes, and that the benefits are realized only after a specific glucose target is met. Although recent guidelines allow for higher targets in patients with multimorbidity and limited life expectancy, intensive glucose control and a fasting glucose level of 15 mmol/L has a very different prognosis than a healthy 75-year-old woman with a fasting glucose level of 7.1 mmol/L.

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The second assumption is that therapies that lower glucose levels will benefit all people who receive a diagnosis of type 2 diabetes, and that the benefits are realized only after a specific glucose target is met. Although recent guidelines allow for higher targets in patients with multimorbidity and limited life expectancy, intensive glucose control and a glycated hemoglobin (HbA1c) target of 7% or less is recommended for most patients. Evidence shows that the benefit of this approach is modest at best, and the incremental benefits of treatment depend on the baseline glucose level. Data from the United Kingdom Prospective Diabetes Study show that the 10-year complication risk for a 50-year-old white man with an HbA1c of 10% is 12.5%. If this patient achieves an HbA1c of 8%, the risk will be substantially reduced, to 6.6%. Nevertheless, physicians are encouraged (some are even offered financial incentives) to achieve an HbA1c of 7% in their patients, which for this patient, would only further reduce the risk, to 4.9%. Patients whose HbA1c levels remain above the target may face the psychological burden of being considered treatment failures.

To lower their HbA1c level from 8% to 7%, patients are usually required to make more intensive efforts, which include taking more medications (which increases the risk of adverse effects, such as hypoglycemia and weight gain), self-monitoring glucose levels and dealing with increased health care visits.

These assumptions need to be challenged for three reasons. First, although diabetes treatment is essential for many patients to alleviate their symptoms and help them avert complications, some patients are labelled and treated without clear benefit while being exposed to potential harms. Second, the patient-borne financial costs for medication and supplies are substantial, ranging from $1000 to $15 000 per year. Third, the growing number of people who receive diagnoses and treatment for type 2 diabetes is causing an unprecedented burden on health care systems. The annual direct cost of diabetes in Canada is about $12 billion, which accounts for 3.5% of public health care spending.

Why do these assumptions prevail? Overinclusive practice guidelines align with the natural tendency of physician experts to ensure that no patient who could potentially benefit from intervention is missed. We also argue that the pharmaceutical industry reinforces these assumptions to maintain a stable and growing demand for medications.

Although pharmaceutical companies have traditionally focused on marketing specific products, there is an increasing shift toward expanding the definition of treatable products as a way to enlarge the market.

Generously funding the societies that produce guidelines, which we believe may be clever marketing disguised as philanthropy, is a means by which the industry can shape prescribing practices. Further, about 94% of authors of diabetes guidelines have declared pharmaceutical relationships. Although most authors do not explicitly recognize their conflicts of interest, evidence shows that their opinions and practice patterns are nonetheless influenced by these relationships.

We need to think differently about type 2 diabetes. The diagnostic definition and treatment targets should be based on baseline risk of complications, not on specific glucose thresholds, and the benefits of treatment should be considered in the context of potential costs and harms. Because these changes may lead to a reduced number of medications prescribed to fewer people, the societies that develop and authors who write clinical practice guidelines need greater independence from pharmaceutical companies.

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