ONTARIO PHARMACISTS ASSOCIATION
Drug Information & Research Centre

MANITOBA SOCIETY OF PHARMACISTS

Therapeutic Options

FOCUS ON DIABETES MELLITUS

The estimated prevalence of diabetes in Canada was 6.8 per cent of the population (2.4 million people) in 2009.[1] Today, more than nine million Canadians have diabetes or prediabetes.[2] These statistics, together with the devastating outcomes associated with diabetes (e.g., cardiovascular mortality, end-stage renal disease, blindness, and amputations[1]), underscore the importance of aggressive disease management.

Recently, the Canadian Diabetes Association (CDA) published its 2013 Clinical Practice Guidelines for the Prevention and Management of Diabetes in Canada.[1] Ultimately, it is hoped that the guidelines will improve quality of care, reduce morbidity and mortality, and lead to better quality of life for people living with diabetes.[1] This article provides a synopsis of the CDA's evidence-based recommendations, with a focus on some of the most important ones relating to drug therapy. It is noteworthy that many recommendations have been omitted due to space constraints, as have the grade/level of evidence associated with the recommendations, and readers are urged to review the full-text guidelines[1] (see References, below, for URL) for details.

MANAGEMENT OF DIABETES

Glycemic Targets

Optimal glycemic control is of paramount importance in diabetes management to help reduce the risk of complications.[1] Most individuals with diabetes should aim to achieve a glycated hemoglobin (A1C) value ≤7.0%, although targets should be individualized[1] (see Table 1). The following plasma glucose

Table 1. Individualized targets for glycemic control[1]

A1C target	Appropriate patient population	Comments
≤7.0%	Most individuals with type 1 or type 2 diabetes	Target provides strong benefits with respect to microvascular complications; might provide significant macrovascular benefits if target achieved early in the course of disease
≤6.5 %	Some patients with type 2 diabetes (e.g., those with a shorter duration of diabetes, no evidence of significant CVD, and longer life expectancy)	Target further lowers the risk of nephropathy and retinopathy, but increases the risk of hypoglycemia
7.1%–8.5%[a]	Patients with type 1 or type 2 diabetes with limited life expectancy, high level of functional dependency, extensive CAD, multiple comorbidities, history of recurrent severe hypoglycemia, hypoglycemia unawareness, or failure to attain established glycemic targets despite treatment intensification[b]	Target balances benefits of lowering glycemia with risks associated with hypoglycemia in higher-risk individuals

A1C = glycated hemoglobin; CAD = coronary artery disease; CVD = cardiovascular disease
a. Higher targets may be appropriate for some individuals.
b. Defined as effective doses of multiple antihyperglycemic agents, including intensified basal-bolus insulin therapy.[1]

targets are recommended to achieve an A1C ≤7.0%:

- fasting plasma glucose or preprandial plasma glucose: 4.0–7.0 mmol/L; and
- two-hour postprandial plasma glucose (PPG): 5.0–10.0 mmol/L.*[1]

Recommendations related to the appropriate frequency of glycemic monitoring are available in the Monitoring Glycemic Control section and Appendix 4 of the full-text guidelines[1] (see References, below, for URL).

Pharmacotherapy – Type 1 Diabetes

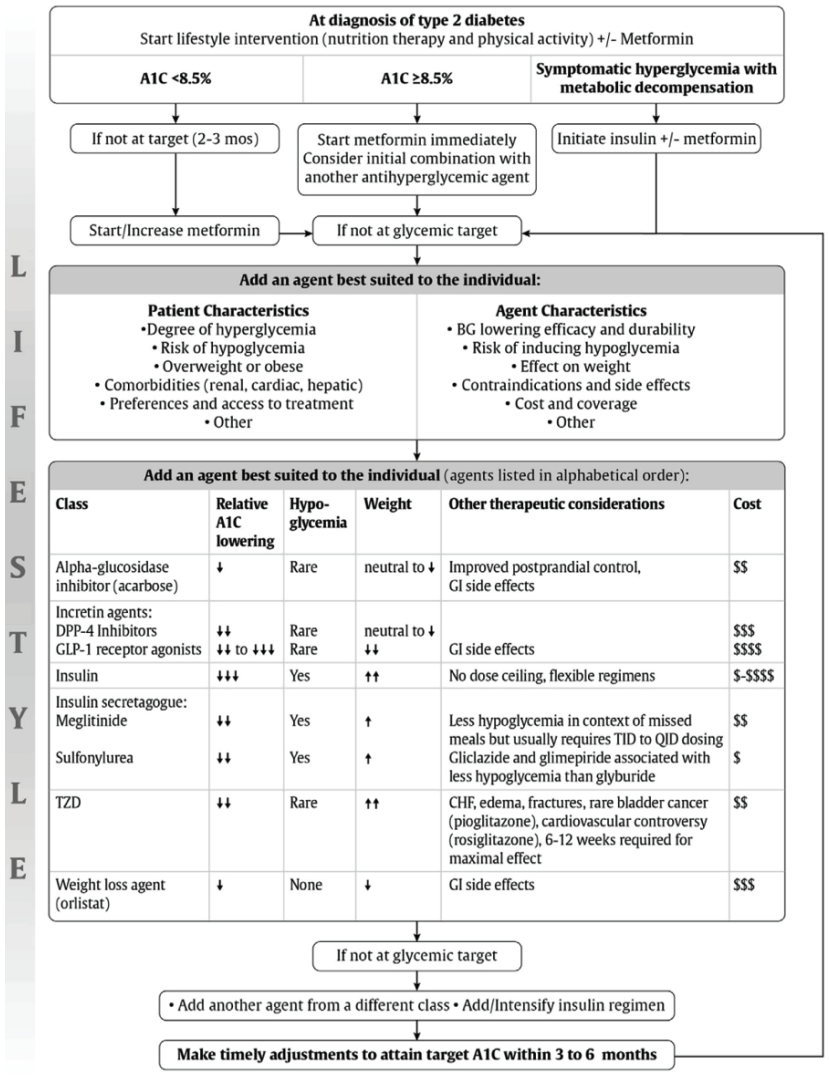
In people with type 1 diabetes, insulin remains the cornersvtone of treatment.[1] Basal-bolus insulin regimens (multiple daily injections) or continuous subcutaneous insulin infusion should be used to achieve glycemic targets.[1] The guidelines recommend rapid-acting insulin analogues (e.g., insulin aspart, insulin glulisine, insulin lispro), in combination with adequate basal insulin, in preference to short-acting regular insulin to minimize the risk of hypoglycemia and improve glycemic control.[1] The guidelines also note that long-acting insulin analogues (e.g., insulin detemir, insulin glargine) may be used as basal insulins to reduce the incidence of hypoglycemia (including nocturnal hypoglycemia) as compared with intermediate-acting NPH insulin.[1]

A summary of the time-action profiles of the insulin products available in Canada is provided in the Pharmacotherapy in Type 1 Diabetes section of the full-text guidelines[1] (see References, below, for URL).

Pharmacotherapy – Type 2 Diabetes

In people with type 2 diabetes, pharmacotherapy is typically initiated with one or more† oral antihyperglycemic agents. As the disease progresses, many patients ultimately require insulin as primary therapy, with or without oral agents.‡ The overall approach to treatment is outlined in Figure 1.

Figure 1. Management of hyperglycemia in type 2 diabetes



A1C = glycated hemoglobin; CHF = congestive heart failure; DPP-4 = dipeptidyl peptidase 4; GI = gastrointestinal; GLP-1 = glucagon-like peptide 1; TZD = thiazolidinedione

Refer to the most recent edition of the Compendium of Pharmaceuticals and Specialties (Canadian Pharmacists Association, Ottawa, Ontario, Canada) for product monographs and for detailed prescribing information.

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Metformin is the initial drug of choice unless contraindicated.[1,3] Additional antihyperglycemic agents should be chosen based on factors listed in Figure 1 and Table 2.

The guidelines explicitly state that when combining antihyperglycemic agents, classes of agents with different mechanisms of action should be used.[1] They also point out that combining agents in the same class, or that have similar mechanisms of action (e.g., sulfonylureas and meglitinides, or dipeptidyl peptidase-4 inhibitors and glucagon-like peptide-1 agonists), is not recommended due to a lack of evidence and the potential for reduced effectiveness.[1]

* If an A1C ≤7.0% cannot be attained with a PPG of 5.0–10.0 mmol/L, PPG lowering to 5.0–8.0 mmol/L should be achieved.[1]

† Initial use of combinations of antihyperglycemic agents at submaximal doses produces more rapid and improved glycemic control with fewer side effects than monotherapy at maximal doses.[1]

‡ Metformin is generally continued with insulin therapy, including intensive basal-bolus regimens, to improve glycemic control and decrease the risk of weight gain/hypoglycemia. Conversely, secretagogues are usually discontinued when rapid- or short-acting insulin is started.[1]

Table 2. Some therapeutic considerations regarding antihyperglycemic agents[1]

Class/agent(s)	Expected A1C ↓[a]	Other therapeutic considerations[b]
Alpha-glucosidase inhibitor (acarbose)	0.6%	• Not recommended as initial therapy in people with marked hyperglycemia (A1C ≥8.5%)
DPP-4 inhibitors (linagliptin, saxagliptin, sitagliptin)	0.7%	• Improved postprandial control • Rare cases of pancreatitis
GLP-1 receptor agonists (exenatide, liraglutide)	1.0%	• Improved postprandial control; significant weight loss • Parenteral administration • Rare cases of pancreatitis
Insulin (various[c])	0.9–1.1%	• May result in greatest A1C reduction • When starting, consider adding a single bedtime dose of basal insulin[d] to oral antihyperglycemic agents; escalate to a basal-bolus[e] regimen as necessary to attain glycemic targets[f] • Insulin products are associated with significant risk of hypoglycemia; risk its highest with regular and NPH insulin
Insulin secretagogues **Meglitinides** (nateglinide, repaglinide) **Sulfonylureas** (gliclazide, glimepiride, glyburide)[g]	0.7%[h] 0.8%	• Relatively rapid blood glucose-lowering effects • Meglitinides particularly reduce postprandial glycemia • Consider using classes other than secretagogues first in patients at high risk of hypoglycemia (e.g., the elderly, those with renal/hepatic failure); meglitinides have a lower risk of hypoglycemia than sulfonylureas (meglitinides have a shorter duration of action, allowing them to be held when skipping a meal); gliclazide has the lowest incidence of hypoglycemia among sulfonylureas
Metformin	1.0–1.5%	• Associated with improved cardiovascular outcomes in overweight subjects • Weight neutral as monotherapy; promotes less weight gain when combined with other antihyperglycemic agents • Contraindicated if CrCl or eGFR is <30 mL/min (caution if <60 mL/min) or in the presence of hepatic failure; associated with GI side effects
TZD (pioglitazone, rosiglitazone)	0.8%	• Contraindicated in patients with clinical heart failure or evidence of LVD • Associated with higher rates of heart failure when combined with insulin (this combination is not an approved indication in Canada) • Clinical utility of drug class significantly limited by possible safety/tolerability issues
Weight loss agent (orlistat)	0.5%	• Promotes weight loss • Associated with GI side effects, including diarrhea

A1C = glycated hemoglobin; CrCl = creatinine clearance; DPP-4 = dipeptidyl peptidase 4; eGFR = estimated glomerular filtration rate; GI = gastrointestinal; GLP-1 = glucagon-like peptide 1; LVD = left ventricular dysfunction; TZD = thiazolidinedione

a. Except for metformin, values listed are reductions expected when an agent from the class is added to metformin.[1]
b. For guidance on drug selection based on renal function, refer to Figure 2 on page S65 of the full-text guidelines[1] (see References, below, for URL).
c. For a listing of the insulin products available and their time-action profiles, refer to pages S57 and S62 of the full-text guidelines[1] (see References, below, for URL).
d. Long-acting analogues (detemir, glargine) reduce the risk of nocturnal and symptomatic hypoglycemia compared with NPH insulin.[1]
e. Rapid-acting analogues (aspart, glulisine, lispro) may improve glycemic control and reduce the risk of hypoglycemia compared with regular insulin.[1]
f. For additional details on initiating/titrating insulin in patients with type 2 diabetes, refer to Appendix 3 of the full-text guidelines[1] (see References, below, for URL).
g. Chlorpropamide and tolbutamide are still available in Canada, but are rarely used.[1]
h. Nateglinide is less effective than other secretagogues.[1]

MACROVASCULAR AND MICROVASCULAR COMPLICATIONS

Macrovascular complications of diabetes include coronary artery disease, cerebrovascular disease, and peripheral vascular disease; microvascular complications include retinopathy, nephropathy, and neuropathy.[1] In order to prevent and manage these complications, a number of pharmacotherapeutic interventions may be employed, as outlined in Table 3. Such interventions should be used in conjunction with health behaviour modifications aimed at reducing cardiovascular risk (e.g., achievement and maintenance of a healthy body weight, healthy eating habits, regular physical activity,§ smoking cessation).[1]

§ Recommendations related to physical activity, nutrition therapy, and weight management are available in the full-text guidelines[1] (see References, below, for URL).

Table 3. Some interventions for prevention/management of diabetes complications[1]

Indication	Intervention	Treatment parameter/ target	Recommended population
Vascular protection/ CV risk reduction	Statin	LDL-C ≤2.0 mmol/L	Adults with type 1 or type 2 diabetes ***and*** (1) clinical macrovascular disease ***or*** (2) age ≥40 years ***or*** (3) age <40 years meeting one of the following criteria: diabetes duration >15 years and age >30 years; microvascular complications; indication for therapy according CCS guidelines[a]
	ACE inhibitor or ARB[b]	NA	Adults with type 1 or type 2 diabetes ***and*** (1) clinical macrovascular disease ***or*** (2) age ≥55 years ***or*** (3) age <55 years and microvascular complications
	ASA[c]	NA	May be used in people with established CVD for secondary prevention;[d] may also be used in people without established CVD but with CV risk factors in addition to diabetes
	Clopidogrel[e]	NA	May be used in patients who cannot tolerate ASA (see above)
Dyslipidemia	Statin[f]	LDL-C ≤2.0 mmol/L	See recommended population for statins above[g]
	Second-line lipid-lowering agents[h]	LDL-C ≤2.0 mmol/L	May be used in combination with a statin to achieve the LDL-C goal when maximum tolerated doses of statin monotherapy fail to achieve the goal[i]
	Fibrate	NA[j]	Patients with serum triglyceride level >10.0 mmol/L (to reduce the risk of pancreatitis)
Hypertension	Antihypertensive agents[k]	SBP <130 mm Hg ***and*** DBP <80 mm Hg	All persons with diabetes and blood pressure levels above targets
CKD[l]	ACE inhibitor or ARB[m]	NA	Adults with diabetes and CKD with either hypertension or albuminuria (to delay progression of CKD)

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; ASA = acetylsalicylic acid; CCS = Canadian Cardiovascular Society; CKD = chronic kidney disease; CV = cardiovascular; CVD = cardiovascular disease; DBP = diastolic blood pressure; LDL-C = low-density lipoprotein-cholesterol; NA = not applicable; SBP = systolic blood pressure

a. Refer to the 2012 update of the Canadian Cardiovascular Society guidelines for the diagnosis and treatment of dyslipidemia for the prevention of cardiovascular disease in the adult[4] for details (see References, below, for URL).
b. At doses that have demonstrated vascular protection (e.g., ramipril 10 mg daily, telmisartan 80 mg daily).[1]
c. Low dose (81–325 mg/day).[1]
d. ASA should not be routinely used for the primary prevention of CVD in people with diabetes.[1]
e. 75 mg/day.[1]
f. Statins are first-line agents to achieve the LDL-C target.[1]
g. Fibrates or niacin should not be added for the sole purpose of further reducing CV risk in patients achieving the LDL-C goal with statin therapy.[1]
h. For example, ezetimibe, bile acid sequestrants, or niacin.[1] For a listing of non-statin lipid-modifying medications and considerations for their use, refer to Table 2B, page S113 of the full-text guidelines[1] (see References, below, for URL).
i. May also be considered in cases of statin intolerance.[1]
j. Specific triglyceride targets are not provided in the CDA guidelines; however, a level <1.5 mmol/L is listed as "optimal".[1]
k. An ACE inhibitor or ARB is recommended as initial therapy in patients with CVD or kidney disease, or with CV risk factors, in addition to diabetes and hypertension. In patients with diabetes and hypertension without the aforementioned conditions, appropriate choices include (in alphabetical order): ACE inhibitors, ARBs, dihydropyridine calcium channel blockers, and thiazide/thiazide-like diuretics. For all patients, combination therapy should be used when standard dose monotherapy fails to meet blood pressure targets. Where combination therapy with an ACE inhibitor is being considered, a dihydropyridine calcium channel blocker is preferable to hydrochlorothiazide.[1]
l. Diagnosed based on the following criteria: a random urine albumin-to-creatinine ratio ≥2.0 mg/mmol and/or an estimated glomerular filtration rate <60 mL/min on at least 2 of 3 samples over a three-month period.[1]
m. Combinations of agents that block the renin-angiotensin-aldosterone system (e.g., ACE inhibitors, ARBs, direct renin inhibitors) should not be routinely used in patients with diabetes and CKD.[1]

References

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