Achieving Glycemic Control in Type 2 Diabetes

Centre for Effective Practice

Adapted from Canadian Diabetes Association 2008 Clinical Practice Guidelines and Updates

Table 1: Diagnostic criteria for diabetes

- **FPG ≥ 7.0 mmol/L***;
  OR
- **Random† PG ≥ 11.1 mmol/L + symptoms‡ of DM;**
  OR
- **2hPG in a 75-g OGTT ≥ 11.1 mmol/L;**
  OR
- **A1C ≥ 6.5%**

(using a standardized, validated assay, in the absence of conditions that affect the A1C)

- A repeat confirmatory laboratory test must be done in all cases on another day in the absence of unequivocal hyperglycemia accompanied by acute metabolic decompensation. (e.g., weight loss, polyuria, ketosis)
- It is preferable that the same test be repeated for confirmation.

* = fasting—no caloric intake for at least 8 hours;
† = random—anytime of the day, without regard to the interval since the last meal;
‡ = classic symptoms of diabetes: polyuria, polydipsia and unexplained weight loss;
Blue = hyperlinked text

Table 2: Management of type 2 diabetes

Lifestyle intervention (initiation of nutrition therapy and physical activity)

A1C < 9.0%	A1C ≥ 9.0%	Symptomatic hyperglycemia with metabolic decompensation
• Initiate **metformin**	• Initiate pharmacotherapy immediately • Consider initiating **metformin** concurrently with another agent from a different class; or initiate **insulin**	• Initiate **insulin** and/or **metformin**

Target: 1. A1C < 7.0% and/or
2. Preprandial PG: 4.0–7.0 mmol/L and/or
3. 2h-Postprandial PG: 5–10 mmol/L (5.0–8.0 mmol/L if A1C not at target)

Targets must be tailored to the individual's risk factors (age, comorbidities, prognosis, duration of diabetes, risk of hypoglycemia, etc.).

If not at target: 1. Add another drug from a different class based on **Tables 3** and **5**; OR
2. Add bedtime basal insulin to other agents (see **Table 4**); OR
3. Intensify insulin regimen

Adjustments should be made to attain target A1C within 6–12 months.

Table 3: Advantages and disadvantages of anti-hyperglycemics

(see **Table 5** for more details)

Class	A1C (%)↓	Hypoglycemia	Wt	Other advantages	Other disadvantages
Alpha-glucosidase inhibitor (acarbose)	0.5–0.8	Rare	– /↓	Improved postprandial control	GI intolerance, flatulence, diarrhea; frequent dosing
Biguanides (metformin)	1–1.5	Rare	↓	↓ all cause mortality	GI intolerance; stop prior to dye or surgery; stop when renal function declines
Dipeptidyl Peptidase (DPP)-4 inhibitors (linagliptin, saxagliptin, sitagliptin)	0.5–1.0	Rare	– /↓	Improved postprandial control	Urticarial/angioedema (rare); pancreatitis (rare); long-term safety unknown
Glucagon-like Peptide (GLP)-1 receptor agonists (exenatide, liraglutide)	1.0	Rare	↓	Potential for improved β-cell mass/function	SC injection; GI side effects; acute pancreatitis (rare); long-term safety unknown; (C-cell/thyroid tumors in animals)
Insulin	> 2	Yes	↑	No dose ceiling; many types; flexible regimen	SC injection(s); requires SMBG
Insulin secretagogues - Meglitinides (nateglinide, repaglinide) - Sulfonylureas (gliclazide, glimepiride, glyburide)	0.5–1.5 1–1.5	Yes Yes	– /↑ ↑	Improved postprandial control - Meglitinides good for people who skip meals	Meglitinides require tid-qid dosing
Thiazolidinediones (TZDs) (pioglitazone, rosiglitazone)	1–1.5	Rare	↑	HDL cholesterol ↑, Triglycerides ↓	6–12 weeks for maximum effect; edema, risk of HF, contraindicated in HF; risk of cardiac ischemia (rosiglitazone); risk of bladder cancer (pioglitazone); fractures (rare); **Patient Consent** required for rosiglitazone
Weight loss agent (orlistat)	< 1.0	None	↓	Non-systemic drug	GI side effects

2hPG = 2-hour plasma glucose; **CV** = cardiovascular; **DM** = diabetes mellitus; **FPG** = fasting plasma glucose; **HF** = heart failure; **OGTT** = oral glucose tolerance test; **PG** = plasma glucose; **SC** = subcutaneous; **SMBG** = self-monitoring of blood glucose; **wt** = weight; **–** = weight neutral; **tid** = three times daily; **qid** = four times daily; Blue = hyperlinked text
Treatment of Hypoglycemia (BS < 4 mmol/L)—Patient Handout http://www.diabetes.ca/documents/about-diabetes/Lows_and_Highs_7.pdf

Table 4: Insulin

If targets not reached or if initial A1C ≥9%, consider insulin. For information on initiating and titrating insulin, see Canadian Diabetes Association 2008 Guidelines—Appendix 3 and the Ontario College of Family Physicians—Insulin Prescription.

Insulin Types (Classified by Duration)		Comments	
Basal	Intermediate-acting: Humulin-N®, Novolin® ge NPHLong-acting: Lantus®, Levemir®	• Usually given at bedtime in addition to oral medications • Can start 10 units hs and titrate by 1 unit/day until fasting blood glucose < 7 mmol/L	• Patients must be able to monitor blood glucose and recognize hypoglycemia • Combinations increase risk of hypoglycemia • Adding insulin to other hypoglycemic medication(s) is an area of controversy - Only metformin, acarbose and glimepiride have Health Canada approval with insulin - Usual care is to: - Stop TZDs - Continue all other agents when patient is only on a basal insulin - Stop all other agents except for metformin with bolus/mixed insulin
Bolus (Prandial)	Short-acting: Humulin® R, Novolin® ge Toronto Rapid-acting: Apidra®, Humalog®, NovoRapid®	• Given before meals (short: 30 minutes before meals; rapid: immediately before meals)	
Bolus/Basal Pre-mixed	Humalog® Mix 25, 50, Humulin® 30/70, Novolin® ge 30/70, 40/60, 50/50, NovoMix® 30	• First/only number refers to proportion of bolus insulin • Given before meals according to bolus component; avoid at bedtime	

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Table 5: Dosing, drug cost, and ODB coverage for non-insulin pharmacotherapy for type 2 diabetes

Agent, Available Dose	Initial Dose ^	Average Dose ^ (Max. Daily Dose)	Renal Dosing (CrCl expressed in mL/min)	Drug Cost* ($/30 Days)	ODB Coverage	Comments
Alpha-Glucosidase Inhibitor						
Acarbose (Glucobay®) 50 mg, 100 mg	25–50 mg daily	50–100 mg tid (300 mg)	**CrCl < 30:** use caution	$24–$33	LU 175, 176	• Titrate up every 1–2 weeks until 50 mg tid to avoid GI side effects; then every 4–8 weeks • Maximum effect may take weeks • Take with first bite of meal
Biguanides						
Metformin (Glucophage®, generics) 500 mg, 850 mg	250–500 mg daily	500–1000 mg bid or 850 mg tid (2550 mg)	**CrCl 30–60:** use caution **CrCl < 30:** contraindicated	$4–$7 $20	✓ (500 mg) × (850 mg)	• Titrate up every 1–2 weeks to avoid GI side effects • Fewer GI side effects with ER formulation • 85% of maximum glucose lowering seen at 1500 mg/day
Metformin ER (Glumetza®) 500 mg, 1000 mg	500 mg daily	1000–2000 mg daily (2500 mg)		$36–$71	×	
Dipeptidyl Peptidase (DPP)-4 Inhibitors						
Linagliptin (Trajenta®) 5 mg	5 mg daily	5 mg daily (5 mg)	**CrCl < 30:** avoid	$81	×	• Linagliptin and sitagliptin have official triple indication with metformin and sulfonylurea
Saxagliptin (Onglyza®) 2.5 mg, 5 mg	5 mg daily	5 mg daily (5 mg)	**CrCl < 60:** 2.5 mg daily	$87	× (2.5 mg) ✓ (5 mg)	
Sitagliptin (Januvia®) 100 mg	100 mg daily	100 mg daily (100 mg)	**CrCl 30–60:** 50 mg daily **CrCl < 30:** 25 mg daily	$84	✓	
Glucagon-like Peptide-1 (GLP-1) Receptor Agonists						
Exenatide (Byetta®) Prefilled pens: 1.2 mL (5 mcg/dose), 2.4 mL (10 mcg/dose)	5 mcg SC bid	5–10 mcg SC bid (20 mcg)	**CrCl < 30:** avoid	$145	×	• Administer within 60 minutes before meal (not after) • Titrate to reduce GI side effects; ↑ after 3–4 weeks • If no response after 3–4 months, consider alternatives
Liraglutide (Victoza®) Multidose pen: 6 mg/mL (3 mL)	0.6 mg SC daily	1.2–1.8 mg SC daily (1.8 mg)	**CrCl < 30:** avoid	$155–$232	×	• Administer without regard for meals • Titrate up after ≥ 1 week to reduce GI symptoms
Insulin Secretagogues – Meglitinides						
Nateglinide (Starlix®) 60 mg, 120 mg	60 mg tid	60–180 mg tid (540 mg)	**CrCl 15–60:** use caution **CrCl < 15:** avoid	$52–$104	×	• Dose given within 30 minutes of meal (not taken if meal skipped) • Greater A1C lowering with repaglinide
Repaglinide (GlucoNorm®, generics) 0.5 mg, 1 mg, 2 mg	0.5 mg tid	0.5–4 mg tid (16 mg)		$20–$46	EAP	
Insulin Secretagogues – Sulfonylureas						
Gliclazide (Diamicron®, generics) 80 mg	40–80 mg bid	80–160 mg bid (320 mg)		$6–$11	✓	• Titrate up every 1–2 weeks when initiating • Risk of hypoglycemia: gliclazide < glimepiride < glyburide • Best administered 15–30 minutes before meals • If CrCL < 30 mL/min, gliclazide is preferred • Chlorpropamide and tolbutamide (first generation) are still available in Canada but rarely used; neither are ODB benefits
Gliclazide (Diamicron MR®, generics) 30 mg, 60 mg	30 mg daily	30–120 mg daily (120 mg)		$4–$15	✓	
Glimepiride (Amaryl®, generics) 1 mg, 2 mg, 4 mg	1 mg daily	1–4 mg daily (8 mg)		$16	×	
Glyburide (Diabeta®, generics) 2.5 mg, 5 mg	1.25 – 2.5 mg daily	5 mg daily–10 mg bid (20 mg)	**CrCl 30–60:** use caution **CrCl < 30:** avoid	$2–$7	✓	
Thiazolidinediones (TZDs)						
Pioglitazone (Actos®, generics) 15 mg, 30 mg, 45 mg	15 mg daily	15–45 mg daily (45 mg)		$50–$105	EAP	• Risk of heart failure, which may be higher if combined with insulin (combination not approved in Canada) • Rosiglitazone may cause cardiac ischemia. **Health Canada Restrictions**: rosiglitazone only to be used when all other oral agents have been tried alone or together and targets not reached
Rosiglitazone (Avandia®) 2 mg, 4 mg, 8 mg	4 mg daily	2–8 mg daily (8 mg)		$44–$98	EAP	
Combination Products						
Avandamet® (rosiglitazone/metformin) 1/500, 2/1000, 4/500, 4/1000 mg	Refer to individual components			$41–$139	×	• Refer to individual components
Janumet® (sitagliptin/metformin) 50/500, 50/850, 50/1000 mg	Refer to individual components			$96	✓	

✓ = general benefit on ODB; **x** = not a benefit; **Max** = maximum; **CrCl** = creatinine clearance; **ODB** = Ontario Drug Benefit; **tid** = three times daily; **bid** = twice daily; **EAP** = Exceptional Access Program; **ER** = extended release; **GI** = gastrointestinal; **LU** = limited use; **MR** = modified release; **SC** = subcutaneous; Blue = hyperlinked text

^ Oral administration unless otherwise noted; * Prices reflect ODB or wholesale cost for generic product where available (January 2012).

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Supplementary Information to Table 5

Acarbose–Limited Use

LU 175 For the treatment of non-insulin-dependent diabetes mellitus (NIDDM) in patients who cannot tolerate or have failed treatment with other oral hypoglycemic agents or in whom other oral hypoglycemic agents are contraindicated. Indefinite authorization.

LU 176 For the treatment of NIDDM in patients who require combination therapy with more than one oral hypoglycemic agent to control their serum glucose concentrations. Indefinite authorization.

https://www.healthinfo.moh.gov.on.ca/formulary/SearchServlet?searchType=luNoteQuery&phrase=exact&keywords=682002012

Repaglinide–EAP

Coverage for **repaglinide** can be requested for a period of 5 years for the treatment of type 2 diabetes in patients with:

- Inadequate glycemic control (A1C > 7%) using maximal doses of a sulfonylurea* AND metformin*, OR on maximal dose of one and demonstrated contraindication, or intolerance to the other; OR
- Demonstrated intolerance or contraindication to both a sulfonylurea AND metformin; OR
- Adequate glycemic control (A1C ≤ 7%) who develop intolerance or a contraindication to sulfonylurea or metformin; OR
- A1C ≤ 7% but with greater than 50% of fasting blood glucose (FBG) or post-prandial glucose (PPG) levels not at target (FBG > 7 mmol/L, PPG > 10 mmol/L), and using maximally tolerated doses of a sulfonylurea and metformin

Pioglitazone–EAP

Coverage for **pioglitazone** can be requested through the EAP for a period of 5 years for type 2 diabetes:

- Dual combination therapy in patients with inadequate glycemic control (A1C > 7%) on maximal doses of metformin* or a sulfonylurea*, and with demonstrated intolerance/contraindication to metformin; OR
- Triple combination therapy in patients with inadequate glycemic control on maximal doses of metformin* and a sulfonylurea*, AND only if the physician has offered insulin as alternative option first, and patient has refused or is not able to take insulin, AND both physician and patient are aware that thiazolidinediones are not indicated for use in triple therapy
- Pioglitazone will NOT be covered for those with type 1 diabetes, as monotherapy (even if patient is intolerant or has contraindications to both metformin and sulfonylureas), in combination use with either nitrates or insulin, in patients with any stage of heart failure, in patients at high risk for bone fracture (post-menopausal women with previously confirmed osteoporosis or osteopenia), or in patients with recent history (in the past 3 months) of ischemic cardiovascular event (myocardial infarction, unstable angina)
- Renewals as well as requests for ongoing treatment in patients previously provided these drugs by other means will be considered for those patients who have not developed a contraindication or precaution for its use in the intervening period AND have demonstrated a recent HbA1C level ≤ 7% while on treatment

Rosiglitazone–EAP

Coverage for **rosiglitazone** can be requested for a period of 5 years for the treatment of type 2 diabetes in patients with:

- Inadequate glycemic control (A1C > 7%) from ALL other oral antidiabetic agents funded through one of the Ontario Drug Benefit Programs (e.g., LU or EAP) except acarbose, in monotherapy or in combination OR
- Where ALL other oral antidiabetic agents are inappropriate due to contraindications or intolerance, AND the patient has refused or is not able to take insulin, AND there is no known contraindication to rosiglitazone
- Renewals will be considered where patients have benefited and continue to benefit from rosiglitazone treatment as demonstrated by recent A1C levels ≤ 7% while on treatment with rosiglitazone AND in those who continue to have no known contraindication(s) to rosiglitazone

http://www.health.gov.on.ca/english/providers/program/drugs/pdf/frequently_requested_drugs.pdf

* For the purpose of EAP approval, maximal doses are metformin 2000 mg/day, glyburide 10 mg/day, gliclazide 160 mg/day, Diamicron MR® 60 mg/day or glimepiride 4 mg/day.

References and Resources

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Health Canada–Advisories and Warnings (Rosiglitazone/Avandia®) http://www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/prof/_2010/avandia_6_hpc-cps-eng.php

Ontario College of Family Physicians' Insulin Prescription http://www.ocfp.on.ca/docs/current-issues/insulin-titration---insulin-prescription.pdf?sfvrsn=1

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