CEP | Providers

Type 2 diabetes: Non-insulin pharmacotherapy

This tool is designed to support family physicians and primary care nurse practitioners to prescribe and manage non-insulin pharmacotherapy for adult patients living with type 2 diabetes. This is an update of the original Achieving glycemic control in type 2 diabetes tool, released in 2012.

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SECTION A: Individualizing targets

Diagnostic criteria for diabetes[1]

Fasting plasma glucose (FPG) ≥7.0 mmol/L*

OR

A1C ≥6.5%†

OR

2-hour plasma glucose (2hPG) in a 75g **oral glucose tolerance test** (OGTT) ≥11.1 mmol/L

OR

Random‡ **plasma glucose** (PG) ≥11.1 mmol/L

- The decision of which test to use for diabetes diagnosis is left to clinical judgment
- Each diagnostic test has advantages and disadvantages[2]

Diagnosis of diabetes is confirmed if:

- Symptomatic hyperglycemia is present (therefore confirmatory tests are not required)

OR

- The results of two laboratory tests are in the diabetes range (in the absence of symptomatic hyperglycemia)
  - The second confirmatory laboratory test must be done on another day, and it is preferable that the same test be repeated for confirmation (in a timely fashion, based on clinical judgment), with the exception of random PG

Factors that affect A1C:

- Factors that can increase A1C: iron deficiency, B12 deficiency, ↓ erythropoiesis, alcoholism, chronic renal failure, splenectomy
- Factors that can decrease A1C: use of erythropoietin, iron or B12, reticulocytosis, chronic liver disease, ingestion of acetylsalicylic acid, vitamin C/E, decreased erythrocyte lifespan (e.g., chronic renal failure, hemoglobinopathies, splenomegaly, rheumatoid arthritis, antiretrovirals, ribavirin, dapsone)

* = fasting – no caloric intake for at least 8 hours, † = using a standardized, validated assay in the absence of factors that affect the accuracy of the A1C, ‡ = random – anytime of the day, without regard to the interval since the last meal

SECTION A: Individualizing targets (continued)

A1C targets and considerations for glycemic control [1,3,4]

Individualize (and reassess) targets considering potential benefits and harms to the patient, and according to each patient's:

- Age and/or frailty
- Comorbidities
- Prognosis
- Duration of diabetes
- Risk of hypoglycemia
- Patient preferences, resources and support system
- Number, complexity and burden of medications

≤ 6.5%
Some adults: if easy/safe to achieve, without hypoglycemia (e.g., with lifestyle modification and metformin).

In others, risks of an A1C of ≤6.5% may warrant deintensification of therapy.[3,5]

≤ 7.0%
"Most" adults: guidelines differ on the target recommended for "most" adults, however they consistently note the need to individualize treatment intensity and therapy based on patient factors.

To achieve A1C ≤ 7.0%, target:

- FPG 4.0–7.0 mmol/L and/or
- PPG 5.0–10.0 mmol/L or if A1C not at target, aim for PPG 5.0–8.0 mmol/L

HOWEVER, this must be balanced against the risk of hypoglycemia.

7.1-8.0%
Functionally dependent adults (Clinical Frailty Scale[11] score = 4-5, on a 9 point scale): deintensification (e.g., reducing dose, discontinuation) of therapy in older, frail adults is often appropriate to reduce potential harms (e.g., hypoglycemia, risk of polypharmacy, lack of time-to-benefit).

7.1-8.5%
Frail older adults (Clinical Frailty Scale[11] score = 6-8, on a 9 point scale) **and/or adults with dementia, limited life expectancy or a history of recurrent severe hypoglycemia and/or hypoglycemia unawareness.**

7.3-7.9%
Adults with cardiovascular disease/risk: patients with A1Cs in the range of 7.3-7.9% have demonstrated reductions in cardiovascular, renal, and/or mortality outcomes. However studies featured a specific drug (an SGLT2i, GLP1-RA, or metformin) and demographic, rather than merely the intensity of glycemic control.[6-10]

Clinical Frailty Scale:[11]

Score	Target A1C
4-5	< 8.0%
6-8	< 8.5%
9	Avoid symptomatic hyper/hypoglycemia

Note: A1C tends to rise over time, even for patients on stable treatments.

SECTION B: Individualizing pharmacotherapy

Management of hyperglycemia in type 2 diabetes[1,12]

At diagnosis of type 2 diabetes
Start and support the ongoing maintenance of healthy lifestyle interventions (nutritional therapy, weight management, physical activity) +/- metformin
✓ **Lifestyle interventions** have a greater potential for A1C lowering than any pharmacotherapy (nutrition A1C 1-2% and exercise A1C 0.5-0.7%)[13]

Select individualized A1C target (see A1C targets and considerations for glycemic control)

A1C < 1.5% above target	**A1C ≥ 1.5% above target**	**Symptomatic hyperglycemia and/or metabolic decompensation** (may include dehydration, diabetic ketoacidosis, hyperosmolar hyperglycemic state)
Add metformin if lifestyle changes not expected to reduce blood glucose levels by 3 months	Start metformin plus a second antihyperglycemic agent, and: • Check renal function before starting agent • Monitor for hypoglycemia when on multiple agents of different classes	Initiate insulin +/- See Type 2 diabetes: insulin therapy tool

If not at A1C target at 3 months

Start metformin (if not already started)

Adjust or advance therapy

If not at A1C target in 3-6 months and/or change in clinical status
(e.g., changes in cardiovascular or renal status, presence of diabetes complications, side effects, and ability to take current medications).

Does patient have:

- Atherosclerotic cardiovascular disease OR
- Chronic kidney disease OR
- Heart failure OR
- Age > 60 years with at least 2 cardiovascular risk factors: smoking (tobacco use), hypertension (untreated BP ≥ 140/95 or current antihypertensive therapy), dyslipidemia (use of lipid-modifying therapy or a documented untreated LDL > 3.4 mmol/L, or HDL-C < 1.0 mmol/L for men and < 1.3 mmol/L for women, or triglycerides > 2.3 mmol/L), central obesity (waist circumference of ≥ 80cm for females, ≥ 90-94cm for males)

NO →

Add or substitute another antihyperglycemic agent based on shared decision-making factors (see the Shared decision-making table)	
Proven cardiorenal benefit in high-risk populations	• Glucagon-like peptide-1 receptor agonists (GLP1-RA) (dulaglutide, liraglutide, subcutaneous semaglutide) • Sodium-glucose co-transporter-2 inhibitors (SGLT2i) (canagliflozin, dapagliflozin, empagliflozin) • Note: benefit potential with GLP1-RA and SGLT2i is less in those with lower cardiovascular risk, so carefully weigh harms
Cardiovascular safety but no proven cardiorenal benefit	• GLP1-RA receptor agonists (exenatide, lixisenatide, oral semaglutide) • Dipeptidyl peptidase-4 inhibitors (DPP4i) (sitagliptin, linagliptin) • Alpha-glucosidase inhibitor (acarbose) • Insulin secretagogues (sulfonylureas and meglitinides) • Insulin • Note: AVOID (due to risk of heart failure) saxagliptin (and possibly alogliptin), thiazolidinediones (TZD)
Minimizing risk of hypoglycemia	• Note: caution use of insulin secretagogues (sulfonylureas and meglitinides), insulin • Other agents have negligible risk as monotherapy
Weight considerations	• Agents that decrease weight: GLP1-RA, SGLT2i, metformin • Agents that increase weight: TZD, insulin secretagogues (sulfonylureas and meglitinides), insulin

YES →

Add or substitute another antihyperglycemic agent with demonstrated cardiorenal benefits

	Patients with existing cardiovascular or renal disease			**Patients with cardiovascular risk factors**
Lower risk observed in outcome trials:	Atherosclerotic cardiovascular disease	Chronic kidney disease	Heart failure	Age > 60 years with 2 cardiovascular risk factors
Major adverse cardiac events	GLP1-RA (dulaglutide, liraglutide) or SGLT2i* (empagliflozin) GLP1-RA (semaglutide SC) or SGLT2i* (canagliflozin)	SGLT2i* (canagliflozin) or GLP1-RA (liraglutide, semaglutide SC) *SGLT2i* (empagliflozin)*		GLP1-RA (dulaglutide) GLP1-RA (liraglutide) *GLP1-RA (semaglutide SC)*
Hospitalization for heart failure	SGLT2i* (canagliflozin, dapagliflozin, empagliflozin)	SGLT2i* (canagliflozin, dapagliflozin, empagliflozin)	SGLT2i* (canagliflozin, **dapagliflozin** [also lowers CV mortality], **empagliflozin**)	SGLT2i* (canagliflozin, dapagliflozin)
Nephropathy progression	SGLT2i* (canagliflozin, dapagliflozin, empagliflozin)	SGLT2i* (**canagliflozin**, dapagliflozin, empagliflozin)		*SGLT2i* (canagliflozin, dapagliflozin)*

Levels of evidence: Grade A | Grade B | *Grade C or D*

Bold = agents with stronger evidence compared to others in the same box

*Start SGLT2i only if eGFR > 30 mL/min

SECTION B: Individualizing pharmacotherapy (continued)

Shared decision-making

- Shared decision-making is an approach to clinical decision-making in which patients and providers jointly consider clinical factors and patient preferences to arrive at a mutually agreeable decision [14]
- Shared decision-making aims to bridge the information gap between patients and providers while prioritizing patient autonomy [14]

Engage patients in a discussion regarding which of the following factors are most important to them:[15,16]
Use this information and a shared decision-making approach to support patients in deciding which diabetes therapy they would prefer see (Non-insulin pharmacotherapy table)

	1. **Affordability of therapy for 100 day supply** • **Green** = < $100 • **Yellow** = $100-$400 • **Red** = > $400
	2. **Therapy that fits with daily routine** • **Green** = twice daily or less administration • **Yellow** = ranges from once daily to 3+ daily • **Red** = 3+ administration per day, inconvenient
	3. **Avoiding therapy that requires injections** • **Yellow** = weekly injection • **Red** = daily injection
	4. **Avoiding therapy that has gastrointestinal side effects** • **Red** = gastrointestinal side effects are common
	5. **Avoiding therapy that increases risk of hypoglycemia** • **Red** = risk of hypoglycemia
	6. **Therapy that impacts weight change** • **Green** = decreases weight • **Red** = increases weight
	7. **Therapy that also provides cardiovascular benefits** • **Green** = cardiovascular benefit • **Red** = cardiovascular risk (e.g., worsening myocardial infarction or heart failure)
	8. **Therapy that also provides kidney protection** • **Green** = provides kidney protection • **Red** = may cause acute renal injury

SECTION B: Individualizing pharmacotherapy (continued)

Non-insulin pharmacotherapy

See page 14 for definitions of acronym used throughout this table

Agent, dosage forms, generic available[G] [17]	A1C reduction (%)[12,18]	Other benefits, CVD outcomes[12,18]	Weight[12,18]	Harms, hypoglycemic risk[12,18] (negligible risk as monotherapy unless stated otherwise)	Comments[12,18] (titration, administration, monitoring, notes)	Dose[18] (I = initial, U = usual, M = max)	Renal dose[12,18]	Coverage (ODB[17], NIHB[19])	Drug cost for usual dose* ($/100 days)[17]
First line									
Biguanides									
Metformin HCL (Glucophage®) [G] Tab: 500mg, 850mg	1.0	• ↓ MI in overweight (>120% IBW) patients • ↓ All-cause mortality • Reduced insulin requirements • Reduced risk of lactic acidosis	Loss of up to 2.9kg in 5 years[20]	• GI intolerance • Vitamin B12 deficiency	• Titrate up every 1–2 weeks to avoid GI AE • Take with largest meal to minimize GI AE • 85% of max glucose lowering seen at 1500 mg daily • Fewer GI side effects with ER formulation • Monitor: hemoglobin and vitamin B12 deficiency (annually), SCr (baseline and periodically) • On SADMANS list[21]	I: 250–500mg po daily cc U: 1000mg po bid cc or 1700mg cc am and 850mg cc pm M: 2550mg daily or 850mg tid	eGFR 30-45mL/min (≤1000mg daily) eGFR <30mL/min (avoid*) *Sometimes used at low dose when eGFR between 15-30 mL/min in renally stable patients	ODB ✓ (500mg) × (850mg) NIHB ✓	G: $20 (1g bid) - $80 (850mg tid) T: $140
(Glumetza®) [G] ER tab: 500mg, 1000mg						I: 250–500mg po daily cc U: 1000–2000mg po cc pm M: 2500 mg daily		ODB × NIHB ×	G: $120 (1g/d) - $235 (2g/d T: $300 (2g/d)
Second line (alphabetical order by class)									
Alpha-glucosidase inhibitor									
Acarbose (Glucobay®) [G] Tab: 50mg, 100mg	0.7–0.8	• Improved postprandial control	—	• GI intolerance, flatulence, diarrhea	• Titrate up every 1–2 weeks until 50 mg tid to avoid GI AE; then every 4–8 weeks • Max effect may take weeks • Take with first bite of meal • Monitor: SCr and LFTs (baseline and periodically)	I: 25mg po daily cc U: 50–100mg po tid cc M: 100mg po tid cc	eGFR <25-30mL/min (contraindication)	ODB ✓ LU 175, 176[22] NIHB ✓	G: $74-$100

SECTION B: Individualizing pharmacotherapy (continued)

Non-insulin pharmacotherapy

Agent, dosage forms, generic available[(G) 17]	A1C reduction (%)[12,18]	Other benefits, CVD outcomes[12,18]	Weight[12,18]	Harms, hypoglycemic risk[12,18] (negligible risk as monotherapy unless stated otherwise)	Comments[12,18] (titration, administration, monitoring, notes)	Dose[18] (I = initial, U = usual, M = max)	Renal dose[12,18]	Coverage (ODB[17], NIHB[19])	Drug cost for usual dose* ($/100 days)[17]
Dipeptidyl peptidase-4 inhibitors (DPP4i) $ Avoid combining DPP4i with GLP1-RA									
†Alogliptin (Nesina®) Tab: 6.25mg, 12.5mg, 25mg[23]	0.5–0.7	• Improved postprandial control • Well tolerated option in older adults • Neutral effect on CVD outcomes	—	• Pancreatitis (rare), severe joint pain (rare) • Alogliptin: possible worsening of HF in patients with acute coronary syndrome without a history of HF • Saxagliptin: HF	• Monitor: SCr (baseline and periodically), LFTs (baseline, especially for alogliptin) • Alogliptin: may ↑ LFTs • Linagliptin: no dosage adjustment in renal impairment • Saxagliptin: avoid in HF	I, U, M: 25mg po daily	eGFR 30-50mL/min (12.5mg po daily) eGFR <30mL/min (6.25mg po daily)	ODB × NIHB ×	T: $265
Linagliptin (Trajenta®) Tab: 5mg						I, U, M: 5mg po daily	eGFR <15mL/min (use with caution). No dosage adjustment	ODB ✓ NIHB ✓	T: $297
Saxagliptin (Onglyza®) Tab: 2.5mg, 5mg						I, U, M: 5mg po daily	eGFR <50mL/min (2.5mg po daily) eGFR <15mL/min (use alternative agent)	ODB ✓ NIHB ✓	T: $337
Sitagliptin (Januvia®) Tab: 25mg, 50mg, 100mg						I, U, M: 100mg po daily	eGFR 30-49mL/min (50mg po daily) eGFR <30mL/min, hemodialysis, peritoneal dialysis - chronic kidney disease (25mg po daily)	ODB ✓ NIHB ✓LU (for patients who did not achieve glycemic control or who demonstrated intolerance to an adequate trial of metformin and a sulfonylurea)	T: $354

SECTION B: Individualizing pharmacotherapy (continued)

Non-insulin pharmacotherapy

Agent, dosage forms, generic available[G] [17]	A1C reduction (%)[12,18]	Other benefits, CVD outcomes[12,18]	Weight[12,18]	Harms, hypoglycemic risk[12,18] (negligible risk as monotherapy unless stated otherwise)	Comments[12,18] (titration, administration, monitoring, notes)	Dose[18] (I = initial, U = usual, M = max)	Renal dose[12,18]	Coverage (ODB[17], NIHB[19])	Drug cost for usual dose* ($/100 days)[17]
Glucagon-like peptide-1 receptor agonists (GLP1-RA) – short acting $ Avoid combining DPP4i with GLP1-RA									
†Exenatide (Byetta®) Pre-filled pen (multiuse): 250µg/mL; 1.2mL, 2.4mL Pk[24]	0.6-1.4	• Unknown	Loss of 1.6-3kg[1]	• SC injection • GI side effects, acute pancreatitis/gallstone disease (rare) • Contraindicated with personal/family hx of medullary thyroid cancer or multiple endocrine neoplasia syndrome type 2	• Administer within 60 minutes before meal • Injection daily or once weekly • Initiate 5ug SC bid within 60 mins ac x 1 month, then 10ug bid • If no improvement in blood glucose control after 3-4 months, consider alternatives • Monitor: SCr (baseline and periodically) • Less A1C lowering with short-acting agents than long-acting agents	I, U: 5µg SC bid ac, prior to main meals ≥6 hour apart M: 10µg SC bid ac	eGFR <50mL/min (caution), <30mL/min (contraindicated)	ODB × NIHB ×	T: $510
Lixisenatide (Adlyxine®) Pre-filled pen (multiuse): 0.05mg/mL, 0.1mg/mL; 3mL Pk		• Neutral effect on CVD outcomes			• Start 10ug SC daily within the hour prior to any meal of the day x 2 weeks then 20ug SC daily • If not tolerated, the dose can be temporarily reduced to 10ug SC daily and consider increasing the dose to 20ug SC once daily within 4 weeks • Monitor: SCr (baseline and periodically)	I: 10mcg SC daily ac x 2 weeks U, M: 20mcg SC daily ac	eGFR <15-20mL/min (contraindicated)	ODB ✓ NIHB ✓	T: $419

SECTION B: Individualizing pharmacotherapy (continued)

Non-insulin pharmacotherapy

Agent, dosage forms, generic available[(G) 17]	A1C reduction (%)[12,18]	Other benefits, CVD outcomes[12,18]	Weight[12,18]	Harms, hypoglycemic risk[12,18] (negligible risk as monotherapy unless stated otherwise)	Comments[12,18] (titration, administration, monitoring, notes)	Dose[18] (I = initial, U = usual, M = max)	Renal dose[12,18]	Coverage (ODB[17], NIHB[19])	Drug cost for usual dose* ($/100 days)[17]
Glucagon-like peptide-1 receptor agonists (GLP1-RA) – longer acting						Avoid combining DPP4i with GLP1-RA			
†Dulaglutide (Trulicity®) Pre-filled pen (single use): 0.75mg/0.5ml, 1.5mg/0.5ml[25]	0.6-1.4	• ↓ MACE in patients with clinical CVD	Loss of 1.6-3kg[1]	• SC injection • GI side effects (less GI side effects with weekly GLP1-RA vs daily), acute pancreatitis/gallstone disease (rare) • Contraindicated in patients with personal/family hx of medullary thyroid cancer or multiple endocrine neoplasia syndrome type 2 (C-cell/thyroid tumors in animals) • SC semaglutide: ↑ retinopathy complications seen in 1 trial in those with retinopathy history (3.0% vs. 1.8% placebo in 2 year trial) • Although similar: •Saxenda® is indicated as an adjunct to a reduced calorie diet and increased physical activity for chronic weight management in adult patients with an initial BMI of ≥ 30 kg/m2 (obese) or ≥ 27 kg/m2 (overweight) in the presence of at least one weight-related comorbidity (e.g., hypertension, type 2 diabetes or dyslipidemia) and who have failed a previous weight management intervention •Victoza® is indicated for once-daily administration for the treatment of adults with type 2 diabetes to improve glycemic control	• With or without meals • Monitor: SCr (baseline and periodically) • Single use disposable (environmental impact)	I: 0.75mg SC once weekly U, M: 1.5mg SC once weekly	eGFR <15mL/min (caution)	ODB × NIHB ×	T: $720 (12 weeks)
†Exenatide (Bydureon®) ER pen (powder, single use): 2mg[26]		• Neutral effect on CVD outcomes			• With or without meals • Monitor: SCr (baseline and periodically) • Supplied as a powder suspension to be reconstituted into a solution	I, U, M: 2mg SC once weekly (must reconstitute)	eGFR <50mL/min (caution), <30mL/min (contraindicated)	ODB × NIHB ×	T: $775 (12 weeks)
†Liraglutide (Victoza®) Pre-filled pen (multiuse): 6mg/mL; 3mL Pk[27]		• ↓ CV death in patients with clinical CVD • ↓ MACE in patients with clinical CVD • ↓ Nephropathy progression			• Administer without regard for meals • Titrate up after 1 week to reduce GI AE (see usual dose) • If >3 missed doses, restart at 0.6mg daily and titrate • Monitor: SCr (baseline and periodically)	I: 0.6mg SC daily U: After ≥1 week, ↑ 1.2mg SC daily x 1 week, then 1.8mg SC daily M: 1.8mg/d	eGFR <15-30mL/min (contraindicated)	ODB × NIHB ×	T: $1095 (1.8mg SC daily x 100 days)
(Saxenda®) Pre-filled 6mg/mL, Pen 5x3mL						I: 0.6mg SC daily U: After ≥1 week, ↑ 1.2mg SC daily x 1 week, then 1.8mg SC daily x 1 week, then 2.4mg SC daily x 1 week, then 3.0mg M: 3.0mg/d			
Semaglutide (Ozempic®) Pre-filled pen (multiuse): 1.34mg/mL; 1.5mL, 3mL Pk	1.5-2.0[10]	• ↓ MACE in patients with clinical CVD	Loss of up to 4kg in 2 years		• Titrate after ≥ 4 weeks to minimize GI AE (see usual dose) • Monitor: SCr (baseline and periodically)	I: 0.25mg SC once weekly U: After ≥4 weeks ↑0.5mg SC once weekly x 4 weeks, then titrate up to 1mg SC weekly as tolerated M: 1mg SC once weekly	eGFR <30mL/min (caution)	ODB ✓ NIHB ✓	T: $390-$772
†(Rybelsus®) Tab: 3mg, 7mg, 14mg[28]	1.1	• Neutral effect on CVD outcomes or MACE	Loss of up to 5kg in 1 year		• Increase dose ≥ 30 days apart to reduce GI AE (see usual dose) • No dose adjustment for hepatic or renal impairment • To be taken with 120mL of water • Monitor: SCr (baseline and periodically)	I: 3mg po daily 30 mins ac U: After 30 days ↑ 7mg daily 30 mins ac M: 14mg daily	Not studied in eGFR < 30mL/min	ODB × NIHB ×	T: $818

SECTION B: Individualizing pharmacotherapy (continued)

Non-insulin pharmacotherapy

Agent, dosage forms, generic available[G] [17]	A1C reduction (%)[12,18]	Other benefits, CVD outcomes[12,18]	Weight[12,18]	Harms, hypoglycemic risk[12,18] (negligible risk as monotherapy unless stated otherwise)	Comments[12,18] (titration, administration, monitoring, notes)	Dose[18] (I = initial, U = usual, M = max)	Renal dose[12,18]	Coverage (ODB[17], NIHB[19])	Drug cost for usual dose* ($/100 days)[17]
Insulin secretagogues – meglitinides									
Repaglinide (Gluconorm®) [G] Tab: 0.5mg, 1mg, 2mg	0.7-1.1	• Neutral CVD events and mortality • Postprandial glycemia is especially reduced by meglitinides • Meglitinides good for patients who skip meals	Gain of 1.4-3.3 kg	• Repaglinide contraindicated when co-administered with clopidogrel or with gemfibrozil • Minimal to moderate risk of hypoglycemia	• Dose given within 30 minutes of meal (not taken if meal skipped) • A minimum of 1 week should elapse between titration steps to assess response after each dose adjustment • Dosage adjustment usually determined by fasting BG • The prepprandial dose can be doubled or increased up to 4mg (e.g., 0.5mg increase to 1mg, 1mg increase to 2mg or 2mg increase to 4mg) • Monitor: SCr and LFTs (baseline and periodically)	I: A1C <8% 0.5mg po tid ac, A1C ≥8% 1-2mg po tid ac U: 1-4mg po bid-qid ac M: 16mg daily	eGFR <30mL/min (caution)	ODB × EAP[29] NIHB ✓	G: $79-$167

SECTION B: Individualizing pharmacotherapy (continued)

Non-insulin pharmacotherapy

Agent, dosage forms, generic available[G] [17]	A1C reduction (%)[12,18]	Other benefits, CVD outcomes[12,18]	Weight[12,18]	Harms, hypoglycemic risk[12,18] (negligible risk as monotherapy unless stated otherwise)	Comments[12,18] (titration, administration, monitoring, notes)	Dose[18] (I = initial, U = usual, M = max)	Renal dose[12,18]	Coverage (ODB[17], NIHB[19])	Drug cost for usual dose* ($/100 days)[17]
Insulin secretagogues – sulfonylureas $ Risk of hypoglycemia: gliclazide < glimepiride < glyburide									
Gliclazide (Diamicron MR®) [G] SR tab: 30mg ER tab: 60mg	0.6-1.2	• Neutral effect on CVD outcomes • Relatively rapid BG lowering response • Gliclazide preferred over glyburide due to potential lower hypoglycemic risk	Gain of 1.2-3.2 kg	• Minimal to moderate risk of hypoglycemia • Caution in older adults	• Titrate up by 30mg every 2 weeks • Gliclazide MR 30mg = gliclazide 80mg • Gliclazide MR can be given once daily with breakfast • If CrCl < 30mL/min, gliclazide is preferred • Monitor: SCr and LFTs (baseline and periodically)	I: 30mg MR po daily U: 60mg MR daily M: 120mg MR daily	eGFR <30mL/min (contra-indicated)	ODB ✓ NIHB ✓	G: $16 T: $37
(Diamicron®) [G] Tab: 80mg				• Minimal to moderate risk of hypoglycemia	• Titrate up by 80mg per week to target BG • For doses of 160mg, administer bid with meals • Monitor: SCr and LFTs (baseline and periodically)	I: 40-80mg po daily in am cc U: 80mg bid cc M: 160mg bid cc		ODB ✓ NIHB ✓	G: $29 T: $94
Glimepiride (Amaryl®) [G] Tab: 1mg, 2mg, 4mg				• Moderate risk of hypoglycemia • Caution in older adults with poor renal function	• After reaching a dose of 2mg, dosage increases should be made in increments of no more than 1mg at 1-2 week intervals based on BG response • Monitor: SCr and LFTs (baseline and periodically)	I: 1-2mg po daily in am cc U: 1-4mg po daily in am cc M: 8mg po daily cc	eGFR <30mL/min (contra-indicated)	ODB × NIHB ×	G: $ 62
Glyburide (Diabeta®) [G] Tab: 2.5mg, 5mg				• Moderate risk of hypoglycemia • Caution in older adults with poor renal function	• Continue initial dose for 5-7 days, then titrate by 2.5mg every 1-2 weeks • If patient consumes a light breakfast, defer 1st dose until lunchtime • If more than 10mg daily is required, the excess should be taken with the largest meal (e.g., evening meal) • To prevent hypoglycemia, do not skip meals after taking glyburide • Monitor: SCr and LFTs (baseline and periodically) • Caution in older adults with poor renal function	I: 1.25-2.5 mg po daily cc U: 5mg daily bid cc M: 10mg bid cc	eGFR <60 (contraindicated)	ODB ✓ NIHB ×	G: $15 T: $37

SECTION B: Individualizing pharmacotherapy (continued)

Non-insulin pharmacotherapy

Agent, dosage forms, generic available[G] [17]	A1C reduction (%)[12,18]	Other benefits, CVD outcomes[12,18]	Weight[12,18]	Harms, hypoglycemic risk[12,18] (negligible risk as monotherapy unless stated otherwise)	Comments[12,18] (titration, administration, monitoring, notes)	Dose[18] (I = initial, U = usual, M = max)	Renal dose[12,18]	Coverage (ODB[17], NIHB[19])	Drug cost for usual dose* ($/100 days)[17]
Sodium-glucose cotransporter-2 inhibitors (SGLT2i) or gliflozins									
Canagliflozin (Invokana®) Tab: 100mg, 300mg	0.5-0.7	• ↓ MACE, ↓ nephropathy progression and HF in patients with clinical CVD	Loss of 2-3kg	• Genital mycotic infections, urinary tract infections, hypotension, ↑ LDL-C, euglycemic diabetic ketoacidosis ± hyperglycemia (rare), fourniere's gangrene (rare), acute kidney injury • Caution with renal dysfunction, loop diuretics and older adults • Withhold treatment prior to major surgery or with serious illness/infections • Canagliflozin: fracture risk, lower extremity amputation – avoid if prior amputation • Dapagliflozin: avoid in bladder cancer • On SADMANS list[21]	• Once daily dosing, usually in the morning because of ↑ urinary frequency and volume • Monitor: blood pressure, weight, SCr, potassium, blood ketones if diabetic ketoacidosis symptoms (baseline, within 2-4 weeks of starting, then periodically)	I, U: 100mg po od daily am M: 300mg daily	eGFR <60mL/min (max dose 100mg daily) eGFR <60mL/min + UGT inducer (avoid) eGFR <45mL/min (caution) eGFR <30mL/min (contra-indicated)	ODB ✓ NIHB ✓ LU (for patients who did not achieve glycemic control or who demonstrated intolerance to an adequate trial of metformin and a sulfonylurea)	T : $321
Dapagliflozin (Forxiga®) Tab: 5mg, 10mg		• ↓ Nephropathy progression, HF or CV death in patients with clinical CVD				I, U: 5mg po daily am M: 10mg po daily am	eGFR < 45mL/min (not recommended) eGFR <30mL/min (contra-indicated)	ODB ✓ NIHB ✓	T: $304
Empagliflozin (Jardiance®) Tab: 10mg, 25mg		• ↓ MACE and ↓ CVD death in patients with clinical CVD • ↓ Nephropathy progression, HF or CV death in patients with HF +/- ↓ in all cause mortality				I, U: 10mg po daily am M: 25mg po daily am	eGFR <60mL/min (caution) eGFR <30mL/min (contra-indicated)	ODB ✓ NIHB ✓	T: $304

SECTION B: Individualizing pharmacotherapy (continued)

Non-insulin pharmacotherapy

Agent, dosage forms, generic available[G] [17]	A1C reduction (%)[12,18]	Other benefits, CVD outcomes[12,18]	Weight[12,18]	Harms, hypoglycemic risk[12,18] (negligible risk as monotherapy unless stated otherwise)	Comments[12,18] (titration, administration, monitoring, notes)	Dose[18] (I = initial, U = usual, M = max)	Renal dose[12,18]	Coverage (ODB[17], NIHB[19])	Drug cost for usual dose* ($/100 days)[17]
Thiazolidinediones (TZD)									
Pioglitazone HCL (Actos®)[G] Tab: 15mg, 30mg, 45mg	0.7-0.9	• ↓ MACE, ↓ MI, ↓ stroke	Gain of 2-5 kg[21]	• Edema, HF, fractures, ↑ HDL-C, macular edema (rare), contraindicated in HF • Pioglitazone: possible bladder risk	• 4–12 weeks for max effect • Pioglitazone: increase by 15mg every 4 weeks • Rosiglitazone: increase to 8mg daily in 8-12 weeks if BG not at target • Monitor: SCr and LFTs (baseline and periodically) • Risk of heart failure, which may be higher if combined with insulin (combination not approved in Canada) • Rosiglitazone: requires special authorization from patient prior to prescribing • Health Canada restrictions: rosiglitazone only to be used when all other oral agents have been tried alone or together and targets not reached[30]	I: 15mg daily po daily U: 30-45mg po daily M: 45mg po daily	eGFR <60mL/min (caution)	ODB × EAP[29] NIHB ✓	G: $247–$366 T: $388-$578
Rosiglitazone (Avandia®)[G] Tab: 2mg, 4mg, 8mg		• Possible MI risk				I: 4mg po daily U: 4mg po daily to bid M: 8mg po daily	eGFR <60mL/min (caution)	EAP[29] ODB × NIHB ×	G: $207 T: $292

SECTION B: Individualizing pharmacotherapy (continued)

Combination products

Refer to individual components in Non-insulin pharmacotherapy table for maximum dose, renal dose, comments

Agent, dosage forms, generic available (G) [17]	Usual dose[18]	Coverage (ODB[17], NIHB[19])	Drug cost for usual dose* ($/100 days)[17]
Insulin degludec/liraglutide (Xultophy®) 100 units/mL insulin degludec, 3.6mg/mL	16 units/0.58mg – 50 units/1.8mg SC daily (50 units insulin daily)	ODB × NIHB ×	T: $370 for 5x3mL
Insulin glargine/lixisenatide (Soliqua®) 100U/mL, 33mcg/mL	15 units/5mcg – 60 units/20mcg SC daily (60 units insulin daily)	ODB ✓ NIHB ✓	T: $215
†Linagliptin/empagliflozin (Glyxambi®) Tab: 5/10mg, 5/25mg[31]	1 tab po daily	ODB × NIHB ×	T: $563
†Metformin/canagliflozin (Invokamet®) Tab: 500/50mg, 850/50mg, 1000/50mg, 500/150mg, 850,150mg, 1000/150mg[32]	1 tab po bid cc	ODB × NIHB ×	T: $386
Metformin/dapagliflozin (Xigduo®) Tab: 850/5mg, 1000/5mg	1 tab po bid cc	ODB ✓ NIHB ✓	T: $273
Metformin/empagliflozin (Synjardy®) Tab: 500/5mg, 850/5mg, 1000/5mg, 500/12.5mg, 850/12.5mg, 1000/12.5mg	1 tab po bid cc	ODB ✓ NIHB ✓	T: $307
Metformin/linagliptin (Jentadueto®) Tab: 500/2.5mg, 850/2.5mg, 1000/2.5mg	1 tab po bid cc	ODB ✓ NIHB ✓	T: $311
Metformin/saxagliptin (Komboglyze®) Tab: 500/2.5mg, 850/2.5mg, 1000/2.5mg[33]	1 tab po bid cc	ODB ✓ NIHB ✓	T: $283
Metformin/sitagliptin (Janumet®) Tab: 500/50mg, 850/50mg, 1000/50mg	1 tab po bid cc	ODB ✓ NIHB ✓	T: $383
(Janumet XR®) ER tab: 500/50mg, 1000/50mg, 1000/100mg	1-2 tab(s) po once daily cc	ODB ✓ NIHB LU (for patients who did not achieve glycemic control or who demonstrated intolerance to an adequate trial of metformin and a sulfonylurea)	T: $196-$383

Blue Text = agents with evidence-based outcome benefits, Orange = important information, ***** = prices reflect cost to consumer and include markup and dispensing fee, **†** = not on Ontario drug formulary, ✓ = general benefit, **x** = not a benefit, **–** = weight neutral, **ac** = before meals, **AE** = adverse events, **BG** = blood glucose, **bid** = twice daily, **cc** = with meal, **CrCl** = creatinine clearance, **CV** = cardiovascular, **CVD** = cardiovascular disease, **EAP** = Exceptional Access Program, **eGFR** = estimated glomerular filtration rate, **ER** = extended release, **G** = generic, **GI** = gastrointestinal, **HCL** = hydrochloric acid, **HDL-C** = high density lipoprotein cholesterol, **HF** = heart failure, **LDL-C** = low density lipoprotein cholesterol, **LFTs** = liver function tests, **LU** = limited use, **MACE** = major adverse cardiovascular event, **max** = maximum, **MI** = myocardial infarction, **µg** = microgram, **mg** = milligram, **mL** = milliliter, **MR** = modified release, **NIHB** = non-insured health benefits for First Nations and Inuit, **ODB** = Ontario Drug Benefit, **po** = by mouth, **qid** = four times daily, **SC** = subcutaneous, **SCr** = serum creatinine, **SR** = sustained release, **T** = trade, **Tab** = tablets, **tid** = three times daily, **UGT** = UDP-glucuronosyltransferase

Patient resources

[i] Diabetes Canada Hypoglycemia low blood sugar in adults

[ii] Diabetes Canada Drive safe with diabetes

[iii] Diabetes Canada Stay safe when you have diabetes and are sick or at risk of dehydration

[iv] RxFiles Type 2 diabetes and sick days: Medications to pause

[v] Centre for Effective Practice local services for patients living with type 2 diabetes

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