CEP | Providers

Type 2 diabetes: Non-insulin pharmacotherapy

This tool is designed to support primary care providers 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.

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

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.

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 +/- metformin

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

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

Non-insulin pharmacotherapy

See page 13 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

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

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

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] (Saxenda®) Pre-filled 6mg/mL, Pen 5x3mL		• ↓ 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 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	eGFR <15-30mL/min (contraindicated)	ODB × NIHB ×	T: $1095 (1.8mg SC daily x 100 days)
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

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

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 (contraindicated)	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 (contraindicated)	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

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 (contraindicated)	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 (contraindicated)	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 (contraindicated)	ODB ✓ NIHB ✓	T: $304

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

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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The Type 2 diabetes: Non-insulin pharmacotherapy tool ('Tool') was developed as part of the Knowledge Translation in Primary Care Initiative, led by the Centre for Effective Practice, in collaboration with the Nurse Practitioners' Association of Ontario. Clinical leadership for the development of the Tool was provided by Dr. Risa Bordman and was subject to external review by health care providers and other relevant stakeholders. This Tool was funded by the Government of Ontario as part of the Knowledge Translation in Primary Care Initiative.

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Developed By: CEP Centre for Effective Practice

In collaboration with: npao Nurse Practitioners' Association of Ontario