

# 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<sup>1</sup>

Fasting plasma glucose (FPG)  $\geq 7.0$  mmol/L\*  
OR  
A1C  $\geq 6.5\%$ †  
OR  
2-hour plasma glucose (2hPG) in a 75g oral glucose tolerance test (OGTT)  $\geq 11.1$  mmol/L  
OR  
Random‡ plasma glucose (PG)  $\geq 11.1$  mmol/L

- The decision of which test to use for diabetes diagnosis is left to clinical judgment
- Each diagnostic test has [advantages and disadvantages](#)<sup>2</sup>

### 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:

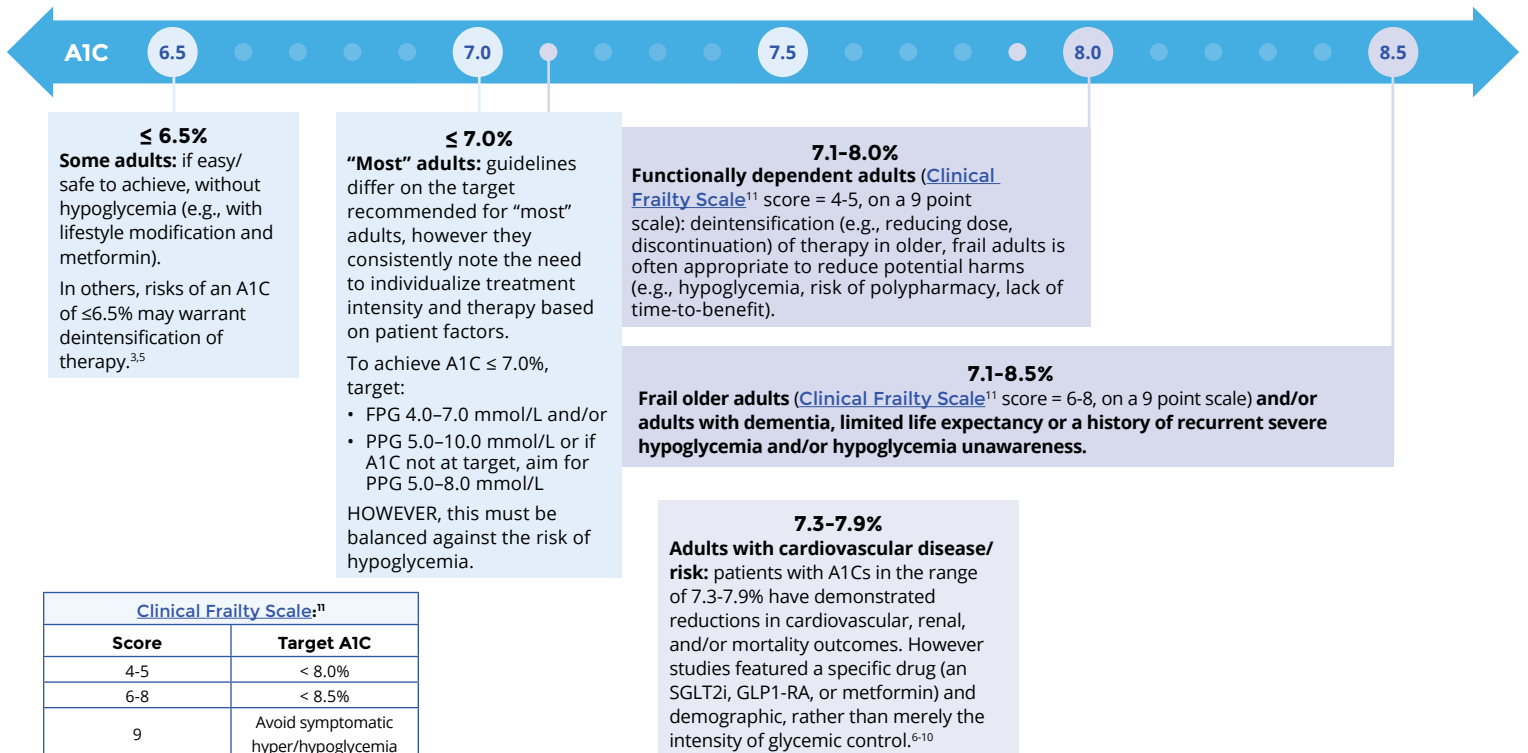
- Factors that can increase A1C: iron deficiency, B12 deficiency, ↓ erythropoiesis, alcoholism, chronic renal failure, splenectomy
- Factors that can decrease A1C: use of erythropoietin, iron or B12, reticulocytosis, chronic liver disease, ingestion of acetylsalicylic acid, vitamin C/E, decreased erythrocyte 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<sup>1,3,4</sup>

**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



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<sup>1,2</sup>

## 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%)<sup>13</sup>

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

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

<p><b>Start metformin</b> (if not already started)</p>	<p><b>Adjust or advance therapy</b></p>
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**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
- 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)
- Chronic kidney disease OR
- Heart failure OR

**NO**

### Add or substitute another antihyperglycemic agent based on shared decision-making factors (see the [Shared decision-making table](#))

<p>Proven cardiorenal benefit in high-risk populations</p>	<ul style="list-style-type: none"> <li>• Glucagon-like peptide-1 receptor agonists (GLP1-RA) (dulaglutide, liraglutide, subcutaneous semaglutide)</li> <li>• Sodium-glucose co-transporter-2 inhibitors (SGLT2i) (canagliflozin, dapagliflozin, empagliflozin)</li> <li>• Note: benefit potential with GLP1-RA and SGLT2i is less in those with lower cardiovascular risk, so carefully weigh harms</li> </ul>
<p>Cardiovascular safety but no proven cardiorenal benefit</p>	<ul style="list-style-type: none"> <li>• GLP1-RA receptor agonists (exenatide, lixisenatide, oral semaglutide)</li> <li>• Dipeptidyl peptidase-4 inhibitors (DPP4i) (sitagliptin, linagliptin)</li> <li>• Alpha-glucosidase inhibitor (acarbose)</li> <li>• Insulin secretagogues (sulfonylureas and meglitinides)</li> <li>• Insulin</li> <li>• Note: AVOID (due to risk of heart failure) saxagliptin (and possibly alogliptin), thiazolidinediones (TZD)</li> </ul>
<p>Minimizing risk of hypoglycemia</p>	<ul style="list-style-type: none"> <li>• Note: caution use of insulin secretagogues (sulfonylureas and meglitinides), insulin</li> <li>• Other agents have negligible risk as monotherapy</li> </ul>
<p>Weight considerations</p>	<ul style="list-style-type: none"> <li>• Agents that decrease weight: GLP1-RA, SGLT2i, metformin</li> <li>• Agents that increase weight: TZD, insulin secretagogues (sulfonylureas and meglitinides), insulin</li> </ul>

**YES**

### Add or substitute another antihyperglycemic agent with demonstrated cardiorenal benefits

	Patients with existing cardiovascular or renal disease			Patients with cardiovascular risk factors
<b>Lower risk observed in outcome trials:</b>	Atherosclerotic cardiovascular disease	Chronic kidney disease	Heart failure	Age > 60 years with 2 cardiovascular risk factors
<b>Major adverse cardiac events</b>	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)
<b>Hospitalization for heart failure</b>	SGLT2i* (canagliflozin, dapagliflozin, empagliflozin)	SGLT2i* (canagliflozin, dapagliflozin, empagliflozin)	SGLT2i* (canagliflozin, dapagliflozin, empagliflozin) [also lowers CV mortality]	SGLT2i* (canagliflozin, dapagliflozin)
<b>Nephropathy progression</b>	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<sup>14</sup>
- Shared decision-making aims to bridge the information gap between patients and providers while prioritizing patient autonomy<sup>14</sup>








### Engage patients in a discussion regarding which of the following factors are most important to them:<sup>15,16</sup>

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)



	<p>1. <b>Affordability of therapy for 100 day supply</b></p> <ul style="list-style-type: none"> <li>• <b>Green</b> = &lt; \$100</li> <li>• <b>Yellow</b> = \$100-\$400</li> <li>• <b>Red</b> = &gt; \$400</li> </ul>
	<p>2. <b>Therapy that fits with daily routine</b></p> <ul style="list-style-type: none"> <li>• <b>Green</b> = twice daily or less administration</li> <li>• <b>Yellow</b> = ranges from once daily to 3+ daily</li> <li>• <b>Red</b> = 3+ administration per day, inconvenient</li> </ul>
	<p>3. <b>Avoiding therapy that requires injections</b></p> <ul style="list-style-type: none"> <li>• <b>Yellow</b> = weekly injection</li> <li>• <b>Red</b> = daily injection</li> </ul>
	<p>4. <b>Avoiding therapy that has gastrointestinal side effects</b></p> <ul style="list-style-type: none"> <li>• <b>Red</b> = gastrointestinal side effects are common</li> </ul>
	<p>5. <b>Avoiding therapy that increases risk of hypoglycemia</b></p> <ul style="list-style-type: none"> <li>• <b>Red</b> = risk of hypoglycemia</li> </ul>
	<p>6. <b>Therapy that impacts weight change</b></p> <ul style="list-style-type: none"> <li>• <b>Green</b> = decreases weight</li> <li>• <b>Red</b> = increases weight</li> </ul>
	<p>7. <b>Therapy that also provides cardiovascular benefits</b></p> <ul style="list-style-type: none"> <li>• <b>Green</b> = cardiovascular benefit</li> <li>• <b>Red</b> = cardiovascular risk (e.g., worsening myocardial infarction or heart failure)</li> </ul>
	<p>8. <b>Therapy that also provides kidney protection</b></p> <ul style="list-style-type: none"> <li>• <b>Green</b> = provides kidney protection</li> <li>• <b>Red</b> = may cause acute renal injury</li> </ul>

## Non-insulin pharmacotherapy


See [page 13](#) for definitions of acronym used throughout this table

Agent, dosage forms, generic available <sup>(G)</sup> 17	A1C reduction (%) <sup>12,18</sup>	Other benefits, CVD outcomes <sup>12,18</sup>	Weight <sup>12,18</sup>	Harms, hypoglycemic risk <sup>12,18</sup> (negligible risk as monotherapy unless stated otherwise)	Comments <sup>12,18</sup> (titration, administration, monitoring, notes)	Dose <sup>18</sup> (I = initial, U = usual, M = max)	Renal dose <sup>12,18</sup>	Coverage (ODB <sup>17</sup> , NIHB <sup>19</sup> )	Drug cost for usual dose* (\$/100 days) <sup>17</sup>
<b>First line</b>									
<b>Biguanides</b>    									
<b>Metformin HCL</b> (Glucophage®) <sup>G</sup> Tab: 500mg, 850mg  (Glumetza®) <sup>G</sup> ER tab: 500mg, 1000mg	1.0	<ul style="list-style-type: none"> <li>• ↓ MI in overweight (&gt;120% IBW) patients</li> <li>• ↓ All-cause mortality</li> <li>• Reduced insulin requirements</li> <li>• Reduced risk of lactic acidosis</li> </ul>	Loss of up to 2.9kg in 5 years <sup>20</sup>	<ul style="list-style-type: none"> <li>• GI intolerance</li> <li>• Vitamin B12 deficiency</li> </ul>	<ul style="list-style-type: none"> <li>• Titrate up every 1–2 weeks to avoid GI AE</li> <li>• Take with largest meal to minimize GI AE</li> <li>• 85% of max glucose lowering seen at 1500 mg daily</li> <li>• Fewer GI side effects with ER formulation</li> <li>• Monitor: hemoglobin and vitamin B12 deficiency (annually), SCr (baseline and periodically)</li> <li>• On <a href="#">SADMANS</a> list<sup>21</sup></li> </ul>	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  I: 250–500mg po daily cc U: 1000–2000mg po cc pm M: 2500 mg daily	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 ✓  ODB × NIHB ×	G: \$20 (1g bid) - \$80 (850mg tid) T: \$140  G: \$120 (1g/d) - \$235 (2g/d) T: \$300 (2g/d)
<b>Second line (alphabetical order by class)</b>									
<b>Alpha-glucosidase inhibitor</b>   									
Acarbose (Glucobay®) <sup>G</sup> Tab: 50mg, 100mg	0.7–0.8	<ul style="list-style-type: none"> <li>• Improved postprandial control</li> </ul>	—	<ul style="list-style-type: none"> <li>• GI intolerance, flatulence, diarrhea</li> </ul>	<ul style="list-style-type: none"> <li>• Titrate up every 1–2 weeks until 50 mg tid to avoid GI AE; then every 4–8 weeks</li> <li>• Max effect may take weeks</li> <li>• Take with first bite of meal</li> <li>• Monitor: SCr and LFTs (baseline and periodically)</li> </ul>	I: 25mg po daily cc U: 50–100mg po tid cc M: 100mg po tid cc	eGFR <25–30mL/min (contraindication)	ODB ✓ <a href="#">LU 175</a> , <a href="#">176</a> <sup>22</sup> NIHB ✓	G: \$74–\$100









## Non-insulin pharmacotherapy

Agent, dosage forms, generic available <sup>(C)</sup> 17	A1C reduction (%) <sup>12,18</sup>	Other benefits, CVD outcomes <sup>12,18</sup>	Weight <sup>12,18</sup>	Harms, hypoglycemic risk <sup>12,18</sup> (negligible risk as monotherapy unless stated otherwise)	Comments <sup>12,18</sup> (titration, administration, monitoring, notes)	Dose <sup>18</sup> (I = initial, U = usual, M = max)	Renal dose <sup>12,18</sup>	Coverage (ODB <sup>17</sup> , NIHB <sup>19</sup> )	Drug cost for usual dose* (\$/100 days) <sup>17</sup>
<b>Dipeptidyl peptidase-4 inhibitors (DPP4i)</b>   <b>Avoid combining DPP4i with GLP1-RA</b>									
†Alogliptin (Nesina®) Tab: 6.25mg, 12.5mg, 25mg <sup>23</sup>	0.5–0.7	<ul style="list-style-type: none"> <li>Improved postprandial control</li> <li>Well tolerated option in older adults</li> <li>Neutral effect on CVD outcomes</li> </ul>	—	<ul style="list-style-type: none"> <li>Pancreatitis (rare), severe joint pain (rare)</li> <li>Alogliptin: possible worsening of HF in patients with acute coronary syndrome without a history of HF</li> <li>Saxagliptin: HF</li> </ul>	<ul style="list-style-type: none"> <li>Monitor: SCr (baseline and periodically), LFTs (baseline, especially for alogliptin)</li> <li>Alogliptin: may ↑ LFTs</li> <li>Linagliptin: no dosage adjustment in renal impairment</li> <li>Saxagliptin: avoid in HF</li> </ul>	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). <b>No dosage adjustment</b>	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 <small>(for patients who did not achieve glycemic control or who demonstrated intolerance to an adequate trial of metformin and a sulfonylurea)</small>	T: \$354






## Non-insulin pharmacotherapy

Agent, dosage forms, generic available <sup>(C)</sup> 17	A1C reduction (%) <sup>12,18</sup>	Other benefits, CVD outcomes <sup>12,18</sup>	Weight <sup>12,18</sup>	Harms, hypoglycemic risk <sup>12,18</sup> (negligible risk as monotherapy unless stated otherwise)	Comments <sup>12,18</sup> (titration, administration, monitoring, notes)	Dose <sup>18</sup> (I = initial, U = usual, M = max)	Renal dose <sup>12,18</sup>	Coverage (ODB <sup>17</sup> , NIHB <sup>19</sup> )	Drug cost for usual dose* (\$/100 days) <sup>17</sup>
<b>Glucagon-like peptide-1 receptor agonists (GLP1-RA) – short acting</b> <span style="float: right;">  </span>									
†Exenatide (Byetta®) Pre-filled pen (multiuse): 250µg/mL; 1.2mL, 2.4mL Pk <sup>24</sup>	0.6-1.4	<ul style="list-style-type: none"> <li>Unknown</li> </ul>	Loss of 1.6-3kg <sup>1</sup>	<ul style="list-style-type: none"> <li>SC injection</li> <li>GI side effects, acute pancreatitis/gallstone disease (rare)</li> <li>Contraindicated with personal/family hx of medullary thyroid cancer or multiple endocrine neoplasia syndrome type 2</li> </ul>	<ul style="list-style-type: none"> <li>Administer within 60 minutes before meal</li> <li>Injection daily or once weekly</li> <li>Initiate 5ug SC bid within 60 mins ac x 1 month, then 10ug bid</li> <li>If no improvement in blood glucose control after 3-4 months, consider alternatives</li> <li>Monitor: SCr (baseline and periodically)</li> <li>Less A1C lowering with short-acting agents than long-acting agents</li> </ul>	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		<ul style="list-style-type: none"> <li>Neutral effect on CVD outcomes</li> </ul>							

## Non-insulin pharmacotherapy





Agent, dosage forms, generic available <sup>(C)</sup> 17	A1C reduction (%) <sup>12,18</sup>	Other benefits, CVD outcomes <sup>12,18</sup>	Weight <sup>12,18</sup>	Harms, hypoglycemic risk <sup>12,18</sup> (negligible risk as monotherapy unless stated otherwise)	Comments <sup>12,18</sup> (titration, administration, monitoring, notes)	Dose <sup>18</sup> (I = initial, U = usual, M = max)	Renal dose <sup>12,18</sup>	Coverage (ODB <sup>17</sup> , NIHB <sup>19</sup> )	Drug cost for usual dose* (\$/100 days) <sup>17</sup>
<b>Glucagon-like peptide-1 receptor agonists (GLP1-RA) – longer acting</b>       <b>Avoid combining DPP4i with GLP1-RA</b>									
†Dulaglutide (Trulicity®) Pre-filled pen (single use): 0.75mg/0.5mL, 1.5mg/0.5mL <sup>25</sup>	0.6-1.4	• ↓ MACE in patients with clinical CVD	Loss of 1.6-3kg <sup>1</sup>	• 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)	• 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 <sup>26</sup>		• 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 <sup>27</sup>		• ↓ CV death in patients with clinical CVD • ↓ MACE in patients with clinical CVD • ↓ Nephropathy progression 		• 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/m <sup>2</sup> (obese) or ≥ 27 kg/m <sup>2</sup> (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	• 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		• Titrate after ≥ 4 weeks to minimize GI AE (see usual dose) • 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 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 <sup>10</sup>		• ↓ 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 10.5mg 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 ✓
†(Rybelsus®) Tab: 3mg, 7mg, 14mg <sup>28</sup>	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	

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<b>Insulin secretagogues – meglitinides</b>     									
Repaglinide (Gluconorm®) <sup>G</sup> Tab: 0.5mg, 1mg, 2mg	0.7-1.1	<ul style="list-style-type: none"> <li>Neutral CVD events and mortality</li> <li>Postprandial glycemia is especially reduced by meglitinides</li> <li>Meglitinides good for patients who skip meals</li> </ul>	Gain of 1.4-3.3 kg	<ul style="list-style-type: none"> <li>Repaglinide contraindicated when co-administered with clopidogrel or with gemfibrozil</li> <li>Minimal to moderate risk of hypoglycemia</li> </ul>	<ul style="list-style-type: none"> <li>Dose given within 30 minutes of meal (not taken if meal skipped)</li> <li>A minimum of 1 week should elapse between titration steps to assess response after each dose adjustment</li> <li>Dosage adjustment usually determined by fasting BG</li> <li>The preprandial 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)</li> <li>Monitor: SCr and LFTs (baseline and periodically)</li> </ul>	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 <sup>29</sup> NIHB ✓	G: \$79-\$167








## Non-insulin pharmacotherapy

Agent, dosage forms, generic available <sup>(C)</sup> 17	A1C reduction (%) <sup>12,18</sup>	Other benefits, CVD outcomes <sup>12,18</sup>	Weight <sup>12,18</sup>	Harms, hypoglycemic risk <sup>12,18</sup> (negligible risk as monotherapy unless stated otherwise)	Comments <sup>12,18</sup> (titration, administration, monitoring, notes)	Dose <sup>18</sup> (I = initial, U = usual, M = max)	Renal dose <sup>12,18</sup>	Coverage (ODB <sup>17</sup> , NIHB <sup>19</sup> )	Drug cost for usual dose* (\$/100 days) <sup>17</sup>
<b>Insulin secretagogues – sulfonylureas</b>     Risk of hypoglycemia: gliclazide < glimepiride < glyburide									
Gliclazide (Diamicon MR®) <sup>G</sup> SR tab: 30mg ER tab: 60mg	0.6-1.2	<ul style="list-style-type: none"> <li>Neutral effect on CVD outcomes</li> <li>Relatively rapid BG lowering response</li> <li>Gliclazide preferred over glyburide due to potential lower hypoglycemic risk</li> </ul>	Gain of 1.2-3.2 kg	<ul style="list-style-type: none"> <li>Minimal to moderate risk of hypoglycemia</li> <li>Caution in older adults</li> </ul>	<ul style="list-style-type: none"> <li>Titrate up by 30mg every 2 weeks</li> <li>Gliclazide MR 30mg = gliclazide 80mg</li> <li>Gliclazide MR can be given once daily with breakfast</li> <li>If CrCl &lt; 30mL/min, gliclazide is preferred</li> <li>Monitor: SCr and LFTs (baseline and periodically)</li> </ul>	I: 30mg MR po daily U: 60mg MR daily M: 120mg MR daily	eGFR <30mL/min (contraindicated)	ODB ✓ NIHB ✓	G: \$16 T: \$37
(Diamicon®) <sup>G</sup> Tab: 80mg				<ul style="list-style-type: none"> <li>Minimal to moderate risk of hypoglycemia</li> </ul>	<ul style="list-style-type: none"> <li>Titrate up by 80mg per week to target BG</li> <li>For doses of 160mg, administer bid with meals</li> <li>Monitor: SCr and LFTs (baseline and periodically)</li> </ul>	I: 40-80mg po daily in am cc U: 80mg bid cc M: 160mg bid cc		ODB ✓ NIHB ✓	G: \$29 T: \$94
Glimepiride (Amaryl®) <sup>G</sup> Tab: 1mg, 2mg, 4mg				<ul style="list-style-type: none"> <li>Moderate risk of hypoglycemia</li> <li>Caution in older adults with poor renal function</li> </ul>	<ul style="list-style-type: none"> <li>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</li> <li>Monitor: SCr and LFTs (baseline and periodically)</li> </ul>	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®) <sup>G</sup> Tab: 2.5mg, 5mg				<ul style="list-style-type: none"> <li>Moderate risk of hypoglycemia</li> <li>Caution in older adults with poor renal function</li> </ul>	<ul style="list-style-type: none"> <li>Continue initial dose for 5-7 days, then titrate by 2.5mg every 1-2 weeks</li> <li>If patient consumes a light breakfast, defer 1st dose until lunchtime</li> <li>If more than 10mg daily is required, the excess should be taken with the largest meal (e.g., evening meal)</li> <li>To prevent hypoglycemia, do not skip meals after taking glyburide</li> <li>Monitor: SCr and LFTs (baseline and periodically)</li> <li>Caution in older adults with poor renal function</li> </ul>	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 <sup>(C)</sup> 17	A1C reduction (%) <sup>12,18</sup>	Other benefits, CVD outcomes <sup>12,18</sup>	Weight <sup>12,18</sup>	Harms, hypoglycemic risk <sup>12,18</sup> (negligible risk as monotherapy unless stated otherwise)	Comments <sup>12,18</sup> (titration, administration, monitoring, notes)	Dose <sup>18</sup> (I = initial, U = usual, M = max)	Renal dose <sup>12,18</sup>	Coverage (ODB <sup>17</sup> , NIHB <sup>19</sup> )	Drug cost for usual dose* (\$/100 days) <sup>17</sup>
<b>Sodium-glucose cotransporter-2 inhibitors (SGLT2i) or gliflozins</b> 									
<b>Canagliflozin</b> (Invokana®) Tab: 100mg, 300mg	0.5-0.7	<ul style="list-style-type: none"> <li>↓ MACE, ↓ nephropathy progression and HF in patients with clinical CVD</li> </ul>	Loss of 2-3kg	<ul style="list-style-type: none"> <li>Genital mycotic infections, urinary tract infections, hypotension, ↑ LDL-C, euglycemic diabetic ketoacidosis ± hyperglycemia (rare),ourniere's gangrene (rare), acute kidney injury</li> </ul>	<ul style="list-style-type: none"> <li>Once daily dosing, usually in the morning because of ↑ urinary frequency and volume</li> <li>Monitor: blood pressure, weight, SCr, potassium, blood ketones if diabetic ketoacidosis symptoms (baseline, within 2-4 weeks of starting, then periodically)</li> </ul>	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 <small>(for patients who did not achieve glycemic control or who demonstrated intolerance to an adequate trial of metformin and a sulfonylurea)</small>	T: \$321
<b>Dapagliflozin</b> (Forxiga®) Tab: 5mg, 10mg		<ul style="list-style-type: none"> <li>↓ Nephropathy progression, HF or CV death in patients with clinical CVD</li> </ul>		<ul style="list-style-type: none"> <li>Caution with renal dysfunction, loop diuretics and older adults</li> </ul>		I, U: 5mg po daily am M: 10mg po daily am	eGFR < 45mL/min (not recommended) eGFR <30mL/min (contraindicated)	ODB ✓ NIHB ✓	T: \$304
<b>Empagliflozin</b> (Jardiance®) Tab: 10mg, 25mg		<ul style="list-style-type: none"> <li>↓ MACE and ↓ CVD death in patients with clinical CVD</li> <li>↓ Nephropathy progression, HF or CV death in patients with HF +/- ↓ in all cause mortality</li> </ul>		<ul style="list-style-type: none"> <li>Withhold treatment prior to major surgery or with serious illness/infections</li> <li>Canagliflozin: fracture risk, lower extremity amputation – avoid if prior amputation</li> <li>Dapagliflozin: avoid in bladder cancer</li> <li>On <a href="#">SAD-MANS</a> list<sup>21</sup></li> </ul>		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 <sup>(C)</sup> 17	A1C reduction (%) <sup>12,18</sup>	Other benefits, CVD outcomes <sup>12,18</sup>	Weight <sup>12,18</sup>	Harms, hypoglycemic risk <sup>12,18</sup> (negligible risk as monotherapy unless stated otherwise)	Comments <sup>12,18</sup> (titration, administration, monitoring, notes)	Dose <sup>18</sup> (I = initial, U = usual, M = max)	Renal dose <sup>12,18</sup>	Coverage (ODB <sup>17</sup> , NIHB <sup>19</sup> )	Drug cost for usual dose* (\$/100 days) <sup>17</sup>
<b>Thiazolidinediones (TZD)</b>   									
Pioglitazone HCL (Actos®) <sup>6</sup> Tab: 15mg, 30mg, 45mg	0.7-0.9	<ul style="list-style-type: none"> <li>• ↓ MACE, ↓ MI, ↓ stroke </li> </ul>	Gain of 2-5 kg <sup>21</sup>	<ul style="list-style-type: none"> <li>• Edema, HF, fractures, ↑ HDL-C, macular edema (rare), contraindicated in HF</li> <li>• Pioglitazone: possible bladder risk</li> </ul>	<ul style="list-style-type: none"> <li>• 4–12 weeks for max effect</li> <li>• Pioglitazone: increase by 15mg every 4 weeks</li> <li>• Rosiglitazone: increase to 8mg daily in 8-12 weeks if BG not at target</li> <li>• Monitor: SCr and LFTs (baseline and periodically)</li> <li>• Risk of heart failure, which may be higher if combined with insulin (combination not approved in Canada)</li> <li>• Rosiglitazone: requires special authorization from patient prior to prescribing</li> <li>• <a href="#">Health Canada restrictions</a>: rosiglitazone only to be used when all other oral agents have been tried alone or together and targets not reached<sup>30</sup></li> </ul>	I: 15mg daily po daily U: 30-45mg po daily M: 45mg po daily	eGFR <60mL/min (caution)	ODB × <a href="#">EAP</a> <sup>29</sup> NIHB ✓	G: \$247–\$366 T: \$388–\$578
Rosiglitazone (Avandia®) <sup>6</sup> Tab: 2mg, 4mg, 8mg		<ul style="list-style-type: none"> <li>• Possible MI risk </li> </ul>				I: 4mg po daily U: 4mg po daily to bid M: 8mg po daily	eGFR <60mL/min (caution)	<a href="#">EAP</a> <sup>29</sup> 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 <sup>(G) 17</sup>	Usual dose <sup>18</sup>	Coverage (ODB <sup>17</sup> , NIHB <sup>19</sup> )	Drug cost for usual dose* (\$/100 days) <sup>17</sup>
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 <sup>31</sup>	1 tab po daily	ODB × NIHB ×	T: \$563
†Metformin/canagliflozin (Invokamet®) Tab: 500/50mg, 850/50mg, 1000/50mg, 500/150mg, 850/150mg, 1000/150mg <sup>32</sup>	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 <sup>33</sup>	1 tab po bid cc	ODB ✓ NIHB ✓	T: \$283
Metformin/sitagliptin (Janumet®) Tab: 500/50mg, 850/50mg, 1000/50mg (Janumet XR®) ER tab: 500/50mg, 1000/50mg, 1000/100mg	1 tab po bid cc	ODB ✓ NIHB ✓	T: \$383
	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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