Stepwise Treatment of Type 2 Diabetes

(Recommendations from Diabetes Canada)


Step 1: At diagnosisa of type 2 diabetes in nonpregnant adults

Lifestyle modification: healthy eating (e.g., DASH diet, Mediterranean style diet, etc), aerobic activity 150 min/week, resistance training two to three days/week, achievement of healthier weight.

Pharmacotherapy:

- Prediabetes: metformin
- **A1C <1.5% above individualized targetb**: lifestyle modification with or without metformin for two to three months, then start or increase metformin if goal A1C not reached.
- **A1C ≥1.5% above individualized targetb**: start metformin with or without another agent (see chart below).
  - Symptomatic hyperglycemia or metabolic decompensation: insulin monotherapy OR insulin plus metformin
- **Overweight**: consider adjunctive orlistat (Xenical).
- **Established cardiovascular disease; age ≥40 years; age >30 years with diabetes duration >15 years; or age <40 years with microvascular disease; or warrants statin per lipid guidelines**: add a statin

Step 2: Add another agent. (See chart below.) For patients with clinical cardiovascular disease, use a drug with cardiovascular benefit: empagliflozin, liraglutide, or canagliflozin [except in patients with amputation]). After giving priority to clinical cardiovascular disease, individualize choice based on degree of hyperglycemia, weight, comorbidities (e.g., heart failure, liver disease), medication side effects (e.g., hypoglycemia), patient preferences, and cost.

Step 3: Add an agent from a different class OR add or intensify insulin.

Goal: Reach target A1C (A1C ≤7% for most adults) in three to six monthsb

a. **A1C of ≥6.5% is diagnostic of diabetes in adults. An A1C 6% to 6.4% indicates prediabetes.**

b. Individualize. Aim for A1C ≤7% (fasting glucose 4 to 7 mmol/L) for most patients. Higher A1C goal (>7% to 8.5%) may be appropriate for some patients (e.g., limited life expectancy, functionally dependent, frailty, dementia, long-standing diabetes, advanced cardiovascular disease, severe hypoglycemic episodes, or hypoglycemic unawareness). Lower goal (≤6.5%) may be appropriate in some patients (e.g., newly diagnosed, long life expectancy, no advanced cardiovascular disease, low hypoglycemia risk, desire to reduce retinopathy or chronic kidney disease risk).
<table>
<thead>
<tr>
<th>Drug or Drug Class</th>
<th>Expected A1C drop when added to metformin</th>
<th>Notable Adverse Effects</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acarbose (<em>Glucobay</em>) <em>(Alpha-glucosidase inhibitor)</em></td>
<td>0.7% to 0.8%</td>
<td>GI</td>
<td>Low risk of hypoglycemia when used as monotherapy</td>
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<tr>
<td>Thiazolidinediones <em>(TZD)</em> *(pioglitazone [e.g., <em>Actos</em>]) <em>(Insulin sensitizer)</em></td>
<td>0.8% to 0.9%</td>
<td>Low risk of hypoglycemia when used as monotherapy</td>
<td>Weight neutral</td>
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<td>Taken with meals¹</td>
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<td>Not for initial therapy if A1C ≥ 8.5%³</td>
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<td>Reduces postprandial glucose²</td>
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<td>Glycemic control better sustained over diabetes course than metformin or sulfonylurea³</td>
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<td>Pioglitazone increases HDL, reduces triglycerides, and increases LDL particle size⁵</td>
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<td>Contraindicated in heart failure (all stages [I to IV])⁵,⁶</td>
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<td>Pioglitazone contraindicated in patients with history of bladder cancer or uninvestigated macroscopic haematuria. Assess risk factors for bladder cancer and counsel patients to report haematuria, dysuria, or urinary frequency.⁵</td>
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*(November 2010: Health Canada announced the restricted use of rosiglitazone-containing products [*Avandia*, etc] due to an increased risk of cardiovascular events. Restricted to patients for whom all other oral agents, as monotherapy or in combination, are ineffective or inappropriate. Requires informed consent.)⁴*
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<td>Insulin</td>
<td>0.9% to 1.2%, or more</td>
<td>Highest risk of hypoglycemia (educate patient to prevent, recognize, and manage)</td>
<td>Consider initial therapy with insulin plus metformin if blood glucose is ≥16.7 mmol/L and/or A1C is ≥10%&lt;sup&gt;7&lt;/sup&gt; Usually start with basal insulin at bedtime</td>
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<tr>
<td>Meglitinides</td>
<td>0.7% to 1.1%</td>
<td>Hypoglycemia (educate patient to prevent, recognize, and manage)</td>
<td>Three or four times daily dosing Can hold dose if skipping meal, to reduce risk of hypoglycemia&lt;sup&gt;3&lt;/sup&gt; Consider over sulfonylureas (less hypoglycemia, better postprandial control) Less weight gain than sulfonylureas Relatively short-lived efficacy Discontinue when more complex insulin regimens (e.g., basal plus prandial insulins) are started</td>
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<tr>
<td>Metformin</td>
<td>1% (as monotherapy)</td>
<td>GI</td>
<td>Weight neutral Ameliorates insulin-associated weight gain&lt;sup&gt;3&lt;/sup&gt; A first-line agent after diet and exercise Metformin can be initiated if eGFR is &gt;45 mL/min/1.73 m&lt;sup&gt;2&lt;/sup&gt;.&lt;sup&gt;8&lt;/sup&gt; Discontinue if eGFR later falls below 30 mL/min/1.73 m&lt;sup&gt;2&lt;/sup&gt;.&lt;sup&gt;8&lt;/sup&gt; Inexpensive</td>
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<td>Lactic acidosis (rare) in patients with cardiovascular, renal, or hepatic dysfunction</td>
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| Alogliptin (*Nesina*), Linagliptin (*Trajenta*), Sitagliptin (*Januvia*), Saxagliptin (*Onglyza*) (*Dipeptidyl peptidase-4 [DPP-4] inhibitors*) | 0.5% to 0.7% | Low risk of hypoglycemia as monotherapy  
May be associated with pancreatitis (rare)  
New or worsening heart failure (saxagliptin, alogliptin)  
May cause severe joint pain | Weight neutral  
Postprandial efficacy  
Dosage modification with renal impairment needed with sitagliptin, saxagliptin, and alogliptin  
CYP3A4 interactions with saxagliptin and linagliptin  
Expensive |
| Sulfonylurea (e.g., glimepiride [e.g., *Amaryl*], glyburide [e.g., *Diabeta*], gliclazide [e.g., *Diamicron*]) (*Insulin secretagogues*) | 0.7% to 1.3% | Hypoglycemia (educate patient to prevent, recognize, and manage)  
Weight gain (highest with glyburide) | Less hypoglycemia with glimepiride or gliclazide vs glyburide  
Tolbutamide rarely used  
Relatively short-lived efficacy  
Discontinue when more complex insulin regimens (e.g., basal plus prandial insulins) are started  
Inexpensive  
Avoid chlorpropamide in elderly or renal impairment |
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<td>Canagliflozin</td>
<td>0.4% to 0.7%</td>
<td>Increased serum creatinine. Acute kidney injury reported with canagliflozin or dapagliflozin (may require dialysis). Urinary tract infection (may be severe) Genital fungal infections (male and female) Increased urination Hypotension Hyperkalemia (canagliflozin) Small LDL increase (0.1 to 0.2 mmol/L, or about 3%) Dapagliflozin may increase risk of bladder cancer. Use with pioglitazone is not recommended. Association with ketoacidosis (rare) May be associated with acute pancreatitis (rare). Rare cases of Fournier’s gangrene in men and women, with onset early (days) and late in therapy (~2 years). Fractures and decrease in</td>
<td>Weight loss 2 to 3 kg Systolic blood pressure reduction 3 to 5 mmHg Low risk of hypoglycemia with monotherapy Canagliflozin and ertugliflozin are contraindicated if eGFR &lt;45 mL/min/1.73m²; do not start if eGFR &lt;60 mL/min/1.73m². Canagliflozin max dose is only for patients with eGFR ≥60 mL/min/1.73 m² and a low risk of harm due to volume depletion. Dapagliflozin contraindicated if eGFR &lt;60 mL/min/1.73m². Empagliflozin contraindicated if eGFR &lt;30 mL/min/1.73m². Canagliflozin may increase digoxin levels. May require dose increase with enzyme inducers. Not recommended in severe hepatic impairment When used as an add-on, consider insulin/sulfonylurea/meglitinide dose reduction Risk factors for acute kidney injury include use of NSAIDs, ACEIs, ARBS, or diuretics, or reduced blood volume, chronic kidney disease, and heart failure. Empagliflozin reduces cardiovascular mortality (NNT = 45 for three years), overall mortality (NNT = 39 for three years), and hospitalization due to heart failure (NNT = 71 for three years) in type 2 diabetes patients with cardiovascular disease. CANVAS (CANagliflozin cardioVascular Assessment Study) found canagliflozin use for about 3.5 years can decrease cardiovascular mortality by 32% and overall mortality by 25% in type 2 diabetes patients with cardiovascular disease. [Evidence level A-1].</td>
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<tr>
<td>Dapagliflozin</td>
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<td>Empagliflozin</td>
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<td>Ertugliflozin</td>
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(Sodium glucose co-transporter 2 [SGLT2] inhibitor)
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<td>SGLT2 inhibitors, continued.</td>
<td></td>
<td>BMD (canagliflozin).(^{16}) Dapagliflozin is also linked to fractures in patients with moderate renal impairment.(^{17}) Amputations may occur in about 6 of every 1,000 patients treated with canagliflozin over one year, compared to about 3 in every 1,000 patients on other diabetes meds.(^{19,20}) Canagliflozin use in patients at high CV risk for about 3.5 years may increase risk of amputations, NNH ~77 [Evidence level A-1].(^{19,21})</td>
<td>years when added to standard glucose-lowering therapy in patients with type 2 diabetes and very high CV risk (&gt;70% of patients had atherosclerotic CV disease), may reduce the combined endpoint of CV mortality, nonfatal MI, or nonfatal stroke (NNT=224). However, when evaluated individually, these endpoints were no longer significantly reduced.(^{19})</td>
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<td>Dulaglutide (Trulicity), Liraglutide (Victoza), Lixisenatide (Adlyxine), Exenatide (Byetta, Bydureon), Semaglutide (Ozempic) (Glucagon-like peptide-1 [GLP-1] agonists) Also see our chart, Comparison of GLP-1 Agonists.</td>
<td>1% (See GLP-1 agonist chart for individual agents)</td>
<td>GI Low risk of hypoglycemia as monotherapy Reports of pancreatitis (rare)(^{23}) Associated with renal insufficiency(^{23}) May be associated with gallbladder disease (liraglutide, exenatide)(^{24}) May lead to retinopathy complications (semaglutide)(^{25})</td>
<td>Weight loss Postprandial efficacy(^3) More weight loss and efficacy than DPP-4 inhibitors Expensive Injectable Liraglutide may reduce cardiovascular death (NNT = 77 for four years) and overall mortality (NNT = 71 for four years) in patients with high cardiovascular risk or cardiovascular disease [Evidence level A-1].(^{26}) Semaglutide use in patients with CV disease, chronic kidney disease, or CV risk factors for about two years may reduce the combined endpoint of CV death, nonfatal MI, or nonfatal stroke (NNT=44) [Evidence level A-1].(^{27}) When evaluated individually, only nonfatal stroke was significant.(^{27})</td>
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Levels of Evidence
In accordance with our goal of providing Evidence-Based information, we are citing the LEVEL OF EVIDENCE for the clinical recommendations we publish.

<table>
<thead>
<tr>
<th>Level</th>
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</table>
| A     | Good-quality patient-oriented evidence.* | 1. High-quality RCT  
2. SR/Meta-analysis of RCTs with consistent findings  
3. All-or-none study |
| B     | Inconsistent or limited-quality patient-oriented evidence.* | 1. Lower-quality RCT  
2. SR/Meta-analysis with low-quality clinical trials or studies with inconsistent findings  
3. Cohort study  
4. Case control study |
| C     | Consensus; usual practice; expert opinion; disease-oriented evidence (e.g., physiologic or surrogate endpoints); case series for studies of diagnosis, treatment, prevention, or screening. | |

*Outcomes that matter to patients (e.g., morbidity, mortality, symptom improvement, quality of life).  
RCT = randomized controlled trial; SR = systematic review  

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References

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Cite this document as follows: Clinical Resource, Stepwise Treatment of Type 2 Diabetes. Pharmacist's Letter/Prescriber’s Letter. June 2018.

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