Not All Oral Anti-Diabetes Medications Are Created Equal

Start treatment with behaviour interventions[1]

Healthy behaviour interventions, such as nutritional therapy, physical activity, and weight management, are recommended as some of the initial treatments (depending on diagnostic levels) in the management of type 2 diabetes (T2DM).

When is it time to consider medication?[2]

In addition to these behaviour interventions, most people will need medication to help keep their blood glucose levels within their target range.

The treatment of T2DM involves a multi-faceted approach to treat and prevent the symptoms of hyperglycemia, including dehydration and fatigue, as well as to reduce the risk of cardiovascular (CV) and microvascular complications.[3]

Deciding on the next step—the role of oral anti-diabetes (OAD) medications[3]

For most patients, the first-line glucose-lowering medication is metformin, because of its safety, low cost, and possible heart benefits. However, if and when metformin and behaviour interventions are not enough, or are not tolerated, to adequately control a person's blood glucose levels, a second-line glucose-lowering medication should be added.

When selecting a second-line glucose-lowering medication, it is important to remember that not all OADs are created equal.

CV, cardiovascular; T2DM, type 2 diabetes mellitus.

Management of Type 2 Diabetes[1,4-6]

HEALTHY BEHAVIOUR INTERVENTIONS

At diagnosis of type 2 diabetes

Start healthy behaviour interventions (nutritional therapy, weight management, physical activity) ± metformin

A1C < 1.5% above target	A1C ≥ 1.5% above target	Symptomatic hyperglycemia and/or metabolic decompensation*
If not at glycemic target within 3 months, start/increase metformin	Start **metformin** immediately Consider a second concurrent antihyperglycemic agent	Initiate insulin† ± metformin
If not at glycemic target		If not at glycemic target

Clinical CVD?

Yes

Start antihyperglycemic agent with demonstrated CV benefit:

Jardiance® (empagliflozin)

Victoza® (liraglutide)

Invokana® (canagliflozin)‡

If not at glycemic target

No

Add additional antihyperglycemic agent best suited to the individual based on the following:

Clinical Considerations	Choice of Agent
Avoidance of hypoglycemia and/or weight gain with adequate glycemic efficacy	DPP-4 inhibitor, GLP-1 receptor agonist, or SGLT2 inhibitor
Other considerations: Reduced eGFR and/or albuminuria, clinical CVD or CV risk factors, degree of hyperglycemia, other comorbidities (CHF, hepatic disease§), planning pregnancy,§ cost/coverage, patient preference	**Look inside to learn about additional factors to consider when selecting an oral anti-diabetes medication**

* May include dehydration, DKA, HHS.
† Insulin may be required at any point for symptomatic hyperglycemia/metabolic decompensation or if unable to achieve glycemic targets with other antihyperglycemic agents.
‡ Avoid in people with prior lower extremity amputation.
§ See respective Product Monographs.
CHF, congestive heart failure; CV, cardiovascular; CVD, cardiovascular disease; DKA, diabetic ketoacidosis; DPP-4, dipeptidyl peptidase-4; eGFR, estimated glomerular filtration rate; GLP-1, glucagon-like peptide-1; HHS, hyperosmolar hyperglycemic state; SGLT2, sodium-glucose cotransporter 2.

Clinical considerations for oral anti-diabetes medication selection[3,4,6-23]

Class	Drug	Dose(s)	A1C lowering (%)	Weight	CV outcomes*	Renal function	Hypoglycemia	Other considerations
Biguanides	**Glucophage®** (Metformin) **Glumetza®** (Metformin ER)	500 mg, 850 mg 500 mg, 1000 mg	~1.0	Neutral	**Metformin** • Reduction in MI in those living with overweight	Not recommended in patients with renal impairment or when renal function is unknown; initial and periodic monitoring of hematologic parameters (e.g., hemoglobin/hematocrit) and renal function (serum creatinine) should be performed at least annually	Rare	Should not be initiated in patients > 80 years of age, unless CrCl demonstrates renal function is not reduced; GI side effects; vitamin B12 deficiency—periodic monitoring of vitamin B12 should be performed; should be avoided in patients with hepatic disease
GLP-1 receptor agonists Injectable GLP-1 receptor agonists are also available	**Rybelsus®** (Semaglutide tablets)	3 mg, 7 mg, 14 mg	0.9–1.4	↓2.2–4.4 kg	Non-inferior to placebo • 21% reduction in MACE	No dosage adjustment recommended based on renal impairment; monitor renal function in patients with renal insufficiency reporting severe adverse GI reactions	Rare	No dosage adjustment required in patients ≥ 65 years of age; greater sensitivity in some older individuals cannot be ruled out; GI side effects common; contraindicated in patients who have a personal or family history of MTC or in patients with MEN 2; patients with a history of diabetic retinopathy should be monitored for worsening and treated according to clinical guidelines

SGLT2 inhibitors	**Forxiga®** (Dapagliflozin)	5 mg, 10 mg	0.4–0.7	↓2.0–3.0 kg	**Dapagliflozin**
					• Non-inferior to placebo
					  ○ 7% reduction in MACE
					Empagliflozin
					• Non-inferior and superior to placebo
					  ○ 14% reduction in 3-point MACE
					Canagliflozin
					• Non-inferior to placebo
					  ○ 18% reduction in MACE
						Caution with loop diuretics; may cause dose-dependent increase in serum creatinine and decrease in eGFR; therefore, renal function must be assessed prior to initiation of therapy and periodically thereafter. If acute kidney injury occurs, discontinue promptly and institute treatment
						Dapagliflozin
						• Not recommended in patients with eGFR < 45 mL/min/1.73 m²
						Empagliflozin
						• Not recommended in patients with eGFR < 30 mL/min/1.73 m²
						Canagliflozin
						• More frequent renal function monitoring recommended in patients whose eGFR is < 60 mL/min/1.73 m²
							Rare	Caution in patients ≥ 65 years of age; reduced progression of nephropathy and reduction in heart failure in participants with clinical CVD (empagliflozin and canagliflozin); genital mycotic infections, urinary tract infections; hypotension; LDL-C levels should be monitored due to small increases in LDL-C; dapagliflozin not to be used with bladder cancer; increased risk of fractures and extremity amputation with canagliflozin (avoid if prior amputation); reduced progression of nephropathy and reduction in heart failure in participants with clinical CVD with empagliflozin and canagliflozin; treatment should be withheld prior to major surgery or with serious illness or infection; careful monitoring of volume status is recommended for patients at risk for volume depletion; may increase blood ketones; rare cases of DKA (which may occur without hyperglycemia), patients should be assessed for DKA immediately if non-specific symptoms occur; if DKA is suspected or diagnosed, treatment should be discontinued immediately

	Jardiance® (Empagliflozin)	10 mg, 25 mg						
	Invokana® (Canagliflozin)	100 mg, 300 mg						
DPP-4 inhibitors	**Januvia®** (Sitagliptin)	25 mg, 50 mg, 100 mg	0.5–0.7	Neutral	Non-inferior to placebo	**Sitagliptin and alogliptin** • Dose adjustment required in patients with moderate or severe renal impairment or ESRD requiring dialysis **Sitagliptin, alogliptin, and saxagliptin** • Renal function must be assessed prior to initiation of therapy and periodically thereafter **Saxagliptin** • Caution in patients with severe renal impairment; not recommended for patients with ESRD requiring hemodialysis **Linagliptin** • Caution in patients with ESRD and patients on dialysis	Rare	No dosage adjustment required in patients ≥ 65 years of age; greater sensitivity in some older individuals cannot be ruled out; rare cases of pancreatitis; rare cases of severe joint pain; caution with saxagliptin in participants with heart failure; use in patients with severe hepatic impairment is not recommended; saxagliptin is also not recommended in patients with moderate hepatic impairment; monitoring for skin disorders is recommended
	Nesina® (Alogliptin)	6.25 mg, 12.5 mg, 25 mg						
	Onglyza® (Saxagliptin)	2.5 mg, 5 mg						
	Trajenta™ (Linagliptin)	5 mg						
Alpha-glucosidase inhibitors	**Glucobay®** (Acarbose)	50 mg, 100 mg	0.7–0.8	Neutral	—	Not recommended in patients with severe renal impairment	Rare	Elderly patients may require more intensive supervision and follow-up; GI side effects common; 3 times daily dosing; contraindicated in patients with IBD, colonic ulceration, partial intestinal obstruction or in patients predisposed to intestinal obstruction; liver enzyme monitoring should be considered during the first 6–12 months of treatment; in patients with history of liver impairment or liver disease, liver enzymes should be measured prior to starting treatment and monitored regularly during the first year
Sulfonylureas	**Diamicron®** (Gliclazide)	80 mg	0.7–1.3	↑1.5–2.5 kg	—	Make dosage adjustments cautiously in patients with renal insufficiency **Gliclazide and gliclazide MR** • Not recommended in patients with severe renal impairment; in patients with impaired renal function; blood and urine glucose should be monitored regularly	Minimal/ moderate risk	Elderly patients are particularly susceptible to hypoglycemia induced by sulfonylureas; elderly patients (malnourished, with impaired hepatic, renal, or adrenal function) will require periodic monitoring and special care; occasional mild-to-moderate elevations of hepatic enzymes, LDH, and creatinine and decrease in natremia have been observed with gliclazide and gliclazide MR; gliclazide preferred over glyburide due to lower risk of hypoglycemia, CV events, and mortality, relatively rapid BG-lowering response; hepatic function should be assessed before initiating therapy and assessed periodically in patients with impaired hepatic function; periodic assessment of cardiovascular, ophthalmic, hematologic, renal, and hepatic status is recommended
	Diamicron® MR (Gliclazide MR)	30 mg, 60 mg						
	Amaryl® (Glimepiride)	1 mg, 2 mg, 4 mg						
	DiaBeta® (Glyburide)	2.5 mg, 5 mg						
Meglitinides	**Starlix®** (Nateglinide)	60 mg, 120 mg	0.7–1.1	↑0.7–1.8 kg	—	**Nateglinide** • No dosage adjustment required in patients with mild-to-severe renal insufficiency **Repaglinide** • Caution in patients with renal impairment or renal failure requiring hemodialysis	Minimal/ moderate risk	No dose adjustment required for patients ≥ 65 years of age; postprandial glycemia is especially reduced; requires 3 times daily dosing; glucose monitoring should be considered in patients at increased risk of hypoglycemia • Repaglinide ○ Not recommended for patients > 75 years of age; monitoring recommended in patients 65–75 years of age with renal, hepatic, or other medical problems; contraindicated when coadministered with clopidogrel or with gemfibrozil
	GlucoNorm® (Repaglinide)	0.5 mg, 1 mg, 2 mg						
Thiazolidinediones	**Actos®** (Pioglitazone)	15 mg, 30 mg, 45 mg	0.8–0.9	↑2.5–5.0 kg	Neutral **Rosiglitazone** • Increase in CV death or CV hospitalization in patients with a history of ischemic heart disease	No dose adjustment required in patients with renal insufficiency **Rosiglitazone** • Caution in patients with severe renal insufficiency	Minimal/ moderate risk	Rosiglitazone should be used with caution in patients > 75 years of age; mild increase in HDL-C, may induce edema and/or congestive heart failure; rare occurrence of macular edema; higher occurrence of fractures; liver enzyme monitoring is recommended prior to initiation of therapy in all patients and periodically thereafter; pioglitazone not to be used with bladder cancer; controversy regarding MI risk for rosiglitazone
	Avandia® (Rosiglitazone)	2 mg, 4 mg, 8 mg						

* CV outcomes derived from the respective Product Monographs.

BG, blood glucose; CrCl, creatinine clearance; CV, cardiovascular; CVD, cardiovascular disease; DKA, diabetic ketoacidosis; DPP-4, dipeptidyl peptidase-4; eGFR, estimated glomerular filtration rate; ER, extended release; ESRD, end-stage renal disease; GI, gastrointestinal; GLP-1, glucagon-like peptide-1; HDL-C, high-density lipoprotein cholesterol; IBD, inflammatory bowel disease; LDH, lactate dehydrogenase; LDL-C, low-density lipoprotein cholesterol; MACE, major cardiovascular event; MI, myocardial infarction; MR, modified release; MTC, medullary thyroid carcinoma; SGLT2, sodium-glucose cotransporter 2.

Refer to the respective Product Monographs and the 2018 Diabetes Canada Guidelines (guidelines.diabetes.ca/cpg/chapter13) for complete recommendations and approaches to individualize patient care

Managing Patients Who Are Sick or at Risk of Dehydration

If a patient begins to feel unwell and is unable to maintain adequate fluid intake, or they experience an acute decline in renal function (e.g., due to GI adverse events or dehydration), give them a "sick day" medication list that instructs them to **hold medications** that will:[3]

1. **Increase their risk for a decline in kidney function, such as:**
   - Angiotensin-converting enzyme inhibitors
   - Angiotensin receptor blockers
   - Direct renin inhibitors
   - Nonsteroidal anti-inflammatory drugs
   - Diuretics
   - SGLT2 inhibitors
2. **Reduce renal clearance and increase the risk of adverse events, such as:**
   - Metformin
   - Sulfonylureas (i.e., gliclazide, glimepiride, glyburide)

When your patients living with T2DM are sick or at risk of dehydration, remember:

S Sulfonylureas
A ACE inhibitors
D Diuretics, direct renin inhibitors

M Metformin
A Angiotensin receptor blockers
N Nonsteroidal anti-inflammatory
S SGLT2 inhibitors

It is also important to inform your patients that when they feel unwell their doses of insulin or noninsulin glucose-lowering medications may need to be adjusted and they will need to increase the frequency of blood glucose self-monitoring.

Refer to the 2018 Diabetes Canada Guidelines (http://guidelines.diabetes.ca/cpg/appendices/appendix8) for complete sick-day medication list instructions

ACE, angiotensin-converting enzyme; GI, gastrointestinal; SGLT2, sodium-glucose cotransporter 2; T2DM, type 2 diabetes mellitus.

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Novo Nordisk Canada Inc., Tel: (905) 629-4222 or 1-800-465-4334. www.novonordisk.ca

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