Table 1
Antihyperglycemic agents for use in type 2 diabetes.

Class and mechanism of action	Drug	Cost*	A1C lowering†	Weight†	Cautions	Other therapeutic considerations
Biguanide: Enhances insulin sensitivity in liver and peripheral tissues by activation of AMP-activated protein kinase	Metformin Metformin extended-release	$ $$	Approx. 1.0%††	Neutral	Use lower dose if eGFR <60ml/min/1.73m^2 Do not initiate if eGFR is <30ml/min/1.73m^2 GI side effects	Hold during acute illnesses associated with risk for dehydration or procedures associated with high risk of acute kidney injury Provide education regarding sick day management (Appendix 8: 2018 CPG) Can reduce vitamin B_{12} absorption
Incretin: Increases glucose dependent insulin release, slows gastric emptying, inhibits glucagon release	**GLP1-RA** Short-acting Exenatide Lixisenatide Longer-acting Dulaglutide Exenatide extended-release Liraglutide Semaglutide	$$$$	0.6-1.4%	Loss of 1.1- 4.4 kg	GI side effects Monitor retinopathy (especially if pre-existing retinopathy) because of risk of progression with rapid drops in A1C Contraindicated with personal/family history of medullary thyroid cancer or multiple endocrine neoplasia syndrome type 2 Caution with a history of pancreatitis or pancreatic cancer	Less A1C reduction with short-acting agents No proven CV benefit with lixisenatide or short-acting exenatide
	DPP4i Alogliptin Linagliptin Saxagliptin Sitagliptin	$$$	0.5-0.7%	Neutral	Risk of heart failure with saxagliptin Caution with a history of pancreatitis or pancreatic cancer	Rare cases of pancreatitis Rare cases of severe joint pain
SGLT2i: Reduces glucose reabsorption by the kidney	Canagliflozin Dapagliflozin Empagliflozin *Ertugliflozin******	$$$	0.5-0.7%	Loss of 2-3 kg	Genital mycotic infections Urinary tract infections Hypotension Rare cases of diabetic ketoacidosis (which may occur without hyperglycemia) Caution required when combined with low carbohydrate eating patterns or with suspected insulin deficiency Good foot care always recommended – particularly in those with high-risk feet (loss of protective sensation, previous foot ulcer or amputation) Dapagliflozin contraindicated with bladder cancer	Less glycemic efficacy at lower GFR Do not initiate if eGFR is <30ml/min/1.73m^2 Hold prior to major surgery or during serious illness or infections Hold during acute illnesses associated with risk for dehydration or procedures associated with high risk of acute kidney injury Provide education regarding sick day management (Appendix 8: 2018 CPG) Small reduction in eGFR (<20%) expected when initiated Only CV safety shown for ertugliflozin
Alpha-glucosidase inhibitor: Inhibits pancreatic α-amylase and intestinal α-glucosidase	Acarbose	$$	0.7-0.8%†††	Neutral	GI side effects common	Requires 3 times daily dosing

(continued on next page)

Table 1 *(continued)*

Class and mechanism of action	Drug	Cost*	A1C lowering†	Weight†	Cautions	Other therapeutic considerations
Insulin: Activates insulin receptors to regulate metabolism of carbohydrate, fat and protein	**Bolus (prandial) Insulins** Rapid-acting analogues Aspart Aspart (faster-acting) Glulisine Lispro U-100 Lispro U-200 Short-acting Regular	$-$$$$ (depending on agent and dose)	0.9-1.2% or more	Gain	Education required regarding • blood glucose monitoring • preventing, detecting and treating hypoglycemia Numerous formulations and delivery systems • increases complexity and risk for errors	Potentially greatest A1C reduction and (theoretically) no maximum dose Dose escalation may be limited by hypoglycemia Numerous formulations and delivery systems • allows for regimen flexibility
	Basal Insulins Intermediate-acting NPH Long-acting analogues Degludec U-100 Degludec U-200 Detemir Glargine U-100 Glargine U-300			Gain of 1.0-2.0 kg		
	Premixed Insulins Premixed regular-NPH Biphasic insulin aspart Lispro/lispro protamine suspension			Gain of 2.0-3.5 kg		
	Other Concentrated U-500 regular			Gain		Recommended in individuals taking >200 units basal insulin per day by 4 or more injections** Used 2 or 3 times daily instead of basal insulin
	Insulin/GLP1 fixed-ratio combinations Degludec/liraglutide Glargine/lixisenatide	$$$-$$$$		Neutral		Can mitigate weight gain seen with initiation or intensification of basal insulin Maximum dose of insulin 50 units for degludec and liraglutide or 60 units for glargine and lixisenatide
Insulin secretagogue: Activates sulfonylurea receptor on β-cell to stimulate endogenous insulin secretion	**Sulfonylureas** Gliclazide Gliclazide-modified release Glimepiride Glyburide	$	0.6-1.2%	Gain of 1.2-3.2 kg	Higher risk of hypoglycemia with glyburide Risk of hypoglycemia increased with fasting or with eGFR <60ml/min/1.73m^2 Provide education regarding sick day management (Appendix 8: 2018 CPG)	Glycemic control is relatively rapid but may not be durable Gliclazide preferred over glyburide due to lower risk of hypoglycemia Glimepiride showed CV safety similar to DPP4 (linagliptin) in CAROLINA trial

(continued on next page)

Table 1 *(continued)*

Class and mechanism of action	Drug	Cost*	A1C lowering†	Weight†	Cautions	Other therapeutic considerations
	Meglitinides Repaglinide	$$	0.7-1.1%	Gain of 1.4-3.3 kg	Repaglinide contraindicated when coadministered with clopidogrel or with gemfibrozil	Useful to reduce postprandial hyperglycemia Requires dosing with each meal (e.g. 3 times daily) Lower risk for hypoglycemia than sulfonylureas in renal impairment
Thiazolidinedione: Enhances peripheral and hepatic insulin sensitivity by activation of peroxisome proliferator activated receptor-gamma receptors	Pioglitazone Rosiglitazone	$$$	0.7-0.9%	Gain of 2.0-2.5 kg	Greater weight gain in some individuals May induce edema and/or congestive heart failure	Durable glycemic control Rare occurrence of macular edema • Higher occurrence of fractures • Pioglitazone not to be used with bladder cancer • Uncertainty about CV safety with rosiglitazone, suggestion of increased risk of MI

Agents are listed in alphabetical order.

* Estimated costs based on recommended daily doses (from DiPiro Pharmacotherapy: A Pathophysiologic Approach, 11th edition) and reviewing provincial formulary costs of generic agents (if available) from AB and ON. Where costs differed between provinces, the higher cost was used. $ = less than 50¢ per day, $$ = 50¢ to $1 per day, $$$ = $1 to $4 per day and $$$$ = >$4 per day.

† Values are the min and max point estimates from 3 meta or network metanalyses (26,27,47). It does not represent the range of responses in treated populations. Large variations between individuals in degree of weight gain can be seen with insulin and thiazolidinediones.

†† Glycated hemoglobin (A1C) lowering vs placebo, Sherifali D, Nerenberg K, Pullenayegum E, Cheng JE, Gerstein HC. *Diabetes Care* 2010;33:1859–64.

††† Based on data from 2 trials in <100 patients.

** Hood RC, Arakaki RF, Wysham C, Li YG, Settles JA, Jackson JA. Two treatment approaches for human regular U-500 insulin in patients with type 2 diabetes not achieving adequate glycemic control on high-dose U-100 insulin therapy with or without oral agents: A randomized, titration-to-target clinical trial. *Endocr Pract* 2015;21:782–93.

*** VERTIS (cardiovascular [CV] outcome trial for ertugliflozin) presented at American Diabetes Association (ADA) June 2020 showed noninferiority for MACE. Manuscript not published at time of writing.

Approx. , approximately; *CPG* , clinical practice guidelines; *DPP4i* , dipeptidyl peptidase-4 inhibitors; *eGFR* , estimated glomerular filtration rate; *GI*, gastrointestinal; *GLP1-RA* , glucagon-like peptide-1 receptor agonists; *MI*, myocardial infarction; *SGLT2i* , sodium-glucose cotransporter 2 inhibitors.