Table 1. Antihyperglycemic agents for use in type 2 diabetes

DRUG	EXPECTED† DECREASE IN A1C	RELATIVE† A1C LOWERING	HYPO-GLYCEMIA	EFFECT IN CV OUTCOME TRIAL	OTHER THERAPEUTIC CONSIDERATIONS
Class* and Mechanism of Action **ALPHA-GLUCOSIDASE INHIBITOR:** inhibits pancreatic alpha-amylase and intestinal alpha-glucosidase					
Acarbose (Glucobay)	0.6%	↓	Negligible risk as monotherapy	–	• Not recommended as initial therapy in people with marked hyperglycemia (A1C ≥ 8.5%) • Weight neutral as monotherapy • GI side effects
Class* and Mechanism of Action **DPP-4 INHIBITOR:** amplifies incretin pathway activation by inhibition of enzymatic breakdown of endogenous GLP-1 and GIP					
Alogliptin (Nesina)	0.7%	↓↓	Negligible risk as monotherapy	Neutral	• Weight neutral • Improved post-prandial control • Rare cases of pancreatitis • Caution with saxagliptin in heart failure
Linagliptin (Trajenta)				–	
Sitagliptin (Januvia)				Neutral	
Saxagliptin (Onglyza)				Neutral	
Class* and Mechanism of Action **GLP-1 RECEPTOR AGONIST:** activates incretin pathway by utilizing DPP-4 resistant analogue to GLP-1					
Albiglutide (Eperzan)	1.0%	↓↓ to ↓↓↓	Negligible risk as monotherapy	–	• Improved postprandial control • Significant weight loss • Nausea and vomiting • Administration parenteral • Rare cases of pancreatitis • Parafollicular cell hyperplasia • Contraindicated with personal/family history of medullary thyroid cancer or multiple endocrine neoplasia syndrome type 2
Dulaglutide (Trulicity)				–	
Exenatide (Byetta)				–	
Exenatide QW (Bydureon)				–	
Liraglutide (Victoza)				–	

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Class* and Mechanism of Action **INSULIN:** activates insulin receptors to regulate metabolism of carbohydrate, fat, and protein					
Bolus (prandial) Insulins **Rapid-acting analogues** • Aspart (NovoRapid) • Glulisine (Apidra) • Lispro (Humalog) • Lispro U200 (Humalog U200) **Short-acting** • Regular (Humulin-R, Novolin geToronto) (Note: Pork regular insulin [Hypurin Regular Insulin Pork] and pork isophane insulin [Hypurin NPH Insulin Isophane] are available but rarely used)	0.9 – 1.1%	↓↓↓	Significant risk	–	• Potentially greatest A1C reduction and no maximal dose • Numerous formulations and delivery systems (including subcutaneous-injectable) • Allows for regimen flexibility • When initiating insulin, consider adding bedtime long-acting basal analogue or intermediate-acting NPH to daytime oral antihyperglycemic agents (although other regimens can be used) • Basal-bolus regimen recommended if above fails to attain glycemic targets • Increased risk of weight gain relative to sulfonylureas and metformin
Basal Insulins **Intermediate-acting** • NPH (Humulin-N, Novolin ge NPH)				–	
Long-acting basal analogues • Detemir (Levemir) • Glargine (Basaglar, Lantus) • Glargine U300 (Toujeo)				Neutral (glargine) – (detemir)	
(Note: Pork isophane insulin [Hypurin NPH Insulin Isophane] is available but rarely used)				–	
Premixed Insulins • Premixed Regular-NPH (Humulin 30/70; Novolin ge 30/70, 40/60, 50/50) • Biphasic insulin aspart (NovoMix 30) • Insulin lispro/lispro protamine suspension (Humalog Mix25, Mix50)	0.9 – 1.1%	↓↓↓	Significant risk	–	

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Class* and Mechanism of Action **INSULIN SECRETAGOGUE:** activates sulfonylurea receptor on beta cell to stimulate endogenous insulin secretion					
Sulfonylureas					• Relatively rapid BG-lowering response • All insulin secretagogues reduce glycemia similarly (except nateglinide, which is less effective) • Post-prandial glycemia is especially reduced by meglitinides • Hypoglycemia and weight gain are especially common with glyburide • Consider using other class(es) of antihyperglycemic agents first in patients at high risk of hypoglycemia (e.g. the elderly, renal/hepatic failure) • If a sulfonylurea must be used in such individuals, gliclazide is associated with the lowest incidence of hypoglycemia and glimepiride is associated with less hypoglycemia than glyburide • Nateglinide and repaglinide are associated with less hypoglycemia than sulfonylureas due to their shorter duration of action allowing medication to be held when forgoing a meal
Gliclazide (Diamicron, Diamicron MR, generic)	0.8%	↓↓	Minimal/ moderate risk	–	
Glimepiride (Amaryl)			Moderate risk	–	
Glyburide (Diabeta, Euglucon, generic) (Note: Chlorpropamide and Tolbutamide are available but rarely used)			Significant risk	–	
Meglitinides					
Nateglinide (Starlix)	0.7%	↓	Minimal/ moderate risk	–	
Repaglinide (GlucoNorm)		↓↓		–	
Class* and Mechanism of Action **METFORMIN:** enhances insulin sensitivity in liver and peripheral tissues by activation of AMP-activated protein kinase					
Metformin (Glucophage, Glumetza)	1.0 – 1.5%	↓↓	Negligible risk as monotherapy	–	• Improved cardiovascular outcomes in overweight subjects • Contraindicated if CrCl/eGFR <30 mL/min or hepatic failure • Caution if CrCl/eGFR <60 mL/min • Weight neutral as monotherapy, promotes less weight gain when combined with other antihyperglycemic agents, including insulin • B12 deficiency • GI side effects

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Class* and Mechanism of Action **SODIUM-GLUCOSE LINKED TRANSPORTER 2 (SGLT2) INHIBITOR:** enhances urinary glucose excretion by inhibiting glucose reabsorption in the proximal renal tubule					
Canagliflozin (Invokana)	0.7 – 1.0%	↓↓ to ↓↓↓	Negligible risk as monotherapy	–	Genital infections, UTI, hypotension, dose-related changes in LDL-C, caution with renal dysfunction and loop diuretics, dapagliflozin not to be used if bladder cancer, rare diabetic ketoacidosis (may occur with no hyperglycemia
Dapagliflozin (Forxiga)				–	
Empagliflozin (Jardiance)				Superiority (empagliflozin in T2DM patients with clinical cardiovascular disease)	
Class* and Mechanism of Action **THIAZOLIDINEDIONE (TZD):** enhances insulin sensitivity in peripheral tissues and liver by activation of peroxisome proliferator-activated receptor-gamma receptors					
Pioglitazone (Actos)	0.8%	↓↓	Negligible risk as monotherapy	Neutral	• Longer duration of glycemic control with monotherapy compared to metformin or glyburide • Mild BP lowering • Between 6 and 12 weeks required to achieve full glycemic effect • Weight gain • May induce edema and/or congestive heart failure • Contraindicated in patients with known clinical heart failure or evidence of left ventricular dysfunction on echocardiogram or other heart imaging • Higher rates of heart failure when combined with insulin‡ • Rare occurrence of macular edema • Higher occurrence of fractures • Cardiovascular controversy (rosiglitazone) • Rare risk bladder cancer with pioglitazone
Rosiglitazone (Avandia)				Neutral	

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Class* and Mechanism of Action **WEIGHT LOSS AGENT:** inhibits lipase					
Orlistat (Xenical)	0.5%	↓	None	–	• Promote weight loss • Orlistat can cause diarrhea and other GI side effects
COMBINED FORMULATIONS					
Avandamet (metformin + rosiglitazone)	See relative A1C lowering for each of the components added to metformin	See expected decrease in A1C for each of the components added to metformin	Negligible risk as monotherapy	–	See metformin, TZDs, DPP-4 inhibitors, and sulfonylureas
Avandaryl (glimepiride + rosiglitazone)	1.6%	↓↓↓	Moderate risk	–	
Janumet/Janumet XR (metformin/metformin ER + sitagliptin)	See relative A1C lowering for each of the components added to metformin	See expected decrease in A1C for each of the components added to metformin	Negligible risk as monotherapy	–	
Jentadueto (linagliptin + metformin)				–	
Kazano (alogliptin + metformin)				–	
Komboglyze (metformin + saxagliptin)				–	
Xigduo (dapagliflozin + metformin)				–	
Oseni (alogliptin + pioglitazone)	1.5%	↓↓↓	Negligible risk as monotherapy	–	

A1C, glycated hemoglobin; **BG,** blood glucose; **BP,** blood pressure; **CrCl,** creatinine clearance; **CV,** cardiovascular; **DPP-4,** dipeptidyl peptidase 4; **eGFR,** estimated glomerular filtration rate; **GI,** gastrointestinal; **GIP,** gastric inhibitory peptide; **GLP-1,** glucagon-like peptide 1; **AMP,** adenosine monophosphate.

Physicians should refer to the most recent edition of the *Compendium of Pharmaceuticals and Specialties* (Canadian Pharmacists Association, Ottawa, Ontario, Canada) for product monographs and detailed prescribing information.

* Listed in alphabetical order.

† A1C percentage/relative reduction expected when agent from this class is added to metformin therapy with exception of metformin where A1C percentage/relative reduction reflects expected monotherapy efficacy.

‡ Combining insulin with a TZD is not an approved indication in Canada.

Adapted from multiple references. See chapters on Pharmacologic Management of T2D for more details:
http://guidelines.diabetes.ca/browse/chapter13
http://guidelines.diabetes.ca/browse/chapter13_2015
http://guidelines.diabetes.ca/browse/chapter13_2016