

Table 7.1—Properties of available glucose-lowering agents in the U.S. and Europe that may guide individualized treatment choices in patients with type 2 diabetes (17)

Class	Compound(s)	Cellular mechanism(s)	Primary physiological action(s)	Advantages	Disadvantages	Cost*
Biguanides	<ul style="list-style-type: none"> Metformin 	Activates AMP-kinase (? other)	<ul style="list-style-type: none"> ↓ Hepatic glucose production 	<ul style="list-style-type: none"> Extensive experience No hypoglycemia ↓ CVD events (UKPDS) 	<ul style="list-style-type: none"> Gastrointestinal side effects (diarrhea, abdominal cramping) Vitamin B₁₂ deficiency Contraindications: CKD, acidosis, hypoxia, dehydration, etc. Lactic acidosis risk (rare) 	Low
Sulfonylureas	2nd Generation <ul style="list-style-type: none"> Glyburide/glibenclamide Glipizide Gliclazide† Glimepiride 	Closes K _{ATP} channels on β-cell plasma membranes	<ul style="list-style-type: none"> ↑ Insulin secretion 	<ul style="list-style-type: none"> Extensive experience Microvascular risk (UKPDS) 	<ul style="list-style-type: none"> Hypoglycemia ↑ Weight 	Low
Meglitinides (glinides)	<ul style="list-style-type: none"> Repaglinide Nateglinide 	Closes K _{ATP} channels on β-cell plasma membranes	<ul style="list-style-type: none"> ↑ Insulin secretion 	<ul style="list-style-type: none"> ↓ Postprandial glucose excursions Dosing flexibility 	<ul style="list-style-type: none"> Hypoglycemia ↑ Weight Frequent dosing schedule 	Moderate
TZDs	<ul style="list-style-type: none"> Pioglitazone‡ Rosiglitazone§ 	Activates the nuclear transcription factor PPAR-γ	<ul style="list-style-type: none"> ↑ Insulin sensitivity 	<ul style="list-style-type: none"> No hypoglycemia Durability ↑ HDL-C ↓ Triglycerides (pioglitazone) ? ↓ CVD events (PROactive, pioglitazone) 	<ul style="list-style-type: none"> ↑ Weight Edema/heart failure Bone fractures ↑ LDL-C (rosiglitazone) ? ↑ MI (meta-analyses, rosiglitazone) 	Low
α-Glucosidase inhibitors	<ul style="list-style-type: none"> Acarbose Miglitol 	Inhibits intestinal α-glucosidase	<ul style="list-style-type: none"> Slows intestinal carbohydrate digestion/absorption 	<ul style="list-style-type: none"> No hypoglycemia ↓ Postprandial glucose excursions ? ↓ CVD events (STOP-NIDDM) Nonsystemic 	<ul style="list-style-type: none"> Generally modest A1C efficacy Gastrointestinal side effects (flatulence, diarrhea) Frequent dosing schedule 	Low to moderate
DPP-4 inhibitors	<ul style="list-style-type: none"> Sitagliptin Vildagliptin† Saxagliptin Linagliptin Alogliptin 	Inhibits DPP-4 activity, increasing postprandial active incretin (GLP-1, GIP) concentrations	<ul style="list-style-type: none"> ↑ Insulin secretion (glucose dependent) ↓ Glucagon secretion (glucose dependent) 	<ul style="list-style-type: none"> No hypoglycemia Well tolerated 	<ul style="list-style-type: none"> Angioedema/urticaria and other immune-mediated dermatological effects ? Acute pancreatitis ? ↑ Heart failure hospitalizations 	High
Bile acid sequestrants	<ul style="list-style-type: none"> Colesevelam 	Binds bile acids in intestinal tract, increasing hepatic bile acid production	<ul style="list-style-type: none"> ? ↓ Hepatic glucose production ? ↑ Incretin levels 	<ul style="list-style-type: none"> No hypoglycemia ↓ LDL-C 	<ul style="list-style-type: none"> Generally modest A1C efficacy Constipation ↑ Triglycerides May ↓ absorption of other medications 	High
Dopamine-2 agonists	<ul style="list-style-type: none"> Bromocriptine (quick release)§ 	Activates dopaminergic receptors	<ul style="list-style-type: none"> Modulates hypothalamic regulation of metabolism ↑ Insulin sensitivity 	<ul style="list-style-type: none"> No hypoglycemia ? ↓ CVD events (Cycloset Safety Trial) 	<ul style="list-style-type: none"> Generally modest A1C efficacy Dizziness/syncope Nausea Fatigue Rhinitis 	High

Continued on p. S56

Table 7.1—Continued

Class	Compound(s)	Cellular mechanism(s)	Primary physiological action(s)	Advantages	Disadvantages	Cost*
SGLT2 inhibitors	<ul style="list-style-type: none"> • Canagliflozin • Dapagliflozin† • Empagliflozin 	Inhibits SGLT2 in the proximal nephron	<ul style="list-style-type: none"> • Blocks glucose reabsorption by the kidney, increasing glucosuria 	<ul style="list-style-type: none"> • No hypoglycemia • ↓ Weight • ↓ Blood pressure • Effective at all stages of type 2 diabetes • Associated with lower CVD event rate and mortality in patients with CVD (EMPA-REG OUTCOME) 	<ul style="list-style-type: none"> • Genitourinary infections • Polyuria • Volume depletion/hypotension/dizziness • ↑ LDL-C • ↑ Creatinine (transient) • DKA, urinary tract infections leading to urosepsis, pyelonephritis 	High
GLP-1 receptor agonists	<ul style="list-style-type: none"> • Exenatide • Exenatide extended release • Liraglutide • Albiglutide • Lixisenatide† • Dulaglutide 	Activates GLP-1 receptors	<ul style="list-style-type: none"> • ↑ Insulin secretion (glucose dependent) • ↓ Glucagon secretion (glucose dependent) • Slows gastric emptying • ↑ Satiety 	<ul style="list-style-type: none"> • No hypoglycemia • ↓ Weight • ↓ Postprandial glucose excursions • ↓ Some cardiovascular risk factors 	<ul style="list-style-type: none"> • Gastrointestinal side effects (nausea/vomiting/diarrhea) • ↑ Heart rate • ? Acute pancreatitis • C-cell hyperplasia/medullary thyroid tumors in animals • Injectable • Training requirements 	High
Amylin mimetics	<ul style="list-style-type: none"> • Pramlintide§ 	Activates amylin receptors	<ul style="list-style-type: none"> • ↓ Glucagon secretion • Slows gastric emptying • ↑ Satiety 	<ul style="list-style-type: none"> • ↓ Postprandial glucose excursions • ↓ Weight 	<ul style="list-style-type: none"> • Generally modest A1C efficacy • Gastrointestinal side effects (nausea/vomiting) • Hypoglycemia unless insulin dose is simultaneously reduced • Injectable • Frequent dosing schedule • Training requirements 	High
Insulins	<ul style="list-style-type: none"> • Rapid-acting analogs <ul style="list-style-type: none"> - Lispro - Aspart - Glulisine - Inhaled insulin • Short-acting <ul style="list-style-type: none"> - Human Regular • Intermediate-acting <ul style="list-style-type: none"> - Human NPH • Basal insulin analogs <ul style="list-style-type: none"> - Glargine - Detemir - Degludec† • Premixed (several types) 	Activates insulin receptors	<ul style="list-style-type: none"> • ↑ Glucose disposal • ↓ Hepatic glucose production • Suppresses ketogenesis 	<ul style="list-style-type: none"> • Nearly universal response • Theoretically unlimited efficacy • ↓ Microvascular risk (UKPDS) 	<ul style="list-style-type: none"> • Hypoglycemia • Weight gain • ? Mitogenic effects • Training requirements • Patient reluctance • Injectable (except inhaled insulin) • Pulmonary toxicity (inhaled insulin) 	Moderate to high#

KKD, chronic kidney disease; CVD, cardiovascular disease; DKA, diabetic ketoacidosis; EMPA-REG OUTCOME, BI 10773 (Empagliflozin) Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (31); GIP, glucose-dependent insulinotropic peptide; HDL-C, HDL cholesterol; LDL-C, LDL cholesterol; MI, myocardial infarction; PPAR-γ, peroxisome proliferator-activated receptor γ; PROactive, Prospective Pioglitazone Clinical Trial in Macrovascular Events (32); STOP-NIDDM, Study to Prevent Non-Insulin-Dependent Diabetes Mellitus (33); TZD, thiazolidinedione; UKPDS, UK Prospective Diabetes Study (34,35). Cycloset trial of quick-release bromocriptine (36). *Cost is based on lowest-priced member of the class (see ref. 17). †Not licensed in the U.S. ‡Initial concerns regarding bladder cancer risk are decreasing after subsequent study. §Not licensed in Europe for type 2 diabetes. #Cost is highly dependent on type/brand (analog > human insulins) and dosage. Adapted with permission from Inzucchi et al. (17).