Table 1—*Properties of currently available glucose-lowering agents that may guide treatment choice in individual patients with type 2 diabetes mellitus*

Class	Compound(s)	Cellular mechanism	Primary physiological action(s)	Advantages	Disadvantages	Cost
Biguanides	• Metformin	Activates AMP-kinase	• ↓ Hepatic glucose production	• Extensive experience • No weight gain • No hypoglycemia • Likely ↓ CVD events (UKPDS)	• Gastrointestinal side effects (diarrhea, abdominal cramping) • Lactic acidosis risk (rare) • Vitamin B_{12} deficiency • Multiple contraindications: CKD, acidosis, hypoxia, dehydration, etc.	Low
Sulfonylureas	2nd generation • Glyburide/ glibenclamide • Glipizide • Gliclazide[b] • Glimepiride	Closes K_{ATP} channels on β-cell plasma membranes	• ↑ Insulin secretion	• Extensive experience • ↓ Microvascular risk (UKPDS)	• Hypoglycemia • Weight gain • ? Blunts myocardial ischemic preconditioning • Low durability	Low
Meglitinides (glinides)	• Repaglinide • Nateglinide	Closes K_{ATP} channels on β-cell plasma membranes	• ↑ Insulin secretion	• ↓ Postprandial glucose excursions • Dosing flexibility	• Hypoglycemia • Weight gain • ? Blunts myocardial ischemic preconditioning • Frequent dosing schedule	High
Thiazolidinediones	• Pioglitazone • Rosiglitazone[c]	Activates the nuclear transcription factor PPAR-γ	• ↑ Insulin sensitivity	• No hypoglycemia • Durability • ↑ HDL-C • ↓ Triglycerides (pioglitazone) • ? ↓ CVD events (ProACTIVE, pioglitazone)	• Weight gain • Edema/heart failure • Bone fractures • ↑ LDL-C (rosiglitazone) • ? ↑ MI (meta-analyses, rosiglitazone) • ? ↑ Bladder cancer (pioglitazone)	High[e]
α-Glucosidase inhibitors[a]	• Acarbose • Miglitol • Voglibose[b,d]	Inhibits intestinal α-glucosidase	• Slows intestinal carbohydrate digestion/absorption	• No hypoglycemia • ↓ Postprandial glucose excursions • ? ↓ CVD events (STOP-NIDDM) • Nonsystemic	• Generally modest HbA_{1c} efficacy • Gastrointestinal side effects (flatulence, diarrhea) • Frequent dosing schedule	Moderate
DPP-4 inhibitors	• Sitagliptin • Vildagliptin[a] • Saxagliptin • Linagliptin • Alogliptin[b,d]	Inhibits DPP-4 activity, increasing postprandial active incretin (GLP-1, GIP) concentrations	• ↑ Insulin secretion (glucose-dependent) • ↓ Glucagon secretion (glucose-dependent)	• No hypoglycemia • Well tolerated	• Generally modest HbA_{1c} efficacy • Urticaria/angioedema • ? Pancreatitis	High

Continued on p. 5

Table 1—*Continued*

Class	Compound(s)	Cellular mechanism	Primary physiological action(s)	Advantages	Disadvantages	Cost
Bile acid sequestrants[a]	• Colesevelam	Binds bile acids in intestinal tract, increasing hepatic bile acid production; ? activation of farnesoid X receptor (FXR) in liver	• Unknown • ? ↓ Hepatic glucose production • ? ↑ Incretin levels	• No hypoglycemia • ↓ LDL-C	• Generally modest HbA_{1c} efficacy • Constipation • ↑ Triglycerides • May ↓ absorption of other medications	High
Dopamine-2 agonists[a]	• Bromocriptine (quick-release)[d]	Activates dopaminergic receptors	• Modulates hypothalamic regulation of metabolism • ↑ Insulin sensitivity	• No hypoglycemia • ? ↓ CVD events (Cycloset Safety Trial)	• Generally modest HbA_{1c} efficacy • Dizziness/syncope • Nausea • Fatigue • Rhinitis	High
GLP-1 receptor agonists	• Exenatide • Exenatide extended release • Liraglutide	Activates GLP-1 receptors	• ↑ Insulin secretion (glucose-dependent) • ↓ Glucagon secretion (glucose-dependent) • Slows gastric emptying • ↑ Satiety	• No hypoglycemia • Weight reduction • ? Potential for improved β-cell mass/function • ? Cardiovascular protective actions	• Gastrointestinal side effects (nausea/vomiting) • ? Acute pancreatitis • C-cell hyperplasia/medullary thyroid tumors in animals • Injectable • Training requirements	High
Amylin mimetics[a]	• Pramlintide[d]	Activates amylin receptors	• ↓ Glucagon secretion • Slows gastric emptying • ↑ Satiety	• ↓ Postprandial glucose excursions • Weight reduction	• Generally modest HbA_{1c} efficacy • Gastrointestinal side effects (nausea/vomiting) • Hypoglycemia unless insulin dose is simultaneously reduced • Injectable • Frequent dosing schedule	High
Insulins	• Human NPH • Human Regular • Lispro • Aspart • Glulisine • Glargine • Detemir • Premixed (several types)	Activates insulin receptors	• ↑ Glucose disposal • ↓ Hepatic glucose production	• Universally effective • Theoretically unlimited efficacy • ↓ Microvascular risk (UKPDS)	• Hypoglycemia • Weight gain • ? Mitogenic effects • Injectable • Training requirements • "Stigma" (for patients)	Variable[f]

[a]Limited use in the U.S./Europe. [b]Not licensed in the U.S. [c]Prescribing highly restricted in the U.S.; withdrawn in Europe. [d]Not licensed in Europe. [e]To be available as a generic product in 2012, with expected significant reductions in cost. [f]Depends on type (analogs > human insulins) and dosage. CKD, chronic kidney disease; CVD, cardiovascular disease; DPP-4, dipeptidyl peptidase 4; GIP, glucose-dependent insulinotropic peptide; GLP-1, glucagon-like peptide 1; HDL-C, HDL-cholesterol; LDL-C, LDL-cholesterol; PPAR, peroxisome proliferator–activated receptor; ProACTIVE, Prospective Pioglitazone Clinical Trial in Macrovascular Events (60); STOP-NIDDM, Study to Prevent Non-Insulin-Dependent Diabetes Mellitus (134); UKPDS, UK Prospective Diabetes Study (29–33).