
بنام خداوند جان و خرد

PHARMACOLOGIC THERAPY FOR ADULTS WITH TYPE ٢ DIABETES

- Patient-centered Approach to choosing appropriate pharmacologic treatment of blood glucose
- ١) important comorbidities such as atherosclerotic cardiovascular disease (ASCVD) and indicators of high ASCVD risk, chronic kidney disease (CKD), and heart failure (HF)
- ٢) hypoglycemia risk
- ٣) effects on body weight
- ٤) side effects
- ٥) cost
- ٦) patient preferences

- Initial Therapy, metformin and comprehensive lifestyle modification
- Additional and/or alternative agents may be considered in special circumstances:
- Increased risk of cardiovascular or renal complications

- **Metformin**:
- Safe
- Inexpensive
- And may reduce risk of cardiovascular events and death
- has beneficial effects on A١C, weight, and cardiovascular mortality
- principal side effects, gastrointestinal intolerance(bloating, abdominal discomfort, and diarrhea)
- metformin to reflect its safety in patients with eGFR >=٣٠ mL/min/١٫٧٣ m٢
- metformin use is associated with vitamin B١٢ deficiency and worsening of symptoms of neuropathy

- When A١C is >=١٫٥% above the glycemic target many patients will require dual combination therapy to achieve their target A١C level .
- **Insulin**
- considered as part of any combination regimen when hyperglycemia is severe
- Catabolic features(weight loss, hypertriglyceridemia, ketosis)
- blood glucose levels >٣٠٠ mg/dL
- A١C >١٠%
- symptoms of hyperglycemia (i.e., polyuria or polydipsia)

- As glucose toxicity resolves, simplifying the regimen and/or changing to noninsulin agents is often possible.

- patients with uncontrolled hyperglycemia associated with type ٢ diabetes can also be effectively treated with a sulfonylurea

- **Combination Therapy**
- monotherapy is often possible for only a few years, after which combination therapy is necessary (stepwise addition)
- Initial combination therapy is superior to sequential addition of medications for extending primary and secondary failure
- Initial combination therapy should be considered in patients presenting with A١C levels ١/٥–٢/٠% above target
- The choice of medication added to initial therapy is based on the clinical characteristics of the patient and their preferences.
- Each new class of noninsulin agents added to initial therapy with metformin generally lowers A١C approximately ٠/٧–١/٠%

- For patients with high ASCVD risk (patients >=٥٥ years of age with coronary, carotid, or lower-extremity artery stenosis >٥٠% or left ventricular hypertrophy), HF, or CKD,

SGLT٢ inhibitor or GLP-١ RA
is recommended as part of the glucose-lowering regimen
independent of A١C, independent of metformin use,

- Greatest reductions in A١C level with insulin regimens and specific GLP-١ RAs added to metformin-based background therapy
- Glycemic efficacy of injectable GLP-١ RA was similar or greater than that of basal insulin
- GLP-١ Ras had a lower risk of hypoglycemia and beneficial effects on body weight compared with insulin, albeit with greater gastrointestinal side effects.

Table 9.2—Drug-specific and patient factors to consider when selecting antihyperglycemic treatment in adults with type 2 diabetes

	Efficacy (60)	Hypoglycemia	Weight change (109)	CV effects		Cost	Oral/SQ	Renal effects		Additional considerations
				ASCVD	HF			Progression of DKD	Dosing/use considerations*	
Metformin	High	No	Neutral (potential for modest loss)	Potential benefit	Neutral	Low	Oral	Neutral	▪ Contraindicated with eGFR <30 mL/min/1.73 m^2	▪ Gastrointestinal side effects common (diarrhea, nausea) ▪ Potential for B12 deficiency
SGLT2 inhibitors	Intermediate	No	Loss	Benefit: empagliflozin†, canagliflozin†	Benefit: empagliflozin‡, canagliflozin, dapagliflozin‡, ertugliflozin	High	Oral	Benefit: canagliflozin§, empagliflozin, dapagliflozin§	▪ See labels for renal dose considerations of individual agents ▪ Glucose-lowering effect is lower for SGLT2 inhibitors at lower eGFR	▪ Should be discontinued before any scheduled surgery to avoid potential risk for DKA ▪ DKA risk (all agents, rare in T2D) ▪ Risk of bone fractures (canagliflozin) ▪ Genitourinary infections ▪ Risk of volume depletion, hypotension ▪ ↑LDL cholesterol ▪ Risk of Fournier's gangrene
GLP-1 RAs	High	No	Loss	Benefit: dulaglutide†, liraglutide†, semaglutide (SQ)† Neutral: exenatide once weekly, lixisenatide	Neutral	High	SQ; oral (semaglutide)	Benefit on renal end points in CVOTs, driven by albuminuria outcomes: liraglutide, semaglutide (SQ), dulaglutide	▪ See labels for renal dose considerations of individual agents ▪ No dose adjustment for dulaglutide, liraglutide, semaglutide ▪ Caution when initiating or increasing dose due to potential risk of nausea, vomiting, diarrhea, or dehydration. Monitor renal function in patients reporting severe adverse GI reactions when initiating or increasing dose of therapy.	▪ **FDA Black Box:** Risk of thyroid C-cell tumors in rodents; human relevance not determined **(liraglutide, dulaglutide, exenatide extended release, semaglutide)** ▪ GI side effects common (nausea, vomiting, diarrhea) ▪ Injection site reactions ▪ Pancreatitis has been reported in clinical trials but causality has not been established. Discontinue if pancreatitis is suspected.

Table 9.2–Drug-specific and patient factors to consider when selecting antihyperglycemic treatment in adults with type 2 diabetes

		Efficacy (60)	Hypoglycemia	Weight change (109)	CV effects		Cost	Oral/SQ	Renal effects		Additional considerations
					ASCVD	HF			Progression of DKD	Dosing/use considerations*	
Metformin		High	No	Neutral (potential for modest loss)	Potential benefit	Neutral	Low	Oral	Neutral	▪ Contraindicated with eGFR <30 mL/min/1.73 m^2	▪ Gastrointestinal side effects common (diarrhea, nausea) ▪ Potential for B12 deficiency
DPP-4 inhibitors		Intermediate	No	Neutral	Neutral	Potential risk: saxagliptin	High	Oral	Neutral	▪ Renal dose adjustment required (sitagliptin, saxagliptin, alogliptin); can be used in renal impairment ▪ No dose adjustment required for linagliptin	▪ Pancreatitis has been reported in clinical trials but causality has not been established. Discontinue if pancreatitis is suspected. ▪ Joint pain
Thiazolidinediones		High	No	Gain	Potential benefit: pioglitazone	Increased risk	Low	Oral	Neutral	▪ No dose adjustment required ▪ Generally not recommended in renal impairment due to potential for fluid retention	▪ **FDA Black Box:** Congestive heart failure **(pioglitazone, rosiglitazone)** ▪ Fluid retention (edema; heart failure) ▪ Benefit in NASH ▪ Risk of bone fractures ▪ Bladder cancer (pioglitazone) ▪ ↑LDL cholesterol (rosiglitazone)
Sulfonylureas (2nd generation)		High	Yes	Gain	Neutral	Neutral	Low	Oral	Neutral	▪ Glyburide: generally not recommended in chronic kidney disease ▪ Glipizide and glimepiride: initiate conservatively to avoid hypoglycemia	▪ FDA Special Warning on increased risk of cardiovascular mortality based on studies of an older sulfonylurea (tolbutamide)
Insulin	**Human insulin**	High	Yes	Gain	Neutral	Neutral	Low (SQ)	SQ; inhaled	Neutral	▪ Lower insulin doses required with a decrease in eGFR; titrate per clinical response	▪ Injection site reactions ▪ Higher risk of hypoglycemia with human insulin (NPH or premixed formulations) vs. analogs
	Analogs						High	SQ			

ASCVD, atherosclerotic cardiovascular disease; CV, cardiovascular; CVOT, cardiovascular outcomes trial; DPP-4, dipeptidyl peptidase 4; DKA, diabetic ketoacidosis; DKD, diabetic kidney disease; eGFR, estimated glomerular filtration rate; GI, gastrointestinal; GLP-1 RAs, glucagon-like peptide 1 receptor agonists; HF, heart failure; NASH, nonalcoholic steatohepatitis; SGLT2, sodium–glucose cotransporter 2; SQ, subcutaneous; T2D, type 2 diabetes. *For agent-specific dosing recommendations, please refer to the manufacturers' prescribing information. †FDA-approved for cardiovascular disease benefit. ‡FDA-approved for heart failure indication. §FDA-approved for chronic kidney disease indication.

Table 34-15 Food and Drug Administration–Approved Noninsulin Pharmacologic Agents for Type 2 Diabetes Mellitus Treatment

Agents (Trade Name[s])	Mode of Action	Safety Concerns, Within-Class Distinctions, and Other Important Considerations
SULFONYLUREAS		
Glyburide (Micronase, Diabeta) Glipizide (Glucotrol) Glipizide-GITS (Glucotrol XL) Glyburide, micronized (Glynase) Glimepiride (Amaryl)	Insulin secretagogue	Increase the risk of hypoglycemia, especially in elderly adults and those with renal insufficiency or weight gain Meta-analysis suggests that sulfonylureas may increase stroke risk (Monami et al., 2013b) Short effective durability of drug except in patients with monogenetic T2DM (i.e., maturity-onset diabetes of the young) Glimepiride lowers fasting and postprandial glucose and has the best safety profile; avoid glyburide in elderly patients and those with CVD
BIGUANIDES		
Metformin (Glucophage) Metformin XL (Fortamet) Metformin XR (Glucophage XR, Glumetza) Metformin oral suspension	Decrease hepatic glucose production and glucose absorption from the GI tract and increase peripheral utilization of glucose	Must take with food to avoid gastritis and GI side effects Caution required for use in elderly patients and those with an estimated GFR rate <45 mL/min Withhold before contrast studies are performed; metformin may be restarted after serum creatinine is repeated and determined to be within a safe targeted range ≤10% of patients may be intolerant to side effect profile May reduce cancer risk in some patients with diabetes May improve fertility in patients with PCOS Some diabetologists prefer a dosing protocol involving rapid titration from 500 mg/day extended release with food to 2 g/day over 2 weeks
α-GLUCOSIDASE INHIBITORS		
Acarbose (Precose) Miglitol (Glyset)	Slow gut absorption of carbohydrates by inhibiting α-glucosidase enzymes	Contraindicated in inflammatory bowel disease, malabsorption syndromes, and partial bowel obstructions May induce hypoglycemia when used in combination therapy; oral glucose (dextrose), whose absorption is not inhibited by α-glucosidase inhibitors, should be used instead of sucrose (cane sugar) for hypoglycemia treatment; hypoglycemia will also respond to glucagon injection Glycemic efficacy of acarbose has been noted to be equal to that of metformin in treatment naive Chinese patients (Yang et al., 2014)

THIAZOLIDINEDIONE		
Pioglitazone (Actos)	Enhances tissue sensitivity to insulin in skeletal muscles by activating intracellular peroxisome proliferator-activated receptors	May cause resumption of ovulation in anovulatory premenopausal women Cases average weight gain of 0.9-2.6 kg Contraindicated in any patient with advanced heart failure (NYHA class III or class IV) or a history of bladder cancer Liver function testing required at baseline and every 2 months for the first year and then periodically thereafter Increases fracture risk in women
GLITINIDES		
Repaglinide (Prandin) Nateglinide (Starlix)	Rapid-acting insulin secretagogue with short (1- to 2-hour) duration of action; same mechanism of action as sulfonylureas but with a different binding site to pancreatic β cells	More effective than metformin, sulfonylureas, and thiazolidinediones at lowering postprandial blood glucose Less risk of hypoglycemia than sulfonylureas because of more rapid kinetics Must be taken 15 minutes before meals Approximately 1 month of therapy is required before fasting blood glucose decreases May either be weight neutral or result in slight weight increase
D2-DOPAMINE AGONIST		
Bromocriptine (Cycoset)	Resets dopaminergic and sympathetic tone within the central nervous system	Reduces glucose, triglycerides, and insulin resistance in patients with T2DM Can be used with all other oral agents and insulin Should be taken daily within 2 hours of rising Consider for use in patients who are shift workers; improving dopaminergic and sympathetic tone within the SCN may reduce insulin resistance; shift workers have disruption in their SCN pacemaker
BILE ACID SEQUESTRANT		
Colesevelam (Welchol)	Uncertain mode of action; may affect secretion of GLP-1	Not indicated as monotherapy in T2DM; may be used with metformin or metformin + sulfonylurea May be considered for off-label use in patients with prediabetes to reduce LDL cholesterol to <100 mg/dL and preserve β-cell function May be considered for use in T2DM patients who have elevated LDL cholesterol

Table 34-15 Food and Drug Administration–Approved Noninsulin Pharmacologic Agents for Type 2 Diabetes Mellitus Treatment (Continued)

Agents (Trade Name[s])	Mode of Action	Safety Concerns, Within-Class Distinctions, and Other Important Considerations
DPP-4 INHIBITORS		
Sitagliptin (Januvia) Sitagliptin + metformin/sitagliptin + metformin, extended release (Janumet/Janumet XR) Saxagliptin (Onglyza) Saxagliptin + metformin, extended release (Kombiglyze XR) Linagliptin (Tradjenta) Linagliptin + metformin (Jentadueto) Alogliptin (Nesina) Alogliptin + metformin (Kazano) Alogliptin + pioglitazone (Oseni)	Block the action of DPP-4 enzymes, resulting in a two- to threefold increase in plasma levels of endogenous GLP-1	Most common side effects are rash and rhinitis Doses of all DPP-4 inhibitors, with the exception of linagliptin, must be adjusted based on renal status (see Table 34-15) As a class, DPP-4 inhibitors do not appear to increase the risk of CAD, HF, or hospitalizations for CHF; they also do not mitigate cardiovascular risk (Monami et al., 2013a) Oseni is contraindicated in patients with established NYHA class III or class IV HF and is not recommended in patients with symptomatic HF
GLP-1 RECEPTOR AGONISTS		
Exenatide (Byetta) Liraglutide (Victoza) Exenatide QW (Bydureon)	Enhance nutrient-stimulated insulin secretion via activation of GLP-1 receptors on β cells; inhibit glucagon secretion; delay gastric emptying; reduce appetite	Associated with weight loss Favorable effect on cardiovascular biomarkers Low rates of hypoglycemia Favor preservation of β-cell function GLP-1 infusion studies demonstrate favorable effects on endothelial cell function in humans Direct link to acute pancreatitis has not been demonstrated Contraindicated in patients with personal or family history of medullary thyroid carcinoma or MEN II (medullary thyroid cancer + pheochromocytoma) Most common adverse effect is nausea, which can be avoided if patients do not eat beyond the point of satiety When used with insulin secretagogue or insulin, reduce dose of secretagogue or insulin to minimize the likelihood of inducing hypoglycemia Exenatide is injected twice daily within 1 hr of eating; liraglutide is injected once daily without regard to meals; exenatide QW is injected once weekly Contraindicated in patients with a history of pancreatitis. Pancreatitis has been observed in patients taking GLP-1 receptor agonists or DPP-4 inhibitors. However, no direct signal has been noted that would implicate the incretin class as inducers of pancreatitis or pancreatic cancer in patients with diabetes Discontinue use in patients suspected of having pancreatitis Exenatide QW may cause injection nodules

Table 34-15 Food and Drug Administration–Approved Noninsulin Pharmacologic Agents for Type 2 Diabetes Mellitus Treatment (Continued)

Agents (Trade Name[s])	Mode of Action	Safety Concerns, Within-Class Distinctions, and Other Important Considerations
SGLT2 INHIBITOR		
Canagliflozin (Invokana)	Reduces the renal threshold of glucose absorption from 180 g/day to approximately 70 g/day by blocking the SGLT2 co-transporter in the distal tubules of the glomeruli. Because glucose is not absorbed in the plasma, insulin resistance improves in a glucose-dependent manner, and patients experience a reduction in fasting and postprandial glucose levels, A1C, weight, and BP.	Side effects include increased frequency of urination, glycosuria, UTIs, mycotic infections, and diarrhea. Elderly patients should be carefully observed for treatment-induced orthostatic hypotension. Contraindicated in patients with renal insufficiency and a GFR <45 mL/min/1.73 m^2 Canagliflozin dose should be 100 mg/day taken in the morning if the estimated GFR is 45-60 mL/min/1.73 m^2; can be titrated to 300 mg if the GFR is >60 mL/min/1.73 m^2 Co-administration with nonselective inducers of UGT enzymes (Rifampin, phenytoin, phenobarbital, ritonavir) will decrease the efficacy of canagliflozin
Dapagliflozin (Farxiga)	Starting dose is 5 mg daily. Can increase to 10 mg daily for patients requiring additional glycemic control	Should not be initiated in patients with an eGFR <60 mL/min/1.73 m^2
	As with other agents in this class, SGLT2 inhibitors interfere with 1,5-anhydroglucitol assays	Results in approximately 70 g of glucose excretion in urine weekly
Empagliflozin (Jardiance)	Doses are 10 and 25 mg daily	Do not initiate in patients with eGFR <45 mL/min/1.73 m^2 and discontinue if eGFR is persistently <45 mL/min/1.73 m^2

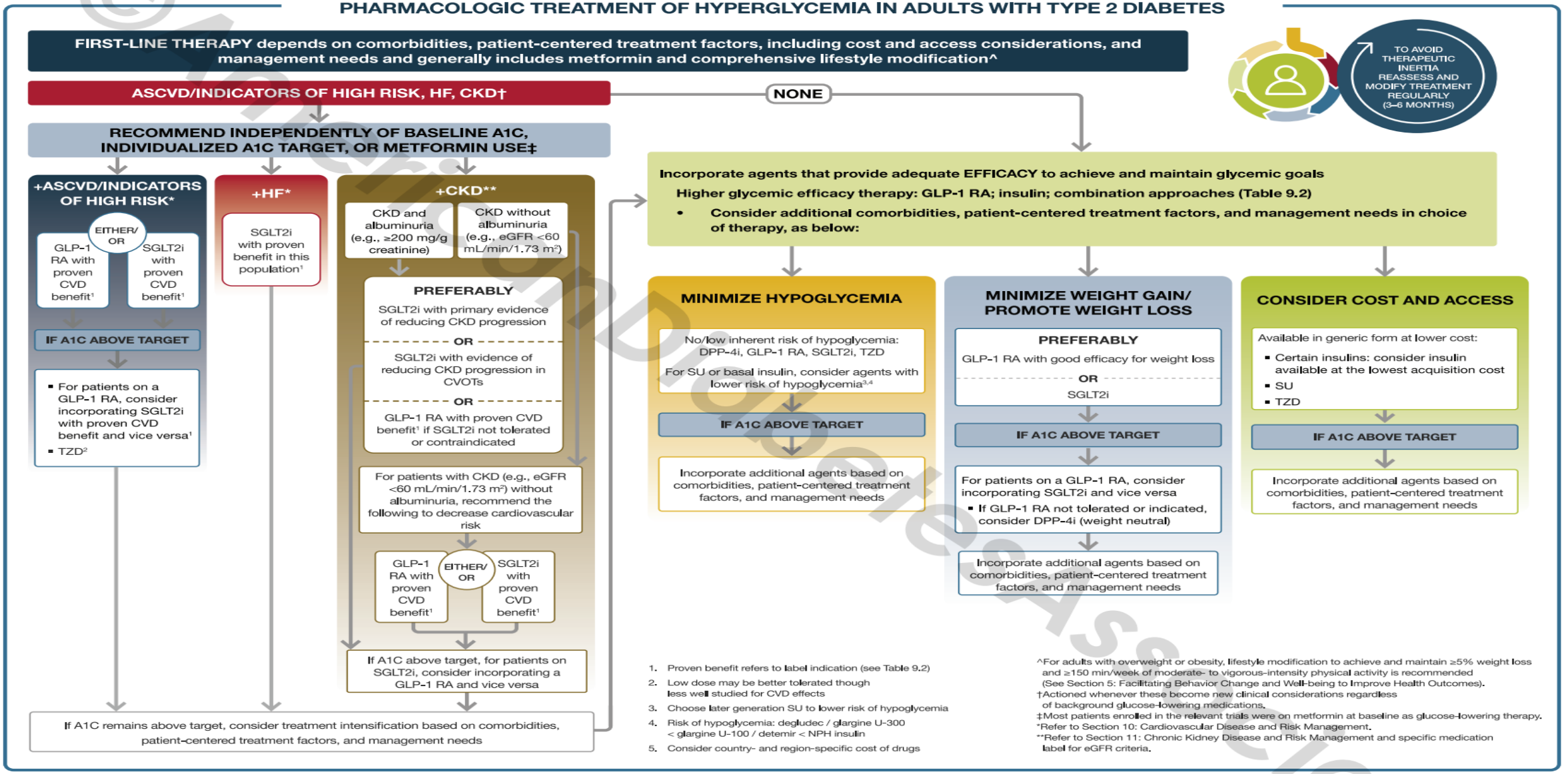

Figure 9.3—Pharmacologic treatment of hyperglycemia in adults with type 2 diabetes. 2022 ADA Professional Practice Committee (PPC) adaptation of Davies et al. (43) and Buse et al. (44). For appropriate context, see **Fig. 4.1**. The 2022 ADA PPC adaptation emphasizes incorporation of therapy rather than sequential add-on, which may require adjustment of current therapies. Therapeutic regimen should be tailored to comorbidities, patient-centered treatment factors, and management needs. ASCVD, atherosclerotic cardiovascular disease; CKD, chronic kidney disease; CVD, cardiovascular disease; CVOTs, cardiovascular outcomes trials; DPP-4i, dipeptidyl peptidase 4 inhibitor; eGFR, estimated glomerular filtration rate; GLP-1 RA, glucagon-like peptide 1 receptor agonist; HF, heart failure; SGLT2i, sodium–glucose cotransporter 2 inhibitor; SU, sulfonylurea; T2D, type 2 diabetes; TZD, thiazolidinedione.