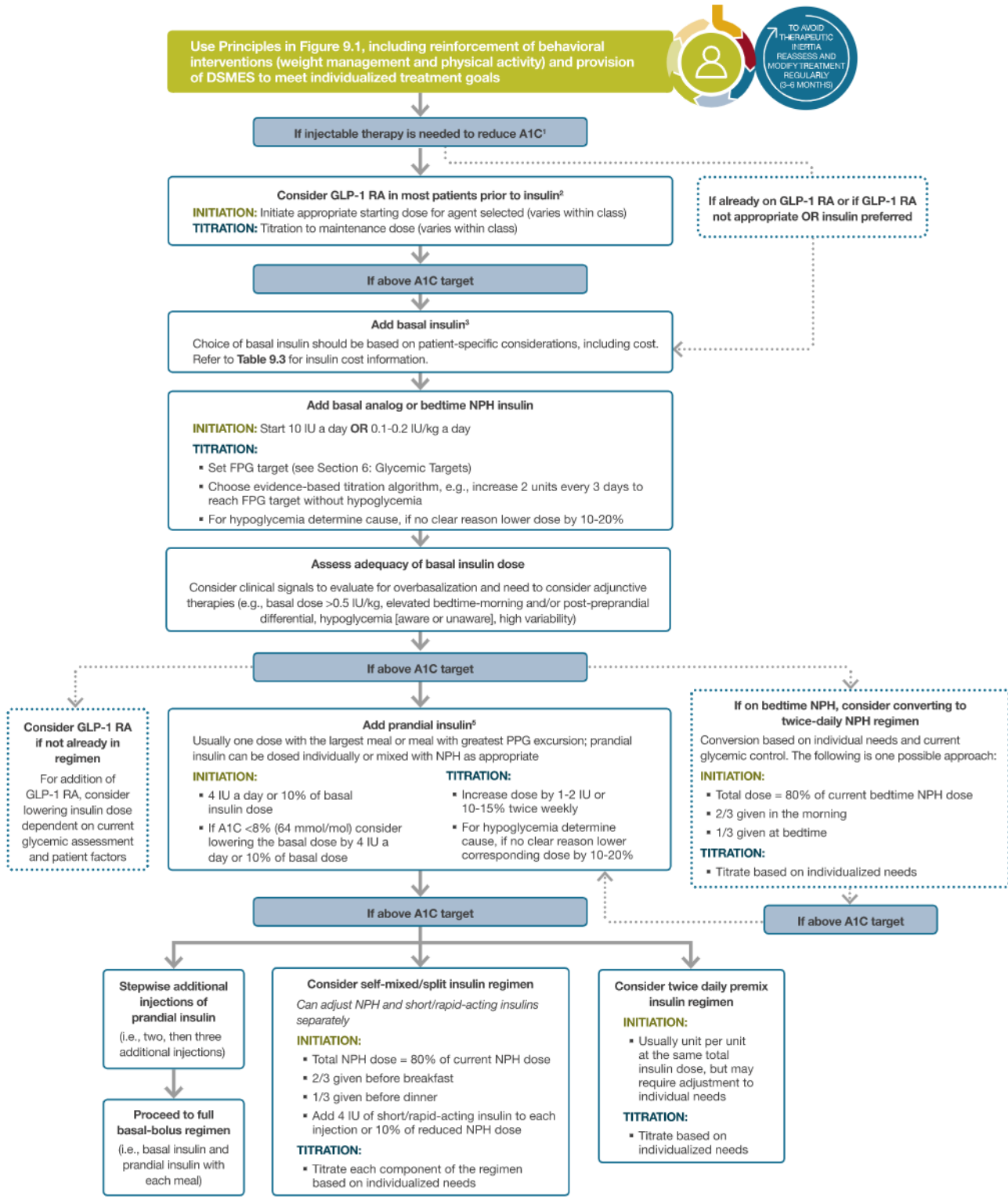


FIGURE 9.1 Glucose-lowering medication in type 2 diabetes: 2021 ADA Professional Practice Committee adaptation of Davies MJ, D'Alessio DA, Fradkin J, et al. Diabetes Care 2018;41:2669–2701 and Buse JB, Wexler DJ, Tsapas A, et al. Diabetes Care 2020;43:487–493. For appropriate context, see Figure 4.1. In this version, the "Indicators of high-risk or established ASCVD, CKD, or HF" pathway was adapted based on trial populations studied. DPP-4i, DPP-4 inhibitor; GLP-1 RA, GLP-1 receptor agonist; LVEF, left ventricular ejection fraction; SGLT2i, SGLT2 inhibitor; SU, sulfonylurea; TZD, type 2 diabetes; TZD, thiazolidinedione.



1. Consider insulin as the first injectable if evidence of ongoing catabolism, symptoms of hyperglycemia are present, when A1C levels (>10% [86 mmol/mol]) or blood glucose levels (≥300 mg/dL [16.7 mmol/L]) are very high, or a diagnosis of type 1 diabetes is a possibility.
 2. When selecting GLP-1 RA, consider: patient preference, A1C lowering, weight-lowering effect, or frequency of injection. If CVD, consider GLP-1 RA with proven CVD benefit. Oral or injectable GLP-1 RA are appropriate.
 3. For patients on GLP-1 RA and basal insulin combination, consider use of a fixed-ratio combination product (iDegLira or iGlarLixi).
 4. Consider switching from evening NPH to a basal analog if the patient develops hypoglycemia and/or frequently forgets to administer NPH in the evening and would be better managed with an AM dose of a long-acting basal insulin.
 5. If adding prandial insulin to NPH, consider initiation of a self-mixed or premixed insulin regimen to decrease the number of injections required.

FIGURE 9.2 Intensifying to injectable therapies. FPG, fasting plasma glucose; FRC, fixed-ratio combination; GLP-1 RA, GLP-1 receptor agonist; max, maximum; PPG, postprandial glucose. Adapted from Davies MJ, D'Alessio DA, Fradkin J, et al. Diabetes Care 2018;41: 2669–2701.

TABLE 9.1 Drug-specific and patient factors to consider when selecting antihyperglycemic treatment in adults with type 2 diabetes

	Efficacy	Hypoglycemia	Weight change	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	<ul style="list-style-type: none"> Contraindicated with eGFR <30 mL/min/1.73 m² 	<ul style="list-style-type: none"> Gastrointestinal side effects common (diarrhea, nausea) Potential for B12 deficiency
SGLT-2 inhibitors	Intermediate	No	Loss	Benefit: empagliflozin, canagliflozin	Benefit: empagliflozin, canagliflozin, dapagliflozin†	High	Oral	Benefit: canagliflozin, empagliflozin, dapagliflozin	<ul style="list-style-type: none"> Renal dose adjustment required (canagliflozin, dapagliflozin, empagliflozin) 	<ul style="list-style-type: none"> 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	Neutral: exenatide once weekly, lixisenatide	Neutral	High	SQ: oral (semaglutide)	Benefit on renal end points in CVOIs, driven by albuminuria outcomes: liraglutide, semaglutide, dulaglutide	<ul style="list-style-type: none"> Exenatide, lixisenatide: avoid for eGFR <30 mL/min/1.73 m² 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. 	<ul style="list-style-type: none"> FDA Black Box: Risk of thyroid C-cell tumors in rodents; human relevance not determined (liraglutide, albiglutide, 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.
DPP-4 inhibitors	Intermediate	No	Neutral	Neutral	Potential risk: saxagliptin	High	Oral	Neutral	<ul style="list-style-type: none"> Renal dose adjustment required (sitagliptin, saxagliptin, alogliptin); can be used in renal impairment No dose adjustment required for linagliptin 	<ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> No dose adjustment required Generally not recommended in renal impairment due to potential for fluid retention 	<ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> Glyburide: not recommended Glipizide and glimepiride: initiate conservatively to avoid hypoglycemia 	<ul style="list-style-type: none"> FDA Special Warning on increased risk of cardiovascular mortality based on studies of an older sulfonylurea (tolbutamide)
Insulin	Highest	Yes	Gain	Neutral	Neutral	Low (SQ)	SQ: inhaled	Neutral	<ul style="list-style-type: none"> Lower insulin doses required with a decrease in eGFR; titrate per clinical response 	<ul style="list-style-type: none"> Injection site reactions Higher risk of hypoglycemia with human insulin (NPH or premixed formulations) vs. analogs
							SQ			

*For agent-specific dosing recommendations, please refer to the manufacturers' prescribing information. †FDA-approved for CVD benefit. ‡FDA-approved for HF indication. §FDA-approved for KGD indication. GI, gastrointestinal; GLP-1 RA, GLP-1 receptor agonist; NASH, nonalcoholic steatohepatitis; SQ, subcutaneous; T2D, type 2 diabetes.