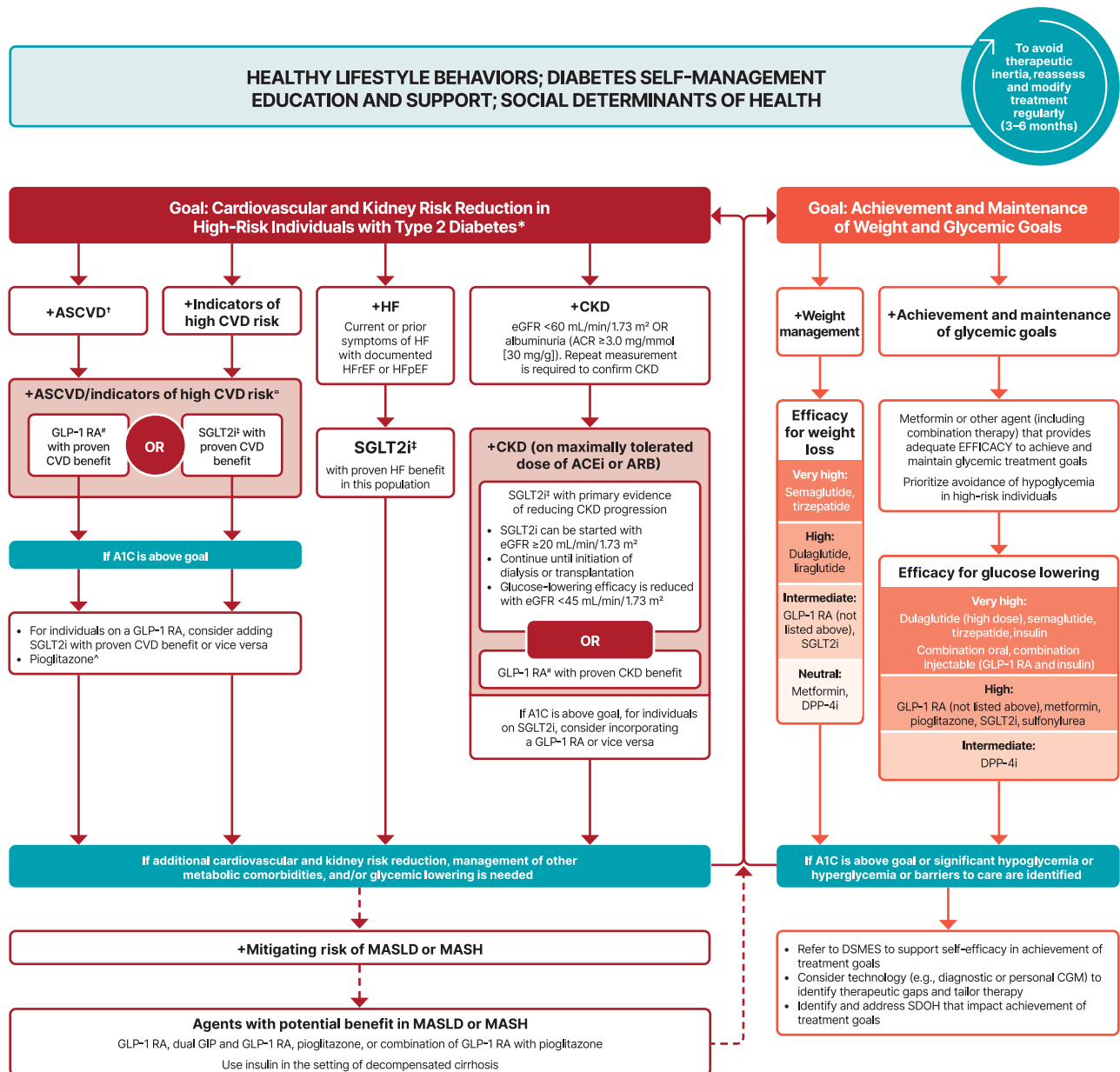


Use of Glucose-Lowering Medications in the Management of Type 2 Diabetes



* In people with HF, CKD, established CVD, or multiple risk factors for CVD, the decision to use a GLP-1 RA or SGLT2i with proven benefit should be made irrespective of background use of metformin or A1C.

† ASCVD: Defined differently across CVOTs but all included individuals with established CVD (e.g., MI, stroke, and arterial revascularization procedure) and variably included conditions such as transient ischemic attack, unstable angina, amputation, and symptomatic or asymptomatic coronary artery disease. Indicators of high risk: While definitions vary, most comprise ≥55 years of age with two or more additional risk factors (including obesity, hypertension, smoking, dyslipidemia, or albuminuria).

‡ A strong recommendation is warranted for people with CVD and a weaker recommendation for those with indicators of high-risk CVD. Moreover, a higher absolute risk reduction and thus lower numbers needed to treat are seen at higher levels of baseline risk and should be factored into the shared decision-making process. See text for details.

For GLP-1 RAs, CVOTs demonstrate their efficacy in reducing composite MACE, CV death, all-cause mortality, MI, stroke, and kidney end points in individuals with T2D with established or high risk of CVD. One kidney outcome trial demonstrated benefit in reducing persistent eGFR reduction and CV death for a GLP-1 RA in individuals with CKD and T2D.

‡ For SGLT2is, CV and kidney outcomes trials demonstrate their efficacy in reducing the risks of composite MACE, CV death, all-cause mortality, MI, HFrEF, and kidney outcomes in individuals with T2D and established or high risk of CVD.

^ Low-dose pioglitazone may be better tolerated and similarly effective as higher doses.

Figure 9.3—Use of glucose-lowering medications in the management of type 2 diabetes. The left side of the algorithm prioritizes mitigation of diabetes-related complications and end-organ effects, while the right side addresses weight and glucose management goals. ACEi, angiotensin-converting enzyme inhibitor; ACR, albumin-to-creatinine ratio; ARB, angiotensin receptor blocker; ASCVD, atherosclerotic cardiovascular disease; CGM, continuous glucose monitoring; CKD, chronic kidney disease; CV, cardiovascular; CVD, cardiovascular disease; CVOT, cardiovascular outcomes trial; DPP-4i, dipeptidyl peptidase 4 inhibitor; DSMES, diabetes self-management education and support; eGFR, estimated glomerular filtration rate; GLP-1 RA, glucagon-like peptide 1 receptor agonist; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; HHF, hospitalization for heart failure; MACE, major adverse cardiovascular events; MASLD, metabolic dysfunction–associated steatohepatitis; MASLD, metabolic dysfunction–associated steatotic liver disease; MI, myocardial infarction; SDOH, social determinants of health; SGLT2i, sodium–glucose cotransporter 2 inhibitor; T2D, type 2 diabetes. Adapted from Davies et al. (89).

Table 9.2—Features of medications for lowering glucose in type 2 diabetes

Medication (route of administration)	Glucose-lowering efficacy ¹	Hypoglycemia risk	Weight effects ²	CV effects		Kidney effects		MASH effects	Clinical considerations and adverse effects
				Effect on MACE	Effect on HF	Progression of CKD	Dosing/use considerations*		
Metformin (oral)	High	No	Neutral (potential for modest loss)	Potential benefit	Neutral	Neutral	<ul style="list-style-type: none"> Contraindicated with eGFR <30 mL/min/1.73 m² 	Neutral	<ul style="list-style-type: none"> GI side effects: mitigate with slow dose titration, extended-release formulations, and administration with food. Potential for vitamin B12 deficiency: monitor and replete as appropriate.
SGLT2 inhibitors (oral)	Intermediate to high	No	Loss (intermediate)	Benefit: canagliflozin, empagliflozin	Benefit: canagliflozin, dapagliflozin, empagliflozin, ertugliflozin	Benefit: canagliflozin, dapagliflozin, empagliflozin	<ul style="list-style-type: none"> See labels of individual agents for dosage considerations for kidney function Glucose-lowering effect is minimal at eGFR <45 mL/min/1.73 m² and lower; continue for cardiovascular and kidney benefit until dialysis or transplantation 	Unknown	<ul style="list-style-type: none"> DKA risk in individuals with insulin deficiency (rare in T2D): discontinue, evaluate, and treat promptly if suspected; be aware of predisposing risk factors and clinical presentations (including euglycemic DKA); mitigate risk with sick-day planning; discontinue before scheduled surgery (e.g., 3–4 days), during critical illness, or during prolonged fasting. Genital mycotic infections: mitigate risk with genital hygiene and avoid use in high-risk individuals. Necrotizing fasciitis of the perineum (Fournier gangrene): rare; prompt treatment if suspected. Intravascular volume depletion: attention to volume status and blood pressure, particularly when ill or fasting; adjust other volume-contracting agents as applicable; monitor kidney function upon initiation.
GLP-1 RAs (SQ; semaglutide also available in oral formulation)	High to very high	No	Loss (intermediate to very high)	Benefit: dulaglutide, liraglutide, semaglutide (SQ) Neutral: exenatide once weekly, lixisenatide	Neutral	Benefit for renal end points in CVOTs, driven by albuminuria outcomes: dulaglutide, liraglutide, semaglutide (SQ) Demonstrated benefit for progression of CKD for semaglutide (SQ)	<ul style="list-style-type: none"> See labels of individual agents for dosage considerations for kidney function No dose adjustment for dulaglutide, liraglutide, or semaglutide Monitor kidney function when initiating or escalating doses in individuals with kidney impairment reporting severe adverse GI reactions 	Potential benefit	<ul style="list-style-type: none"> Thyroid C-cell tumors identified in rodents; human relevance not determined. Ileus: risk level is not well established; provide guidance on discontinuation prior to surgical procedures. Pancreatitis: acute pancreatitis has been reported, but causality has not been established. Do not initiate if at high risk for pancreatitis, and discontinue if pancreatitis is suspected. Biliary disease: evaluate for gallbladder disease if cholelithiasis or cholecystitis is suspected; avoid use in at-risk individuals. Diabetic retinopathy: close monitoring of retinopathy in those at high risk (older individuals and those with longer duration of T2D [≥10 years]).
Dual GIP and GLP-1 RA (SQ)	Very high	No	Loss (very high)	Under investigation	Under investigation	Under investigation	<ul style="list-style-type: none"> See labels of individual agents for dosage considerations for kidney function No dose adjustment Monitor kidney function when initiating or escalating doses in individuals with kidney impairment reporting severe adverse GI reactions 	Potential benefit	<ul style="list-style-type: none"> Impact on drug absorption: orally administered drug absorption may be impaired during dose titration (including of oral contraceptives). GI side effects: counsel on potential for GI side effects; provide guidance on dietary modifications to mitigate GI side effects (reduction in meal size, mindful eating practices [e.g. stop eating once full], decreasing intake of high-fat or spicy food); consider slower dose titration for those experiencing GI challenges. Not recommended for individuals with gastroparesis.
DPP-4 inhibitors (oral)	Intermediate	No	Neutral	Neutral	Neutral (potential risk: saxagliptin)	Neutral	<ul style="list-style-type: none"> Dose adjustment required based on kidney function (sitagliptin, saxagliptin, alogliptin) No dose adjustment required for linagliptin 	Unknown	<ul style="list-style-type: none"> Pancreatitis has been reported, but causality has not been established. Discontinue if pancreatitis is suspected. Postmarketing concerns about joint pain (consider discontinuing if debilitating and other treatment options are feasible) and bullous pemphigoid (discontinue if suspected).
Pioglitazone (oral)	High	No	Gain	Potential benefit	Increased risk	Neutral	<ul style="list-style-type: none"> No dose adjustment required Generally not recommended in kidney impairment due to potential for fluid retention 	Potential benefit	<ul style="list-style-type: none"> Increased risk of HF and fluid retention. Do not use in the setting of HF. Risk of bone fractures. Bladder cancer: do not use in individuals with active bladder cancer, and use caution in those with prior history of bladder cancer.
Sulfonylureas (2nd generation) (oral)	High	Yes	Gain	Neutral	Neutral	Neutral	<ul style="list-style-type: none"> Glyburide: generally not recommended in CKD Glipizide and glimepiride: initiate conservatively to avoid hypoglycemia 	Unknown	<ul style="list-style-type: none"> FDA Special Warning on increased risk of CV mortality based on studies of an older sulfonylurea (tolbutamide); glimepiride shown to be CV safe (see text). Use with caution in individuals at risk for hypoglycemia, particularly if in combination with insulin.
Insulin (human) (SQ; regular insulin also available as inhaled formulation) Insulin (analogs) (SQ)	High to very high	Yes	Gain	Neutral	Neutral	Neutral	<ul style="list-style-type: none"> Lower insulin doses required with a decrease in eGFR; titrate per clinical response 	Unknown	<ul style="list-style-type: none"> Injection site reactions Higher risk of hypoglycemia with human insulin (NPH or premixed formulations) vs. analogs Risk of hypoglycemia and duration of activity increases with the severity of impaired kidney function. Refer to device-specific instructions for insulins compatible with different delivery systems (i.e., pumps, connected insulin pens, insulin patches).

CKD, chronic kidney disease; CV, cardiovascular; DKA, diabetic ketoacidosis; DPP-4, dipeptidyl peptidase 4; eGFR, estimated glomerular filtration rate; FDA, U.S. Food and Drug Administration; GI, gastrointestinal; GIP, glucose-dependent insulinotropic polypeptide; GLP-1 RA, glucagon-like peptide 1 receptor agonist; HF, heart failure; MACE, major adverse cardiovascular events; MASH, metabolic dysfunction-associated steatohepatitis; SGLT2, sodium–glucose cotransporter 2; SQ, subcutaneous; T2D, type 2 diabetes. *For agent-specific dosing recommendations, please refer to manufacturers' prescribing information. ¹Tsapas et al. (106). ²Tsapas et al. (241). Adapted from Davies et al. (89).