



Key Considerations in use of SGLT2 Inhibitors and GLP-1RAs for CV Risk Reduction in Patients with T2D

Purpose:

- This tool complements the *2020 ACC Expert Consensus Decision Pathway on Novel Therapies for Cardiovascular Risk Reduction in Patients with Type 2 Diabetes*, which helps clinicians determine which patients are appropriate for the use of specific glucose-lowering agents (**SGLT2 Inhibitors** or **GLP-1RAs**) that have been shown to lower cardiovascular (CV) risk.
- Once patient eligibility has been determined and a decision to begin one of the suggested therapies has been made through clinician-patient discussion including patient preference and cost consideration, this tool provides clinicians with a reference for the initiation and monitoring of these two novel classes of therapies with the goal of reducing CV risk in patients with Type 2 Diabetes (T2D).
- For tips to facilitate clinician-patient conversations about T2D and CV risk, use the discussion guide [“Getting to the Heart of the Matter: What You and Your Patients Need to Know About Managing Diabetes and CV Risk.”](#)
- The decision pathway and this tool, are primarily focused on management in the outpatient ambulatory setting, although implementing relevant portions in the acute inpatient setting may be reasonable.

Overview:

- To date, several large, well-conducted, randomized clinical trials have demonstrated that two novel classes of therapies originally developed for glucose lowering can directly improve CV outcomes.
- The two classes of therapies are **SGLT2** (sodium-glucose cotransporter 2) **Inhibitors** and **GLP-1RAs** (glucagon-like peptide 1 receptor agonists). The specific drugs in each class that have demonstrated a reduction in major adverse CV events are:

SGLT2 Inhibitors	canagliflozin, dapagliflozin, empagliflozin
GLP-1RAs	dulaglutide, liraglutide, injectable semaglutide

- Because most morbidity and mortality in T2D comes from CV events, the CV specialist has a key role in optimizing these patients' care and is well-positioned to address 3 key areas in the management of patients with T2D: 1) Screening for T2D in their patients with or at high risk of CV disease; 2) Aggressively treating CV risk factors; and 3) Incorporating newer glucose-lowering agents with evidence for improving CV outcomes into routine practice.
- CV specialists who care for patients with T2D, who also have one or more of the following: atherosclerotic cardiovascular disease (ASCVD)*, heart failure (HF), diabetic kidney disease (DKD)†, at high risk for ASCVD‡§, should recommend guideline-based therapy for prevention (lifestyle, blood pressure, lipids, glucose, antiplatelet), and initiate a patient-clinician discussion about the addition of an SGLT2 inhibitor or GLP-1RA with demonstrated CV benefit.

* ASCVD is defined as a history of an acute coronary syndrome or MI, stable or unstable angina, coronary heart disease with or without revascularization, other arterial revascularization, stroke, or peripheral artery disease assumed to be atherosclerotic in origin.

† DKD is a clinical diagnosis marked by reduced eGFR, the presence of albuminuria, or both.

‡ Consider an SGLT2 inhibitor when your patient has established ASCVD, HF, DKD or is at high risk for ASCVD. Consider a GLP-1RA when your patient has established ASCVD or is at high risk for ASCVD.

§ Patients at high risk for ASCVD include those with end organ damage such as left ventricular hypertrophy or retinopathy or with multiple CV risk factors (e.g., age, hypertension, smoking, dyslipidemia, obesity).

Reference: Das SR, Everett BM, Birtcher KK, Brown JM, Januzzi JL, Kalyani RR, Kosiborod M, Magwire ML, Neumiller JJ, Morris PB, Sperling LS. 2020 expert consensus decision pathway on novel therapies for cardiovascular risk reduction in patients with type 2 diabetes: a report of the American College of Cardiology Solution Set Oversight Committee. *J Am Coll Cardiol* 2020;**xx:xxx-xx**.





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SGLT2 Inhibitors			
DOSAGE INFORMATION			
Drug	Recommended Doses for CV Benefit*	Dose Modification	Indications
Canagliflozin	100 mg PO daily	<ul style="list-style-type: none"> eGFR 30 to 59 ml/min/1.73m²: max dose 100 mg daily eGFR <30 ml/min/1.73m²: use is not recommended for glycemic control 	<ul style="list-style-type: none"> Improve glycemic control in adults with T2D as an adjunct to diet and exercise Reduce risk of MI, stroke, or CV death in adults with T2D and CV disease Reduce the risk of end-stage kidney disease, doubling of serum creatinine, CV death, and hospitalization for HF in patients with T2D and diabetic nephropathy with albuminuria
Dapagliflozin	10 mg PO daily	<ul style="list-style-type: none"> eGFR <45 ml/min/1.73m²: use is not recommended for glycemic control eGFR <30 ml/min/1.73 m²: use is contraindicated 	<ul style="list-style-type: none"> Improve glycemic control in adults with T2D as an adjunct to diet and exercise Reduce the risk of hospitalization for HF in adults with T2D and established CV disease or multiple CV risk factors Reduce the risk of CV death and hospitalization for HF in adults with HFrEF
Empagliflozin	10 mg PO daily	<ul style="list-style-type: none"> eGFR <45 ml/min/1.73m²: use is not recommended 	<ul style="list-style-type: none"> Improve glycemic control in adults with T2D as an adjunct to diet and exercise Reduce risk of CV death in adults with T2D and established CV disease

Please note: Information regarding “Considerations for Drug Initiation and Monitoring”, “Contraindications”, and “Patient Education” for SGLT2 Inhibitors are continued on the next page.

CV = cardiovascular; eGFR = estimated glomerular filtration rate; GLP-1RA = glucagon-like peptide-1 receptor agonist; HF = heart failure; HFrEF = heart failure with reduced ejection fraction; MI = myocardial infarction; PO = “per os”, by mouth; SGLT2 = sodium-glucose cotransporter-2; T2D = type 2 diabetes

*Because there is no evidence of a graded dose response regarding CV and renal effects, SGLT2 inhibitors with CV benefit should be initiated at the lowest dose tested in CV and renal outcomes trials. Those doses are listed here. No further dose titration is needed for CV or renal risk reduction. However, dose increases may provide further glucose reduction benefits, if indicated.





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SGLT2 Inhibitors

CONTINUED:

CONSIDERATIONS FOR DRUG INITIATION AND MONITORING

- Discontinue at least three days before a planned surgery to prevent postoperative ketoacidosis.
- May contribute to intravascular volume contraction; consider stopping or reducing diuretic dose if applicable.
- Use with caution in patients with prior amputation, severe peripheral neuropathy, severe peripheral vascular disease, or active diabetic foot ulcers or soft tissue infections.
- Possible increased risk of bone fractures (canagliflozin).
- If HbA1c is well-controlled at baseline or known history of frequent hypoglycemic events, wean or stop sulfonylurea and consider reducing total daily insulin dose by ~20% when starting therapy.
- Avoid hypovolemia. May need to reduce diuretic dose if the patient has symptoms of dehydration. Educate patients regarding symptoms of dehydration (lightheadedness, orthostasis, weakness) and to hold medication if low oral intake.
- Instruct patients to more closely monitor glucose at home for the first 4 weeks of therapy (especially if on insulin, sulfonylurea, and/or glinides). Consider discontinuing any sulfonylurea or glinide. For patients taking insulin, consider modestly reducing total daily insulin dose (by up to 20%).
- Adverse effects to monitor:
 - Genital fungal infections
 - Urinary tract infections
 - Euglycemic diabetic ketoacidosis
 - Lower limb ulcerations and soft tissue infections

CONTRAINDICATIONS

- History of serious hypersensitivity reaction to drug
- Pregnancy or breastfeeding
- On dialysis
- eGFR <30 ml/min/1.73m² (dapagliflozin)
- ESRD (dapagliflozin and empagliflozin)
- Severe renal impairment (empagliflozin)

PATIENT EDUCATION

Educate patients on:

- Potential for genital mycotic infections and importance of genital hygiene.
- Symptoms of diabetic ketoacidosis (nausea, vomiting, abdominal pain, weakness) and that diabetic ketoacidosis can occur even if blood glucose readings are in the 150–250 mg/dL range. If patient experiences diabetic ketoacidosis-like symptoms, he/she should be instructed to seek urgent medical attention.
- Foot care, especially in patients with diabetic neuropathy. Ask patients to report any foot wounds immediately.

eGFR = estimated glomerular filtration rate; ESRD = end stage renal disease; GLP-1RA = glucagon-like peptide-1 receptor agonist; HbA1c = hemoglobin A1c; SGLT2 = sodium-glucose cotransporter-2; T2D = type 2 diabetes

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GLP-1RAs				
DOSAGE INFORMATION				
Drug	Recommended Doses for CV Benefit*	Titration	Dose Modification	Indications
Dulaglutide	0.75 mg SC per week	Titrate slowly to 1.5 mg or maximally tolerated dose based on prescribing information	<ul style="list-style-type: none"> Up-titrate slowly to reduce nausea and vomiting Discontinue if pancreatitis is suspected and do not restart if pancreatitis is confirmed No dose adjustment necessary with renal or hepatic impairment; data in end-stage renal disease are limited 	<ul style="list-style-type: none"> Improve glycemic control in adults with T2D Reduce MACE for people with T2D with and without established CV disease
Liraglutide	0.6 mg SC daily	Titrate slowly to 1.8 mg or maximally tolerated dose based on prescribing information	<ul style="list-style-type: none"> Up-titrate slowly to reduce nausea and vomiting Discontinue if pancreatitis is suspected and do not restart if pancreatitis is confirmed No dose adjustment is necessary with renal or hepatic impairment 	<ul style="list-style-type: none"> Improve glycemic control in adults with T2D Reduce risk of MI, CVA, or CV death in adults with T2D and CV disease
Injectable Semaglutide	0.25 mg SC per week	Titrate slowly to 1 mg once weekly or maximally tolerated dose based on prescribing information	<ul style="list-style-type: none"> Up-titrate slowly to reduce nausea and vomiting Discontinue if pancreatitis is suspected and do not restart if pancreatitis is confirmed No dose adjustment is necessary with renal or hepatic impairment 	<ul style="list-style-type: none"> Improve glycemic control in adults with T2D Reduce risk of MI, CVA, or CV death in adults with T2D and CV disease

Please note: Information regarding “Considerations for Drug Initiation and Monitoring” and “Contraindications” for **GLP-1RAs** are continued on the next page.

CV = cardiovascular; CVA = cerebrovascular accident; GLP-1RA = glucagon-like peptide-1 receptor agonist; MACE = major adverse cardiovascular events; MI = myocardial infarction; SC = subcutaneous; SGLT2 = sodium-glucose cotransporter-2; T2D = type 2 diabetes



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GLP-1RAs

CONTINUED:

CONSIDERATIONS FOR DRUG INITIATION AND MONITORING

- Hypoglycemia risk increased with insulin, sulfonylureas, or glinides.
- May delay gastric emptying; not recommended in patients with clinically meaningful gastroparesis. This effect is usually transient with longer-acting GLP-1RAs.
- Care should be taken in patients with prior gastric surgery, including bariatric surgery.
- Diabetic retinopathy complications were reported with semaglutide (injectable), although it is unclear if this is a direct effect of the drug or due to other factors such as rapid improvement in blood glucose control.
- Adverse effects to monitor:
 - Nausea, vomiting, diarrhea, headache, weakness, or dizziness
 - Hypoglycemia when given with insulin, sulfonylureas, or glinides
 - Weight loss
 - Injection site reactions
- If HbA1c is well-controlled at baseline or known history of frequent hypoglycemic events, wean or stop sulfonylurea and consider reducing total daily insulin dose by ~20% when starting therapy.
- Instruct patients to more closely monitor glucose at home for the first 4 weeks of therapy. Consider discontinuing any sulfonylurea or glinide. For patients taking insulin, consider modestly reducing total daily insulin dose (by up to 20%).
- Discontinue DPP-4 inhibitor before starting.
- To mitigate nausea, recommend small portion sizes for meals, start at the lowest dose, and up-titrate as tolerated toward the goal doses used in CV outcome trials.
- Advise patients to undergo appropriate, guideline-recommended eye examinations before starting therapy if not done within the last 12 months.
- Discuss potential risk of diabetic retinopathy complications (for dulaglutide or injectable semaglutide).
- Avoid in patients with diabetic gastroparesis or active gallbladder disease.

CONTRAINDICATIONS

- History of serious hypersensitivity reaction to drug
- Pregnancy or breast feeding
- Personal or family history of medullary thyroid cancer
- Personal or family history of MEN2

CV = cardiovascular; DPP4 = dipeptidyl peptidase-4; GLP-1RA = glucagon-like peptide-1 receptor agonist; HbA1c = hemoglobin A1c; MEN2 = multiple endocrine neoplasia, type 2; MI = myocardial infarction; SGLT2 = sodium-glucose cotransporter-2; T2D = type 2 diabetes

