



Key Considerations in use of GLP1-RAs and SGLT2is for CV Risk Reduction in Patients with ASCVD and T2D

Purpose:

- This tool complements the 2018 ACC Expert Consensus Decision Pathway on Novel Therapies for Cardiovascular Risk Reduction in Patients with Type 2 Diabetes and Atherosclerotic Cardiovascular Disease, which helps clinicians determine which atherosclerotic cardiovascular disease (ASCVD) 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) and established ASCVD.
- The pathway document, 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	empagliflozin, canagliflozin
GLP-1RAs	liraglutide, semaglutide

- The CV specialist is well-positioned to address 3 key areas in the management of ASCVD patients with T2D: screening of high-risk CV patients for T2D, aggressively treating CV risk factors in patients with established T2D and ASCVD, and incorporating these new agents into practice based on the recent data.
- CV specialists who care for patients with ASCVD and T2D should recommend guideline-based therapy with lifestyle changes, metformin, and initiate a clinician-patient discussion about the addition of an SGLT2 inhibitor or GLP-1RA with demonstrated CV benefit.

*The EMPA-REG OUTCOME and the CANVAS and CANVAS-R trials have demonstrated significant reductions in MACE in patients randomized to receive SGLT2 inhibitor therapy as compared with placebo. The LEADER trial showed that liraglutide has been definitively shown to significantly reduce CV events. A similar benefit was observed in the moderately sized trial of semaglutide, SUSTAIN-6. Benefits of exenatide QW were suggested in studies but not definitive and therefore not currently included in this tool.

Reference: Das SR, Everett BM, Birtcher KK, Brown JM, Cefalu WT, Januzzi JL Jr, Rastogi Kalyani R, Kosiborod M, Magwire ML, Morris PB, Sperling LS. 2018 ACC expert consensus decision pathway on novel therapies for cardiovascular risk reduction in patients with type 2 diabetes and atherosclerotic cardiovascular disease: a report of the American College of Cardiology Task Force on Expert Consensus Decision Pathways. *J Am Coll Cardiol* 2018;2018 Nov 26 [E-pub ahead of print]: <https://doi.org/10.1016/j.jacc.2018.09.020>

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GLP-1RAs (*glucagon-like peptide-1 receptor agonist*)

DOSAGE INFORMATION

Drug	Initiation	Titration	Dose Modifications
Liraglutide (Currently Preferred)	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 prevent 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.
Semaglutide	0.25 mg SC per week	Titrate slowly to maximally tolerated dose based on prescribing information	<ul style="list-style-type: none"> Up-titrate slowly to prevent nausea and vomiting. Discontinue if pancreatitis is suspected, and do not restart if pancreatitis is confirmed. Agents listed above offer reductions in MACE but are associated with transient nausea and vomiting. Route of administration is subcutaneous, but given with a small needle and pen device to ease administration and patient acceptance. No dose adjustment necessary with renal or hepatic impairment. Data in end-stage renal disease are limited.

CONSIDERATIONS FOR DRUG INITIATION AND MONITORING

- Agents listed above offer reductions in MACE but are associated with transient nausea and vomiting.
- Route of administration is subcutaneous, but given with a small needle and pen device to ease administration and patient acceptance.
- If A1C well-controlled at baseline, or known history of frequent hypoglycemic events, reduce dose of sulfonylurea by 50% or basal insulin dose by 20% when starting therapy.
- Discontinue DPP-4 inhibitor before starting (if applicable).
- To mitigate nausea, start at lowest dose and up-titrate slowly to the doses used in CV outcome trials.*
- Monitor for increase in diabetic retinopathy complications (for semaglutide).
- Educate patients on:
 - Need for close monitoring of glucose at home for the first 4 weeks of therapy.
 - Need for undergoing appropriate, guideline-recommended eye exams before starting therapy if not done within the last 12 months.

Abbreviations: A1C = hemoglobin A1C; CrCl = Creatinine clearance; CV = cardiovascular; DPP4 = dipeptidyl peptidase-4; GLP-1RA = glucagon-like peptide-1 receptor agonist; T2D = type 2 diabetes; SC = subcutaneous; QW = once daily

*Higher doses of GLP1-RA can sometimes be used for weight loss, but have not been shown to offer additional CV risk reduction

Reference: Das SR, Everett BM, Birtcher KK, Brown JM, Cefalu WT, Januzzi JL, Rastogi Kalyani R, Kosiborod M, Magwire ML, Morris PB, Sperling LS. 2018 ACC Expert Consensus Decision Pathway on novel therapies for cardiovascular risk reduction in patients with type 2 diabetes and atherosclerotic cardiovascular disease: a report of the American College of Cardiology Task Force on Expert Consensus Decision Pathways. *J Am Coll Cardiol* 2018; 2018 Nov 26 [E-pub ahead of print]: <https://doi.org/10.1016/j.jacc.2018.09.020>.

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SGLT2 inhibitors (sodium-glucose cotransporter 2)

DOSAGE INFORMATION

Drug	Initiation	Titration	Dose Modifications
Empagliflozin (Currently Preferred)	10 mg PO daily	May increase to 25 mg daily	<ul style="list-style-type: none"> eGFR \geq45 mL/min/1.73 m²: No dose adjustment required. eGFR <45 mL/min/1.73 m²: Do not initiate; discontinue if eGFR persistently below 45 mL/min/1.73 m². *
Canagliflozin	100 mg PO daily	May increase to 300 mg daily if needed in those who have an eGFR \geq 60 mL/min/1.73 m ²	<ul style="list-style-type: none"> eGFR \geq60 mL/min/1.73 m²: No dose adjustment required. eGFR 45 to <59 mL/min/1.73 m²: Do not exceed 100 mg/day. eGFR <45 mL/min/1.73 m²: Do not initiate; discontinue if eGFR persistently below 45 mL/min/1.73 m².

CONSIDERATIONS FOR DRUG INITIATION AND MONITORING

- Agents listed above appear to reduce both MACE and HF risk but increase the risk of genital mycotic infections with possible additional risk of rare events.
- Route of administration is oral.
- Cardiovascular benefits were seen at the lowest doses of both drugs, so dose titration is not necessary to achieve cardiovascular risk reduction.
- If A1c well controlled at baseline, or known history of frequent hypoglycemic events, reduce dose of sulfonylurea by 50% or insulin dose by 20% when starting therapy.
- Avoid hypovolemia. May need to reduce thiazide or loop diuretic dose.
- Monitor kidney function.
- Educate patients on:
 - Need for close monitoring of glucose at home for the first 4 weeks of therapy.
 - Symptoms of low blood pressure (light headedness, orthostasis, weakness).
 - Symptoms of diabetic ketoacidosis (nausea, vomiting, 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, they should be instructed to seek immediate medical attention.
 - Foot care and follow up foot pulse exam (particularly canagliflozin).
 - Potential for genital mycotic infections.

Abbreviations: eGFR = estimated glomerular filtration rate; PO = orally; SGLT2 = sodium-glucose cotransporter-2; T2D = type 2 diabetes.

*SGLT2 inhibitor doses are modified in patients with impaired renal function because the medications are less effective in lowering glucose concentrations when renal function is impaired, rather than because of specific safety concerns. The CV benefit of these medications appears to be present down to eGFR of 30 mL/min/1.73m². Trials of SGLT2 inhibitors are underway in patients with CKD using progression of kidney disease as their key clinical outcomes.

Reference: Das SR, Everett BM, Birtcher KK, Brown JM, Cefalu WT, Januzzi JL, Rastogi Kalyani R, Kosiborod M, Magwire ML, Morris PB, Sperling LS. 2018 ACC Expert Consensus Decision Pathway on novel therapies for cardiovascular risk reduction in patients with type 2 diabetes and atherosclerotic cardiovascular disease: a report of the American College of Cardiology Task Force on Expert Consensus Decision Pathways. *J Am Coll Cardiol* 2018; 2018 Nov 26 [E-pub ahead of print]: <https://doi.org/10.1016/j.jacc.2018.09.020>.

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