

Connect to the Heart of Type 2 Diabetes:

ACC Handbook on ASCVD and Type 2 Diabetes



AMERICAN
COLLEGE *of*
CARDIOLOGY

This brochure is intended to aid cardiovascular (CV) clinicians who are managing patients with type 2 diabetes (T2D) with established ASCVD or at high risk for ASCVD.

When considering such guidance, it is important to remember:

- ASCVD is defined as a history of an acute coronary syndrome or myocardial infarction, 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.
- High risk* for ASCVD is defined as end organ damage such as left ventricular hypertrophy, retinopathy, or multiple risk factors (e.g., age, hypertension, smoking, obesity, dyslipidemia).

*As discussed in the 2020 Diabetes Expert Consensus Decision Pathway, this definition for “high risk” is consistent with the inclusion/exclusion criteria of the clinical trials for SGLT2 inhibitors and GLP-1RAs and the ADA’s Standards of Medical Care in Diabetes. It is not necessarily equivalent to the definition of “high risk” as categorized by the pooled cohort equations used in the ASCVD Risk Estimator apps.

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Resources

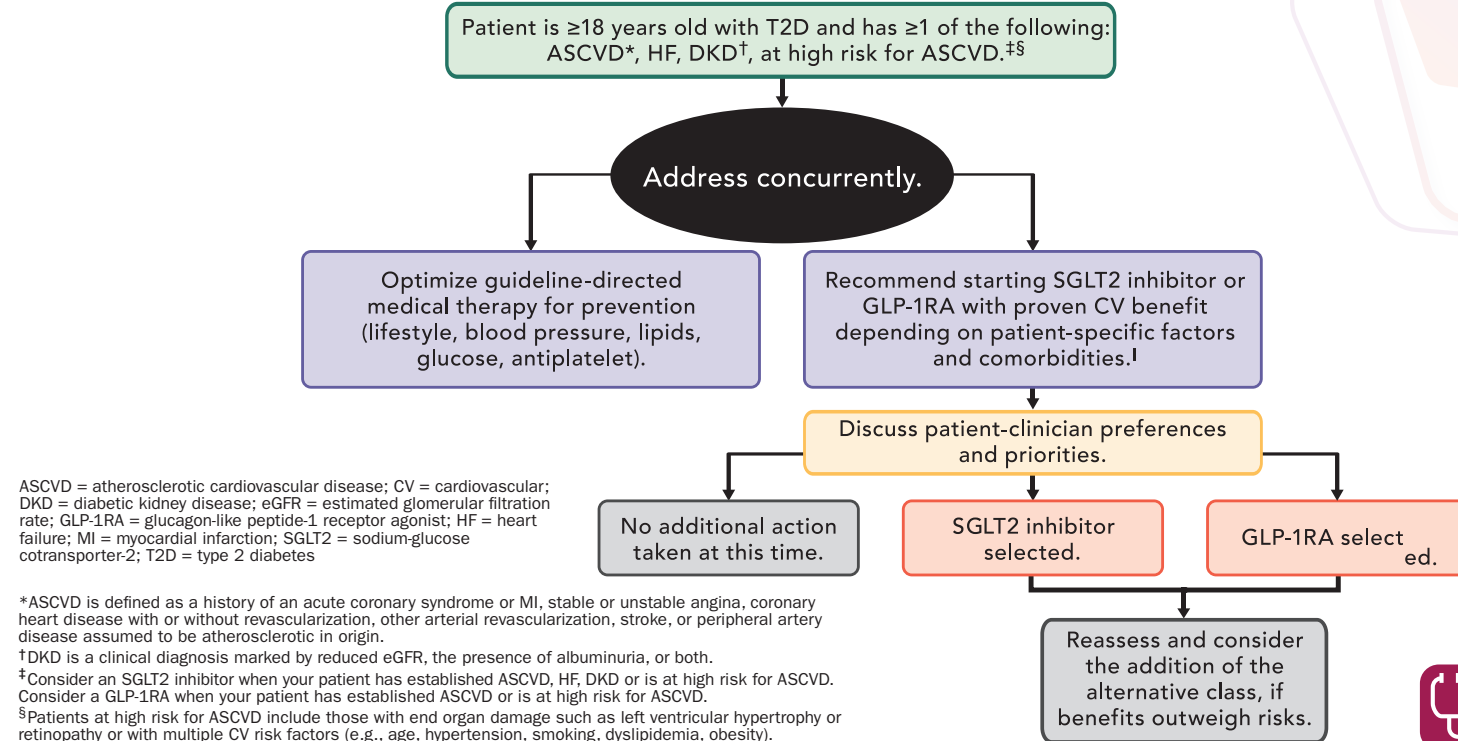
- ASCVD Risk Stratification
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- CV disease remains the leading cause of morbidity and mortality in patients with T2D.
- Comprehensive CV risk factor control reduces events and improves survival in patients with T2D. This includes encouraging a healthy diet, regular physical activity, weight loss, smoking cessation, assiduous control of blood pressure, lowering of atherogenic blood lipids, and use of antiplatelet agents in accordance with current treatment guidelines.
- Beyond these core recommendations, CV specialists should be aware of the strong clinical evidence regarding specific therapies proven to improve CV outcomes in patients with T2D.
- Drugs from two new classes—SGLT2 inhibitors and GLP-1RAs—have demonstrated important cardiovascular benefits that appear to be independent of the glucose lowering effects.

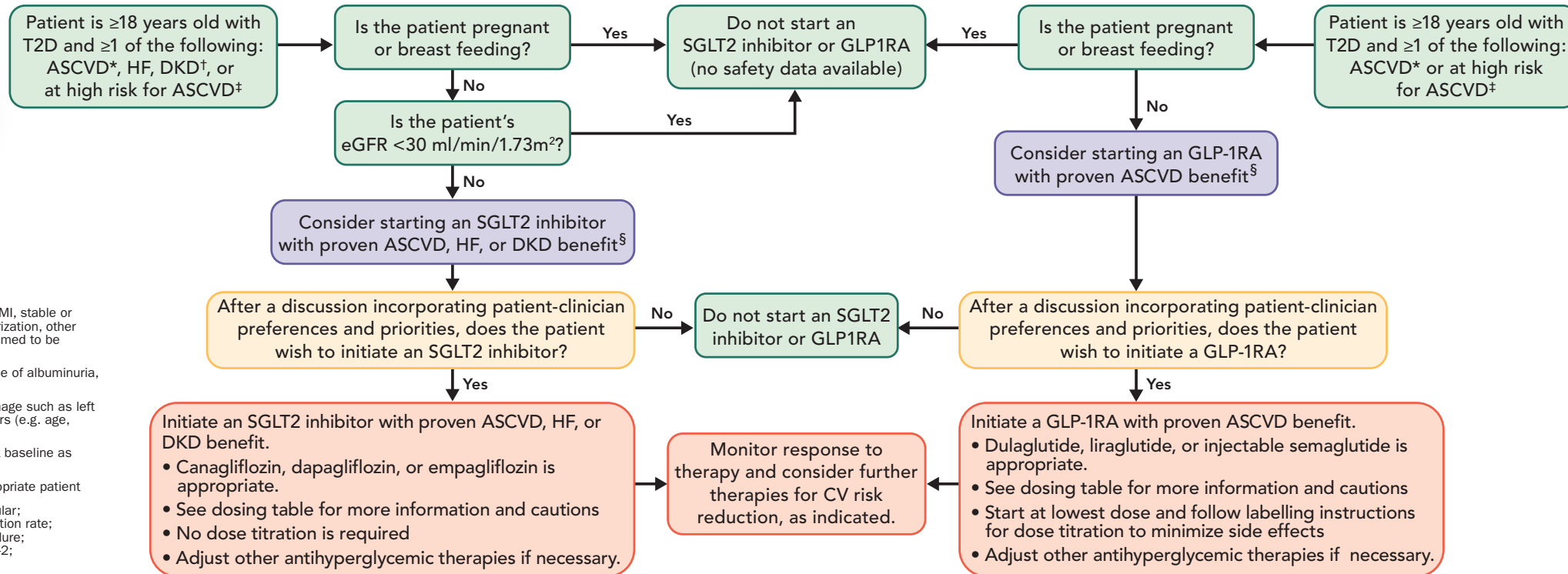
The CV specialist has a key role in optimizing the care of patients with T2D and is well-positioned to address 3 key areas in the management of these patients:

1. Screening for T2D in their patients with or at high risk of CV disease
2. Aggressively treating CV risk factors
3. Incorporating newer glucose-lowering agents with evidence for improving CV outcomes into routine practice



Algorithm for Using an SGLT2 Inhibitor to Manage ASCVD, HF, or DKD Risk

Algorithm for Using a GLP-1RA to Manage ASCVD Risk



*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

‡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)

§Most patients enrolled in the relevant trials were on metformin at baseline as glucose-lowering therapy

¶This may include the addition of a GLP-1RA or SGLT2i in the appropriate patient

ASCVD = atherosclerotic cardiovascular disease; CV = cardiovascular; DKD = diabetic kidney disease; eGFR = estimated glomerular filtration rate; GLP-1RA = glucagon-like peptide-1 receptor agonist; HF = heart failure; MI = myocardial infarction; SGLT2 = sodium-glucose cotransporter-2; T2D = type 2 diabetes



These Medications Should be Used:

- In concert with established risk factor modification guidelines for the prevention of MACE in patients with T2D, including guidelines on lipids, blood pressure, and antiplatelet therapy
- In the context of guideline-directed diabetes care, including those described in the ADA Standards of Medical Care in Diabetes

Opportunities to Initiate an SGLT2 Inhibitor or a GLP-1RA With Demonstrated CV or Renal Benefit in Patients With T2D:

- In a patient with T2D and ASCVD (SGLT2 inhibitor or GLP-1RA)
- At the time of diagnosis of clinical ASCVD (SGLT2 inhibitor or GLP-1RA), DKD (SGLT2 inhibitor), and/or HF (SGLT2 inhibitor)[†] in a patient with T2D on a drug regimen that does not include an SGLT2 inhibitor or GLP-1RA with CV benefit
- At the time of diagnosis of T2D in a patient with clinical ASCVD (SGLT2 inhibitor or GLP-1RA), DKD (SGLT2 inhibitor), and/or HF (SGLT2 inhibitor)^{†‡}
- At hospital discharge (with close outpatient follow-up) after admission for an ASCVD^{||} (SGLT2 inhibitor or GLP-1RA) or HF (SGLT2 inhibitor) event[§]
- In a patient with T2D and diabetic kidney disease (SGLT2 inhibitor, alternatively GLP-1RA for eGFR <30 ml/min/1.73 m²)[‡]
- In patients determined to be at high risk of ASCVD II (SGLT2 inhibitor or GLP-1RA) or HF (SGLT2 inhibitor)^{†‡}

Key Points About SGLT2 Inhibitors and GLP-1RAs with Demonstrated CV Benefit:

- An SGLT2 inhibitor with demonstrated CV benefit is recommended for patients with T2D and HF, especially HF with reduced ejection fraction (HFrEF), or who are at high risk of developing HF, DKD, clinically evident ASCVD, or any combination of these conditions
- A GLP-1RA with demonstrated CV benefit is recommended for patients with established or at very high risk for ASCVD
- A patient-clinician discussion about the use of an SGLT2 inhibitor and/or a GLP-1RA with demonstrated CV benefit is recommended at the time of a clinical follow up visit for patients with T2D who have or who are at very high risk for clinical ASCVD, HF, and/or DKD

*At the time of hospital discharge or in the outpatient setting. Increased vigilance regarding hypoglycemia surveillance is warranted, especially if on background insulin, sulfonylurea, or gliinide therapy.

[†]A minority of patients included in the CANVAS, LEADER, SUSTAIN-6, and EXSCEL trials and a majority of patients in the REWIND trial could be characterized as high-risk primary prevention patients. These patients did not have established ASCVD but did have prespecified ASCVD risk factors.

[‡]Use clinical judgement when initiating an SGLT2 inhibitor in a patient who will be starting or up-titrating an ACE inhibitor or ARB if the patient's renal function is impaired.

[§]Hospitalized patients were not included in most of the CV outcome trials discussed here. There is a lack of practical and safety data regarding in-hospital addition of SGLT2 inhibitors or GLP-1RAs to a patient's regimen.

^{||}Consider for patients at very high risk of ASCVD to include patients with end-organ damage such as left ventricular hypertrophy or retinopathy or with multiple CV risk factors (e.g., age, hypertension, smoking, dyslipidemia, obesity).

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; ASCVD = atherosclerotic cardiovascular disease; CANVAS = Canagliflozin Cardiovascular Assessment Study; CV = cardiovascular; DKD = diabetic kidney disease; eGFR = estimated glomerular filtration rate; EXSCEL = Exenatide Study of Cardiovascular Event Lowering Trial; GLP-1RA = glucagon-like peptide-1 receptor agonist; HF = heart failure; LEADER = Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results; MACE = major adverse cardiovascular event; REWIND = Researching CV Events With a Weekly Incretin in Diabetes; SGLT2 = sodium-glucose cotransporter-2; SUSTAIN-6 = Trial to Evaluate CV and Other Long-term Outcomes With Semaglutide in Subjects With T2D; T2D = type 2 diabetes



Reference Sheet: Key Considerations in Use of SGLT2 Inhibitors With Demonstrated CV Benefit

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

CV = cardiovascular; CVA = cerebrovascular accident; 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; MACE = major adverse cardiovascular events; MI = myocardial infarction; SC = subcutaneous; 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.

Reference Sheet: Key Considerations in Use of SGLT2 Inhibitors With Demonstrated CV Benefit

Considerations for Drug Initiation and Monitoring	Contraindications
<ul style="list-style-type: none"> 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: <ul style="list-style-type: none"> Genital fungal infections Urinary tract infections Euglycemic diabetic ketoacidosis Lower limb ulcerations and soft tissue infections 	<ul style="list-style-type: none"> 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
	<p>Educate patients on:</p> <ul style="list-style-type: none"> 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.



Reference Sheet: Key Considerations in Use of GLP-1RAs With Demonstrated CV Benefit

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

*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.

Reference Sheet: Key Considerations in Use of GLP-1RAs With Demonstrated CV Benefit

Considerations for Drug Initiation and Monitoring
<ul style="list-style-type: none"> 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: <ul style="list-style-type: none"> Nausea, vomiting, diarrhea, headache, weakness, or dizziness <ul style="list-style-type: none"> 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
<ul style="list-style-type: none"> 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; CVA = cerebrovascular accident; DPP4 = dipeptidyl peptidase-4; GLP-1RA = glucagon-like peptide-1 receptor agonist; HbA1c = hemoglobin A1c; MACE = major adverse cardiovascular events; MEN2 = multiple endocrine neoplasia, type 2; MI = myocardial infarction; SC = subcutaneous; SGLT2 = sodium-glucose cotransporter-2; T2D = type 2 diabetes



Patient and Clinician Preferences and Priorities for Considering SGLT2 Inhibitors With Demonstrated CV Benefit Versus GLP-1RAs With Demonstrated CV Benefit

Preference or Priority	Consider Using an SGLT2 Inhibitor First When Patient and Clinician Priorities Include:	Consider Using a GLP-1RA First When Patient and Clinician Priorities Include:
MACE Prevention	+++	+++
HF Prevention	+++	
Weight Loss	+	+++
Renal disease progression prevention	+++	+
Mode of administration	Oral	Subcutaneous
Considerations that may prompt use of an alternative class	<ul style="list-style-type: none"> Severely reduced kidney function*,† History of prior amputation, severe peripheral arterial disease, or active diabetic foot ulcers (caution with canagliflozin) History of recurrent genital candidiasis History of diabetic ketoacidosis History of fracture (caution with canagliflozin) The patient is considering pregnancy The patient is breast feeding 	<ul style="list-style-type: none"> Persistent nausea, despite appropriate dietary education and low doses History of gastroparesis Active gallbladder disease History of MEN2 or medullary thyroid cancer History of proliferative retinopathy (caution with semaglutide or dulaglutide) The patient is considering pregnancy The patient is breast feeding

*eGFR <45 mL/min/1.73m² is currently a caution due to a decrease in glycemic efficacy (not due to safety), but ongoing studies are testing whether SGLT2 inhibitors offer renal benefits in these patients. The FDA label for canagliflozin allows use of canagliflozin to an eGFR of 30 ml/min/1.73m² specifically for patients with DKD.

†Use clinical judgement when initiating an SGLT2 inhibitor in a patient who will be starting or up-titrating an ACE inhibitor or ARB if the patient's renal function is impaired.

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; CV = cardiovascular; DKD = diabetic kidney disease; eGFR = estimated glomerular filtration rate; FDA = Food and Drug Administration; GLP-1RA = glucagon-like peptide-1 receptor agonist; HF = heart failure; MACE = major adverse cardiovascular event; MEN2 = multiple endocrine neoplasia type 2; SGLT2 = sodium-glucose cotransporter-2.

ASCVD Risk Stratification: Assessing Risk With ACC ASCVD Risk Estimator Apps*

The screenshot displays the ACC ASCVD Risk Estimator Plus app interface. At the top, there are three tabs: 'Estimate Risk', 'Therapy Impact', and 'Advice'. The 'Estimate Risk' tab is active, showing a 'Current 10-Year ASCVD Risk' of 16.6% (Intermediate). Below this, it indicates 'Lifetime ASCVD Risk: 50%' and 'Optimal ASCVD Risk: 2.0%'. The user input fields are: Current Age (56), Sex (Female), Race (African American), Systolic Blood Pressure (146 mm Hg), Diastolic Blood Pressure (83 mm Hg), Total Cholesterol (278 mg/dL), HDL Cholesterol (55 mg/dL), LDL Cholesterol (112 mg/dL), History of Diabetes? (Yes), and Smoker? (Current).

ACC ASCVD Risk Estimator Plus

- Mobile and web-based app
- Estimate a patient's initial 10-year risk, lifetime risk, and optimal risk
- Receive an individualized, evidence-based intervention approach for managing primary prevention of ASCVD
- Guide patient-clinician discussions about lowering risk

ACC Multilingual ASCVD Risk Estimator

- Web-based app
- Estimate a patient's initial 10-year risk, lifetime risk, and optimal risk with multiple language options
- Simplified for quick calculation of risk assessment

*Risk stratification categories in the apps are based on risk factors included in the pooled cohort equations. The definition of "high risk" in the apps is not necessarily equivalent to the definition of "high risk" as defined in the 2020 Diabetes Expert Decision Consensus Pathway.



How to access the ASCVD Risk Estimator Plus app:

- Online at: <https://tools.acc.org/ASCVD-Risk-Estimator-Plus>
- Download on a mobile device (Apple or Android) by searching “ASCVD Risk Estimator Plus” in the iTunes or Google Play stores.
- Scan the QR code below:



How to access the Multilingual ASCVD Risk Estimator web app:

- Online at: <https://tools.acc.org/Multilingual-ASCVD-Risk-Estimator>
- Scan the QR code below:



References

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Das SR, Everett BM, Birtcher KK, Brown JM, Januzzi Jr 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 Sep, 76 (9) 1117-1145. <https://doi.org/10.1016/j.jacc.2020.05.037>

ACC 2019 Type 2 Diabetes and Cardiovascular Risk Discussion Guide

Links to Prescribing Information

Canagliflozin: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/204042s026lbl.pdf

Dapagliflozin: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/202293s021lbl.pdf

Empagliflozin: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/204629s023lbl.pdf

Dulaglutide: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/125469s007s008lbl.pdf

Liraglutide: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/022341s027lbl.pdf

Injectable Semaglutide: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/209637lbl.pdf

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