U.S. Department of Veterans Affairs
Veterans Health Administration
PBM Academic Detailing Services

Provider Factsheet

Sodium Glucose Co-Transporter 2 (SGLT2) Inhibitors and Glucagon-Like Peptide-1 Receptor Agonists (GLP-1 RA) Cardiorenal Benefits and Roles in Therapy

SGLT2 inhibitors and **GLP-1 RAs** are beneficial across multiple clinical conditions as outlined in the table below. **The benefits of these agents extends beyond their glucose lowering effects.**[1,2]

SGLT2 inhibitor and GLP-1 RA's role in therapy for cardiorenal benefits*,[1-15]

ASCVD	• Use SGLT2 Inhibitor (empagliflozin) in T2DM and ASCVD or high risk of ASCVD • If a SGLT2 inhibitor cannot be used, use a GLP-1 RA (injectable semaglutide)
HF	• Use SGLT2 inhibitor (empagliflozin) in addition to other GDMT for HF with reduced, mid-range, or preserved ejection fraction (HFrEF, HFmrEF, HFpEF) in patients with and without T2DM • GLP-1 RA (injectable semaglutide) improved quality of life in HFpEF and obesity; evidence does not show reduction in hospitalizations or mortality
CKD	• Use SGLT2 inhibitor (empagliflozin) in T2DM and CKD. In those without T2DM, use SGLT2 inhibitor if eGFR ≥ 20 ml/min/1.73 m^2 and uACR > 200 mg/g, or eGFR 20-45 ml/min/1.73 m^2 and uACR < 200 mg/g — Use with maximally tolerated doses of ACE I or ARB • If SGLT2 inhibitor cannot be used in patients with T2DM and CKD, use GLP-1 RA

*Before starting a SGLT2 inhibitor, ensure eGFR ≥ 20 mL/min/1.73 m^2 and continue until ESRD/dialysis. ASCVD: established cardiovascular disease (acute coronary syndrome, myocardial infarction [MI], stable or unstable angina, peripheral artery disease, stroke, or any revascularization procedure). High risk indicators of ASCVD: age ≥ 55 years with ≥ 2 risk factors (obesity, hypertension, smoking, dyslipidemia, or albuminuria). HF: all types of heart failure. CKD: eGFR < 60 mL/min/1.73 m^2 or uACR ≥ 30 mg/g. ACE I = angiotensin-converting enzyme inhibitor; ARB = angiotensin II receptor blocker; ASCVD = atherosclerotic cardiovascular disease; CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate; ESRD = end stage renal disease; GDMT = guideline directed medical therapy (**ADS Heart Failure SharePoint**); HbA1c = hemoglobin A1c; HF = heart failure; uACR = urine albumin-creatinine ratio. **Evidence for tirzepatide, a glucose dependent insulinotropic polypeptide/glucagon-like peptide-1 (GIP/GLP-1) receptor agonist, is still emerging and was not included in this review.**

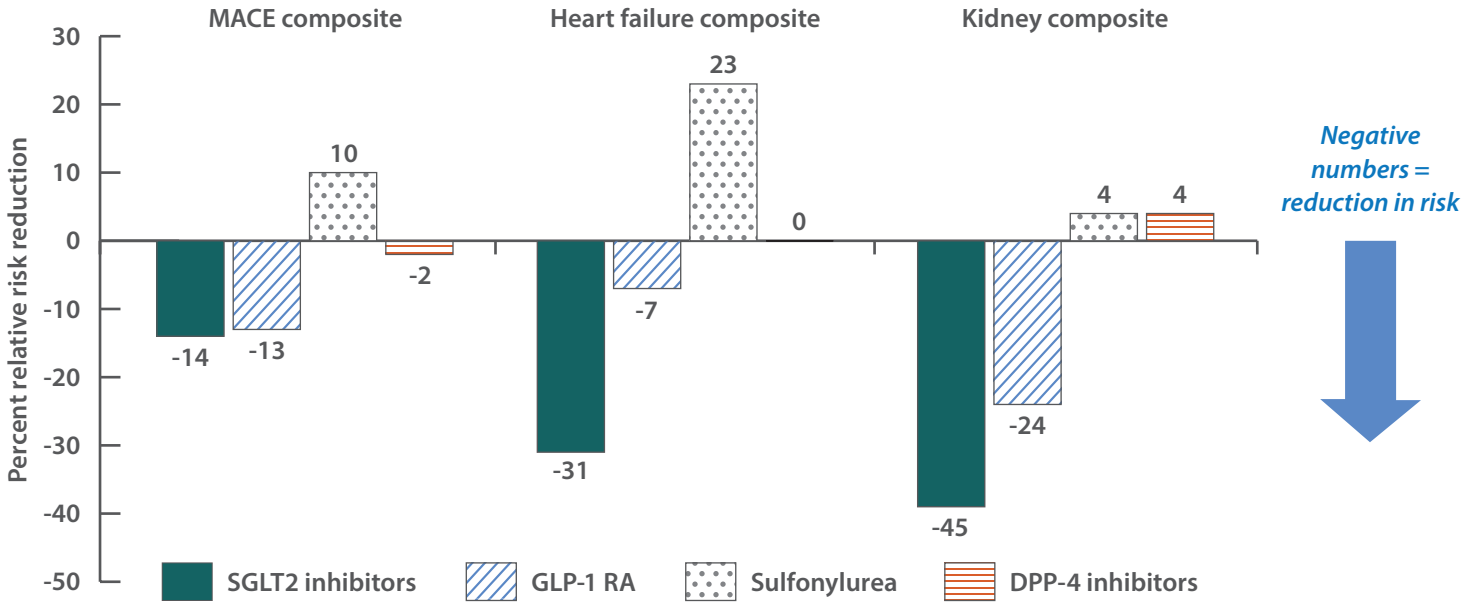
Monitoring and effects of SGLT2 inhibitors and GLP-1 RAs[2-8]

Monitoring		Estimated effects over time	
		< 1 month	**> 3 months**
SGLT2 inhibitors			
Lab monitoring	eGFR*	↓3-9 ml/min/1.73 m^2	eGFR stabilizes and protective effects start
	HbA1c		↓0.5-1%
Home monitoring	Blood glucose	↓fasting reading 18-36 mg/dL	
	Blood pressure	↓systolic BP 3-8 mmHg	
	Weight	↓3-5 lbs	
GLP-1 receptor agonists (injectable)			
Lab monitoring	eGFR		protective effects start
	HbA1c		↓1-2%
Home monitoring	Blood glucose	↓fasting reading 36-72 mg/dL	
	Blood pressure	no significant change	
	Weight	↓4-14 lbs	

*SGLT2 inhibitors may initially worsen eGFR in the first 4 weeks like what is seen with ACE I. The eGRF is expected to stablize over time and may improve in some patients. SGLT2 inhibitors may be continued if eGFR decrease is < 30%. If eGFR declines ≥ 30% after initiation, further evaluation is warranted to determine if discontinuation is needed and evaluation of risks versus benefits.

Consider cardiorenal benefits when choosing therapy in Veterans with type 2 diabetes[9-31]

In Veterans with T2DM, use a SGLT2 inhibitor first for patients with ASCVD, HF, or CKD and add metformin if additional glycemic control is needed. Metformin is beneficial for glycemic control and may reduce cardiovascular mortality and progression to ESRD. Consider combination empagliflozin/metformin tablets for patients taking both agents. If a sulfonylurea or DPP-4 inhibitor is being used in a patient with ASCVD, HF, or CKD, consider replacing the sulfonylurea or DPP-4 inhibitor with a SGLT2 inhibitor when HbA1c is in target range. In cases where HbA1c is not controlled, then add a SGLT2 inhibitor to existing therapy.



MACE composite: major adverse cardiovascular events (nonfatal stroke, nonfatal MI, and cardiovascular death); HF composite: cardiovascular (CV) death and HF hospitalization; Kidney composite: end stage renal disease, eGFR < 10-15 mL/min/1.73 m^2, or death from renal/CV causes. For ASCVD, use SGLT2 inhibitors **empagliflozin** or canagliflozin, and GLP-1 RA injectable semaglutide, liraglutide, or dulaglutide. For HF, use SGLT2 inhibitors **empagliflozin**, dapagliflozin, or sotagliflozin. For CKD, use SGLT2 inhibitors **empagliflozin**, canagliflozin, or dapagliflozin and GLP-1 RA injectable semaglutide (other GLP-1 RAs reduce albuminuria). (**Bolded** = formulary agent). DPP4-I = dipeptidyl peptidase 4 inhibitor. Negative numbers indicate a reduction in risk, therefore provide cardiorenal benefits.

Dosing information for SGLT2 inhibitor–empagliflozin (oral)[1-3]

Mechanism of action: Blocks glucose and sodium reabsorption in the kidney, decreases plasma volume, and increases urinary excretion of glucose, sodium, and uric acid.

DOSE:

- Initial dose 10 mg or 12.5 mg daily (cardiorenal benefit achieved at this dose)*
- Maximum dose 25 mg daily (for glycemic control in T2DM)
- Less effective for glucose lowering when eGFR is < 45 mL/min/1.73 m^2 but retains cardiorenal benefits

TIPS TO IMPROVE ADHERENCE:

- Take in the morning with or without food
- Use empagliflozin/metformin combination tablet*

DO NOT INITIATE:

- Pregnant or breastfeeding
- Type 1 diabetes
- eGFR < 20 mL/min/1.73 m^2

Empagliflozin is on the VA National Formulary. See VA National Formulary: **VA Formulary Advisor**. If using empagliflozin for cardiorenal benefit alone, the 10 mg or 12.5 mg daily dose is used. Empagliflozin dose is typically only increased to 25 mg daily when used for T2DM and further glycemic control is needed. *Available with metformin immediate or sustained release formulations.

Managing side effects—SGLT2 inhibitors[3,4,32,33]

SGLT2 inhibitors		
Side effect	**Risk factors**	**Considerations**
Frequent urination	• HbA1c > 9% • Taking SGLT2 inhibitor at bedtime	• Lower glucose readings to target levels • Recommend taking SGLT2 inhibitor in the morning
Hypovolemia or hypotension	• Age > 75 years or frailty • Concomitant blood pressure-lowering agents or diuretics	• Reduce non-renin-angiotensin system agents • Reduce diuretic if not having fluid overload • Provide counseling to maintain adequate hydration
Genitourinary infections (GU)	• Uncontrolled T2DM, obesity • Female birth sex or uncircumcised male • History of genital yeast infection, urinary tract infection, or Fournier's gangrene • Barriers to adequate hygiene • Severe incontinence or catheter use • Immunosuppression	• Encourage preventative measures (e.g., daily perineal hygiene, clean after urinating and sex, keep area dry, avoid tight-fitting clothing) • Provide education on infection signs and symptoms with action plan • Continue SGLT2 inhibitor if clinically stable GU. Cardiorenal benefits end quickly after stopping
Diabetic ketoacidosis (DKA)	• Hemoglobin A1c > 10% • Very low carbohydrate or ketogenic diet • Excessive alcohol use • Sudden excessive insulin dose reductions • Surgery or procedures • Reduced oral intake during acute illness or prolonged fasting	• Address elevated glucose when HbA1c > 10% with other agents before starting SGLT2 inhibitors • Do not abruptly discontinue insulin • Provide information on signs/symptoms of DKA/ euglycemic DKA (< 250 mg/dL) with action plan • Hold SGLT2 inhibitor 3-4 days prior to surgery/ procedures and provide sick day planning
Sick day planning	• Higher risk for DKA with fever, infection, poor appetite, vomiting or diarrhea	• Stop SGLT2 inhibitor; restart when symptoms resolve. If symptoms continue, follow up with healthcare team

Discussion points for SGLT2 inhibitors with Veterans[3,4,32,33]

- Stop SGLT2 inhibitors 3 days before surgery or procedures with anesthesia or moderate sedation (ertugliflozin =4 days prior). See **VA Peri-Procedural Management of Diabetes Medications and Devices Guidance.**
- Significant dietary changes, particularly following a very low carbohydrate diet < 50 gm/day may increase risk of DKA. Provide information on DKA and develop an action plan.
- Avoid use during pregnancy and breastfeeding. Potential risk to fetus in second and third trimester.[4]

Dosing information for GLP-1 RA—semaglutide (injection)[1,2,4]

Mechanism of action: Increases insulin secretion in response to elevated blood glucose, decreases glucagon secretion, and slows gastric emptying.

DOSE:

- Initial dose: 0.25 mg weekly for 4 weeks
- Increase to 0.5 mg weekly for cardiorenal benefit; may further increase dose every 4 weeks to 1 mg or 2 mg weekly as needed to achieve glycemic goals
- Maximum dose 2 mg weekly (Ozempic®)
- Subcutaneous injection in abdomen, thigh, or upper arm
- In T2DM, need an eye exam before starting; follow up with ophthalmology if a history of diabetic retinopathy

DO NOT INITIATE:

- Pregnant or breastfeeding
- Severe gastrointestinal dysmotility
- Active risk of pancreatitis, history of pancreatitis, or gallbladder disease with current risk factors*
- Personal or family history of MTC or MEN 2
- History of suicidal attempts or active suicidal ideation. Mental health consultation needed

Semaglutide injection (Ozempic®) is VA National Formulary with criteria for use. See **VA Formulary Advisor.** MEN 2 = multiple endocrine neoplasia syndrome type 2; MTC = medullary thyroid cancer. *Risk factors: > 1000 mg/dL triglycerides, known gallstones with intact gallbladder, or alcohol abuse.

Managing side effects—GLP-1 RAs[3,5,33,34]

GLP-1 receptor agonist		
Side effect	**Risk factors**	**Considerations**
Nausea, stomach upset/ dyspepsia	• Eating high fat or spicy foods • Large meals or overeating • Having an empty stomach • Drinking alcohol • Injecting before a meal	• Eat foods low in fat and include fruits/vegetables • Reduce portion size by 50% for first couple of weeks • Eat small snacks if feeling nauseated • Avoid alcohol and caffeine • Inject after a meal • Ginger chews or peppermint tea may help
Constipation	• Not eating enough fiber • Dehydration • Immobility	• Slowly add fruits, vegetables, and other high fiber foods • Stay hydrated; try one meal with a liquid consistency • Exercise or do a form of movement every day • Use stool softeners, fiber supplements, or osmotic laxatives as needed
Belching and gassiness	• Drinking carbonated beverages • Taking large bites/eating too quickly • Foods that cause gas	• Limit carbonated beverages and avoid using straws • Eat smaller bites and chew food thoroughly • Limit beans, lentils, and other gas-producing foods
Diarrhea	• Eating dairy, high fat, high sugar, or spicy foods	• Stay hydrated and limit dairy and sugary beverages • Temporarily reduce fiber in diet
Pancreatitis	• History of pancreatitis or gallstones with current risk factors, elevated triglycerides, or alcohol misuse	• Consider alternative agent if severe hypertriglyceridemia, excessive alcohol use, gallbladder disease, or pancreatitis

Discussion points for GLP-1 RA with Veterans[3,5,33,34]

- Start semaglutide injection at 0.25 mg weekly and titrate slowly (every 4 weeks or longer) to improve tolerability. Cardiorenal benefits are achieved with semaglutide injection 0.5 mg weekly.
- If vomiting occurs repeatedly, contact your healthcare team and stay hydrated.
- Abdominal pain that radiates to the back with or without nausea could be gallbladder disease or pancreatitis; contact healthcare team if experiencing.
- If scheduled for a surgery or procedure requiring anesthesia or moderate sedation, see **VA Peri-Procedural Management of Diabetes Medications and Devices Guidance.**
- Avoid use during pregnancy and breastfeeding. Stop at least 2 months before planned pregnancy.[5]

1. U.S. Department of Veterans Affairs. *VA/DoD Clinical Practice Guidelines for the Management of Type 2 Diabetes Mellitus.* 2023; **https://www.healthquality.va.gov/guidelines/cd/diabetes**. Assessed 10/12/2024. **2**. American Diabetes Association. *Standards of medical care in diabetes–2025 Diabetes Care.* 2024;48(Suppl 1): S1-S352. **3**. UpToDate Lexidrug. 2025. UpToDate, Inc. **4**. Jardiance (empagliflozin) package insert. Ridgefield CT: Boehringer Ingelheim Pharmaceuticals, Inc. 2023. **5**. Ozempic (semaglutide) package insert. Indianapolis, IN: Eli Lilly and Company; 2025. **6.** Maddox TM, et.al. *J Am Coll Cardiol.* 2024;83(15):1444-1488. **7.** Ferdinand KC, et.al. *Circulation.* 2019;139(18):2098-2109. **8.** Zhang X, Zhao Q. *Journal of Hypertension.* 2016;34(2):167-75. **9.** Zinman B, et al. *N Engl J Med.* 2015;373(22): 2117-2128. **10.** Packer M, et al. *N Engl J Med.* 2020;383(15):1,413-24. **11.** McGuire DK, et al. *JAMA Cardiol.* 2021;6(2):148-58. **12.** Salah HM, et al. *Am Heart J.* 2021;232:10-22. **13.** Zelniker TA, et.al. *Circulation.* 2019;139:2022-2031. **14.** Giugliano D, et al. *Diabetes Obes Metab.* 2020;22(8):1,397-405. **15.** Kawai Y, et al. *Diabetes Res Clin Pract.* 2022;183:109146. **16.** Heidenreich PA, et al. *Circulation.* 2022;145(18):e895-e1032. **17.** Straw S, et al. *Open Heart.* 2021;8(1):e001585. **18.** Anker SD, et al. *N Engl J Med.* 2021;385(16):1451-61. **19.** Chalmoukou K, et al. *Eur J Intern Med.* 2022; 97:78-85. **20.** Wanner C, et al. *N Engl J Med.* 2016;375(4):323-334. **21.** Herrington WG, et al. *N Engl J Med.* 2023;388(2):117-127. **22.** Husain M, et al. *N Engl J Med.* 2019;381(9):841-851. **23.** Marso SP, et al. *N Engl J Med.* 2016;375(19):1834-1844. **24.** Perkovic V, et.al. *N Engl J Med.* 2024;391(2):109-121. **25.** Kosiborod MN, et al. *N Engl J Med.* 2023;389(12):1069-1084. **26.** Wexler DJ, et al. *JAMA Intern Med.* 2023;183(7):705-714. **27.** Kahn MS, et al. *JACC Heart Fail.* 2022;10(3):198-210. **28.** Phung OJ, et al. *Diabetic Medicine.* 2013;30(10):1160-1171. **29.** Green JB, et al. *N Engl J Med.* 2015;373(3):232. **30.** Rosenstock J, et al. *JAMA.* 2019;321(1):69. **31.** Mascolo A, et al. *Front Cardiovasc Med.* 2022;9:1010693. **32.** Kittipibul V, et al. *J Am Coll Cardiol.* 2024;83(16):1568-1578. **33.** Drucker DJ. *Diabetes Care.* 2024;47(11):1873-1888. **34.** Gorgojo-Martinez, et al. *J Clin Med.* 2022;12(1):145.