What You Need to Know About SGLT2 Inhibitors

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Diabetes prevention and adequate management is essential for preventing progression of chronic kidney disease (CKD). Preventive measures should include blood pressure and glucose control with initiation of sodium-glucose cotransporter 2 inhibitors (SGLT2i) in addition to either an angiotensin-converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB) when able. An analysis of adults with type 2 diabetes in the United States showed that diabetes control has improved from 1999 to the early 2010s, but this progress has since stalled, and even declined, by certain metrics.[1] Since 2010, the use of combination therapy had declined among patients with uncontrolled blood pressure and plateaued for those with poor glycemic control.[1]

It is critical to improve the health of patients at risk of developing end-stage renal disease (ESRD) with the tools available. It is estimated that the annual incidence of ESRD will increase from 3.7 per 100,000 of the general population in 2014 to 5.7 per 100,000 by 2040.[2] Incorporating diabetes prevention, it is projected that the annual incidence of ESRD could instead be between 5.2 and 5.5 per 100,000 by 2040.[2] It is important to note that if 50% of eligible patients with type 2 diabetes start an SGLT2i, the annual incidence of ERSD could instead be 4.7 per 100,000 by 2040.[2]

Q What are SGLT2i?

A SGLT2i work by inhibiting sodium-glucose cotransporter 2, which is expressed in the proximal renal tubule and is responsible for most glucose reabsorption. Inhibiting sodium-glucose cotransporter 2 reduces reabsorption of filtered glucose and increases glucose excretion through the kidneys. In addition to increasing glucosuria, SGLT2i also reduce sodium reabsorption and appear to act as an osmotic diuretic. In several studies, which are discussed in more detail below, SGLT2i have exhibited cardiorenal-protective properties in patients with and without type 2 diabetes.

Q What are the indications for SGLT2i use?

A Currently, 4 SGLT2i are approved by the US Food and Drug Administration (Table). Dapagliflozin is the only SGLT2i that is approved for patients with and without type 2 diabetes. In addition to diabetes, dapagliflozin is indicated to reduce the risk of cardiovascular death and hospitalization for heart failure in both adults with and without diabetes. It is also indicated to reduce the risk of sustained estimated glomerular filtration rate (eGFR) decline, cardiovascular death, and hospitalization for heart failure in adults with CKD who are at risk of progression, both with and without diabetes.[3]

The other SGLT2i currently available are indicated only for patients with type 2 diabetes. Canagliflozin is indicated to reduce the risk of ESRD, doubling of serum creatinine, cardiovascular death, and hospitalization for heart failure in adults with diabetes and diabetic nephropathy with albuminuria.[4] It is also indicated to reduce the risk of major adverse cardiovascular events in adults with diabetes and established cardiovascular disease.[4] Empagliflozin is indicated to reduce the risk of cardiovascular death in adults with diabetes and established cardiovascular disease.[5] Ertugliflozin is indicated for the management of type 2 diabetes alone.[6]

Q What are the cardiovascular benefits associated with SGLT2i?

A In the CANVAS trials, canagliflozin demonstrated a 14% reduction in major adverse cardiac events in patients with a history of cardiovascular disease—the study's primary end point.[7] In the EMPA-REG OUTCOME trial, empagliflozin significantly reduced the risk of the first occurrence of any primary

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Table. Comparison of US-Approved SGLT2i

	DAPAGLIFLOZIN[3]	CANAGLIFLOZIN[4]	EMPAGLIFLOZIN[5]	ERTUGLIFLOZIN[6]
Combination options	Dapagliflozin and metformin XR Dapagliflozin and saxagliptin	Canagliflozin and metformin Canagliflozin and metformin XR	Empagliflozin and linagliptin Empagliflozin and metformin Empagliflozin and metformin XR	Ertugliflozin and metformin Ertugliflozin and sitagliptin
Doses	5-10 mg daily	100-300 mg daily	10-25 mg daily	5-15 mg daily
Indications	Type 2 diabetes Reduce the risk of hospitalization for heart failure in adults with type 2 diabetes and either established CVD or multiple risk factors Reduce the risk of CVD death and hospitalization for heart failure in adults with HFrEF To reduce the risk of sustained eGFR decline, CVD death and hospitalization for heart failure in adults with CKD at risk of progression	Type 2 diabetes Reduce the risk of ESRD, doubling of creatinine, CVD death, and hospitalization for heart failure in adults with type 2 diabetes and diabetic nephropathy with albuminuria Reduce the risk of major adverse cardiovascular events in adults in type 2 diabetes with established CVD	Type 2 diabetes Reduce the risk of CVD death in adults with type 2 diabetes and established CVD	Type 2 diabetes
Renal dosing	eGFR, > 25; no adjustment, 5-10 mg daily eGFR, < 25; Initiation is not recommended but may be continued to reduce risk of eGFR decline, ESRD, CVD death, and heart failure	eGFR, > 60; up to 300 mg once daily eGFR, 30-59; 100 mg daily eGFR, < 30; initiation is avoided but if already taking then may continue at 100 mg daily	eGFR, < 45; avoid use	eGFR, < 30; avoid use

Abbreviations: CVD, cardiovascular disease; HFrEF, heart failure with reduced ejection fraction; XR, extended-release; ESRD, end-stage renal disease; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate

composite endpoint—cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke (hazard ratio, 0.86)—in patients with type 2 diabetes and a documented history of coronary artery disease, stroke, or peripheral artery disease.[8] In the EMPEROR-Reduced trial, empagliflozin reduced the primary outcome of cardiovascular death and hospitalization for heart failure by 25% in patients with an ejection fraction of less than or equal to 40%.[9]

In the DECLARE-TIMI trial, dapagliflozin reduced the risk of cardiovascular death and hospitalization for heart failure by 17% in adults who had or were at risk for heart disease.[10] In the DAPA-HF trial, dapagliflozin reduced the worsening of heart failure and cardiovascular death by 26% in patients with a reduced ejection fraction.[11]

Q What are the renal benefits associated with SGLT2i?

A For the CREDENCE trial, researchers followed 4401 participants with type 2 diabetes who were taking canagliflozin for more than 2 years.[12] The mean hemoglobin A1c level was 8.3%, and the mean eGFR was 56.2 mL/min/1.73 m^2. This trial showed that canagliflozin, 100 mg, significantly reduced the risk of progression to

ESRD, doubling of serum creatinine, and cardiovascular death by 30%, in addition to reducing the risk of hospitalization for heart failure by 39%.[12]

The DAPA-CKD trial included 4304 patients with CKD and with or without type 2 diabetes who were assigned to either dapagliflozin, 10 mg, or placebo. These patients were also followed for more than 2 years. The mean eGFR was 43.1±12.4 mL/min/1.73 m^2, and 68% of participants had type 2 diabetes. The results showed that dapagliflozin reduced the incidence of 50% or more sustained decline in eGFR, progression to ESRD, and cardiovascular or renal death by 36% in patients with type 2 diabetes and by 50% in patients without diabetes.[13]

It is important to note that nearly all patients in both studies were taking the maximally tolerated dose of ACEi or ARB. It is also important to remember that initiation of SGLT2i causes a small increase in serum creatinine and decrease in eGFR. However, these changes typically occur within 2 weeks of starting therapy and then resolve.[3-6]

Q Is there a risk of genitourinary infections with SGLT2i?

A A slightly higher incidence of urinary tract infections was observed among patients taking SGLT2i in early studies. However, a definitive relationship has not been established. The most recent data on canagliflozin in the CANVAS trial,[7] empagliflozin in the EMPA-REG trial,[8] and dapagliflozin in the DECLARE-TIMI trial[10] showed no significant increase in urinary tract infections among patients taking an SGLT2i vs placebo. In contrast, genital mycotic infections have been frequently observed with the initiation of SGLT2i. However, very few patients required discontinuation of therapy because of genital mycotic infections.[3-6]

Q Is there a risk of limb amputation with SGLT2i?

A An increased risk of lower limb amputations associated with canagliflozin vs placebo was observed in the CANVAS trial (5.9 vs 2.8 events per 1000 patient-years) and the CANVAS-R trial (7.5 vs 4.2 events per 1000 patient-years) in patients with type 2 diabetes who either had or were at risk for cardiovascular disease.[7] However, results of the CREDENCE trial did not show an elevated risk of lower extremity amputation.[12] Data on empagliflozin from the EMPA-REG trial8 and dapagliflozin from the DECLARE-TIMI trial[10] showed no significant increase in the risk of amputation.

Of note, lower limb infections, gangrene, and diabetic foot ulcers were the most common precipitating medical events leading to the need for amputation. The risk of amputation was highest among those with a history of previous amputation, peripheral vascular disease, and neuropathy.[14]

Q What is the risk of diabetic ketoacidosis associated with SGLT2i?

A Incidence rates of diabetic ketoacidosis (DKA) events were overall low in clinical trials but varied for each SGLT2i. The event rate for empagliflozin was 0.1 vs less than 0.1 for placebo, for canagliflozin was 0.6 vs 0.3 for placebo, and for dapagliflozin was 0.3 vs 0.1 for placebo.[7-10] Risk factors for DKA with SGLT2i use may include low C-peptide level, underlying autoimmune diabetes, inadequate insulin doses, carbohydrate intake restriction, volume depletion, and hyperglucagonemia.[14]

Q When should I not use an SGLT2i?

A Although renal dosing varies for each SGLT2i, none should be started in the setting of advanced CKD (defined as an eGFR of < 25 mL/min/1.73 m^2), ESRD, or dialysis. These medications should not be prescribed for patients with type 1 diabetes and are not recommended for patients who are pregnant or breastfeeding.[3-6]

In clinical trials for glycemic control, canagliflozin was associated with a dose-dependent increase in the incidence of volume-depletion-related adverse reactions (eg, hypotension, postural dizziness, orthostatic hypotension, syncope, and dehydration).[4] An increased incidence was observed in patients taking the 300-mg dose. The 3 factors associated with the largest increase in volume-depletion-related adverse events in these trials were the use of loop diuretics, moderate renal impairment (defined as an eGFR, 30-60 mL/min/1.73 m^2), and age 75 years or older.[4]

Q Can it be safely combined with other diabetes medications?

A Combination therapy with SGLT2i, glucagon-like peptide 1 receptor agonists (GLP1-RA), and metformin has been found to be beneficial and safe. In the AWARD 10 study, adding dulaglutide to stable treatment with any approved SGLT2i resulted in an additional 0.66% to 0.79% decrease in hemoglobin A1c without increasing hypoglycemia.[15] In addition, weight loss was 3.1 kg in the dulaglutide, 1.5 mg, group vs 2.1 kg in the placebo group.[15] Results of the DURATION 8 study showed similar findings among patients taking combination therapy of dapagliflozin plus exenatide.[16] No episodes of hypoglycemia were reported. The effect on weight loss also appeared beneficial (3.6 kg in the combination group vs 2.2 kg in the dapagliflozin-only group and 1.6 kg in the exenatide-only group).[16]

Both studies[15,16] suggest that SGLT2i and GLP1-RA as combination therapy can be used safely, with significant improvement in hemoglobin A1c and weight loss than either therapy alone.

SGLT2i therapy alone has not been observed to increase the risk of hypoglycemia. However, the risk of hypoglycemia increased when an SGLT2i was added to a sulfonylurea or insulin. Thus, lowering insulin doses and possibly discontinuing sulfonylureas should be considered when starting an SGLT2i.[3-6]

References

1. Fang M, Wang D, Coresh J, Selvin E. Trends in diabetes treatment and control in U.S. adults, 1999-2018. *N Engl J Med.* 2021;384(23):2219-2228. https://doi.org/10.1056/nejmsa2032271
2. Morton JI, McDonald SP, Salim A, Liew D, Shaw JE, Magliano DJ. Projecting the incidence of type 2 diabetes-related end-stage kidney disease until 2040: a comparison between the effects of diabetes prevention and the effects of diabetes treatment. *Diabetes Care.* Published online May 23, 2021. https://doi.org/10.2337/dc21-0220
3. FARXIGA® (dapagliflozin). Package insert. AstraZeneca Pharmaceuticals LP; 2021. https://www.farxiga-hcp.com/
4. INVOKANA®. Prescribing information. Janssen Pharmaceuticals, Inc.; 2021. https://www.invokanahcp.com/
5. Jardiance (empagliflozin) tablets. Prescribing information. Boehringer Ingelheim International; 2020. https://jardiancehcp.com/
6. Steglatro (ertugliflozin) 5 mg, 15 mg tablets. Dosing information. MERCK& Co., Inc.; 2021. https://www.merckconnect.com/steglatro/dosing-administration/
7. Neal B, Perkovic V, Mahaffey KW, et al; CANVAS Program Collaborative Group. Canagliflozin and cardiovascular and renal events in type 2 diabetes. *N Engl J Med.* 2017;377(7):644-657. https://doi.org/10.1056/nejmoa1611925
8. Zinman B, Wanner C, Lachin JM, et al; EMPA-REG OUTCOME Investigators. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med.* 2015;373(22):2117-2128. https://doi.org/10.1056/nejmoa1504720
9. Packer M, Anker SD, Butler J, et al. Effect of empagliflozin on the clinical stability of patients with heart failure and a reduced ejection fraction: the EMPEROR-Reduced trial. *Circulation.* 2021;143(4):326-336. https://doi.org/10.1161/circulationaha.120.051783
10. Wiviott SD, Raz I, Bonaca MP, et al. Dapagliflozin and cardiovascular outcomes in type 2 diabetes. *N Engl J Med*. 2019;380(4):347-357. https://doi.org/10.1056/nejmoa1812389
11. McMurray JJV, Solomon SD, Inzucchi SE, et al; DAPA-HF Trial Committees and Investigators. Dapagliflozin in patients with heart failure and reduced ejection fraction. *N Engl J Med.* 2019;381(21):1995-2008. https://doi.org/10.1056/nejmoa1911303
12. Perkovic V, Jardine MJ, Neal B, et al; CREDENCE Trial Investigators. Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. *N Engl J Med*. 2019;380(24):2295-2306. https://doi.org/10.1056/nejmoa1811744
13. Heerspink HJL, Stefánsson BV, Correa-Rotter R, et al; DAPA-CKD Trial Committees and Investigators. Dapagliflozin in patients with chronic kidney disease. *N Engl J Med.* 2020;383(15):1436-1446. https://doi.org/10.1056/nejmoa2024816
14. Scheen AJ. An update on the safety of SGLT2 inhibitors. *Expert Opin Drug Saf.* 2019;18(4):295-311. https://doi.org/10.1080/14740338.2019.1602116
15. Ludvik B, Frías JP, Tinahones FJ, et al. Dulaglutide as add-on therapy to SGLT2 inhibitors in patients with inadequately controlled type 2 diabetes (AWARD-10): a 24-week, randomised, double-blind, placebo-controlled trial. *Lancet Diabetes Endocrinol.* 2018;6(5):370-381. https://doi.org/10.1016/s2213-8587(18)30023-8
16. Frías JP, Guja C, Hardy E, et al. Exenatide once weekly plus dapagliflozin once daily versus exenatide or dapagliflozin alone in patients with type 2 diabetes inadequately controlled with metformin monotherapy (DURATION-8): a 28 week, multicentre, double-blind, phase 3, randomised controlled trial. *Lancet Diabetes Endocrinol.* 2016;4(12):1004-1016. https://doi.org/10.1016/s2213-8587(16)30267-4