Use of SGLT-2 Inhibitors to Treat Chronic Kidney Disease in Primary Care

George Bakris, MD

doi: 10.12788/jfp.0389

KEY TAKEAWAYS

- Chronic kidney disease (CKD) remains underrecognized by patients and clinicians in the primary care setting, largely due to its asymptomatic presentation in early stages.
- Sodium-glucose cotransporter-2 (SGLT-2) inhibitors have demonstrated kidney-protective effects in clinical trials—including in patients with and without type 2 diabetes (T2D)—and there are several proposed mechanisms for these benefits.
- Dapagliflozin and canagliflozin are SGLT-2 inhibitors with indications for CKD, and only dapagliflozin is indicated for CKD in patients without T2D.
- Clinically relevant adverse events associated with SGLT-2 inhibitors include volume depletion, diabetic ketoacidosis, and genital mycotic infections.

FACULTY

George Bakris, MD, Professor of Medicine, Director, AHA Comprehensive Hypertension Center, The University of Chicago Medicine, Chicago, IL

DISCLOSURES

Drs. Bakris and Ulrich have no disclosures to report.

ACKNOWLEDGMENT

Editorial support was provided by Austin Ulrich, PharmD, BCACP, of Primary Care Education Consortium.

Additional resources can be found at **https://www.pcmg-us.org/toolkit/ckd.**

SPONSORSHIP

This activity is sponsored by Primary Care Education Consortium and the Primary Care Metabolic Group and supported by funding from AstraZeneca.

INTRODUCTION

CASE SCENARIO

BT is a 59-year-old man who presents to a primary care clinic to establish care after moving to a new area. BT's medical records indicate diagnoses of hypertension, dyslipidemia, prediabetes, obesity, osteoarthritis, and gout. He states that he feels that his current medications are working well for him, and he "just needs an annual check-up" because his wife told him he needs one.

Lab work: glycated hemoglobin (A1c) 6.0%, estimated glomerular filtration rate (eGFR) 54 mL/min/1.73 m^2, urinary albumin-to-creatinine ratio (UACR) 140 mg/g, and lipid panel within normal limits; from 6 months ago at an outside clinic, the patient's eGFR was 50 mL/min/1.73 m^2

Vitals: Body mass index 32.4 kg/m^2, blood pressure 144/72 mmHg in clinic today

Current medications: losartan 50 mg daily, atorvastatin 10 mg daily, allopurinol 300 mg daily, and ibuprofen 200 mg 1-2 tablets twice daily as needed (uses once monthly)

The patient in this case scenario has chronic kidney disease (CKD), although this appears to be a new diagnosis based on his past medical records. He has several risk factors for CKD due to comorbidities and medications that can worsen kidney function. Although he is still in the earlier, and likely asymptomatic, stages of CKD, intervention is needed to address modifiable risk factors, prevent progression, and reduce the risk of adverse clinical outcomes from CKD.

CKD is defined as abnormality in kidney function or structure persistent for longer than 3 months.[1-3] It is commonly encountered in primary care, yet it remains underrecognized and underappreciated by many clinicians and patients.[2,4] CKD is thought to affect 8%-16% of the population globally, with a prevalence of 37 million (15%) adults in the United States.[5,6] Due to its often asymptomatic presentation, many patients with early CKD are unaware of the disease, underscoring the need for routine screening and awareness. Primary care practitioners (PCPs) can play a key role in reducing the burden of CKD by identifying and managing CKD, especially in earlier stages.

TABLE 1. **Risk factors for chronic kidney disease**

Clinical risk factors	
• Diabetes	• Kidney stones
• Hypertension	• Recurrent urinary tract infections
• Smoking	• Urinary tract obstruction
• Obesity	• Malignancy
• Autoimmune diseases	• Reduced kidney mass (low birth weight, nephrectomy, etc)
• Systemic infections (such as hepatitis B, hepatitis C, HIV)	• History of acute kidney injury
• Nephrotoxic drugs (such as NSAIDs, herbal products, lithium)	• Intravenous drug use
	• Family history of kidney disease
Sociodemographic risk factors	
• Older than 60 years of age	• Low education
• Non-white race	• Low income
Genetic risk factors	
• Polycystic kidney disease	• Sickle cell trait and disease
• Congenital anomalies of the kidney and urinary tract	• APOL1 risk alleles
• Other familial causes	• Alport syndrome

Abbreviations: APOL1, apolipoprotein L1; HIV, human immunodeficiency virus; NSAIDs, nonsteroidal anti-inflammatory drugs.

Source: Adapted from: Chen TK, Knicely DH, Grams ME. Chronic kidney disease diagnosis and management: a review. *JAMA*. 2019;322(13):1294-1304. doi:10.1001/jama.2019.14745

CKD is characterized by a glomerular filtration rate (GFR) <60 mL/min/1.73 m^2, UACR ≥30 mg/g, or by other markers of kidney damage such as hematuria or structural abnormalities.[1,3] In the United States, estimates suggest that >50% of individuals will develop a GFR <60 mL/min/1.73 m^2 during their lifetime. Notably, GFR declines with age, with a loss of about 1 mL/min/1.73 m^2 per year of life beginning around age 60.[7] Thus, there is a need for early detection and treatment to avoid adverse outcomes from progressive CKD, such as atherosclerotic cardiovascular disease (ASCVD), end-stage kidney disease (ESKD), and death.[8-10] Risk factors for CKD include many clinical, sociodemographic, and genetic characteristics (**TABLE 1**).[2,11]

Historically, sodium-glucose cotransporter-2 (SGLT-2) inhibitors have been studied and approved by the US Food and Drug Administration as antihyperglycemic drugs to treat type 2 diabetes mellitus (T2D).[12] However, in recent years, clinical evidence has confirmed cardiovascular and kidney benefits for certain SGLT-2 inhibitors, leading to added indications for heart failure with reduced ejection fraction (dapagliflozin), heart failure regardless of ejection fraction (empagliflozin) and kidney disease for patients with (dapagliflozin and canagliflozin) and without (dapagliflozin) T2D.[13-15]

Managing CKD in primary care should include reducing cardiovascular risk; managing hypertension, diabetes, and other comorbidities; avoiding nephrotoxins; ensuring correct medication dosing; and monitoring kidney function and other pertinent laboratory tests.[2] Drug therapy that is often considered includes statin therapy, renin-angiotensin-aldosterone system (RAAS) blockade with an angiotensin-converting enzyme (ACE) inhibitor or angiotensin II receptor blocker (ARB) and/or an aldosterone receptor antagonist; and antihyperglycemic agents in patients with T2D.[2] Based on recent evidence, as noted subsequently in this article, SGLT-2 inhibitors may become standard therapy for reducing the risk of adverse clinical outcomes from CKD, including diabetic kidney disease (DKD).

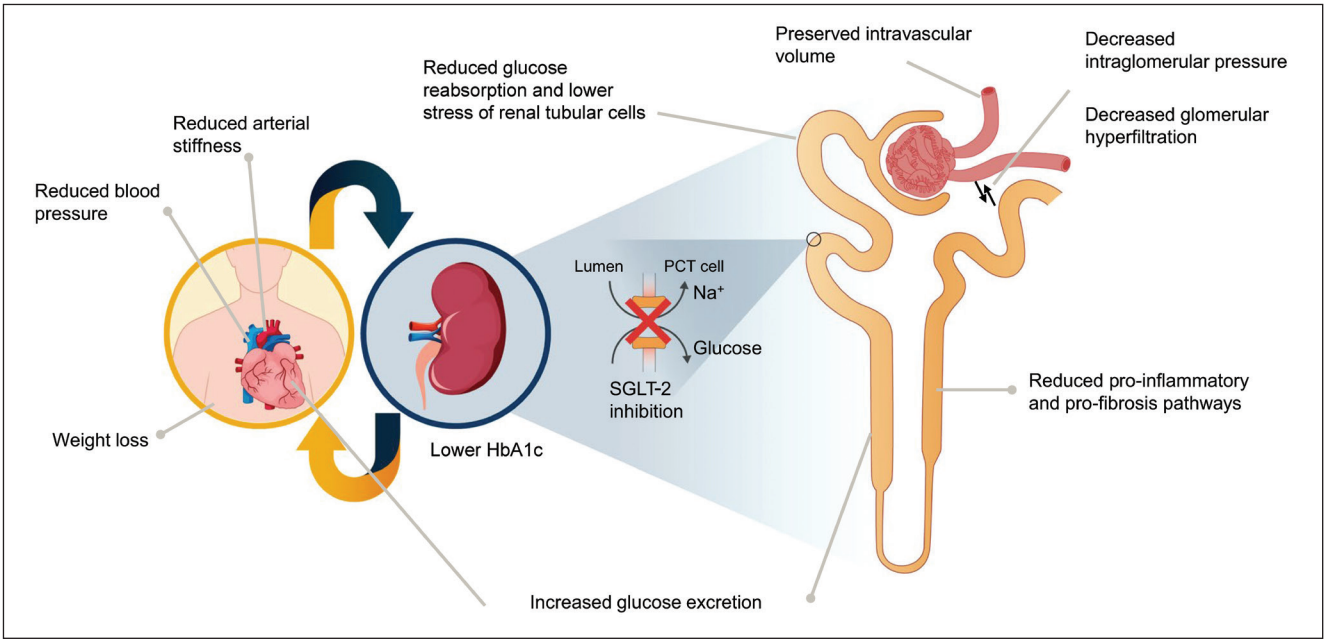
KIDNEY-PROTECTIVE MECHANISMS OF SGLT-2 INHIBITORS

There are several proposed mechanisms for the kidney benefits observed from SGLT-2 inhibitor therapy; most are independent of effects on blood glucose (**FIGURE**).[16] Based on results from trials of dapagliflozin and canagliflozin, SGLT-2 inhibitors can provide kidney benefits in patients with CKD. Specifically, the benefits are evident in those with T2D, an eGFR of 25 mL/min/1.73 m^2 (dapagliflozin) to 30 mL/min/1.73 m^2 (canagliflozin) or greater, and coadministration of an ACE inhibitor or ARB.[17-20] Only dapagliflozin has shown kidney benefits in patients without T2D.[20]

SGLT-2 inhibitors are thought to exert the following effects directly on the kidneys as well as effects on body systems interconnected with the kidneys[12]:

- *Improvement in tubuloglomerular feedback;* however,

FIGURE. **Proposed kidney-protective pathways for SGLT-2 inhibitors**[16]



Source: Giorgino F, Vora J, Fenici P, Solini A. Renoprotection with SGLT2 inhibitors in type 2 diabetes over a spectrum of cardiovascular and renal risk. *Cardiovasc Diabetol*. 2020;19(1):196. doi:10.1186/s12933-020-01163-9

The figure text was simplified and original superscript references from the source publication were removed prior to its reproduction in this article.

effects on glomerular hemodynamics are unclear

- *Reduction of tubular workload and hypoxia* by reducing sodium and glucose reabsorption
- *Reduction in glucose metabolic fluxes,* improving mitochondrial function
- *Enhancement of diuresis and natriuresis* leading to reductions in interstitial fluid in the kidneys and alleviating kidney hypoxia
- *Limiting inflammation and fibrosis* through reductions in various inflammatory components, including uric acid

Overwhelmingly, more research is needed to elucidate mechanisms of kidney protection clearly, but trial data affirm the benefits of SGLT-2 inhibitors in patients with CKD, including DKD.[12] Notably, SGLT-2 inhibitors also provide kidney protection through less direct mechanisms by simply improving risk factors for CKD and ASCVD, including reducing blood glucose levels and blood pressure.

ROLE OF SGLT-2 INHIBITORS IN DIABETIC AND NON-DIABETIC CKD

Guideline recommendations for SGLT-2 inhibitors in CKD

Society clinical guidelines have recognized the kidney benefits of SGLT-2 inhibitors in patients with diabetes, and to a lesser extent, those without diabetes. The American Diabetes Association recommends the use of SGLT-2 inhibitors in patients with stage 3 CKD or higher and T2D, regardless of glycemic control, to slow CKD progression and reduce the risk of heart failure.[21]

The Kidney Disease Improving Global Outcomes (KDIGO) guidelines recommend using SGLT-2 inhibitors as a first-line therapy, along with metformin, in patients with T2D and CKD with eGFR ≥ 30 mL/min/1.73 m^2.[22] KDIGO also suggests reducing doses of other antihyperglycemic drugs, if needed, to accommodate initiation of an SGLT-2 inhibitor. The guidelines recommend prioritizing SGLT-2 inhibitors with documented kidney or cardiovascular benefits and obtaining a baseline eGFR. Additionally, KDIGO suggests that once an SGLT-2 inhibitor is started, it can be continued even if the eGFR drops below 30 mL/min/1.73 m^2, unless it is not tolerated or dialysis is needed.[22]

The American Heart Association recognized the beneficial effects of SGLT-2 inhibitors on cardiovascular and kidney outcomes in a scientific statement that recommends use of SGLT-2 inhibitors in patients with T2D and CKD based on adequate eGFR per drug labeling.[23] Lastly, a joint guideline from the European Society of Cardiology and the European Association for the Study of Diabetes acknowledges the kidney-protective effects of SGLT-2 inhibitors and recommends

their use in patients with T2D who are already on metformin or who are treatment naïve.[24]

Evidence and indications for SGLT-2 inhibitors in CKD

Several cardiovascular and renal outcomes trials form the evidence base for using SGLT-2 inhibitors in patients with CKD. Patients in each trial had varying levels of kidney disease, and although many outcomes are similar between the agents, there are a few key inter-drug differences.[16]

Dapagliflozin: indicated for adults with CKD at risk of progression to reduce the risk of sustained eGFR decline, ESKD, cardiovascular death, and hospitalization for heart failure.[13] In the Dapagliflozin Effect on Cardiovascular Events-Thrombolysis in Myocardial Infarction 58 (DECLARE-TIMI 58) trial, patients with T2D who had or were at risk for ASCVD received dapagliflozin or placebo.[25] Results demonstrated a reduction in a secondary renal composite endpoint (≥40% reduction in eGFR to <60 mL/min/1.73 m^2, kidney failure, or death due to kidney disease), as well as lower rates of progression to a higher category of albuminuria and prevention of new-onset albuminuria. In a kidney-specific analysis from DECLARE-TIMI 58, dapagliflozin was found to prevent and reduce progression of kidney disease in a population where about 93% of patients had an eGFR >60 mL/min/1.73 m^2.[26]

In the Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease (DAPA-CKD) trial, patients with or without T2D, an eGFR of 25-75 mL/min/1.73 m^2 and a UACR of 200-5000 mg/g received dapagliflozin or placebo.[20,27,28] The dapagliflozin group experienced a reduction in the primary cardio-renal composite endpoint (sustained decline in eGFR of at least 50%, ESKD, or death from kidney disease or cardiovascular causes), a slower mean rate of eGFR decline, and a reduction in albuminuria. These benefits were observed regardless of diabetes or glycemic status.

Canagliflozin: indicated to reduce the risk of ESKD, doubling of serum creatinine, cardiovascular death, and hospitalization for heart failure in adults with T2D and diabetic nephropathy with albuminuria.[14] The Canagliflozin Cardiovascular Assessment Study (CANVAS) program enrolled patients with T2D and high cardiovascular risk.[29] The canagliflozin group showed a reduction in a secondary renal composite endpoint (sustained 40% reduction in eGFR, need for kidney replacement therapy, or death from kidney disease) and prevention of new-onset albuminuria.

In the Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE) trial, patients with T2D and albuminuric CKD (eGFR of 30-90 mL/min/1.73 m^2 and a UACR of >300-5000 mg/g) received canagliflozin or placebo.[17] Trial results indicated a reduction in the primary cardio-renal composite endpoint (serum creatinine doubling, kidney failure treated by kidney replacement therapy, or death from kidney disease or cardiovascular causes). Kidney benefits also included a slower mean rate of eGFR decline and reduction in mean UACR.

Empagliflozin: not currently indicated for patients with CKD or DKD.[15] The Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG OUTCOME) trial enrolled patients with T2D and established ASCVD, and assigned them to either empagliflozin or placebo.[30,31] The empagliflozin group experienced a reduction in a secondary renal composite endpoint (incident or worsening nephropathy or cardiovascular death), progression to macroalbuminuria, doubling of serum creatinine, and initiation of renal-replacement therapy.[31]

The Study of Heart and Kidney Protection with Empagliflozin (EMPA-KIDNEY) clinical trial to evaluate the effect of empagliflozin in patients with CKD, was stopped early due to evidence of positive efficacy, with published results expected later in 2022.[32]

Ertugliflozin: not currently indicated for patients with CKD or DKD.[33] In the Evaluation of Ertugliflozin Efficacy and Safety Cardiovascular Outcomes (VERTIS CV) trial, patients with T2D and ASCVD received ertugliflozin or placebo.[34] The ertugliflozin group demonstrated a nonsignificant reduction in a secondary renal composite outcome (doubling of serum creatinine, renal replacement therapy, and death from renal causes) as well as a significant reduction in an exploratory renal composite outcome (sustained 40% reduction from baseline in eGFR, chronic dialysis/kidney transplant, or renal death).[34,35]

Evidence-based treatment of CKD with SGLT-2 inhibitors in primary care

When considering initiating an SGLT-2 inhibitor for patients with CKD, PCPs should consider patient-specific factors in light of trial data and guideline recommendations to select an agent (**TABLE 2**). Of note, SGLT-2 inhibitors can safely and effectively be combined with ACE inhibitors and ARBs for treatment of kidney disease, and the vast majority of patients with CKD in the trials mentioned earlier were receiving concurrent treatment with an ACE inhibitor or ARB.[36] Patients' eGFR, albuminuria status, CKD stage, and diabetes status may render them ineligible for certain SGLT-2 inhibitors. Notably, dapagliflozin is the only SGLT-2 inhibitor with a renal-specific indication including patients with and without T2D and spanning CKD stages (including earlier stages of CKD such as eGFR >60 mL/min/m^2 and UACR >30 mg/g).

ADVERSE EVENTS OF SGLT-2 INHIBITORS

Clinically relevant adverse events of SGLT-2 inhibitors include volume depletion (1.2%-1.5%), genital mycotic infections

TABLE 2. **SGLT-2 inhibitors, their eGFR criteria, and their indications**

Drug	CV/renal outcomes clinical trial(s)	Selected trial outcomes	eGFR criteria[a] and relevant indications
Dapagliflozin[13]	DECLARE-TIMI 58[25]	Incidence of secondary renal composite: 4.3% in dapagliflozin group vs 5.6% in placebo group (HR 0.76; 95% CI: 0.67, 0.87) Reduction in eGFR decline by at least 40% to <60 mL/min/1.73 m^2 by 46% with dapagliflozin compared to placebo (HR 0.54; 95% CI: 0.43, 0.67)	≥25 CKD (with or without T2D) and T2D
	DAPA-CKD[20,28]	Incidence of primary cardio-renal composite: 9.2% in dapagliflozin group vs 14.5% in placebo group (HR 0.61; 95% CI: 0.51, 0.72) Reduction in mean UACR by 29.3% with dapagliflozin compared with placebo (95% CI: -33.1, -25.2; *P* <.0001)	
Canagliflozin[14]	CANVAS[29]	Incidence of secondary renal composite: 5.5 vs 9.0 participants per 1000 patient-years for canagliflozin vs placebo (HR 0.60; 95% CI: 0.47, 0.77) Albuminuria progression occurred in 89.4 vs 128.7 per 1000 patient-years with canagliflozin compared to placebo (HR 0.73; 95% CI: 0.67, 0.79)	≥30 DKD, T2D
	CREDENCE[17]	Incidence of primary cardio-renal composite: 43.2 vs 61.2 events per 1000 patient-years for canagliflozin vs placebo (HR 0.70; 95% CI: 0.59, 0.82) Reduction in mean UACR by 31% with canagliflozin compared to placebo (95% CI: -25, -35)	
Empagliflozin[15]	EMPA-REG OUTCOME[30]	Incidence of secondary renal composite: 12.7% in empagliflozin group vs 18.8% in placebo group (HR 0.54; 95% CI: 0.40, 0.75) Progression to macroalbuminuria: 11.2% in empagliflozin group vs 16.2% in placebo group (HR 0.62; 95% CI: 0.54, 0.72) Doubling of serum creatinine: 1.5% in empagliflozin group vs 2.6% in placebo group (HR 0.56; 95% CI: 0.39, 0.79) Initiation of renal-replacement therapy: 0.3% in empagliflozin group vs 0.6% in placebo group (HR 0.45; 95% CI: 0.21, 0.97)	≥30 T2D
Ertugliflozin[33]	VERTIS CV[34,35]	Incidence of secondary renal composite: 3.2% in ertugliflozin group vs 3.9% in placebo group (HR 0.81; 95% CI: 0.63, 1.04) Incidence of exploratory renal composite: 6.0 vs 9.0 events per 1000 person-years for ertugliflozin vs placebo (HR 0.66; 95% CI: 0.50, 0.88)	≥45 T2D

[a]eGFR measured in mL/min/1.73 m^2

Abbreviations: CI, confidence interval; CV, cardiovascular; HR, hazard ratio.

(2%-4% in men, 3%-7% in women), and diabetic ketoacidosis (DKA).[12] One study estimates that DKA occurs in about 1 in 800 patients with diabetes receiving an SGLT-2 inhibitor, about twice as often as those not taking an SGLT-2 inhibitor.[37] For patients with a history of these adverse events, especially severe or recurrent events, clinicians should carefully consider whether pursuing therapy with an SGLT-2 inhibitor is the most appropriate clinical decision. PCPs should engage patients in shared decision-making when discussing SGLT-2 inhibitors and provide a clear, simple discussion of their risks and benefits.

Although there may be an initial, acute decrease in eGFR (≥10% decrease in about half of patients) when starting an SGLT-2 inhibitor, the eGFR tends to stabilize thereafter and can ultimately be reversed with discontinuation of therapy.[38] Additionally, the small initial eGFR drop is not associated with progressive long-term kidney injury or loss of function and should not be a reason for discontinuation.[39] Initial drop in eGFR >30% occurred in 0.5% of patients and was associated with a slightly increased risk of kidney-related adverse events.[39] Since volume depletion can occur with SGLT-2 inhibitors, monitoring volume status and kidney function can help identify this trend. However, adjusting diuretic or antihypertensive therapy is usually not necessary when starting an SGLT-2 inhibitor.[12]

Although DKA is rare, SGLT-2 inhibitors have a warning for DKA, which may be euglycemic.[12] Factors that may increase the risk of DKA include insulin use, surgery, and acute illness. Clinicians should consider holding SGLT-2 inhibitors for 3 days prior to surgery or during acute illness.[12]

Women are more likely than men to experience genital mycotic infections when taking an SGLT-2 inhibitor, and the risk of these infections can be improved by proper personal hygiene (such as rinsing the genital area with water after voiding and before bed and wearing cotton underwear) and optimized T2D management.[40]

SUMMARY

CKD is a common condition encountered in primary care, and PCPs are well positioned for early identification and treatment of the disease to slow progression and prevent adverse outcomes. SGLT-2 inhibitors now have data and indications to support use in kidney disease in patients with T2D (dapagliflozin and canagliflozin) and without T2D (dapagliflozin). Clinicians should consider treating patients with CKD with an SGLT-2 inhibitor consistent with clinical evidence and guideline recommendations, based on eGFR, albuminuria, and diabetes status. Engaging patients in shared decision-making discussions can help them accurately weigh the benefits and risks of treatment with an SGLT-2 inhibitor. ●

REFERENCES

1. Chapter 1: Definition and classification of CKD. *Kidney Int Suppl (2011)*. 2013;3(1):19-62. doi:10.1038/kisup.2012.64
2. Chen TK, Knicely DH, Grams ME. Chronic kidney disease diagnosis and management: a Review. *JAMA*. 2019;322(13):1294-1304. doi:10.1001/jama.2019.14745
3. Shlipak MG, Tummalapalli SL, Boulware LE, et al. The case for early identification and intervention of chronic kidney disease: conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference. *Kidney Int*. 2021;99(1):34-47. doi:10.1016/j.kint.2020.10.012
4. Plantinga LC, Boulware LE, Coresh J, et al. Patient awareness of chronic kidney disease: trends and predictors. *Arch Intern Med*. 2008;168(20):2268-2275. doi:10.1001/archinte.168.20.2268
5. Jha V, Garcia-Garcia G, Iseki K, et al. Chronic kidney disease: global dimension and perspectives. *The Lancet*. 2013;382(9888):260-272. doi:10.1016/S0140-6736(13)60687-X
6. Chronic Kidney Disease in the United States, 2021. Published July 8, 2021. Accessed December 10, 2021. https://www.cdc.gov/kidneydisease/publications-resources/ckd-national-facts.html
7. Waas T, Schulz A, Lotz J, et al. Distribution of estimated glomerular filtration rate and determinants of its age dependent loss in a German population-based study. *Sci Rep*. 2021;11(1):10165. doi:10.1038/s41598-021-89442-7
8. Grams ME, Chow EKH, Segev DL, Coresh J. Lifetime incidence of CKD stages 3-5 in the United States. *Am J Kidney Dis Off J Natl Kidney Found*. 2013;62(2):245-252. doi:10.1053/j.ajkd.2013.03.009
9. Astor BC, Matsushita K, Gansevoort RT, et al. Lower estimated glomerular filtration rate and higher albuminuria are associated with mortality and end-stage renal disease. A collaborative meta-analysis of kidney disease population cohorts. *Kidney Int*. 2011;79(12):1331-1340. doi:10.1038/ki.2010.550
10. Matsushita K, Coresh J, Sang Y, et al. Estimated glomerular filtration rate and albuminuria for prediction of cardiovascular outcomes: a collaborative meta-analysis of individual participant data. *Lancet Diabetes Endocrinol*. 2015;3(7):514-525. doi:10.1016/S2213-8587(15)00040-6
11. Van den Bulck SA, Vankrunkelsven P, Goderis G, et al. Developing quality indicators for chronic kidney disease in primary care, extractable from the electronic medical record. A RAND-modified Delphi method. *BMC Nephrol*. 2020;21(1):161. doi:10.1186/s12882-020-01788-8
12. Tuttle KR, Brosius FC, Cavender MA, et al. SGLT2 Inhibition for CKD and Cardiovascular Disease in Type 2 Diabetes: report of a scientific workshop sponsored by the National Kidney Foundation. *Diabetes*. 2021;70(1):1-16. doi:10.2337/dbi20-0040
13. Farxiga [package insert]. https://den8dhaj6zs0e.cloudfront.net/50fd68b9-106b-4550-b5d0-12b045f8b184/0be9cb1b-3b33-41c7-bfc2-04c9f718e442/0be9cb1b-3b33-41c7-bfc2-04c9f718e442_viewable_rendition__v.pdf. Updated April 2021. Accessed December 10, 2021.
14. Invokana [package insert]. https://www.janssenlabels.com/package-insert/product-monograph/prescribing-information/INVOKANA-pi.pdf. Updated August 2020. Accessed December 10, 2021.
15. Jardiance [package insert]. https://docs.boehringer-ingelheim.com/Prescribing%20Information/PIs/Jardiance/jardiance.pdf. Updated March 2022. Accessed April 19, 2022.
16. Giorgino F, Vora J, Fenici P, Solini A. Renoprotection with SGLT2 inhibitors in type 2 diabetes over a spectrum of cardiovascular and renal risk. *Cardiovasc Diabetol*. 2020;19(1):196. doi:10.1186/s12933-020-01163-9
17. Perkovic V, Jardine MJ, Neal B, et al. Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. *N Engl J Med*. 2019;380(24):2295-2306. doi:10.1056/NEJMoa1811744
18. Cannon CP, Perkovic V, Agarwal R, et al. Evaluating the effects of canagliflozin on cardiovascular and renal events in patients with type 2 diabetes mellitus and chronic kidney disease according to baseline HbA1c, including those with HbA1c <7%: results from the CREDENCE trial. *Circulation*. 2020;141(5):407-410. doi:10.1161/CIRCULATIONAHA.119.044359
19. Jhund PS, Solomon SD, Docherty KF, et al. Efficacy of dapagliflozin on renal function and outcomes in patients with heart failure with reduced ejection fraction: results of DAPA-HF. *Circulation*. 2021;143(4):298-309. doi:10.1161/CIRCULATIONAHA.120.050391
20. Heerspink HJL, Stefánsson BV, Correa-Rotter R, et al. Dapagliflozin in patients with chronic kidney disease. *N Engl J Med*. 2020;383(15):1436-1446. doi:10.1056/NEJMoa2024816
21. American Diabetes Association Professional Practice Committee. 11. Chronic Kidney Disease and Risk Management: *Standards of Medical Care in Diabetes—2022*. *Diabetes Care*. 2022;45(Supplement_1):S175-S184. doi:10.2337/dc22-S011
22. de Boer IH, Caramori ML, Chan JCN, et al. KDIGO 2020 Clinical Practice Guideline for Diabetes Management in Chronic Kidney Disease. *Kidney Int*. 2020;98(4):S1-S115. doi:10.1016/j.kint.2020.06.019
23. Rangaswami J, Bhalla V, de Boer IH, et al. Cardiorenal protection with the newer antidiabetic agents in patients with diabetes and chronic kidney disease: a scientific statement from the American Heart Association. *Circulation*. 2020;142(17). doi:10.1161/CIR.0000000000000920
24. Cosentino F, Grant PJ, Aboyans V, et al. 2019 ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD. *Eur Heart J*. 2020;41(2):255-323. doi:10.1093/eurheartj/ehz486
25. 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. doi:10.1056/NEJMoa1812389
26. Mosenzon O, Wiviott SD, Cahn A, et al. Effects of dapagliflozin on development and progression of kidney disease in patients with type 2 diabetes: an analysis from the DECLARE-TIMI 58 randomised trial. *Lancet Diabetes Endocrinol*. 2019;7(8):606-617. doi:10.1016/S2213-8587(19)30180-9
27. Wheeler DC, Stefansson BV, Batiushin M, et al. The dapagliflozin and prevention of adverse outcomes in chronic kidney disease (DAPA-CKD) trial: baseline characteristics. *Nephrol Dial Transplant*. 2020;35(10):1700-1711. doi:10.1093/ndt/gfaa234
28. Jongs N, Greene T, Chertow GM, et al. Effect of dapagliflozin on urinary albumin excretion in patients with chronic kidney disease with and without type 2 diabetes: a prespecified analysis from the DAPA-CKD trial. *Lancet Diabetes Endocrinol*. 2021;9(11):755-766. doi:10.1016/S2213-8587(21)00243-6
29. Neal B, Perkovic V, Mahaffey KW, et al. Canagliflozin and cardiovascular and renal events in type 2 diabetes. *N Engl J Med*. 2017;377(7):644-657. doi:10.1056/NEJMoa1611925
30. Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med*. 2015;373(22):2117-2128. doi:10.1056/NEJMoa1504720
31. Wanner C, Inzucchi SE, Lachin JM, et al. Empagliflozin and progression of kidney disease in type 2 diabetes. *N Engl J Med*. 2016;375(4):323-334. doi:10.1056/NEJMoa1515920
32. EMPA-KIDNEY trial stops early due to evidence of efficacy. https://www.empakidney.org/news/empa-kidney-trial-stops-early-due-to-evidence-of-efficacy. Updated March 16, 2022. Accessed April 5, 2022.
33. Steglatro [package insert]. https://www.merck.com/product/usa/pi_circulars/s/steglatro/steglatro_pi.pdf. Updated September 2021. Accessed December 10, 2021.
34. Cannon CP, Pratley R, Dagogo-Jack S, et al. Cardiovascular outcomes with ertugliflozin in type 2 diabetes. *N Engl J Med*. 2020;383(15):1425-1435. doi:10.1056/NEJMoa2004967
35. Cherney DZI, Charbonnel B, Cosentino F, et al. Effects of ertugliflozin on kidney composite outcomes, renal function and albuminuria in patients with type 2 diabetes mellitus: an analysis from the randomised VERTIS CV trial. *Diabetologia*. 2021;64(6):1256-1267. doi:10.1007/s00125-021-05407-5
36. Zou H, Zhou B, Xu G. SGLT2 inhibitors: a novel choice for the combination therapy in diabetic kidney disease. *Cardiovasc Diabetol*. 2017;16(1):65. doi:10.1186/s12933-017-0547-1
37. Wang Y, Desai M, Ryan PB, et al. Incidence of diabetic ketoacidosis among patients with type 2 diabetes mellitus treated with SGLT2 inhibitors and other antihyperglycemic agents. *Diabetes Res Clin Pract*. 2017;128:83-90. doi:10.1016/j.diabres.2017.04.004
38. Kitamura K, Hayashi K, Ito S, et al. Effects of SGLT2 inhibitors on eGFR in type 2 diabetic patients-the role of antidiabetic and antihypertensive medications. *Hypertens Res*. 2021;44(5):508-517. doi:10.1038/s41440-020-00590-1
39. Heerspink HJL, Cherney DZI. Clinical implications of an acute dip in eGFR after SGLT2 inhibitor initiation. *Clin J Am Soc Nephrol*. 2021;16(8):1278-1280. doi:10.2215/CJN.02480221
40. Engelhardt K, Ferguson M, Rosselli JL. Prevention and management of genital mycotic infections in the setting of sodium-glucose cotransporter 2 inhibitors. *Ann Pharmacother*. 2021;55(4):543-548. doi:10.1177/1060028020951928