Use of SGLT-2 Inhibitors in Patients with Chronic Kidney Disease

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doi: 10.12788/jfp.0225

KEY TAKEAWAYS

- Chronic kidney disease (CKD) is common, occurring in 1 of 7 adults in the United States.
- 9 out of 10 adults with CKD are unaware of it.
- People with CKD have the same risk for cardiovascular (CV) death as people with known atherosclerotic heart disease.
- The risk for CV events and death increases with worsening albuminuria and estimated glomerular filtration rate (eGFR).
- Patients with risk factors for CKD (hypertension, diabetes, family history of CKD, or advancing age) should be screened by measuring both eGFR and urinary albumin-to-creatinine ratio.
- Sodium-glucose cotransporter-2 inhibitors are first-line agents for treatment of patients with type 2 diabetes mellitus and CKD or a history of atherosclerotic CV disease.
- Dapagliflozin has demonstrated equivalent efficacy for reducing kidney events in patients with CKD irrespective of diabetes status, and a similar, ongoing trial with empagliflozin may provide potential confirmation.

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DISCLOSURES

Dr. Mottl discloses that she serves on the advisory board for Bayer. Gregory Scott, PharmD, has no disclosures to report.

ACKNOWLEDGMENT

Editorial support was provided by Gregory Scott, PharmD, RPh, at the Primary Care Education Consortium.

SPONSORSHIP

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

INTRODUCTION

Chronic kidney disease (CKD) is defined as abnormalities of kidney structure or function present for >3 months, and it carries significant risk for cardiovascular (CV) health.[1] Three criteria are used to classify CKD: etiology, glomerular filtration rate stage (G1 to G5), and albuminuria category (A1 to A3).[1] Numerous factors have been shown to independently increase the risk of CKD, including uncontrolled diabetes mellitus, uncontrolled hypertension, obesity, heart failure, age >60 years, tobacco use, family history of CKD, history of acute kidney injury, and genetic factors.[2-5] In turn, CKD increases the risk for a wide variety of CV diseases, including hypertension, myocardial infarction, stroke, chronic heart failure, peripheral vascular disease, and end-stage kidney disease (ESKD),[6-8] making clear the extensive interaction between the kidney and heart.

Of the estimated 37 million adults (15%) in the United States who have CKD, an estimated 9 out of 10 are unaware, particularly those with early-stage disease.[9] This is a concern since patients with early-stage CKD may not be receiving appropriate treatments or, worse yet, may be receiving potentially nephrotoxic medications, leading to more rapid rates of disease progression.[5,10] Diabetes and hypertension are the 2 principal causes of CKD and ESKD,[5] accounting for 47% and 29%, respectively, of the 124,500 incident ESKD cases diagnosed in 2017.[11] ESKD is defined as kidney failure treated with dialysis or kidney transplant. Fewer than half (44.9%) of individuals who develop ESKD survive 5 years.[11] Given the extensive morbidity and mortality associated with CKD, greater and earlier awareness among individuals at risk for CKD is urgently needed, with primary care clinicians (PCCs) playing a sentinel role in early diagnosis and treatment.

SCREENING FOR CKD

Routine screening of kidney function in post-pubertal children with diabetes and all individuals with type 2 diabetes mellitus has been recommended by the American Diabetes Association (ADA) since the 1990s.[12] Since that time, the ADA recommendations have become more defined, with their 2021 *Standards of Medical Care in Diabetes* providing specific screening recommendations for individuals with type 1 diabetes (T1D) or type 2 diabetes (T2D) **(TABLE 1)**.[13-15] Updated recommendations released in 2020 by Kidney Disease: Improving Global Outcomes (KDIGO) mirror the ADA's recommendations.[1]

A key point in both the ADA and KDIGO screening recommendations is that adults with T1D or T2D should be screened for kidney disease by measuring both estimated

TABLE 1. **ADA recommendations for screening for CKD in individuals with diabetes mellitus**[13-15]

	Adults[a]	Children/adolescents
Who?	T1D: Duration ≥5 years T2D: All	At puberty or age >10 years, whichever is earlier, once the child has had diabetes 5 years
How?	Urinary albumin (eg, spot urine for UACR) and eGFR	Urinary albumin with a random (morning preferred) spot urine for UACR
When?	At least annually	Annually

[a]Adults with diabetes and UACR >300 mg/g and/or eGFR 30-60 mL/min/1.73 m^2 should be monitored twice annually to guide therapy.

glomerular filtration rate (eGFR) and urinary albumin-to-creatinine ratio (UACR). Annual measurement of kidney function in individuals with diabetes is a new quality care indication for public and private payers introduced in 2021. Measuring both eGFR and UACR is essential since one may become abnormal in advance of the other. Approximately 40% of patients with T2D will have an eGFR of <60 mL/min/1.73 m^2 in the absence of albuminuria.[16,17] Albuminuria can occur a decade or more before a noticeable decline in the eGFR, which typically does not occur until there is advancing glomerulosclerosis.[18,19] Thus, small changes in a patient's eGFR, such as a serum creatinine that is 0.9 to 1.1 mg/dL compared to 0.7 to 0.9 mg/dL several years ago, should be investigated to identify the cause.

Clinical evidence demonstrates that there is a graded increase in risk for all-cause and CV mortality, as well as adverse kidney outcomes, with increasing levels of albuminuria and decreasing eGFR. These effects are independent of one another, but interact in an additive fashion.[20,21] Even for individuals with an eGFR of >60 mL/min/1.73 m^2, the risks are significantly increased for a UACR of ≥30 mg/g. For example, for an individual with an eGFR of 75 to 90 mL/min/1.73 m^2, the risk of CV mortality is doubled if the UACR is 30 mg/g vs <10 mg/g.[22]

TREATMENT OVERVIEW

Once an individual is identified as having CKD, evidence-based therapy should be initiated to prevent further deterioration in kidney function.[1,14] As part of comprehensive treatment,[1,14] it is critically important to treat the underlying cause of the kidney disease. Equally important is the avoidance of nephrotoxic medications, particularly nonsteroidal anti-inflammatory drugs, which are commonly used in individuals with CKD.[5] Moreover, care must be taken to appropriately dose medications that are principally cleared by the kidneys, of which antibiotics are among the most frequent offenders.

Use of an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker is essential for most individuals with albuminuric CKD to reduce the risk of worsening albuminuria and progressive deterioration of eGFR.[1,14] In individuals with T1D or T2D, intensive glycemic control, ie, glycated hemoglobin (A1c) of <7.0%, to achieve near-normoglycemia delays the onset and progression of albuminuria and reduced eGFR.[1,14] Less intensive glycemic control, ie, A1c of <8.0%, may be appropriate in some individuals with advanced CKD, significant CV disease, or limited life expectancy.[1]

While early-stage or uncomplicated CKD can often be managed by the PCC, early referral to a nephrologist (eGFR of ≥30 mL/min/1.73 m^2) is advised in some situations. These include 1) uncertain etiology of kidney disease, particularly in the setting of persistent microscopic hematuria or atypically elevated UACR, eg, ≥1000 mg/g; 2) rapidly increasing albuminuria or nephrotic-range proteinuria; 3) rapidly decreasing eGFR (>3 mL/min/1.73 m^2 per year); and 4) particularly challenging management issues, eg, anemia, metabolic bone disease, secondary hyperparathyroidism, resistant hypertension, and electrolyte disturbances.[14] Additionally, the absence of retinopathy in individuals with T1D suggests alternative or additional causes of kidney disease.[14] All individuals with CKD with an eGFR of <30 mL/min/1.73 m^2 should be evaluated by a nephrologist unless life expectancy is limited (<1 year).

USE OF SGLT-2 INHIBITORS IN T2D AND CARDIOVASCULAR SAFETY AND BENEFITS

The sodium-glucose cotransporter-2 inhibitor (SGLT-2i) class of medications have several pharmacodynamic advantages for the treatment of individuals with T2D. First, they are administered orally once daily. Second, their unique glucosuric mechanism of action is complementary to all other glucose-lowering medications. Third, they do not cause hypoglycemia unless combined with sulfonylureas or insulin. Fourth, they promote modest weight loss. For these latter 2 reasons, the ADA recommends SGLT-2i therapy when hypoglycemia or overweight/obesity are a concern.[23] Lastly, SGLT-2i therapy causes modest reduction in blood pressure, which can be advantageous as hypertension is common in individuals with T2D.

TABLE 2. **Efficacy outcomes from CVOTs**

	Canagliflozin (CANVAS)[24]	Dapagliflozin (DECLARE-TIMI 58)[25]	Empagliflozin (EMPA-REG OUTCOME)[26,27]	Ertugliflozin (VERTIS-CV)[28]
N; % male	10,142; 64.2	17,160; 62.6	7020; 71.5	8246; 70.0
% with established atherosclerotic CV disease	65.6	40.6	99.2	–[a]
Primary MACE endpoint; HR (95% CI)	0.86 (0.75-0.97)[b]	0.93 (0.84-1.03)[c]	0.86 (0.74-0.99)[b]	0.97 (0.85-1.11)[b]
CV death or hospitalization for heart failure; HR (95% CI)	0.78 (0.67-0.91)	0.83 (0.73-0.95)[d]	0.66 (0.55-0.79)[e]	0.88 (0.75-1.03)
CV death; HR (95% CI)	0.87 (0.72-1.06)	0.98 (0.82-1.17)	0.62 (0.49-0.77)	0.92 (0.77-1.11)
Myocardial infarction; HR (95% CI)	0.85 (0.69-1.05)[f]	0.89 (0.77-1.01)	0.87 (0.70-1.09)[f]	1.04 (0.86-1.27)[f]
Stroke; HR (95% CI)	0.90 (0.71-1.15)[f]	1.01 (0.84-1.21)[g]	1.24 (0.92-1.67)[f]	1.00 (0.76-1.32)[f]
Renal composite endpoint; HR (95% CI)	0.60 (0.47-0.77)[h]	0.53 (0.43-0.66)[i]	0.54 (0.40-0.75)[j]	0.81 (0.63-1.04)[k]
Hospitalization for heart failure; HR (95% CI)	0.67 (0.52-0.87)	0.73 (0.61-0.88)	0.65 (0.50-0.85)	0.70 (0.54-0.90)

Boxes shaded in gray indicate significant benefit favoring SGLT-2 inhibitor vs placebo.

CANVAS, Canagliflozin Cardiovascular Assessment Study; DECLARE-TIMI 58, Dapagliflozin Effect on Cardiovascular Events–Thrombolysis in Myocardial Infarction 58; EMPA-REG OUTCOME, Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients; VERTIS-CV, Evaluation of Ertugliflozin Efficacy and Safety Cardiovascular Outcomes Trial.

[a]Not specified, but established coronary, cerebrovascular, or peripheral atherosclerotic CV disease was a required inclusion criterion.

[b]Cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke.

[c]Cardiovascular death, myocardial infarction, or ischemic stroke.

[d]Co-primary endpoint.

[e]Excluding fatal stroke.

[f]Nonfatal.

[g]Ischemic.

[h]40% reduction in eGFR, renal-replacement therapy, or renal death.

[i]≥40% reduction in eGFR to <60 mL/min/1.73 m^2, ESKD, or renal death.

[j]Doubling of serum creatinine accompanied by eGFR ≤45 mL/min/1.73 m^2, renal-replacement therapy, or renal death.

[k]Renal death, renal-replacement therapy, or doubling of the serum creatinine level.

Multiple large CV outcomes trials (CVOTs) have demonstrated the CV safety of all 4 SGLT-2 inhibitors currently available in the United States **(TABLE 2)**.[24-28] CV safety was based on major adverse CV events (MACE), a composite endpoint of CV death, nonfatal myocardial infarction, or nonfatal stroke. All CVOTs involving an SGLT-2i included individuals who had suffered a CV event, ie, secondary prevention, while some included individuals who were at high CV risk but who had not suffered a CV event, ie, primary prevention.

Some but not all CVOTs showed significant reductions in CV death; however, all showed reductions in hospitalization for heart failure.[24-26,28] While reductions in CV death were restricted to those with baseline CV disease, reductions in hospitalization rates for heart failure were irrespective of baseline CV disease status.[29]

The results of these CVOTs led the ADA[23] and the American College of Cardiology/American Heart Association (ACC/AHA)[30] to recommend SGLT-2i therapy as a preferred option for secondary CV prevention. The ADA recommends the addition of an SGLT-2i as an option for individuals with T2D and established CV disease who do not achieve glycemic control with optimized metformin and lifestyle management.[23] The ACC/AHA also suggest considering combined use of an SGLT-2i and a glucagon-like peptide-1 receptor agonist for primary prevention of CV disease in patients with T2D and additional risk factors for CV disease.[30]

TABLE 3. **Baseline demographics and efficacy outcomes in kidney disease trials**

Average	Canagliflozin (CREDENCE)[32]	Dapagliflozin (DAPA-CKD)[33]
N; % male	4401; 66.1	4304; 66.9
Mean age, y	63.0	61.9
Mean eGFR, mL/min/1.73 m^2	56.2	43.1
UACR (median), mg/g	927	949
% with T2D	100	67.5
% with CV disease	50.4	37.4
% with HTN	96.8	NR
% on RAAS inhibitor	99.9	98.2
Randomized treatment	Canagliflozin 100 mg/d or placebo	Dapagliflozin 10 mg/d or placebo
Follow-up (median), y	2.6	2.4
Primary composite endpoint; HR (95% CI)	0.70 (0.59-0.82)[a]	0.61 (0.51-0.72)[b]
CV death; HR (95% CI)	0.78 (0.61-1.00)	0.81 (0.58-1.12)
All-cause death; HR (95% CI)	0.83 (0.68-1.02)	0.69 (0.53-0.88)
CV death or hospitalization for heart failure; HR (95% CI)	0.69 (0.57-0.83)	0.71 (0.55-0.92)
Doubling of SCr; HR (95% CI)	0.60 (0.48-0.76)	–
eGFR decline ≥50%; HR (95% CI)	–	0.53 (0.42-0.67)
ESKD; HR (95% CI)	0.68 (0.54-0.86)	0.64 (0.50-0.82)
eGFR <15 mL/min/1.73 m^2; HR (95% CI)	0.60 (45-0.80)	0.67 (0.51-0.88)
Dialysis or kidney transplantation; HR (95% CI)	0.74 (0.55-1.00)	0.66 (0.49-0.90)
Long-term dialysis; HR (95% CI)	–	0.66 (0.48-0.90)

Boxes shaded in gray indicate significant benefit favoring SGLT-2 inhibitor vs placebo.

HTN, hypertension; NR, not reported; SCr, serum creatinine.

Outcomes are shown as hazard ratio (95% confidence interval).

[a]Dialysis, kidney transplantation, sustained eGFR <15 mL/min/1.73 m^2, doubling of serum creatinine level, renal death, or CV death.

[b]Sustained decline in eGFR ≥50%, dialysis for ≥28 days, transplantation, sustained eGFR <15 mL/min/1.73 m^2, CV death, or renal death.

KIDNEY OUTCOMES AND SGLT-2 INHIBITORS

The CVOTs all had prespecified secondary kidney endpoints, and dapagliflozin, empagliflozin, and canagliflozin (but not ertugliflozin) showed reductions in major kidney outcomes (those being a 40% decline in eGFR and/or doubling of serum creatinine, or renal death). Despite the lack of a statistically significant reduction in these hard events, ertugliflozin was found to slow the rate of eGFR decline,[28] with results consistent with the other CVOT trials.[31] The vast majority of patients in the CVOTs had minimal or no evidence of CKD at baseline, suggesting primary or early benefit of these drugs to prevent progression of CKD in T2D.

Two kidney outcomes trials, CREDENCE (Canagliflozin and Renal Events in Diabetes With Established Nephropathy Clinical Evaluation)[32] and DAPA-CKD (Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease),[33] have been conducted exclusively in individuals with CKD and their results reported. A third, EMPA-KIDNEY (The Study of Heart and Kidney Protection With Empagliflozin), is in progress.[34] CREDENCE included only individuals with T2D, whereas DAPA-CKD and EMPA-KIDNEY include individuals with or without T2D. Inclusion criteria were: 1) CREDENCE, eGFR of 30 to <90 mL/min/1.73 m^2 and UACR of >300 to 5000 mg/g; 2) DAPA-CKD, eGFR of 25 to 75 mL/min/1.73 m^2 and UACR of 200 to 5000 mg/g; and 3) EMPA-KIDNEY, eGFR of 20 to <45 mL/min/1.73 m^2 or eGFR of 45 to <90 mL/min/1.73 m^2 and UACR of ≥200 mg/g.

CREDENCE and DAPA-CKD both demonstrated significant kidney and CV benefits with canagliflozin and dapagliflozin, respectively. Key baseline demographics are shown in **TABLE 3**; all of the individuals in CREDENCE and two-thirds in DAPA-CKD had T2D and nearly all were treated with a renin-angiotensin-aldosterone system (RAAS) blocker.[32,33]

TABLE 4. **Adverse events of special interest in clinical trials of SGLT-2 inhibitors focused on patients with CKD**

Adverse event	CREDENCE[32]			DAPA-CKD[33]		
	Canagliflozin, %	**Placebo, %**	**HR (95% CI)**	**Dapagliflozin, %**	**Placebo, %**	***P***
Any adverse event	81.1	84.7	0.87 (0.82-0.93)	–	–	–
Any serious adverse event	33.5	36.7	0.87 (0.79-0.97)	29.5	33.9	–
Amputation	3.2	3.9	1.11 (0.79-1.56)	1.6	1.8	0.73
DKA	0.5	<0.1	10.80 (1.39-83.65)	0	<0.1	0.50
Fracture	3.0	3.1	0.98 (0.70-1.37)	4.0	3.2	0.22
Major hypoglycemia[a]	–	–	–	0.7	1.3	0.04
Hypoglycemia[b]	10.2	10.9	0.92 (0.77-1.11)	–	–	–
Hyperkalemia	6.9	8.2	0.80 (0.65-1.00)	–	–	–
Volume depletion	6.5	5.2	1.25 (0.97-1.59)	5.9	4.2	0.01
Renal-related	13.2	17.7	(0.71 (0.61-0.82)	7.2	8.7	0.07
Acute kidney injury	3.9	4.5	0.85 (0.64-1.13)	1.8	2.4	–

[a]Characterized by symptoms of severe impairment in consciousness or behavior, need of external assistance, intervention to treat hypoglycemia, and prompt recovery from acute symptoms after the intervention.

[b]Symptomatic and asymptomatic.

In CREDENCE, canagliflozin was superior to placebo for preventing the primary renal outcome (composite of dialysis, transplantation, sustained eGFR of <15 mL/min/1.73 m^2, doubling of serum creatinine, CV death, or renal death) (hazard ratio [HR] 0.70; 95% confidence interval [CI]: 0.59-0.82).[32] The number needed to treat (NNT) for the primary renal outcome was estimated to be 22 over 2.5 years.

Similarly, DAPA-CKD demonstrated significant reductions with dapagliflozin in the primary renal outcome (composite of sustained decline in eGFR of ≥50%, dialysis, transplantation, sustained eGFR of <15 mL/min/1.73 m^2, or CV or renal death) (HR 0.61; 95% CI: 0.51-0.72), with an NNT of 19 over 2.4 years.[33] The significant reduction of the primary renal outcome was observed in individuals with T2D (HR 0.64; 95% CI: 0.52-0.79) and without T2D (HR 0.50; 95% CI: 0.35-0.72); *P* for interaction = 0.24. Treatment with dapagliflozin also resulted in a significant reduction in the primary renal outcome in individuals with an eGFR of ≥45 mL/min/1.73 m^2 (HR 0.49; 95% CI: 0.34-0.69) and an eGFR of <45 mL/min/1.73 m^2 (HR 0.63; 95% CI: 0.51-0.78), as well as a UACR of ≤1000 mg/g (HR 0.54; 95% CI: 0.37-0.77) and a UACR of >1000 mg/g (HR 0.62; 95% CI: 0.50-0.76).[33] Moreover, dapagliflozin reduced the risk of kidney failure, CV death, or hospitalization for heart failure, and prolonged survival in individuals with CKD independent of the presence of concomitant CV disease.[35]

The overwhelming evidence for SGLT-2 inhibitors as a risk mitigation strategy in diabetes and CKD led to the recent recommendation by KDIGO for an SGLT-2i as initial therapy in combination with lifestyle management and metformin in individuals with T2D and CKD with an eGFR of ≥30 mL/min/1.73 m^2.[36] Moreover, based on the results from DAPA-CKD, dapagliflozin was approved by the US Food and Drug Administration in April 2021 to reduce the risk of kidney function decline, kidney failure, CV death, and hospitaliza-

tion for heart failure in adults with CKD who are at risk of disease progression.

ADVERSE EVENTS

SGLT-2i trials have shown fairly consistently that the adverse effects of this drug class include genital mycotic infections and a small but statistically significant increased risk of euglycemic diabetic ketoacidosis (DKA).[37] Experts across disciplines generally agree that while the risk of DKA is real, it can be mitigated by instructions to hold medication during conditions that predispose to DKA, such as fasting or acute illness. The risk of amputation was a concern raised by the CANVAS study, involving canagliflozin[24]; however, the CREDENCE trial did not show a difference compared to placebo **(TABLE 4)**.[32] Notably, an increased risk of urinary tract infections has not been shown in meta-analyses.[37] Increased rates of volume depletion or hypotension have been seen, but these are infrequent adverse effects and easily avoided by decreasing concurrent diuretic medications in patients who are euvolemic at the time of initiating SGLT-2i therapy. Moreover, the risk of acute kidney injury is actually mitigated by SGLT-2i therapy.

IMPLICATIONS FOR PRIMARY CARE

Both canagliflozin and dapagliflozin significantly reduce renal events in individuals with baseline CKD, regardless of the severity of albuminuria or low eGFR. In addition, dapagliflozin provides kidney benefits in individuals with or without T2D. These findings have prompted the question: Are SGLT-2 inhibitors glucose-lowering medications with cardiorenal benefits or are they cardiorenal medications that lower glycemia?[38-40] Advances in the treatment of CKD emphasize the key role of PCCs in the early identification and diagnosis of these individuals. SGLT-2 inhibitors have become an important treatment option in individuals with T2D and established CV disease, including CKD, as recommended in current guidelines and reflected in approved product labeling.[41-44]

REFERENCES

1. International Society of Nephrology. KDIGO 2020 Clinical Practice Guideline for Diabetes Management in Chronic Kidney Disease. *Kidney Int*. 2020;98(4S):S1-S115.
2. Gatwood J, Chisholm-Burns M, Davis R, et al. Evidence of chronic kidney disease in veterans with incident diabetes mellitus. *PLoS One*. 2018;13(2):e0192712.
3. Tarver-Carr ME, Powe NR, Eberhardt MS, et al. Excess risk of chronic kidney disease among African-American versus white subjects in the United States: a population-based study of potential explanatory factors. *J Am Soc Nephrol*. 2002;13(9):2363-2370.
4. Chen TK, Knicely DH, Grams ME. Chronic kidney disease diagnosis and management: a review. *JAMA*. 2019;322(13):1294-1304.
5. Tuttle KR, Alicic RZ, Duru OK, et al. Clinical characteristics of and risk factors for chronic kidney disease among adults and children: an analysis of the CURE-CKD registry. *JAMA Netw Open*. 2019;2(12):e1918169.
6. Sasso FC, Chiodini P, Carbonara O, et al; Nephropathy in Type 2 Diabetes Study Group. High cardiovascular risk in patients with Type 2 diabetic nephropathy: the predictive role of albuminuria and glomerular filtration rate. *Nephrol Dial Transplant*. 2012;27(6):2269-2274.
7. Pálsson R, Patel UD. Cardiovascular complications of diabetic kidney disease. *Adv Chronic Kidney Dis*. 2014;21(3):273-280.
8. Tuttle KR, Bakris GL, Bilous RW, et al. Diabetic kidney disease: a report from an ADA Consensus Conference. *Diabetes Care*. 2014;37(10):2864-2883.
9. Centers for Disease Control and Prevention. Chronic kidney disease in the United States, 2019. Accessed May 25, 2021. https://www.cdc.gov/kidneydisease/pdf/2019_National-Chronic-Kidney-Disease-Fact-Sheet.pdf
10. Murphy DP, Drawz PE, Foley RN. Trends in angiotensin-converting enzyme inhibitor and angiotensin II receptor blocker use among those with impaired kidney function in the United States. *J Am Soc Nephrol*. 2019;30(7):1314-1321.
11. US Renal Data System. 2019 USRDS annual report: epidemiology of kidney disease in the United States. 2019. Accessed May 25, 2021. https://www.usrds.org/annual-data-report/
12. American Diabetes Association. Standards of medical care for patients with diabetes mellitus. *Diabetes Care*. 1994;17(6):616-623.
13. American Diabetes Association. 4. Comprehensive Medical Evaluation and Assessment of Comorbidities: *Standards of Medical Care in Diabetes–2021. Diabetes Care*. 2021;44(Suppl 1):S40-S52.
14. American Diabetes Association. 11. Microvascular Complications and Foot Care: *Standards of Medical Care in Diabetes–2021. Diabetes Care*. 2021;44(Suppl 1):S151-S167.
15. American Diabetes Association. 13. Children and Adolescents: *Standards of Medical Care in Diabetes–2021. Diabetes Care*. 2021;44(Suppl 1):S180-S199.
16. Mottl AK, Kwon KS, Mauer M, Mayer-Davis EJ, Hogan SL, Kshirsagar AV. Normoalbuminuric diabetic kidney disease in the U.S. population. *J Diabetes Complications*. 2013;27(2):123-127.
17. Vistisen D, Andersen GS, Hulman A, Persson F, Rossing P, Jørgensen ME. Progressive decline in estimated glomerular filtration rate in patients with diabetes after moderate loss in kidney function—even without albuminuria. *Diabetes Care*. 2019;42(10):1886-1894.
18. Alicic RZ, Rooney MT, Tuttle KR. Diabetic kidney disease: Challenges, progress, and possibilities. *Clin J Am Soc Nephrol*. 2017;12(12):2032-2045.
19. Afkarian M. Diabetic kidney disease in children and adolescents. *Pediatr Nephrol*. 2015;30(1):65-74.
20. Ninomiya T, Perkovic V, de Galan BE, et al. Albuminuria and kidney function independently predict cardiovascular and renal outcomes in diabetes. *J Am Soc Nephrol*. 2009;20(8):1813-1821.
21. Fox CS, Matsushita K, Woodward M, et al. Associations of kidney disease measures with mortality and end-stage renal disease in individuals with and without diabetes: a meta-analysis. *Lancet*. 2012;380(9854):1662-1673.
22. KDIGO. Chapter 1: Definition and classification of CKD. *Kidney Int Suppl (2011)*. 2013;3(1):19-62.
23. American Diabetes Association. 9. Pharmacologic Approaches to Glycemic Treatment: *Standards of Medical Care in Diabetes–2021. Diabetes Care*. 2021;44(Suppl 1):S111-S124.
24. 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.
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.
26. 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.
27. 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.
28. 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.
29. Zelniker TA, Wiviott SD, Raz I, et al. SGLT2 inhibitors for primary and secondary prevention of cardiovascular and renal outcomes in type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials. *Lancet*. 2019;393(10166):31-39.
30. Arnett DK, Blumenthal RS, Albert MA, et al. 2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation*. 2019;140(11):e596-e646.
31. Johansen ME, Argyropoulos C. The cardiovascular outcomes, heart failure and kidney disease trials tell that the time to use sodium glucose cotransporter 2 inhibitors is now. *Clin Cardiol*. 2020;43(12):1376-1387.
32. 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.
33. 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.
34. Herrington WG, Preiss D, Haynes R, et al. The potential for improving cardio-renal outcomes by sodium-glucose co-transporter-2 inhibition in people with chronic kidney disease: a rationale for the EMPA-KIDNEY study. *Clin Kidney J*. 2018;11(6):749-761.
35. McMurray JJV, Wheeler DC, Stefánsson BV, et al. Effect of dapagliflozin on clinical outcomes in patients with chronic kidney disease, with and without cardiovascular disease. *Circulation*. 2021;143(5):438-448.
36. KDIGO 2020 Clinical Practice Guideline for Diabetes Management in Chronic Kidney Disease. *Kidney Int*. 2020;98(4S):S1-S115.
37. Barbarawi M, Al-Abdouh A, Barbarawi O, Lakshman H, Al Kasasbeh M, Chen K. SGLT2 inhibitors and cardiovascular and renal outcomes: a meta-analysis and trial sequential analysis. *Heart Fail Rev*. 2021. doi:10.1007/s10741-021-10083-z.
38. Packer M. SGLT2 inhibitors produce cardiorenal benefits by promoting adaptive cellular reprogramming to induce a state of fasting mimicry: a paradigm shift in understanding their mechanism of action. *Diabetes Care*. 2020;43(3):508-511.
39. Wanner C. EMPA-REG OUTCOME: the nephrologist's point of view. *Am J Cardiol*. 2017;120(1S):S59-S67.
40. Sattar N, McGuire DK. Pathways to cardiorenal complications in type 2 diabetes mellitus: a need to rethink. *Circulation*. 2018;138(1):7-9.
41. Invokana [package insert]. Titusville, NJ: Janssen Pharmaceuticals, Inc.; August 2020.
42. Farxiga [package insert]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; May 2020.
43. Jardiance [package insert]. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals, Inc.; February 2021.
44. Steglatro [package insert]. Whitehouse Station, NJ: Merck Sharp & Dohme Corp.; March 2021.