

SGLT2 Inhibition for CKD and Cardiovascular Disease in Type 2 Diabetes: Report of a Scientific Workshop Sponsored by the National Kidney Foundation



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Diabetes is the most frequent cause of chronic kidney disease (CKD), leading to nearly half of all cases of kidney failure requiring replacement therapy. The principal cause of death among patients with diabetes and CKD is cardiovascular disease (CVD). Sodium/glucose cotransporter 2 (SGLT2) inhibitors were developed to lower blood glucose levels by inhibiting glucose reabsorption in the proximal tubule. In clinical trials designed to demonstrate the CVD safety of SGLT2 inhibitors in type 2 diabetes mellitus (T2DM), consistent reductions in risks for secondary kidney disease end points (albuminuria and a composite of serum creatinine doubling or 40% estimated glomerular filtration rate decline, kidney failure, or death), along with reductions in CVD events, were observed. In patients with CKD, the kidney and CVD benefits of canagliflozin were established by the CREDENCE (Canagliflozin and Renal Events in Diabetes With Established Nephropathy Clinical Evaluation) trial in patients with T2DM, urinary albumin-creatinine ratio > 300 mg/g, and estimated glomerular filtration rate of 30 to <90 mL/min/1.73 m². To clarify and support the role of SGLT2 inhibitors for treatment of T2DM and CKD, the National Kidney Foundation convened a scientific workshop with an international panel of more than 80 experts. They discussed the current state of knowledge and unanswered questions to propose therapeutic approaches and delineate future research. SGLT2 inhibitors improve glomerular hemodynamic function and are thought to ameliorate other local and systemic mechanisms involved in the pathogenesis of CKD and CVD. SGLT2 inhibitors should be used when possible by people with T2DM to reduce risks for CKD and CVD in alignment with the clinical trial entry criteria. Important risks of SGLT2 inhibitors include euglycemic ketoacidosis, genital mycotic infections, and volume depletion. Careful consideration should be given to the balance of benefits and harms of SGLT2 inhibitors and risk mitigation strategies. Effective implementation strategies are needed to achieve widespread use of these life-saving medications.

Complete author and article information provided before references.

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Introduction

Diabetes and chronic kidney disease (CKD) commonly co-exist and are associated with high risk for morbidity and mortality. In the United States, 34.2 million adults (10.5% of the population) are estimated to have diabetes, with only 26.9 million aware of the diagnosis.¹ Type 2 diabetes mellitus (T2DM) accounts for 90% to 95% of cases of diagnosed diabetes.¹ Worldwide, 463 million had diabetes in 2019, with a predicted growth in prevalence to nearly 700 million by 2045.² Diabetic kidney disease (DKD), CKD in diabetes, occurs in ~30% of people with type 1 diabetes mellitus (T1DM) and in ~40% of those with T2DM.³ Diabetes is the leading cause of CKD globally, accounting for nearly half of all cases of kidney failure requiring replacement therapy. However, patients with T2DM and CKD are more likely to die than progress to kidney failure.^{2,4} As such, the population with diabetes requiring kidney replacement therapy (KRT) is a survivor cohort of ~10% of those who originally had CKD.⁵ The most common causes of death in patients with T2DM and CKD are atherosclerotic cardiovascular disease (ASCVD) and heart failure (HF).^{6,7}

Glycemic control is the cornerstone of optimal diabetes care. For those with CKD, hypertension control and use of

an angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB) are also foundations of optimal care. Many glucose-lowering medications are now available. Until recently, no class of glucose-lowering agent was considered as preferred treatment. Rather, the recommendation was to achieve a glycemic target determined by hemoglobin A_{1c} (HbA_{1c}) level. People with diabetes and CKD have had limited choice of glucose-lowering agents due to safety issues, adverse effects, or lack of evidence in people with low glomerular filtration rates (GFR).

Sodium/glucose cotransporter 2 (SGLT2) inhibitors lower blood glucose levels by preventing glucose and sodium reabsorption in the proximal tubule.⁸⁻¹⁰ The US Food and Drug Administration (FDA) has approved 4 SGLT2 inhibitors for the treatment of hyperglycemia in T2DM: canagliflozin, dapagliflozin, empagliflozin, and ertugliflozin. The first reported cardiovascular disease (CVD) outcome trial (CVOT) to demonstrate safety of an SGLT2 inhibitor, the EMPA-REG OUTCOME trial, was also the first to show clear benefit of a particular glucose-lowering agent for protection against major adverse cardiovascular events (MACE) in people with T2DM and ASCVD. Empagliflozin also reduced the risk for secondary

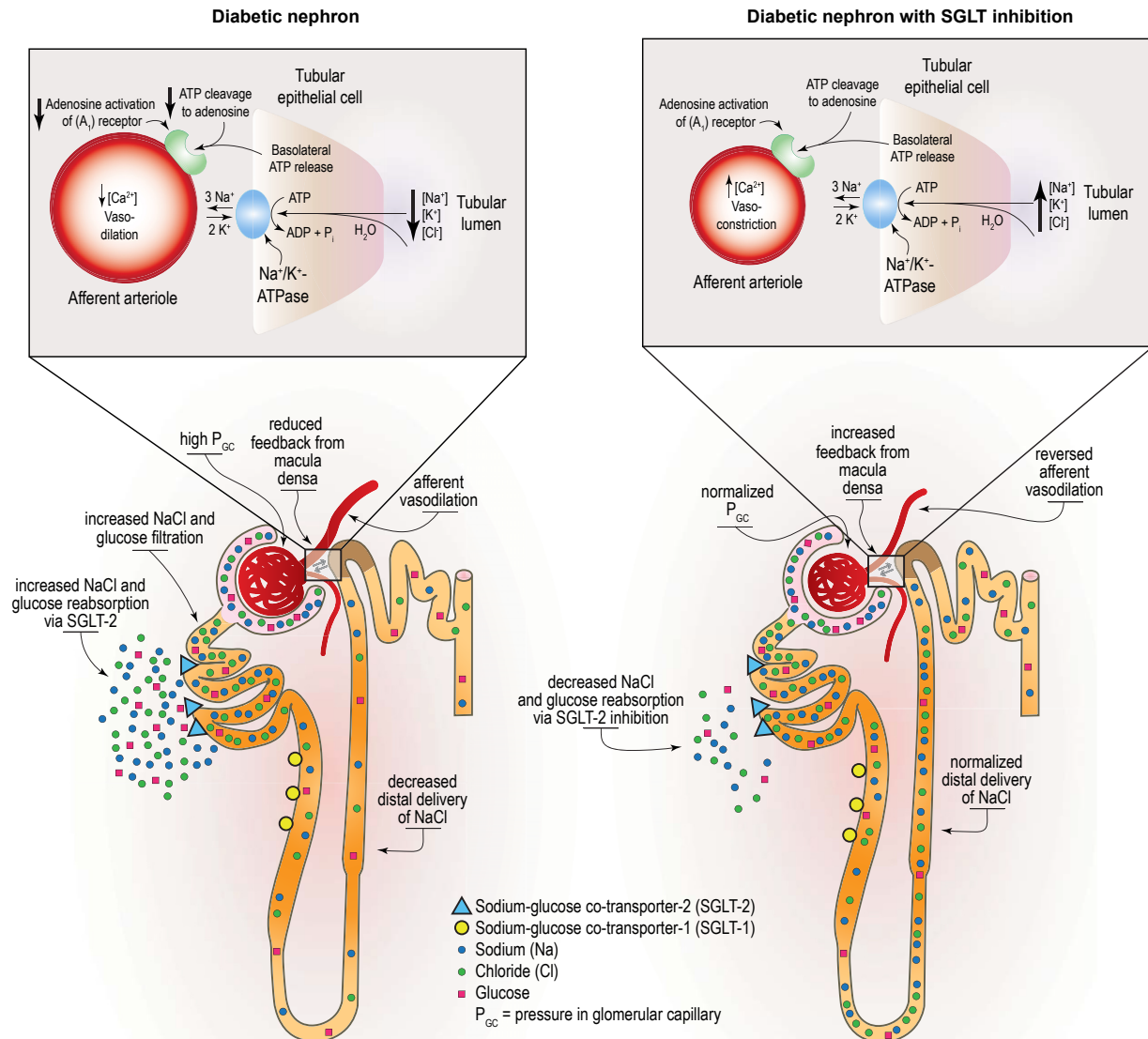


Figure 1. Sodium/glucose cotransporter 2 (SGLT-2) inhibition and glomerular hemodynamics in diabetes. Abbreviations: ADP, adenosine diphosphate; ATP, adenosine triphosphate; P, phosphate. Reproduced from Alicic et al¹⁸ with permission of the copyright holder; original graphic © 2018 by the National Kidney Foundation.

kidney disease end points (albuminuria progression, serum creatinine doubling, kidney failure, and death).¹¹ These results have subsequently been demonstrated across the class of SGLT2 inhibitors with canagliflozin¹² and dapagliflozin¹³ in their respective CVOTs. These collective findings were subsequently proven by the CREDENCE trial, the first to show superiority of an SGLT2 inhibitor added to the standard of care for CKD in T2DM for a primary outcome of kidney disease end points.¹⁴

To address the groundbreaking science for the emerging role of SGLT2 inhibition for the treatment of

patients with T2DM and CKD, the National Kidney Foundation (NKF) held a scientific workshop in June 2019 with an international panel of more than 80 experts in nephrology, endocrinology, cardiology, primary care, pharmacology, regulatory affairs, public health, and physiology. These experts deliberated on the current state of knowledge, methods to improve clinical care, and research that is needed to advance the field. The objective of this report is to publicly disseminate the conference proceedings and recommendations with an ultimate goal of providing knowledge that will improve CKD and CVD outcomes for people with T2DM.

Mechanisms of Kidney Protection by SGLT2 Inhibitors

The kidney benefits of SGLT2 inhibitors appear to be largely independent of glycemic control based on a growing series of observations. Their glucose-lowering effects are modest, especially in people with baseline estimated GFR (eGFR) < 45 mL/min/1.73 m². Nevertheless, kidney protection is consistent and substantial in this population.¹⁴ SGLT2 inhibitors also have kidney benefits in people with well-controlled glycemia (HbA_{1c} < 7%) in whom further glucose lowering was minimal.¹⁵ In the DAPA-HF trial, which included people with or without diabetes, the effects on HF and kidney disease end points were consistent regardless of diabetes status.¹⁶ Finally, kidney protection of this type and magnitude has not been observed with other glucose-lowering agents.

Tubuloglomerular Feedback and Glomerular Hemodynamics

In addition to improvement in CKD and CVD risk factors, many other mechanisms have been postulated.¹⁷ The concept of restoring tubuloglomerular feedback is frequently used to explain the salutary kidney effects of SGLT2 inhibitors (Fig 1¹⁸). Restoration of tubuloglomerular feedback occurs as a consequence of increased sodium chloride delivery to the macula densa.^{19,20} When sodium chloride enters the macula densa, vasoactive substances such as adenosine are locally formed and released. In a paracrine manner, adenosine constricts the afferent arteriole through the adenosine 1 receptor, thereby decreasing glomerular perfusion and hyperfiltration, a central mechanism for progressive glomerular injury.^{21,22} Consistent with this concept, SGLT2 inhibition by empagliflozin was observed to reduce kidney blood flow and increase vascular resistance in hyperglycemic patients with T1DM through afferent arteriolar vasoconstriction.²³ Another recent study in patients with T2DM reported that SGLT2 inhibition reduced GFR through efferent arteriolar dilation.²⁴ Notably, preclinical data suggest that tubuloglomerular feedback may also occur by locally produced adenosine binding receptors that activate vasodilation in the efferent arteriole.²⁵ Thus, although the acute reduction in GFR is consistent in patients with T1DM and T2DM, the underlying glomerular hemodynamic effectors may differ.

Tubular Workload and Hypoxia

Reabsorption of electrolytes and organic solutes in the proximal tubule is energy and adenosine triphosphate (ATP) dependent. The proximal tubule accounts for the largest amount of oxygen consumption in the kidney.²⁶ In patients with diabetes, proximal tubular glucose reabsorption through SGLT2 is increased due to an increase in luminal glucose driven by hyperglycemia and glomerular

hyperfiltration.²⁷ The resulting increased glucose and sodium reabsorption increases oxygen demand, which in turn renders the proximal tubule relatively hypoxic.²⁸

Tubular hypoxia may be a major mechanism of kidney disease progression in diabetes.²⁹ By reducing sodium and glucose reabsorption, SGLT2 inhibitors reduce tubular workload and mitigate hypoxia in the proximal tubule. However, the shift of glucose and sodium reabsorption downstream to the S3 segment of the proximal tubule and medullary thick ascending limb of the loop of Henle increases oxygen demand, making these tubular segments vulnerable to ischemia. Lower medullary oxygen tension stimulates hypoxia-inducible factors, including erythropoietin, to increase red blood cell production and improve oxygen-carrying capacity.²⁸ Hypoxia in the kidney cortex can be quantified using blood oxygen level–dependent magnetic resonance imaging (BOLD-MRI).³⁰ Different BOLD-MRI techniques lead to varying results and current technology is not sufficiently sensitive to identify tubular segments. Thus, insight into where SGLT2 inhibitors alleviate hypoxia will require advances in techniques for more precise imaging.

Glucose Metabolic Fluxes and Mitochondrial Dysfunction

Glucose metabolic flux increases in the kidney cortex in early experimental and human diabetes, as indicated by higher urinary levels of tricarboxylic acid cycle and glycolytic metabolites.^{31,32} This process occurs by increased proximal tubular glucose uptake. Moreover, higher urinary levels of tricarboxylic acid cycle metabolites predict kidney disease progression, and higher glucose metabolic flux promotes proximal tubular mitochondrial dysfunction.³² Glucose metabolic flux decreases over time in progressive DKD with worsening mitochondrial dysfunction.³³ Mitochondrial dysfunction may further aggravate ATP deficiency and hypoxia, which could conceivably be alleviated by SGLT2 inhibition.

Diuresis and Natriuresis

SGLT2 inhibitors promote diuresis due to glucosuria and natriuresis.³⁴ Diuresis is an important mechanism for reducing blood pressure and risk for HF events.^{11-16,35} Lack of a compensatory increase in heart rate suggests commensurate blunting of sympathetic nervous system activity, which may also contribute to salutary effects of SGLT2 inhibitors compared with other diuretics.^{36,37} In addition, a study that coupled plasma and urinary water and electrolyte data with mathematical modeling to compare effects of dapagliflozin and bumetanide on volumes of blood and interstitial fluid suggested that SGLT2 inhibitors have a preferential effect to mobilize fluid from the interstitial compartment rather than the intravascular space.³⁸ Reduction in interstitial fluid in the kidney and

Table 1. Proposed Research for Kidney-Protective Mechanisms of SGLT-2 Inhibitors

Study	Rationale/Objective
Glomerular Hemodynamics	
Evaluate glomerular hemodynamics in younger patients with T2DM, patients with T1DM, and patients with obesity but not diabetes.	Provide insight on effects of SGLT2 inhibitors in different populations with varying glomerular hemodynamic status and glucose metabolism.
Tubular Workload and Hypoxia	
Elucidate effects of SGLT2 inhibition on urine metabolomics and kidney oxygenation using advanced imaging techniques such as PET.	Knowledge about metabolism and hypoxia in the pathogenesis of DKD and effects of SGLT2 inhibition are needed.
Diuretic Effects	
Investigate effects of SGLT2 inhibition on SNS in patients with and without DKD.	Mechanisms for reduction in SNS activity of SGLT2 inhibitors are unknown. Studying patients with nondiabetic CKD could help understand these effects.
Anti-inflammatory and Antifibrotic Effects	
Determine anti-inflammatory and antifibrotic effects of SGLT2 inhibitors in patients with and without DKD. Consider kidney biopsies to determine effects at the tissue level.	Mechanisms for anti-inflammatory and antifibrotic effects of SGLT2 inhibitors are unknown. Studying patients with nondiabetic CKD could help understand these effects.

Abbreviations: CKD, chronic kidney disease; DKD, diabetic kidney disease; PET, positron emission tomography; SGLT2, sodium/glucose cotransporter 2; SNS, sympathetic nervous system; T2(1)DM, type 2 (1) diabetes mellitus.

reduced proximal tubular energy requirements may alleviate cortical and outer medullary hypoxia.

Inflammation and Fibrosis

SGLT2 inhibitors reduce levels of nuclear factor- κ B (NF κ B), interleukin 6 (IL-6), monocyte chemoattractant protein 1 (MCP-1), and other factors implicated in inflammation and tissue fibrosis in experimental models of diabetes.^{39,40} Similar effects on urinary IL-6 and MCP-1, as well as serum tumor necrosis factor receptor 1 (TNFR1) and IL-6, were observed in clinical trials of SGLT2 inhibitors in patients with T2DM.^{41,42} Although the mechanism for reduced inflammation with SGLT2 inhibition is unknown, study participants receiving canagliflozin had lower plasma levels of inflammatory and fibrotic mediators compared with those receiving glimepiride despite similar levels of glycemia, suggesting a glucose-independent effect.⁴² Hyperuricemia may induce kidney inflammation and has been reported to be a risk factor for incident DKD in T2DM.⁴³ A meta-analysis suggested that SGLT2 inhibitors reduce serum uric acid levels in patients with T2DM.⁴⁴

Future Research

SGLT2 inhibitors have numerous effects on local and systemic factors involved in DKD onset and progression. The mechanistic hierarchy and pleiotropy of these agents are unknown. More comprehensive understanding of the kidney-protective pathways is crucial to facilitate research that will elucidate SGLT2 inhibitor actions and optimize their use (Table 1).

Cardiovascular Protection by SGLT2 Inhibitors

Three SGLT2 inhibitors (empagliflozin, canagliflozin, and dapagliflozin) were studied across 6 large-scale completed

CVD and CKD clinical trials,^{12-16,35} with assessment of ertugliflozin⁴⁵ in a subsequent clinical trial.

Atherosclerotic CVD

The CVOTs designed to test safety and a CKD trial (CREDENCE) were comparable in key aspects: participants with T2DM, placebo controls, SGLT2 inhibitor dose not based on glycemia, all participants treated by standard of care, and similarly defined and adjudicated outcomes. There were differences in risk profiles of participants in the CVOTs, ranging from 100% to 40% with prevalent ASCVD at baseline, the balance having 1 or more ASCVD risk factors. Although the findings across these trials on the composite outcome of MACE (3-point MACE; CVD death, myocardial infarction, and stroke) were consistent,⁴⁶ differences in study design may explain varying effect estimates of SGLT2 inhibition on ASCVD events.

The EMPA-REG OUTCOME trial randomly assigned 7,020 patients with established ASCVD including coronary, peripheral vascular, or cerebral artery disease.⁴⁷ After a median follow-up of 3.1 years, patients treated with empagliflozin had a 14% lower relative risk for cardiovascular death, myocardial infarction, or stroke (hazard ratio [HR], 0.86; 95% CI, 0.74-0.99).³⁵ The benefit of empagliflozin on the primary CVD composite outcome was largely driven by a significant reduction in CVD death rates (3.7% vs 5.9%; HR, 0.62 [95% CI, 0.49-0.77]).

The CANVAS trials program evaluated the CVD safety and efficacy of canagliflozin.¹² This program integrated data from 2 separate trials that included a total of 10,142 participants in combination. Most patients included in these trials had established ASCVD at baseline, whereas ~35% met eligibility criteria based on the presence of ASCVD risk factors with T2DM. In the CANVAS program, canagliflozin reduced the risk for the primary outcome of MACE (HR, 0.86; 95% CI, 0.75-0.97). Although formal

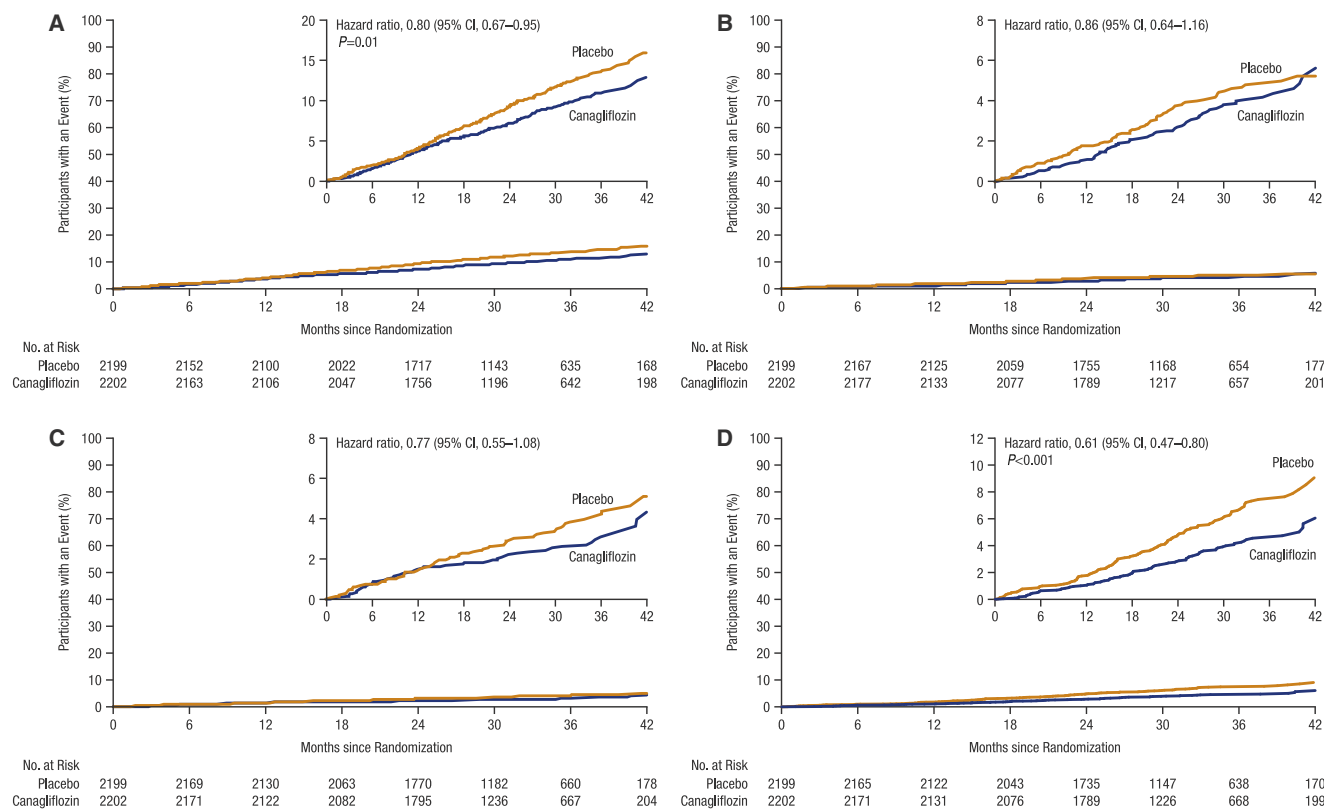


Figure 2. Effects of canagliflozin on cardiovascular outcomes in the overall population. (A) Cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke. (B) Fatal or nonfatal myocardial infarction. (C) Fatal or nonfatal stroke. (D) Hospitalization for heart failure. Reproduced from Mahaffey et al⁴⁹ with permission of Wolters Kluwer Health, Inc; original graphic © 2019 by Mahaffey et al.

interaction testing did not identify statistically significant differences in the effect of canagliflozin in patients with or without established ASCVD, HRs in participants with and without ASCVD were 0.82 (95% CI, 0.72-0.95) and 0.98 (95% CI, 0.74-1.30), respectively.⁴⁸

The DECLARE-TIMI 58 trial randomly assigned 17,160 patients with T2DM to treatment with either dapagliflozin or placebo. This trial had dual primary outcomes: (1) MACE and (2) composite of CVD death or HF hospitalization. Unlike the EMPA-REG OUTCOME trial and CANVAS program, most participants in the DECLARE-TIMI 58 trial did not have established ASCVD (59%; n = 10,186). The overall effect of dapagliflozin on MACE was not statistically significantly different versus placebo (HR, 0.93; 95% CI, 0.84-1.03).¹³ The point estimate of efficacy was numerically lower in participants with ASCVD (HR, 0.90; 95% CI, 0.79-1.02) than in those without ASCVD (HR, 1.01; 95% CI, 0.86-1.20), but results in neither subgroup achieved statistical significance nor was the interaction significant.

The CREDENCE trial, although primarily designed to assess efficacy on kidney outcomes, analyzed 3-point MACE as part of the primary analysis hierarchy in participants with T2DM and DKD.¹⁶ CREDENCE participants were at high CVD risk, with 3-point MACE occurring in 16.1% and 8.3% during a mean of 2.6 years in those

with and without established ASCVD, respectively.⁴⁹ Risk for 3-point MACE was significantly reduced with canagliflozin versus placebo overall (HR, 0.80; 95% CI, 0.67-0.95) and in the primary prevention cohort for ASCVD (HR, 0.68; 95% CI, 0.49-0.94), and was numerically similar in the secondary prevention cohort (HR, 0.85; 95% CI, 0.69-1.06; Fig 2).

Heart Failure

In a systematic review and meta-analysis of the CVOTs with data from 34,322 patients with T2DM with or at high risk for ASCVD, relative risk for CVD death or hospitalization for HF was reduced by 23% in patients treated with an SGLT2 inhibitor versus placebo (HR, 0.77; 95% CI, 0.71-0.84).⁴⁶ Reductions in hospitalizations for HF were seen in EMPA-REG OUTCOME, CANVAS, and DECLARE-TIMI 58, including patients with and without prevalent ASCVD and those with and without a history of HF. Results from these CVOTs and CREDENCE revealed more robust and consistent benefits on HF than on MACE with SGLT2 inhibitors.¹⁴

DAPA-HF was the first clinical trial of an SGLT2 inhibitor to assess HF events as the primary outcome and to include participants with and without diabetes.⁵⁰ DAPA-HF was conducted in 4,744 participants with New York Heart Association classes II to IV HF with an ejection

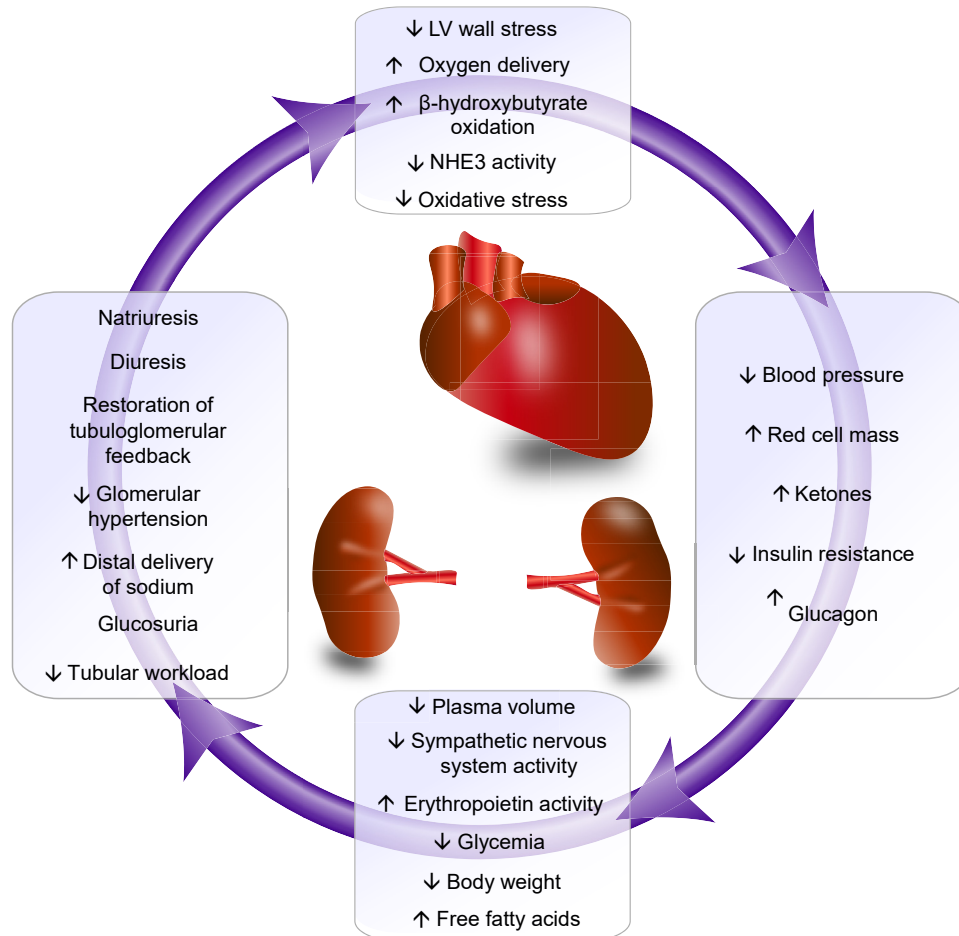


Figure 3. The kidney-heart connection for organ protection. Abbreviations: LV, left ventricular; NHE3, sodium–hydrogen exchanger 3. Reproduced courtesy of Emily J. Cox, PhD; original graphic © 2020 E.J. Cox.

fraction $\leq 40\%$ who were treated by the standard of care, including β -blocker; ACE enzyme inhibitor, ARB, or sacubitril-valsartan; mineralocorticoid receptor antagonist; and cardiac device therapy (if indicated). The primary outcome of worsening HF or CVD death was significantly reduced, 16.3% versus 21.2% for dapagliflozin compared to placebo (HR, 0.74; 95% CI, 0.65–0.85). These results were consistent across subgroups including those with and without diabetes or CKD.

In summary, all clinical trials to date have shown a consistent beneficial effect of the SGLT2 inhibitors on HF events. This observation has been also corroborated by real-world data from clinical practice that has found consistent associations between the use of SGLT2 inhibitors and lower risk for HF hospitalization across a broad spectrum of patients.^{51,52}

Potential Mechanisms of Cardiovascular Benefits

Patients with T2DM are at high risk for ASCVD and HF compared with nondiabetic individuals.^{50,53} However, glycemic control per se does not meaningfully reduce the risk for these events.^{54–56} The concept that benefits of

SGLT2 inhibitors are mediated by nonglycemic mechanisms is further supported by observations that reduction in CVD events occurred irrespective of concomitant use of other glucose-lowering agents. Furthermore, the observed CVD risk reductions were not related to either baseline or achieved HbA_{1c} levels in participants with diabetes.⁵⁷ In DAPA-HF, dapagliflozin reduced the risk for worsening HF or CVD death irrespective of diabetes status.⁵⁸ Thus, the mechanisms by which SGLT2 inhibitors reduce the risk for HF are not attributable to improved glycemic control.⁵⁹ A variety of potential mechanisms have been proposed to explain beneficial effects of SGLT2 inhibitors on CVD (Fig 3).^{19,59–63} Those that appear particularly plausible include effects on volume status, natriuresis, expansion of red blood cell mass, and myocardial energetics.^{34,36,59,62,64}

Future Research

SGLT2 inhibitors reduce HF risks in broad cohorts of patients with T2DM and in those with reduced ejection fraction HF with or without diabetes.^{46,58} Results from post hoc analyses of the DECLARE-TIMI 58 trial and the

CANVAS program have suggested that patients with reduced ejection fraction may have greater benefit.^{65,66} Whether HF benefits also apply to patients with preserved ejection fraction are being addressed in ongoing clinical trials evaluating empagliflozin and dapagliflozin (ClinicalTrials.gov identifiers NCT03057951 and NCT03619213, respectively). Despite robust evidence for CVD benefits of SGLT2 inhibitors, there remain important unanswered questions. Mechanistic studies will offer insights into the modes by which these agents improve CVD outcomes. Knowledge of mechanisms could help tailor therapy, identify additional populations who may benefit or may face enhanced risk for adverse effects, and elucidate new pathways or targets (Table 2).

Kidney Protection by SGLT2 Inhibitors

Kidney Disease Events

EMPA-REG OUTCOME was the first CVOT to demonstrate that treatment with an SGLT2 inhibitor, empagliflozin, reduced the risk for a secondary kidney disease outcome (severely increased albuminuria, doubling of serum creatinine accompanied by $eGFR \leq 45$ mL/min/1.73 m², initiation of KRT, or death from kidney disease) to 12.7% versus 18.8% in the placebo group (HR, 0.61; 95% CI, 0.53-0.70).¹¹ Mean baseline eGFR was 74 mL/min/1.73 m², 26% of participants had $eGFR < 60$ mL/min/1.73 m², and 40% had albuminuria. Importantly, after the first 4 weeks of treatment during which eGFR declined with empagliflozin, eGFR stabilized in the empagliflozin groups and declined steadily in the placebo group. These findings were confirmed in the CANVAS program, in which mean baseline eGFR was 76 mL/min/1.73 m², 20% had $eGFR < 60$ mL/min/1.73 m², and 30% had albuminuria.¹² The secondary kidney disease outcome (sustained 40% reduction in eGFR, need for KRT, or death from kidney disease) occurred less frequently among

participants in the canagliflozin group versus placebo (HR, 0.60; 95% CI, 0.47-0.77). DECLARE-TIMI 58 included participants with a mean baseline eGFR of 85 mL/min/1.73 m², of whom 7.4% had $eGFR < 60$ mL/min/1.73 m². The proportion with albuminuria was 30%, similar to other CVOTs. This trial demonstrated that dapagliflozin significantly decreased the risk for the secondary kidney disease outcome comprising 40% reduction in eGFR to <60 mL/min/1.73 m², kidney failure, or death due to kidney disease (HR, 0.53; 95% CI, 0.43-0.66).

CREDESCENCE was the first clinical trial to be stopped early for overwhelming efficacy proving the kidney protective effects of SGLT2 inhibition for DKD. The trial was conducted in 4,401 participants with T2DM and severely increased albuminuria (urinary albumin-creatinine ratio of >300 to $<5,000$ mg/g) with eGFR of 30 to <90 mL/min/1.73 m² who were treated by the standard of care with either an ACE inhibitor or ARB.¹⁴ Starting at a mean baseline eGFR of 56 mL/min/1.73 m², risk for the primary outcome (serum creatinine doubling, kidney failure treated by KRT, or death from kidney disease or CVD) was substantially reduced (HR, 0.70; 95% CI, 0.59-0.82). After 3 weeks of treatment, the mean rate of eGFR decline was significantly slower in patients receiving canagliflozin compared with placebo (-1.85 vs -4.59 mL/min/1.73 m² per year; Figs 4 and 5). The number needed to treat with canagliflozin to prevent a primary outcome event was 22 during a mean of 2.6 years. These kidney-protective effects were accomplished with nominal between-group differences in HbA_{1c} levels or blood pressure.

Albuminuria

In CREDESCENCE, urinary albumin-creatinine ratio was reduced by 31%.¹⁴ The CVOTs consistently showed a corresponding reduction in albuminuria by 30% to 40% in patients with albuminuria. Treatment with SGLT2 inhibitors also increases the likelihood to regress from severely to moderately increased albuminuria or normal albuminuria and from moderately increased albuminuria to normal albuminuria. The albuminuria-lowering effect occurs within weeks after initiation of treatment and is presumably due to glomerular hemodynamic effects. For prevention of new-onset albuminuria, CVOT results have been less consistent. This effect was observed in CANVAS¹² and DECLARE-TIMI-58,⁶⁷ but not in the EMPA-REG OUTCOME trial.¹¹ However, in the latter study, the absolute level of albuminuria in patients with normal albuminuria at baseline was lower in patients receiving empagliflozin compared with placebo by trial end.⁶⁸

Subgroup Responses

In the CVOTs and CREDESCENCE, kidney-protective effects are consistent overall (Fig 6) and in participants with different levels of glycemic control (HbA_{1c} $< 7\%$ or $> 9\%$) or eGFR strata (>90 , 60-90, or 30-60 mL/min/1.73 m²).^{11,12,14,70}

Table 2. Proposed Research to Understand Effects of SGLT2 Inhibitors for CVD Safety or Benefit in Additional Populations

Study	Rationale/Objective
Prediabetes and obesity	High risk for ASCVD events
Initial monotherapy in T2DM	High risk for ASCVD and HF events
T1DM	High risk for ASCVD events
Post-acute coronary syndrome, peripheral arterial disease	High risk for ASCVD events
Acute HF, HF with preserved ejection fraction	High risk for HF events
Atrial fibrillation	High risk for ASCVD and HF events
Hypertensive urgency	High risk for ASCVD and HF events
Nondiabetic CKD	High risk for ASCVD and HF events

Abbreviations: ASCVD, atherosclerotic cardiovascular disease; CKD, chronic kidney disease; CVD, cardiovascular disease; HF, heart failure; SGLT2, sodium/glucose cotransporter 2; T2(1)DM, type 2 (1) diabetes mellitus.

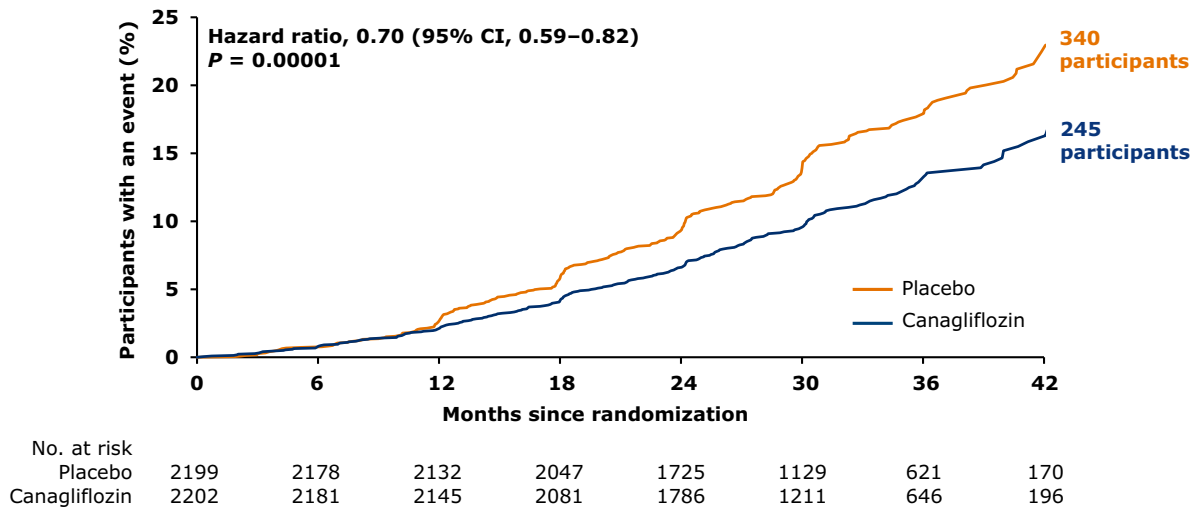


Figure 4. CREDENCE (Canagliflozin and Renal Events in Diabetes With Established Nephropathy Clinical Evaluation) primary outcome: kidney failure, serum creatinine doubling, kidney or cardiovascular disease death. Adapted with permission from Perkovic et al¹⁴ with permission of the copyright holder; original graphic © 2019 Massachusetts Medical Society.

In CREDENCE, 29.8% (1,313/4,401) of participants had a baseline eGFR of 30 to 45 mL/min/1.73 m², and kidney benefits did not differ from those in patients with higher eGFR.^{14,69} Given consistent effects over time and across stages of CKD, no particular eGFR subgroup appears to derive more prominent benefits than the others.⁷¹ This observation is clinically relevant because in patients with eGFR < 45 mL/min/1.73 m², SGLT2 inhibitors have nominal effects on glycemia, although reductions in eGFR decline, blood pressure, and body weight are maintained.^{72,73} The effects of SGLT2 inhibitors on kidney disease end points do not differ in patients with established ASCVD or those with multiple CVD risk factors.^{12,14,70} The effects on kidney disease outcomes are also similar irrespective of background use of renin-angiotensin system blockade.¹⁴ Importantly, in all clinical trials of SGLT2

inhibitors reported to date, patients with baseline eGFR < 30 mL/min/1.73 m² were excluded. Current studies will determine whether SGLT2 inhibitors have kidney benefits in patients with and without diabetes who have eGFR below this level (EMPA-KIDNEY: ClinicalTrials.gov identifier NCT03594110; DAPA-CKD: ClinicalTrials.gov identifier NCT03036150). Importantly, on March 30, 2020, DAPA-CKD was stopped early at the recommendation of an Independent Data Monitoring Committee due to overwhelming efficacy.⁷⁴

Future Research

The influence of diuretic treatment on effects of SGLT2 inhibitors are unclear, although overall diuretics do not seem to have much effect on their kidney benefits.^{11,12,70} More research on this aspect is needed, especially

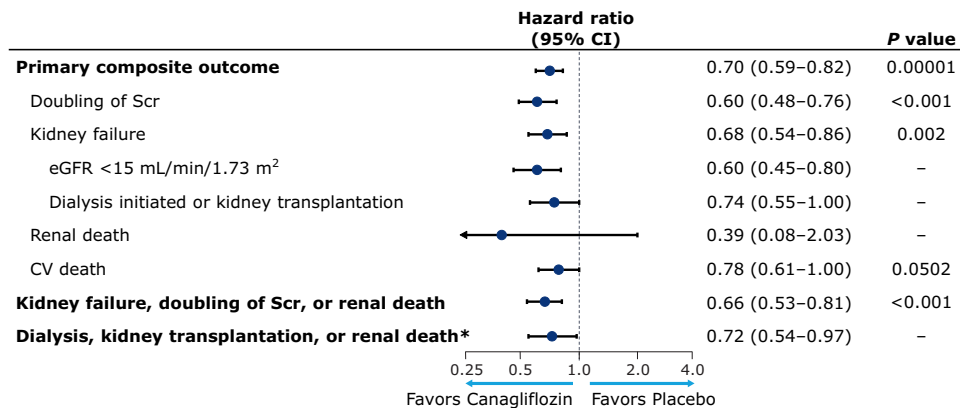


Figure 5. CREDENCE (Canagliflozin and Renal Events in Diabetes With Established Nephropathy Clinical Evaluation): summary forest plot. *Post hoc analysis. Abbreviations: CV, cardiovascular; eGFR, estimated glomerular filtration rate; Scr, serum creatinine. Developed with data from Perkovic et al.¹⁴

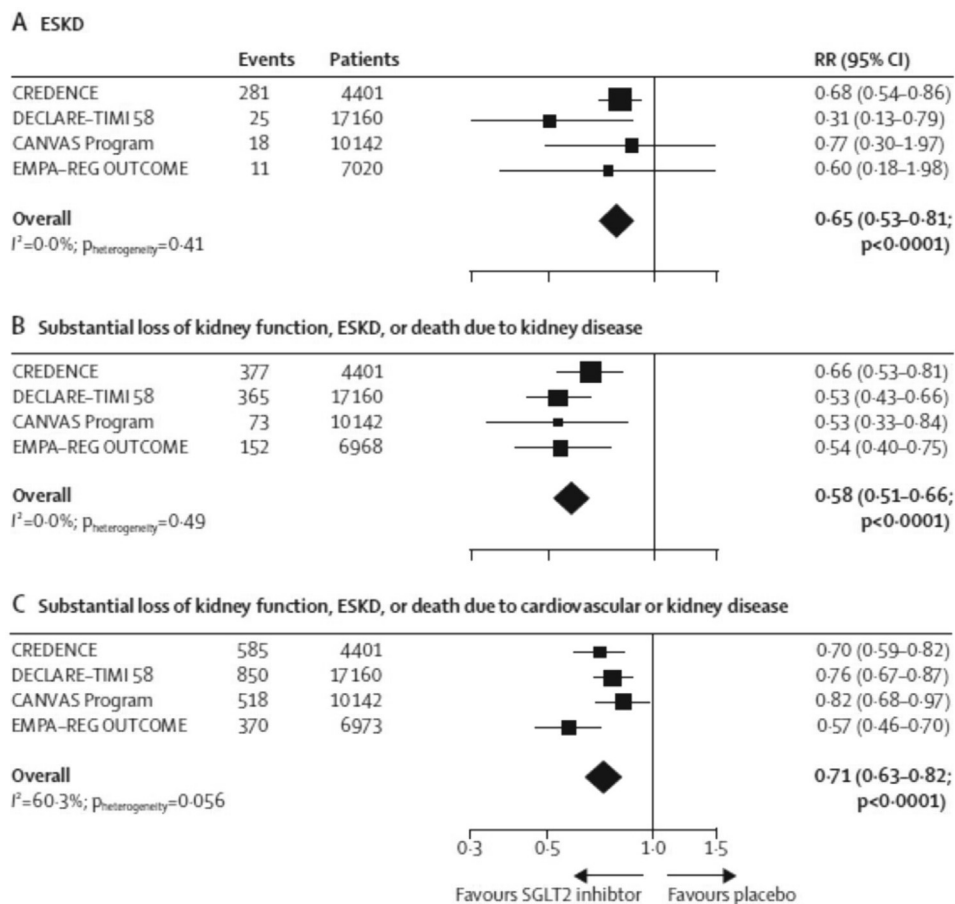


Figure 6. Effects of sodium/glucose cotransporter 2 (SGLT2) inhibitors on chronic kidney disease end points in the cardiovascular disease outcome trials and CREDESCENCE (Canagliflozin and Renal Events in Diabetes With Established Nephropathy Clinical Evaluation). Random effects meta-analysis. Abbreviations: ESKD, end-stage kidney disease; RR, relative risk. Reproduced from Neuen et al⁶⁹ with permission of the copyright holder; original graphic © 2019 Elsevier Ltd.

differentiating thiazide and loop diuretics. The effects of other treatments that alter glomerular hemodynamics, for example, nonsteroidal anti-inflammatory drugs, remain to be clarified.⁷⁵ Better prediction of SGLT2 inhibitor response is needed because neither clinical characteristics nor various risk factors identify albuminuria responders (>30% reduction).⁷⁶ Only a subset of patients with T2DM and CKD have purely diabetic glomerulopathy (30%-50%), whereas others commonly have tubulointerstitial or vascular disease with or without diabetic glomerulopathy.^{77,78} Patients with different structural lesions may respond differently to SGLT2 inhibition, so their effects on structural lesions in DKD should be studied. Additionally, whether other patient groups (diabetes with glomerular hyperfiltration, T1DM, nondiabetic CKD, or post-kidney and post-heart transplant diabetes) benefit from SGLT2 inhibitors warrants study. Several glucagon-like peptide 1 (GLP1) receptor agonists have demonstrated ASCVD or CKD benefits in CVOTs for T2DM and in a clinical trial in moderate to severe CKD with T2DM.^{79,80} Available data have shown additive benefits with an SGLT2 inhibitor and

a GLP1 receptor agonist on glycemia, blood pressure, and weight.^{81,82} Therefore, combination therapy with these classes of agents could be studied for effects on clinical CKD and CVD outcomes (Table 3).

Integration of SGLT Inhibition Into Clinical Practice

Glycemic Control Regimens

SGLT2 inhibitors were initially approved for T2DM as glucose-lowering agents without increased risk for hypoglycemia. Dapagliflozin and sotagliflozin also have regulatory approval in Europe as glucose-lowering agents adjunctive to insulin for T1DM. Although the glucose-lowering effect of SGLT2 inhibitors is attenuated with reduced eGFR, adjustment of concomitant glucose-lowering agents may be required to avoid hypoglycemia if administered with insulin, sulfonylureas, or glinides. Because the CKD and CVD benefits are largely independent of SGLT2 inhibitor dose, preservation of insulin dosing with SGLT2 inhibitor dose reduction is preferable to mitigate the risk for ketoacidosis.

Table 3. Proposed Research to Understand Clinical Effects of SGLT2 Inhibitors on Kidney Disease

Study	Rationale/Objective
Responder Status	
Identify responders and nonresponders to SGLT2 inhibition for kidney protection.	Develop a precision approach to apply SGLT2 inhibition to patients most likely to benefit.
Albuminuria and eGFR	
Determine whether the initial change in albuminuria or eGFR predicts subsequent GFR.	Identifying so-called initial “decliners” vs “nondecliners” would be helpful for therapeutic applications.
Structural Basis of Treatment Response	
Perform kidney biopsies, as well as measure corresponding urinary and blood biomarkers, to predict responsiveness to SGLT2 inhibition.	Understanding structural basis of response to SGLT2 inhibition to advance therapeutic applications.
Combination Treatments	
Test efficacy and safety of SGLT2 inhibitors and GLP-1 receptor agonists as a first-line agents in patients with diabetes and CKD for potential benefits of combination therapy.	Determine benefits and risks of treatments and their combinations to optimize CKD and CVD outcomes.
Benefits and Risks in Different Populations	
Identify additional groups who benefit from SGLT2 inhibitors for kidney protection.	Learn whether SGLT2 inhibition provides similar benefits for patients with diabetes and glomerular hyperfiltration, T1DM, nondiabetic CKD, or post-kidney and post-heart transplant diabetes.
Identify groups at high risk for SGLT2 inhibitor side effects such as ketoacidosis, genital mycotic infections, and volume depletion.	More precisely characterize the clinical features of at-risk groups as well as categories and rates of adverse outcomes from SGLT2 inhibitors.

Abbreviations: CKD, chronic kidney disease; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; GLP1, glucagon-like peptide 1; SGLT2, sodium/glucose cotransporter 2; T1DM, type 1 diabetes mellitus.

Prevention and Treatment of Kidney Disease and CVD

The FDA granted regulatory approval for canagliflozin to reduce the risks for doubling of serum creatinine level, kidney failure, hospitalization for HF, and CVD death in adults with T2DM and CKD (urinary albumin-creatinine ratio, 300-5,000 mg/g and eGFR, 30- $<$ 90 mL/min/1.73 m²) based on CREDENCE.⁸³ Most participants enrolled in the clinical trials of SGLT2 inhibitors were concomitantly treated with metformin, although some were not. For example, in the EMPA-REG OUTCOME trial, 1,827 (26%) participants were not treated with metformin.⁸⁴ Whether SGLT2 inhibitors should instead be used as first-line agents in people with T2DM for ASCVD, HF, or CKD is a point of debate.⁸⁴ Major national and international organizations are rapidly updating recommendations and guidelines (Table 4).⁸⁵⁻⁸⁸ All recommend SGLT2 inhibition for patients with T2DM and eGFR as low as 30 mL/min/1.73 m², particularly if severely increased albuminuria is present. Moreover, SGLT2 inhibitor withdrawal is not required if eGFR decreases to $<$ 30 mL/min/1.73 m², as per the CREDENCE protocol. Because DAPA-CKD was stopped early for overwhelming efficacy, the eGFR cutoff could be reduced to 25 mL/min/1.73 m². If results are comparable in nondiabetic patients with CKD, they also may be recommended for SGLT2 inhibitor treatment.

Risks of SGLT2 Inhibitors

Important risks of SGLT2 inhibitors include euglycemic ketoacidosis, genital mycotic infections, and volume depletion. For those with a history of these side effects,

particularly if recent or recurrent, careful consideration should be given to the balance of benefits and harms of SGLT2 inhibitors. Inclusion of patients in shared decision making and counseling regarding use of an SGLT2 inhibitor are paramount to safe implementation. Whether to permanently discontinue SGLT2 inhibitor therapy following a single episode of ketoacidosis, a genital mycotic infection, or volume depletion should be individualized according to the clinical scenario, patient concerns, and potential for benefits. These risks occur across the SGLT2 inhibitor class.

Euglycemic ketoacidosis with minimal to no elevation in blood glucose levels may occur in patients taking SGLT2 inhibitors due to increased fatty acid oxidation and glucagon release along with decreased insulin secretion.^{89,90} Patients with either T1DM or T2DM taking insulin are at particular risk, with the greatest risk for ketoacidosis in T1DM. To mitigate risk, it is important to maintain insulin doses and pause SGLT2 inhibitor treatment during periods of acute illness or other stressors. Blood or urine ketone monitoring may be used for early detection of ketosis. Patients should be informed that if they experience signs or symptoms of ketoacidosis, such as nausea, vomiting, and abdominal pain, they should discontinue SGLT2 inhibitor therapy and immediately seek medical attention. Genital mycotic infections occur more often in SGLT2 inhibitor users (2%-4% in men and 3%-7% in women) than nonusers ($<$ 2% in both sexes).⁹¹ In a recent report, advice given for daily rinsing of the genital area after voiding and before bedtime significantly lessened the risk for genital mycotic infections (6/125 vs

Table 4. SGLT2 Guidelines for CKD and CVD in Diabetes

Professional Group Recommendations	SGLT2i Recommended in CKD	SGLT2i Recommended in ASCVD	SGLT2i Recommended in HF	SGLT2i Recommended Independent of Metformin
European Society of Cardiology/ European Association for the Study of Diabetes Guidelines 2019 ⁸⁷	Yes ^a	Yes	Yes	Yes (patients drug naive for glucose-lowering agents)
American Diabetes Association Standards of Medical Care in Diabetes 2020 ⁸⁵	Yes ^b (if GFR adequate based on drug approval label)	Yes (if GFR adequate based on drug approval label)	Yes (if GFR adequate based on drug approval label)	No
Kidney Disease: Improving Global Outcomes Diabetes and CKD Guideline 2020 ⁸⁸	Yes ^c (if GFR adequate based on drug approval label)	Yes (if GFR adequate based on drug approval label)	Yes (if GFR adequate based on drug approval label)	No
American Heart Association Scientific Statement on Cardiorenal Protection in Diabetes and CKD 2020 ⁸⁶	Yes ^d (if GFR adequate based on drug approval label)	Yes (if GFR adequate based on drug approval label)	Yes (if GFR adequate based on drug approval label)	No comment

Abbreviations: ASCVD, atherosclerotic cardiovascular disease; CKD, chronic kidney disease; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; HF, heart failure; SGLT2, sodium/glucose cotransporter 2; SGLT2i, sodium/glucose cotransporter 2 inhibitor.

^aeGFR of 30 to <90 mL/min/1.73 m².

^beGFR of 30 to 60 mL/min/1.73 m² or urinary albumin-creatinine ratio > 30 mg/g, particularly urinary albumin-creatinine ratio > 300 mg/g.

^ceGFR ≥ 30 mL/min/1.73 m².

^deGFR ≥ 30 or ≥45 mL/min/1.73 m² depending on agent; for canagliflozin, eGFR of 30 to 45 mL/min/1.73 m² and urinary albumin-creatinine ratio > 300 mg/g.

51/125; $P = 0.015$) and improved adherence to SGLT2 inhibitor treatment over a 3-year period.⁹² SGLT2 inhibitors may cause volume depletion due to their diuretic effect. However, stopping or reducing doses of other diuretics on SGLT2 inhibitor initiation is generally not necessary, but monitoring of electrolyte levels and kidney function is important for dose titration or adjustment of other antihypertensive or diuretic agents. To minimize risk for volume depletion, SGLT2 inhibitor treatment should be paused during periods of acute illness or other stressors.

Among putative side effects of SGLT2 inhibitors, Fournier gangrene is rare (1 in 10,000 patients) but serious and has been reported in post-market approval safety reports to the FDA.⁹³ It is unclear how much of this risk is attributable to SGLT2 inhibitors per se versus secular trends for increased rates of skin infections in diabetes.⁹⁴ Despite theoretical concerns for acute kidney injury and urinary tract infection, SGLT2 inhibitors do not increase these risks and acute kidney injury is less common.^{69,95} Higher risks for lower extremity amputation, mainly toe or metatarsal (6.3 vs 3.4 per 1,000 person-years), and fractures (15.4 vs 11.9 per 1,000 person-years) were reported for canagliflozin versus placebo in the CANVAS program.¹² Whether these are chance findings or they represent a class effect is uncertain. Higher risks for amputation and fracture were not observed in CVOTs of other SGLT2 inhibitors or with canagliflozin in the CREDENCE trial.^{14,69,95}

Optimizing Uptake of SGLT2 Inhibitors

The clinical benefits provided by SGLT2 inhibition can only be realized with increased use. Nearly 20 years ago,

similar expectations were held for ACE inhibitors and ARBs, but implementation of this standard of care for diabetes and CKD is strikingly low, in the range of 20% to 40%, even in contemporary reports from communities and health care systems.^{96,97} The newfound opportunity with SGLT2 inhibitors highlights the urgent need for better CKD screening and detection.^{11-14,97-99} Education and activation of patients regarding the benefits of receiving renin-angiotensin system inhibitors and SGLT2 inhibitors can be accomplished through focused discussion and information dispersed in clinical settings, communities of high-risk groups, and public media platforms. For example, the NKF and CVS Kidney Care have partnered on a campaign to promote kidney health and screening for CKD.¹⁰⁰

Even with greater awareness of the benefits of SGLT2 inhibitors, their high cost poses a barrier to use. Using a participant-level simulation model and United Kingdom health care costs, empagliflozin in addition to standard of care is projected to be cost-effective.¹⁰¹ The model predicted that although patients would incur increased out-of-pocket cost, empagliflozin in addition to standard of care would result in longer survival by 2.1 life-years. Market exclusivity practice is another major barrier because brand name monopolies may delay widespread access to SGLT2 inhibitors.¹⁰² Patient advocacy and professional organizations can lead the education of clinicians and patients with concentrated efforts to increase SGLT2 inhibitor use in appropriate patients.^{103,104} Clinicians who provide care in nephrology, endocrinology, cardiology, and primary care must master competency in prescribing and managing SGLT2 inhibitors. Considering the broad indications for the treatment of T2DM, CKD, and CVD, dissemination and implementation science is

Table 5. Proposed Research to Increase Uptake of SGLT2 Inhibitors

Study	Rationale/Objective
Dissemination and Implementation	
Test whether multiprofessional clinics (in which patients are seen by nephrologist, cardiologist, diabetes care provider, and pharmacist) improve uptake of SGLT2 inhibitors.	Identify new models of care to increase dissemination and implementation of SGLT2 inhibitor use.
Availability of Insurance Coverage for SGLT2 Inhibitors	
Perform detailed risk-benefit and economic analyses using large claims databases.	Encourage coverage for SGLT2 inhibitors for CKD and CVD from health insurers.

Abbreviations: CKD, chronic kidney disease; CVD, cardiovascular disease; SGLT2, sodium/glucose cotransporter 2.

needed to generate data that health care administrators and policy makers can use to support ready availability of SGLT2 inhibitors (Table 5).

Conclusions

Diabetes is the leading cause of CKD worldwide, with high risks for kidney failure, ASCVD, HF, and premature mortality. The concept that benefits of SGLT2 inhibitors are mediated by nonglycemic mechanisms is supported by many observations that the CKD and CVD risk reductions in the clinical trials of these agents occurred irrespective of glycemic control or use of other glucose-lowering agents. SGLT2 inhibitors have numerous effects, from improving glomerular hemodynamics to modifying local and systemic mechanisms involved in the pathogenesis of CKD and CVD. More comprehensive understanding of these mechanisms is crucial for optimal application and to facilitate research that will elucidate actions of SGLT2 inhibitors. Clinicians have a responsibility to maximize the known benefits by prescribing and managing SGLT2 inhibitors in patients likely to benefit. Dedicated efforts are required to disseminate information, provide education, and ensure appropriate SGLT2 inhibitor use.

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