Renal and Cardiovascular Effects of Sodium Glucose Co-Transporter 2 Inhibitors in Patients with Type 2 Diabetes and Chronic Kidney Disease: Perspectives on the Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation Trial Results

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Abstract
Background: Chronic kidney disease (CKD) risk is elevated in patients with type 2 diabetes mellitus (T2DM). Disease management in these patients has been generally focused on glycemic control and controlling other renal and cardiac risk factors as, historically, few protective therapies have been available. The Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE) trial of canagliflozin was the first study to demonstrate renal protection with a sodium glucose co-transporter 2 inhibitor in patients with T2DM and CKD, and these results could have important implications for clinical practice. ***Summary:*** In CREDENCE, participants with T2DM and estimated glomerular filtration rate 30–<90 mL/min/1.73 m^2 and urinary albumin-creatinine ratio >300–5,000 mg/g who were treated with an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker for ≥4 weeks prior to randomization at either the maximum labeled or tolerated dose were randomized to receive either canagliflozin 100 mg or placebo. Canagliflozin significantly reduced the risk of the primary composite outcome of doubling of serum creatinine, end-stage kidney disease, or renal or cardiovascular (CV) death compared with placebo (hazard ratio 0.70, 95% CI 0.59–0.82; $p = 0.00001$). Canagliflozin also reduced the risk of secondary renal and CV outcomes. The safety profile of canagliflozin in CREDENCE was generally similar to previous studies of canagliflozin. No imbalances were observed between canagliflozin and placebo in the risk of amputation or fracture in the CREDENCE population. ***Key Messages:*** The positive renal and CV effects of canagliflozin observed in the CREDENCE trial could have a substantial impact on improving outcomes for patients with T2DM and CKD.

Introduction

Burden and Mechanisms of Chronic Kidney Disease

Chronic kidney disease (CKD) is defined by the Kidney Disease: Improving Global Outcomes working group as abnormalities of kidney structure or function present for >3 months, with implications for health. The Kidney Disease: Improving Global Outcomes CKD risk score is classified based on estimated glomerular filtration rate (eGFR) and albuminuria [1]. The prevalence of CKD has been estimated to be between 10 and 13% globally and 14.8% in the United States and is expected to increase due to the aging global population and rising prevalence of diabetes and hypertension [2, 3].

CKD affects approximately 40% of patients with type 2 diabetes mellitus (T2DM), and diabetes is the leading cause of CKD [3]. It is recommended that all patients with T2DM have urinary albumin-creatinine ratio (UACR) and eGFR screenings annually because progression to substantial proteinuria (protein excretion >300 mg/g) is a strong predictor of rapid progression of CKD to end-stage kidney disease (ESKD). Despite this, CKD awareness among health care providers is low, which can be a barrier to providing effective care; in the United States, 48% of those with severely reduced kidney function who are not on dialysis are unaware that they have CKD [4, 5].

Unlike cardiovascular (CV) disease, for which many cardioprotective medications are available, physicians have limited treatment options beyond glycemic control and antihypertensive therapy to slow CKD progression. There have been no new treatments in 18 years, since the development of renin-angiotensin-aldosterone system (RAAS) inhibitors, including angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs), leaving a substantial residual risk for renal failure to occur [6, 7].

Several key potentially modifiable factors, including obesity, hyperglycemia, and systemic hypertension, may work together to drive maladaptive processes, such as insulin resistance, glomerular hyperfiltration, inflammation, proteinuria, and CV disease, that contribute to the development and progression of CKD in patients with T2DM. Additionally, patients with CKD are at an increased risk for several safety concerns as a result of their progressive renal insufficiency, including hypoglycemia, hyperlipidemia, hypertension, hyperkalemia, hyperphosphatemia, hyperuricemia, anemia, fluid retention and heart failure, metabolic bone disease, amputation, and altered drug clearance [8–13].

Current Treatment Options for Patients with T2DM and CKD

Treatment for patients with T2DM and CKD aimed at reducing the rate of progression to ESKD is limited to management of underlying risk factors, including hypertension, dyslipidemia, and hyperglycemia, and limiting dietary protein intake [14–16]. In patients with hypertension, reducing blood pressure (BP) to <140/90 mm Hg is recommended to slow CKD progression, though a target of <130/80 mm Hg may be appropriate for some patients, and treatment with an ACE inhibitor or ARB is recommended [16]. At least annual screening of creatinine, eGFR, and UACR is recommended for patients with T2DM, and monitoring of electrolytes, eGFR, and UACR should be more frequent after a diagnosis of CKD [16].

The current treatment paradigm for managing renal outcomes in patients with T2DM and CKD is largely based on results from 2 landmark trials of ARBs: Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan Study (RENAAL) and Irbesartan Diabetic Nephropathy Trial (IDNT) [6, 7]. In RENAAL, treatment with losartan was associated with a 16% reduction in the risk of the composite outcome of doubling of serum creatinine, ESKD, or death compared with placebo in patients with T2DM and nephropathy [6]. In IDNT, treatment with irbesartan reduced the risk of a composite outcome of doubling of serum creatinine, ESKD, or death with irbesartan by 20% compared with placebo and by 23% compared with amlodipine (a calcium channel blocker) in patients with hypertension, T2DM, and proteinuria [7].

Though RAAS inhibitors can ameliorate hypertension and hyperfiltration, only 3 agents are indicated for the treatment of nephropathy in patients with diabetes (i.e., captopril for type 1 diabetes mellitus [T1DM]; losartan and irbesartan for T2DM) [17–19]. Consistent effects on ESKD endpoints are not observed across all RAAS inhibitors, and these agents are not thought to affect hyperglycemia or obesity and do not reduce the risk of CV outcomes, independent of BP control [20]. However, not all agents have been studied, and there may be differences based on dose. Furthermore, increased risk of hyperkalemia and changes in serum creatinine are viewed as safety concerns by clinicians [21]. Additionally, despite a 22% reduction in the risk of doubling of serum creatinine or renal replacement therapy, meta-analytic results suggest that as a class, RAAS inhibitors do not significantly reduce the risk of ESKD [22, 23]. However, these observations need to be tempered because not all

studies were adequately powered to examine this endpoint.

One observational study of patients with T2DM and stages 3/4 CKD showed that 84% are being treated with RAAS inhibitors and only 26% are being treated with the maximum dose [24]. Thus, either undertreatment or the inability to tolerate the maximum dose of a RAAS inhibitor may contribute to higher risk of CKD progression in people with T2DM and CKD, especially as the severity of CKD worsens [25]. In addition, even when patients are treated with the maximum dose of a RAAS inhibitor, there is still a high residual risk of progression of CKD [20]. In light of these observations, new treatments are needed that can slow CKD progression, studied in properly designed trials of patients with CKD [26].

Renal effects of sodium glucose co-transporter 2 (SGLT2) inhibitors were suggested in CV outcomes trials (CVOTs) of patients with T2DM and high CV risk [27–29]. The Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE) trial of canagliflozin has provided the first definitive evidence of renal protection with an SGLT2 inhibitor in patients with T2DM and CKD. This article reviews the evidence for the effects of SGLT2 inhibitors on renal outcomes, with a focus on the results from CREDENCE and the implications for clinical practice.

Defining Renal Endpoints in Patients with CKD

Due to variability in CKD progression, it can be challenging to measure the impact of new therapies on renal outcomes, even in high-risk populations [30]. In addition to hard renal outcomes like ESKD and renal death, surrogate endpoints like the doubling of serum creatinine (roughly equivalent to a 57% reduction in eGFR) and albuminuria have been used in clinical trials of patients with CKD. However, there may be some limitations associated with these endpoints because accumulating a reasonable number of these events requires large numbers of patients and long follow-up duration, and changes in surrogate endpoints do not always correlate with hard renal outcomes [30–35]. Additionally, albuminuria alone is not considered a surrogate endpoint because it does not predict the endpoint of interest and is subject to high levels of variance [36, 37]. Although there is ongoing work on identifying novel renal endpoints to predict progression to ESKD [38], clinically meaningful renal outcomes, such as ESKD, remain important to definitively demonstrate renal benefits in patients with T2DM and CKD [39].

Supporting Renal Evidence from Large Outcomes Trials of SGLT2 Inhibitors

The CVOTs of SGLT2 inhibitors (Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes [EMPA-REG OUTCOME] trial of empagliflozin, CANagliflozin cardioVascular Assessment Study [CANVAS] Program trials of canagliflozin, and Dapagliflozin Effect on Cardiovascular Events [DECLARE] trial of dapagliflozin) were designed to evaluate CV safety for the endpoints of nonfatal myocardial infarction, nonfatal ischemic stroke, and CV death in patients with T2DM and either prevalent CV disease or high risk for CV events. Though the populations in these studies did not have high proportions of patients with CKD (<26% of patients had eGFR <60 mL/min/1.73 m^2 and <12% of patients had UACR >300 mg/g) and were not powered for renal outcomes, positive effects on renal outcomes were demonstrated in EMPA-REG OUTCOME [28], the CANVAS Program [27], and DECLARE [29].

While participants had low renal risk, these results suggested that SGLT2 inhibitors may provide reductions in the risk of renal composite endpoints compared with placebo (Table 1). Variation in baseline renal function and the endpoints selected are likely largely responsible for the differences in renal outcomes among these CVOTs [40]. Furthermore, renal endpoints in these trials were exploratory.

The effects of dapagliflozin were also studied in the Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure (DAPA-HF) trial of patients with heart failure and reduced ejection fraction, which included those with and without diabetes. A higher proportion of patients in DAPA-HF had renal impairment (41% had eGFR <60 mL/min/1.73 m^2) compared with the CVOTs, and dapagliflozin showed a positive effect on the renal outcome of ≥50% eGFR reduction, ESKD, or renal death (hazard ratio [HR] 0.71, 95% CI 0.44–1.16) [41].

Renal Outcomes with Canagliflozin in Patients with T2DM and CKD in the CREDENCE Trial

The CREDENCE trial was the first dedicated renal outcomes trial of an SGLT2 inhibitor designed for patients with T2DM and CKD who were receiving clinically appropriate RAAS inhibition and powered for renal endpoints [42]. The CREDENCE trial, which was conceived in 2012 and enrolled its first patient in early 2014 prior to data availability from any CVOTs, provided the first efficacy and safety data for a population with T2DM and CKD that was not selected based on their CV risk.

CREDENCE enrolled patients ≥30 years of age with T2DM, glycated hemoglobin A1c (HbA1c) ≥6.5–≤10.5%,

Table 1. Renal outcomes from CVOTs of SGLT2 inhibitors [27–29, 89, 90]

	EMPA-REG OUTCOME Empagliflozin vs. placebo	CANVAS Program* Canagliflozin vs. placebo	DECLARE Dapagliflozin vs. placebo
Doubling of serum creatinine†, ESKD, or renal death	6.3 vs. 11.5 per 1,000 PY HR 0.54 ($p < 0.001$)	1.5 vs. 2.8 per 1,000 PY HR 0.53 (95% CI 0.33–0.84)	
Doubling of serum creatinine, ESKD, or renal or CV death		13.2 vs. 15.8 per 1,000 PY HR 0.82 (95% CI 0.68–0.97)	
Doubling of serum creatinine†, ESKD, renal death, or new-onset macroalbuminuria	47.8 vs. 76.0 per 1,000 PY HR 0.61 ($p < 0.001$)	15.1 vs. 27.4 per 1,000 PY HR 0.58 (95% CI 0.50–0.67)	
Doubling of serum creatinine†, ESKD, renal death, new-onset macroalbuminuria, or CV death	60.7 vs. 95.9 per 1,000 PY HR 0.61 ($p < 0.001$)		
40% eGFR reduction‡, ESKD, or renal death		5.5 vs. 9.0 per 1,000 PY HR 0.60 (95% CI 0.47–0.77)	3.7 vs. 7.0 per 1,000 PY HR 0.53 (95% CI 0.43–0.66)
40% eGFR reduction‡, renal death, ESKD, or renal or CV death		16.9 vs. 21.6 per 1,000 PY HR 0.77 (95% CI 0.66–0.89)	10.8 vs. 14.1 per 1,000 PY HR 0.76 (95% CI 0.67–0.87)
40% eGFR reduction, ESKD, renal death or development of macroalbuminuria		18.6 vs. 33.3 per 1,000 PY HR 0.57 (95% CI 0.50–0.66)	
Doubling of serum creatinine†	5.5 vs. 9.7 per 1,000 PY HR 0.56 ($p < 0.001$)	1.2 vs. 2.4 per 1,000 PY HR 0.50 (95% CI 0.30–0.84)	
40% eGFR reduction		5.3 vs. 8.7 per 1,000 PY HR 0.60 (95% CI 0.47–0.78)	
ESKD	1.0 vs. 2.1 per 1,000 PY HR 0.45 ($p = 0.04$)	0.4 vs. 0.6 per 1,000 PY HR 0.77 (95% CI 0.30–1.97)	
ESKD or renal death		0.4 vs. 0.8 per 1,000 PY HR 0.56 (95% CI 0.23–1.32)	
New-onset albuminuria	252.5 vs. 266.0 per 1,000 PY HR 0.95 (ns)	100.4 vs. 130.8 per 1,000 PY HR 0.80 (95% CI 0.73–0.88)	
New-onset microalbuminuria		96.7 vs. 127.3 per 1,000 PY HR 0.80 (95% CI 0.73–0.87)	
New-onset macroalbuminuria§	41.8 vs. 64.9 per 1,000 PY HR 0.62 ($p < 0.001$)	15.1 vs. 27.6 per 1,000 PY HR 0.58 (95% CI 0.50–0.68)	
Progression of albuminuria		89.4 vs. 128.7 per 1,000 PY HR 0.73 (95% CI 0.67–0.79)	

* While prespecified, the renal outcomes reported for the CANVAS Program are outside the formal hypothesis testing sequence; therefore, no *p* values are reported.

† With eGFR ≤45 mL/min/1.73 m^2 in EMPA-REG OUTCOME.

‡ With eGFR <60 mL/min/1.73 m^2 in DECLARE.

§ UACR >300 mg/g with a UACR in EMPA-REG OUTCOME.

CVOT, cardiovascular outcomes trial; SGLT2, sodium glucose co-transporter 2; EMPA-REG OUTCOME, Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes; CANVAS, CANagliflozin cardioVascular Assessment Study; DECLARE, Dapagliflozin Effect on Cardiovascular Events; ESKD, end-stage kidney disease; PY, patient-years; HR, hazard ratio; CV, cardiovascular; eGFR, estimated glomerular filtration rate; ns, not significant; UACR, urinary albumin-creatinine ratio.

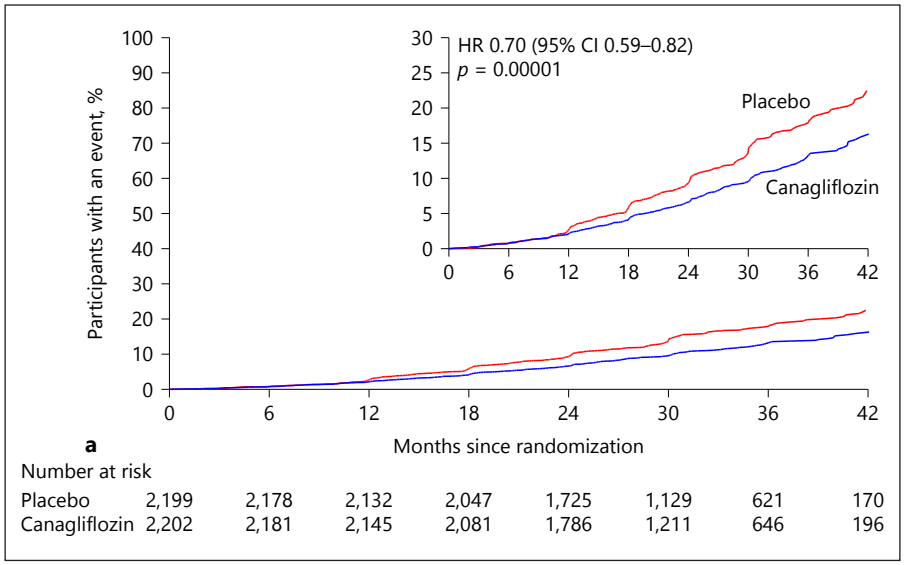

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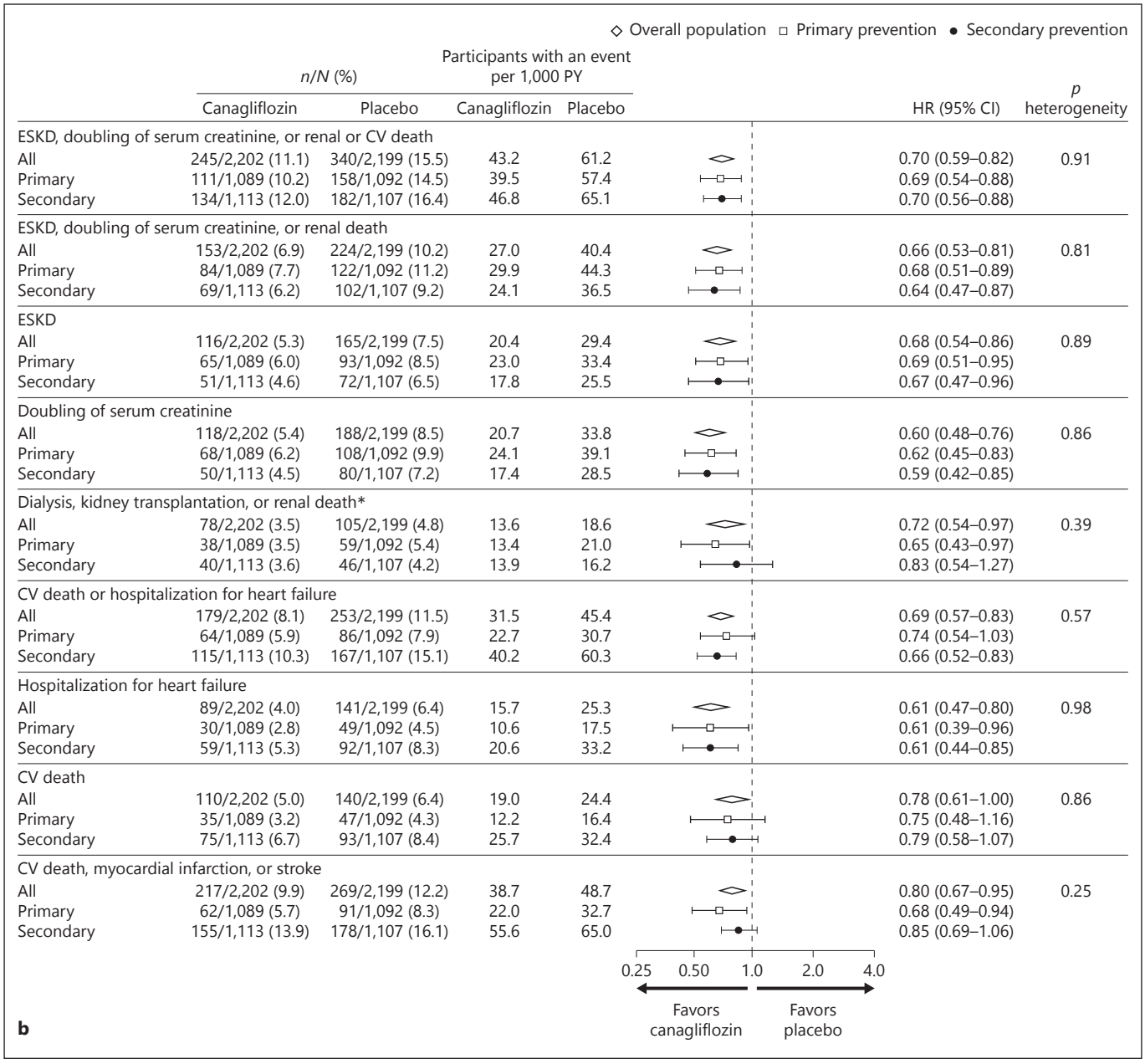
Fig. 1. Effects of canagliflozin on (**a**) the primary composite outcome of ESKD, doubling of serum creatinine, or renal or CV death in the overall CREDENCE population [43], (**b**) renal, CV, and mortality outcomes in primary and secondary prevention cohorts [44], and (**c**) renal, CV, and mortality outcomes in subgroups defined by screening eGFR [45]. **a** From Perkovic et al. [43]. Copyright © 2019 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society. **b** Reprinted with permission from Mahaffey et al. [44]. * Exploratory outcome. ESKD, end-stage kidney disease; CV, cardiovascular; CREDENCE, Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation; eGFR, estimated glomerular filtration rate; HR, hazard ratio; PY, patient-years.

(Figure continued on next pages.)

and CKD (defined as eGFR 30–<90 mL/min/1.73 m^2 and albuminuria [UACR >300–5,000 mg/g]) [43]. Patients were required to be on an ACE inhibitor or ARB for ≥4 weeks prior to randomization at either the maximum labeled or tolerated dose. A total of 4,401 patients were randomized to canagliflozin 100 mg or placebo. At baseline, patients had a mean age of 63 years, HbA1c of 8.3%, eGFR of 56.2 mL/min/1.73 m^2, and median UACR of 927.0 mg/g. About half (50.4%) of patients had a history of CV disease and 14.8% had a history of heart failure.

The primary outcome of CREDENCE was the composite of doubling of serum creatinine, ESKD (requirement for renal replacement therapy in the form of chronic dialysis or transplantation or sustained eGFR <15 mL/min/1.73 m^2), and renal or CV death. Canagliflozin treatment was associated with a 30% lower relative risk of the primary outcome compared with placebo (HR 0.70, 95% CI 0.59–0.82; $p = 0.00001$; Fig. 1a), with all components of the composite contributing to the outcome [43]. Consistent effects on the primary outcome were observed across prespecified subgroups including by screening eGFR (30–<45, 45–<60, and 60–<90 mL/min/1.73 m^2) and baseline UACR (≤1,000 or >1,000 mg/g) at baseline, independent of effects on HbA1c. In exploratory analyses of the components of the primary outcome, canagliflozin treatment was associated with a 32% reduction in ESKD (HR 0.68, 95% CI 0.54–0.86; $p = 0.002$) and a reduction in dialysis, kidney transplantation, or renal death (HR 0.72, 95% CI 0.54–0.97). Canagliflozin reduced the risk of the secondary renal composite outcome of doubling of serum creatinine, ESKD, or renal death (HR 0.66, 95% CI 0.53–0.81; $p < 0.001$; Fig. 1b) [43]. In addition to the effects on renal outcomes, canagliflozin was also associated with reductions in the CV composite outcomes of CV death or hospitalization for heart failure (HR 0.69, 95% CI 0.57–0.83; $p < 0.001$); CV death, myocardial infarction, or stroke (HR 0.80, 95% CI 0.67–0.95; $p = 0.01$); and hospitalization for heart failure (HR 0.61, 95% CI 0.47–0.80; $p < 0.001$; Fig. 1b) [43]. In the overall population, the number needed to treat for 2.5 years to prevent 1 event was 22 for the primary composite outcome; 28 for the ESKD, doubling of serum creatinine, or renal death; 43 for ESKD; 46 for hospitalization for heart failure; 29 for CV death or hospitalization for heart failure; and 40 for CV death, nonfatal myocardial infarction, and nonfatal stroke [43, 44]. The effects of canagliflozin on renal and CV outcomes, including the primary renal outcome and the composite of CV death, myocardial infarction, or stroke, were consistent in subgroups of participants with and without prior CV disease (Fig. 1b); canagliflozin was the first treatment to show a benefit for the composite of nonfatal myocardial infarction, nonfatal stroke, or CV death in primary prevention patients with T2DM and CKD [44]. The effects of canagliflozin on renal and CV outcomes were also consistent in subgroups by screening eGFR (30–<45, 45–<60, and 60–<90 mL/min/1.73 m^2; all p for heterogeneity ≥0.11; Fig. 1c) [45]. Although CREDENCE participants had eGFR 30–<90 mL/min/1.73 m^2 at screening, 174 patients had eGFR <30 mL/min/1.73 m^2 at baseline; the effects of canagliflozin on renal and mortality outcomes in these participants were consistent with the overall population [46].



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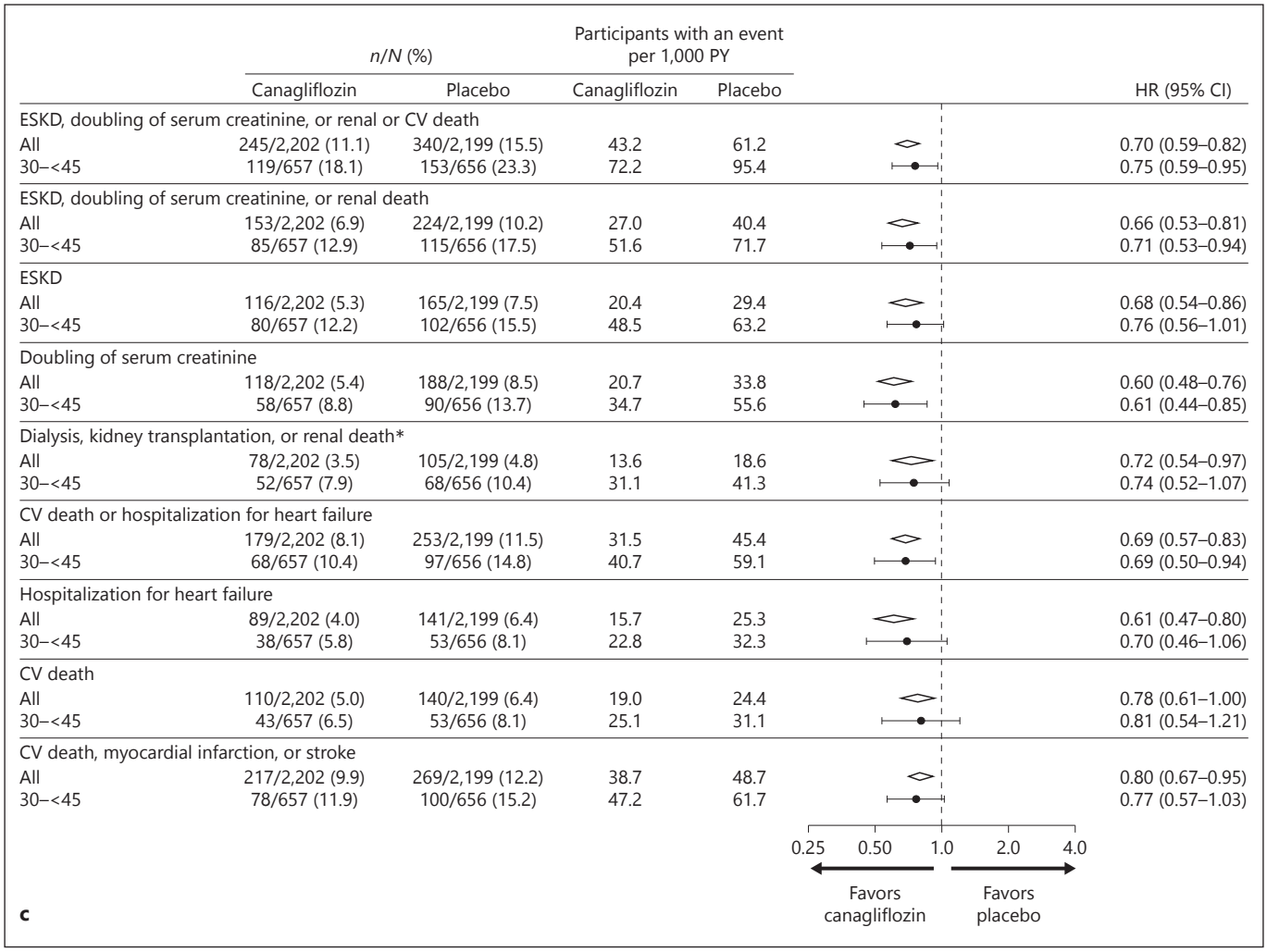
As expected, due to the acute hemodynamic effects of SGLT2 inhibition, there was a greater reduction in eGFR with canagliflozin than placebo over the first 3 weeks of treatment (between-group difference, –3.17 mL/min/1.73 m^2; Fig. 2) [43]. However, after the first 3 weeks, patients treated with canagliflozin had an approximately 60% slower annual rate of eGFR decline than with placebo (–1.85 vs. –4.59 mL/min/1.73 m^2, respectively; between-group difference, 2.74 mL/min/1.73 m^2), suggesting that canagliflozin changes renal hemodynamics [43]. Off-treatment effects on eGFR were not tested in CREDENCE, but reversible acute effects of SGLT2 inhibitors on eGFR were demonstrated in EMPA-REG OUTCOME and CANVAS-R [27, 28].

Patients with later stages of CKD and T2DM have fragile health and are at high risk of renal and nonrenal complications [47], so higher rates of adverse events would be expected in CREDENCE compared with other clinical trials of SGLT2 inhibitors. The safety profile of canagliflozin in CREDENCE was generally similar to previous studies of canagliflozin. Overall, there were fewer adverse events (HR 0.87, 95% CI 0.82–0.93) and serious adverse events (HR 0.87, 95% CI 0.79–0.97) with canagliflozin



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versus placebo [43]. The risk of renal-related adverse events was lower with canagliflozin versus placebo (HR 0.71, 95% CI 0.61–0.82) and there was no difference in the risk of acute kidney injury (HR 0.85, 95% CI 0.64–1.13). The risk of diabetic ketoacidosis was low in both groups, but higher with canagliflozin than placebo (2.2 vs. 0.2 events per 1,000 patient-years, respectively; HR 10.80, 95% CI 1.39–83.65); 11 of the 12 participants with diabetic ketoacidosis events were on insulin [43]. Consistent with previous studies, including the CANVAS Program, an increased risk of genital mycotic infections was seen with canagliflozin compared with placebo (males: HR 9.30, 95% CI 2.83–30.60; females: HR 2.10, 95% CI 1.00–4.45). There were no differences in risks of hyperkalemia, hypoglycemia, osmotic diuresis, or volume depletion events with canagliflozin versus placebo.

Increased risk of amputation and fracture were identified as safety signals in the CANVAS Program CVOT of canagliflozin [27]. The separation in amputation event rates between canagliflozin and placebo became apparent at ~6 months after randomization, but no specific cause, mechanism, or at-risk subgroup for increased amputation risk has been identified despite extensive post hoc analyses [48]. When the increased risk of amputation was identified in the CANVAS Program, a protocol amendment was introduced in CREDENCE that asked investigators to examine patients' feet at each trial visit, in accordance with good clinical practice, and to temporarily interrupt the assigned treatment in patients with any active condition that might lead to amputation [43]. CREDENCE participants had a higher baseline risk and rate of amputation than those in the CANVAS Program (5.3 vs. 2.3% with prior amputation at baseline, respectively) [27, 43]. Consistent with the higher risk of amputation at baseline, placebo-treated participants had higher rates of amputation in CREDENCE than the CANVAS

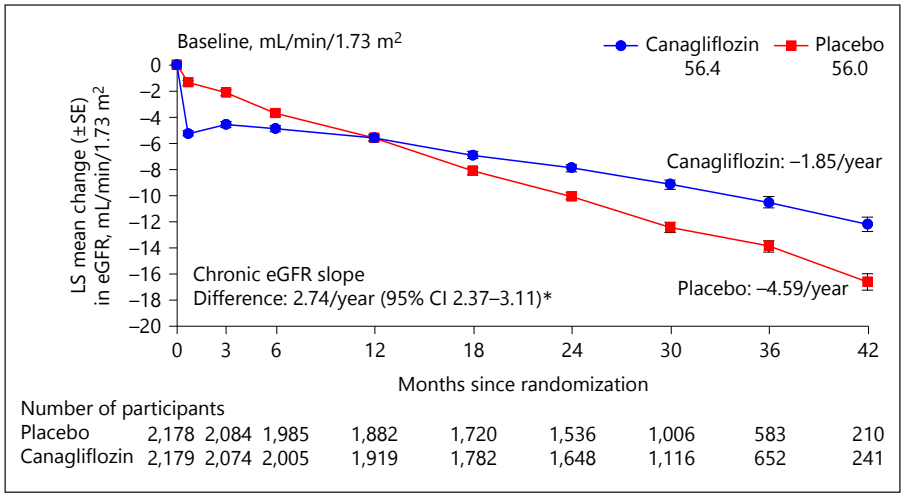

Fig. 2. Effects on eGFR in CREDENCE. Reprinted with permission from Perkovic et al. [43]. * Sixty percent reduction in the rate of eGFR decline with canagliflozin. eGFR, estimated glomerular filtration rate; CREDENCE, Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation; LS, least squares.

Program (11.2 and 3.4 events per 1,000 patient-years, respectively) [27, 43]. However, no difference in the risk of amputation was observed comparing canagliflozin- to placebo-treated patients in CREDENCE (12.3 vs. 11.2 events per 1,000 patient-years, respectively; HR 1.11, 95% CI 0.79–1.56) over a mean follow-up time of 2.6 years [27, 43]. In the CANVAS Program, an increased risk of fracture was seen in the CANVAS study, but not in CANVAS-R [27]. There was no difference in the risk of adjudicated fracture with canagliflozin versus placebo (11.8 vs. 12.1 events per 1,000 patient-years, respectively; HR 0.98, 95% CI 0.70–1.37) [43], consistent with all but 1 trial of canagliflozin (the CANVAS study). Despite extensive post hoc analyses, no specific cause to explain this discrepancy has been identified, though an unidentified fall-related mechanism remains a possibility [49].

Clinical Perspective

The lack of new treatments for and increased prevalence of CKD over the last 2 decades has presented a challenge for both patients and physicians. The emergence of positive renal results from CREDENCE suggests that canagliflozin may have the therapeutic potential to substantially improve outcomes for people with T2DM and CKD on top of standard-of-care treatment with an ACE inhibitor or ARB. In real-world clinical practice, 5% of patients with T2DM would meet eligibility criteria for CREDENCE (~2 million US adults; Fig. 3) [50, 51]. Although CVOTs provided some evidence of external validity in terms of renoprotection with SGLT2 inhibitors, CVOT participants had substantially better renal function than those in CREDENCE (Fig. 3); therefore, dedicated trials examining the risk of renal failure and death in patients with T2DM and CKD were needed to provide definitive evidence for the effects of SGLT2 inhibitors on renal outcomes and safety [40].

CREDENCE demonstrated that in patients with T2DM and CKD, treatment with canagliflozin significantly reduced the risk of doubling of serum creatinine, ESKD, or renal or CV death compared with placebo. Canagliflozin also reduced the risk of ESKD alone and CV endpoints, including the composite of CV death, myocardial infarction, or stroke and hospitalization for heart failure, suggesting that canagliflozin may provide both renal and CV protection for patients with T2DM and CKD, with and without prior atherosclerotic CV disease. As a result, the FDA has recently approved canagliflozin for reducing the risk of ESKD, doubling of serum creatinine, CV death, and hospitalization for heart failure in adults with T2DM and diabetic nephropathy with albuminuria [52].

CREDENCE provided the first-ever safety data of an SGLT2 inhibitor in patients with T2DM and CKD. Reassuringly, the overall safety profile of canagliflozin in CREDENCE was consistent with known adverse events, with no increased risk of hypoglycemia or acute kidney injury. Unlike the CANVAS Program, there were no imbalances between canagliflozin and placebo for amputation or fracture, indicating that although this population has a higher baseline risk of these outcomes, these are not safety concerns with canagliflozin for the population studied in CREDENCE when used in the manner studied – namely, good clinical practice with respect to diabetic foot care and peripheral artery disease including exclusion of patients with a history of traumatic amputa-

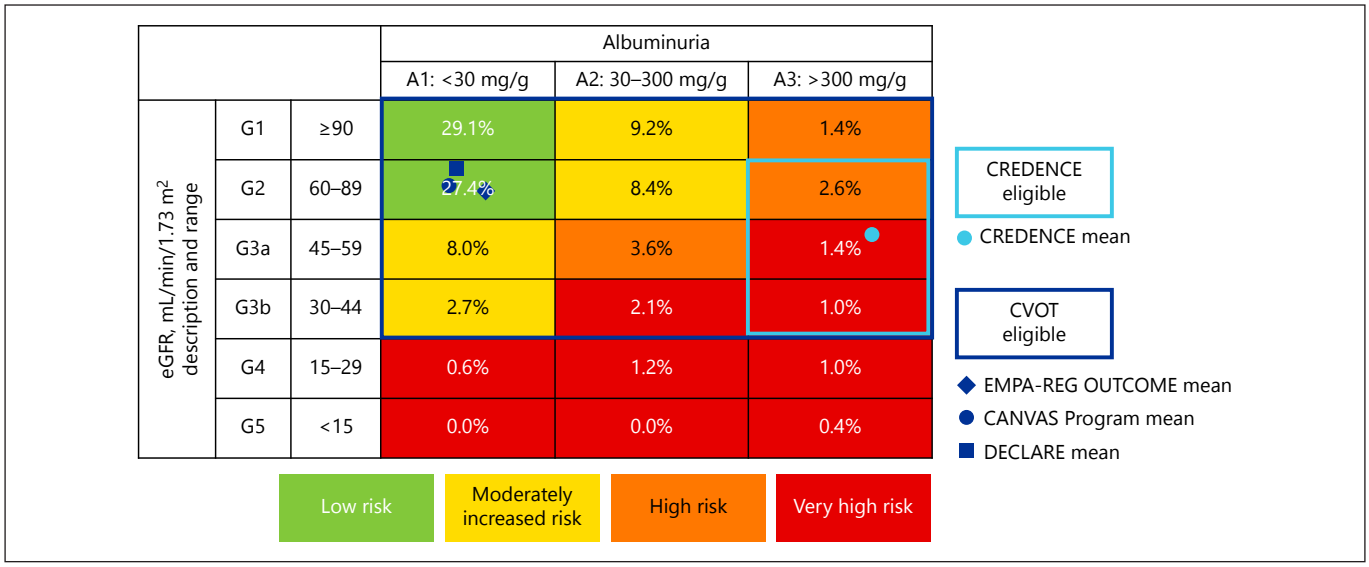

Fig. 3. Proportion of patients with T2DM and CREDENCE and CVOT eligibility by Kidney Disease: Improving Global Outcomes risk score. Proportion of patients with T2DM in each eGFR and UACR category based on US EHR data from Bailey et al. [50]. Position of mean eGFR and albuminuria shown for each trial are estimates. T2DM, type 2 diabetes mellitus; CREDENCE, Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation; CVOT, cardiovascular outcomes trial; eGFR, estimated glomerular filtration rate; UACR, urinary albumin-creatinine ratio; EMPA-REG OUTCOME, Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes; CANVAS, CANagliflozin cardioVascular Assessment Study; DECLARE, Dapagliflozin Effect in Cardiovascular Events.

tion within 12 months, or an active foot ulcer, osteomyelitis, gangrene, or critical ischemia of the lower extremity within 6 months and interruption of therapy upon the emergence of any of the above with careful consideration of the individual risks and benefits prior to restarting canagliflozin after resolution of the event. Additionally, unlike studies of RAAS inhibitors, no increase in the risk of hyperkalemia was seen in CREDENCE, even on top of maximum-tolerated ACE inhibitor or ARB therapy.

However, there are some limitations associated with the study. Although CREDENCE was stopped early for efficacy at a planned interim analysis for the primary endpoint, the resulting follow-up time was relatively short (median of 2.6 years), which may have limited the power for some secondary outcomes and increased the risk of overestimating effect size [43].

The interest in the effects of antihyperglycemic agents in patients with CKD has led to plans for studies with other agents in people with and without T2DM [53–55]. The ongoing DAPA-CKD and EMPA-KIDNEY studies of dapagliflozin and empagliflozin will provide additional data on the potential for SGLT2 inhibitors to slow the progression of CKD in people with CKD with or without T2DM, and other studies will provide data on the effects of empagliflozin on hyperfiltration in patients with T1DM [53, 54, 56]. Future studies could investigate whether therapy with canagliflozin and other agents, such as nonsteroidal mineralocorticoid receptor agonists, which are currently in development, could have synergistic effects in the kidney and heart [57].

Several mechanisms may contribute to the renal protective effects seen with canagliflozin, including reductions in HbA1c, body weight, BP, and albuminuria [58–63]. The effects of SGLT2 inhibitors on BP and body weight are independent of urinary glucose excretion [64–66]. However, data from CREDENCE suggest that the effects of canagliflozin on renal outcomes may be independent of effects on blood glucose, particularly because renoprotection is seen in patients with low eGFR levels who have negligible glucosuria [45, 67]. In addition, SGLT2 inhibitors have negligible long-term effects on serum potassium and an acute effect on serum creatinine that provides stable long-term benefits [58, 68]. Furthermore, SGLT2 inhibition may confer renal protection via renal hemodynamic changes, such as attenuation of renal hyperfiltration and normalization of tubuloglomerular feedback by blocking sodium reabsorption at renal proximal tubules, thereby increasing sodium delivery to the macula densa [62, 69–72]. In response, there is increased afferent arteriole tone, decreased glomerular hyperfiltration, and normalization of

intraglomerular pressure [62, 70–72]. The renal hemodynamic hypothesis is further supported by results of a study of empagliflozin in patients with T1DM [69] and by animal studies of empagliflozin and dapagliflozin [73, 74]. Global hemodynamic effects of SGLT2 inhibitors on interstitial fluid may also contribute to renoprotection. SGLT2 inhibition reduces interstitial fluid with minimal impact on blood volume and perfusion [75, 76]. Another hypothesis has suggested that SGLT1 senses increased glucose in the macula densa, which increases production of nitric oxide, thereby blunting tubuloglomerular feedback and promoting glomerular hyperfiltration [77]. Additional putative renoprotective mechanisms have been postulated or proposed, which include reduction of albuminuria; reduction of glucose-mediated inflammation, proliferation, and fibrosis; proximal tubule hypertrophy; reduction of oxidative stress; and competitive inhibition of the family of sodium-hydrogen exchanger (NHE) channels in target organs including the heart and kidneys [73, 74, 78–80]. In addition, reductions in interstitial fluid and normalization of endothelial dysfunction may provide renal and CV protection [66, 75, 76, 81].

SGLT2 inhibitors may also contribute to renal protection through their effects on CV disease, including increases in lipolysis and ketogenesis, which change cellular energetics; increases in natriuresis and osmotic diuresis, which reduce pressure and volume overload; and off-target inhibition of the NHE family of channels which are responsible for rapid restoration of intracellular pH [40, 82–84]; and through favorable effects via NHE1 inhibition in ischemia-reperfusion [85]. In the kidney, SGLT2 inhibition may also inhibit NHE3 in the proximal tubule, with implications on natriuretic, GFR, and BP effects [86]. Another interesting mechanistic hypothesis is that the ketonemia among those treated with SGLT2 inhibitors may influence the relative utilization of glucose and fatty acids in cellular respiration that could be partially responsible for the observed CV and renal effects [87]. Details of these potential mechanisms are beyond the scope of this review.

SGLT2 inhibition may provide a more "user friendly" approach to kidney protection compared with RAAS inhibitors because there is less of a change in eGFR and limited to no effect on serum potassium. Thus, clinicians may be more likely to use these drugs, specifically in people with reduced kidney function. Based on data from CREDENCE, the American Diabetes Association guidelines were updated in June 2019 to suggest consideration of use of an SGLT2 inhibitor in patients with T2DM and CKD with eGFR ≥30 mL/min/1.73 m^2 and particularly those with >300 mg/g albuminuria to reduce the risk of CKD progression, CV events, or both [16]. Treatment guidelines in Europe were recently updated to recommend SGLT2 inhibitors as first-line therapy in patients with T2DM who are at high risk of heart failure and for the prevention and management of CKD in patients who are at a high associated risk of CV disease [88]. In September 2019, the US prescribing information for canagliflozin was updated to allow initiation in people with eGFR ≥30 mL/min/1.73 m^2 and continuation of treatment in those already on canagliflozin who reach eGFR <30 mL/min/1.73 m^2 and albuminuria >300 mg/day until initiation of dialysis or kidney transplantation [52]. These changes should work to broaden the population eligible for treatment to reduce the progression of CKD.

In conclusion, the CREDENCE trial provided evidence that patients with T2DM and CKD treated with canagliflozin have a lower risk of kidney failure and CV events compared with placebo with an acceptable safety profile. Data from additional dedicated outcomes trials in patients with CKD will be important to confirm whether renal benefits are a class effect of SGLT2 inhibitors and whether benefits may extend to patients with CKD without diabetes to build further evidence on the renal efficacy and safety of this class of drugs.

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Statement of Ethics

This review article does not contain new data from studies performed by the authors.

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