REVIEW

Canagliflozin for the Treatment of Diabetic Kidney Disease and Implications for Clinical Practice: A Narrative Review

Davida Kruger · Virginia Valentine

ABSTRACT

Type 2 diabetes mellitus (T2DM) affects millions of people worldwide, elevating their risk of developing a range of complications, including chronic kidney disease (CKD). People with T2DM and CKD (i.e., diabetic kidney disease, DKD) have an increased risk of progressing to end-stage kidney disease (ESKD), experiencing cardiovascular complications, and premature death. Despite this, DKD is primarily addressed through management of risk factors, and there are few pharmaceutical treatments capable of reversing or delaying disease progression. Canagliflozin is a sodium glucose co-transporter 2 inhibitor that was initially developed as a blood glucose–lowering agent for people with T2DM. Evidence from clinical trials of canagliflozin in people with T2DM, as well as evidence from cardiovascular outcomes trials in people with T2DM and high cardiovascular risk, provided preliminary evidence suggesting that it may also have beneficial renal effects. The Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE) trial was a dedicated renal outcomes trial of canagliflozin that assessed its renal effects in people with DKD. Overall, the CREDENCE trial demonstrated that canagliflozin improves renal outcomes and slows early disease progression in people with DKD. These data supported the approval of canagliflozin for the treatment DKD, the first new treatment in almost 20 years; therefore, it is important for clinicians to understand how to implement this treatment in their clinical practice.

Keywords: Canagliflozin; Cardiovascular disease; Diabetic kidney disease; Randomized trials; Sodium glucose co-transporter 2 inhibitor; Type 2 diabetes

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Key Summary Points

People with type 2 diabetes have a high risk of developing diabetic kidney disease (DKD), which is the leading cause of end-stage kidney disease

There are few pharmaceutical treatments capable of reversing or delaying the progression of DKD

The Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE) trial was a dedicated renal outcomes trial of the sodium glucose co-transporter 2 inhibitor canagliflozin in people with DKD

Results from CREDENCE demonstrated that canagliflozin improves renal outcomes and slows early disease progression in people with DKD

This article reviews the key results from CREDENCE, along with context and guidance for clinicians on how to implement canagliflozin treatment in their clinical practice

DIABETIC KIDNEY DISEASE: BURDEN AND TREATMENT

More than 34 million Americans have diabetes, and over 90% have type 2 diabetes mellitus (T2DM) [1, 2]. People with T2DM are at high risk of developing microvascular and macrovascular complications such as chronic kidney disease (CKD), which affects approximately 40% of people with T2DM and is the leading cause of end-stage kidney disease (ESKD) globally and in the USA [3–7]. CKD represents a variety of kidney-related diseases that are not necessarily related to T2DM; however, kidney disease that is pathologically related to T2DM can be classified as diabetic kidney disease (DKD). Clinically, DKD is identified by persistent urinary albumin to creatinine ratio

(UACR) $\geq$ 30 mg/g and/or sustained estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m^2 [8]. People diagnosed with DKD will experience continued reductions in eGFR, increased albuminuria, and glomerular hyperfiltration, all of which increase their cardiovascular risk [9–13]. DKD increases the rate of 10-year cumulative all-cause mortality in people with T2DM by almost 20%, with the majority of this residual risk attributed to death from cardiovascular complications [8, 14]. Heart failure is the most common cardiovascular complication among people with DKD, and the risk of developing heart failure is 2.5 times higher for people with T2DM compared to non-diabetic individuals, with this risk increasing with decreasing eGFR [15]. Osteoporosis, fracture, retinopathy, neuropathy, and amputation are also complications commonly seen in people with DKD [16–20].

Despite the risks associated with DKD, awareness of kidney disease is low among people with T2DM, particularly at early stages when the disease is generally asymptomatic; just 40–50% of people with stage 4 or 5 CKD are aware of their condition (Fig. 1) [21, 22]. The prevalence and major life-threatening risks associated with CKD make this condition costly for the health care system. In 2016, approximately 20% of overall Medicare expenditures were attributed to CKD (excluding ESKD), and more than 40% of Medicare spending in people with diabetes was allocated to the management of CKD [23]. The substantial impact of kidney disease led the US Department of Health and Human Services to announce its Advancing American Kidney Health initiative, which has a goal of reducing the number of Americans developing ESKD by 25% by 2020 [24].

Currently, the recommended approach to slow the progression of DKD is management of underlying risk factors, including hypertension, hypoxemia, hyperglycemia, albuminuria, and increased adiposity, along with refraining from smoking and following a low-protein diet [9, 25–28]. Beyond this, people have few treatment options, and little progress has been made in this area over the past two decades, which has left a substantial proportion of people with DKD at high risk for progression to renal failure,
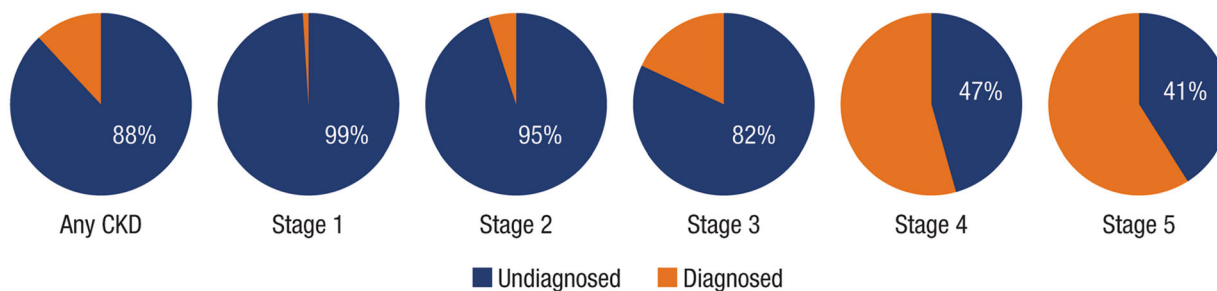
Fig. 1 Prevalence and awareness of CKD in adults with T2DM [11]. CKD chronic kidney disease, T2DM type 2 diabetes mellitus

cardiovascular morbidity, and cardiovascular mortality.

Renin–angiotensin–aldosterone system (RAAS) inhibitors, such as angiotensin-converting enzyme (ACE) inhibitors and/or angiotensin receptor blockers (ARBs), are recommended for the management of hypertension and heart failure [29–31]. Evidence from clinical trials in people with T2DM suggested that RAAS inhibitors may provide renal benefits in this population; however, only two ARBs (losartan and irbesartan) and no ACE inhibitors are approved for the prevention of kidney function decline in people with T2DM and albuminuria (> 300 mg/g) [29, 30, 32–35]. Additionally, RAAS inhibitors have been associated with safety risks such as hyperkalemia and acute kidney injury [9, 26]. Considering the current state of treatment for DKD, new medications capable of preventing or delaying the progression of this disease are needed.

Recent studies have investigated the potential renal benefits associated with sodium glucose co-transporter 2 (SGLT2) inhibitors, which were first developed and approved for the management of hyperglycemia in people with T2DM [36–38]. Unlike other classes of antihyperglycemic agents (AHAs), SGLT2 inhibitors work independently of insulin by lowering the renal threshold for glucose excretion (RT_G) in people with T2DM, thereby increasing urinary glucose excretion (UGE) and leading to a mild osmotic diuresis and a net caloric loss that contribute to improvements in glycemic control, weight loss, and blood pressure reduction [39, 40]. SGLT2 inhibition has also been associated with renal hemodynamic changes, such

as attenuation of renal hyperfiltration and normalization of tubuloglomerular feedback, which may contribute to renal benefits (Fig. 2) [41].

Evidence from cardiovascular outcome trials (CVOTs) of SGLT2 inhibitors in people with T2DM and established cardiovascular disease or cardiovascular risk provided evidence suggesting that this class may also have beneficial renal effects [42–44]. However, the patient populations enrolled in the CVOTs were generally at low renal risk, with eGFR ranging from 60 to < 90 mL/min/1.73 m^2 and UACR < 30 mg/g. In addition, the number of events accumulated was not enough to definitively establish the effects on renal outcomes [43]. For example, in the CANagliflozin cardioVascular Assessment Study (CANVAS) Program, which was the CVOT for the SGLT2 inhibitor canagliflozin, participants had mean eGFR of 76.5 mL/min/1.73 m^2, median UACR of 12.3 mg/g, and 80.0% were receiving a RAAS inhibitor [43]. CVOTs for other SGLT2 inhibitors, including EMPA-REG OUTCOME (empagliflozin) and DECLARE-TIMI 58 (dapagliflozin), recruited a similar population with low renal risk. As a result of this population profile, the number of renal outcomes accumulated in these trials was too low to definitively determine the impact of SGLT2 inhibitors on renal outcomes; there were only 69 confirmed renal replacement therapy or renal death events across the three studies, which included more than 34,000 participants [42–44]. Additionally, these studies were not designed to specifically assess the impact of intervention on renal endpoints, so all renal studies were based on secondary, exploratory,
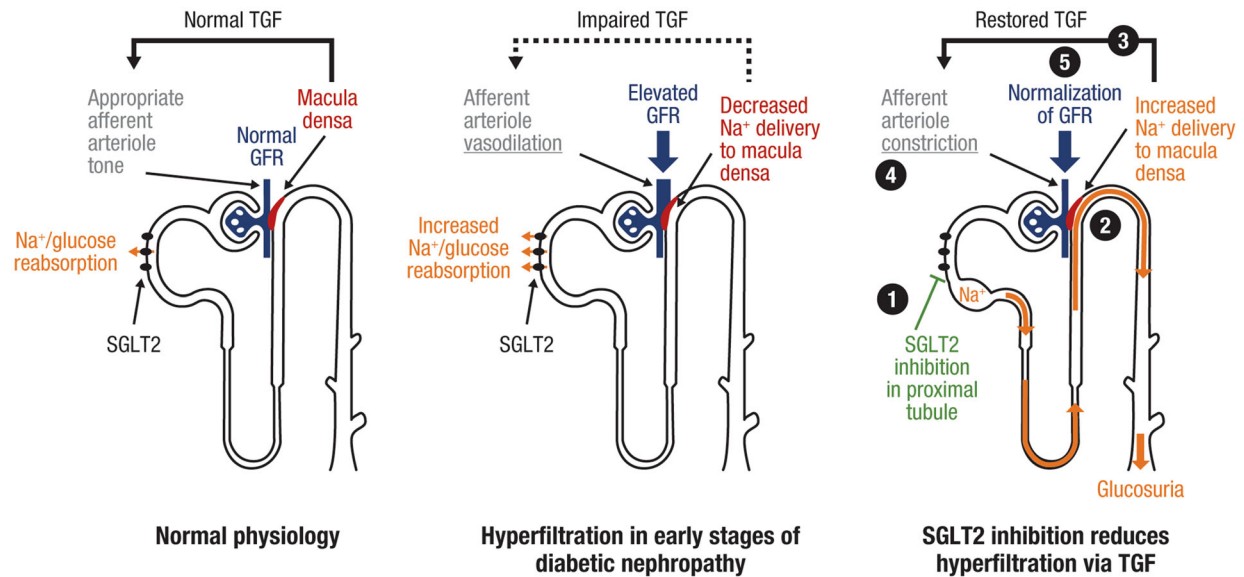
Fig. 2 Tubuloglomerular feedback mechanisms encountered under normal physiology, in the early stages of diabetic nephropathy, and after SGLT2 inhibition [41]. SGLT2 sodium glucose co-transporter 2, TGF tubuloglomerular feedback, GFR glomerular filtration rate. Reproduced with permission from Cherney et al. [41]

or post hoc analyses. Thus, dedicated trials of SGLT2 inhibitors in people with DKD were necessary to assess the renal benefits afforded through treatment of this population with this class of medications. This article describes the dedicated renal outcomes trial, Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE), which was the first study to demonstrate the renal effects of canagliflozin in people with T2DM and compromised kidney function (i.e., DKD) [45].

COMPLIANCE WITH ETHICS GUIDELINES

This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

CREDENCE STUDY DESIGN

CREDENCE was an event-driven trial designed to formally test whether canagliflozin lowers the risk of kidney failure and cardiovascular outcomes in people with T2DM and established diabetic nephropathy [45, 46]. The CREDENCE trial was initiated in 2014 before the conclusion of the CVOTs and its initiation was motivated by renal data measured in phase 3 studies of canagliflozin [45]. The study population included adults at least 30 years of age with T2DM (HbA1c $\geq$ 6.5% and $\leq$ 12.0%), eGFR $\geq$ 30 and < 90 mL/min/1.73 m^2, and UACR > 300 and $\leq$ 5000 mg/g [45, 46]. People were also required to be receiving a maximally tolerated dose of an ACE inhibitor or ARB for at least 4 weeks prior to randomization [45, 46]. The CREDENCE trial was stopped 2 years early on the advice of an independent data monitoring committee on the basis of the efficacy and safety findings observed in an interim analysis conducted in July 2018 after a planned 405 primary endpoint events had occurred [46].

The primary endpoint of the CREDENCE trial was the composite of ESKD (defined as the need for chronic dialysis for 30 days or more, kidney transplantation, or eGFR < 15 mL/min/1.73 m^2 sustained for at least 30 days by central laboratory assessment), doubling of serum

creatinine, or renal or cardiovascular death [45, 46]. Secondary endpoints were tested according to a prespecified hierarchical testing sequence as follows: cardiovascular death or hospitalization for heart failure; cardiovascular death, myocardial infarction, or stroke (i.e., 3-point major adverse cardiovascular event, MACE); hospitalization for heart failure; the composite of ESKD, doubling of serum creatinine, or renal death; cardiovascular death; all-cause mortality; and the composite of cardiovascular death, myocardial infarction, stroke, hospitalization for heart failure, or hospitalization for unstable angina [45, 46]. All renal and cardiovascular endpoints that were part of planned primary and secondary composite endpoints were adjudicated by a blinded end-point adjudication committee [45, 46]. Other outcomes of interest included the effects on intermediate outcomes, including eGFR, UACR, HbA1c, and blood pressure.

## EFFICACY OUTCOMES WITH CANAGLIFLOZIN IN CREDENCE

A total of 4401 people were enrolled in the CREDENCE trial and randomized (1:1) to canagliflozin 100 mg or placebo. Participants had a mean age of 63 years, HbA1c of 8.3%, body mass index of 31.3 kg/m^2, and had T2DM for an average duration of 16 years. Most CREDENCE trial participants were male (66%) and white (67%) [46]. In addition, 60% of people had eGFR < 60 mL/min/1.73 m^2 at baseline. Overall, participants had a mean eGFR of 56.2 mL/min/1.73 m^2, a median UACR of 927 mg/g, and 99.9% were taking a maximally tolerated dose of a RAAS inhibitor.

Canagliflozin treatment was associated with a 30% relative risk reduction of the primary composite outcome of ESKD, doubling of serum creatinine, or renal or cardiovascular death compared with placebo (hazard ratio [HR], 0.70; 95% confidence interval [CI] 0.59–0.82; $P = 0.00001$; Fig. 3) [46]. Consistent effects were seen for the components of the primary composite endpoint, as well as the secondary renal, cardiovascular, and mortality endpoints (Fig. 4).

The effects of canagliflozin on reducing the risk of the primary outcome were observed consistently across participant subgroups, including those defined by history of cardiovascular disease, screening eGFR, race, ethnicity, and baseline HbA1c; effects were also generally similar across subgroups for other renal, cardiovascular, and mortality outcomes [47–50]. Of note, canagliflozin was the first AHA to demonstrate renal and cardiovascular benefits in a population without cardiovascular disease history [50]. The renal and cardiovascular effects of canagliflozin were also consistent across eGFR subgroups, including in participants with screening eGFR of 30 to < 45 mL/min/1.73 m^2 [48, 51]. A post hoc analysis in participants with baseline eGFR < 30 mL/min/1.73 m^2 ($n = 174$) also demonstrated consistent effects of canagliflozin on renal, cardiovascular, and mortality outcomes as those seen in the overall population, with no differences in the risk of renal-related adverse events or other safety outcomes compared to the overall population [46, 48].

As seen in previous studies, canagliflozin treatment was associated with an acute drop in eGFR from baseline to week 3 (Fig. 5) [46]. This initial decline in eGFR was seen rapidly and attenuated over time [52]. After this initial drop, the rate of eGFR decline was reduced by approximately 60% with canagliflozin compared to placebo, suggesting that canagliflozin treatment may help to delay progression of renal function decline [46]. In addition, canagliflozin was also associated with a 31% reduction in UACR compared with placebo over the course of the trial.

The number needed to treat (NNT) has been reported for key outcomes from the CREDENCE trial (Fig. 6). The NNT to prevent one event from the primary composite outcome was 22 (95% CI 15–38). NNTs for other outcomes were 28 (95% CI 19–54) for the composite renal outcomes of ESKD, doubling of the serum creatinine level, or renal death; 43 (95% CI 26–121) for ESKD events; and 46 (95% CI 29–124) for hospitalization for heart failure. These findings further demonstrate the beneficial effects of canagliflozin on renal and cardiovascular outcomes in people with DKD.
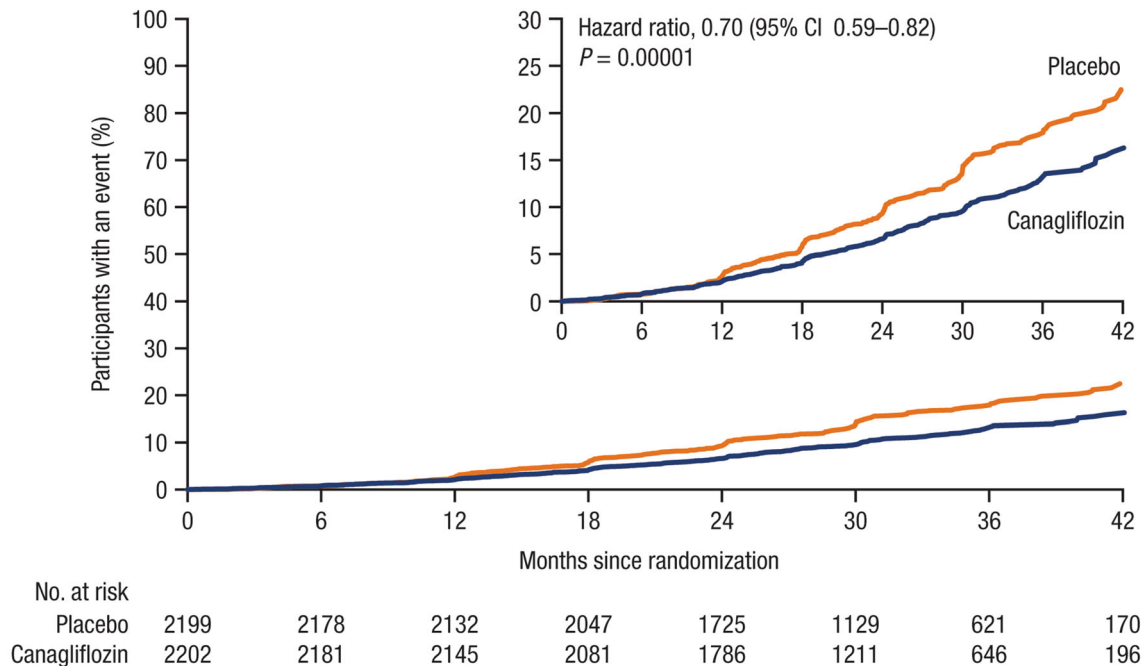
Fig. 3 Primary composite outcome of ESKD, doubling of serum creatinine, or renal or cardiovascular death in CREDENCE [46]. ESKD end-stage kidney disease. From Perkovic et al. [46]. Copyright © 2020 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society
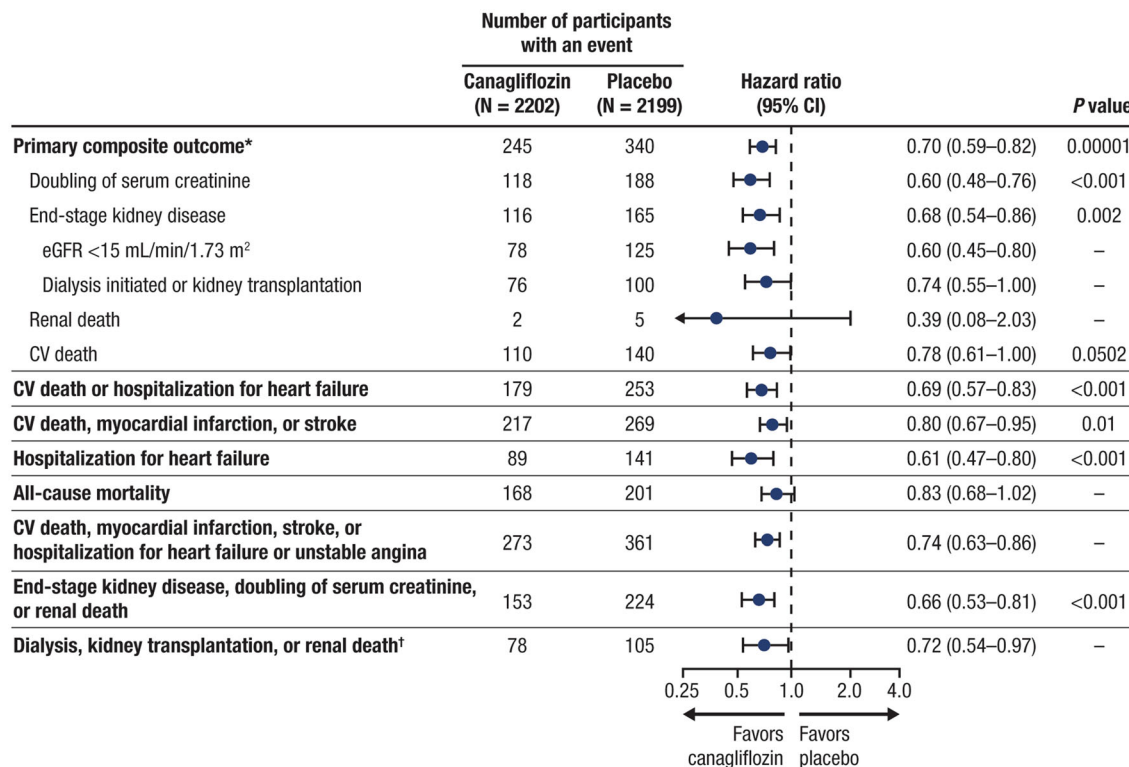
SAFETY OUTCOMES WITH CANAGLIFLOZIN IN CREDENCE

The overall safety profile of canagliflozin in the CREDENCE trial was generally consistent with the previous studies of canagliflozin (Fig. 7) [46]. In CREDENCE, overall adverse events and serious adverse events were lower among participants receiving canagliflozin compared with placebo. There was no difference between canagliflozin and placebo for the incidence of adverse events of interest, including malignancies, urinary tract infections, volume depletion, hypoglycemia, osmotic diuresis, and hypersensitivity/cutaneous reactions [46]. Furthermore, canagliflozin treatment resulted in a lower risk of renal-related adverse events compared to those treated with placebo (HR, 0.71; 95% CI 0.61–0.82) [46]. There was no difference observed in the risk of acute kidney injury between the participants receiving canagliflozin and placebo (HR, 0.85; 95% CI 0.64–1.13) [46].

Notably, in CREDENCE there was no difference between canagliflozin and placebo in the rates of amputation (HR, 1.11; 95% CI 0.79–1.56) or fracture (HR, 0.98; 95% CI 0.70–1.37) [46]. These results are in contrast with the CANVAS Program, which found an increased risk of amputation (HR, 1.97; 95% CI 1.41–2.75), and the CANVAS trial, which found an increased risk of fracture (HR, 1.55; 95% CI 1.21–1.97) in participants treated with canagliflozin [43]. The reason for this discrepancy is not known and, with the exception of an increased risk of amputation observed in studies of ertugliflozin, other clinical studies of SGLT2 inhibitors, including phase 3 trials of canagliflozin, have not shown this same risk [44, 53–55].

CLINICAL PERSPECTIVE

DKD is a devastating disease that puts people with T2DM at an increased risk for developing several serious and life-threatening conditions. The dearth of new treatments for DKD over the

	Number of participants with an event				
	Canagliflozin (N = 2202)	Placebo (N = 2199)	Hazard ratio (95% CI)		P value
Primary composite outcome*	245	340	⊢●⊣	0.70 (0.59–0.82)	0.00001
Doubling of serum creatinine	118	188	⊢●⊣	0.60 (0.48–0.76)	<0.001
End-stage kidney disease	116	165	⊢●⊣	0.68 (0.54–0.86)	0.002
eGFR <15 mL/min/1.73 m^2	78	125	⊢●⊣	0.60 (0.45–0.80)	–
Dialysis initiated or kidney transplantation	76	100	⊢●⊣	0.74 (0.55–1.00)	–
Renal death	2	5	←●—————⊣	0.39 (0.08–2.03)	–
CV death	110	140	⊢●⊣	0.78 (0.61–1.00)	0.0502
CV death or hospitalization for heart failure	179	253	⊢●⊣	0.69 (0.57–0.83)	<0.001
CV death, myocardial infarction, or stroke	217	269	⊢●⊣	0.80 (0.67–0.95)	0.01
Hospitalization for heart failure	89	141	⊢●⊣	0.61 (0.47–0.80)	<0.001
All-cause mortality	168	201	⊢●⊣	0.83 (0.68–1.02)	–
CV death, myocardial infarction, stroke, or hospitalization for heart failure or unstable angina	273	361	⊢●⊣	0.74 (0.63–0.86)	–
End-stage kidney disease, doubling of serum creatinine, or renal death	153	224	⊢●⊣	0.66 (0.53–0.81)	<0.001
Dialysis, kidney transplantation, or renal death†	78	105	⊢●⊣	0.72 (0.54–0.97)	–

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        0.25   0.5   1.0   2.0   4.0
              ←——————     ——————→
              Favors      Favors
           canagliflozin  placebo
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Fig. 4 Effects of canagliflozin on cardiovascular and renal outcomes in CREDENCE [46]. CI confidence interval, eGFR estim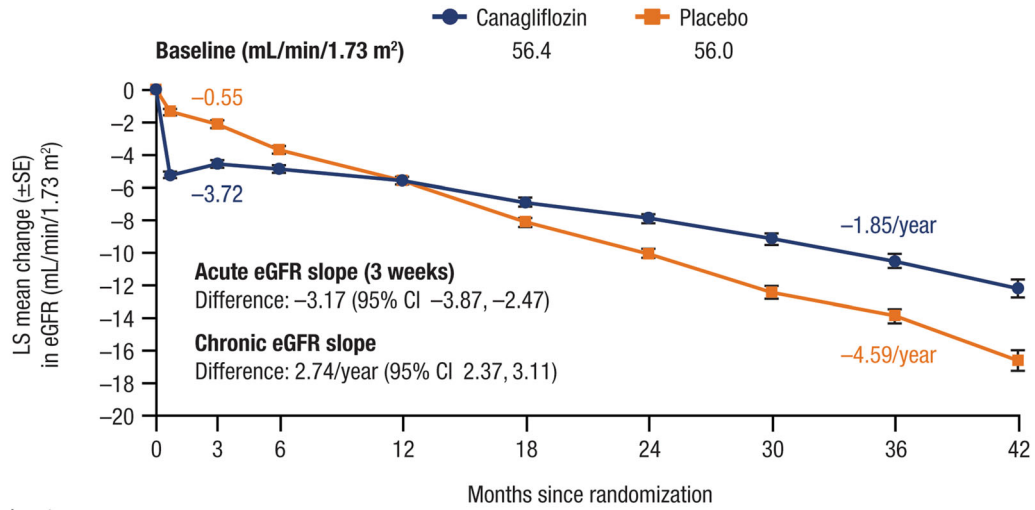ated glomerular filtration rate, CV cardiovascular. *The primary composite outcome included end-stage kidney disease, doubling of serum creatinine, or renal or CV death. †This outcome was exploratory

last two decades has presented a challenge for disease management and created an immense economic burden. The CREDENCE trial was uniquely designed compared with previous trials because of its focus on renal outcomes and its study population, which included people with DKD. Thus, CREDENCE was the first study to provide definitive evidence demonstrating the effects of canagliflozin in slowing kidney function decline in this population with compromised kidney function. In addition to its renal benefits, CREDENCE was the first study to show the efficacy of an AHA for preventing cardiovascular events in those without a history of cardiovascular disease [46].

In addition to providing evidence for the beneficial effects of canagliflozin in slowing kidney function decline in people with DKD, results from the CREDENCE trial demonstrated a favorable safety profile that did not result in an increased risk of amputation or fracture with canagliflozin. It remains important for clinicians to remember that good clinical practice and proper foot care are always crucial in people with DKD, who are at an inherently heightened baseline risk for amputation and fracture.

The mechanism responsible for the renal benefits associated with canagliflozin treatment in the CREDENCE trial is unclear; however, a number of potential hypotheses have been generated. It has been proposed that the renal benefits associated with SGLT2 inhibition are achieved through a renal hemodynamic effect that may attenuate renal hyperfiltration and normalization of tubuloglomerular feedback by blocking sodium reabsorption at renal proximal tubules, ultimately increasing sodium delivery to the macula densa [41, 56–59]. A number of alternative mechanisms have been proposed and are under investigation, including effects on albuminuria; glucose-mediated inflammation, proliferation, and fibrosis; proximal tubule hypertrophy; oxidative stress; and

Fig. 5 Effects of canagliflozin on eGFR slope over time [46]. eGFR estimated glomerular filtration rate, LS least squares, SE standard error, CI confidence interval. From

Perkovic et al. [46] Copyright © 2020 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society
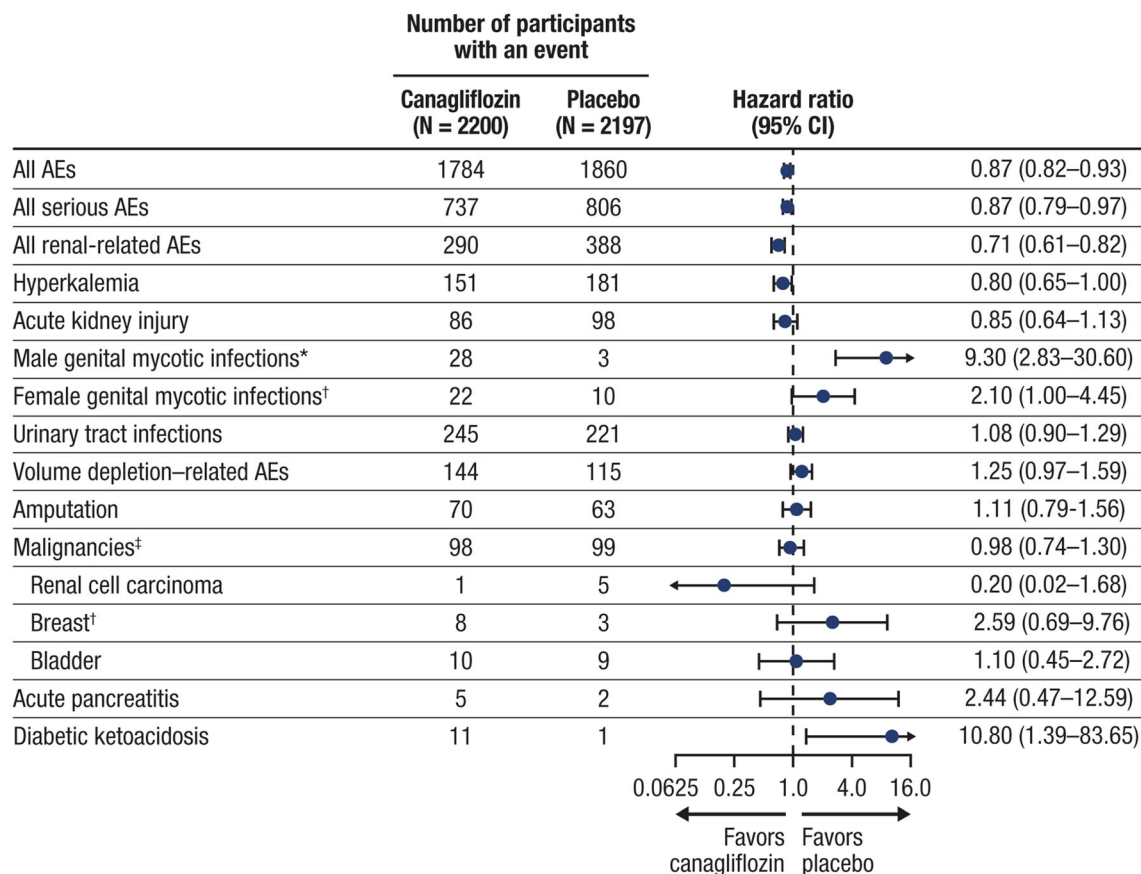

Fig. 6 Number needed to treat to prevent one event from the **a** primary composite outcome; **b** composite renal outcomes of end-stage kidney disease, doubling of the serum creatinine level, or renal death; **c** end-stage kidney disease; **d** hospitalization for heart failure [46]. eGFR estimated glomerular filtration rate. *ESKD (defined as the

need for chronic dialysis for at least 30 days, kidney transplantation, or eGFR < 15 mL/min/1.73 m² sustained for at least 30 days by central laboratory assessment), doubling of serum creatinine, or renal or cardiovascular death

sodium–hydrogen exchanger expression [60–64]. Furthermore, it has been hypothesized that SGLT2 inhibitors complement the mechanism of RAAS inhibition to improve renal and

cardiovascular outcomes in people receiving ACE inhibitors and/or ARBs [65]. Indeed, the renal benefits associated with canagliflozin treatment were observed in addition to standard

	Number of participants with an event		Hazard ratio (95% CI)	
	Canagliflozin (N = 2200)	Placebo (N = 2197)		
All AEs	1784	1860		0.87 (0.82–0.93)
All serious AEs	737	806		0.87 (0.79–0.97)
All renal-related AEs	290	388		0.71 (0.61–0.82)
Hyperkalemia	151	181		0.80 (0.65–1.00)
Acute kidney injury	86	98		0.85 (0.64–1.13)
Male genital mycotic infections*	28	3		9.30 (2.83–30.60)
Female genital mycotic infections†	22	10		2.10 (1.00–4.45)
Urinary tract infections	245	221		1.08 (0.90–1.29)
Volume depletion–related AEs	144	115		1.25 (0.97–1.59)
Amputation	70	63		1.11 (0.79-1.56)
Malignancies‡	98	99		0.98 (0.74–1.30)
Renal cell carcinoma	1	5		0.20 (0.02–1.68)
Breast†	8	3		2.59 (0.69–9.76)
Bladder	10	9		1.10 (0.45–2.72)
Acute pancreatitis	5	2		2.44 (0.47–12.59)
Diabetic ketoacidosis	11	1		10.80 (1.39–83.65)

0.0625   0.25   1.0   4.0   16.0

← Favors canagliflozin   Favors placebo →

Fig. 7 Effects of canagliflozin on safety outcomes in CREDENCE [46]. CI confidence interval, AE adverse event. *Includes male participants only (canagliflozin, $n = 1439$; placebo, $n = 1466$). †Includes female participants only (canagliflozin, $n = 761$; placebo, $n = 731$). ‡Includes malignant tumors of unspecified type

of care with RAAS inhibitors, which were being taken by more than 99% of CREDENCE trial participants. Future studies will be helpful to decipher the mechanism responsible for the renal benefits observed with canagliflozin, which may help to inform future prescribing recommendations related to the combined use of SGLT2 inhibitors and RAAS inhibitors.

Renal outcomes data for people with DKD are not yet available for other SGLT2 inhibitors; however, trials for the SGLT2 inhibitors dapagliflozin and empagliflozin that include this population as well as people with CKD (without T2DM) are ongoing and expected to be completed in late 2020 and 2022, respectively [66, 67]. These data may help to clarify whether the renal benefits seen with canagliflozin in CREDENCE trial participants are a class effect of

SGLT2 inhibitors and whether these effects may extend to people with CKD who do not have T2DM to further establish the renal efficacy and safety of this class of drugs.

The results from the CREDENCE trial prompted the US Food and Drug Administration (FDA) to expand the indication for canagliflozin to a new patient population [68]. Prior to CREDENCE, canagliflozin was approved for two indications: (1) as an adjunct to diet and exercise to improve glycemic control in adults with T2DM and (2) to reduce the risk of MACE in adults with T2DM and established cardiovascular disease. On the basis of results from the CREDENCE trial, the FDA approved canagliflozin to reduce the risk of ESKD, doubling of serum creatinine, cardiovascular death, and hospitalization for heart failure in adults with

Indication	Patient characteristics required for initiation of treatment				Patient characteristics required for continuation of treatment		
	HbA1c (%)	eGFR (mL/min/1.73 m²)	CVD	UACR (mg/g)	HbA1c (%)	eGFR (mL/min/1.73 m²)	UACR (mg/g)
Glycemic control	Baseline HbA1c >7*	Baseline eGFR ≥45	CVD history not required	Any baseline UACR	Any HbA1c level	eGFR ≥45†	Any UACR level
Reduction in MACE	Any baseline HbA1c	Baseline eGFR ≥45	History of CVD	Any baseline UACR	Any HbA1c level	eGFR ≥45	Any UACR level
Reduction in renal outcomes, CV death, and HHF	Any baseline HbA1c	Baseline eGFR ≥30	CVD history not required	Baseline UACR >300	Any HbA1c level	Any eGFR until dialysis	UACR >300‡

● No restrictions ● Some restrictions

Fig. 8 Updated dosing and eligibility guidelines for canagliflozin [68]. eGFR estimated glomerular filtration rate, CVD cardiovascular disease, UACR urinary albumin to creatinine ratio, MACE major adverse cardiovascular events, CV cardiovascular, HHF hospitalization for heart failure. Note that "No restrictions" and "Some restrictions" refer to the eligibility requirements of patients for treatment with canagliflozin based on the criteria specified in each row/column. For those with "Some restrictions," the specific thresholds are provided in the figure. *Varies depending on specific goals of patient. †Dose can be increased to 300 mg for better glycemic control if eGFR > 60 mL/min/1.73 m². ‡Patient can continue treatment with eGFR < 30 mL/min/1.73 m² as long as UACR is > 300 mg/g

T2DM and diabetic nephropathy with albuminuria (> 300 mg/day). The US prescribing information for canagliflozin was also updated to allow the continuation of canagliflozin 100 mg in people already receiving therapy whose eGFR falls to < 30 mL/min/1.73 m² with a UACR > 300 mg/g until initiation of dialysis or kidney transplantation [68]. Evidence from the CREDENCE trial also prompted the American Diabetes Association to update its guidelines in June 2019 to recommend that people with T2DM with an eGFR ≥ 30 mL/min/1.73 m² and albuminuria (> 300 mg/g) consider using an SGLT2 inhibitor to reduce their risk of DKD progression and/or cardiovascular events [69]. Further updates to these guidelines published in 2020 suggested that SGLT2 inhibitors should be considered independently of HbA1c for people when atherosclerotic cardiovascular disease, heart failure, or CKD predominates or for people with T2DM and CKD who require treatment in addition to metformin to attain target HbA1c [70]. Taken together, these new recommendations demonstrate that canagliflozin treatment is beneficial to a diverse array of people in a broad range of circumstances, and physicians should consider the unique characteristics of each patient when determining if canagliflozin is an appropriate treatment option (Fig. 8).

CONCLUSION

The CREDENCE trial has demonstrated the effects of canagliflozin that improve renal outcomes and slow early disease progression in people with T2DM and DKD. In addition to the positive effects on kidney function, treatment with canagliflozin also decreased the prevalence of all comorbid complications in CREDENCE trial participants, demonstrating the potential this treatment has to reduce the DKD-related expenditures in the health care industry. Data from other trials investigating the use of SGLT2

inhibitors will be crucial for further establishing the value and efficacy of this class of drugs in people at high renal risk and probing the extension of these benefits to a wider range of people.

ACKNOWLEDGEMENTS

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