Estimated Renal and Cardiovascular Outcomes and Cost Offsets in Patients With Type 2 Diabetes and Diabetic Nephropathy Treated With Canagliflozin

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BACKGROUND

- Chronic kidney disease (CKD) is characterized by gradual and permanent loss of kidney function[1]
- When unchecked, CKD can progress over time until dialysis or a kidney transplant is needed to maintain life
- The Canagliflozin and Renal Endpoints in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE) trial was the first dedicated renal outcomes study for any sodium glucose co-transporter 2 inhibitor to report results in participants with type 2 diabetes and CKD[2]
- As compared with standard of care (SoC) that included the use of the maximum tolerated dose of a renin–angiotensin–aldosterone system inhibitor in >99% of patients, canagliflozin 100 mg plus SoC was shown to reduce the risk of experiencing the primary endpoint (composite of end-stage kidney disease [ESKD], doubling of serum creatinine [DoSCr], renal death, or cardiovascular [CV] death) by 30% (P = 0.00001) in the CREDENCE trial[2]
  - Canagliflozin 100 mg plus SoC also reduced the risk of secondary and exploratory endpoints compared with SoC, such as a 26% reduction for starting maintenance dialysis, a 20% risk reduction in major adverse cardiovascular events (MACE; CV death, nonfatal myocardial infarction [MI], or nonfatal stroke) and a 39% risk reduction in hospitalization for heart failure (HHF)[2]
- Properly informing health care decision-makers of the cost implications of treatment for patients with diabetic kidney disease (DKD) can be accomplished using economic modeling methods, which allow customization of cost inputs for specific health care systems and extrapolation of CREDENCE trial outcomes to longer decision-making time horizons

OBJECTIVE

- To estimate cost offsets associated with using canagliflozin 100 mg plus SoC versus SoC alone in patients matching the CREDENCE population from the 3rd party payer perspective in the United States over a 5-year time horizon

METHODS

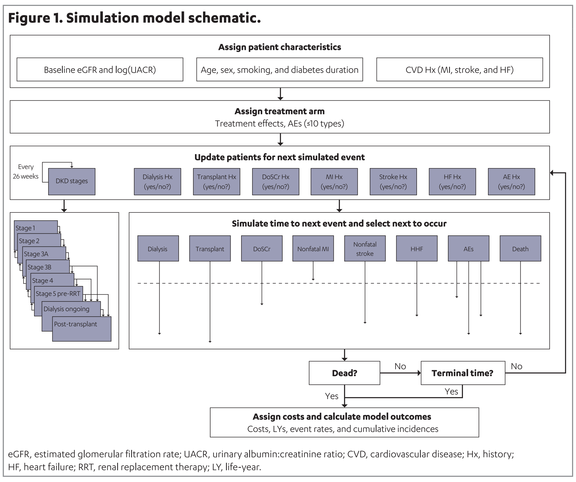
Model Overview

- CREDEM-DKD is a discrete event simulation model that included both 1st order (Monte Carlo) and 2nd order (parameter) uncertainty (**Figure 1**)
  - 1,000 cohorts of 1,000 hypothetical patients based on the CREDENCE trial population were created
  - Hypothetical patients received either canagliflozin 100 mg plus SoC or SoC alone (with treatment effects applied for the canagliflozin study arm), and their health histories were simulated over 5 years
- CREDEM-DKD was constructed to match the participants and the key renal and CV outcomes in the CREDENCE trial
  - Model outcomes are driven by risk prediction equations that were estimated using patient-level data from the CREDENCE trial[2]
- The model attaches unit costs to patient histories
  - State costs were applied for each health state (i.e., years following an event)
  - Event costs were applied for nonfatal MI events, nonfatal stroke events, and nonfatal HHF events
  - Drug costs are applied at a fixed cost per year, and treatment-related adverse event (AE) costs were applied as an event cost
  - An annual discount rate of 3% was used[3]
- To confirm robustness and to examine the evolution of clinical benefits and cost offsets over time, simulations were performed with a time horizon of 3 years (which is similar to the median 2.62 years of follow-up for participants in CREDENCE) and 10 years (providing an estimate of the longer-term economic outcomes)

Model Inputs

- Baseline characteristics for simulated cohorts were sampled from distributions published for the CREDENCE population of patients with type 2 diabetes and CKD[2]
- Treatment effects were also sourced from CREDENCE, notably as hazard ratios (HRs) for dialysis (0.74), HHF (0.61), MI (0.81), and stroke (0.80) events[2]
- Cost assumptions came from published sources and represented a US payer perspective[4,5]

Figure 1. Simulation model schematic.



eGFR, estimated glomerular filtration rate; UACR, urinary albumin:creatinine ratio; CVD, cardiovascular disease; Hx, history; HF, heart failure; RRT, renal replacement therapy; LY, life-year.

RESULTS

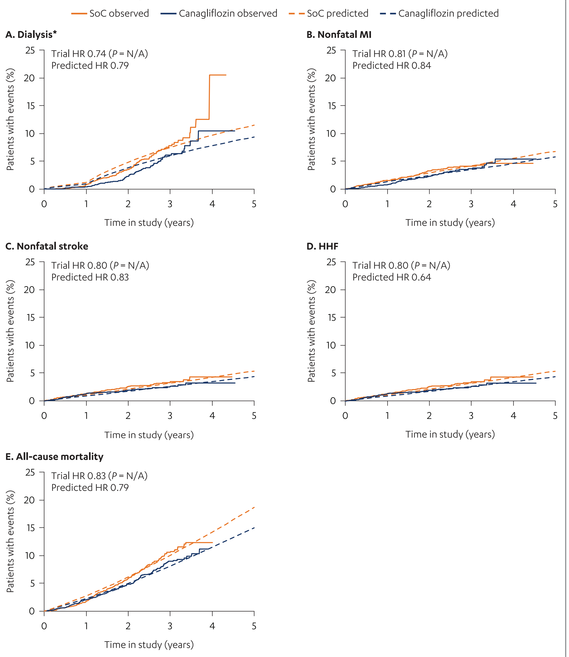
- In a population of 1,000 patients, canagliflozin was associated with 21% fewer dialysis starts (approximately 220 events avoided), 36% fewer HHF events, 16% fewer MI events (approximately 85 events avoided), 17% fewer stroke events (approximately 75 events avoided), and 21% fewer deaths (**Table 1**)
- The estimated cumulative incidence for both study arms matched the CREDENCE trial fairly well (**Figure 2**)
  - The model tended to overpredict the start of maintenance dialysis, but the difference between arms was similar to that in the trial
  - By Year 3, however, model predictions matched closely with the CREDENCE trial
- AE rates modeled in the simulation were numerically higher for canagliflozin, notably for male genital mycotic infection (GMI; **Table 1**)
- Cost offsets estimated for dialysis, HHF, MI, and stroke were estimated at $3,815, $1,040, $627, and $317, respectively (**Figure 3**)
- In the 10-year sensitivity analysis, the cost offsets for dialysis and HHF were estimated at $7,635 and $1,429, respectively (**Figure 3**)

Table 1. Events per 100 Patient-years Over 5 Years

	Canagliflozin	SoC	HR
All-cause mortality	3.22	4.08	0.79
CV death	1.77	2.29	0.77
Death due to other causes	1.45	1.78	0.82
Renal			
Dialysis	2.09	2.64	0.79
ESKD	2.09	3.67	0.57
CV			
Nonfatal MI	1.20	1.44	0.84
Nonfatal stroke	1.00	1.21	0.83
HHF	1.50	2.35	0.64
MACE	2.19	2.64	0.83
CV death or HHF	1.50	2.35	0.64
AEs			
UTI	4.65	4.29	1.08
Male GMI	0.52	0.05	9.82
Female GMI	0.45	0.22	2.05

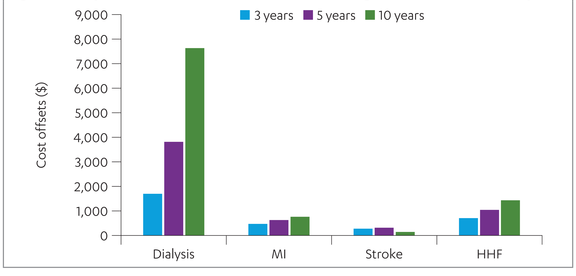
UTI, urinary tract infection.

Figure 2. Kaplan-Meier cumulative incidence curves for predicted and observed CREDENCE values, by outcome.



N/A, not applicable.
*The risk prediction equation for dialysis includes a 1st year indicator to adjust for the limited number of events in the 1st year in CREDENCE.

Figure 3. Per-patient cost offsets associated with canagliflozin over 3, 5, and 10 years.



DISCUSSION

- Economic simulation modeling using a model derived from patient-level data from the CREDENCE trial was used to extrapolate the findings of the trial to a 5-year time horizon, and cost offsets for avoided renal and CV events were estimated
- The model captures the full spectrum National Kidney Foundation–Kidney Disease Outcomes Quality Initiative (NKF-KDOQI) stages for CKD and other important outcomes, such as dialysis, MI, stroke, and HHF
- The results from the simulation suggest that estimated renal and CV benefits associated with the use of canagliflozin added to SoC compared with SoC alone leads to important cost offsets for the health care sector, primarily from lowering the need for dialysis. Sensitivity analysis showed that the magnitude of potential cost offsets increases over time

LIMITATIONS

- By design, the model includes only renal and CV outcomes and therefore does not address other diabetes outcomes, such as glucose control, retinopathy, and transplants
- Costs for fatal events were not included, which may underestimate benefits of canagliflozin
- Estimating risk prediction equations with randomized controlled trial data risks incorporation of bias, as study recruitment criteria may lead to non-representative samples and protocols steering treatment (e.g., glycemic equipoise) can affect outcomes

CONCLUSION

- **Results of these simulations suggest that for this high unmet need US patient population, canagliflozin use is associated with cost offsets due to fewer renal, CV, and mortality events compared to SoC**

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