



# Linear Projection of Estimated Glomerular Filtration Rate Decline with Canagliflozin and Implications for Dialysis Utilization and Cost in Diabetic Nephropathy

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Received: August 25, 2020 / Accepted: October 20, 2020 / Published online: December 18, 2020  
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## ABSTRACT

**Introduction:** Diabetes is a common cause of end-stage kidney disease leading to dialysis or kidney transplantation. Estimated glomerular filtration rate (eGFR) measures kidney function, and differences in the rate (slope) of eGFR decline can be used to assess treatment effects on kidney function over time. In the CREDENCE trial, the sodium glucose co-transporter 2 inhibitor canagliflozin slowed the rate of eGFR decline by 60% compared to placebo in patients with diabetes and chronic kidney disease. This analysis utilized eGFR slopes from CREDENCE to estimate the difference in time to dialysis by treatment arm and estimated the economic value of that delay.

**Methods:** A linear decline in eGFR and maintenance of stable therapy were assumed for the canagliflozin and placebo arms in CREDENCE. Mean eGFR over time was calculated using acute (baseline to week 3) and chronic (week 3 onward) slopes. Reaching eGFR of 10 ml/min/1.73 m<sup>2</sup> was

assumed to represent the need for chronic dialysis. The difference in time to dialysis between treatments was calculated. Based on the average duration of dialysis, annual dialysis costs were determined, discounting 2020 US dollars at an inflation rate of 4%.

**Results:** Following the acute and chronic eGFR slopes, the projected time to dialysis was 22.85 years for canagliflozin and 9.90 years for placebo. Based on 95% confidence intervals from CREDENCE, the model-estimated difference in time to dialysis was 9.27–17.48 years. With a mean baseline participant age of 63 years, the delay in dialysis with canagliflozin would be associated with a reduction in dialysis costs of approximately \$170,000 per patient in 2020 dollars.

**Conclusion:** Using clinical trial data, canagliflozin treatment was projected to delay dialysis by approximately 13 years, which could translate to a substantial cost savings. More precise estimates should be investigated with considerations for nonlinear eGFR slope trajectory, competing risks, and patient characteristics.

**Trial Registration:** ClinicalTrials.gov identifier, NCT02065791.

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**Electronic supplementary material** The online version of this article (<https://doi.org/10.1007/s13300-020-00953-4>) contains supplementary material, which is available to authorized users.

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**Keywords:** Canagliflozin; Cost of illness; Diabetes mellitus, Type 2; Dialysis; Renal insufficiency, chronic; Sodium glucose co-transporter 2 inhibitors

## Key Summary Points

### Why carry out this study?

End-stage kidney disease (ESKD) commonly results from diabetes and leads to dialysis, which has substantial impacts on patients' quality and quantity of life and health care spending.

Canagliflozin, a sodium glucose co-transporter 2 inhibitor indicated for type 2 diabetes mellitus, was shown to reduce the risk of ESKD by 32% and slow the rate of estimated glomerular filtration rate (eGFR) decline by 60% in the Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (CREDESCENCE) trial.

This analysis estimated the delay in time to dialysis and the economic value of delaying dialysis in patients treated with canagliflozin using linear projections of eGFR slope from the CREDESCENCE trial.

### What was learned from the study?

For patients with diabetic nephropathy who are similar to CREDESCENCE trial participants, canagliflozin was projected to delay the initiation of dialysis by 12.95 years relative to placebo, with an estimated cost savings of approximately \$170,000 per patient treated with canagliflozin.

The use of eGFR slopes from clinical trial data allowed straightforward estimation of important health care outcomes, indicating a substantial delay in the need for dialysis and reduction in costs in a population of patients treated with canagliflozin based on the CREDESCENCE study.

These findings support further analysis using disease models that consider nonlinear eGFR slopes, competing risk factors, and varying baseline patient characteristics.

## DIGITAL FEATURES

This article is published with digital features, including a summary slide, to facilitate understanding of the article. To view digital features for this article go to <https://doi.org/10.6084/m9.figshare.13110887>.

## INTRODUCTION

Diabetes is the most common cause of end-stage kidney disease (ESKD), which affects approximately 750,000 people per year in the USA [1–4]. The estimated glomerular filtration rate (eGFR) measures kidney function and shows a linear decline over time [5]. Once individuals reach ESKD, renal replacement therapy with either dialysis or kidney transplantation is required. In 2017, dialysis was the most common renal replacement therapy, with 97.1% of incident ESKD patients beginning dialysis and only 2.9% receiving a preemptive kidney transplant [1]. The current Kidney Disease: Improving Global Outcomes (KDIGO) guidelines recommend initiation of renal replacement therapy in the presence of symptoms or signs attributable to kidney failure, which usually occurs when eGFR reaches 5–10 ml/min/1.73 m<sup>2</sup> [6–9]. According to the US Renal Data System (USRDS) report for 2017, patients had a mean eGFR of 10 ml/min/1.73 m<sup>2</sup> at initiation of dialysis [1].

Numerous studies have assessed the predictive value of eGFR slope in terms of kidney disease progression, demonstrating a consistent association with subsequent development of ESKD, even for relatively small differences in slope [10]. Workshops held jointly with the National Kidney Foundation (NKF), the US Food and Drug Administration (FDA), and the European Medicines Agency have led to the acceptance of eGFR slope as a standard endpoint in chronic kidney disease (CKD) trials, and the NKF established in 2018 that a difference of 0.5–1.0 ml/min/1.73 m<sup>2</sup>/year supports clinical benefit [10, 11]. Thus, the chronic slope of eGFR is a marker of future disease progression and could be a useful tool for estimating when a patient might reach ESKD or require dialysis [10, 12, 13]. Research presented at the

workshops supported chronic slope as the appropriate slope measure for any comparison of treatments with acute hemodynamic effects, such as renin-angiotensin-aldosterone system inhibitors or sodium glucose co-transporter 2 (SGLT2) inhibitors [5].

Research has shown that dialysis severely compromises multiple domains of a patient's health-related quality of life (HRQoL) [1, 14–16]. Moreover, the long-term prognosis of dialysis is poor, with survival times for elderly patients < 5 years after starting dialysis [21, 22]. Overall mortality rates for patients with ESKD have declined since 2001, with a current rate among hemodialysis patients of 167 per 1000 patient-years. Initiating dialysis earlier based on eGFR values has not been shown to impact clinical outcomes or HRQoL [23], but delaying the time to dialysis may benefit a patient's HRQoL in two ways: by providing a patient with more years at a better quality of life before dialysis and reducing the duration of time a patient spends on dialysis with poor quality of life.

The economic impact of dialysis is also substantial, with costs estimated at approximately \$95,000 per patient per year for patients with diabetes in 2017 [1]. Medicare spending for ESKD patients was \$35.9 billion in 2017 and accounted for 7.2% of the overall paid claims in the fee-for-service system [1]. Delays in time to the initiation of dialysis can reduce the duration of dialysis, as the expected number of years on dialysis decreases with increasing age of initiation. Furthermore, health care systems can realize economic benefit by pushing out dialysis spending to future time periods.

The dedicated renal outcomes trial Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE) demonstrated the beneficial effects of the SGLT2 inhibitor canagliflozin on renal endpoints in patients with type 2 diabetes mellitus (T2DM) and CKD [24, 25]. Patients were  $\geq 30$  years of age with T2DM (hemoglobin A1c  $\geq 6.5\%$  and  $\leq 12.0\%$ ), eGFR  $\geq 30$  and  $< 90$  ml/min/1.73 m<sup>2</sup>, and urinary albumin:creatinine clearance  $> 300$  and  $\leq 5000$  mg/g. They were also required to be receiving a maximum tolerated dose of an angiotensin-converting enzyme inhibitor and/or angiotensin receptor

blocker for  $\geq 4$  weeks prior to randomization. A stratified Cox proportional-hazards model was used to analyze the primary and secondary trial outcomes according to the category of eGFR at screening. Canagliflozin treatment was associated with a 30% relative risk reduction of the primary composite outcome of ESKD (defined as the composite of maintenance dialysis sustained for  $\geq 30$  days, renal transplantation, or a sustained eGFR  $< 15$  ml/min/1.73 m<sup>2</sup>), doubling of serum creatinine, or renal or cardiovascular death compared with placebo [hazard ratio 0.70; 95% confidence interval (CI) 0.59, 0.82;  $P = 0.00001$ ] [25]. Canagliflozin treatment was associated with an acute (reversible) drop in eGFR from baseline to week 3 compared with placebo (least squares mean change  $\pm$  standard error of  $-3.72 \pm 0.25$  vs.  $-0.55 \pm 0.25$  ml/min/1.73 m<sup>2</sup>/year). This initial drop in eGFR was followed by stabilization in eGFR decline compared to placebo from week 3 to the end of the study ( $-1.85 \pm 0.13$  vs.  $-4.59 \pm 0.14$  ml/min/1.73 m<sup>2</sup>/year), which is consistent with known renal hemodynamic effects of SGLT2 inhibition [26]. Importantly, as a result of these findings, the FDA issued a new indication for canagliflozin to reduce the risk of ESKD, doubling of serum creatinine, cardiovascular death, and hospitalization for heart failure in adults with T2DM and diabetic nephropathy with albuminuria  $> 300$  mg/day [27]; this represented the first new indication for the reduction of ESKD risk in 20 years [28, 29].

The objective of this analysis was to utilize a linear projection of eGFR slopes reported for patients treated with canagliflozin or placebo in the CREDENCE trial to estimate the delay in the need for dialysis that would be anticipated with long-term canagliflozin treatment. Furthermore, the economic value of delaying dialysis costs was estimated and presented in terms of current dollars.

## METHODS

To estimate a difference in time for the mean eGFR of each CREDENCE treatment cohort to reach a threshold representing the need for dialysis, a linear eGFR decline was assumed for

patients persisting on stable treatment beyond the actual CREDENCE follow-up period. Trajectories of eGFR for patients meeting the criteria for CREDENCE, with a mean baseline eGFR of 56 ml/min/1.73 m<sup>2</sup> and treated with either canagliflozin or placebo, were modeled as a linear function over time using the published eGFR slopes from CREDENCE [25]. Mean eGFR over time for each cohort was estimated using the acute slopes [ml/min/1.73 m<sup>2</sup> (95% CI); canagliflozin, − 3.72 (− 4.21, − 3.23); placebo, − 0.55 (− 1.04, − 0.06)] to calculate eGFR values at week 3 and chronic slopes [ml/min/1.73 m<sup>2</sup>/year (95% CI); canagliflozin, − 1.85 (− 2.10, − 1.60); placebo, − 4.59 (− 4.86, − 4.32)] from week 3 to future years. An eGFR value of 10 ml/min/1.73 m<sup>2</sup> was used to represent the level of kidney function that would require the initiation of dialysis [1]. Assuming patients in each cohort persisted on assigned treatment, the difference in time to dialysis between canagliflozin and placebo was calculated.

For each treatment arm, the mean eGFR could be estimated at any time point using the published acute and chronic slope. In this model, eGFR at week 3 was calculated as baseline eGFR in ml/min/1.73 m<sup>2</sup> plus the acute slope. The time from week 3 to an eGFR level of 10 ml/min/1.73 m<sup>2</sup> was equal to (10 − eGFR value at week 3) divided by the chronic slope in units of ml/min/1.73 m<sup>2</sup>/year. Upper and lower bounds for modeled time estimates were calculated by using the 95% CI ranges for the acute and chronic slopes for canagliflozin and placebo published in the primary CREDENCE manuscript [25]. A lower bound for the difference between canagliflozin and placebo time to eGFR of 10 ml/min/1.73 m<sup>2</sup> was calculated using the least steep slope values in the 95% CI ranges for acute and chronic slopes for placebo and the steepest slope values in the 95% CI ranges for acute and chronic slopes for canagliflozin. The corresponding upper bound for the difference in time was calculated using the steepest slope values in the 95% CI ranges for placebo acute and chronic slopes and the shallowest slope values in the 95% CI ranges for canagliflozin. To assess how results may differ in models based on lower or higher eGFR thresholds representing

the need for dialysis, eGFR thresholds of 5 and 15 ml/min/1.73 m<sup>2</sup> were also modeled [1, 6, 30].

An estimation of the economic impact of a delay in dialysis was made by projecting the age at which a patient would begin dialysis and valuing the average number of years on dialysis expected for a patient initiating at that age for each of the therapies based on data from the USRDS [22]. The cost of dialysis per year used in these calculations was estimated at \$100,000 (estimate based on USRDS data for 2017 indicating a cost of \$95,457 per patient per year for dialysis in a patient with a primary diagnosis of diabetes [1]). To account for the time value of money, the lump sum of multiyear dialysis costs was converted to current US dollars through factoring in the initiation year and assuming a medical cost inflation rate of 4% [31], using the standard discounting equation:

Cost of dialysis (\$100,000) ×

Dialysis duration per patient (1.04)<sup>years to initiation</sup>

### Compliance with Ethics Guidelines

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

## RESULTS

The population for this projection model is intended to represent the 4401 patients randomized to treatment with canagliflozin or placebo in the CREDENCE trial, with a median follow-up of 2.62 years [25]. Assuming a mean baseline eGFR of 56 ml/min/1.73 m<sup>2</sup> in both cohorts, the mean eGFR of the canagliflozin cohort fell to 52.28 ml/min/1.73 m<sup>2</sup> during the initial 3 weeks because of the reported hemodynamic effect, while the placebo cohort declined to 55.45 ml/min/1.73 m<sup>2</sup> during the same period (Table 1). The chronic eGFR slope of each treatment cohort from the CREDENCE trial was then used to project eGFR values in each group until an eGFR-defined threshold for dialysis of 10 ml/min/1.73 m<sup>2</sup> was reached.

**Table 1** Calculations for time to dialysis (eGFR of 10 ml/min/1.73 m<sup>2</sup>) in placebo and canagliflozin cohorts of the CREDENCE trial [25, 33]

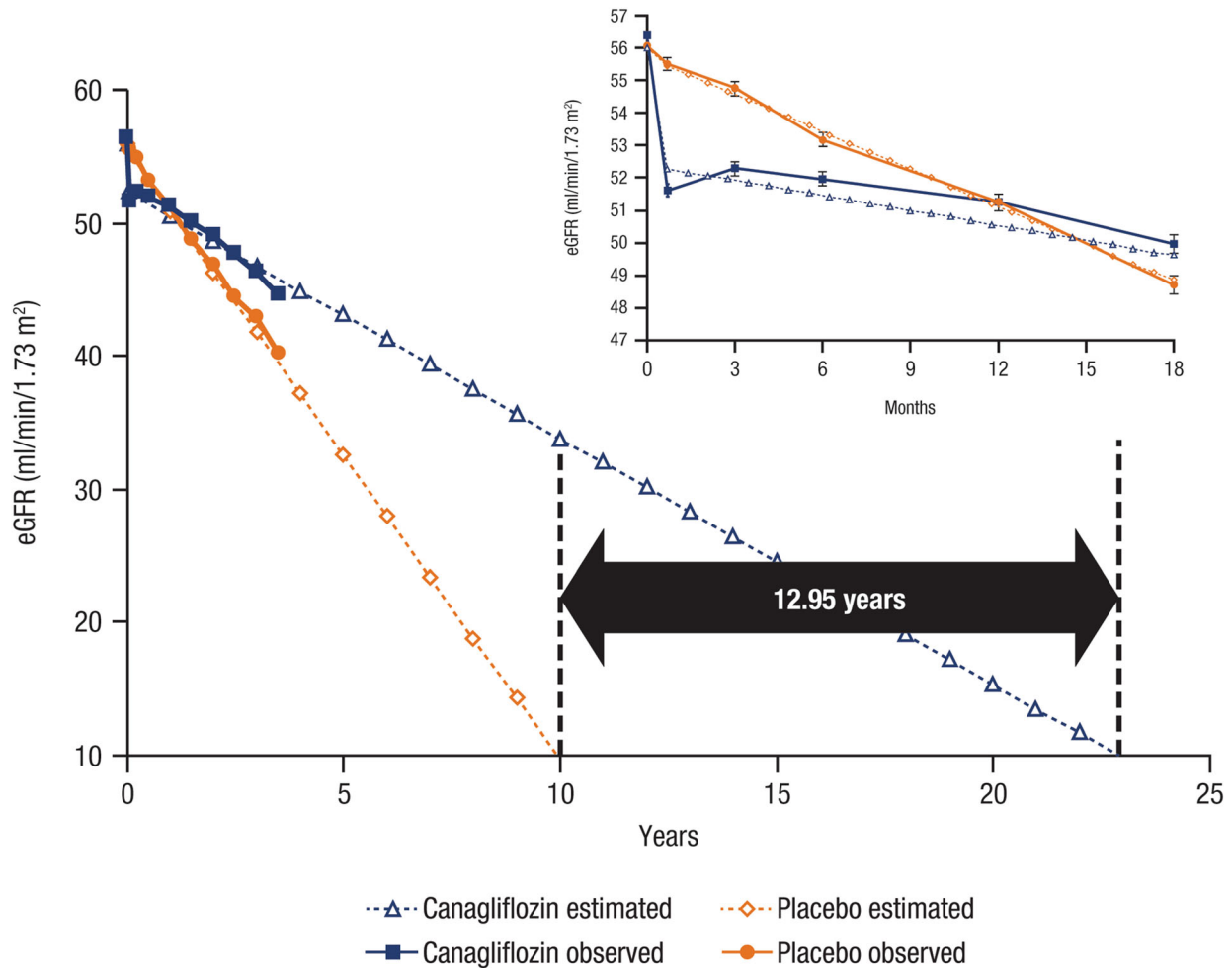
Calculations	Placebo cohort	Canagliflozin cohort
<b>Base case</b>		
eGFR at week 3 = baseline eGFR + acute slope, ml/min/1.73 m <sup>2</sup>	$56 + (-0.55) = 55.45$	$56 + (-3.72) = 52.28$
Time to dialysis = (10 – eGFR at week 3)/chronic slope	$(10 - 55.45)/(-4.59) = 9.90$ years	$(10 - 52.28)/(-1.85) = 22.85$ years
Delay in time to dialysis = canagliflozin time to dialysis – placebo time to dialysis	$22.85 - 9.90 = 12.95$ years	
<b>Lower bound</b> (within 95% CIs, least steep slopes for placebo; steepest slopes for canagliflozin)		
eGFR at week 3 = baseline eGFR + acute slope 95% CI, ml/min/1.73 m <sup>2</sup>	$56 + (-0.06) = 55.94$	$56 + (-4.21) = 51.79$
Time to dialysis = (10 – eGFR at week 3)/chronic slope	$(10 - 55.94)/(-4.32) = 10.63$ years	$(10 - 51.79)/(-2.10) = 19.90$ years
Delay in time to dialysis = canagliflozin time to dialysis – placebo time to dialysis	$19.90 - 10.63 = 9.27$ years	
<b>Upper bound</b> (within 95% CIs, steepest slopes for placebo; least steep slopes for canagliflozin)		
eGFR at week 3 = baseline eGFR + acute slope 95% CI, ml/min/1.73 m <sup>2</sup>	$56 + (-1.04) = 54.96$	$56 + (-3.23) = 52.77$
Time to dialysis = (10 – eGFR at week 3)/chronic slope	$(10 - 54.96)/(-4.86) = 9.25$	$(10 - 52.77)/(-1.60) = 26.73$
Delay in time to dialysis = canagliflozin time to dialysis – placebo time to dialysis	$26.73 - 9.25 = 17.48$ years	

CI confidence interval, eGFR estimated glomerular filtration rate

These estimated eGFR values are depicted next to the actual eGFR measurements from participants in the CREDENCE trial in Fig. 1.

Based on these projections, the time to reach the eGFR-defined threshold for dialysis was 22.85 years for canagliflozin and 9.90 years for

placebo. Under these assumptions, treatment of a population similar to CREDENCE with canagliflozin is projected to delay the initiation of dialysis by 12.95 (range 9.27, 17.48) years relative to placebo. Lower- and upper-bound



**Fig. 1** Estimated eGFR values used to project the delay in time to dialysis (eGFR of 10 ml/min/1.73 m<sup>2</sup>) by treatment in the CREDENCE trial (overlaid with observed data). *eGFR* estimated glomerular filtration rate

calculations based on slopes in the CREDENCE 95% CIs are provided in Table 1.

As expected, estimates of the time for eGFR to decline to an even lower eGFR threshold than the base case of 10 ml/min/1.73 m<sup>2</sup> were longer, and, conversely, shorter times were estimated for eGFR to decline to higher thresholds than the base case. Sensitivity analysis on the effect of lower (5 ml/min/1.73 m<sup>2</sup>) and higher (15 ml/min/1.73 m<sup>2</sup>) eGFR thresholds for dialysis projected delays of 14.57 years and 11.34 years, respectively (Table 2).

An economic evaluation of a delay in the time to dialysis was made by projecting the expected timing and cost of dialysis for each therapy scaled in 2020 US dollars. We assumed that all patients would persist on their cohort

therapy and none would die from competing risks. Historical durations of dialysis, by age of initiation, provided estimates of how long canagliflozin and placebo patients would continue dialysis, given the mean baseline age for CREDENCE of 63 years, followed by the projected times to eGFR of 10 ml/min/1.73 m<sup>2</sup> [22]. The estimated reductions in dialysis costs, under these assumptions, would be approximately \$170,000 per patient treated with canagliflozin (see Online Appendix).

## DISCUSSION

The treatment of patients with diabetes and chronic kidney disease remained relatively

**Table 2** Sensitivity analysis of calculations for time to dialysis using lower and higher eGFR thresholds for dialysis [33]

Calculations	Placebo cohort	Canagliflozin cohort
<b>eGFR threshold = 5 ml/min/1.73 m<sup>2</sup></b>		
Time to dialysis = (5 – eGFR at week 3)/chronic slope	$(5 - 55.45)/(-4.59) = 10.99$ years	$(5 - 52.28)/(-1.85) = 25.56$ years
Delay in time to dialysis = canagliflozin time to dialysis – placebo time to dialysis	$25.56 - 10.99 = 14.57$ years	
<b>eGFR threshold = 15 ml/min/1.73 m<sup>2</sup></b>		
Time to dialysis = (15 – eGFR at week 3)/chronic slope	$(15 - 55.45)/(-4.59) = 8.81$ years	$(15 - 52.28)/(-1.85) = 20.15$ years
Delay in time to dialysis = canagliflozin time to dialysis – placebo time to dialysis	$20.15 - 8.81 = 11.34$ years	

eGFR estimated glomerular filtration rate

unchanged for nearly two decades before the CREDENCE trial, with no new treatments for diabetic nephropathy approved during this time. Given the lack of recent data in this area, payers are likely unfamiliar with how to assess the value of improved treatment in kidney disease, specifically delaying dialysis. The current results using clinical trial data for the eGFR slope projected that canagliflozin could delay the typical CREDENCE patient's progression to dialysis by nearly 13 years, with an estimated savings in dialysis costs of approximately \$170,000 per patient treated with canagliflozin. Delaying the initiation of dialysis has profound implications for patients' HRQoL, by reducing associated symptoms and HRQoL impacts of dialysis [17, 19].

There are important factors to consider in applying the modeled results to populations treated in actual clinical practice or to settings and populations that differ from patients in the CREDENCE trial. The patient characteristics and trial data published from CREDENCE provided the clinical inputs for the calculations of time to dialysis and dialysis costs avoided in this analysis. However, the generalizability of the findings to populations with different clinical characteristics, such as baseline eGFR values, comorbidities, and concomitant medications, is

unknown. The treatment that CREDENCE patients received while in this trial may not be reflective of treatment in actual clinical practice, and therefore the trajectories of eGFR could be affected, which would result in a different set of outcomes in terms of time to dialysis and costs avoided. Patients within a clinical trial can be expected to be more adherent to study treatments during a trial than patients would be after many years of real-world use. Patients whose adherence or persistence to canagliflozin in real-world use is poorer than that of patients in the trial would experience lower benefits in terms of delaying dialysis.

A limit to this analysis is the assumption that the mean eGFR of the population will decline linearly over time, which may not hold over the long term or at the lower eGFR levels considered here. Even if the linear assumption holds true, there will likely be individual patients whose real-world kidney function does not change in a linear fashion. Moreover, the results of this analysis cannot be generalized to all patients with diabetic nephropathy, as the results are based on participants from the CREDENCE trial who met all eligibility criteria outlined for that study. There is no set level of eGFR universally defined as representing the need for dialysis, and the assumed level of 10 ml/min/1.73 m<sup>2</sup>

may not be representative of typical dialysis initiation in some settings. This issue was also addressed by generating results for lower and higher eGFR thresholds for dialysis. No adjustments were made for the effect of competing risks on the changing composition of patient cohorts over time. Given the decades-long time to dialysis projected for some patients, it is expected that some patients in each group would die before ever initiating dialysis. This analysis focused solely on the costs of dialysis and therefore makes no estimates of the costs or savings from other effects of treatment, such as adverse events, medication costs, improvements in glycemic control, or reductions in cardiovascular events. Finally, the safety of canagliflozin when used for many years has not been extensively investigated, so the long-term tolerability of canagliflozin for the period of time that dialysis may be delayed is not known. However, prior studies indicate canagliflozin has a favorable safety profile over extended use up to 6.5 years [32].

By delaying the initiation of dialysis, the patient benefits from a longer time at a higher quality of life before dialysis and a shorter time living with the quality of life degradations of dialysis [1, 14–16]. The health care system can benefit financially from delays to dialysis by pushing any dialysis costs to future years accompanied by expected reductions in the duration of dialysis for older initiators of dialysis. We have approximated future dialysis costs under some broad assumptions, and the results suggest the potential for savings to be substantial.

## CONCLUSION

Through application of the eGFR slopes published for the CREDENCE trial, a linear model representing a CREDENCE-like population projected delays in time to the need for dialysis associated with continued persistence on canagliflozin and provided rationale for expectations of lower dialysis costs per patient. More precise estimates on dialysis delays and reduced costs than projected by this simple linear model should be investigated by disease models that

account for competing hazards of death and discontinuation and that assess the effect of nonlinear renal function declines on projections of time to dialysis.

## ACKNOWLEDGEMENTS

We thank all the patients, investigators, and trial teams for their participation in the CREDENCE trial, which informed this analysis. Medical writing support was provided by Michelle McDermott, PharmD, of MedErgy and was funded by Janssen Scientific Affairs, LLC.

**Funding.** This article and the fee for the journal's Rapid Service were supported by Janssen Scientific Affairs, LLC (Titusville, NJ, USA).

**Authorship.** All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

**Disclosures.** Michael Durkin and Jaime Blais are employees of Janssen Scientific Affairs, LLC.

**Compliance with Ethics Guidelines.** This article is based on previously conducted studies and does not contain any new studies with humans participants or animals performed by any of the authors.

**Data Availability.** Data from the CREDENCE trial will be made available in the public domain via the Yale University Open Data Access Project (<https://yoda.yale.edu/>) once the product and relevant indication studied have been approved by regulators in the USA and European Union, and the study has been completed for 18 months.

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