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Kidney protection with canagliflozin: A combined analysis of the randomized CANVAS program and CREDENCE trials

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Abstract

Aim: In the CANVAS Program and CREDENCE trials, the sodium glucose co-transporter 2 inhibitor canagliflozin reduced the risk of cardiovascular and kidney events in patients with type 2 diabetes. The current study analysed a pooled population to ascertain the kidney protection provided by canagliflozin across the full spectrum of kidney parameters.

Methods: This post-hoc pooled analysis of the CANVAS Program (N = 10 142) and CREDENCE trial (N = 4401), assessed the risk of the primary kidney composite (doubling of serum creatinine, end-stage kidney disease, renal death), in all patients and subgroups defined by baseline estimated glomerular filtration rate (<30, 30 to <45, 45 to <60 and ≥60 ml/min/1.73 m^2), albuminuria [<30, 30-300, >300 mg/g (<3.39, 3.39-33.9, >33.9 mg/mmol)] and 2012 Kidney Disease: Improving Global Outcomes (KDIGO) classification of chronic kidney disease (low/moderate, high and very high risk).

Results: In the overall population, the risk for the primary kidney composite outcome was 37% lower in the canagliflozin group versus placebo (HR: 0.63; 95% CI: 0.53, 0.77; $p < .001$). There was no evidence of heterogeneity in the kidney protective effects of canagliflozin across a range of kidney risks when stratified by baseline estimated glomerular filtration rate, albuminuria or KDIGO risk category (all $p_{interaction} > .05$). A statistically significant risk reduction of the primary kidney composite outcome was sustained by approximately 18 months after randomization.

Conclusions: These results emphasize a critical role of canagliflozin in kidney protection across a broad spectrum of participants with type 2 diabetes with varying levels of kidney function.

KEYWORDS
canagliflozin, cardiovascular disease, diabetic nephropathy, SGLT2 inhibitors, type 2 diabetes

1 | INTRODUCTION

Sodium glucose co-transporter 2 (SGLT2) inhibitors reduce the risk of kidney disease progression in a growing number of patient populations. Secondary analyses of cardiovascular (CV) outcome trials first reported kidney protection in patients with type 2 diabetes (T2D) at high CV risk.[1] For participants at intermediate CV risk, canagliflozin reduced the risk of the composite kidney outcome of sustained doubling in serum creatinine, end-stage kidney disease (ESKD) or renal death by 47% in the CANVAS Program.[2] With additional evidence of kidney protection from SGLT2 inhibition in real-world observational data[3] and heart failure trials,[4] dedicated kidney outcome trials were eagerly anticipated.

The CREDENCE trial was the first dedicated kidney outcomes trial that showed evidence of kidney protection with canagliflozin in participants who have diabetic kidney disease (DKD) and a high risk of kidney disease progression.[5] This was followed by the DAPA-CKD trial, which recruited participants with chronic kidney disease (CKD) with and without T2D,[6] and the EMPA-KIDNEY trial, which included participants with the lowest estimated glomerular filtration rate (eGFR; lower limit, 20 ml/min/1.73 m^2) and without albuminuria (in participants with eGFR 20-44 ml/min/1.73 m^2).[7] Despite these trials, there remain knowledge gaps regarding the kidney protection conferred by SGLT2 inhibitors in patients with CKD, including in lower CKD stages, normoalbuminuric patients and advanced CKD stages approaching dialysis. Indeed, the EMPA-KIDNEY trial did not identify any benefit on the primary composite outcome in people with moderately elevated albuminuria, although a slower rate of eGFR loss was reported.

The generation of novel evidence supporting the clinical benefits of guideline-directed therapies in CKD populations is an important strategy to address the therapeutic inertia that serves as a barrier to the effective use and application of these therapies.[8] In particular, this may be an issue in those with advanced DKD where, faced with an increasing number of therapies in DKD management that have multiple potential side effects, clinicians may defer initiation of novel therapies with resultant loss in clinical benefits and preventable adverse outcomes. More recently, time to clinical benefit analyses have served to highlight the clinical consequences of therapeutic inertia and delayed drug initiation.[9,10]

Accordingly, our aim was to conduct a post-hoc pooled analysis of the CANVAS Program and CREDENCE to assess evidence of heterogeneity in the kidney protective effects of canagliflozin across a broad cohort of participants with T2D at varying risk of kidney disease progression. In response to the therapeutic inertia that exists with these agents, an additional aim was to examine the time at which statistically significant benefits are achieved with canagliflozin to understand better the potential consequences of delaying initiation of SGLT2 inhibition in high-risk patients.

2 | METHODS

2.1 | Trial populations

The CANVAS Program consisted of 10 142 participants with T2D, eGFR of ≥30 ml/min/1.73 m^2 who had established CV disease or were at high risk of CV disease. The CREDENCE trial consisted of 4401 participants with T2D, eGFR of 30 to <90 ml/min/1.73 m^2 and albuminuria of >300 to ≤5000 mg/g (>33.9 to ≤565.6 mg/mmol). Participants in each study were randomized to canagliflozin or placebo. Detailed study methods, statistical analysis plan and results of the CANVAS Program (ClinicalTrials.gov identifiers: NCT01032629, NCT01989754) and CREDENCE trial (NCT02065791) have been previously published.[11,12] The protocols were approved by the ethics committees at each site and the study was conducted in accordance with the ethical principles of the Declaration of Helsinki. All participants provided written informed consent.

2.2 | Participant categorization

For the purposes of this pooled analysis, the cohorts were analysed as a whole and by baseline eGFR (<30, 30 to <45, 45 to <60 and ≥60 ml/min/1.73 m^2), albuminuria [<30, A1; 30-300, A2; >300 mg/g, A3 (<3.39, 3.39-33.9, >33.9 mg/mmol, respectively)] and 2012 Kidney Disease: Improving Global Outcomes (KDIGO) classification of CKD (low/moderate risk, high risk, very high risk). While all participants had an eGFR ≥30 ml/min/1.73 m^2 at screening, some eGFR values decreased by the time of randomization assessment to <30 ml/min/1.73 m^2.

2.3 | Outcomes

This post-hoc pooled analysis examined a primary composite kidney outcome comprised of doubling of serum creatinine from baseline (average of randomization and pre-randomization values and doubling sustained for ≥30 days according to central laboratory assessment), ESKD (dialysis for ≥30 days, kidney transplantation, or an eGFR of <15 ml/min/1.73 m^2 sustained for ≥30 days according to central laboratory assessment), or death from renal disease. Secondary outcomes included components of the primary composite outcome. Analysis of eGFR slope was also performed on the cohort as a whole and in the eGFR subgroups described above. The slope of the eGFR was defined as the annual mean difference in eGFR between canagliflozin and placebo, and was reported as acute, chronic and total. Calculations of eGFR were performed using the 2021 CKD-EPI formula.

2.4 | Statistical analysis

The intention-to treat population was used for analysis of outcomes. Hazard ratios (HRs), 95% confidence intervals (CIs) and *p* values were

TABLE 1 Baseline characteristics for the pooled CANVAS Program and CREDENCE trial by baseline eGFR

Characteristics[a]	eGFR <30 ml/min/1.73 m^2 (n = 202)	eGFR 30 to <45 ml/min/1.73 m^2 (n = 1717)	eGFR 45 to <60 ml/min/1.73 m^2 (n = 2751)	eGFR ≥60 ml/min/1.73 m^2 (n = 9870)	Total population (n = 14540)
Age, years	5 (9.5)	66 (9.2)	65 (8.5)	62 (8.2)	63.2 (8.5)
Female, n (%)	78 (38.6)	615 (35.8)	1052 (38.2)	3380 (34.2)	5125 (35.2)
Race, n (%)					
Asian	27 (13.4)	317 (18.5)	430 (15.6)	1387 (14.1)	2161 (14.9%)
Black or African American	10 (5.0)	77 (4.5)	100 (3.6)	373 (3.8)	560 (3.9%)
White	135 (66.8)	1195 (69.6)	2036 (74.0)	7506 (76.0)	10 872 (74.8%)
Other[b]	30 (14.9)	128 (7.5)	185 (6.7)	604 (6.1)	947 (6.5%)
History hypertension, n (%)	196 (97.0)	1666 (97.0)	2624 (95.4)	8896 (90.1)	13 382 (92.0%)
History of HF, n (%)	25 (12.4)	294 (17.1)	431 (15.7)	1361 (13.8)	2111 (14.5%)
History CV disease, n (%)	103 (51.0)	1014 (59.1)	1705 (62.0)	6052 (61.3)	8874 (61.0%)
Diabetes duration, year	17 (9.3)	179 (8.7)	16 (8.4)	13 (7.7)	14.2 (8.1)
SBP, mmHg	138 (16.7)	139 (17.1)	139 (15.7)	137 (15.5)	138(15.8)
DBP, mmHg	75.5 (10.4)	76.3 (10.0)	77.1 (9.7)	78.4 (9.4)	77.9 (9.6)
HbA1c, %	8.1 (1.2)	8.2 (1.2)	8.2 (1.1)	8.3 (1.0)	8.3 (1.1)
eGFR, ml/min/1.73 m^2	26 (3.3)	38 (4.1)	53 (4.3)	82 (16.1)	70.3 (21.9)
Median UACR, mg/mmol (IQR)	108.0 (44.6, 253)	74.4 (21.9, 194)	28.8 (1.6, 113)	1.8 (0.8, 15.9)	3.8 (1.0, 59.2)

Abbreviations: CV, cardiovascular disease; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HF, heart failure; IQR, interquartile range; SBP, systolic blood pressure; SD, standard deviation; UACR, urinary albumin/creatinine ratio.

[a]Data are mean ± SD unless otherwise noted.

[b]Includes American Indian, Alaska Native, Native Hawaiian, Pacific Islander, multiple, other and unknown.

estimated with Cox regression models,[13] with stratification according to trial for all canagliflozin groups combined versus placebo. Discrete methods were used to address ties in failure times as these events were frequently determined by protocol-specified laboratory tests. Annualized incidence rates were calculated per 1000 patient-years of follow-up.

We graphed time trajectories for the effect [HR (95% CI)] of pooled canagliflozin versus placebo on the primary kidney composite outcome by calculating the HR on each day following randomization until the last observation of the last patient using the Cox proportional hazards model that included a fixed effect for treatment and stratification, according to the trial.[14] Thus, all (cumulative) events for each post-randomization day were considered and subjects without events by that post-randomization day were censored on that day. We then assessed the timing when the treatment effect first reached statistical significance based on a $p < .05$, with all subsequent estimates also <.05.

We used mixed models for repeated measures to analyse the trajectory of eGFR over time in the on-treatment analysis population. To account for differences in visit schedules across time, we used the within-subject average of Weeks 3, 6 and 13 and the within-subject average of Weeks 18 and 26. These models assumed an unstructured covariance where possible (compound symmetry for eGFR <30 ml/min/1.73 m^2, due to lack of convergence) and adjusted for the baseline eGFR value, trial, trial visit interaction between treatment group and visit, and interaction between baseline value and visit as fixed effects.

Slope analyses regarding the on-treatment eGFR for the acute phase (baseline to Week 13), chronic phase (Week 13 to end of treatment) and total slope through Week 130 were performed using a two-slope model with a knot at Week 13, including the fixed effects of treatment, baseline eGFR, study, continuous time, time spline (one knot at Week 13), with two-way interactions of treatment by time, treatment by time spline, study by time, study by time spline, and the random effects of intercept, time and time spline. Total slope at Week 130 was calculated as a linear contrast of the acute and chronic phases based on the two-slope model. To assess interaction in effects on slope outcomes, we performed slope analyses separately for each eGFR subgroup to obtain treatment effects and their standard errors. We then compared the estimated effects between subgroups while accounting for the estimated standard error within each subgroup using χ^2 test with degrees of freedom equal to 1 less than the number of subgroups being compared.[15]

3 | RESULTS

3.1 | Pooled analysis

The pooled cohort consisted of 14 540 participants with baseline mean eGFR of 70 ± 22 ml/min/1.73 m^2. Baseline characteristics of the pooled cohort divided by eGFR subgroups are reported in Table 1. Across the entire cohort, the risk of the primary kidney composite

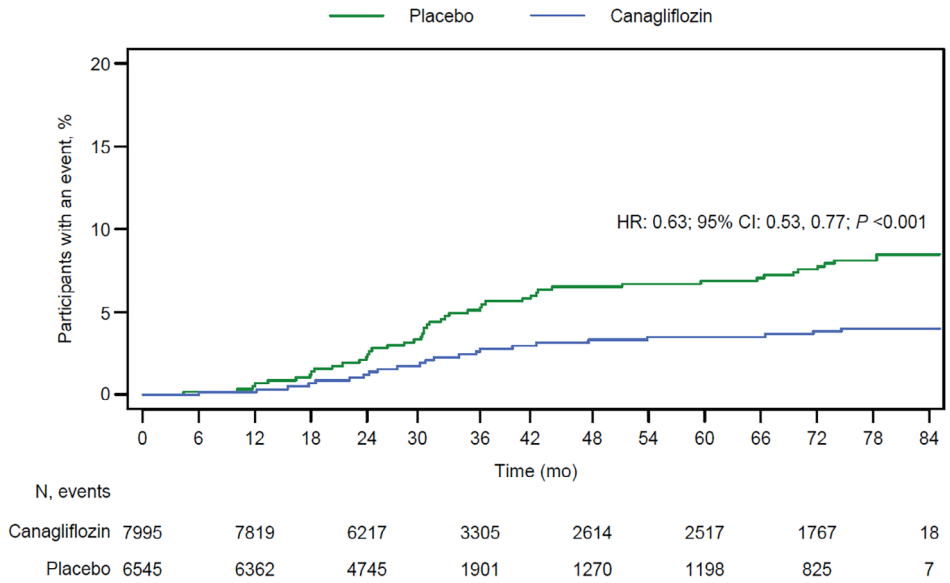

FIGURE 1 Risk for the primary kidney composite outcome over time. CI, confidence interval; HR, hazard ratio; mo, months.

outcome was 37% lower in the canagliflozin group compared with the placebo group (HR: 0.63; 95% CI: 0.53, 0.77; $p < .001$; Figure 1). The HRs for individual components of the composite outcome were as follows: doubling of serum creatinine (HR: 0.58; 95% CI: 0.47, 0.72) and ESKD (HR: 0.69; 95% CI: 0.55, 0.87). There were too few renal deaths to estimate reliably the treatment effects on this outcome alone, thus the HR for the composite of ESKD and renal death was estimated (HR: 0.68; 95% CI: 0.54, 0.86).

3.2 | Subgroup analyses

The effect of canagliflozin on the primary kidney composite outcome did not vary across participants' albuminuria categories (A1, A2 and A3; $p_{interaction} = .16$). This was also the case for the individual components of the composite outcome (Figure 2A). Similarly, there was no evidence of heterogeneity for the effect of canagliflozin versus placebo across participants with baseline eGFR categories <30, 30 to <45, 45 to <60 and ≥60 ml/min/1.73 m^2 ($p_{interaction} = .77$; Figure 2B). Figure S1 shows the Kaplan-Meier curves that illustrate consistent separation of the canagliflozin and placebo curves across all eGFR subgroups. There was no evidence of heterogeneity among subgroups of KDIGO risk categories ($p_{interaction} = .75$; Figure S2).

3.3 | Estimated glomerular filtration rate slope analyses

Acute, chronic and total slopes for the combined cohort and eGFR subgroups are reported in Table S1. Over the first 13 weeks, treatment with canagliflozin resulted in an acute reduction in eGFR of 1.92 ml/min/1.73 m^2 (95% CI: −2.25, −1.60) compared with placebo. There was some evidence that the magnitude of the acute effect attenuated across progressively lower eGFR subgroups ($p_{interaction} = .045$). Indeed, for those with eGFR <30 ml/min/1.73 m^2 at baseline, eGFR increased for both participants allocated to canagliflozin and placebo (Table S1). Thereafter, canagliflozin attenuated long-term decline in eGFR (chronic slope) by 1.91 ml/min/1.73 m^2/year (95% CI: 1.68, 2.13). Effects on chronic slope were consistent across eGFR subgroups ($p_{interaction} = .13$). Over the entire follow-up period of 130 weeks (total slope), canagliflozin attenuated eGFR decline by 0.95 ml/min/1.73 m^2/year (95% CI: 0.75, 1.16). The effect on total slope appeared larger across progressively lower eGFR subgroups ($p_{interaction} = .003$), driven partly by the more rapid loss of eGFR in the lower eGFR subgroups (Table S1). eGFR over time in the entire cohort and eGFR subgroups are displayed in Figure 3.

3.4 | Time to statistical significance

A statistically significant reduction in the risk of the primary kidney composite outcome was sustained approximately 18 months after randomization (HR at ~18 months: 0.68; 95% CI: 0.47, 0.99; $p < .05$), after which the upper bound of the 95% CI fell below 1 for the remaining follow-up period (Figure 4). While not immediately statistically significant, the HR curve was flat and <1.0 for the entire duration of the observation period with the CI narrowing as more events accrued over time. When analysed by baseline eGFR, time to statistical significance was shorter in low eGFR subgroups compared with higher eGFR subgroups, probably driven by a greater number of events accrued sooner (~18, 30 and 66 months in participants with baseline eGFR of 30 to 45, 45-60 and ≥60 ml/min/1.73 m^2, respectively).

4 | DISCUSSION

This post-hoc pooled analysis was conducted in a large cohort of 14 540 participants with T2D from the CANVAS Program and the CREDENCE trial, representing a diverse range of people at risk for

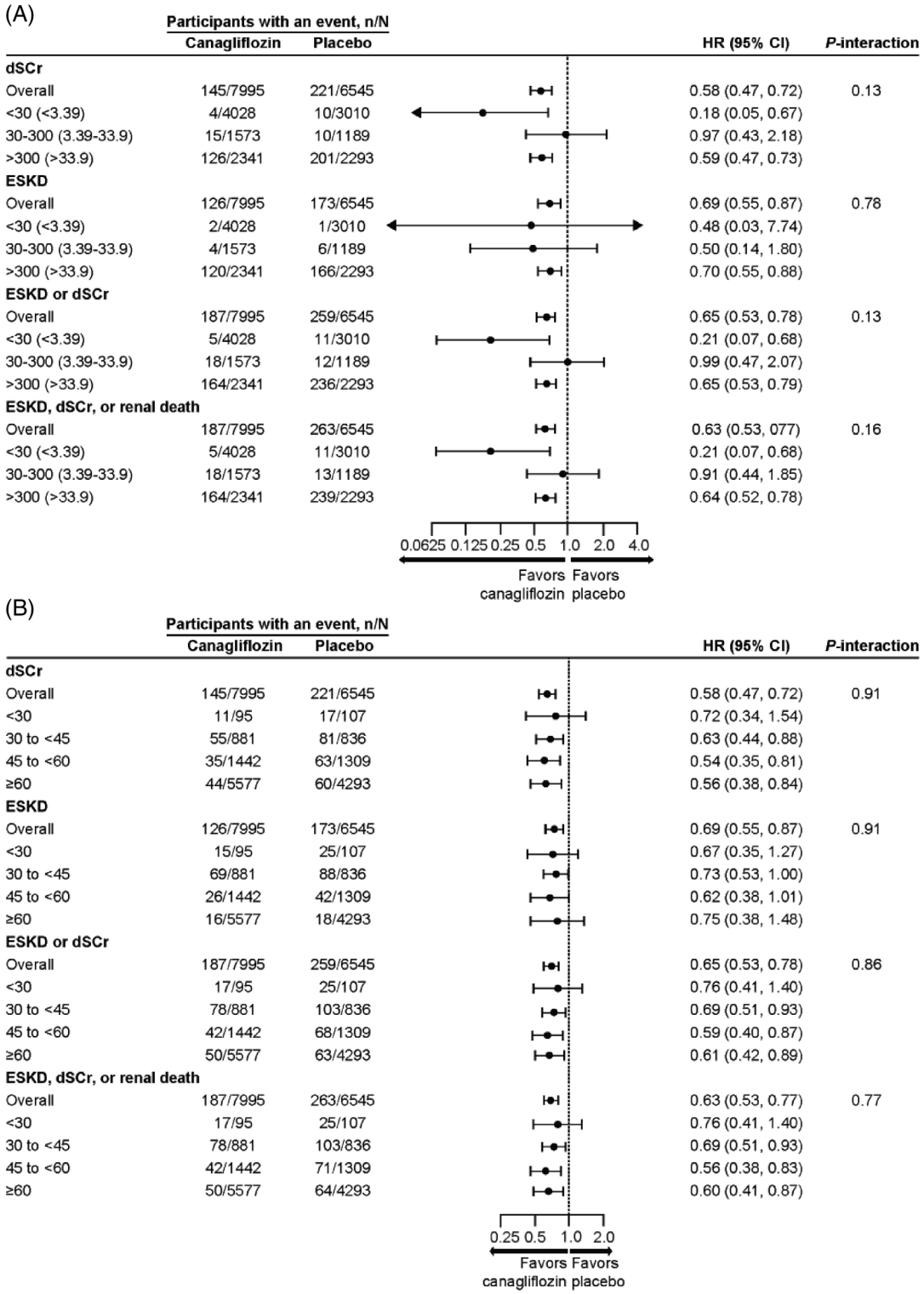

FIGURE 2 Risk for events by (A) UACR [mg/g (mg/mmol)] and (B) eGFR subgroups (ml/min/1.73 m^2). CI, confidence interval; dSCr, doubling of serum creatinine; eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; HR, hazard ratio; UACR, urine albumin/creatinine ratio.

kidney disease progression. There were three important findings in this analysis. First, there was no evidence of heterogeneity in the effect of canagliflozin on the composite kidney outcome of the doubling of serum creatinine, ESKD, or renal death across subgroups defined by baseline albuminuria, eGFR or KDIGO risk category. This contrasts with recent results from the EMPA-KIDNEY trial, which reported evidence of statistical heterogeneity between albuminuria subgroups.[7] Second, the beneficial effects of canagliflozin on kidney

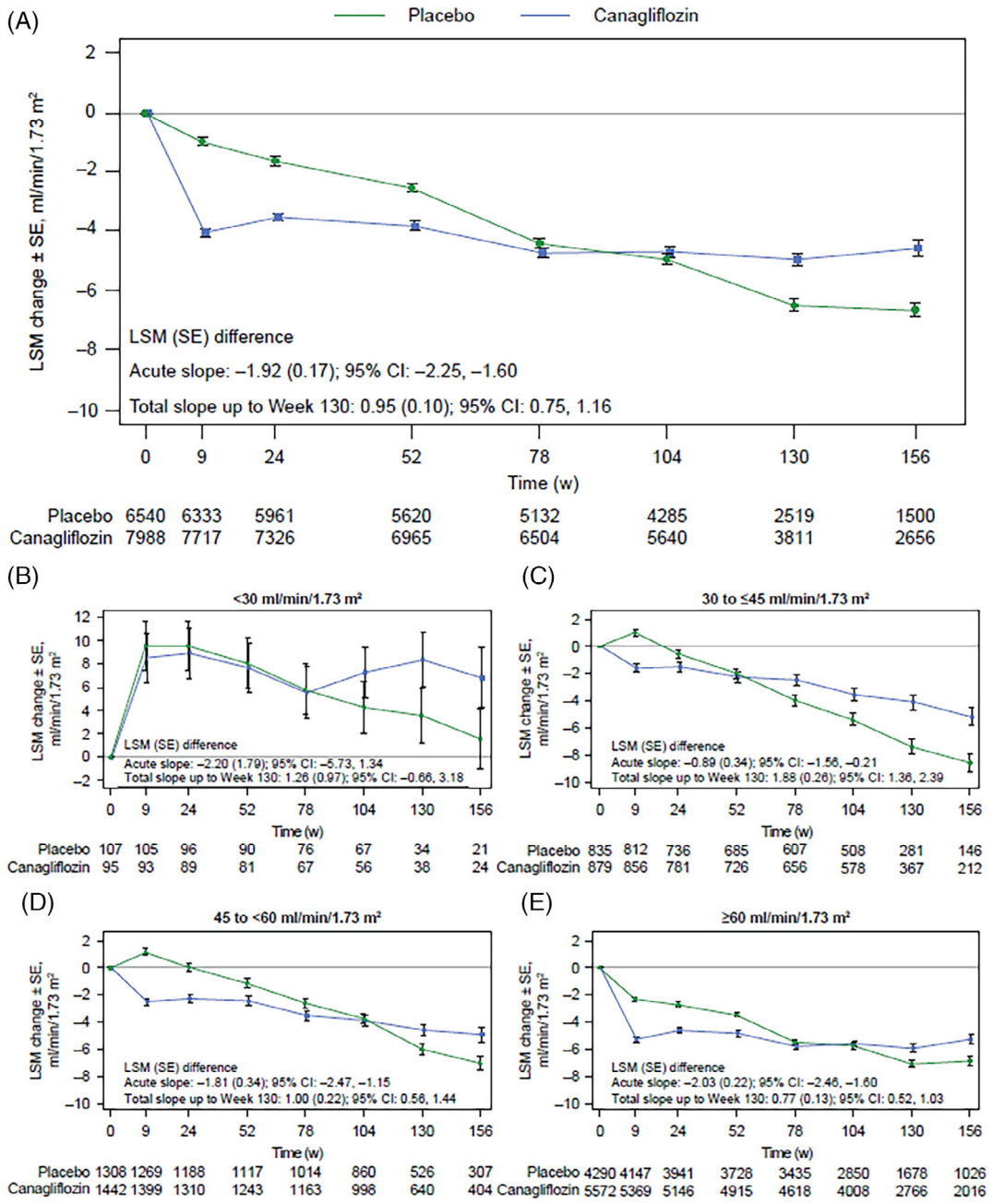

FIGURE 3 Change in eGFR over time (A) in the whole cohort and (B-E) by baseline eGFR subgroups. LSM (SE) difference = canagliflozin–placebo. CI, confidence interval; eGFR, estimated glomerular filtration rate; LSM, least-squares mean; SE, standard error; w, weeks.

disease progression, as represented by chronic and total eGFR slope, were evident across the range of kidney function studied, including those with eGFR <30 ml/min/1.73 m^2. Third, statistically and clinically significant reduction in the risk of the kidney composite outcome with canagliflozin was observed within 18 months of treatment initiation.

The consistent effect of canagliflozin on kidney outcomes across a broad range of kidney risk as represented by albuminuria, eGFR and KDIGO subgroups is in line with previous secondary analyses and meta-analyses of SGLT2 inhibitor trials where no evidence of interaction with baseline risk of kidney disease progression has been identified.[16] This analysis extends these findings to a broader range of participants, including those with eGFR <30 ml/min/1.73 m^2 and those with clinically preserved kidney function (albeit with CV risk factors). The absence of effect modification across albuminuria subgroups, while consistent with preceding analyses, does differ from EMPA-KIDNEY, a dedicated kidney outcome trial designed to have a lower median albuminuria and more participants without severely increased albuminuria. With respect to the primary composite outcome of CV death or kidney disease progression studied in EMPA-KIDNEY, there was some evidence that the magnitude of benefit increased with rising albuminuria.[7] One important caveat is that the present analysis was performed entirely in participants with T2D

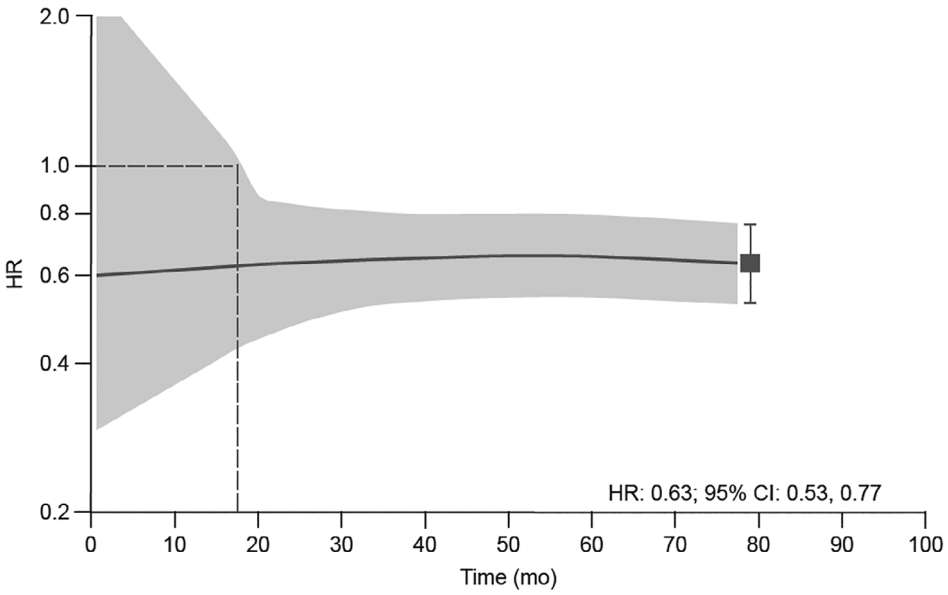

FIGURE 4 Time to statistical significance of renal composite. CI, confidence interval; HR, hazard ratio; mo, months.

while EMPA-KIDNEY included participants with and without diabetes, and a large proportion of patients with urine albumin/creatinine ratio in the A1 or A2 range. It remains to be seen the extent to which baseline albuminuria, eGFR and diabetes status together modify the effect of SGLT2 inhibition on kidney outcomes.

The effectiveness of SGLT2 inhibition in patients with CKD with severely decreased eGFR approaching ESKD is another clinical question that has yet to be completely answered. Our results are consistent with other analyses in the CREDENCE,[17] DAPA-CKD[18] and EMPA-KIDNEY trials showing effectiveness in patients with eGFR <30 ml/min/1.73 m^2, without evidence of heterogeneity. Until the EMPA-KIDNEY trial, all analyses to date, including patients with low eGFR, also had albuminuria due to the design of the original kidney outcome trials. The effectiveness of SGLT2 inhibition in patients with eGFR <30 ml/min/1.73 m^2 without albuminuria remains to be determined once more granular results from the EMPA-KIDNEY trial, which enrolled participants with eGFR from ≥20 to <45 ml/min/1.73 m^2 without a requirement for baseline albuminuria, are reported.

Canagliflozin-treated participants experienced stabilization of eGFR trajectories compared with a gradual decline in the placebo group. Chronic and total slope are validated surrogate endpoints that can predict kidney disease progression; treatment effects leading to eGFR preservation by ≥0.75 ml/min/1.73 m^2/year over 3 years have been shown to predict hard kidney endpoints.[19] In the present analysis, all eGFR subgroups experienced placebo-subtracted differences in chronic slope in excess of this treatment effect threshold, consistent with long-term kidney protection with canagliflozin. The magnitude of benefit on total slope appeared greater in participants with lower baseline eGFR, which may be at least partly reflect the more rapid loss of GFR in the low eGFR subgroups made up of individuals largely from CREDENCE with severely increased albuminuria. These results are consistent with other studies reporting greater absolute benefit of SGLT2 inhibition on CV and kidney outcomes in patients at higher baseline risk of kidney disease progression.[15,20]

Statistical significance with respect to the primary composite kidney outcome was attained approximately 18 months after randomization. While this reflects when the upper limit of the CI fell below 1, the HR for the treatment effect remained mostly flat during the entire observation period, potentially suggesting an even earlier benefit on kidney outcomes. Time to clinical significance for CV outcomes, including hospitalization for heart failure, has been previously measured in other SGLT2 inhibitor outcome trials,[9,10,14] although our work represents the first such analysis of its kind with respect to a primary kidney outcome. Dapagliflozin and empagliflozin both had a sustained clinical benefit of reducing CV death or worsening heart failure as early as 1 month after randomization.[9,14] The difference between the kidney and heart failure outcomes may be explained by the nature of these outcomes and the physiological effects of SGLT2 inhibition. Relevant to heart failure outcomes, SGLT2 inhibition causes an acute and sustained plasma volume contraction, reductions in cardiac preload and myocardial stretch, and reductions in natriuretic peptides.[21,22] These acute physiological changes can be expected to translate to relatively quick reductions in adverse heart failure outcomes. In contrast, loss of kidney function can take many years to occur and thus sufficient follow-up is required for events to accrue. Indeed, the albuminuria-lowering effect of SGLT2 inhibitors in CKD is observed after only 14 days of treatment.[23] These data contrast with other interventions that protect kidney function in people with T2D, such as intensive glucose lowering, the benefits of which are observed over a median follow-up of 5 years.[24]

The probable rapid clinical benefit of canagliflozin treatment, statistically confirmed at just under 18 months after randomization, not only underscores the importance of timely initiation of SGLT2 inhibition but also the importance of medication compliance and sustained use of the drug to obtain clinical benefits. Unfortunately, despite high-quality evidence, uptake of guideline-directed therapies in the management of DKD and CKD remains suboptimal, including for medications that block the renin-angiotensin-aldosterone system

and SGLT2 inhibitors.[8] While solutions to improve uptake of guideline-directed therapies in DKD are complex, time to clinical benefit analyses may facilitate appropriate and timely use of these novel and effective therapies.

The strengths of this analysis include the large number of participants studied in a high-quality trial environment with blinded expert outcome adjudication. Participants were on optimal medical management at baseline with both trials having high rates of renin-angiotensin-aldosterone system blockade prescription as well as other agents conferring cardiorenal protection. Results of this study are relevant to the typical nephrology practice considering the broad range of kidney function and kidney risk represented in this combined cohort.

There are limitations to consider. This was an exploratory integrated analysis of two distinct clinical trials that were not originally designed to detect treatment effects in specific subgroups of eGFR, albuminuria and KDIGO risk category. The low number of participants and events in the eGFR <30 ml/min/1.73 m^2 subgroup means that analyses were probably insufficiently powered to draw definite conclusions on the totality of the benefits of canagliflozin in this cohort.

In conclusion, this analysis of the combined CANVAS Program and CREDENCE trial cohorts, showed no evidence of heterogeneity in the kidney protective effects of canagliflozin across a range of kidney risk as determined by baseline eGFR, albuminuria, or KDIGO risk stratification. These results emphasize the central role of SGLT2 inhibition in kidney protection across a broad spectrum of individuals with T2D.

AUTHOR CONTRIBUTIONS

Vikas S. Sridhar, Brendon L. Neuen, Fernando G. Ang, Clare Arnott, David Z. Cherney, Robert A. Fletcher, Vlado Perkovic, Wally Rapattoni, David C. Wheeler and Adeera Levin contributed to the conceptualization, data curation and data interpretation. April Slee performed the formal analysis. Vikas S. Sridhar wrote the original draft the manuscript, and all authors were involved in the review and editing of the manuscript.

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CONFLICT OF INTEREST STATEMENT

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DATA AVAILABILITY STATEMENT

The data sharing policy of Janssen Pharmaceutical Companies of Johnson & Johnson is available at https://www.janssen.com/clinical-trials/transparency. As noted on this site, requests for access to the study data can be submitted through Yale Open Data Access (YODA) Project site at http://yoda.yale.edu.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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