Effects of newer kidney protective agents on kidney endpoints provide implications for future clinical trials

OPEN

Hiddo J.L. Heerspink[1,2], Niels Jongs[1], Brendon L. Neuen[2,3], Patrick Schloemer[4], Muthiah Vaduganathan[5], Lesley A. Inker[6], Robert A. Fletcher[2], David C. Wheeler[7], George Bakris[8], Tom Greene[9], Glenn M. Chertow[10,11] and Vlado Perkovic[12]

[1]*Department of Clinical Pharmacy and Pharmacology, University Medical Center Groningen, University of Groningen, Groningen, Netherlands;* [2]*The George Institute for Global Health, Sydney, Australia;* [3]*Department of Renal Medicine, Royal North Shore Hospital, Sydney, Australia;* [4]*Statistics & Data Insights, Bayer AG, Berlin, Germany;* [5]*Harvard Medical School, Boston, Massachusetts, USA;* [6]*Division of Nephrology, Tufts Medical Center, Boston, Massachusetts, USA;* [7]*Department of Renal Medicine, University College London, London, UK;* [8]*Department of Medicine, University of Chicago, Chicago, Illinois, USA;* [9]*Division of Biostatistics, Department of Population Health Sciences, University of Utah Health, Salt Lake City, Utah, USA;* [10]*Department of Medicine, Epidemiology and Biostatistics, Stanford University School of Medicine, Stanford, California, USA;* [11]*Department of Health Policy, Stanford University School of Medicine, Stanford, California, USA; and* [12]*Faculty of Medicine & Health, University New South Wales, Sydney, Australia*

Doubling of serum creatinine (equivalent to a 57% decline in the estimated glomerular filtration rate (eGFR)) is an accepted component of a composite kidney endpoint in clinical trials. Smaller declines in eGFR (40%, 50%) have been applied in several recently conducted clinical trials. Here, we assessed the effects of newer kidney protective agents on endpoints including smaller proportional declines in eGFR to compare relative event rates and the magnitude of observed treatment effects. We performed a post hoc analysis of 4401 patients in the CREDENCE, 4304 in the DAPA-CKD, 5734 in the FIDELIO-DKD, and 3668 in the SONAR trials, which assessed the effects of canagliflozin, dapagliflozin, finerenone and atrasentan in patients with chronic kidney disease. Effects of active therapies versus placebo on alternative composite kidney endpoints incorporating different eGFR decline thresholds (40%, 50%, or 57% eGFR reductions from baseline) with kidney failure or death due to kidney failure were compared. Cox-proportional hazards regression models were used to assess and compare treatment effects. During follow-up, event rates were higher for endpoints incorporating smaller versus larger eGFR decline thresholds. Compared to the treatment effects on kidney failure or death due to kidney failure, the magnitude of relative treatment effects was generally similar when considering composite endpoints incorporating smaller declines in eGFR. Hazard ratios for the four interventions ranged from 0.63 to 0.82 for the endpoint incorporating 40% eGFR decline and 0.59 to 0.76 for the endpoint incorporating 57% eGFR decline. Clinical trials incorporating a 40% eGFR decline in a composite endpoint would require approximately half the number of participants compared to a 57% eGFR decline with equivalent statistical power. Thus, in populations at high risk of CKD progression, the relative effects of newer kidney protective therapies appear generally similar across endpoints based on varying eGFR decline thresholds.

Kidney International (2023) **104,** 181–188; https://doi.org/10.1016/j.kint.2023.03.037

KEYWORDS: kidney failure; mineralocorticoid receptor antagonist; randomized controlled clinical trial; SGLT2 inhibitor

Lay Summary

The established endpoint for clinical trials in nephrology includes a large decline in estimated glomerular filtration rate (eGFR; 57%). To assess drug effects, the established endpoint requires large sample sizes and trials of long duration. Alternative endpoints that include smaller declines in eGFR have been proposed and applied in recent clinical trials. In this new study, we demonstrate in 4 recently completed clinical trials that the effects of newer nephroprotective agents are generally similar across endpoints using varying eGFR declines. Because endpoints based on smaller declines in eGFR occur more often, the sample size needed to detect treatment effects would be smaller if less-stringent eGFR thresholds are used, thereby facilitating conduct of clinical trials.

Kidney failure is the most significant long-term complication of chronic kidney disease (CKD), for clinicians, patients, and caregivers.[1] Given this, clinical trials aiming to develop new therapies for CKD have traditionally used kidney failure as a component of a composite endpoint, together with a relatively large decline in kidney function

Correspondence: *Hiddo J.L. Heerspink, Department of Clinical Pharmacy and Pharmacology, University of Groningen, Hanzeplein 1, PO Box 30 001, Groningen, The Netherlands E-mail: h.j.lambers.heerspink@umcg.nl*

Received 8 January 2023; revised 2 March 2023; accepted 24 March 2023; published online 28 April 2023

(e.g., doubling of serum creatinine). Because kidney failure and doubling of serum creatinine are late manifestations of CKD progression, drug development for CKD has historically focused on patients with more advanced disease, to avoid protracted follow-up times and mitigate operational complexities. Surrogate endpoints that can reliably reflect longer-term, well-established endpoints could facilitate the conduct of clinical trials at earlier stages of CKD.[2]

In the past decade, significant progress has been made in validating surrogate endpoints. Initial studies focused on the validity of using declines in eGFR of less than 57% (equivalent to a doubling of serum creatinine) as a component of a composite endpoint.[3–5] A meta-analysis of clinical trials supported the validity of using a 30% eGFR decline in some circumstances, and a 40% decline in eGFR could be more broadly acceptable as a surrogate endpoint. However, for both surrogate endpoints, the pattern of acute effects on eGFR should be examined, specifically because the acute eGFR lowering effects can attenuate the treatment effect estimate in confirmatory phase 3 trials.[6]

The validity of kidney endpoints defined by smaller declines in eGFR was demonstrated with established therapies, using data from clinical trials conducted mostly in the 1990s and early 2000s, with the majority being agents that inhibit the renin–angiotensin system. Newer classes of agents for attenuating CKD progression have emerged since then, including sodium–glucose co-transporter-2 (SGLT2) inhibitors (canagliflozin, dapagliflozin, and empagliflozin); a nonsteroidal mineralocorticoid receptor antagonist (finerenone); and an endothelin receptor antagonist (atrasentan).[7–10] These newer interventions all have acute eGFR-lowering effects, although of varying magnitude; whereas atrasentan exerts a modest eGFR-lowering acute effect (–0.8 ml/min per 1.73 m^2), the acute effect is 3- to 4-fold larger with finerenone and SGLT2 inhibitors.

Understanding the implications of alternative eGFR decline thresholds on the relative (and absolute) effects of these and other therapeutic agents will help inform clinical decision making in the near term, and the design of future clinical trials.

METHODS

Overall study design

In this study, we used data from pivotal placebo-controlled randomized clinical trials that assessed the efficacy and safety of either an SGLT2 inhibitor, a nonsteroidal mineralocorticoid receptor antagonist, or an endothelin receptor antagonist on composite endpoints of kidney failure or death due to kidney disease, with eGFR decline thresholds of 40%, 50%, and 57%. We selected pivotal phase 3 clinical trials enrolling patients with type 2 diabetes and CKD that demonstrated a significant risk reduction in the respective composite kidney endpoint with the newer pharmacologic intervention. We therefore included the following trials: Canagliflozin and Renal Endpoints in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE [clinicaltrials.gov NCT02065791]); Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease (DAPA-CKD [NCT03036150]); Finerenone in Reducing Kidney Failure and Disease Progression in Diabetic Kidney Disease (FIDELIO-DKD [NCT02540993]); and the Study of Diabetic Nephropathy with Atrasentan (SONAR [NCT01858532]).

Clinical trials

CREDENCE. Between 2014 and 2017, the CREDENCE trial randomized 4401 patients who were at least 30 years of age, had a diagnosis of type 2 diabetes, an eGFR between 30 and 90 ml/min per 1.73 m^2, and a urinary albumin:creatinine ratio (UACR) between 300 and 5000 mg/g (>33.9–565.6 mg/mmol).[7] Eligible patients were prescribed an angiotensin-converting enzyme (ACE)–inhibitor or an angiotensin receptor blocker (ARB). Eligible participants were randomly assigned to receive either canagliflozin at a dose of 100 mg daily or placebo and were followed for a median duration of 2.6 years.

DAPA-CKD. Between 2017 and 2020, the DAPA-CKD trial enrolled 4304 patients aged 18 years or older who had CKD, with or without a diagnosis of type 2 diabetes, an eGFR between 25 and 75 ml/min per 1.73 m^2, and a UACR between 200 and 5000 mg/g (>22.6–565.6 mg/mmol).[8] Eligible patients were prescribed an ACE-inhibitor or ARB if tolerated. Participants were randomly assigned to receive either dapagliflozin at a dose of 10 mg once daily or placebo and were followed for a median of 2.4 years.[2]

FIDELIO-DKD. Between 2015 and 2018, the FIDELIO-DKD trial enrolled 5734 patients aged 18 years or older who had CKD and a diagnosis of type 2 diabetes.[10] Participants had an eGFR of 25 to <60 ml/min per 1.73 m^2, a UACR of 30 to <300 mg/g (3.9–<33.9 mg/mmol), and diabetic retinopathy; or an eGFR of 25 to <75 ml/min per 1.73 m^2 and a UACR between 300 and 5000 mg/g (33.9–565.6 mg/mmol). Eligible patients were prescribed an ACE-inhibitor or ARB and were randomized to receive either finerenone or placebo and were followed for a median duration of 2.6 years.

SONAR. Between 2013 and 2017, the SONAR trial enrolled 5117 patients aged 18 to 85 years who had a diagnosis of type 2 diabetes, an eGFR between 25 and 75 ml/min per 1.73 m^2, and a UACR between 300 and 5000 mg/g (>33.9–565.6 mg/mmol).[9] All patients were prescribed an ACE-inhibitor or ARB. All eligible participants received atrasentan at a dose of 0.75 mg during an open-label active run-in "enrichment period" aimed to select patients who were likely to respond to atrasentan, defined as a reduction in UACR of 30% or more, and exclude patients prone to atrasentan-induced fluid retention, defined as an increase of at least 3 kg in body weight or an increase in brain natriuretic peptide to at least 300 pg/ml. All responder patients who tolerated atrasentan ($n = 2648$) and a selection of nonresponder patients ($n = 1020$) proceeded to the randomization visit and were assigned in a 1:1 ratio to either continue receiving atrasentan at a dose of 0.75 mg/d or transition to receiving placebo. For the current analysis, we combined the responder and nonresponder strata, as no evidence indicated that the effect of atrasentan on the primary composite kidney outcome was different in responders and nonresponders. The median duration of follow-up was 2.2 years.

Endpoints

The kidney endpoints evaluated in this analysis were a composite of kidney failure (defined as requiring maintenance dialysis for at least 28 days [90 days in the FIDELIO-DKD trial], having undergone kidney transplantation, or having an eGFR <15 ml/min per 1.73 m^2 sustained for at least 28 days), death due to kidney failure, or decline in eGFR sustained for at least 28 days (thresholds

of ≥40%, ≥50%, and ≥57%). A sustained eGFR <15 ml/min per 1.73 m^2 was not a component of the kidney failure definition in the FIDELIO-DKD trial.

Statistical analyses

We performed all statistical analyses following the intention-to-treat principle. We used proportional hazards (Cox) regression models to assess the effect of the active intervention, compared to placebo, on the risk for first relevant composite kidney endpoint. The kidney endpoint in each analysis was defined as kidney failure, death due to kidney failure, or varying eGFR thresholds—57%, 50%, or 40% decline in eGFR from baseline. We also assessed the effects of the interventions on the composite endpoint of kidney failure or death due to kidney failure. We adjusted Cox models for stratification factors used at randomization as originally defined in each clinical trial.

To estimate treatment effects on the acute and chronic eGFR slope, we used a shared parameter mixed-effects model, as previously described, based on a linear eGFR slope starting at 3 months post-randomization, while accounting for informative censoring due to kidney failure or death.[11–13] The model adjusts for baseline eGFR and accounts for different sources of variation in eGFR between and within participants and treatment arms. Differences between the randomized groups in the mean eGFR at the 3-months follow-up, and the mean slopes from 3 months onward factored by the follow-up duration, represented the treatment effects on the acute and chronic eGFR slopes, respectively.

We calculated required sample sizes for future kidney outcome trials with PASS version 14.07.6 (PASS NCSS, LLC). We used observed hazard ratios as the assumed relative risk reduction for each composite endpoint and the event rate for that endpoint in participants assigned to placebo. We calculated the required sample size to provide 90% power at a 2-sided α-level of 0.05 with an allocation ratio of 1, assuming 18 months of enrollment and 48 months of total trial duration.

RESULTS

Patient characteristics of the CREDENCE, DAPA-CKD, FIDELIO-DKD, and SONAR trials are shown in Table 1. Mean age ranged between 61.8 and 65.6 years; mean eGFR ranged between 42.3 and 56.2 ml/min per 1.73 m^2, and median UACR ranged between 828 and 949 mg/g. An ACEi or ARB was prescribed for all participants in the SONAR, CREDENCE, and FIDELIO-DKD trials, and for 97% of participants in the DAPA-CKD trial. In all clinical trials, baseline characteristics were well balanced across randomized patient groups.

Initiation of canagliflozin, dapagliflozin, or finerenone led to larger acute eGFR-lowering effects, compared to atrasentan (Table 2). During follow-up, the chronic eGFR slope was significantly reduced, with all interventions with numerically larger effects observed with canagliflozin (Table 2).

Table 1 | Baseline characteristics

Characteristic	CREDENCE (N = 4401)	DAPA-CKD (N = 4304)	FIDELIO-DKD (N = 5674)	SONAR (N = 3668)
Enrollment period	2014–2017	2016–2018	2015–2018	2013–2018
Age, yr	63.0 (9)	61.8 (12)	65.6 (9)	64.5 (8.8)
Female sex	494 (33.9)	1425 (33.1)	1691 (29.8)	946 (25.8)
Race				
Asian	877 (19.9)	1467 (34.1)	1440 (25.4)	1198 (32.7)
Black	224 (5.1)	191 (4.4)	264 (4.7)	224 (6.1)
Other	369 (8.4)	356 (8.3)	378 (6.7)	136 (3.7)
White	2931 (66.6)	2290 (53.2)	3592 (63.3)	2110 (57.5)
Blood pressure, mm Hg				
Systolic	140.0 (16)	137.1 (17)	138.0 (14)	133.3 (15)
Diastolic	78.3 (9)	77.5 (11)	75.8 (10)	71.5 (10)
Body weight, kg	87.1 (20.7)	81.7 (21)	87.2 (20)	85.7 (20)
Hba1c, %	8.3 (1.3)	7.06 (1.7)	7.7 (1.3)	7.8 (1.5)
eGFR, ml/min per 1.73 m^2	56.2 (18)	43.1 (12)	44.3 (13)	42.3 (14)
eGFR, ml/min per 1.73 m^2				
>60	1769 (40.2)	454 (10.5)	656 (11.6)	468 (12.8)
<60	2632 (59.8)	3850 (89.5)	5016 (88.4)	3191 (87.0)
UACR, mg/g	927 (463–1833)	949 (477–1885)	852 (446–1634)	828 (458–1556)
UACR, mg/g				
≥1000	2053 (46.7)	2079 (48.3)	2480 (43.7)	892 (24.5)
≤1000	2348 (53.3)	2225 (51.7)	3191 (56.2)	2771 (75.5)
Baseline medications				
ACEi	1922 (43.7)	1353 (31.4)	1942 (34.2)	1319 (36.0)
ARB	2480 (56.4)	2870 (66.7)	3725 (65.7)	2391 (65.2)
Diuretics	2057 (46.7)	1882 (43.7)	3214 (56.6)	3157 (86.1)
Insulin	2884 (65.5)	1598 (37.1)	3637 (64.1)	2315 (63.1)
Statins	3036 (69.0)	2794 (64.9)	4215 (74.3)	2707 (73.8)

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin-receptor blocker; CREDENCE, Canagliflozin and Renal Endpoints in Diabetes with Established Nephropathy Clinical Evaluation; DAPA-CKD, Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease; eGFR, estimated glomerular filtration rate; FIDELIO-DKD, Finerenone in Reducing Kidney Failure and Disease Progression in Diabetic Kidney Disease; HbA1c, hemoglobin A1c; SONAR, Study of Diabetic Nephropathy with Atrasentan; UACR, urinary albumin-to-creatinine ratio.
Values are presented as mean (SD) or n (%), except for UACR, which is presented as median (25th–75th percentile).

Table 2 | Acute and chronic effects of the interventions on eGFR decline

Clinical trial	Intervention	Acute eGFR change, ml/min per 1.73 m^2 per mo			Chronic eGFR slope, ml/min per 1.73 m^2 per yr		
		Active	Placebo	Difference (95% CI)	Active	Placebo	Difference (95% CI)
CREDENCE	Canagliflozin	−0.93 (0.06)	−0.33 (0.07)	−0.60 (−0.78, −0.42)	−2.5 (0.14)	−5.0 (0.15)	2.5 (2.1, 2.8)
DAPA-CKD	Dapagliflozin	−0.88 (0.05)	−0.45 (0.05)	−0.43 (−0.57, −0.30)	−2.4 (0.16)	−3.9 (0.11)	1.5 (1.2, 1.8)
FIDELIO-DKD	Finerenone	−0.95 (0.04)	−0.19 (0.04)	−0.76 (−0.88, −0.64)	−3.1 (0.08)	−4.4 (0.09)	1.3 (1.1, 1.6)
SONAR	Atrasentan	−0.20 (0.05)	−0.11 (0.05)	−0.09 (−0.23, 0.05)	−3.0 (0.13)	−3.7 (0.13)	0.7 (0.3, 1.1)

CI, confidence interval; CREDENCE, Canagliflozin and Renal Endpoints in Diabetes with Established Nephropathy Clinical Evaluation; DAPA-CKD, Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease; eGFR, estimated glomerular filtration rate; FIDELIO-DKD, Finerenone in Reducing Kidney Failure and Disease Progression in Diabetic Kidney Disease; SONAR, Study of Diabetic Nephropathy with Atrasentan.

Treatment effects on composite kidney outcomes

During follow-up, 284 (6.5%), 272 (6.3%), 444 (7.8%), and 287 (7.8%) kidney failure or death due to kidney failure events occurred in the CREDENCE, DAPA-CKD, FIDELIO-DKD, and SONAR trials, respectively. The composite endpoint of 57% eGFR decline, end-stage kidney disease, or death due to kidney failure occurred in 319 (7.2%), 313 (7.3%), 578 (10.2%), and 323 (8.8%) participants during the follow-up of the respective trials. As expected, incorporating lesser declines in eGFR within the composite kidney endpoint increased the number of events (Figure 1). The number of 40% eGFR decline endpoints during the first 3 to 6 months of follow-up was higher in the canagliflozin and finerenone groups, compared to the placebo group, of the relevant trials, triggered by the initial decline, an effect not observed with dapagliflozin or atrasentan (Supplementary Table S1).

Treatment effects of the active, compared to placebo, groups in each trial are shown in Figure 1. The precision of the treatment effect increased for endpoints with lesser declines in eGFR, as reflected by the narrower 95% confidence interval and decreased standard error (for example, the standard error of the log hazard ratio was 0.058 for 57% eGFR decline, compared to 0.043 for 40% eGFR decline in the DAPA-CKD trial). The magnitudes of the treatment effects of canagliflozin, dapagliflozin, and atrasentan on the composite endpoint of end-stage kidney disease or death due to kidney failure were similar, compared to the composite endpoint of kidney failure, death due to kidney failure, or 57% eGFR decline (Figure 1). The effect of finerenone on the composite endpoint of end-stage kidney disease or death due to kidney failure was somewhat smaller, compared to the composite endpoints that included an eGFR decline threshold. Overall, the direction and magnitude of these effect sizes in all 4 trials remained generally similar when the 57% eGFR decline was replaced by a 50% or 40% eGFR reduction.

Sample size

Figure 2 shows the impact on the statistical power for the composite kidney endpoints based on each of the eGFR thresholds to detect the observed relative risk reduction. As a result of higher event rates and similar relative risk reductions, required sample sizes would have been smaller in all trials if less-stringent eGFR thresholds had been used.

DISCUSSION

This analysis of 4 recently completed clinical trials in CKD primarily associated with type 2 diabetes compared event rates, treatment effect sizes, and required sample sizes of different kidney endpoints, including different eGFR decline thresholds. The results demonstrated that the SGLT2 inhibitors canagliflozin and dapagliflozin, the nonsteroidal mineralocorticoid receptor antagonist finerenone, and the endothelin receptor antagonist atrasentan showed benefit on all kidney endpoints irrespective of the eGFR threshold included in this analysis. Because the number of endpoints was higher, with no appreciable difference in relative risk reduction, the required sample size to detect the observed treatment effect would be smaller if less-stringent thresholds were used.

Many treatments that affect CKD progression cause acute effects on eGFR that differ from their long-term effects.[14] Analyses prepared for a workshop organized by the National Kidney Foundation and the US Food and Drug Administration concluded that for interventions that cause large acute reductions in eGFR (such as use of SGLT2 inhibitors and mineralocorticoid receptor antagonists), a 50% or 57% eGFR decline is the preferred endpoint.[6,15] These recommendations were made based on clinical trial results and simulations that demonstrated that the acute decline in eGFR contributes to additional endpoints in the active treatment arm. Presumably, this impact is at least in part due to random variations in eGFR over time, which can periodically exceed the eGFR endpoint threshold. Consistent with these prior findings, our results also showed a higher number of events in the active treatment arm in the canagliflozin and finerenone trials early in follow-up. In contrast to prior analyses demonstrating that the treatment effects of ACE inhibitors and ARBs are attenuated when lower eGFR decline thresholds are used,[3] our analyses show generally similar treatment effects across eGFR decline thresholds. This similarity is most likely explained by the balance between the magnitude of the acute and chronic treatment effects on eGFR. The SGLT2 inhibitors and finerenone exert relatively large acute reductions in eGFR but also show a profound stabilization of the rate of eGFR decline during maintenance treatment, which appears to be sufficient to overcome the acute reduction in eGFR.[7,10,16] Indeed, the chronic treatment effects of canagliflozin, dapagliflozin, and finerenone were

Composite kidney outcome	Events (N/%) Active	Events (N/%) Placebo	Event rate (events per 100 pt years) Active	Event rate (events per 100 pt years) Placebo	HR (95% CI)
Sustained eGFR decline, kidney failure, or death due to kidney failure					
CREDENCE					
40% eGFR reduction	212 (9.6)	320 (14.6)	3.8	5.9	0.63 (0.53, 0.75)
50% eGFR reduction	153 (6.9)	230 (10.5)	2.7	4.1	0.64 (0.52, 0.79)
57% eGFR reduction	126 (5.7)	193 (8.8)	2.2	3.4	0.63 (0.50, 0.79)
Kidney failure or death due to kidney failure	118 (5.4)	166 (7.5)	2.0	2.9	0.69 (0.54, 0.87)
DAPA-CKD					
40% eGFR reduction	235 (10.9)	345 (16.0)	5.6	8.5	0.64 (0.54, 0.76)
50% eGFR reduction	142 (6.6)	243 (11.3)	3.3	5.8	0.56 (0.45, 0.68)
57% eGFR reduction	120 (5.6)	193 (8.9)	2.8	4.6	0.59 (0.47, 0.75)
Kidney failure or death due to kidney failure	109 (5.1)	163 (7.6)	2.5	3.8	0.64 (0.50, 0.81)
FIDELIO-DKD					
40% eGFR reduction	504 (17.8)	600 (21.1)	7.6	9.1	0.82 (0.73, 0.93)
50% eGFR reduction	320 (11.3)	413 (14.5)	4.7	6.1	0.76 (0.66, 0.88)
57% eGFR reduction	252 (8.9)	326 (11.5)	3.6	4.7	0.76 (0.65, 0.90)
Kidney failure or death due to kidney failure	208 (7.3)	236 (8.3)	3.0	3.4	0.87 (0.72, 1.05)
SONAR					
40% eGFR reduction	257 (14.0)	300 (16.4)	6.7	7.9	0.73 (0.61, 0.86)
50% eGFR reduction	181 (9.9)	209 (11.4)	4.7	5.5	0.76 (0.62, 0.92)
57% eGFR reduction	146 (8.0)	177 (9.7)	3.8	4.7	0.73 (0.58, 0.91)
Kidney failure or death due to kidney failure	126 (6.9)	161 (8.8)	3.3	4.2	0.70 (0.55, 0.88)

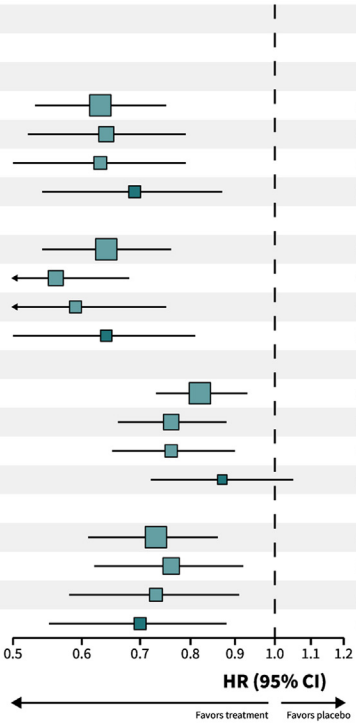

Figure 1 | New interventions for patients with chronic kidney disease decrease the risk of a composite kidney endpoint on the basis of a 57%, 50%, or 40% estimated glomerular filtration rate (eGFR) decline, compared with placebo. eGFR decline thresholds were defined based on 2 consecutive measurements at least 28 days apart. The endpoints are a composite of varying eGFR thresholds, kidney failure, or death due to kidney failure. The treatment effect on the composite endpoint of kidney failure or death due to kidney failure is shown in the bottom row for each trial. The solid square indicates the point estimate, and the horizontal line indicates its 95% confidence interval (CI). The size of each square is proportional to the standard error of the log hazard ratio (HR). CREDENCE, Canagliflozin and Renal Endpoints in Diabetes with Established Nephropathy Clinical Evaluation; DAPA-CKD, Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease; FIDELIO-DKD, Finerenone in Reducing Kidney Failure and Disease Progression in Diabetic Kidney Disease; pt years, patient years; SONAR, Study of Diabetic Nephropathy with Atrasentan.

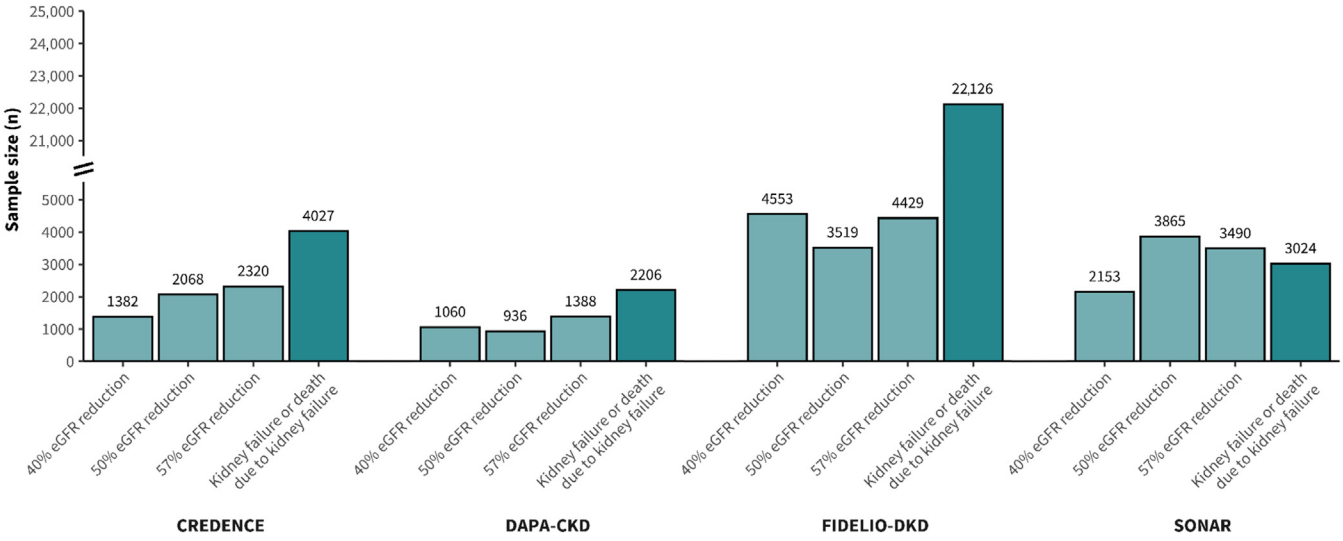

Figure 2 | Sample size for different endpoints. CREDENCE, Canagliflozin and Renal Endpoints in Diabetes with Established Nephropathy Clinical Evaluation; DAPA-CKD, Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease; eGFR, estimated glomerular filtration rate; FIDELIO-DKD, Finerenone in Reducing Kidney Failure and Disease Progression in Diabetic Kidney Disease; SONAR, Study of Diabetic Nephropathy with Atrasentan.

approximately twice as large as those observed with losartan and irbesartan in the Reduction of Endpoints in Non–Insulin-Dependent Diabetes Mellitus with the Angiotensin II Antagonist Losartan (RENAAL) trial and the Irbesartan Diabetic Nephropathy Trial (IDNT), respectively, although these trials were conducted 2 decades ago when standards of care were different. Thus, in settings in which acute eGFR-lowering effects are balanced by marked attenuation of eGFR decline, a 50% eGFR threshold as a component of a composite kidney endpoint seems appropriate for balancing the relatively higher event rates with sufficient protection against the acute eGFR-lowering effects.

Compared with a 57% eGFR reduction, use of 50% or 40% eGFR decline thresholds did not result in an attenuation of the treatment effect size with atrasentan in the SONAR trial. The acute effect of atrasentan of –0.09 ml/min per 1.73 m^2 per month is considerably smaller relative to those of RAAS or SGLT2 inhibitors. Other clinical trials of endothelin receptor antagonists have also demonstrated relatively small acute effects on GFR.[17,18] For interventions with little to no acute effect on GFR, lower eGFR decline thresholds should increase statistical power without influencing the magnitude of observed treatment effects. The lack of attenuation of treatment effects with endothelin receptor antagonists is consistent with other interventions without acute (negative) GFR effects.

Our analysis of the DAPA-CKD and CREDENCE trials contrasts with SGLT2 outcome trials in patients with type 2 diabetes who are at high cardiovascular risk but low risk of CKD progression. Analyses from these trials showed that the treatment effects of canagliflozin and empagliflozin were attenuated when lower eGFR decline thresholds were incorporated in the composite kidney endpoint.[19,20] The attenuation of the treatment effect in the Canagliflozin Cardiovascular Assessment Study (CANVAS Program) and Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPAREG-OUTCOME trial) may be attributed to the populations enrolled in these trials, in which most participants had normal or near-normal kidney function, and normal or low levels of albuminuria. The rate of kidney function decline in these trials was much slower relative to that in the trials included in our analysis.[21,22] As a result of the considerably slower rate of eGFR decline in the control arm, smaller eGFR decline thresholds were more likely to be susceptible to the relatively large acute reduction in eGFR with SGLT2 inhibitors, thereby "diluting" the treatment effect. This hypothesis is supported by a previous simulation study that demonstrated that kidney endpoints based on smaller declines in GFR may not increase statistical power for drugs with acute eGFR-lowering effects, in clinical trial cohorts with higher baseline eGFR, or slower rates of progression, such as cohorts with low levels of albuminuria, as in the CANVAS Program and EMPAREG OUTCOME trials.[23] This notion may also explain, at least in part, some of the findings of the Study of Heart and Kidney Protection with Empagliflozin (EMPA-KIDNEY) trial. In that trial, the effect on CKD progression appeared larger when a 50% eGFR decline threshold was used, compared to a 40% eGFR decline threshold.[24,25] The apparent attenuation in the treatment effect using a 40% decline threshold may be partly explained by the greater heterogeneity of the trial population in the EMPA-KIDNEY trial—48% had a UACR <300 mg/g, which resulted in a considerably slower rate of eGFR decline compared to that in the CREDENCE and DAPA-CKD trials. Attenuation of the treatment effect size based on smaller eGFR decline thresholds may also occur when the treatment effect is proportional to the underlying rate of kidney function decline or when the acute eGFR-lowering effect attenuates when eGFR declines.[14] Thus, the choice of endpoint must consider the context of the specific clinical trial population, including the level of baseline kidney function and the expected rate of eGFR decline, as well as specific drug characteristics.

The strengths of this study are that we used data from multiple, relatively large, international, rigorously conducted, kidney disease–dedicated outcome trials involving drugs with different mechanisms of action. The clinical endpoints—kidney failure and death due to kidney failure—were adjudicated in all trials by independent event adjudication committees, although the precise definitions varied slightly across trials. This study also has limitations. First, the eGFR-based endpoints were confirmed by a subsequent measurement, but the timing of these measurements varied for different endpoints. The primary eGFR-based endpoint varied across trials and was confirmed by a second measurement after approximately 1 month in all trials, whereas the other eGFR-based endpoints were confirmed at the next scheduled study visit according to the trial protocol, except in the FIDELIO-DKD trial, in which a 57% eGFR decline was confirmed after 4 weeks as well. The primary eGFR-based endpoint varied across trials (57% in the CREDENCE and SONAR trials; 50% in the DAPA-CKD trial; and 40% in the FIDELIO trial) and the cadence of follow-up visits also varied across trials (3 months in the FIDELIO-DKD and SONAR trials; 4 months in the DAPA-CKD trial; and 6 months in the CREDENCE trial). Because of the subtle differences in endpoint definitions, and differences in trial design and study populations, the efficacy data for each eGFR-based endpoint should not be compared across trials. The sample-size calculations assume that the observed treatment effects reflect the true treatment effect but do not account for sampling errors and random variations and therefore should be interpreted cautiously. Although smaller eGFR thresholds may increase event rates and decrease required sample sizes or shorten follow-up, this effect may subsequently limit proper drug safety assessment. Future trials should thus balance the choice of the eGFR-decline threshold and sample size with appropriate safety assessment, with greater need for more-robust safety assessment for interventions earlier in the drug-development process. Finally, other than the DAPA-CKD trial, for which patients with and without type 2 diabetes were recruited, the vast majority of participants in the 4 selected trials had type 2 diabetes with substantial albuminuria; these results may not generalize to the broader population of patients with CKD,

particularly those with earlier-stage disease and/or lower levels of albuminuria and or therapeutic interventions with different mechanisms of action.

In conclusion, these prespecified exploratory analyses of 4 major kidney disease outcome trials show that the relative effects of newer therapies on kidney disease progression are similar across different eGFR-decline thresholds, as long as background rates of eGFR decline are sufficiently brisk. Because threshold events are more frequent when eGFR endpoints are based on smaller declines in eGFR, we can expect higher statistical power when lower eGFR thresholds are incorporated into composite kidney endpoints.

DISCLOSURE

HJLH is a consultant for AstraZeneca, Bayer, Boehringer Ingelheim, Chinook, CSL Behring, Dimerix, Eli-Lilly, Gilead, Janssen, Merck, Novo Nordisk, ProKidney, Travere Therapeutics, and Vifor Fresenius; and has received research support from AstraZeneca, Boehringer Ingelheim, Janssen, and Novo Nordisk. NJ has received travel grants from AstraZeneca. MV has received research grant support or served on advisory boards for American Regent, Amgen, AstraZeneca, Bayer AG, Baxter Healthcare, Boehringer Ingelheim, Chiesi, Cytokinetics, Lexicon Pharmaceuticals, Novartis, Novo Nordisk, Pharmacosmos, Relypsa, Roche Diagnostics, Sanofi, and Tricog Health; has had speaker engagements with AstraZeneca, Novartis, and Roche Diagnostics; and participates on clinical trial committees for studies sponsored by Galmed, Novartis, Bayer AG, Occlutech, and Impulse Dynamics. GB is supported by T32 NIH grant DK07011 and is a consultant to Bayer, Janssen, KBP Biosciences, Ionis, Alnylam, AstraZeneca, Glaxo Smith Kline, Novo Nordisk, Janssen, and InREGEN. GMC has received fees from AstraZeneca for the DAPA-CKD trial steering committee; has received research grants from National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), National Institute of Allergy and Infectious Diseases (NIAID), and CSL Behring; is on the board of directors for Satellite Healthcare; has received fees for advisory boards for Cricket, DiaMedica, and Reata; holds stock options for Ardelyx, CloudCath, Durect, DxNow, Outset, Renibus, and Unicycive; has received fees from Akebia, Gilead, Sanifit, and Vertex for trial steering committees; and has received fees for DSMB service from Bayer, Gilead, Mineralys, Palladio and ReCor. DCW has received honoraria and/or consultancy fees from Amgen, AstraZeneca, Boehringer Ingelheim, Bayer, GlaxoSmithKline, Gilead, Janssen, Napp, Mundipharma, Medscape, Merck Sharp and Dohme, Reata, Takeda, Tricida, Vifor Fresenius, and Zydus. BLN has received fees for advisory boards, steering committee roles, scientific presentations, and travel support from AstraZeneca, Bayer, Boehringer Ingelheim, Cambridge Healthcare Research, Medscape, and Janssen, with all honoraria paid to his institution. TG has received consulting fees from Janssen, CSL Behring, Boehringer Ingelheim, and AstraZeneca. LAI reports funding from the National Institutes of Health (NIH), the National Kidney Foundation (NKF), Omeros, Dialysis Clinics, Inc., and Reata Pharmaceuticals for research and contracts to Tufts Medical Center; consulting agreements to Tufts Medical Center with Tricida and HealthLogistics Interactive; and consulting agreements to Dimerix. VP serves as a Board Director for St. Vincents Health Australia, George Clinical, and several Medical Research Institutes; and has received honoraria for Steering Committee roles, scientific presentations, and/or advisory board attendance from Abbvie, Amgen, AstraZeneca, Bayer, Baxter, Boehringer Ingelheim, Chinook, Durect, Eli Lilly, Gilead, GSK, Janssen, Merck, Mitsubishi Tanabe, Mundipharma, Novartis, Novo Nordisk, Otsuka, Pharmalink, Pfizer, Reata, Travere, Relypsa, Roche, Sanofi, Servier, and Tricida. PS is a Bayer employee. The other author declared no competing interests.

DATA STATEMENT

The data supporting the findings of this study are openly available in repository (vivli) at https://vivli.org or may be obtained in accordance with AstraZeneca's data sharing policy described at https://astrazenecagrouptrials.pharmacm.com/ST/Submission/disclosure (pertains only to data from the DAPA-CKD trial).

ACKNOWLEDGMENT

The authors thank all investigators, patients, and research teams for their contributions to the reported clinical trials.

AUTHOR CONTRIBUTIONS

All authors were involved in the design, data collection, and interpretation of the clinical trials. NJ and PS analyzed the data. HJLH and BLN wrote the first draft of the manuscript. All authors reviewed the manuscript drafts, provided approval of the final version for submission, and take responsibility for the accuracy and integrity of the data. All authors had access to the analysis and had final responsibility for submission for publication.

SUPPLEMENTARY MATERIAL

Supplementary File (Word)

Supplementary Table S1. Number of kidney endpoints in the first 4 and 6 months after randomization.

REFERENCES

1. Webster AC, Nagler EV, Morton RL, Masson P. Chronic kidney disease. *Lancet*. 2017;389:1238–1252.
2. Levey AS, Gansevoort RT, Coresh J, et al. Change in albuminuria and GFR as end points for clinical trials in early stages of CKD: a scientific workshop sponsored by the National Kidney Foundation in Collaboration with the US Food and Drug Administration and European Medicines Agency. *Am J Kidney Dis*. 2020;75:84–104.
3. Heerspink HJL, Weldegiorgis M, Inker LA, et al. Estimated GFR decline as a surrogate end point for kidney failure: a post hoc analysis from the Reduction of End Points in Non-Insulin-Dependent Diabetes With the Angiotensin II Antagonist Losartan (RENAAL) Study and Irbesartan Diabetic Nephropathy Trial (IDNT). *Am J Kidney Dis*. 2014;63:244–250.
4. Levey AS, Inker LA, Matsushita K, et al. GFR decline as an endpoint for clinical trials in CKD: a scientific workshop sponsored by the National Kidney Foundation and the US Food and Drug and Administration. *Am J Kidney Dis*. 2014;64:821–835.
5. Levin A, Agarwal R, Herrington WG, et al. International consensus definitions of clinical trial outcomes for kidney failure: 2020. *Kidney Int*. 2020;98:849–859.
6. Inker LA, Lambers Heerspink HJ, Mondal H, et al. GFR decline as an alternative end point to kidney failure in clinical trials: a meta-analysis of treatment effects from 37 randomized trials. *Am J Kidney Dis*. 2014;64:848–859.
7. Perkovic V, Jardine MJ, Neal B, et al. Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. *N Engl J Med*. 2019;380:2295–2306.
8. Heerspink HJL, Stefansson BV, Correa-Rotter R, et al. Dapagliflozin in patients with chronic kidney disease. *N Engl J Med*. 2020;383:1436–1446.
9. Heerspink HJL, Parving H-H, Andress DL, et al. Atrasentan and renal events in patients with type 2 diabetes and chronic kidney disease (SONAR): a double-blind, randomised, placebo-controlled trial. *Lancet*. 2019;393:1937–1947.
10. Bakris GL, Agarwal R, Anker SD, et al. Effect of finerenone on chronic kidney disease outcomes in type 2 diabetes. *N Engl J Med*. 2020;383:2219–2229.
11. Inker LA, Heerspink HJL, Tighiouart H, et al. GFR slope as a surrogate end point for kidney disease progression in clinical trials: a meta-analysis of treatment effects of randomized controlled trials. *J Am Soc Nephrol*. 2019;30:1735–1745.

12. Vonesh E, Tighiouart H, Ying J, et al. Mixed-effects models for slope-based endpoints in clinical trials of chronic kidney disease. *Stat Med*. 2019;38:4218–4239.
13. Vonesh EF, Greene T. Biased estimation with shared parameter models in the presence of competing dropout mechanisms. *Biometrics*. 2022;78:399–406.
14. Neuen BL, Tighiouart H, Heerspink HJL, et al. Acute treatment effects on GFR in randomized clinical trials of kidney disease progression. *J Am Soc Nephrol*. 2022;33:291–303.
15. Greene T, Teng CC, Inker LA, et al. Utility and validity of estimated GFR-based surrogate time-to-event end points in CKD: a simulation study. *Am J Kidney Dis*. 2014;64:867–879.
16. Heerspink HJL, Jongs N, Chertow GM, et al. Effect of dapagliflozin on the rate of decline in kidney function in patients with chronic kidney disease with and without type 2 diabetes: a prespecified analysis from the DAPA-CKD trial. *Lancet Diabetes Endocrinol*. 2021;9:22–31.
17. Dhaun N, Ferro CJ, Davenport AP, et al. Haemodynamic and renal effects of endothelin receptor antagonism in patients with chronic kidney disease. *Nephrol Dial Transplant*. 2007;22:3228–3234.
18. Smeijer JD, Kohan DE, Webb DJ, et al. Endothelin receptor antagonists for the treatment of diabetic and nondiabetic chronic kidney disease. *Curr Opin Nephrol Hypertens*. 2021;30:456–465.
19. Perkovic V, Koitka-Weber A, Cooper ME, et al. Choice of endpoint in kidney outcome trials: considerations from the EMPA-REG OUTCOME(R) trial. *Nephrol Dial Transplant*. 2020;35:2103–2111.
20. Oshima M, Neal B, Toyama T, et al. Different eGFR decline thresholds and renal effects of canagliflozin: data from the CANVAS Program. *J Am Soc Nephrol*. 2020;31:2446–2456.
21. Perkovic V, de Zeeuw D, Mahaffey KW, et al. Canagliflozin and renal outcomes in type 2 diabetes: results from the CANVAS Program randomised clinical trials. *Lancet Diabetes Endocrinol*. 2018;6:691–704.
22. Wanner C, Inzucchi SE, Lachin JM, et al. Empagliflozin and progression of kidney disease in type 2 diabetes. *N Engl J Med*. 2016;375:323–334.
23. Greene T, Ying J, Vonesh EF, et al. Performance of GFR slope as a surrogate end point for kidney disease progression in clinical trials: a statistical simulation. *J Am Soc Nephrol*. 2019;30:1756–1769.
24. EMPA-Kidney Collaborative Group, Herrington WG, Staplin N, et al. Empagliflozin in patients with chronic kidney disease. *N Engl J Med*. 2023;388:117–127.
25. Nuffield Department of Population Health Renal Studies Group, SGLT2 Inhibitor Meta-Analysis Cardio-Renal Trialists' Consortium. Impact of diabetes on the effects of sodium glucose co-transporter-2 inhibitors on kidney outcomes: collaborative meta-analysis of large placebo-controlled trials. *Lancet*. 2022;400:1788–1801.