Original Investigation

GFR Decline as an Alternative End Point to Kidney Failure in Clinical Trials: A Meta-analysis of Treatment Effects From 37 Randomized Trials

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Background: There is increased interest in using alternative end points for trials of kidney disease progression. The currently established end points of end-stage renal disease and doubling of serum creatinine level, equivalent to a 57% decline in estimated glomerular filtration rate (eGFR), are late events in chronic kidney disease (CKD), requiring large clinical trials with long follow-up. As part of a comprehensive evaluation of lesser declines in eGFR as alternative end points, we describe the consistency of treatment effects of intervention on the alternative and established end points in past trials.

Study Design: Diagnostic test study.

Setting & Population: 9,488 participants from 37 randomized controlled trials of CKD progression across 5 intervention types.

Index Test: Alternative end points including percentage change in eGFR from baseline (20%, 30%, 40%, and 57%) throughout study duration and to 12, 18, and 24 months. eGFR change confirmed versus nonconfirmed at the next visit.

Reference Test: The historically established end point of time to composite of treated kidney failure (end-stage renal disease), untreated kidney failure (GFR $<$ 15 mL/min/1.73 m^2), or doubling of serum creatinine level throughout study duration.

Results: Over a median of 3.62 years' follow-up, there were 3,070 established end points. Compared to the established end point, the number of alternative end points was greater for smaller versus larger declines in eGFR and longer versus shorter follow-up intervals. There was a general trend toward attenuation of the treatment effect with end points defined by a lesser eGFR decline, with greater attenuation with nonconfirmed end points, except for the low-protein-diet intervention, for which a stronger treatment effect was observed. The ratio (95% credible interval) of the HR for the alternative to established end point for the 5 intervention types ranged from 0.91 (0.64-1.43) to 1.12 (0.89-1.40) for 40% decline and from 0.88 (0.63-1.39) to 1.15 (0.88-1.54) for 30% decline for the overall study duration, indicating consistency of treatment effects.

Limitations: Limited variety of interventions tested and low statistical power for many CKD clinical trials.

Conclusions: These results provide some support for the use of lesser eGFR declines as a surrogate end point, with stronger support for the 40% than 30% decline.

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INDEX WORDS: Kidney end point; renal end point; kidney disease outcome; surrogate end point; chronic kidney disease (CKD); estimated glomerular filtration rate (eGFR) decline; eGFR trajectory; renal function; kidney disease progression; end-stage renal disease (ESRD); treatment effect.

Chronic kidney disease (CKD) is a major public health issue due to its increasing prevalence, poor outcomes, and high cost of treatment for kidney failure. However, despite the availability of simple laboratory tests to identify people with earlier stages of CKD, there are not as many randomized clinical trials for kidney disease as for other common diseases, and therapies to slow the progression of kidney disease to kidney failure

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are scarce. The US Food and Drug Administration (FDA) accepts kidney failure and halving of glomerular filtration rate (GFR), assessed as doubling of serum creatinine level as an end point for clinical trials of kidney disease progression, but these are late events in CKD. It is widely accepted that decreased estimated GFR (eGFR) is a strong risk factor for kidney failure and mortality.[1] However, these associations are not sufficient to validate eGFR decline as a surrogate end point. Alternative end points based on lesser declines in GFR need to be evaluated empirically as end points prior to their use.

In December 2012, the National Kidney Foundation (NKF) and FDA cosponsored a scientific workshop "GFR Decline as an Endpoint for Clinical Trials in CKD" to critically examine data that might support new definitions of GFR decline as end points in clinical trials of CKD-related therapies. The workshop report is included in this issue of *AJKD*.[2] As part of the process, the workshop planning committee appointed an analytic group to design and conduct analyses using data from observational studies, randomized clinical trials, and simulation studies. This article is the second in a series of 4 by the analytic group to report the results of these analyses. The first article examined the associations of decline in eGFR with subsequent kidney failure and mortality from a meta-analysis of observational studies.[1] This article examines the consistency of treatment effects on the established and alternative end points from a meta-analysis of clinical trials. The third article examines effect modification by cause of kidney disease or type of intervention on the associations of decline in eGFR with subsequent kidney failure in a meta-analysis of the same clinical trials,[3] and the fourth article examines the validity and utility of alternative end points in simulations.[4]

Use of lesser GFR decline as alternative end points for trials of kidney disease progression could increase the number of end point events during the trials. For example, a greater number of events with consistent treatment effects of an alternative compared to the established end point would lead to more precise estimates of the treatment effects, providing greater statistical power, enabling shorter trials or with smaller sample size. In this study, we used an individual-patient meta-analysis of 37 randomized controlled trials of 5 types of interventions in progressive kidney disease to compare the number of end points and consistency of the treatment effect of several alternative end points based on lesser decline compared with the established end points.

METHODS

A more detailed description of the methods is available in Item S1 (provided as online supplementary material).

Data Sets and Analytical Groups

We previously described the creation of the pooled individual-patient–level data set for the purpose of investigating an early change in proteinuria as a surrogate end point for kidney disease progression.[5,6] Briefly, we performed a systemic review of the literature for kidney disease randomized controlled trials until May 15, 2007, and requested individual-patient data from the investigators (figure *a* of Item S1).[7-36] As part of a separate study investigating proteinuria in immunoglobulin A (IgA) nephropathy, we performed a separate systematic review until July 9, 2012, and also received individual-patient data from 5 additional trials.[37-41] Thus, in total, data from 37 trials of 5 intervention types accounting for 9,488 participants were included in the final data set used in the analyses reported here (See table *a* of Item S1 for list of studies and references).

For trials that evaluated more than one intervention, we included a separate group for each independent treatment comparison, such that some participants were included in more than one analytical comparison,[16,17,22,23] for a total of 43 analytical comparisons (herein referred to as "studies"), with 12,821 participant-level comparisons. We categorized the studies by intervention type: (1) renin-angiotensin system (RAS) blockade versus control; (2) RAS blockade versus calcium channel blocker (CCB); (3) intensive blood pressure control; (4) low-protein diet; and (5) immunosuppressive therapy. For the other interventions, we defined the active treatment as the treatment hypothesized to produce the larger reduction in the risk of the clinical end point for each study.

Estimated GFR

GFR was estimated using the CKD-EPI (CKD Epidemiology Collaboration) 2009 creatinine equation.[42] Creatinine level was standardized to isotope-dilution mass spectroscopy–traceable reference methods using direct comparison or values were reduced by 5%, as has been described previously.[43]

Reference Test: Clinical Outcome—Established End Points

We defined established end points for clinical trials as treated kidney failure (end-stage renal disease [ESRD], defined as initiation of treatment with dialysis or transplantation), untreated kidney failure (defined as eGFR < 15 mL/min/1.73 m^2 in those with eGFRs > 25 mL/min/1.73 m^2 at baseline), or doubling of serum creatinine level that occurred over the full study duration. The primary analysis was time to the first occurrence of ESRD or the composite of the 3, censoring for death. In secondary analyses, we included time to death in the composite end point.

Index Tests: Surrogate Outcome—Alternative eGFR-Based End Points

We defined the alternative end point as time to first occurrence of a decline in eGFR of 20%, 30%, 40%, or 57% (approximately equivalent to a doubling of serum creatinine using the CKD-EPI creatinine equation[42]) and then determined whether the decline occurred within 12, 18, or 24 months or the complete study duration. In sensitivity analyses, we also examined time to an absolute decline in eGFR of 10, 20, and 30 mL/min/1.73 m^2. For both the percent and absolute decline end points, we also determined whether the magnitude of eGFR decline was confirmed by an eGFR determination at the next visit. If the end point occurred at the last visit, we considered it as confirmed. We used the confirmed end point in the primary analyses and the nonconfirmed end point in the secondary analyses.

Analyses

The overall goal of the analyses was to compare number of events and mean treatment effects (ie, hazard ratio [HR]) computed using each of the proposed alternative end points with those computed using the established end point. Item S1 contains further details of the rationale and methods.

The first step was to summarize the number of end points and treatment effects across each intervention. Within each study, we

computed the number of events for the alternative and established end points over the full duration of the study and the shorter intervals. Cox regression analyses were performed separately in each study to obtain HRs on each of the established and alternative end points. Next, we summarized treatment effects across each intervention by pooling HRs across studies from the same intervention using random-effects meta-analyses with a restricted maximum-likelihood estimator.[44] Meta-analyses were performed in R statistical software, version 2.15.1 (R Foundation for Statistical Computing) with the metafor package.[44] We summarized variation in mean HRs using 95% confidence intervals and heterogeneity across studies using the prediction interval across which 90% of future studies would be expected to fall.[45,46]

The second step was to describe agreement between the alternative and established end points using the ratios, or relative effects, between HRs for the alterative and established end points as the metric of agreement. We used Bayesian mixed models to obtain posterior estimates of treatment effects and then computed ratios. Ratios were computed for each study and pooled across interventions.[47] A ratio near 1.0 would imply agreement between treatment effects on the established and alternative end points, whereas a ratio greater than 1.0 would imply attenuation of the treatment effect for the alternative compared to the established end point and a ratio less than 1.0 would imply strengthening of the treatment effect. We summarized variation in the mean estimate using Bayesian 95% credible intervals and heterogeneity across studies using prediction intervals across the middle 90% of studies.[45,46]

In addition to the mentioned R version, analyses were performed using SAS, version 9.2 (SAS Institute Inc), and JAGS ("Just Another Gibbs Sampler").[48]

RESULTS

Table 1 shows characteristics of the studies and patients. The data set included 43 studies of 12,821 participants across 5 intervention types: RAS blockade versus control (5,748 participants), RAS blockade versus CCB (2,295 participants), intensive blood pressure control (2,655 participants), low-protein diet (839 participants), and immunosuppressive therapy (1,284 participants). Over a median of 3.62 years' follow-up across studies, there were 3,070 established events (2,029 cases of ESRD, 1,151 cases of eGFR $<$ 15 mL/min/1.73 m^2, and 2,086 doublings of serum creatinine). Results differed among the interventions by participant and study characteristics. For example, studies of RAS blockade had lower eGFRs at baseline and also were of shorter duration compared with studies of immunosuppressive therapy.

The second visit for the confirmed end point occurred at a median of 3.16 months after the initial visit. In general, compared to the established end point, the number of confirmed alternative end points was greater for smaller versus larger declines in eGFR and longer versus shorter follow-up intervals (Fig 1; table *b* of Item S1). For example, for the overall study duration, there were ~30% more end points for the 40% decline and 60% more for the 30% decline compared to the established end point, whereas at 24 months, the 30% decline continued to result in more end points and the 40% decline resulted in fewer end points compared to the established end point during the overall study duration. Use of nonconfirmed end points resulted in 10% to 50% more events than the confirmed end points (table *d* compared to table *b* of Item S1).

Figure 2 and table *b* of Item S1 show pooled HRs for treatment effects on the established and alternative outcomes for each of the 5 intervention groups. For all interventions, point estimates for the HR for the composite established end point (ESRD, eGFR $<$ 15 mL/min/1.73 m^2, and doubling of serum creatinine) and 57% eGFR decline during the total follow-up interval were similar compared to ESRD alone. Despite the greater number of events, in each interval, there was a general trend toward higher HRs (attenuation, weaker treatment effects) with end points defined by lesser eGFR declines, except for the low-protein-diet intervention. However, there were some important differences among the interventions. For the RAS blockade versus control intervention, eGFR declines of 40% and 30% had lower HRs (stronger treatment effects) compared to the established end point at shorter intervals. The RAS blockade versus CCB comparison showed greater attenuation of the HRs with lesser eGFR declines at all intervals compared to the RAS blockade versus control intervention; nonetheless, a 40% eGFR decline had the lowest HR for follow-up of 18 months or less. For the intensive blood pressure control comparison, HRs for the lesser eGFR declines showed less attenuation than for both RAS blockade interventions and were similar to the established end point for all durations of follow-up. For the immunosuppressive therapy intervention, the pattern of attenuation of the HRs was similar to the general trend for the full study duration; at shorter follow-up intervals, all alternative end points showed substantially weaker HRs than at the full study duration. In contrast to the general trend of attenuation of HRs with lesser eGFR decline, for the low-protein-diet intervention, we observed lower HRs for lesser eGFR declines compared to the established end point for all durations of follow-up. Among individual studies, the pattern of results generally was consistent with the pooled analyses, with moderate heterogeneity (see table *b* of Item S1 for the prediction interval across 90% of studies and table *c* for results for HRs for individual studies for the established end points and 4 of the alternative end points).

There was no change to the pattern of results with inclusion of death in the established end point (figure *b* of Item S1). Use of nonconfirmed end points resulted in greater attenuation of the HRs, particularly for 20% and 30% eGFR declines for 4 of 5 of the interventions (figure *c* of Item S1). Use of absolute change in eGFR showed similar patterns with attenuation of the HRs with lesser change in eGFR (table *e* of Item S1).

Table 1. Clinical Characteristics by 5 Interventions

Study	N	Disease	Participant Characteristics					Events				
			Age (y)	Female Sex	Black	eGFR	Urine Protein (g/d)	Median F/U (mo)	ESRD	2×Scr	eGFR < 15[a]	Composite
A. RAS Blockade vs Control												
A1[7]	55	CKD	50 ± 12	28 (51)	0 (0)	14.8 ± 9.0	1.09 [2.16]	28.3	21	9	0	41.8%
A2[8]	67	CKD	46 ± 13	34 (51)	0 (0)	16.5 ± 6.7	1.43 [2.20]	21.2	15	11	2	34.3%
A3[9]	224	CKD	45 ± 15	113 (50)	0 (0)	16.8 ± 4.4	1.69 [1.18]	30.9	83	47	5	49.6%
A4[10]	98	CKD	51 ± 14	47 (48)	0 (0)	23.4 ± 7.8	1.60 [2.60]	27.4	26	25	14	37.8%
A5[11]	106	CKD	47 ± 13	38 (36)	37 (35)	35.4 ± 17.2	1.25 [2.88]	29.7	15	13	9	22.6%
A6[11]	122	CKD	52 ± 12	44 (36)	74 (61)	37.0 ± 17.5	0.23 [0.88]	34.2	10	14	8	18.9%
A7[12]	562	CKD	51 ± 13	157 (28)	0 (0)	38.6 ± 11.6	0.84 [2.33]	35.1	2	77	51	15.7%
A8[13]	1,513	DM	60 ± 7	557 (37)	230 (15)	41.4 ± 13.2	2.44 [3.99]	33.5	341	360	274	33.6%
A9[14]	322	CKD	49 ± 14	73 (23)	2 (1)	41.5 ± 18.8	2.75 [2.81]	25.7	58	40	34	23.6%
A10[15]	103	CKD	51 ± 13	35 (34)	1 (1)	48.1 ± 19.3	0.50 [2.40]	44.0	7	10	4	9.7%
A11[16]	877	HTN	55 ± 11	339 (39)	877 (100)	48.9 ± 15.8	0.12 [0.57]	52.3	135	134	76	22.6%
A12[17]	1,137	DM	59 ± 8	363 (32)	139 (12)	50.1 ± 19.5	3.03 [3.64]	30.1	182	231	118	25.4%
A13[18]	409	DM	35 ± 8	191 (47)	32 (8)	73.0 ± 25.3	1.86 [2.83]	37.5	35	82	34	20.5%
A14[19]	109	IgAN	41 ± 9	79 (72)	0 (0)	75.1 ± 29.0	1.60 [1.56]	34.9	3	7	6	7.3%
A15[20]	44	IgAN	32 ± 11	17 (39)	0 (0)	98.1 ± 26.5	1.70 [1.30]	75.0	15	6	1	34.1%
B. RAS Blockade vs CCB												
B16[21]	121	CKD	55 ± 11	47 (39)	0 (0)	24.9 ± 10.1	1.00 [2.18]	36.0	21	22	10	26.5%
B11[16]	653	HTN	54 ± 11	255 (39)	653 (100)	48.7 ± 15.8	0.11 [0.53]	52.3	106	93	54	21.8%
B12[17]	1,129	DM	59 ± 8	400 (35)	147 (13)	50.1 ± 18.7	2.91 [3.43]	30.2	185	242	122	28.2%
B17[22]	392	DM	59 ± 8	130 (33)	63 (16)	72.1 ± 18.7	0.15 [0.77]	60.3	0	24	5	6.1%
C. Intensive Blood Pressure Control												
C18[23]	255	CKD	51 ± 13	104 (41)	13 (5)	20.3 ± 5.9	0.71 [1.87]	26.5	136	63	16	58.0%
C19[24]	330	CKD	54 ± 15	82 (25)	0 (0)	32.3 ± 18.2	2.39 [2.15]	16.0	71	42	28	25.8%
C20[23]	584	CKD	52 ± 12	228 (39)	53 (9)	40.7 ± 11.0	0.20 [1.06]	27.5	58	74	45	16.4%
C11[16]	1,094	HTN	55 ± 11	425 (39)	1,094 (100)	48.7 ± 15.7	0.12 [0.54]	52.3	179	164	97	23.0%
C17[22]	392	DM	59 ± 8	130 (33)	63 (16)	72.1 ± 18.7	0.15 [0.77]	60.3	0	24	5	6.1%
D. Low-Protein Diet												
D18[23]	255	CKD	51 ± 13	104 (41)	13 (5)	20.3 ± 5.9	0.71 [1.87]	26.5	136	63	16	58.0%
D20[23]	584	CKD	52 ± 12	228 (39)	53 (9)	40.7 ± 11.0	0.20 [1.06]	27.5	58	74	45	16.4%

(Continued)

Table 1 (Cont'd). Clinical Characteristics by 5 Interventions

			Participant Characteristics					Events				
Study	N	Disease	Age (y)	Female Sex	Black	eGFR	Urine Protein (g/d)	Median F/U (mo)	ESRD	2×Scr	eGFR < 15[a]	Composite
E. Immunosuppressive Therapy												
E21[40]	46	IgAN	42 ± 12	9 (20)	0 (0)	27.8 ± 7.0	2.50 [2.50]	50.3	19	9	7	41.3%
E22[25]	73	IgAN	46 ± 13	13 (18)	2 (3)	40.7 ± 14.4	1.62 [2.41]	26.3	13	11	5	23.3%
E23[26]	29	IgAN	38 ± 12	5 (17)	0 (0)	42.2 ± 26.6	2.29 [1.66]	19.5	7	0	1	24.1%
E24[27]	83	Lupus	33 ± 12	69 (83)	18 (22)	55.9 ± 35.9	4.40 [6.24]	23.5	24	13	11	31.3%
E25[28]	34	IgAN	45 ± 11	10 (29)	0 (0)	62.2 ± 19.0	1.00 [2.08]	45.0	2	2	2	5.9%
E26[29]	97	IgAN	39 ± 13	26 (27)	0 (0)	65.9 ± 22.5	2.10 [2.25]	35.8	16	4	3	18.6%
E27[30]	62	Lupus	40 ± 10	52 (84)	0 (0)	71.0 ± 26.4	3.94 [4.44]	48.0	2	1	1	4.8%
E28[41]	197	IgAN	39 ± 13	55 (28)	0 (0)	74.7 ± 25.5	2.00 [1.20]	72.8	9	14	6	7.1%
E29[31]	83	Lupus	33 ± 11	79 (95)	2 (2)	80.6 ± 29.2	2.50 [2.26]	100.0	5	8	0	9.6%
E30[32]	91	MN	50 ± 11	28 (31)	0 (0)	82.5 ± 19.9	5.50 [4.70]	42.0	2	3	3	3.3%
E31[38]	83	IgAN	39 ± 12	25 (30)	0 (0)	87.2 ± 21.6	1.90 [1.00]	102.0	7	14	8	16.9%
E32[33]	75	MN	44 ± 11	15 (20)	0 (0)	87.7 ± 23.0	4.80 [4.10]	138.0	10	19	12	25.3%
E33[34]	76	MN	47 ± 13	26 (34)	0 (0)	89.0 ± 25.2	5.40 [3.65]	27.0	2	10	2	13.2%
E34[35]	48	MN	47 ± 13	8 (17)	0 (0)	89.4 ± 20.3	7.25 [5.32]	24.0	0	4	0	8.3%
E35[37]	95	IgAN	34 ± 11	29 (31)	0 (0)	91.3 ± 23.7	1.64 [1.18]	57.2	8	15	5	15.8%
E36[36]	31	MN	49 ± 11	12 (39)	0 (0)	92.6 ± 22.2	5.60 [4.10]	24.0	0	1	1	3.2%
E37[39]	81	IgAN	36 ± 11	48 (59)	0 (0)	98.8 ± 21.4	1.33 [1.64]	78.0	5	7	5	8.6%

Note: Unless otherwise indicated, values for categorical variables are given as number (percentage) and values for continuous variables are given as mean ± standard deviation or median [interquartile range]. Each study is referred by an alphanumeric code. Each letter refers to treatment comparisons, and each number refers to the individual studies. A is RAS blockade versus control, B is RAS blockade versus CCB, C is intensive blood pressure control, D is low-protein diet, and E is immunosuppressive therapy. See table *a* of Item S1 for study name for each study number.

Abbreviations and definitions: 2×Scr, doubling of serum creatinine; CCB, calcium channel blocker; CKD, chronic kidney disease without specified etiology; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate (in mL/min/1.73 m^2); ESRD, end-stage renal disease; F/U, follow-up; HTN, hypertension; IgAN, immunoglobulin A nephropathy; MN, membranous nephropathy; RAS, renin-angiotensin system.

[a]Outcome of eGFR < 15 mL/min/1.73 m^2 restricted to those with eGFRs > 25 mL/min/1.73 m^2 at baseline.

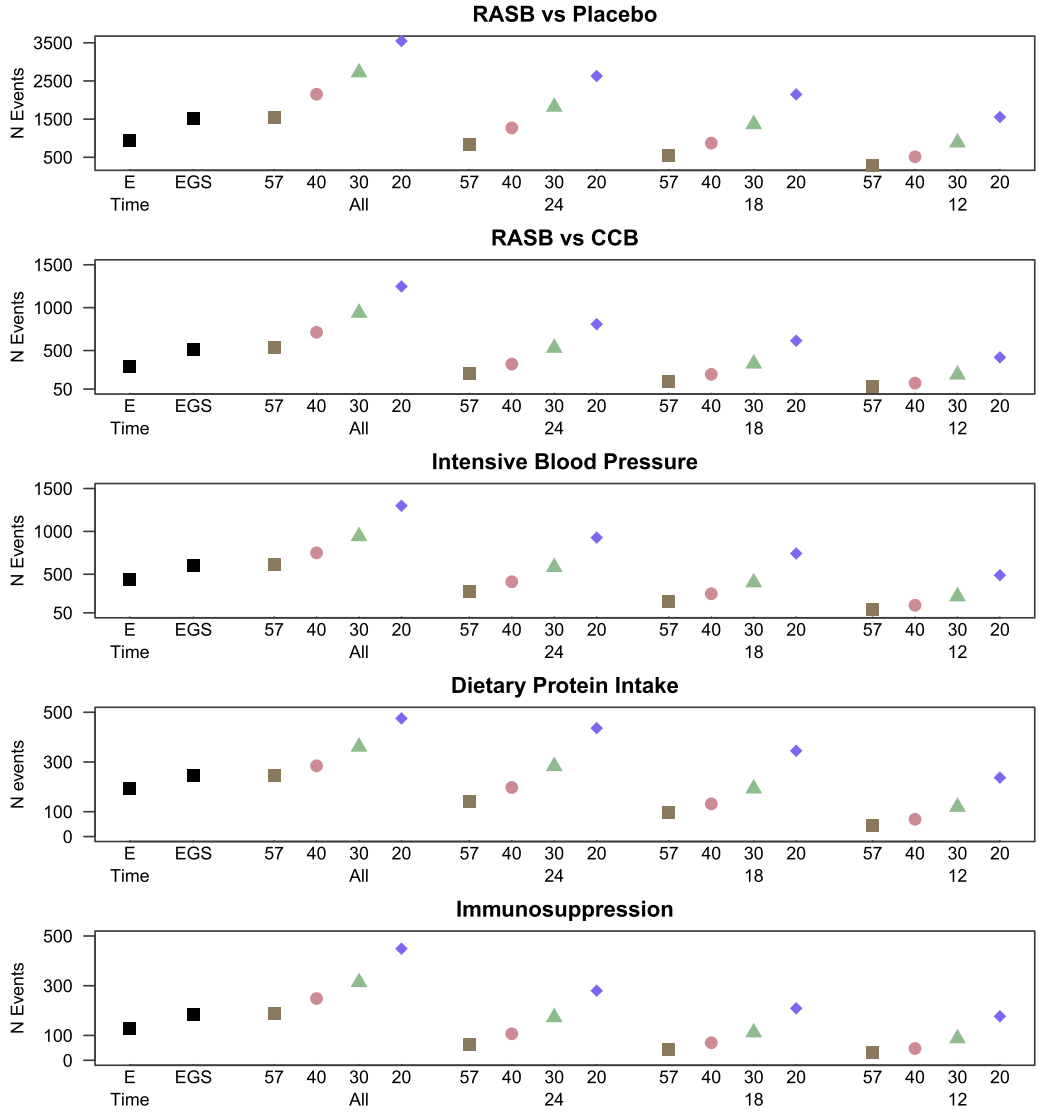

Figure 1. Number of events for the established end point (time to end-stage renal disease [ESRD], glomerular filtration rate [GFR] < 15 mL/min/1.73 m^2, or doubling of serum creatinine) for the overall study duration and on the alternative end points (time to 20%, 30%, 40%, and 57% decline in GFR) during the overall study duration and at 24, 18, and 12 months aggregated for the 5 interventions. Abbreviations: CCB, calcium channel blocker; E, ESRD; EGS, ESRD, estimated GFR < 15 or doubling of serum creatinine; RASB, renin-angiotensin system blockade.

Figure 3 compares treatment effects for 40% and 30% eGFR declines for the overall study duration and at the 24-month interval compared with treatment effects for the established end point. The direction of the pooled treatment effects for each alternative end point was consistent with the established end points for all interventions. For the 4 interventions other than low-protein diet, the point estimate for the ratio of the HR for the alternative to established end point was greater than 1.0 in 13 of 16 comparisons, indicating attenuation of the HR for lesser eGFR declines (Table 2). For the low-protein diet, the point estimate for the ratio for all 4 comparisons was less than 1.0, indicating strengthening of the HR for all end points. However, treatment effects on both the established and alternative end points, as well as the ratios between the end points, are not estimated with sufficient precision to make definitive conclusions about agreement between the established and alternative end points in most cases. There was moderate variation across studies, which varied across the end points and interventions (Fig 3; Table 2).

DISCUSSION

Use of surrogate end points for clinical trials of CKD progression potentially might shorten the duration of clinical trials and decrease the participant number needed to achieve statistical power. However, in other fields there are examples of discrepancies between treatment effects on the surrogate and clinical end points

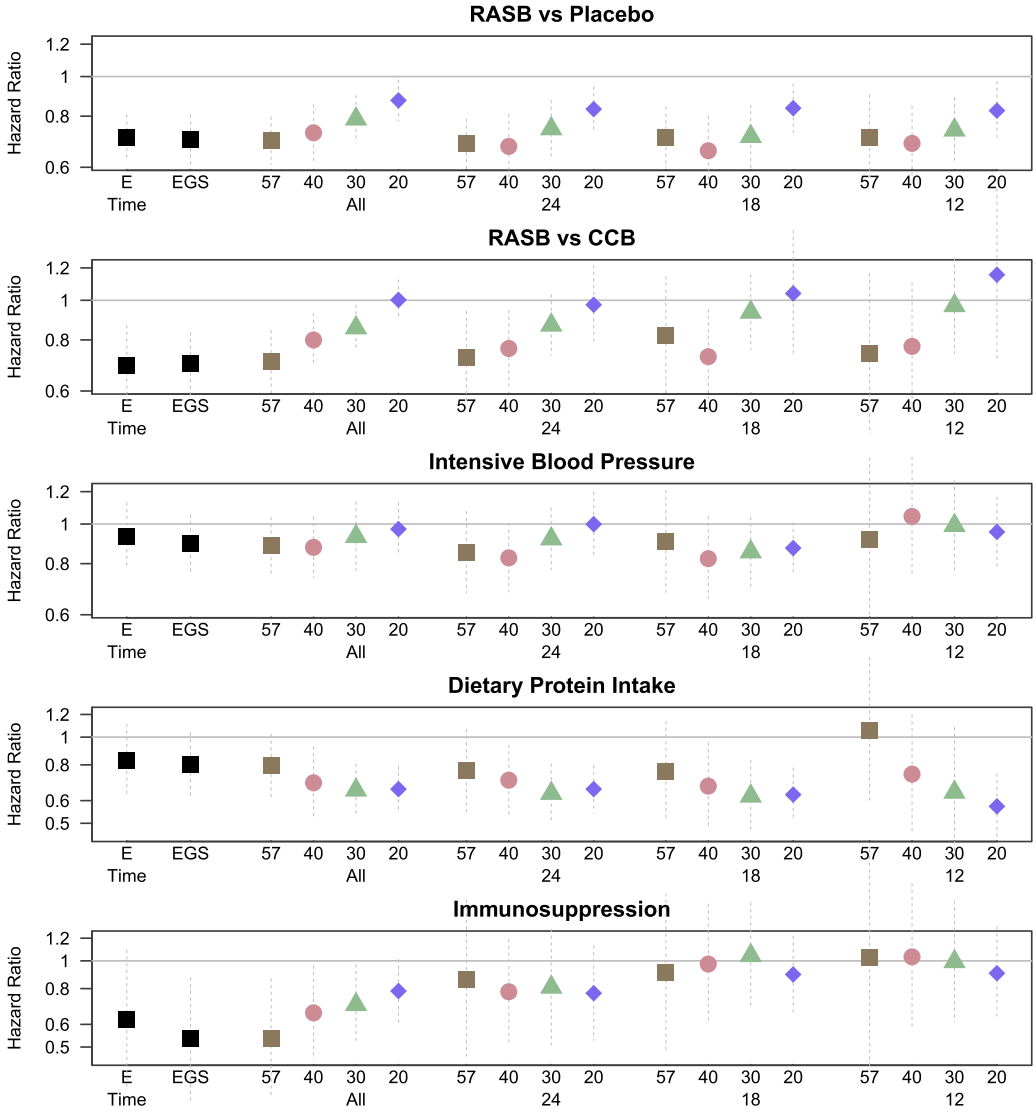

Figure 2. Estimated treatment effects on the established end point (time to end-stage renal disease [ESRD], glomerular filtration rate [GFR] < 15 mL/min/1.73 m^2, or doubling of serum creatinine) for the overall study duration and on the alternative end points (time to 20%, 30%, 40%, and 57% decline in GFR) during the overall study duration and at 24, 18, and 12 months aggregated for the 5 interventions. Treatment effects are expressed as hazard ratios (HRs). Dashed gray lines show the confidence interval around the point estimates. Thin horizontal line indicates HR of 1, consistent with a nonsignificant treatment effect. Abbreviations: CCB, calcium channel blocker; E, ESRD; EGS, ESRD, estimated GFR < 15 or doubling of serum creatinine; RASB, renin-angiotensin system blockade.

in definitive trials.[49] The first article describing the analyses performed as part of the NKF-FDA scientific workshop to investigate new definitions of GFR decline as end points for CKD trials showed strong associations of 30% and 40% declines in eGFR over a 1-, 2-, or 3-year baseline period with subsequent kidney failure and mortality.[1] Although these associations are a necessary criterion for surrogacy, they are not sufficient.[50-52] The current report addresses another component of the evaluation of alternative end points for use as end points in kidney disease trials; whether treatment effects using the alternative end points are consistent with those observed using the established end point.

In this study, we showed that use of a 57% eGFR decline, equivalent to doubling of serum creatinine level using the CKD-EPI 2009 creatinine equation, led to consistent or stronger treatment effects compared to use of the end point of ESRD alone. Although doubling of creatinine level has been used for many years as an end point in trials of kidney disease progression to increase the number of end points compared to treated kidney failure, this is first large-scale validation of its use. We were able to show that this relationship was consistent across studies and interventions. Because one must progress through lesser eGFR declines to reach a 57% eGFR decline,

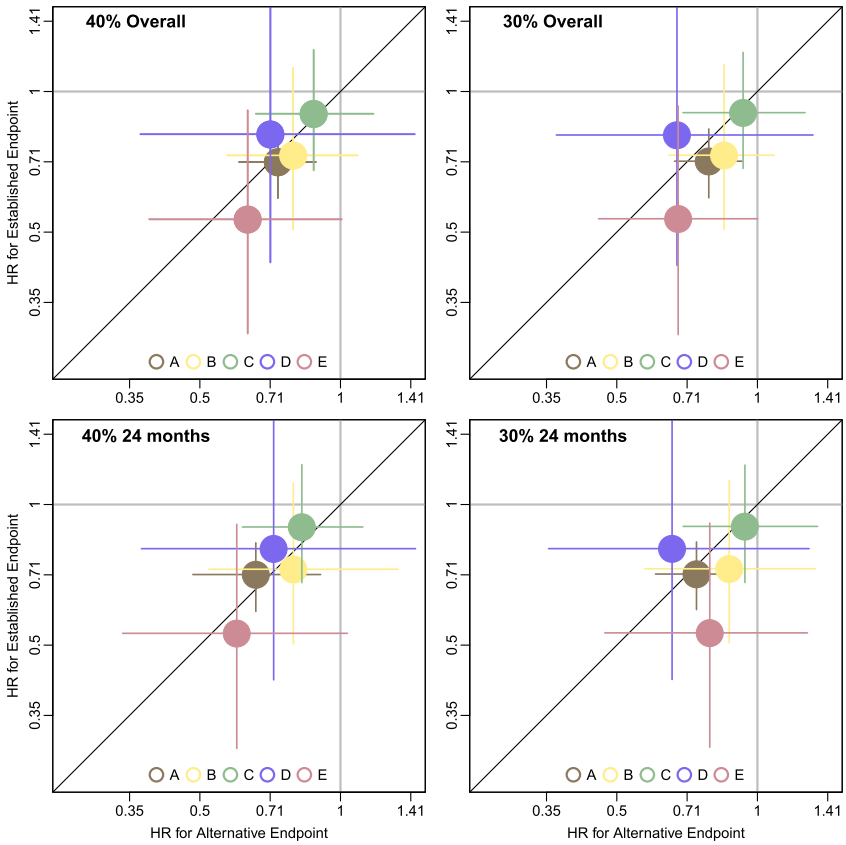

Figure 3. Relationship between estimated treatment effects on the established end point (end-stage renal disease, glomerular filtration rate [GFR] < 15 mL/min/1.73 m^2, or doubling of serum creatinine) on the vertical axis to estimated treatment effects on the alternative end points (on the horizontal axis) aggregated for the 5 interventions. Treatment effects are expressed as hazard ratios (HRs). Diagonal line is the line of identity. Dashed lines around each circle indicate the Bayesian credible intervals for the treatment effect on the established and alternative end points. Colors indicate intervention type. Dark gray, (A) renin-angiotensin system blockade versus control; yellow, (B) renin-angiotensin system blockade versus calcium channel blocker; green, (C) intensive blood pressure control; blue, (D) low-protein diet; pink, (E) immunosuppressive therapies. GFR decline of (top left) 40% in the overall study duration, (top right) 30% in the overall study duration, (bottom left) 40% at 24 months, and (bottom right) 30% at 24 months.

we hypothesized that even lesser declines in GFR would result in an even greater number of end points and similar or stronger treatment effects, particularly at shorter periods of follow-up. Consistent with this hypothesis, we observed a greater number of events for end points defined by lesser eGFR declines for all interventions at some intervals and consistency between the alternative and established end points for most comparisons. However, we also observed a trend toward attenuation of HRs with lesser eGFR declines for 4 of 5 interventions.

Prior studies have suggested possible mechanisms for the variation in the HRs observed using GFR decline as an end point. The first mechanism is acute effects on GFR of the intervention or the control that are different in direction or magnitude to their long-term effects. RAS blockade, lower blood pressure targets, and low-protein diets have been shown to cause an initial decline in GFR (a negative acute effect) followed by a slower rate of GFR decline.[16,23,53,54] In contrast, CCBs, higher blood pressure targets, and high-protein diets lead to an initial increase in GFR (a positive acute effect) followed by a faster rate of GFR decline.[10] Because acute effects are more likely to lead to small rather than large declines in GFR, the presence of acute effects is likely to lead to greater variation in the HR when using smaller versus larger declines in GFR as alternative end points. Both RAS blockade and CCB treatments lead to acute effects, but in the opposite direction, and therefore this mechanism likely explains the greater attenuation in the HR observed for the RAS blockade versus CCB intervention compared to the RAS blockade versus control intervention. The second mechanism is greater effects of the interventions for those with faster progression (proportional effects). This is a well-recognized phenomenon in other domains[55,56] and has been shown to be a factor in studies of low-protein diets.[57] In studies in which treatment effects are greater for the faster versus slower progressors, use of end points based on lesser eGFR declines may be expected to lead to smaller magnitudes for estimated treatment effects. This mechanism may have contributed to the attenuation of the HR that was observed for the RAS blockade and immunosuppressive therapies. The third mechanism is effects of interventions on serum creatinine level not related to changes in GFR.[58] Low-protein diets acutely decrease creatinine generation, thereby lowering serum creatinine level and increasing eGFR despite lowering measured GFR. The net effect would be to augment the treatment effect, as we observed. The potential effect of interventions on non-GFR determinants of endogenous filtration markers is relevant to all filtration markers, not only creatinine. A fourth mechanism is that lesser declines are subject to greater degrees of measurement error and are more likely to lead to false events. While

Table 2. Ratios for Comparison of Alternative End Points of 30% and 40% Decline in eGFR to Established End Point at Overall Study Duration and 24 Months

Intervention	Alternative End Point		Ratio[a]	95% Credible Intervals Around Mean	Prediction Interval for Agreement of Studies Across 90% of Studies
	Time	eGFR Decline			
A. RAS blockade vs control	Overall	40%	1.06	0.98-1.14	0.93-1.19
		30%	1.13	1.01-1.26	0.91-1.40
	24 mo	40%	0.98	0.89-1.07	0.84-1.14
		30%	1.08	0.95-1.20	0.86-1.33
B. RAS blockade vs CCB	Overall	40%	1.07	0.80-1.35	0.67-1.60
		30%	1.12	0.80-1.48	0.62-1.83
	24 mo	40%	1.11	0.68-2.04	0.62-1.94
		30%	1.15	0.81-1.53	0.68-1.93
C. Intensive blood pressure control	Overall	40%	0.98	0.85-1.11	0.81-1.16
		30%	1.05	0.87-1.21	0.83-1.30
	24 mo	40%	0.96	0.79-1.16	0.69-1.30
		30%	1.05	0.88-1.24	0.83-1.32
D. Low-protein diet	Overall	40%	0.91	0.64-1.43	0.47-1.84
		30%	0.88	0.63-1.39	0.48-1.69
	24 mo	40%	0.93	0.64-1.44	0.48-1.88
		30%	0.86	0.61-1.42	0.47-1.78
E. Immunosuppressive therapy	Overall	40%	1.12	0.89-1.40	0.80-1.57
		30%	1.15	0.88-1.54	0.69-1.98
	24 mo	40%	1.12	0.83-1.49	0.69-1.89
		30%	1.27	0.92-1.74	0.69-2.37

Abbreviations: CCB, calcium channel blocker; eGFR, estimated glomerular filtration rate; RAS, renin-angiotensin system.

[a]Ratio is the exponentiation of difference of log hazard ratio of established end point minus the log hazard ratio of the altnerative end point. Established end point is the composite of end-stage renal disease, eGFR < 15 mL/min/1.73 m^2, and doubling of serum creatinine level.

none of these analyses can prove the existence of these 4 mechanisms, the observed results are consistent with prior studies. Overall, these results emphasize the complexity of the effect of interventions and control on lesser eGFR declines and the importance of understanding these potential mechanisms prior to the design of phase 3 trials. Other potential solutions require further study, such as evaluation for acute effects during the trial and a prespecified adaptation of the trial design if an acute effect is detected.

We presented results from multiple studies that were pooled using rigorous meta-analytical techniques. The advantage of this approach is that larger studies with more precise results are weighted more than smaller studies, which limits conclusions to be drawn from small outlier studies. The disadvantage is that the pooled results may not detect differences among trials that are due to different mechanisms and do not allow us to determine the improvement in statistical power that could be obtained from using the alternative end points for a specific trial. In general, results in individual studies followed the general pattern within an intervention. We previously have published a report of the impact of these alternative outcomes in 2 trials of angiotensin receptor blockers for diabetic kidney disease.[59] In that report, we showed an increase in number of events and a trend toward attenuation of treatment effects when using lesser eGFR declines. These effects counterbalanced each other such that there was no improvement in statistical power when using lesser eGFR declines. In addition, we presented results using the 3-month time point as the baseline and show less attenuation of treatment effects with lesser decline. Our data from the current study reinforce the importance of understanding the effects of the intervention on GFR in specific populations. The final articles from the series of reports from the workshop analytical group explore the impact of these mechanisms and their combination on design of clinical trials.

We found that use of confirmed end points results in stronger treatment effects for all magnitudes of eGFR decline, particularly at shorter follow-up. The likely explanation is that the "noise" in eGFR that could be related to short-term fluctuation in measured GFR (eg, due to acute kidney injury) or in non-GFR determinants of serum creatinine level are not sustained across a subsequent visit. Based on these data, a reasonable approach in the design of future trials would be to confirm the end point with a repeat measurement. Our

data cannot identify the appropriate timing for the next visit. Because the change in GFR would not have been a specified event in the study design, the next visit used in our analyses was the next planned visit.

Strengths of this study include a systematic literature search to include all available studies, uniform definitions of exposures and outcomes, and a rigorous evaluation using complementary meta-analytical methods. In particular, the trial-level analysis to characterize agreement between the alternative and established end points used Bayesian analyses to account for statistical noise resulting from limited sample sizes from some studies. Similar analyses using less formal methods have been interpreted as supporting reductions in blood pressure and serum cholesterol level as surrogate end points for cardiovascular disease protection.[60-62]

There are several limitations. First, our analyses are restricted to the specific diseases and interventions included in the published and unpublished literature available at the beginning of our study in 2007, as well as the additional IgA studies that we included. Inclusion of new trials and in particular large trials could overcome some of the limitations of our current analysis. Second, the limitations in sample size and variation in treatment effects among well-powered CKD trials limited statistical power, particularly for the trial-level ratio analysis. Thus, we cannot with certainty say that that the ratio of treatment effects for the alternative to established end points does or does not include 1. These limitations in size and variation also made estimation of between-study variability sensitive to assumptions about its prior distribution and did not allow for a comprehensive subgroup analyses by varying factors of disease, level of proteinuria, and eGFR. This also prevented evaluation of the ability of treatment effects on GFR decline to predict treatment effects on the established outcome, which is of key relevance for the design of future studies. Third, the confirmed result was not a planned visit as part of the study design, but was the next available visit and may have occurred long after the original visit.

In summary, the results presented here, together with those of the workshop report and the other 3 articles from the workshop analytical group, suggest that a confirmed eGFR decline of 40% and possibly 30% may be used as an end point for a trial of kidney disease progression in certain circumstances. Acute effects of interventions of GFR, nonproportional effects of interventions on GFR decline, and effects of interventions on the endogenous filtration markers used to estimate GFR could affect the utility of one or both of these end points, depending on the magnitude of the effect. Exploration as to the existence of these factors should be undertaken early in the design of drug development and potentially could be evaluated during phase 3 trials that use eGFR decline as an end point.

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The participating CKD-EPI clinical trials/collaborators are listed in Item S2.

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Contributions: Research idea and study design: LAI, HJLH, THG, ASL; data acquisition: LAI; data analysis/interpretation: LAI, HJLH, HM, CHS, HT, FN, JC, TG, ASL; statistical analysis: LAI, HJLH, HM, CHS, HT, FN, THG; supervision or mentorship: LAI, THG, ASL. Each author contributed important intellectual content during manuscript drafting or revision and accepts accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved. LAI takes responsibility that this study has been reported honestly, accurately, and transparently; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

SUPPLEMENTARY MATERIAL

Item S1: Supplemental methods, figures, and tables.

Item S2: List of participating CKD-EPI clinical trials/collaborators.

Note: The supplementary material accompanying this article (http://dx.doi.org/10.1053/j.ajkd.2014.08.017) is available at www.ajkd.org

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