Original Investigation

GFR Decline and Subsequent Risk of Established Kidney Outcomes: A Meta-analysis of 37 Randomized Controlled Trials

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Background: The currently established end points for clinical trials of progression of chronic kidney disease (CKD) are end-stage renal disease and doubling of serum creatinine level, which approximates a 57% decline in estimated glomerular filtration rate (eGFR). There is increased interest in using alternative end points in clinical trials to shorten trial duration and reduce sample size. As part of an evaluation of using lesser declines in GFR as alternative end points, we examined the associations of various levels of eGFR decline with the subsequent development of established end points and assess the consistency of alternate levels of eGFR decline across varying clinical manifestations of kidney disease and interventions.

Study Design: Observational analysis of randomized controlled trials.

Setting & Participants: 9,488 participants in 37 randomized controlled trials in CKD.

Predictor: Alternative end points, defined as 30% and 40% declines in eGFR from baseline to month 12. Effect modification by baseline eGFR, proteinuria, cause of disease, and interventions.

Outcomes: Established end point, defined as end-stage renal disease, eGFR < 15 mL/min/1.73 m^2, or doubling of serum creatinine level.

Results: From baseline to 12 months, 16.1% and 7.8% of participants had eGFR declines of $\geq$30% or $\geq$40%, respectively. Over a median follow-up of 2.0 (IQR, 1.2-3.1) years after the 12-month baseline period, 2,661 established end points were observed. A strong linear association was observed between eGFR decline and subsequent established end points. HRs for the established end point for 30% and 40% decreases in eGFR compared to a 0% decline were 9.6 (95% CI, 7.3-12.6) and 20.3 (95% CI, 14.1-29.3), respectively. The associations were consistent regardless of baseline eGFR, proteinuria, causes of disease, and interventions.

Limitations: Observational study subject to residual confounding.

Conclusions: The strong associations between lesser declines in eGFR and the subsequent development of established end points were consistent across different clinical characteristics of kidney disease and interventions and support implementation of alternative end points in clinical trials of CKD progression.

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INDEX WORDS: Randomized controlled trial; nephropathy; meta-analysis; kidney end point; renal end point; kidney disease outcome; surrogate end point; chronic kidney disease (CKD); estimated glomerular filtration rate (eGFR) decline; renal function; kidney disease progression; end-stage renal disease (ESRD).

This article is the third in a series of 4 articles to report the analyses undertaken in conjunction with a 2012 workshop, "GFR Decline as an Endpoint for Clinical Trials in CKD," sponsored by the National Kidney Foundation (NKF) and the US Food and Drug Administration (FDA). The workshop report is included in this issue of *AJKD*.[1]

The FDA accepts halving of glomerular filtration rate (GFR), assessed as doubling of serum creatinine level, as a surrogate end point for the clinical end point of kidney failure in clinical trials of kidney disease progression, but it is a late event in chronic kidney disease (CKD). A doubling of serum creatinine level corresponds to a 57% decline in estimated GFR (eGFR) using the 2009 CKD-EPI (CKD Epidemiology Collaboration) creatinine equation.[2] Lesser declines in GFR need to be evaluated as alternative surrogate end points for kidney disease progression. Establishing the validity of such end points includes quantification of the strength of their association with future progression

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to established kidney end points and consistency of the association among various subgroups.

The first article in this series showed strong and consistent associations between 30% and 40% declines in eGFR and subsequent kidney failure and mortality in cohorts participating in the CKD Prognosis Consortium.[3] However, it is important to evaluate the consistency of these associations across different causes of kidney diseases and types of interventions used to slow the progression of CKD. Moreover, although the cohort studies included in the first article had complete data for eGFR, data for proteinuria, an important prognostic factor, were not available in all cohorts. In this study, we evaluate the relationship of lesser declines in eGFR with subsequent kidney failure and describe the effect modification by cause of kidney disease and type of intervention, as well as baseline eGFR and level of proteinuria, in a meta-analysis of 37 clinical trials participating in CKD-EPI. The second article in this series described this database of clinical trials and the consistency of treatment effects on the established and alternative end points from a meta-analysis of clinical trials,[4] and the fourth article examines the validity and utility of alternative end points in simulations.[5]

METHODS

Data Sources and Study Selection

We used an individual-patient data set of clinical trials that was created previously for the purpose of investigating early change in proteinuria as a surrogate end point for kidney disease progression. The development of the pooled data set, available data, and characteristics of included studies are described in detail elsewhere.[6] In brief, to create the database, we performed a systematic review of the literature for kidney disease randomized controlled trials as of May 15, 2007, and requested individual-patient data from the investigators.[6] For the purpose of this analysis, we excluded one study with no end-stage renal disease (ESRD) outcomes.[7] As part of a separate study investigating the effects of interventions on proteinuria in immunoglobulin A (IgA) nephropathy, we performed a separate systematic review as of July, 9, 2012, and also received individual-patient data from 5 additional studies. Altogether, we included 37 unique studies (see Table S1, available as online supplementary material, for a list of studies and references). We excluded 103 participants who did not have a baseline or follow-up serum creatinine value, leading to a total of 9,488 individuals (Table 1). Some trials had more than one treatment comparison[8-11]; thus, for analyses by intervention, there were 43 treatment comparisons (herein referred to as studies) including 12,821 participants.

Estimated GFR

GFR was estimated from serum creatinine level at baseline and 12 months using the 2009 CKD-EPI creatinine equation. Creatinine was calibrated to standardized methods using direct comparison or by assuming the calibration factor in the MDRD (Modification of Diet in Renal Disease) Study laboratory.[12]

Established End Points

Established end points for clinical trials include treated kidney failure (ESRD, defined as initiation of treatment with dialysis or

Table 1. Baseline Characteristics, Percentage Change in eGFR During First 12 Months, and Number of Kidney Outcomes After 12 Months, by Cause of Kidney Disease

Disease	Baseline Characteristics						After 12 mo			
	No. of Studies	No. of Patients	Age (y)	Female Sex	eGFR (mL/min/1.73 m^2)	Proteinuria (g/d)	ΔeGFR at 12 mo[a]	F/U (mo)	No. of ESRD Events	No. of EGS Events
CKD unspecified	13	2,949	51 ± 13	1,030 (34.9)	33.5 ± 16.1	1.2 [0.2-2.7]	−11.1% ± 20.8%	17.4 ± 10.4	457	690
Diabetes and nephropathy	4	4,008	55 ± 11	425 (38.9)	51.3 ± 21.2	2.4 [1.2-4.7]	0.4% ± 22.0%	39.0 ± 15.9	154	222
Hypertensive nephrosclerosis	1	1,094	57 ± 11	1,444 (36.0)	48.7 ± 15.7	0.1 [0.0-0.6]	−12.2% ± 21.6%	24.2 ± 13.3	538	940
IgA nephropathy	11	888	39 ± 12	316 (35.6)	73.3 ± 30.2	1.8 [1.3-2.8]	−2.0% ± 20.9%	46.9 ± 32.4	87	116
Lupus nephritis	3	228	35 ± 12	200 (87.7)	70.0 ± 32.8	3.1 [1.9-6.2]	36.3% ± 83.6%	48.7 ± 32.2	22	26
Membranous nephropathy	5	321	47 ± 12	89 (27.7)	87.3 ± 22.3	5.5 [4.0-8.4]	2.7% ± 27.7%	37.1 ± 39.2	14	33
Total[b]	37	9,488	52 ± 13	3,504 (36.9)	49.2 ± 24.9	1.7 [0.6-3.6]	−7.7% ± 26.3%	28.0 ± 21.0	1,272	2,027

Note: Unless otherwise indicated, values for categorical variables given as number (percentage); values for continuous variables are given as mean ± standard deviation or median [interquartile range].

Abbreviations and definitions: CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; EGS, composite of ESRD, eGFR < 15 mL/min/1.73 m^2, or doubling of serum creatinine; ESRD, end-stage renal disease; F/U, follow-up; IgA, immunoglobulin A.

[a]For participants who did not reach EGS by 12 months.

[b]Totals differ from that reported in the text because those numbers were totaled across treatment comparisons, whereas for some studies with more than 2 treatment arms, participants were included more than once.

transplantation), kidney failure not treated with dialysis or transplantation (eGFR < 15 mL/min/1.73 m^2 for people who started the study with eGFRs > 25 mL/min/1.73 m^2), or doubling of serum creatinine level. We defined the primary outcome as time to the first occurrence of the composite of all 3 outcomes, censoring for death that occurred over the full study duration. All trials with at least 10 established end points were included in this analysis. Outcome ascertainment started from the date of the 12-month creatinine measurement until the end of each trial.

Predictor: Change in eGFR

Percent change in eGFR at 12 months was calculated as follows: $[(eGFR_{12mo} - eGFR_{baseline})/eGFR_{baseline}] \times 100\%$. Percentage change in eGFR subsequently was categorized into 30%, 40%, and 57% declines in eGFR (equivalent to 34%, 53%, and 100% increases in serum creatinine levels).

Statistical Analysis

Baseline characteristics are summarized by cause of CKD and presented as mean ± standard deviation for normally distributed variables or median (interquartile range) for skewed variables. We classified cause of disease as diabetes and nephropathy, hypertensive nephrosclerosis, IgA nephropathy, lupus nephritis, membranous nephropathy, and CKD of unspecified or other cause. We classified intervention types as renin-angiotensin system blockade versus control, renin-angiotensin system blockade versus calcium channel blocker, intensive blood pressure control, low-protein diet, and immunosuppressive therapy.

A 2-stage analytical meta-analysis approach was applied in which each study was analyzed separately followed by random-effects meta-analysis. In each study, a Cox proportional hazard regression analysis was constructed to estimate the adjusted risk of the established end points according to percent change in eGFR. We used a spline function with one knot at eGFR change of 0% to allow for a possible nonlinear relationship. To verify that the linearity above and below the knot was satisfied, we fitted a restricted cubic spline for each part of the curve and tested the global effect and deviation from linearity for each part separately. The multivariable Cox proportional hazard regression was adjusted for age, sex, race (black vs nonblack), baseline eGFR, proteinuria, systolic blood pressure, diabetes (yes vs no), and treatment assignment in each study. Active treatment was defined as the treatment hypothesized to produce the greatest reduction in the risk of the clinical end point. If a study did not enroll patients with diabetes or enrolled only whites, the variable was not included in the multivariable Cox regression for that study. We used multivariable adjusted hazard ratios (HRs) from the continuous model to calculate the risk of established end points for a 30%, 40%, and 57% decline in eGFR.

The second stage of the 2-stage meta-analytic approach involved random-effects meta-analysis of all individual study results. Heterogeneity among studies was quantified by I^2 statistic (total variance in point estimates that can be attributed to heterogeneity) and τ^2 statistic (between-study variance of true effects).[13] We also assessed agreement defined as the proportion of individual studies that showed a statistically significant association between percentage decline in eGFR and the established end point. To explore baseline eGFR, proteinuria, cause of disease, and intervention type as potential sources of heterogeneity, we performed univariate metaregression analyses.[13] In addition, we performed subgroup analysis by treatment intervention to examine whether the strength of the association between eGFR decline and the established end point was different between the control and active treatment arms.

We performed various sensitivity analyses. First, we assessed whether the addition of all-cause mortality to the established end point changed the relationship. Second, we calculated percentage change in eGFR over the first 18 months of the trial because the strength of the association between changes in eGFR and established end points may depend on the duration of the baseline period. Third, we adjusted each Cox model for a minimal set of covariates: age, sex, race, baseline eGFR, proteinuria, and treatment assignment.

Analyses were performed using SAS, version 9.2 (SAS Institute Inc); Stata/SE, version 12 software (StataCorp LP), for random-effects meta-analysis; and R software, version 2.14.1 (R Foundation for Statistical Computing).

RESULTS

Key baseline characteristics of the study population summarized by cause of disease are shown in Table 1. Baseline characteristics of individual studies are shown in Table S1. Mean age of the population was 52 years, 37% of the population were women, and eGFR and proteinuria levels ranged (5th to 95th percentile) from 16.8 to 99.1 mL/min/1.73 m^2 and 0.05 to 9.03 g/d, respectively.

Overall, mean percent eGFR change during the first 12 months in the pooled data set was −7.7% ± 26.3% (SD; 5th to 95th percentile, −44.1% to 29.1%; Table 1). Changes in eGFR during the first 12 months varied among studies from −29% to +46.2% (Table S1). The distribution was skewed toward negative values, indicating that most patients had a decline in eGFR (Fig 1). The cumulative prevalence of at least 30% or 40% decline in eGFR was 16.1% and 7.8%, respectively. By comparison, the cumulative prevalence of at least 57% decline in eGFR was 0.5%. Twenty-seven percent had an increase in eGFR. Patients with a lesser decline in eGFR during the 12-month baseline period were younger, had lower systolic blood pressure and proteinuria, had higher eGFRs, and were less likely to have a diagnosis of diabetes at baseline (Table S2).

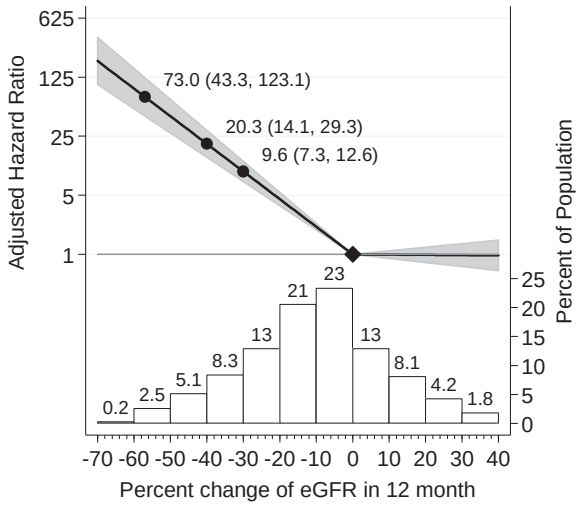

Figure 1. Adjusted hazard of the composite established kidney end point associated with percent change in estimated glomerular filtration rate (eGFR) during a 1-year baseline period. Hazard ratios for 30%, 40%, and 57% decline in eGFR are shown in the graph. The histogram in the bottom of the graph shows the distribution of percent change in eGFR.

Over a median follow-up of 2.0 (interquartile range, 1.2-3.1) years after the 12-month baseline period, 2,661 composite established end points were observed (Table 1). Forty-five percent of patients with an established kidney end point had a −30% change in eGFR over 12 months, whereas only 2% of cases reached −57% eGFR change in this time frame, although the rate of the established kidney end point was higher in people with greater versus less decline (Table S3). As shown in Fig 1, the association between eGFR change during a 12-month baseline period and subsequent risk of the established kidney end point was nonlinear. For GFR declines (negative change in eGFR), the association was linear on the logarithmic scale. After adjustment for baseline covariates, HRs were exponentially larger for larger percentage declines in eGFR compared to no change (Fig 1). HRs for the composite established end point at a 30% and 40% eGFR decline were 9.6 (95% confidence interval [CI], 7.3-12.6) and 20.3 (95% CI, 14.0-29.2), respectively (Table 2) compared to a 0% decline. By comparison, the HR for a 57% eGFR decline, equivalent to a doubling of serum creatinine level, which is included in the composite established end point, was 73.0 (95% CI, 43.3-123.1). For increases in GFR (positive change in eGFR), the association was not significant (adjusted HR, 1.0; 95% CI, 0.8-1.4; Fig 1).

The strength of the association between a 30% and 40% eGFR decline and subsequent risk of established end points in each individual study is presented in forest plots in Fig S1. Although heterogeneity across studies for the association of GFR decline with established end points was present ($I^2 = 69.3\%$; $P < 0.01$; Fig S1), >80% of individual studies showed a statistically significant association between percentage decline in eGFR and established end points (Table 2). Heterogeneity to a large extent was caused by one outlying study contributing 5.0% to the overall analysis (study number 3).[14] After exclusion of this study, heterogeneity was reduced substantially ($I^2 = 34.5\%$; $P = 0.05$). Strong associations were observed when analyses were repeated in the active and control arms of the trials separately (Fig S2). Differences between the active and control arms were eliminated when the outlying study was excluded.

Using metaregression, we explored several study-level factors as potential sources of heterogeneity. Univariate metaregression analysis revealed that the associations between 30% and 40% eGFR declines and established end points were consistent regardless of baseline eGFR ($P = 0.08$), baseline proteinuria ($P = 0.07$), cause of disease, or type of intervention (Fig 2). After exclusion of the outlying study,[14] there was no evidence of effect modification by any of these factors (all $P \geq 0.1$). Additionally, a pooled patient-level analysis showed no significant interaction between baseline proteinuria or eGFR with 12-month change in eGFR for the composite established end point (P for interaction proteinuria = 0.9; P for interaction eGFR = 0.3).

In sensitivity analyses, essentially similar results were obtained when ESRD alone was used as the end point or when all-cause mortality was included with the established end point (Table 2; Figs S3 and S4). Analysis of percentage change in eGFR during an 18-month baseline period also showed strong associations with established end points (Fig S5). In addition, results were not different when associations were adjusted for age, sex, treatment assignment, baseline eGFR, and proteinuria treatment intervention alone (Table 2).

DISCUSSION

In this large observational meta-analysis of clinical trials, we documented more frequent occurrence of

Table 2. Association Between 30% and 40% eGFR Decline and Established Kidney End Points and Measures of Heterogeneity

End Point[a]	Model[b]	HR for 30% eGFR decline (CI)[c]	HR for 40% eGFR decline (CI)[c]	I^2	τ^2	Qualitative Agreement Among Studies[d]
EGS	Fully adjusted	9.6 (7.3-12.6)	20.3 (14.1-29.2)	69.3%	0.2279	22 of 25 (88%)
E	Fully adjusted	9.8 (7.0-13.7)	21.0 (13.4-32.7)	70.7%	0.2495	13 of 18 (72%)
EGSX	Fully adjusted	7.3 (5.6-9.5)	14.2 (10.0-20.2)	74.1%	0.2536	22 of 27 (82%)
EGS	Minimally adjusted	10.0 (7.7-13.1)	21.6 (15.2-30.8)	73.8%	0.2467	22 of 25 (88%)
E	Minimally adjusted	9.5 (7.0-12.9)	20.1 (13.3-30.2)	75.0%	0.2393	14 of 18 (78%)
EGSX	Minimally adjusted	7.9 (6.2-10.1)	15.7 (11.3-21.7)	75.1%	0.2264	22 of 27 (82%)

Abbreviations: CI, confidence interval; eGFR, estimated glomerular filtration rate; HR, hazard ratio.

[a]End points defined as follows: E, end-stage renal disease; G, eGFR < 15 mL/min/1.73 m^2; S, doubling of serum creatinine; X, death; more than 1 letter indicates a composite end point.

[b]Minimally adjusted model shows results of Cox proportional hazard regression adjusted for age, sex, treatment intervention, eGFR, and proteinuria. Fully adjusted models additionally adjust for race (nonblack vs black), diabetes, and systolic blood pressure.

[c]HRs are calculated from a continuous multivariable-adjusted Cox proportional hazard model and represent the risk for established kidney end points at a 30% and 40% eGFR decline compared to a 0% decline at 12 months.

[d]Indicates number of individual studies that showed a statistically significant association between percentage decline in eGFR and kidney end points.

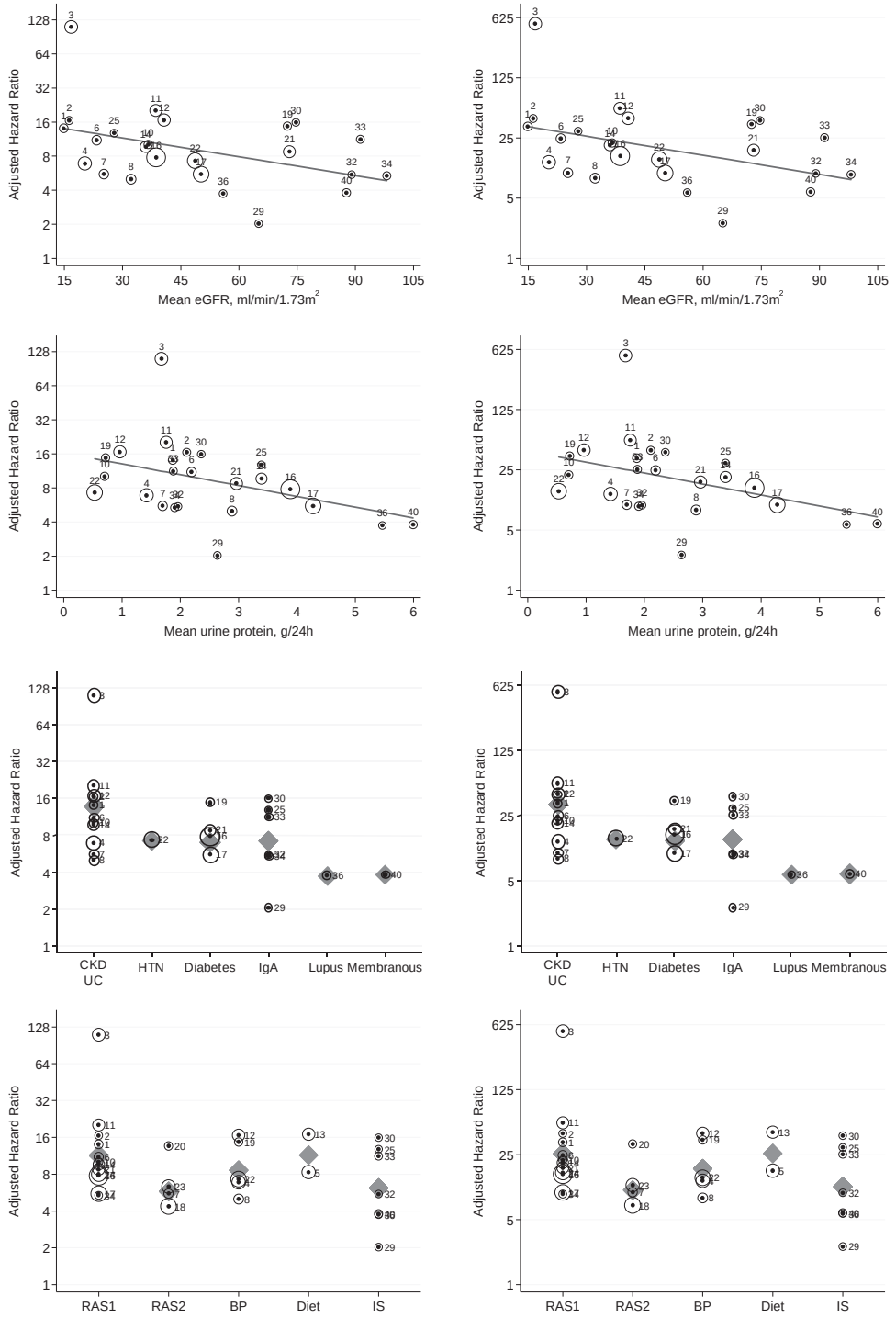

Figure 2. Metaregression of (left graphs) 30% and (right graphs) 40% estimated glomerular filtration rate (eGFR) declines with established kidney end point. Abbreviations: BP, blood pressure; CKD UC, chronic kidney disease unspecified cause; HTN, hypertension; IgA, immunoglobulin A; IS, immunosuppression; RAS1, renin-angiotensin-system blockers versus placebo; RAS2; renin-angiotensin system blockers versus calcium antagonists. Labels refer to study numbers in Table S1.

lesser eGFR declines compared with doublings of serum creatinine level during the first 12 months of the trial and strong associations of lesser eGFR declines with the subsequent development of established end points for kidney disease progression. Associations did not differ significantly by level of baseline eGFR and proteinuria, cause of disease, or type of intervention. Moreover, strong associations were observed when the control and active treatment arms were analyzed separately. These data indicate that associations of

lesser declines in eGFR with established end points were strong and consistent under a variety of circumstances in these clinical trials.

A doubling of serum creatinine level is accepted as an established surrogate end point in clinical trials of CKD progression because it represents a large change in eGFR and patients who experience a doubling in serum creatinine level are likely to receive renal replacement therapies in the near future. However, a doubling of serum creatinine level is a late event in CKD and necessitates clinical trials of long duration and large sample size. The first article in this series, involving more than 1.5 million participants, showed that eGFR declines of 30% during a 2-year observation period are associated with a 5-fold increased risk of ESRD and 2-fold increased risk of mortality after adjustment for potential confounders.[3] Our study includes 3 of the same studies as reported in the cohorts,[8,11,15] but focuses specifically on well-characterized clinical trial populations with CKD and provides additional information on clinical manifestations of kidney disease and treatment. Analyses from cohort studies could not address whether the associations between lesser declines in eGFR and established kidney end points are consistent in treated and control patients. However, our results show strong associations in both the treated and control groups, which suggests that there is less confounding by treatment. The strong and consistent results support the hypothesis that lesser eGFR declines may be suitable as surrogate end points in a wide range of patient populations and interventions.

There is a growing consensus that surrogate end points should be used in clinical trials only when they are sufficiently validated and reflect a clinical end point.[16] Surrogate outcomes are valid if the surrogate strongly and consistently correlates with the clinical end point and a treatment effect on the surrogate end point reflects a similar treatment effect (direction and magnitude) on the clinical end point.[17] The consistent associations that we observed are not sufficient to claim surrogacy and should be interpreted in conjunction with additional analyses, as described in the accompanying article in this series that compares the treatment effect of interventions on a lesser decline in eGFR (ie, 30% or 40%) with the treatment effect on established end points of kidney disease progression.[4] Additionally, simulation studies, as described in another accompanying article,[5] are needed to assess the utility and validity of these alternative end points using a wide range of scenarios because empirical data in trials of CKD progression do not capture all circumstances.

Our meta-analysis benefited from a large volume of individual-patient data, which increases the precision of the effect estimates. However, there also are limitations. Although we adjusted for multiple potential confounding factors, we cannot exclude residual confounding. The follow-up period for ascertainment of established end points was short, but in accord with the duration of contemporary clinical trials. In addition, we restricted the analysis to events that occurred after 12 months to focus on lesser declines versus rapid declines. Although heterogeneity among studies was present as assessed by conventional measures of heterogeneity, it appeared that agreement of the association among individual studies was high and the heterogeneity was driven largely by one outlying study.[14] In particular, we recognize that the number of studies with high eGFRs or low proteinuria was small. Therefore, we are unable to precisely delineate the strength of the associations in patients with these characteristics. Additionally, variability between laboratories in creatinine measurements may have been present. We also did not assess whether the 30% or 40% decline in eGFR after 12 months was sustained over time. These issues may have resulted in less precise estimates of the percentage decline in eGFR and could have led to underestimation of the strength of the reported associations. Finally, use of an existing database means that we are missing recent trials, including trials in transplant recipients and more recently tested agents such as erythropoiesis-stimulating agents, endothelin antagonists, or anti-inflammatory drugs. We suggest that these findings should be confirmed in additional clinical trial populations with these characteristics.

In conclusion, the strong association between lesser declines in eGFR and the subsequent development of clinical end points is consistent across different causes of kidney disease and interventions used to slow the progression of kidney disease. These results provide further support for the validity of these alternative eGFR-based end points in clinical trials of CKD progression and, together with those of the other 3 studies reporting analyses conducted in conjunction with the NKF-FDA workshop, suggest that a confirmed eGFR decline of 40% and possibly 30% may be used as an end point for clinical trials of kidney disease progression in certain circumstances.

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The participating CKD-EPI clinical trials/collaborators are listed in Item S1.

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institution, University of Groningen. Dr Matsushita reports receiving honorarium from Mitsubishi Tanabe Pharma. Dr Coresh reports receiving a research grant from Amgen during the past 3 years. Dr Levey reports funding to Tufts Medical Center for research and contracts with the National Institutes of Health, NKF, Amgen, Pharmalink AB, and Gilead Sciences. Dr Inker reports receiving research grants from Pharmalink AB and a Gilead Sciences and consulting agreement with Otsuka. The other authors declare that they have no other relevant financial interests.

Contributions: Research idea and study design: HJLH, KM, JC, ASL, LAI; data acquisition: HT, LAI, ASL; data analysis/interpretation: HJLH, HT, KM, JC, ASL, LAI; statistical analysis: HT, HM, SB, YS. 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. HJLH 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

Table S1: Baseline characteristics, percentage change in eGFR, and clinical outcomes for individual studies included in current report.

Table S2: Baseline characteristics according to percentage change in eGFR during 12-mo baseline period.

Table S3: Number of events and annual event rates for composite established endpoint according to change in eGFR at 12 mo.

Figure S1: Forest plot of individual studies for 30% and 40% eGFR decline.

Figure S2: Forest plot of association of 30% and 40% decline in eGFR with composite established endpoint stratified by control and active treatment.

Figure S3: Adjusted hazard of ESRD associated with percent change in eGFR during 1-y baseline period.

Figure S4: Adjusted hazard of composite established endpoint or all-cause mortality associated with percent change in eGFR during a 1-y baseline period.

Figure S5: Adjusted hazard of composite established endpoint with percentage change in eGFR during an 18-mo baseline period.

Item S1: List of participating CKD-EPI clinical trials/collaborators.

Note: The supplementary material accompanying this article (http://dx.doi.org/10.1053/j.ajkd.2014.08.018) is available at www.ajkd.org

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