AJKD

Original Investigation

Early Change in Proteinuria as a Surrogate End Point for Kidney Disease Progression: An Individual Patient Meta-analysis

*Lesley A. Inker, MD, MS,[1] Andrew S. Levey, MD,[1] Kruti Pandya, MS,[1] Nicholas Stoycheff, MD,[1] Aghogho Okparavero, MBBS, MPH,[1] and Tom Greene, PhD,[2] on behalf of the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI)**

Background: It is controversial whether proteinuria is a valid surrogate end point for randomized trials in chronic kidney disease.

Study Design: Meta-analysis of individual patient-level data.

Setting & Population: Individual patient data for 9,008 patients from 32 randomized trials evaluating 5 intervention types.

Selection Criteria for Studies: Randomized controlled trials of kidney disease progression until 2007 with measurements of proteinuria both at baseline and during the first year of follow-up, with at least 1 further year of follow-up for the clinical outcome.

Predictor: Early change in proteinuria.

Outcomes: Doubling of serum creatinine level, end-stage renal disease, or death.

Results: Early decline in proteinuria was associated with lower risk of the clinical outcome (pooled HR, 0.74 per 50% reduction in proteinuria); this association was stronger at higher levels of baseline proteinuria. Pooled estimates for the proportion of treatment effect on the clinical outcome explained by early decline in proteinuria ranged from −7.0% (95% CI, −40.6% to 26.7%) to 43.9% (95% CI, 25.3% to 62.6%) across 5 intervention types. The direction of the pooled treatment effects on early change in proteinuria agreed with the direction of the treatment effect on the clinical outcome for all 5 intervention types, with the magnitudes of the pooled treatment effects on the 2 end points agreeing for 4 of the 5 intervention types. The pooled treatment effects on both end points were simultaneously stronger at higher levels of proteinuria. However, statistical power was insufficient to determine whether differences in treatment effects on the clinical outcome corresponded to differences in treatment effects on proteinuria between individual studies.

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

Conclusions: These results provide new evidence supporting the use of an early reduction in proteinuria as a surrogate end point, but do not provide sufficient evidence to establish its validity in all settings.

Am J Kidney Dis. ■(■):■-■. © *2014 by the National Kidney Foundation, Inc.*

INDEX WORDS: Proteinuria; surrogate endpoint; kidney disease progression; disease trajectory; end-stage renal disease (ESRD); prognostic marker.

Chronic kidney failure is a major public health issue worldwide because of its increasing prevalence, poor outcomes, and high cost of treatment.[1] Based on the idea that treatments initiated early in the course of a disease might slow progression and postpone the onset of kidney failure, guidelines and public health campaigns have concentrated on early detection and treatment of chronic kidney disease.[1,2] Because many kidney diseases progress gradually, a large decline in glomerular filtration rate, assessed as a doubling of serum creatinine level from baseline, often is used as a surrogate end point for kidney failure in randomized clinical trials (RCTs). However, the time required to reach this end point for patients enrolled early in the course of kidney disease often exceeds 10 years. Hence, RCTs using doubling of serum creatinine level as an end point require long durations of follow-up to detect the end point, increasing expense and complexity, and often are infeasible for early-stage disease. This problem likely has contributed to the small number of RCTs in nephrology compared with other fields and the paucity of therapies to slow kidney disease progression.[3,4]

The hypothesis that an early change in proteinuria is a valid surrogate end point for kidney disease progression in RCTs has a fairly firm biological basis.[5,6] Proteinuria has been established as a marker of

From the [1]Division of Nephrology, Tufts Medical Center, Boston, MA; and [2]Department of Medicine, University of Utah School of Medicine, Salt Lake City, UT.

**A list of the CKD-EPI collaborators appears in the Acknowledgements.*

Received October 28, 2013. Accepted in revised form February 24, 2014.

Because an author of this manuscript is an editor for AJKD, the peer-review and decision-making processes were handled entirely by an Associate Editor (Jonathan C. Craig, MD, PhD, MM [Clin Epi]) who served as Acting Editor-in-Chief. Details of the journal's procedures for potential editor conflicts are given in the Information for Authors & Editorial Policies.

Address correspondence to Lesley A. Inker, MD, MS, Division of Nephrology, Tufts Medical Center, 800 Washington St, Box #391, Boston, MA 02111. E-mail: linker@tuftsmedicalcenter.org

0272-6386/$36.00

http://dx.doi.org/10.1053/j.ajkd.2014.02.020

kidney damage in experimental studies and has been widely reported to be prognostic for long-term disease progression at all stages of kidney disease.[7-15] However, as evidenced by high-profile past failures in other disciplines, premature acceptance of surrogate end points carries a risk that ineffective or harmful therapies could be approved for use in practice.[16] The National Institutes of Health and the US Food and Drug Administration have organized several conferences to address this controversy, which had concluded that there is only preliminary empirical evidence in support of this hypothesis.[15,17]

We report an individual patient-level meta-analysis of a pooled data set of 9,008 individuals from 32 RCTs to provide an integrated systematic evaluation of an early change in proteinuria as a surrogate end point for trials of kidney disease progression.

METHODS

A complete description of methods is included in Item S1 (provided as online supplementary material).

Data Sources, Searches, and Study Selection

We previously described the creation of the pooled individual-level patient-level data set.[18] In brief, we performed a systemic review of the literature for RCTs of kidney disease progression as of May 15, 2007, and requested individual patient data from the investigators. Inclusion criteria were availability of urine protein measurements at baseline and at least once within 13 months after randomization and at least one participant with a clinical outcome during 1 further year of follow-up. A total of 32 studies accounting for 9,008 individuals that investigated 5 intervention types were used in the analyses reported here (A, renin-angiotensin system [RAS] blockade vs control[19-32]; B, RAS blockade vs calcium channel blocker[19,32-34]; C, intensive blood pressure control[19,33,35,36]; D, low-protein diet[35]; and E, immunosuppressive therapy[37-50]; see Table S1 for list of studies). For studies that evaluated more than one intervention,[19,32,33,35] we included a separate group for each independent treatment comparison, such that some participants were included more than once. We combined the smaller studies that tested immunosuppressive therapies by disease type (immunoglobulin A [IgA] nephropathy, lupus nephritis, and membranous nephropathy) into 3 separate study groups (for study-specific details, see Table S2).[37-50] Overall, we had 29 analytical comparisons (herein referred to as "studies") across the 5 intervention types. We defined the active treatment as the treatment hypothesized to produce the greater reduction in risk for the clinical end point.

Proteinuria

We defined an early change in proteinuria as the change in log-transformed 24-hour urine protein excretion from baseline to the first follow-up measurement between 2.5 and 13 months thereafter. We selected this interval because treatment effects on urine protein are expected to peak at about 2-4 months and some clinical trials obtained measurements only yearly. For 2 studies that measured urine albumin,[30,31] urine total protein was estimated from urine albumin excretion.

Clinical Outcome

We defined the primary clinical outcome as time to the first doubling of serum creatinine level, end-stage renal disease (defined as the initiation of dialysis therapy or transplantation), or death. We considered the composite of time to first doubling of serum creatinine level or end-stage renal disease (censoring death) in sensitivity analyses. We used the study-defined censoring times[19-25,27,28,30-36,38-41,43-45,48,49] or approximated this as time from randomization to final visit date plus 6 months plus the study-specific 90th percentile of the average interval between serum creatinine measurements.[26,29,37,42,45-47,50]

Data Synthesis and Analysis

Overview

We performed 3 standard categories of analyses that are widely used for validation of surrogate end points: (1) association between the clinical outcome and early change in proteinuria at the individual level,[51] (2) proportion of treatment effect on the clinical outcome explained by the early change in proteinuria (Prentice-Freedman criterion),[52,53] and (3) association between treatment effects on the clinical outcomes and treatment effects on early change in proteinuria across different trials and/or across subgroups within trials.[54-57] For all 3 categories, we first obtained appropriate measures of association within each study, followed by joint analyses that summarized results across studies. We used Bayesian mixed models for analyses of individual- and trial-level associations to account for variation between trials when summarizing overall results.[55,58,59] We used credible intervals, which in some respects are analogous to confidence intervals in frequentist statistics, to characterize the precision of parameter estimates from Bayesian analyses.[59]

Individual-Level Association

Demonstration of a consistent patient-level epidemiologic association between a surrogate and the clinical outcome is widely regarded as necessary, although not sufficient, for establishing the validity of the surrogate end point in clinical trials.[60-62] We evaluated individual-level association by performing separate Cox regressions to relate the clinical outcome to early change in proteinuria in each study, with results expressed as the hazard ratio (HR) associated with a halving of proteinuria. The primary analyses were adjusted for baseline proteinuria. Additional models adjusted for age, sex, baseline serum creatinine level, and mean arterial pressure in addition to proteinuria. The study-specific results subsequently were analyzed under Bayesian mixed-effect models to summarize the distribution of individual-level association across all studies, within each of the 5 interventions, and in relation to level of baseline proteinuria.[58] For the pooled result across all studies, we included only one intervention per study, such that participants were not represented more than once.

Proportion of Treatment Effect Explained (Prentice-Freedman criterion)

The proportion of the treatment effect on a clinical outcome "explained by the surrogate" has been used widely as an index of the validity of surrogate end points.[52,53,63] The proportion of treatment effect is defined as the ratio of the treatment effect on the clinical outcome that remains after statistically controlling for the surrogate to the treatment effect without controlling for the surrogate. Large proportions of treatment effect close to one are regarded as supporting the surrogacy hypothesis.[54,64]

We performed Cox regressions to estimate treatment effects on the clinical outcomes for each study, first adjusting for only baseline proteinuria. Then for studies in which the treatment effect on the clinical outcome approached statistical significance ($P < 0.10$), we repeated the Cox regression adjusting also for early change in proteinuria. The proportion of treatment effect was calculated as 1 minus the ratio of the log-transformed Cox regression coefficients for the treatment with and without adjusting for early change in proteinuria. These analyses were repeated with additional adjustment for the extended covariate set described above.