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# Early change in proteinuria as a surrogate outcome in kidney disease progression: a systematic review of previous analyses and creation of a patient-level pooled dataset

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## Abstract

**Background.** Proteinuria is a candidate surrogate end point for randomized controlled trials (RCTs) in chronic kidney disease (CKD). There is a reasonably sound biological basis for this hypothesis, but only preliminary empirical evidence currently exists.

**Methods.** A systematic review and creation of a patient-level dataset of randomized controlled trials (RCTs) in CKD that reported changes in proteinuria and assessed progression of kidney disease as defined by dialysis, transplantation, death, or changes in GFR or creatinine were performed.

**Results.** *Systematic review.* Seventy RCTs met the eligibility criteria; 17 eligible RCTs contained analyses of proteinuria as a predictor of outcomes; 15 RCTs concluded that greater proteinuria was associated with adverse outcomes. A majority were studies of diabetic or hypertensive kidney disease and tested renin–angiotensin system blockade. Definitions of predictor and outcome variables were too variable to conduct a meta-analysis of group data. *Database creation.* Over 4 years was required to create the patient-level dataset. The final dataset included 34 studies and >9000 patients with a variety of CKD types and interventions.

**Conclusions.** There are a relatively small number of RCTs designed to rigorously test therapies for kidney disease progression. Current analyses of change in proteinuria as a predictor of CKD progression are heterogeneous and incomplete, indicating further evaluation in a pooled individual patient-level database is necessary to advance knowledge in this field.

**Keywords:** chronic kidney disease; proteinuria; randomized clinical trials; surrogate markers; systematic review

## Introduction

Many chronic kidney diseases worsen over time by transitions through a sequence of stages, regardless of the specific cause or rate of progression. Recent guidelines and public health campaigns have focused on early detection and treatment of chronic kidney disease based on the rationale that treatments initiated early in the disease course can slow progression of the disease and delay onset of kidney failure.

Kidney failure, defined as the initiation of dialysis or transplantation and doubling of serum creatinine, is an accepted end point for kidney disease progression in clinical trials. However, because many chronic kidney diseases progress slowly, a long duration of follow-up is required, increasing the expense and complexity of trials and leading to a paucity of therapies to slow progression. The use of surrogate end points may accelerate testing of new therapies, particularly in earlier stages of CKD.

Proteinuria is commonly considered as a candidate for a surrogate end point for kidney disease progression. There is a reasonably sound biological basis for this hypothesis [1,2], but to date, there is only preliminary empirical evidence [3–9]. A rigorous evaluation of the surrogacy of proteinuria will avoid erroneous conclusions in instances where the effect of the intervention on proteinuria does not predict the effect on the clinical end point. In May 2008, the National Kidney Foundation (NKF) and the Food and Drug Administration (FDA) co-sponsored a scientific workshop on 'proteinuria as a surrogate outcome in chronic kidney disease', with the objectives to (i) evaluate the strengths and limitations of criteria for assessment of proteinuria as a potential surrogate end point in CKD, (ii) explore the strengths and limitations of available data on proteinuria as a potential surrogate end point, focusing on specific clinical circumstances and therapeutic agents, and (iii) delineate what else needs to be done to evaluate proteinuria as a potential surrogate end point [10]. Preceding this conference, the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) charged a research group, Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI),

to undertake a formal evaluation of proteinuria as a surrogate marker [11]. CKD-EPI will accomplish the formal evaluation using a systematic review and a pooled individual patient-level meta-analysis of randomized controlled trials (RCT). The purpose of this manuscript is to describe, first, the results of the systematic review of prior analyses addressing this question as proteinuria as a surrogate marker for kidney disease progression, and second, the formation of the collaborative group and mechanics of development of a pooled individual patient-level dataset to be used in the formal evaluation of proteinuria as a surrogate marker, the results of which will be published separately.

## Materials and methods

### *Literature search*

We conducted a comprehensive search of the literature in MEDLINE on 7 April 2005 and updated it on 15 May 2007 to identify articles to address the following research question: 'Does the short-term effect of treatment on changes in proteinuria predict the long-term effect of treatment on changes in GFR during randomized controlled trials in chronic kidney disease?' The search strategy retrieved articles using the following key or text words restricted to RCTs: kidney disease, chronic renal insufficiency, chronic kidney disease, renal disease, IgA nephropathy, lupus nephritis, diabetic nephropathy, glomerular disease, polycystic kidney disease, kidney transplant, focal sclerosis, membranous nephropathy, and proteinuria or albuminuria. All abstracts were screened according to the criteria listed in Table 1. Abstracts were excluded in instances where they clearly did not meet one of the criteria. Articles were obtained for the remaining abstracts and screened again against the inclusion criteria. The above search was repeated restricting to meta-analyses, and the resulting studies were searched for additional RCTs. Finally, studies were added from the general knowledge of CKD-EPI investigators and collaborators.

### *Systematic review of prior analyses*

The resulting papers from the literature search were examined to determine if analyses of proteinuria as a predictor of kidney disease progression were performed. To determine if such analyses were reported separately, we conducted an additional MEDLINE search for each study with >150 participants. Analyses were subdivided into four types depending upon the use of proteinuria as the predictor of outcomes: (i) Baseline—level of proteinuria at baseline, (ii) Intermediate change—change from proteinuria at baseline to an intermediate time point, (iii) Residual—level of proteinuria at an intermediate time point, and (iv) Prentice/Freedman—comparison of treatment effect with and without adjustment for change in proteinuria, where loss of a significant treatment effect after adjustment indicates support for proteinuria as a surrogate marker [12].

**Table 1.** Inclusion criteria for literature search

1. Population: CKD (as defined by GFR <60 mL/min/1.73 $m^2$ or microalbuminuria)
2. Design: randomized controlled trial (RCT)
3. Intervention: any
4. Comparator: any
5. Outcome: dialysis, transplant, death or serum creatinine. At least one person in the study had progression of kidney disease defined by 50% increase in creatinine in at least one patient
6. Sample size: >100 in non-glomerular disease except IgA nephropathy ($n$ >25)
7. Measurements: urine protein at baseline and at 6–12 months; GFR or GFR estimate or serum creatinine at baseline and serially in follow-up
8. Duration: at least 1 year after the second measure of proteinuria

### *Creation of a patient-level pooled database*

*Obtaining data.* Once a study was determined to meet the inclusion criteria (Table 1), the study's primary author was invited to join CKD-EPI as a collaborator. Invitations were sent initially via electronic mail. Follow-up messages were sent if no response was received. If collaborators expressed potential interest, a subsequent message was sent to explain the specifics of the overall project, study design, and analytical methods as well as publication and ancillary study policies. After agreement to participate was received, a discussion about the required variables and definitions, timing, and method for data transfer occurred.

*Pooled dataset development.* Once data were received from a study, variables that were to be included in the pooled dataset were selected, and where necessary, units of numeric variables were converted from SI to traditional units; any character variables, such as sex and race, were changed to numeric variables (e.g. 0 = male and 1 = female) and renamed to be consistent with the pooled dataset. Once a dataset was in acceptable format, the output's descriptive statistics were gathered, and outliers were manually checked and compared with the original study publication. Inquiries were sent to the collaborators for questions that arose in the data.

Baseline was defined as the date closest to randomization where not otherwise specified. The diagnosis of aetiology of kidney disease and diabetes was as assigned based on the individual patient-level data or explicit study inclusion criteria. The specific type and collection method for urine protein were recorded. Hypertension was defined by diagnosis provided, taking antihypertensive medication or baseline blood pressure >140/90 mmHg. If only the haematocrit was provided, then the haemoglobin was estimated by dividing haematocrit by 3. Information on assignment to treatment or control arm, and specific interventions given in each arm was included, including both treatments included in a factorial design. In some studies, data on non-study medications were available, but only information on angiotensin-converting enzyme inhibitors or renin–angiotensin receptor blockers were retained in the study datasets.

Follow-up variables included in the datasets consisted of urine protein, serum creatinine and blood pressure. Among the included studies, urine protein was measured in a 24-h collection or a spot sample, as total protein or albumin, and given as a total value, a concentration, or as a protein to creatinine ratio.

Outcomes included doubling of serum creatinine, ESRD (dialysis or transplant) or death. Doubling of serum creatinine was either provided in the dataset or calculated from the follow-up creatinine. Administrative censoring data or the last follow-up dates were included.

*Data pooling.* After data cleaning, studies were combined into pooled datasets suitable for analysis. Five pooled datasets were created: baseline, follow-up visits (urine protein, serum creatinine and blood pressure) and outcomes. The baseline dataset included baseline demographic information, clinical information and laboratory values. The follow-up datasets included multiple observations per patient and included serial follow-up measurements of blood pressure, urine protein, and serum creatinine with time from randomization specified for each measurement. The outcome dataset included information on administrative censoring date, doubling of serum creatinine, ESRD, and death and dates for each event.

## Results

### *Literature search*

Based on review of abstracts, a total of 93 RCTs met the inclusion criteria (Figure 1, upper half). One study is now known to have been falsified, and was removed from further consideration [13]. Manuscripts were reviewed, and additional RCTs were included based on investigators' knowledge. At the end of the selection process, 70 RCTs met the inclusion criteria (Table 2, first column). Of the 23 205 participants, 9811 (42%) were included in trials of diabetic kidney disease, 6737 (23%) in non-diabetic kidney disease and 3257 (14%) in transplant kidney disease. Of the 70 studies, angiotensin-converting enzymes (ACE) inhibitors or angiotensin receptor blockers (ARB)

($n$ = 23) and immunosuppressives ($n$ = 27) were the most common interventions. In addition, low protein diets ($n$ = 5), other antihypertensives ($n$ = 4), varying blood pressure goals ($n$ = 2), and new investigational therapies ($n$ = 3) are also represented.

*Systematic review of prior analyses*

Figure 1 (lower left) describes the additional steps required for the systematic review. Of 70 eligible RCTs, 12 contained analyses of proteinuria as a predictor of CKD progression in the original manuscript. In a second MEDLINE search for relevant analyses that were published separately, we identified 1510 abstracts, of which 25 manuscripts were retrieved for further review. From these, five additional RCTs were included in which an analysis of proteinuria was reported in the ancillary paper but not in the original manuscript (Table 3).

*Baseline*. A total of 13 individual RCTs [3–5,8,14–25] examined the association of baseline proteinuria to kidney disease outcomes, with proteinuria quantified as total urine protein, log-transformed urine protein, protein to creatinine ratio, and albumin to creatinine ratio. Analyses were heterogeneous and included both linear regression of GFR slope and time-dependent outcomes. Twelve of the 13 analyses found a statistically significant relationship between baseline proteinuria and outcome [3–5,8,14–16,18–25]. The exception was one study testing enalapril in 44 patients with IgA nephropathy [17].

*Intermediate change.* Ten studies examined intermediate change in proteinuria [3–5,8,16–18,20,21,24,26–28]. Here too, the measures of proteinuria varied (i.e. 24-h urine protein and albumin to creatinine ratio) as did time intervals (e.g. absolute change over 4 months, quartile decrease in proteinuria over 6 months, or percent decrease). Analyses included both linear regression of GFR slope and time-dependent outcomes. All published analyses of intermediate change in proteinuria found that greater reduction in proteinuria was associated with a favourable effect on the outcome measure.

*Residual.* Two studies examined residual proteinuria [3,18,20,21]. One study examined 24-h total urine protein at 3 months [20,21], while the other examined spot albumin to creatinine ratio at 6 months. Both analyses found that greater reduction in proteinuria was associated with a favourable effect on the outcome measure.

*Prentice–Freedman.* Five studies employed the Prentice–Freedman type of analysis [3,8,16,18,20,21,28,29], examining treatment effect with and without adjustment for proteinuria. Time intervals varied in that two studies adjusted for baseline proteinuria [8,29], while one study each adjusted for 6-month change [8,28], time-dependent change [18], and 6-month residual proteinuria [3]. Of these five studies, four found that the main treatment effect lost statistical significance when adjusted for its measure of proteinuria [3,8,16,18,20,21,28]. The exception was a study testing eprodisate in 183 patients with AA amyloidosis with a median baseline proteinuria of 3.1 g/day and a composite time-dependent outcome followed up for 24 months, where the treatment effect was maintained after adjustment for baseline urine protein [29].

*Creation of a patient-level pooled database*

Figure 1 (lower right) describes additional steps for creation of the patient-level pooled database.

*Process of data transfer.* The majority of authors were willing to collaborate, although in some instances, the process of obtaining agreement required several iterations. Altogether, the time from initial contact to agreement to participate ranged from immediately to 6 months, and multiple contacts were often needed with some ranging up to 16.

Data transfer required even more intense follow-up with time from agreement to data transfer ranged from 9 to 108 weeks, and number of contacts ranged from 3 to 31, with a mean of 11. Of the 70 studies contacted, we did not receive a reply from seven authors [28,30–35], 13 studies were disqualified after initial discussion with the authors [25,36–47], the data was never received for 7 studies despite initial agreement [27,29,42,48–51] and 9 studies were disqualified after data were received for insufficient data [14,52–59], leaving 34 studies included in the dataset (Table 2, second, third and fourth columns) [15,17,19,22,26,42,43,60–84]. Overall, more than 3 years have passed since the first author contact to the transfer of the last dataset. The final dataset included studies published from 1989 to 2007, multi-centre ($n$ = 27) and single centre ($n$ = 7), with a range of participants from 11 to 1715, per each study (Table 4).

*Database description.* Table 5 shows the variables that were provided according to number of participants and number of studies. Most studies did not provide all the requested variables.

Three studies were multifactorial in design with all three studies including a blood pressure arm as well as a second intervention (drug class of diet) [62,77,84]. A total of 16 studies used placebo in the control arms [22,26,42,60,61,63,64,66–68,75,76,79,81,83], whereas 18 studies used a different intervention [15,17,19,43,62,65,69–74,77,78,80,82,84] (Table 4).

Urine protein was measured using 24-h measurement of total urine protein in 30 studies [15,17,19,22,26,42,43,61, 64–79,81–84], and 24-h measurement of total urine albumin was used in two studies [62,80] (Table 4). One study [60] assayed both urine protein and urine albumin in a 24-h urine collection, while another used spot urine albumin as the primary measurement, but a subset of participants collected a 24-h urine collection, and total protein was measured [63].

For most studies, hypertension status was defined as provided in the dataset, except in one study [71] where hypertensive status was defined as systolic blood pressure $\geq$140 or diastolic blood pressure $\geq$90 mmHg. In 11 studies, baseline sitting measurements of blood pressure were used [19,22,26,61,77–83]. BMI was calculated in all studies except for two that had already provided the calculated value. Haemoglobin was estimated by dividing haematocrit by 3 in 10 studies [19,22,26,77–83].

Some of the original study datasets were organized into one observation per visit with multiple observations per patient [4,5,19,22,24,42,60–65,69,75,78–82,85], while other

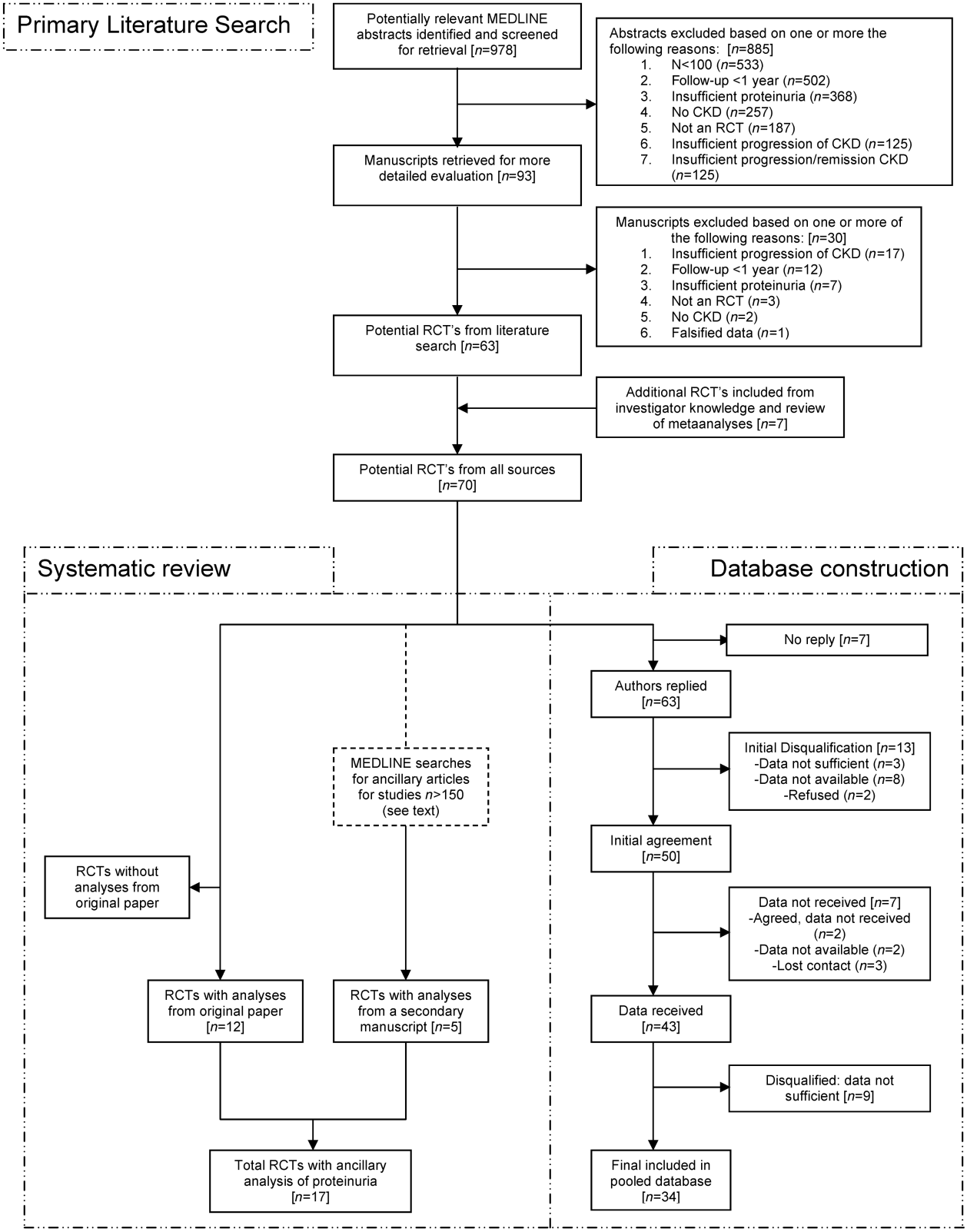


**Fig. 1.** Steps involved in the primary literature search, systemic review and database construction.

**Table 2.** Number of patients and studies by disease for systematic review and creation of patient-level pooled database

| Disease | Requested Subjects (studies) | Initial agreement Subjects (studies) | Data received Subjects (studies) | Final Subjects (studies) |
|---|---|---|---|---|
| **Diabetic kidney disease** | | | | |
| Type 1 | 409 (1) | 409 (1) | 409 (1) | 409 (1) |
| Type 2 | 9402 (6) | 9300 (5) | 8610 (4) | 3620 (3) |
| Subtotal | 9811 (7) | 9709 (6) | 9019 (5) | 4029 (4) |
| **Non-diabetic kidney disease** | | | | |
| IgA | 807 (12) | 593 (9) | 593 (9) | 387 (6) |
| Lupus | 481 (7) | 315 (4) | 315 (4) | 228 (3) |
| Membranous | 581 (9) | 514 (8) | 391 (6) | 334 (6) |
| FSGS | 106 (2) | 49 (1) | 49 (1) | 11 (1) |
| MPGN | 59 (1) | 0 | 0 | 0 |
| Hypertension | 1094 (1) | 1094 (1) | 1094 (1) | 1094 (1) |
| Amyloid | 183 (1) | 183 (1) | 0 | 0 |
| ADPKD | 89 (1) | 89 (1) | 89 (1) | 0 |
| Various | 6737 (23) | 3678 (16) | 3492 (15) | 3030 (13) |
| Subtotal | 10 137 (57) | 6518 (41) | 6023 (37) | 5084 (30) |
| **Transplant** | | | | |
| Transplant | 3257 (6) | 814 (3) | 581 (1) | 0 |
| Subtotal | 3257 (6) | 814 (3) | 581 (1) | 0 |
| **Total** | 23 205 (70) | 17 038 (50) | 15 623 (43) | 9113 (34) |

The number of authors initially approached is indicated in the 'Requested' column. Authors who responded that were interested in participating in the collaboration are indicated in the 'Initial agreement' column. We only received data on a subset of these studies, indicated in the 'Data received' column, and all of the data received was not eligible for inclusion; thus, the final dataset is indicated in the 'Final' column. In all columns, 'Subjects' refers to the number of participants, and 'studies' refers to the number of studies.

study datasets were organized into one observation per visit, with multiple observations per patient [15,17,26,43,66–68,70–74,76]. The later form datasets were converted into one observation per visit.

Determination of the last follow-up time differed among studies. Of the 34 studies included, the study end date was determined using an administrative censoring date ($n = 4$) [60,63,77,84], the last follow-up date or end date ($n = 9$) [43,64,65,67–69,72–74], or the last available serum creatinine value or outcome in comparison with randomization date ($n = 3$) [17,26,42,62,66,75]. Four studies [15,61,70,76] did not have either an administrative censoring date or the last follow-up date.

## Discussion

In principle, the rationale for the use of surrogate end points is that they may facilitate the conduct of clinical trials and identification of novel therapies. Surrogates can often be measured earlier, more easily or frequently and with higher precision, are less subject to competing risks, and are less affected by other treatment modalities, all of which allow for reduced sample size requirements, less expensive trials and faster decision making. Surrogate end points can be used in a moderately low-risk manner in earlier phases of development of new interventions, as exploratory subgroup analyses, extension of established findings to related patient populations with less severe disease, or with greater risk in extension of established findings to related interventions and in the establishment of the benefit of new interventions. Many in the nephrology community have suggested proteinuria as changes in proteinuria occur earlier than changes in GFR [10]. However, while proteinuria is indeed easy to measure, complete 24-h urine collections are difficult to obtain, and levels may be biased by exercise and treatments. The goal of the CKD-EPI Collaboration is to determine if early reduction in proteinuria can be used as a surrogate marker for hard clinical end points, and as we previously suggested, the creation of a joint dataset of multiple RCT databases is the ideal statistical approach of evaluating change in proteinuria as surrogate [11]. In this publication, we summarize the literature search, evaluate the current literature on the topic, and describe the process by which this joint dataset was created. Analyses underway will describe the results of our evaluation to empirically test proteinuria as a surrogate marker.

### *Literature search*

The treatment of kidney disease is a fundamental problem in nephrology, yet our review of the literature identified only a relatively small number of RCTs designed to rigorously test therapies for kidney disease progression. The majority of studies were of small sample size, and despite the chronic nature of the disease, most studies had less than 1-year follow-up. We were able to identify studies of a variety of CKD aetiologies and therapies; however, some areas are less well represented, and the majority of treatments involve blockade of the renin–angiotensin system. In part, the limitation reflects the lack of studies in the field, but it also reflects the limitations of variables collected among the available studies. For instance, we were able to find studies of transplant patients, but none measured proteinuria or had data available that could be shared with the collaboration. It is likely that in part, the lack of available studies has been due to little enthusiasm by industry for investigations into novel therapeutics for kidney disease because of the need for long and expensive trials.

**Table 3.** Systematic review of previous analyses relating proteinuria to kidney disease progression

| Author, year, reference (study name) | Number | Population | Treatment | Protein modality | Control | Observation | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | Baseline | Intermediate change | Residual | Prentice/ Freedman analysis |
| Dember 2007 [29] | 183 | Non-diabetic (glomerular disease) | Eprodisate | 24-h P | Placebo | | | | ○ |
| Hou 2006 [26] | 422 | Non-diabetic (various) | Benazapril | 24-h P | Placebo | | ● | | |
| Hogg 2006 [14] | 96 | Non-diabetic (glomerular disease) | Fish oil/ prednisone | Spot A | Placebo | ● | | | |
| Ruggenenti 2005 [15] (REIN-2) | 338 | Non-diabetic (various) | Intensive BP | 24-h P | Conventional BP | ● | | | |
| Lea 2005 [5] (AASK) | 1094 | Non-diabetic (hypertensive) | Ramipril or metoprolol/ intensive BP[a] | 24-h P | Amlodipine/ conventional BP | ● | ● | | |
| Bolton 2004 [27] | 690 | Diabetic | Pimagedine | | Placebo | | ● | | |
| Atkins 2005 [16] | 1715 | Diabetic | Irbesartan or amlodipine | 24-h P | Placebo | ● | ● | | ● |
| Hunsicker 2004 [8] (IDNT) | | | | | | | | | |
| Praga 2003 [17] | 44 | Non-diabetic (glomerular disease) | Enalapril | 24-h P | Conventional BP except ACEI | ○ | ● | | |
| De Zeeuw 2004 [3] | 1513 | Diabetic | Losartan | Spot A | Placebo | ● | ● | ● | ● |
| Shahinfar 2002 [18] (RENAAL) | 1513 | | | | | | | | |
| Pozzi 1999 [28] | 86 | Non-diabetic (glomerular disease) | Methylprednisolone | 24-h P | Supportive therapy | | ● | | ● |
| van Essen 1997 [19] | 103 | Non-diabetic (various) | Enalapril/atenolol | 24-h P | β-blocker | ● | | | |
| Ruggenenti 2003 [20] | 273 | Non-diabetic (various) | Ramipril | 24-h P | Placebo; conventional BP | ● | ● | ● | ● |
| GISEN 1997 [21] (REIN) | 166 | | | | | | | | |
| Ihle 1996 [22] | 70 | Non-diabetic (various) | Enalapril | 24-h P | Placebo | ● | | | |
| Breyer 1996 [23] (CSG) | 409 | Diabetic | Captopril | 24-h P | Placebo | ● | | | |
| Hunsicker 1997 [4] | 585 | Non-diabetic | Low protein diet/ | 24-h P | Usual protein diet/ | ● | ● | | |
| Peterson 1995 [24] (MDRD Study A) | 255 | (various) | intensive BP[a] | | conventional BP | ● | ● | | |
| Hunsicker 1997 [4] | 585 | Non-diabetic | Very low protein diet/ | 24-h P | Low protein diet/ | ● | ● | | |
| Peterson, 1995 [24] (MDRD Study B) | 255 | (various) | intensive BP[a] | | conventional BP | ● | ● | | |
| D'Amico 1994 [25] | 128 | Non-diabetic (various) | Low protein diet | 24-h P | Controlled protein diet | ● | | | |

Filled circles, significant; unfilled circles, not significant; 24-h P, 24-h measurement of total urinary protein excretion over 24 h; 24-h A, urinary albumin excretion over 24 h; spot P, urine albumin to creatinine ratio from a single urine specimen.
[a]Factorial study design.

*Systematic review of prior analyses*

In our systematic review of the published literature, the majority of analyses found that increasing proteinuria at any time point is associated with kidney disease progression, although we recognize the possibility of publication bias. Despite the apparent homogeneity of the results, these individual associations are not sufficient to determine proteinuria as a surrogate marker. First, these analyses were absent in a majority of studies. Second, as mentioned above, the vast majority of analyses are of patients with diabetic or hypertensive kidney disease, in trials of renin–angiotensin system blockade. Third, there was much heterogeneity in analytic approaches used, with variable definitions for predictor and outcome variables, making it difficult to compare results from individual studies. Until there is consensus on the definition of an early change in proteinuria, it will not be possible to combine the results of clinical trials. Finally, the few studies where proteinuria did not predict CKD progression or fulfil the Prentice–Freedman approach serve as an important reminder that proteinuria as a surrogate marker candidate may depend on its context or pathophysiology [10]. For instance, in amyloidosis, proteinuria may be due to overflow of light chains and not correlated with the degree of glomerular kidney damage [29]. It is thus evident that the pooled dataset will improve generalizability and may assist in explaining the heterogeneity of the current knowledge

**Table 4.** Characteristics of studies included in the pooled dataset

| Disease | Study/author/ reference | Year | Site | Number | Intervention in treatment arm | Intervention in control arm | Protein modality | Baseline protein (mean) |
|---|---|---|---|---|---|---|---|---|
| Type 1 DM | CSG [61] | 1993 | MC | 409 | ACEI | Placebo | 24-h P | 2.8 |
| Type 2 DM | IDNT [60] | 2001 | MC | 1715 | ARB | CCB, placebo | 24-h P, 24-h A | 2.9 |
| | RENAAL [63] | 2001 | MC | 1513 | ARB | Placebo | Spot A | 1.25 g/g |
| | ABCD[a] [62] | 2000 | MC | 392 | Intensive BP | Moderate BP | 24-h A | 171 μg/min |
| IgA | Donadio [64] | 1999 | MC | 97 | Fish oil | Placebo | 24-h P | 2.9 |
| | Donadio [65] | 2001 | MC | 73 | High-dose fish oil | Low-dose fish oil | 24-h P | 1.7 |
| | Praga [17] | 2003 | SC | 44 | ACEI | Standard medical therapy | 24-h P | 1.9 |
| | Maes [66] | 1999 | SC | 34 | ACEI; MMF | Placebo | 24-h P | 1.7 |
| | Appel [67] | 2003 | SC | 30 | MMF | Placebo | 24-h P | 2.7 |
| | HKVIN [68] | 2006 | MC | 109 | ARB | Placebo | 24-h P | 2.1 |
| Lupus | Lupus CSG [69] | 1992 | MC | 83 | Prednisone CYC | Prednisone CYC + plasmapheresis | 24-h P | 5.5 |
| | Chan [70] | 2005 | MC | 62 | MMF prednisolone | CTX-AZA prednisolone | 24-h P | 5.3 |
| | Euro lupus [71] | 2002 | MC | 83 | High-dose CYC | Low-dose CYC | 24-h P | 3 |
| Membranous | Ponticelli AJKD [72] | 2006 | MC | 31 | Steroids chlorambucil or CYC | Steroids | 24-h P | 6.1 |
| | Ponticelli JASN [43] | 1997 | MC | 91 | Steroids + Chlorambucil | Steroids + cyclophosphamide | 24-h P | 7.4 |
| | Ponticelli NEJM [74] | 1992 | MC | 76 | Steroids + chlorambucil | Steroids alone | 24-h P | 7.3 |
| | Ponticelli NEJM [73] | 1989 | MC | 77 | Steroids + chlorambucil | Supportive therapy | 24-h P | 5.8 |
| | Cattran[b] [42] | 2001 | MC | 11 | Cyclosporine | Placebo | 24-h P | 9.3 |
| | Spain, Praga [76] | 2007 | SC | 48 | Tacrolimus | Placebo | 24-h P | 7.8 |
| FSGS | Cattran[c] [75] | 1999 | MC | 11 | Cyclosporine | Placebo | 24-h P | 7.8 |
| Hypertension | AASK [77] | 2002 | MC | 1094 | ACEI intensive BP | CCB BB conventional BP | 24-h P | 0.5 |
| Various | Hannedouche [78] | 1994 | MC | 99 | ACEI | BB | 24-h P | 2.2 |
| | Ihle [22] | 1996 | SC | 70 | ACEI | Placebo | 24-h P | 2.2 |
| | Brenner [79] | 1993 | MC | 112 | ACEI | Placebo | 24-h P | 2.3 |
| | Toto [79] | 1993 | MC | 124 | ACEI | Placebo | 24-h P | 0.7 |
| | Kamper [80] | 1992 | SC | 69 | ACEI | Standard medical therapy | 24-h A | 0.02 |
| | Maschio [81] | 1996 | MC | 583 | ACEI | Placebo | 24-h P | 1.8 |
| | Zuchelli [82] | 1992 | MC | 121 | ACEI | CCB | 24-h P | 1.6 |
| | Hou [26] | 2006 | SC | 224 | ACEI | Placebo | 24-h P | 1.6 |
| | REIN [83] | 1999 | MC | 351 | ACEI | Placebo | 24-h P | 3.6 |
| | REIN 2 [15] | 2005 | MC | 333 | ACEI (conventional) | ACEI + CCB (intensive) | 24-h P | 2.9 |
| | van Essen [19] | 1997 | MC | 103 | ACEI | BB | 24-h P | 3.3 |
| | MDRD-A [84] | 1997 | MC | 585 | Intensive BP, low protein | Conventional BP, usual protein | 24-h P | 0.9 |
| | MDRD-B [84] | 1997 | MC | 255 | Intensive BP, very low protein | Conventional BP, low protein | 24-h P | 1.4 |

Units for urine protein are g/24 h.
[a]This is a subset of the 470 study participants with microalbuminuria.
[b]This is a subset of the 51 study participants.
[c]This is a subset of the 54 study participants.
MC, multiple centre; SC, single centre; CCB, calcium channel blocker; CTX-AZA, cyclophosphamide–azathioprine; BB, beta-blocker; 24-h P, 24-h measurement of total urinary protein excretion over 24 h; 24-h A, urinary albumin excretion over 24 h; Spot A, urine albumin to creatinine ratio from a single urine specimen.

**Table 5.** Available data for inclusion in the pooled dataset

| Variable | Studies | Patients |
|---|---|---|
| Study population | 34 | 9113 |
| **Baseline variables** | | |
| **Age** | 34 | 9051 |
| **Sex** | 34 | 9111 |
| **Race** | 33 | 9087 |
| **Kidney disease diagnosis** | 34 | 9113 |
| **Duration of kidney disease** | 15 | 3329 |
| **Diabetes status** | 25 | 8525 |
| **HTN status**[a] | 32 | 8678 |
| **Systolic BP**[a] | 30 | 8742 |
| **Diastolic BP**[a] | 30 | 8742 |
| **Height** | 25 | 7609 |
| **Weight** | 29 | 8591 |
| **BMI**[a] | 25 | 7597 |
| Medications[a] | 26 | 8629 |
| **Treatment assignment**[a] | 34 | 9113 |
| **BUN** | 13 | 6604 |
| **Serum creatinine** | 34 | 9008 |
| GFR (measured)[a] | 9 | 2340 |
| Creatinine clearance (measured) | 14 | 3229 |
| **Urine protein measurements**[a] | 34 | 9112 |
| **Haemoglobin**[a] | 16 | 6346 |
| **Albumin** | 19 | 7150 |
| **Glucose** | 34 | 9112 |
| **Calcium** | 12 | 5790 |
| **Phosphate** | 12 | 6784 |
| **Potassium** | 7 | 3173 |
| PTH | 1 | 224 |
| CRP | 2 | 258 |
| **Cholesterol** | 17 | 6889 |
| **HDL** | 10 | 5271 |
| **LDL** | 11 | 4810 |
| **Triglycerides** | 16 | 6376 |
| **Follow-up** | | |
| **Systolic blood pressure** | 30 | 8467 |
| **Diastolic blood pressure** | 30 | 8472 |
| **Serum creatinine** | 34 | 8970 |
| **Urine protein** | 34 | 8577 |
| Measured GFR | 9 | 1832 |
| Measured creatinine clearance | 15 | 3842 |

Bold indicates variables included in the dataset.
[a]Variables provided by the study authors needed to be defined, calculated from existing data or selected from multiple potential choices.

by allowing for greater flexibility in defining predictors and outcomes, although we will still be limited by the measures collected in the original trials.

### *Patient-level pooled database*

In general, we were impressed that most investigators were very willing to share data and to work with us to clean the dataset, even in the absence of monetary compensation. However, each study defined variables differently and collected different information, which contributed to the time-consuming and labour-intensive nature of this work. The pooled dataset therefore does not contain complete information on all potentially relevant participant characteristics, which would assist in exploring the causes and the likely study heterogeneity we will observe, ultimately restricting our analyses of these datasets. In the future, we would advocate for patterning of academia, industry, the NIDDK, and the NKF to encourage collaborations for development of similar data structures and for data sharing after the completion of the trials. Process and rules about governance of the data would need to be established but are doable. Lack of establishment of such structures could delay recognition of surrogates.

In conclusion, the lack of available treatments for kidney disease progression is a critical problem. Validation of reduction of proteinuria as a surrogate marker will undoubtedly facilitate and accelerate the conduct of studies and the availability of treatments. However, few studies have been used to test treatments for kidney disease, and of those, rigorous analyses of the role of proteinuria are limited. We will address this question in a joint analysis of a pooled dataset in anticipation that positive results will facilitate conduct of studies to bring new therapies more rapidly to the aid of people with chronic kidney disease.

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