SPECIAL ARTICLE

Proteinuria as a Surrogate Outcome in CKD: Report of a Scientific Workshop Sponsored by the National Kidney Foundation and the US Food and Drug Administration

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Changes in proteinuria have been suggested as a surrogate outcome for kidney disease progression to facilitate the conduct of clinical trials. This report summarizes a workshop sponsored by the National Kidney Foundation and US Food and Drug Administration (FDA) with the following goals: (1) to evaluate the strengths and limitations of criteria for assessment of proteinuria as a potential surrogate end point for clinical trials in chronic kidney disease (CKD), (2) to explore the strengths and limitations of available data for proteinuria as a potential surrogate end point, and (3) to delineate what more needs to be done to evaluate proteinuria as a potential surrogate end point. We review the importance of proteinuria in CKD, including the conceptual model for CKD, measurement of proteinuria and albuminuria, and epidemiological characteristics of albuminuria in the United States. We discuss surrogate end points in clinical trials of drug therapy, including criteria for drug approval, the definition of a surrogate end point, and criteria for evaluation of surrogacy based on biological plausibility, epidemiological characteristics, and clinical trials. Next, the report summarizes data for proteinuria as a potential surrogate outcome in 3 broad clinical areas: early diabetic kidney disease, nephrotic syndrome, and diseases with mild to moderate proteinuria. We conclude with a synthesis of data and recommendations for further research. At the present time, there appears to be sufficient evidence to recommend changes in proteinuria as a surrogate for kidney disease progression in only selected circumstances. Further research is needed to define additional contexts in which changes in proteinuria can be expected to predict treatment effect. We recommend collaboration among many groups, including academia, industry, the FDA, and the National Institutes of Health, to share data from past and future studies.
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INDEX WORDS: Proteinuria; glomerular filtration rate (GFR); chronic kidney disease (CKD).

Chronic kidney disease (CKD) is now widely acknowledged as a public health problem in the United States and around the world.[1,2] Approximately 13% of the US adult population is estimated to have CKD, corresponding to approximately 26 million individuals.[3] Outcomes of CKD include complications of decreased kidney function, increased risk of cardiovascular disease, and progression to kidney failure requiring treatment by dialysis or transplantation. Earlier stages of CKD can be detected in populations at increased risk by using simple laboratory tests; however, there are few therapies to slow the progression to kidney failure. The increasing incidence and prevalence of treated kidney failure, with poor outcomes and high cost, highlight the urgent need to facilitate the development of therapies for CKD.

Nephrology lags behind other fields in medicine in the conduct of clinical trials.[4,5] One

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Box 1. Importance of Proteinuria as a Biomarker

Marker of kidney damage
Clue to the diagnosis of CKD
Risk factor for progression (causal in animal models)
Modifier for efficacy of ACE-inhibitor therapy in nondiabetic kidney disease
Hypothesized marker of vascular permeability ("generalized endothelial dysfunction")
Risk factor for CVD at low levels (less than the threshold for the definition of CKD)
Hypothesized surrogate outcome for kidney disease progression and CVD risk reduction

Abbreviations: ACE, angiotensin-converting enzyme; CKD, chronic kidney disease; CVD, cardiovascular disease.
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problem in conducting clinical trials in CKD is defining end points. The progression of CKD is often slow, and until late stages, it is often asymptomatic. Thus, end points for clinical trials may be long delayed from disease onset and the time that interventions may be effective. Surrogate end points may provide an opportunity to detect early evidence of effectiveness. Proteinuria is an accepted marker for kidney damage; is related to diagnosis, prognosis, and treatment in kidney disease; and has been suggested as a surrogate outcome for clinical trials of kidney disease progression (Box 1).[6-8]

The US Food and Drug Administration (FDA) approves drugs for use in the United States based on demonstration of efficacy on clinically meaningful end points in pivotal clinical trials. Kidney failure requiring dialysis or transplantation is an example of an accepted clinically meaningful end point in CKD. The FDA also accepts change in kidney function, assessed as doubling of serum creatinine level, as a surrogate end point for clinical trials of kidney disease progression because it is expected to predict the development of kidney failure. Except in a very limited sense, change in proteinuria has not been accepted as a surrogate end point for pivotal clinical trials for drug approval.

In May, 2008, the National Kidney Foundation (NKF) and FDA cosponsored a scientific workshop entitled "Proteinuria as a Surrogate Outcome in Chronic Kidney Disease." The objectives of the conference were to: (1) evaluate the strengths and limitations of criteria for assessment of proteinuria as a potential surrogate end point in CKD; (2) explore the strengths and limitations of available data for proteinuria as a potential surrogate end point, focusing on specific clinical circumstances and therapeutic agents; and (3) delineate what more needs to be done to evaluate proteinuria as a potential surrogate end point.

1. SCOPE OF WORKSHOP

This conference built upon a prior workshop cosponsored by the NKF and National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), "Proteinuria and Other Markers of Chronic Kidney Disease."[9] Recommendations from that workshop included standardization of measurement and terminology for proteinuria and albuminuria, periodic clinical assessment of proteinuria as a marker of kidney damage, and research on proteinuria as a surrogate end point for kidney disease progression. Since then, there has been substantial progress.

Topics for the current conference included: (1) the importance of proteinuria in CKD, (2) evaluation of surrogacy in clinical trials, and (3) evaluation of change in proteinuria as a surrogate outcome in kidney disease progression in 3 broad clinical areas: early diabetic kidney disease, nephrotic syndrome, and diseases with mild to moderate proteinuria. The conference agenda and slide presentations are posted on the NKF website[10]; attendees are listed in the online supplementary material (Item S1; available with this article at www.ajkd.org). This report briefly reviews the conference proceedings and discusses some of the research recommendations that resulted from the conference. The synthesis was prepared by the planning committee, with input from representatives from the FDA and other attendees.

2. THE IMPORTANCE OF PROTEINURIA IN CKD

2.1. Conceptual Model for CKD

CKD is a heterogeneous condition, with many different causes, manifestations, comorbid conditions, and factors affecting prognosis.[11] It is defined as kidney damage or decreased glomerular filtration rate (GFR) for 3 months or more, with assessment of kidney damage from kidney biopsy or markers of damage or a history of kidney transplantation and with estimation of

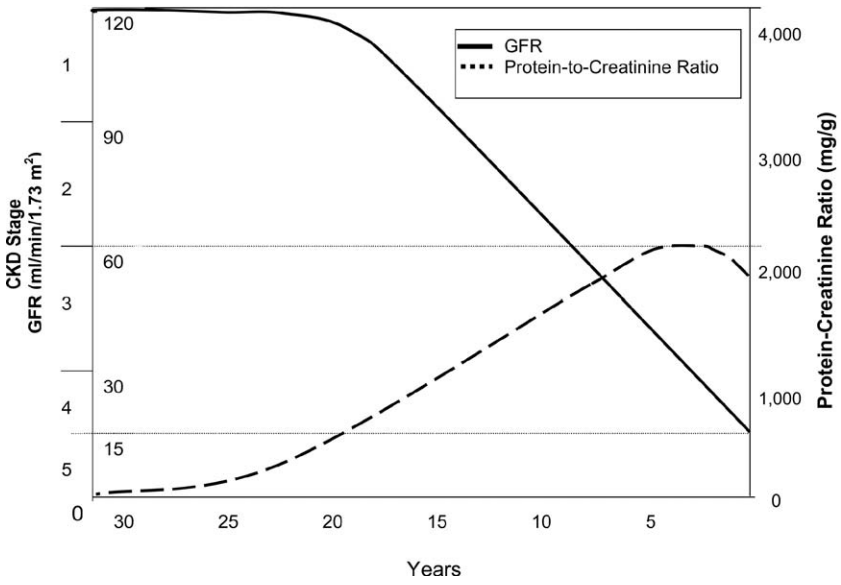

Figure 1. Hypothetical example of change in glomerular filtration rate (GFR) and proteinuria during 30-year course of kidney disease before kidney failure. Stages of chronic kidney disease (CKD) are indicated on the outer left vertical axis, and GFR is shown on the inner left vertical axis. Total protein-creatinine ratio is shown on the right vertical axis. Time in years is shown as elapsed time since the onset of kidney failure on the horizontal axis. Proteinuria appears early in the course of kidney disease and remains increased throughout. GFR remains normal for approximately 15 years, then decreases, reaching levels associated with kidney failure after 30 years. Conversion factor for GFR in mL/min/1.72 m^2 to mL/s/1.72 m^2, $\times 0.01667$. Reproduced with permission of the American Society of Nephrology from Stevens et al.[8]

GFR from equations using serum creatinine level, age, sex, and race. Stages of CKD are defined according to level of GFR, with kidney failure defined as GFR less than 15 mL/min/1.73 m^2 or treatment by dialysis or transplantation. Symptoms caused by decreased kidney function generally appear at or shortly before the stage of kidney failure. Figure 1 shows a hypothetical example of the change in GFR and proteinuria during the course of progressive kidney disease.[8] In practice, there is a wide range for protein excretion and rate of decrease in GFR in CKD.

Proteinuria is one of many markers of kidney damage. As described next, urine contains a large number of proteins, including albumin. Urine albumin, rather than total protein, is now recommended for early detection of kidney damage in adults, with albumin-creatinine ratio greater than 30 mg/g as the threshold level.[9,11] The rationale for this threshold is that it is 2 to 3 times greater than the level in young healthy adults, is indicative of kidney damage in patients with diabetes and other glomerular diseases, and is associated with risk of progression to greater levels of proteinuria and subsequent GFR decrease in diabetic and nondiabetic individuals. Levels even less than this threshold also are associated with increased risk of cardiovascular disease. Some have suggested that very low levels of albuminuria may reflect generalized endothelial dysfunction rather than kidney disease per se. This latter argument is difficult to resolve because the kidney is a highly vascular organ and appears to be affected prominently in disorders of the microvasculature.

Specific proteins other than albumin may reflect damage to renal tubules in some disease conditions.[12] In particular, low-molecular-weight proteins may originate from failure of tubular reabsorption of filtered proteins. In addition, proteins with molecular weight greater than albumin reflect greater severity of kidney damage in glomerular disease.

2.2. Measurement of Proteinuria and Albuminuria

Normal urine contains a large number of proteins. In healthy individuals, albumin makes up a small fraction of total protein, but in individuals with increased urine total protein levels, albumin

Table 1. Definitions of Total Proteinuria and Albuminuria

Total Protein*

Assay	Normal	Elevated (formerly termed clinical proteinuria)
24-h Excretion	<200 mg/d	>200 mg/d
Spot urine protein-creatinine ratio†	<200 mg/g‡	>200 mg/g‡

Albumin

Assay	Normal	Low	High (formerly termed microalbuminuria)	Very High (formerly termed macroalbuminuria)
24-h Excretion	<10 mg/d	10-29 mg/d	30-300 mg/d	>300 mg/d
Spot urine ACR† (sex-specific values§)	<10 mg/g	10-29 mg/g	30-300 mg/g (17-250 mg/g for men, 25-355 mg/g for women)	>300 mg/g (>250 mg/g for men, >355 mg/g for women)

Note: Correspondence among terms is inexact; therefore, threshold levels are not consistent. Conversion factor for albumin-creatinine ratio in mg/g to mg/mmol, ×0.113.

Abbreviations: ACR, albumin-creatinine ratio; NA, not applicable.

*Values vary according to assay.

†Average creatinine excretion exceeds 1,000 mg/d and varies according to age, sex, and race. For simplicity, assumed average value for this table is 1,000 mg/d.

‡Threshold values for children are 500 mg/g in children 6 to 24 months of age and 200 mg/g in children 2 years or older.

§Sex-specific cutoff values are from a single study.[13] Use of the same cutoff value for men and women leads to greater values of prevalence for women than men.

Source: National Kidney Foundation.[11]

is predominant. Traditional methods for measurement of proteinuria detect all proteins, but are not sensitive enough to detect quantities of albumin just greater than the normal range. Specific assays for albumin are now available that are more sensitive, and levels of urine albumin detected by using these assays, but not assays for urine total protein, have been termed "microalbuminuria." However, this term is a misnomer because urine albumin detected by using these tests is not "small." Microalbuminuria originally was studied in diabetes, but has now been studied in patients with other conditions, such as hypertension, and in general population studies. Table 1 lists threshold levels for definitions of clinically relevant abnormalities in urine total protein and albumin according to methods for urine collection.[11,13]

Methods for measurement of urine total protein are inexpensive and widely used in clinical medicine, but are limited by the absence of a gold-standard reference method and large variability among methods. Currently available methods for urine albumin measurement are less variable than methods for urine total protein measurement, but are not standardized across clinical laboratories. The National Kidney Disease Education Program of the NIDDK and the International Federation of Clinical Chemistry and Laboratory Medicine have undertaken a standardization program for urine albumin measurement and issued the following recommendations[14]: urine albumin-creatinine ratio should be reported as either "mg/mmol" or "mg/g," albumin concentration (miligrams per liter) is difficult to interpret and should not be reported alone, first morning urine sample has lower biological variability than a random collection, albumin should be measured in fresh (nonfrozen) urine, and the term "urine albumin" should replace "microalbumin." The implications for clinical trials are to use a central laboratory and, for most kidney diseases, measure urine albumin rather than urine total protein unless there is a specific rationale for measuring nonalbumin proteins.

Possible alternatives for terms to define categories of albumin-creatinine ratio and corresponding quantities would be as follows: normal, less than 10 mg/g; low, 10 to 29 mg/g; high, 30 to 300 mg/g; and very high, greater than 300 mg/g

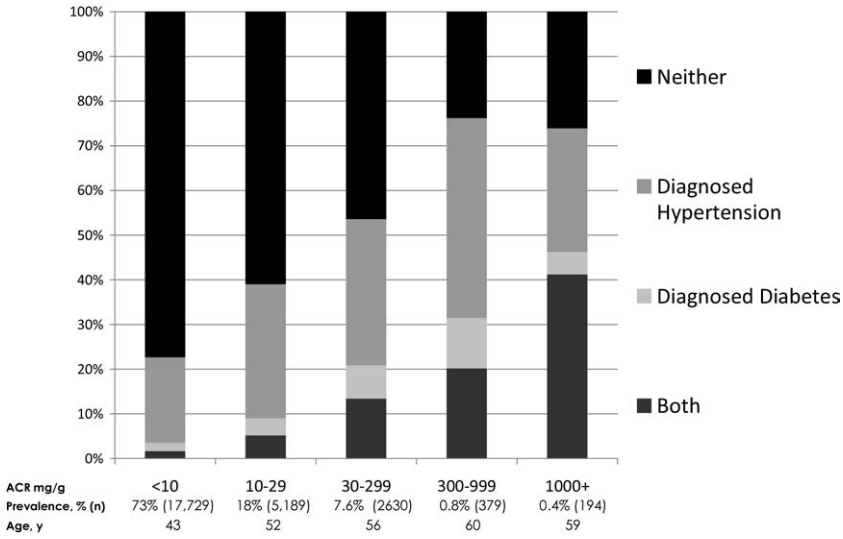

Figure 2. Distribution of albumin-creatinine ratios (ACRs) in the United States. Number and percentage of participants according to ACR in the National Health and Nutrition Examination Survey 1988-2004. Within each category, the prevalence of diagnosed diabetes and hypertension, both and neither, are shown. Figure courtesy of Josef Coresh.

(Table 1). It would be reasonable to create an additional category above the very high range for the equivalent of nephrotic syndrome. Differing threshold values by age, sex, and race based on known variation in urinary creatinine excretion rates have been investigated; however, consensus on utility has not been reached.[15,16]

2.3. Epidemiological Data for Albuminuria in the United States

Variations in methods for measurement and lack of standardized definitions for levels of urine total protein have hampered epidemiological studies. Data from the US National Health and Nutrition Examination Surveys show an increase in prevalence of high levels of albuminuria (defined as spot albumin-creatinine ratio $>$ 30 mg/g) from 7.1% to 8.2% during the survey periods 1988 to 1994 and 1999 to 2004.[3] The increase was attributed to the older age of the population, greater proportion of minority groups, and greater prevalence of hypertension and diabetes and greater body mass index. Figure 2 shows associations of high levels of albuminuria with older age and greater prevalence of diagnosed hypertension, diabetes, or both. A wealth of epidemiological data shows that greater levels of albuminuria, even less than the threshold of 30 mg/g, are associated with lower estimated GFR, subclinical cardiovascular disease, and increased risk of subsequent kidney failure and cardiovascular and all-cause mortality, even after adjustment for confounding factors.[11,17-19] Some have even proposed that a decrease in albuminuria might be a surrogate marker for cardiovascular disease events, as well as for kidney disease progression.

3. EVALUATION OF CANDIDATE SURROGATE END POINTS FOR CLINICAL TRIALS

The growth of biotechnology has created novel methods to measure and monitor disease, including the use of biomarkers that can serve as surrogate end points for pivotal clinical trials. However, important lessons have been learned from other fields in which initial beliefs about the efficacy of drug treatment on the basis of trials that used surrogate outcomes subsequently were reversed with additional evidence based on clinical end points.[20,21] Thus, it is critical that any new potential surrogate be rigorously tested before it is accepted.

In this section, we review criteria for drug approval by the FDA, definitions of types of outcomes for clinical trials, criteria for surrogacy, and applications of these concepts to clinical trials of kidney disease progression.

3.1. Criteria for Drug Approval

Approval of a drug by the FDA requires demonstration of "substantial evidence" of effectiveness consisting of "adequate and well-controlled investigations." Phases of drug development are listed in Box 2.[22,23] To establish a drug's efficacy, a development program must establish that

Box 2. Phases of Drug Development

Preclinical Studies

Preclinical studies include evaluation of the drug's toxic and pharmacological effects through in vitro and in vivo laboratory animal testing. Genotoxicity screening is performed, as well as investigations on drug absorption and metabolism, the toxicity of the drug's metabolites, and the speed with which the drug and its metabolites are excreted from the body.

Clinical Studies

The clinical investigation of a previously untested drug generally is divided into 3 phases. Although in general, the phases are conducted sequentially, they may overlap.

Phase 1 includes the initial introduction of an investigational new drug into humans. These studies usually are conducted in healthy volunteer participants. These studies are designed to determine the metabolic and pharmacological actions of the drug in humans, the side effects associated with increasing doses, and, if possible, to gain early evidence on effectiveness. Phase 1 studies also evaluate drug metabolism, structure-activity relationships, and the mechanism of action in humans.

Phase 2 includes the early controlled clinical studies conducted to obtain some preliminary data on the effectiveness of the drug for a particular indication or indications in patients with the disease or condition. This phase of testing also helps determine the common short-term side effects and risks associated with the drug.

Phase 3 studies are intended to gather the additional information about effectiveness and safety that is needed to evaluate the overall benefit-risk relationship of the drug. Phase 3 studies also provide an adequate basis for extrapolating the results to the general population and transmitting that information in the physician labeling.

Source: Food and Drug Administration.[22,23]

a drug has an effect on a clinically meaningful end point.[24,25] Alternatively, a surrogate end point that reliably predicts a clinically meaningful benefit can be used. Thus, although a number of biomarkers commonly are used in the early phases of drug development, clinically meaningful end points or reliable surrogates must be used for phase 3 clinical trials.

Established surrogates are widely used in phase 3 clinical trials in lieu of direct measures of clinical benefit. In certain settings, other biomarkers also can be used as end points in phase 3 clinical trials even if there is uncertainty about the relation of the outcome to clinical benefit. Passed in the late 1990s, the FDA Modernization Act (Subpart H) gave the FDA authority to approve drugs for serious or life-threatening disease with no good available therapy on the basis of an effect of a drug on an end point that is "reasonably likely" to predict clinical benefit.[26] Approval under this expanded authority requires a phase 4 commitment to verify that the effect on the surrogate translates into improved clinical outcomes. An important premise of subpart H is that approval can be granted for accelerated entry of a drug to the market, but a confirmatory trial then is required, showing an effect on the clinical end point. Subpart H has been used infrequently in drug development, partly because of the inherent difficulties of completing a phase 4 commitment after a drug has entered the market. Although Subpart H may be a viable option for some development programs, such an approval pathway may not be feasible for long-term therapies for which the anticipated clinical benefits may not manifest for many years.

3.2. Definitions of Types of Outcomes

Figure 3 shows the overlapping relationships for various potential outcome measures for clinical trials. In practice, a "clinically meaningful" end point refers to a direct measure of how a patient feels, functions, or survives. Mortality and measures of morbidity, functional status, and quality of life are accepted end points for phase 3 clinical trials.

A surrogate end point is a laboratory measurement or physical sign that is used in therapeutic trials as a substitute for a clinically meaningful end point and is expected to predict the effect of

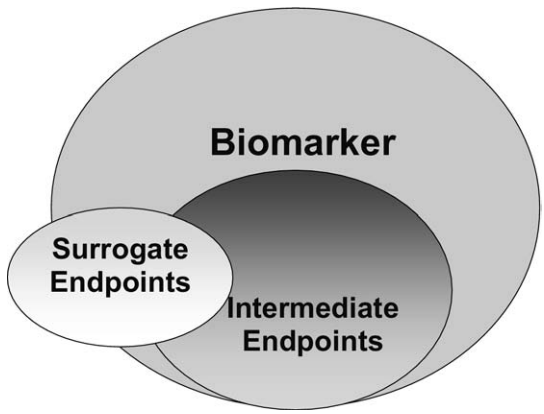

Figure 3. Definitions and relationships. For explanations, see text. Figure courtesy of Tom Greene.

Box 3. Rationale for Using Surrogate Outcomes as End Points in Phase 3 Clinical Trials

Earlier measurement
Easier or more frequent measurement
Greater measurement precision
Less subject to competing risks
Less affected by other treatment modalities
Reduced sample size requirements
Faster decision making

Reprinted with permission of the American Society of Nephrology from Stevens et al.[8]

the therapy.[21] Box 3 lists rationales for the use of surrogate end points in phase 3 clinical trials. Examples of accepted surrogate end points in other fields include blood pressure and low-density lipoprotein cholesterol level for cardiovascular diseases. In CKD, surrogate end points may be useful to establish the efficacy of a drug for treating early stages of CKD, in which it is otherwise difficult to show a benefit. Because surrogate end points can reduce the duration, size, and cost of clinical trials, they also can facilitate the development of drugs intended to treat later stages of CKD.

A biomarker is a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacological responses to a therapeutic intervention.[27] By definition, proteinuria and decreased GFR are biomarkers for CKD and potentially could be surrogate end points for kidney failure because in general, they precede the development of kidney failure.

An intermediate end point is a biomarker that is intermediate in the causal pathway between an intervention and a clinical end point. Decreased GFR also is an intermediate end point because it is on the causal pathway to kidney failure. Doubling of serum creatinine level is accepted as a surrogate end point because it reflects a large decrease in GFR and predicts the development of kidney failure. As shown in Fig 1, the increase in proteinuria potentially could be a surrogate outcome for a large decrease in GFR in clinical trials.

3.3. Criteria for Surrogacy

Although there is no formally defined "evidentiary standard," the surrogate must be able to predict reliably the effect of a treatment on an outcome of interest; this generally means the demonstration that the clinical outcomes track the marker regardless of how the marker is affected by the various interventions. There are 3 general lines of evidence that support the acceptance of a surrogate end point (Box 4).[28] These include biological plausibility, epidemiological data (observational studies and clinical data), and evidence from clinical trials (intervention studies). The evidence supporting claims for changes in proteinuria as a surrogate end point for kidney disease progression is described next.

Box 4. Criteria for Surrogacy

Biological plausibility: sometimes intuitive, sometimes supported by animal data or by favorable responses in extreme cases
Epidemiological data: increases (or decreases) in the putative surrogate are correlated with unfavorable (or favorable) clinical outcomes
Clinical trials: changes in the putative surrogate resulting from at least 1 type of intervention, and preferably many types, working by different mechanisms, affect clinical outcomes in a predictable manner that is fully accounted for by the effect on the surrogate

Source: Desai et al.[28]

3.3.1. Biological Plausibility

Biological plausibility refers to the biological basis that a putative surrogate will predict the effect of an intervention on an outcome of interest. Such evidence usually derives from in vitro or animal studies, but sometimes may arise from favorable clinical responses in extreme circumstances. Biological plausibility is greatest when the marker is a necessary intermediate on the causal pathway of disease. For proteinuria as a potential surrogate for CKD progression, biological plausibility is based on the hypothesized effects of drugs on established mechanisms of kidney damage that cause proteinuria and lead to kidney failure, but it is not usually believed to be on the causal pathway.

Figure 4 shows a variety of mechanisms by which drug treatment could reduce proteinuria.[29-31] The heterogeneity among kidney diseases in the biological mechanisms for proteinuria suggest that response to drug treatment also may be diverse. Currently, there is a wealth of data relating proteinuria in experimental and clinical diabetic kidney disease and for some other glomerular diseases. These relationships are less well known for other kidney diseases,

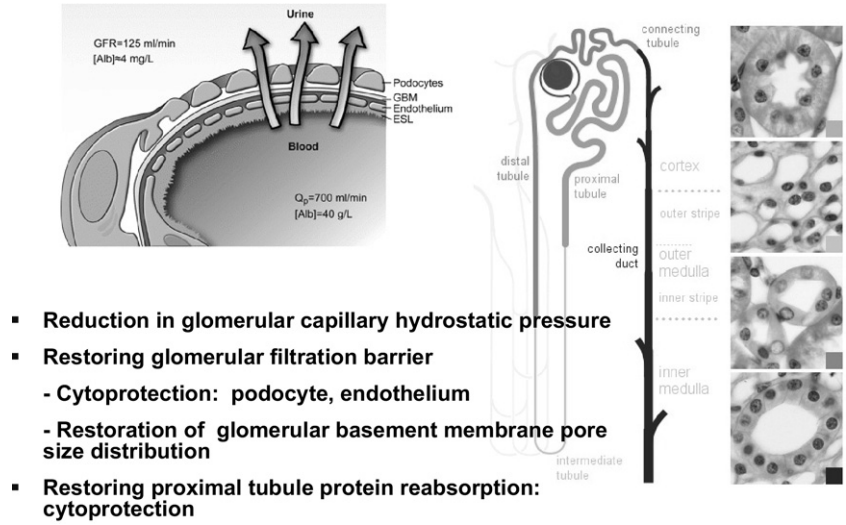

Figure 4. Possible mechanisms for proteinuria reduction. Schematic view of a glomerulus (left), nephron (center), and cross-section of nephron segments (right). Abbreviations: [Alb], albumin; ESL, endothelial cell surface layer (glycocalyx); GBM, glomerular basement membrane; GFR, glomerular filtration rate; Q_p, plasma flow.[29,30] Left panel reproduced with permission of the American Physiological Society from Haraldsson et al.[30] Right panel courtesy of Lutz Slomianka, University of Western Australia.

such as vascular, tubulointerstitial, and cystic kidney diseases, and there is little information for kidney transplant recipients. In addition, when proteinuria appears, it may cause further damage to the glomerular mesangium or tubules, thereby hastening progression of kidney disease.[32] Thus, the response to treatment may differ depending on the stage of kidney disease. Heterogeneity in response to treatment suggests that proteinuria may be an acceptable surrogate for progression in some kidney diseases and some settings, but not in others.

The time course of response of proteinuria to drugs is critically important for the design and interpretation of clinical trials. Biological plausibility is considerably strengthened if long-term reduction in proteinuria persists after withdrawal of the drug. Of interest, in some kidney diseases, the mechanisms for proposed beneficial effects of drugs on proteinuria reflect hemodynamic rather than structural mechanisms.[33,34] In principle, alterations in hemodynamic effects could ameliorate proteinuria without reducing structural damage. Although reduction in glomerular capillary hydrostatic pressure may be beneficial in kidney disease, reversing or halting progression of the underlying structural damage is an even greater clinical benefit. Evidence for a beneficial effect of a drug on structure rather than function can be inferred from persistence of the effect on proteinuria after withdrawal of the drug for several months. However, the exact duration of persistence of the effect after withdrawal of the drug is uncertain because beneficial effects on structure may also diminish over time. Furthermore, drug therapy may be intended for long-term use in practice, rather than for withdrawal after short-term use.

3.3.2. Epidemiological Data (observational studies)

Epidemiological data refer to observational studies or, in some circumstances, clinical observations of the relationship of the surrogate to the clinical outcome of interest. For proteinuria as a potential surrogate for CKD progression, epidemiological data refer to the relationship of increases or decreases in proteinuria to worsening or improving GFR, respectively. In the statistical literature, these relationships are described as "individual-level associations." A large body of evidence is now available to show that a greater initial level of proteinuria and an increase over time are independent predictors of both faster GFR decrease and development of kidney failure in patients with a wide variety of types of kidney disease.[11] These results appear strong across all segments of the population and all levels of proteinuria, including levels of albuminuria less than the threshold for the definition of CKD. In many studies, proteinuria is associated more strongly with kidney disease outcomes than all other factors tested. Although these associations provide preliminary support, clinical tri-

als are required to show that the effect of treatments on change in proteinuria predicts the effect of the same treatment on kidney disease progression.

3.3.3. Clinical Trials (intervention studies)

The strongest evidence for surrogacy comes from clinical trials, in which changes in proteinuria resulting from at least 1 type of intervention, and preferably many types, working by different mechanisms would affect clinical outcomes in a predictable manner that is fully accounted for by the effect on the surrogate.[28] There are 2 limitations to the current body of evidence. First, no large-scale clinical trial with clinically meaningful end points has specifically targeted different levels of proteinuria as the intervention; however, a number of trials have evaluated change in proteinuria as a secondary end point of other interventions, such as levels of blood pressure, classes of antihypertensive agents, glycemic control in diabetes, lipid-lowering therapy, and dietary modification. Thus, all the evidence derives from secondary analysis of interventions designed to affect a different pathway of disease. Second, because of the variability in proteinuria among patients in most studies and the slow progression of most kidney diseases, analyses relating change in proteinuria to the occurrence of clinically meaningful end points can be conducted in only large clinical trials with a long duration of follow-up. Although there are some large trials of angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs), there are few large trials of other interventions. Given these limitations, as described next, no method of analysis is likely to fulfill strict definitions of the terms "predictable" and "fully accounted for"; some interpretation will be required.

The statistical community has repeatedly cautioned that simply observing a correlation between the putative surrogate and clinical end point is not sufficient to conclude that the putative surrogate is valid.[35] Figure 5 shows possible scenarios for the relationship among treatment, change in proteinuria, and clinical end points.[8] In Fig 5A, proteinuria is on the causal pathway to kidney disease progression and the treatment causes a change in proteinuria; however, treatment also affects progression by a separate causal pathway. Depending on the size of the effect through this second pathway, the treatment effect on progression may differ markedly from its effect on proteinuria. Alternatively, in Fig 5C, treatment affects both proteinuria and progression, but these effects are unrelated. Statistical treatment of the relationships between effects of treatment on the surrogate and the clinical end point has been reviewed.[8] In addition to evaluation of the individual-level associations described previously, statisticians have focused on 2 other general approaches to validation of surrogate end points in the clinical trials reviewed here. Other statistical treatments, not reviewed here, have considered the problem of validating surrogate end points by using formal causal models that incorporate counterfactual variables to express causal effects.[36,37]

Prentice Criteria. Formal statistical criteria for validation of surrogate end points first were proposed by Prentice.[8] In practice, these criteria are evaluated by testing whether an estimate of the treatment effect on the clinical end point is reduced to zero after statistical adjustment for the surrogate. Under certain models for causal inference, fulfillment of this criterion would, with strong assumptions, show the absence of a causal pathway independent of proteinuria (Fig 5B). Unfortunately, reduction in the effect size to zero holds only rarely, even for end points that generally have been accepted as valid surrogates. Other investigators have proposed relaxing the Prentice criterion to stipulate that the proportion of the treatment effect (PTE) that remains after statistical adjustment for the surrogate should not exceed a designated threshold (for example, 0.5 to 0.75). Substantial variation in PTE across clinical trials can arise from different analytic approaches and likely reflects low precision with which the PTE can be determined within a single study. Another limitation of applying the Prentice criteria is undercorrection for measurement error in the surrogate. Most important, recent work under formal statistical frameworks for causal modeling has clarified that even exact fulfillment of the Prentice criteria fails to establish the validity of the surrogate except under the unlikely assumption that there are no confounding factors that influence both the surrogate and the clinical end point (Fig 5D). In the case of proteinuria, it is plausible that other factors influ-

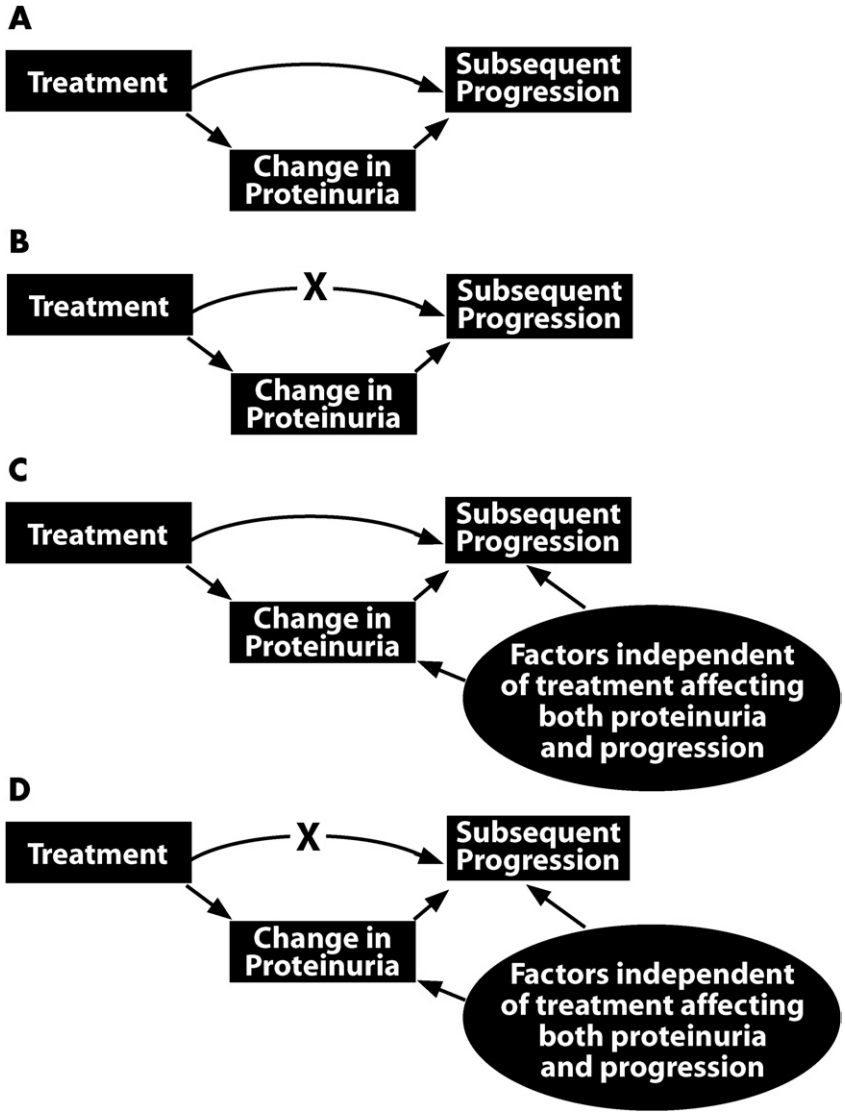

Figure 5. Possible scenarios for relationships among treatment, change in proteinuria, and clinical end points. (A) Treatment affects both change in proteinuria and clinical end points, but there are separate causal pathways. (B) Treatment effect is mediated only through reduction in proteinuria. (C) Treatment affects both proteinuria and progression, but these effects are unrelated. (D) Treatment affects both proteinuria and progression, and there are no confounding factors that influence both. Reproduced with permission of the American Society of Nephrology from Stevens et al.[8]

ence both the initial change in proteinuria and rate of progression. All these considerations discourage sole reliance on the Prentice criteria to assess proteinuria as a surrogate outcome.

Trial-Level Association. The trial-level approach directly evaluates the association between treatment effects on the surrogate and treatment effects on clinical end points. This approach requires joint analysis or meta-analysis of multiple randomized trials. A regression model is developed from previous trials to predict the treatment effect and confidence interval on the clinical end point from the treatment effect on the surrogate (Fig 6).[8,38] The most important limitation of the trial-level approach is the assumption that previous studies are representative of a new study to

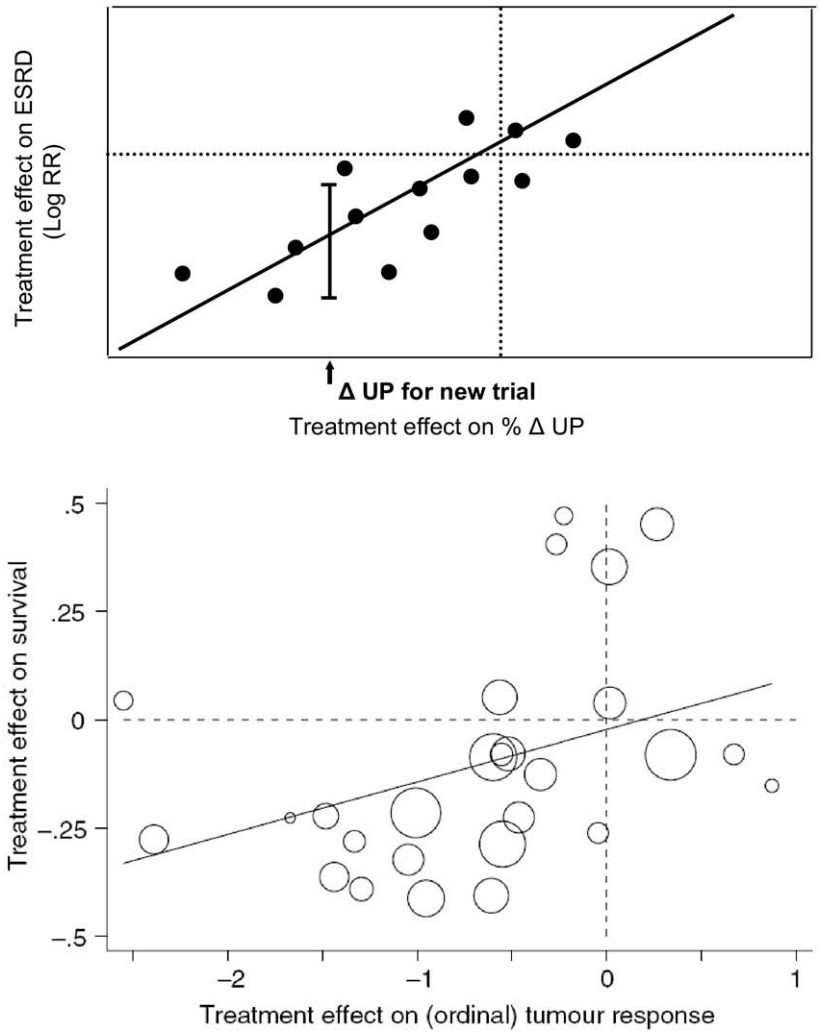

Figure 6. Trial-level analysis of the relationship between treatment effect on the clinical end point and treatment effect on the surrogate. (Top panel) Hypothetical relationship between treatment effect on end-stage renal disease (ESRD) (vertical axis) and percentage of change in urine protein (%ΔUP) (horizontal axis). (Bottom panel) Observed relationship between treatment effect on survival (vertical axis) and treatment effect on tumor response. In both panels, each plot character represents a single clinical trial. In the top panel, the arrow on the horizontal axis represents the hypothetical observed effect on ΔUP in a new trial, and the vertical line reflects the confidence interval for the predicted effect on ESRD in the new trial. In the bottom panel, the size of plot characters is proportional to the sample size of the clinical trial.[8,38] Top panel courtesy of Tom Greene. Bottom panel reproduced with permission of the Royal Statistical Society from Burzykowski et al.[39]

which the surrogate outcome is to be applied. Extrapolation to studies with features substantially different from the original validation studies will entail an additional level of uncertainty beyond that captured by error in the statistical model and must rely primarily on biological arguments. This limitation is critically important in studies of new populations or new therapeutic agents.

Another limitation of this approach is the requirement for sufficient variation across trials in the effect of the intervention on the surrogate. If treatment effect on the surrogate is relatively uniform, it will require a large number of studies to relate the magnitude of the effect on the surrogate to the effect on the hard clinical outcome. In principle, including trials of different agents or different kidney diseases could increase the variation in the treatment effect on the surrogate, but there may be reluctance to make conclusions from such comparisons.

4. APPLICATION TO SPECIFIC CLINICAL CIRCUMSTANCES AND THERAPEUTIC AGENTS

A large number of studies were reviewed by the presenters for discussion during the conference. Although the searches were not systematic, the articles reviewed permit some general observations. Table S1 (provided as online supplementary material available with this article at www.ajkd.org) shows the studies grouped according to clinical context and level of proteinuria.[40-89] Except for

early diabetic kidney disease,[40-54] the conference focused predominantly on clinical trials.

4.1. Early Diabetic Kidney Disease

4.1.1. Biological Plausibility

Early structural changes in the glomerulus in diabetic kidney disease include podocyte loss, widening of the glomerular basement membrane, and expansion of mesangial and total glomerular volume.[90-92] Of these changes, an increase in the fraction of mesangial to glomerular volume is considered the most specific marker for diabetic kidney disease, with a reasonable correlation between increased mesangial-glomerular volume ratio and microalbuminuria. However, the relationship can be variable, with some examples of structural changes in the absence of increased albumin excretion.

4.1.2. Epidemiological Characteristics

The natural history of diabetic kidney disease has been well characterized, although it may have changed since the introduction of treatment with ACE inhibitors and ARBs. The earliest clinical abnormality is microalbuminuria, usually between 5 and 15 years after the onset of type 1 or type 2 diabetes. Thereafter, worsening albuminuria, increasing blood pressure, and decreasing GFR give rise to symptomatic kidney failure by approximately 20 years (as shown in the hypothetical example in Fig 1). Observational studies show a strong and graded relationship between level of albuminuria and risk of decreasing GFR and the development of kidney failure in patients with type 1 and type 2 diabetes.[46,93-99] In type 2 diabetes, the competing risk from cardiovascular disease is greater than the risk of kidney failure and may obscure this relationship.

Data from large cohorts presented at the conference showed that 70% to 90% of participants who develop an estimated GFR less than 60 mL/min/1.73 m^2 had prior macroalbuminuria or microalbuminuria. In 1 study, this proportion has decreased in the more recent era, possibly because of treatment with ACE inhibitors and ARBs.[43] In all studies, virtually all individuals who developed kidney failure had prior macroalbuminuria. The main limitation of these studies is that few patients beginning with normal albumin excretion were followed up long enough for the development of low levels of estimated GFR. Other limitations are related to variation in laboratory methods and definitions, such as urine albumin and serum creatinine assays, definitions for microalbuminuria, imprecision and bias (underestimation of measured GFR) of GFR-estimating equations, and effects of ACE inhibitors and ARBs on GFR, independent of their effects on the underlying kidney disease.

4.1.3. Clinical Trials

A comprehensive review of clinical trials is included in the NKF's Kidney Disease Outcomes Quality Initiative (KDOQI) clinical practice guidelines on diabetes and CKD.[7] Briefly, better glycemic control reduces the risk of transitions from normal albumin excretion to microalbuminuria and from microalbuminuria to macroalbuminuria. Better blood pressure control and treatment with agents that interfere with the renin-angiotensin system (ACE inhibitors, ARBs, direct renin inhibitors, and aldosterone antagonists) reduce urinary albumin excretion or slow the progression from microalbuminuria to macroalbuminuria. When studied, withdrawal of antihypertensive agents was followed by an increase in albuminuria, but often not to pretreatment levels.

The main limitation of these studies is that the duration of follow-up was not sufficient to observe clinical end points. Thus, it is difficult to relate the reduction in albuminuria to reduction in clinical end points, as required by the Prentice criteria or evaluation of the trial-level association.

4.1.4. Conclusions

The NKF-KDOQI work group concluded there was not sufficient evidence for acceptance of changes in proteinuria as a surrogate outcome for progression of early diabetic kidney disease[7]:

> Interventions that reduce albuminuria or delay its increase may be promising as potential therapies for diabetic kidney disease. However, in the opinion of the Work Group, there currently is insufficient evidence to assume that lowering albuminuria levels will necessarily lead to improvements in clinical outcomes, such as progression to CKD stage 5, cardiovascular disease event, or death. Conversely, the failure to reduce albuminuria does not preclude a beneficial clinical effect on diabetic kidney disease from a potential intervention.

> Therefore, to be considered efficacious, potential treatments for diabetic kidney disease must demonstrate benefits not only on albuminuria reduction, but also on such clinical end points as CKD stage 5, cardiovascular disease events, or death.

Although there was general agreement during the conference with the conclusion of the NKF-KDOQI work group, there was support for extending this conclusion to acceptance of transitions from normal albumin excretion to macroalbuminuria or from macroalbuminuria to normal albumin excretion as surrogates for the development and remission of diabetic kidney disease, respectively. Justification for this opinion is based on the greater risk of decreasing GFR and the development of kidney failure in patients with macroalbuminuria than microalbuminuria and the lower risk of misclassification of response in participants with greater changes in albuminuria. This approach is consistent with the guidelines in that macroalbuminuria in the setting of either type 1 or type 2 diabetes is an acceptable criterion for the diagnosis of diabetic kidney disease unless there are features to suggest another form of disease. Persistence of the response after withdrawal of therapy also would be important to have confidence that the drug has had an effect on underlying structural damage, rather than a transient hemodynamic effect, although the optimal interval for assessing durability is not established. Unfortunately, the development of macroalbuminuria in participants with normal albumin excretion requires a long follow-up, and complete disappearance of macroalbuminuria appears to occur infrequently. Therefore, adoption of these transitions as surrogate outcomes may not have a meaningful impact on clinical trial design for drug development in early diabetic kidney disease. Possibly, considering intermediate changes on a continuous scale may have more utility. More work is needed to determine the magnitude of change that will reliably predict the effect of a treatment on outcome.

4.2. Nephrotic Syndrome

4.2.1. Biological Plausibility

Nephrotic syndrome[55-74] is an infrequent, but dramatic, constellation of signs and symptoms, defined as urine total protein excretion greater than 3.5 g/d, low serum albumin level, increased serum cholesterol level, and edema. In 1 study, the corresponding urine albumin level was greater than 2.2 g/d.[100] Urinary loss of large amounts of protein represents a major disruption of the size and charge-selective filtration barrier of a normal glomerulus and is central to the pathophysiological process of other signs and symptoms of nephrotic syndrome.[98,101,102] Patient-reported outcomes, such as discomfort from edema or fatigue or side effects of drugs used to treat the underlying disease or symptoms, are common, but generally not well quantified. Deep-vein thrombosis, infections, and acute kidney injury are life-threatening complications from persistent nephrotic syndrome. Kidney failure may develop over months to years.

Initially, corticosteroids were the mainstay of therapy for adults and children, and there is a large amount of literature documenting some impressive responses, particularly in children. With the development of percutaneous kidney biopsy, pathological and etiologic classification of glomerular diseases became increasingly sophisticated. It now is recognized that there are a large variety of kidney diseases associated with nephrotic syndrome, a wide range of responses to corticosteroids and other therapies, and a wide range of rates of decrease in kidney function according to the cause of pathological types of kidney disease.

4.2.2. Epidemiological Data

Observational studies show a strong relationship between the presence of nephrotic-range proteinuria and increased risk of future GFR decrease irrespective of the cause and pathological state of kidney disease, with the exception of minimal change disease. The risk of progression to kidney failure during 5 to 10 years is 20% to 90% in adults with primary kidney diseases. The same general pattern is observed for patients with nephrotic syndrome caused by systemic diseases. Conversely, complete remission of nephrotic syndrome (to normal urine total protein levels) is associated with a greater likelihood of stability of GFR and freedom from development of kidney failure. Partial remission (to abnormal urine total protein levels) is not strictly defined, although most studies have required a decrease in urine total protein excretion to less than 3.5 g/d. The relationship of partial remissions to risk of kidney failure is not clear, in large part be-

cause of variability in the definitions for partial remissions and GFR decrease. Both complete and partial remissions (to < 3.5 g/d) are associated with improvement in symptoms, biochemical abnormalities, and quality of life.

4.2.3. Clinical Trials

There have been a large number of clinical trials in adults and children with nephrotic syndrome caused by primary kidney diseases and systemic diseases involving the kidneys, including a wide variety of interventions and comparison groups (usually not placebo controlled). Most trials have focused on decrease in proteinuria and subsequent GFR decrease. Unfortunately, most trials have been relatively small, and there is little firm evidence of benefit for most diseases. Complete remissions are not common, and there is not a standardized definition for partial remissions. Altogether, these limitations make it difficult to apply the Prentice criteria or evaluate the trial-level association.

4.2.4. Conclusions

There was general support at the conference for remission of nephrotic syndrome as a surrogate end point based on the association of nephrotic syndrome with important symptoms and high risk of future GFR decrease. These symptoms could be considered as clinically meaningful outcomes for end points in phase 3 clinical trials. Complete remission is relatively well defined and uniformly associated with good outcomes. Partial remission is poorly defined, and standardization of the definition would clarify the relationship of partial remission to resolution of symptoms and future course of GFR decrease. Another suggestion to facilitate testing of new drugs would be to define a standard for the efficacy of corticosteroids and other therapies in inducing remission of nephrotic syndrome in patients with more common glomerular diseases, such as lupus nephritis, to define an acceptable noninferiority margin for the evaluation of new drugs.

4.3. Diseases With Mild to Moderate Proteinuria

4.3.1. Biological Plausibility

Many kidney diseases are characterized by mild to moderate proteinuria[54,74-89] (urine total protein from a lower level of 0.5 to 1.0 g/d to an upper level of 3.5 g/d [just less than nephrotic range]). Diabetic and various nondiabetic kidney diseases are considered together in this section because they share certain common features, etiologic and pathological diagnoses are often uncertain, and they often are grouped together in epidemiological studies and clinical trials. The corresponding level of albuminuria has not been precisely defined, but probably corresponds to a lower level greater than 300 mg/g and an upper level of approximately 2 g/d.

Irrespective of the cause of kidney damage, progression of kidney disease leads to uniform pathophysiological, pathological, and clinical features, suggesting a "common final pathway."[103] There are numerous theories for the progressive nature of CKD, giving rise to a number of hypothesized treatments to slow progression. In many experimental models, the course of kidney disease is reflected in the proportion of sclerotic glomeruli and magnitude of proteinuria, and in these models, drug effects on proteinuria often mirror drug effects on glomerular pathological states and survival. Some of the strongest evidence linking proteinuria to kidney disease progression derives from experiments in which proteinuria is induced by intravenous administration of high-molecular-weight proteins, leading to transglomerular passage of proteins into the urinary space, tubulointerstitial damage, glomerular sclerosis, and the development of kidney failure.[104]

4.3.2. Epidemiological Data

Reliable data about the prevalence and diagnosis of kidney diseases with this level of proteinuria are not readily available. Figure 2 shows that only approximately 1.2% of US adults have albuminuria with albumin greater than 300 mg/g (which is likely to correspond to this range of proteinuria), with a mean age of 60 years, and the vast majority have hypertension, diabetes, or both. In most series, the most common diagnoses are diabetic kidney disease and other glomerular disease, although hypertensive nephrosclerosis, tubulointerstitial and cystic diseases, and kidney disease in transplant recipients occasionally may have urinary protein levels this high. These diseases are associated with a wide range in rates of GFR decrease and risk of the development of kidney failure. As discussed, despite this heterogene-

ity, a wealth of epidemiological data relate baseline level of proteinuria and changes in proteinuria during follow-up to subsequent rate of GFR decrease and risk of the development of kidney failure.

4.3.3. Clinical Trials

A large number of clinical trials across a wide range of types of kidney disease and types of drugs have shown strong relationships between changes in proteinuria and GFR decrease during treatment.[11] However, there have been few studies relating treatment effects of drugs or other treatments on changes in proteinuria and later changes in GFR. Most of the largest clinical trials have used agents that act on the renin-angiotensin system. These studies have uniformly shown a beneficial effect of ACE inhibitors and ARBs to decrease blood pressure, decrease proteinuria, and slow the decrease in GFR in both diabetic and nondiabetic kidney diseases. The beneficial effects appear to be independent of the antihypertensive effects and greater in patients with greater baseline proteinuria.[74,78,80] In several of these studies, the control arm was treated with a dihydropyridine calcium channel blocker, which increases proteinuria. In 2 of 3-arm studies,[75,81] treatment with a dihydropyridine calcium channel blocker led to an increase in proteinuria and faster GFR decrease compared with the β-blocker arm. In 1 study not reviewed at the conference,[105] combination therapy with ACE inhibitors and ARBs led to a greater decrease in proteinuria than either agent alone and a slower rate of GFR decrease, although a recent letter of concern raises questions about this study.[106] Despite adequate blood pressure control and treatment with ACE inhibitors and ARBs, many patients continue to show GFR decrease and progression to kidney failure proportionate to residual proteinuria.[74,75,78,80,107,108]

Despite the relative uniformity of treatment effects of ACE inhibitors and ARBs on proteinuria and GFR decrease, a review of selected studies in 2006 showed a wide range of PTE.[8] Review of additional data at the conference did not suggest a strong trial-level association; the magnitudes of the treatment effects of ACE inhibitors and ARBs on clinical end points across different randomized trials were not predicted accurately by the magnitudes of treatment effects on proteinuria. However, as noted, the PTE can be confounded by other factors, and the uniformity of treatment effects of ACE inhibitors and ARBs may make it difficult to fulfill the trial-level association criterion. Additional analyses are necessary, according to baseline level of proteinuria and magnitude of change early in follow-up, and after inclusion of trials of agents other than ACE inhibitors and ARBs.

In contrast to the kidney disease studies, the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), a large study of high-risk hypertensive patients, ACE inhibitors did not reduce the risk of kidney disease progression compared with the diuretic and calcium channel blocker arm, even in the subgroup with CKD.[109-111] Urine protein was not measured in this study, and it was hypothesized that the discrepancy between ALLHAT and the kidney disease studies cited previously was attributable to lower levels of proteinuria in ALLHAT.[112] Subsequent to the conference, the Ongoing Telmisartan Alone and in Combination With Ramipril Global Endpoint Trial (ONTARGET), a large study comparing ACE inhibitors, ARBs, or both for the treatment of cardiovascular disease, showed a greater decrease in proteinuria with the combination therapy, but no additional benefit on cardiovascular disease, and a faster decrease in GFR and increased risk of kidney failure and death.[113,114] In this study, the geometric mean baseline urine albumin-creatinine ratio was approximately 10 mg/g, with microalbuminuria and macroalbuminuria in 13% and 4% of participants, respectively. In subgroups with CKD, including "overt diabetic nephropathy" defined as macroalbuminuria in the setting of diabetes or CKD stage 3 or higher, no benefit of combination therapy was observed for kidney disease end points individually or combined. Moreover, in subgroups without diabetes, hypertension, or CKD, the risk of these kidney disease end points was increased.

4.3.4. Conclusions

CKD with mild to moderate proteinuria constitutes a heterogeneous set of diseases. The large number of trials and uniformity of responses across a range of kidney diseases suggests that a

reduction in mild to moderate proteinuria may be a suitable surrogate for changes in kidney disease progression in clinical trials with ACE inhibitors and ARBs. However, there is not a sufficient number of trials of other interventions or other populations to extend this conclusion beyond this narrow setting. For other agents, innovative trial designs to fulfill criteria for FDA approval through Subpart H may allow the use of proteinuria as a surrogate outcome. For example, in the trial of the glycosaminoglycan sulodexide in diabetic kidney disease, 2 concurrent trials were planned; a study of patients with less severe disease (microalbuminuria) with a primary end point of decrease in albuminuria to normal or by 50% of the baseline level that persisted after drug withdrawal, and a study of patients with more advanced disease (urine total protein $>$ 900 mg/d) with a primary end point of decrease in incidence of doubling of baseline serum creatinine level or kidney failure. In both studies, the control group received an ACE inhibitor or ARB.[54] A significant beneficial effect in the trial of patients with less severe disease would enable accelerated entry of the drug into the market while the trial of patients with more severe disease was continuing. One disadvantage of this approach is that an early "null" effect in the trial in patients with less severe disease may diminish enthusiasm to complete the trial in patients with more severe disease, thus overlooking the possible later benefit of an agent that has a beneficial effect on kidney disease progression without decreasing proteinuria more than an ACE inhibitor or ARB.

Additional studies are necessary to establish more firmly the validity of changes in proteinuria as a surrogate for kidney disease progression. Randomized trials comparing treatment regimens targeting a higher versus lower level of proteinuria would be helpful. A recent study by Ruggenenti et al[115] comparing kidney disease progression in 2 cohorts treated with a multimodality therapy (including ACE inhibitors and ARBs) to achieve either target

Table 2. Conclusions for Use of Change in Proteinuria as a Surrogate Outcome for Kidney Disease Progression in Clinical Trials

	Conditions	Drugs
	Sufficient evidence for surrogacy	
(1)	Preventing development of kidney disease (progression from normal albuminuria to macroalbuminuria) in diabetes, with persistence of effect after drug withdrawal	Any
(2)	Complete remission of macroalbuminuria in diabetes, with persistence of effect after drug withdrawal	Any
(3)	Complete remission of nephrotic syndrome, with persistence after withdrawal of drug	Any
(4)	Reduction in mild to moderate proteinuria, with persistence of effect after drug withdrawal	ACE inhibitors or ARBs
	Surrogate is reasonably likely to predict treatment effect*	
(1)	Slowing progression from microalbuminuria to macroalbuminuria in diabetes, with persistence of effect after drug withdrawal	Any
(2)	Complete remission of microalbuminuria in diabetes, with persistence of effect after drug withdrawal	Any
(3)	Partial remission of nephrotic syndrome, with persistence after drug withdrawal	Any
(4)	Reduction in mild to moderate proteinuria, with persistence of effect after drug withdrawal	ACE inhibitors or ARBs in combination; RAS drugs other than ACE inhibitors or ARBs (direct renin inhibitors, aldosterone inhibitors)

Note: Conclusions do not necessarily represent Food and Drug Administration opinion. Additional details not specified, such as specific kidney diseases, duration of kidney disease, glomerular filtration rate, absolute or relative change in proteinuria, and duration for persistence of effect after drug withdrawal.

Abbreviations: ACE, angiotensin-converting enzyme; ARBs, angiotensin reuptake blockers; RAS, renin-angiotensin system.

*Consider approval under Subpart H with phase 4 commitment.

Table 3. Research Recommendations for Use of Change in Proteinuria as a Surrogate Outcome for Kidney Disease Progression in Clinical Trials

Population	Recommendations
	Existing data
All kidney disease populations	Standardize indices of proteinuria; relate levels of urine total protein to albumin, and excretion rates in timed urine collections to ratios of concentrations of total protein-creatinine and albumin-creatinine in untimed spot urine samples Relate absolute and relative changes in urinary albumin and total protein on a continuous scale to subsequent GFR decline; determine absolute and relative changes that are most predictive of GFR decline, doubling of serum creatinine and onset of kidney failure
Early diabetes	Determine if there is an intermediate level between microalbuminuria and macroalbuminuria that is more predictive of subsequent GFR decrease than microalbuminuria
Nephrotic syndrome	Compile data on prognosis and response to treatment from studies of specific diseases and histopathologic patterns Standardize definition of remission and partial remission of nephrotic syndrome Relate present level of urine protein to patient reported outcomes Define a standard for treatment efficacy for remission and partial remission of nephrotic syndrome in specific diseases (for example, SLE) for purpose of defining acceptable noninferiority margin for new drugs in comparison to older drugs
Mild to moderate proteinuria	Compile data from existing clinical trials for trial level analysis; investigate heterogeneity due to baseline levels of proteinuria, relative or absolute changes during follow-up and specific kidney diseases
	New clinical trials
All clinical populations	Use a central laboratory and standardize methods for urine albumin assay Measure urine proteins other than albumin if there is a specific rationale; relate measures of albumin, nonalbumin proteins, and total protein Assess persistence of change in proteinuria after drug withdrawal in clinical trials Measure proteinuria in clinical trials exploring effects of therapy on clinical end points; relate baseline levels, absolute and relative changes to clinical end points Relate measures of proteinuria to other markers of kidney damage and biomarkers Concurrent trials in severe and mild study populations Compare interventions targeting different urine protein levels

Abbreviations: GFR, glomerular filtration rate; SLE, systemic lupus erythematosus.

blood pressure or target urine protein excretion provides promising preliminary data.

5. SUMMARY OF CONCLUSIONS AND RECOMMENDATIONS

There is an urgent need to facilitate the investigation of new drugs to slow the progression of CKD. Because most kidney diseases progress slowly and are not symptomatic until late in the course, validation of surrogate markers for kidney disease progression would greatly facilitate drug development. The criteria for surrogacy developed for other disease appear reasonable for evaluation of changes in proteinuria as a surrogate for disease progression in CKD.

Proteinuria is a biomarker. It is not a direct measure of how a patient feels, functions, or survives (a clinical end point), and it is not necessarily an intermediate end point on the path to kidney failure. It is unlikely that proteinuria will be useful as a surrogate in all settings of kidney disease. At the present time, there appears to be sufficient evidence to recommend changes in proteinuria as a surrogate for kidney disease progression in only selected circumstances (Table 2).

Further research is needed to define limited contexts in which changes in proteinuria can be expected to predict treatment effect (Table 3). Attention perhaps should focus on particular disease states in which, given what is known about the pathogenesis of disease, there is greater reason to believe that proteinuria, even if not on the causal pathway, is a consistent intermediate on the pathway to kidney failure. Research should continue to explore the consistency of the relationship between changes in proteinuria (direction and magnitude) and clinical outcomes of interest. Analyses also should attempt to define the magnitude of change in proteinuria (relative or absolute) that reliably predicts outcome. Systematic search strategies are necessary to avoid bias, and meta-analysis to quantify effects would be desirable. Additional intervention trials are needed to establish the relationship between changes in proteinuria and clinically meaningful end points. As research on proteinuria continues, it also is important to search for other biomarkers to aid in the diagnosis and prognosis in CKD and perhaps serve as surrogate end points for clinical trials in the future.

Progress in this field will require collaboration among investigators to share data from past and future studies. Based on the experience with this conference, it appears that substantial data already are available and investigators may be willing to share data from past clinical trials. The FDA is in a unique position to facilitate these efforts. The FDA should be involved in collaborative efforts with academia, industry, and the National Institutes of Health to collect and share these data. Some of the trials presented at this conference are on file at the FDA, and the FDA has data on file from other trials that should be made available to investigators for research on this topic. However, many of the trials reviewed for this conference were small and not submitted to the FDA for drug approval. There are other examples of successful collaborative efforts to improve the tools used to evaluate the safety and efficacy of drugs.[116,117] Governance of the database is an important issue for such a collaboration, and to address confidentiality issues, the FDA could act as a trusted party to hold the data. For future clinical trials, it will be important to include patients with CKD and assess drug effects on proteinuria so that we can better understand the relationship between changes in proteinuria and clinically meaningful end points.[39]

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SUPPLEMENTARY MATERIALS

Item S1: List of Meeting Participants.

Table S1: Compilation of Studies Reviewed for the Conference Report.

Note: The supplementary material accompanying this article (doi:10.1053/j.ajkd.2009.04.029) is available at www.ajkd.org.

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