Published in final edited form as:

Pediatr Nephrol. 2015 February ; 30(2): 193–198. doi:10.1007/s00467-014-2995-0.

Defining New Surrogate Markers for CKD Progression[⊕]

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Abstract

At a recent meeting of international experts on clinical aspects of progressive chronic kidney disease (CKD), an extensive analysis of extant clinical trials was used to develop more effective and economical surrogate markers for CKD outcomes in adults. This article describes the reasons for this undertaking, the methods and conclusions of the meeting, and the relevance of these findings to pediatric nephrology.

Introduction

On December 2–4, 2012, a meeting was held in Baltimore, Maryland, USA, to discuss the utility of GFR decline as an endpoint for clinical trials of interventions to slow progression in chronic kidney disease (CKD). Co-sponsored by the U.S. National Kidney Foundation and the U.S. Food and Drug Administration, a gathering of leaders in the field considered alternative markers for disease progression. The rationale for this inquiry was that the currently accepted surrogate marker, doubling of serum creatinine, requires a considerable number of participants and long follow-up time if enrolled subjects do not already have fairly advanced CKD. This delays the availability of new treatments, precludes trials of interventions that may have an effect early in CKD progression and drives up the cost of clinical trials. As described in a preliminary report in *JAMA* [1] and in a summary paper in the *American Journal of Kidney Diseases* [2], the meeting: 1) more fully validated the previously accepted “gold standard” of doubling in serum creatinine (equivalent to a 57% reduction in GFR), and 2) proposed two new surrogate endpoints, reduction of GFR by either 30% or 40% over two years. The purpose of this editorial commentary is to provide a context for the meeting outcome, describe the methods and conclusion of the meeting, and consider the relevance of these findings to pediatric nephrology.

[⊕]The views expressed in this article are not intended to represent the views of the US Food and Drug Administration.

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Defining and validating surrogate endpoints

In order for a drug or biological product to be approved for use by the FDA, effectiveness of the product must be established through adequate and well-controlled studies. Generally, such studies contain seven elements [3]:

1. A clear, prospectively defined statement of purpose (i.e., hypothesis to be tested).
2. Study design permitting a valid comparison with a control (either concurrent or historical).
3. A method of selecting subjects that provides adequate assurance that they have the disease or condition being studied.
4. A method of assigning patients to treatment and control groups that minimizes bias and is intended to assure comparability of the groups. In most circumstances, assignment is by randomization.
5. Adequate measures to minimize bias for study subjects and study personnel, including observers and analysts.
6. Methods of assessment (e.g., study endpoints and outcome measures) that are well defined and reliable.
7. Analysis of the results, such as statistical analysis methods used, that is adequate to assess the effects of the treatment.

Additionally, endpoints used to support the effectiveness of a treatment should be *clinically meaningful*. A clinically meaningful endpoint is one that directly measures how a patient functions, feels, or survives [4]. Identification of such a meaningful endpoint to support the design of adequate and well-controlled trials is the cornerstone of evidence needed to support FDA approval of drugs and biological products in the U.S. [5].

Biomarkers are potentially useful in all phases of clinical development of a therapy, and can be used as an endpoint in clinical trials. A biomarker is defined as “a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention.” [6] Biomarkers are attractive as clinical endpoints because their changes may accurately predict outcome much earlier than a clinically meaningful endpoint such as survival. However, establishing a biomarker as a *validated* surrogate endpoint (i.e., a biomarker that is intended to substitute for a clinical endpoint) requires robust scientific evidence and a stringent review process. Thus, not all biomarkers are acceptable for use as a clinical endpoint in a trial. Indeed, although a biomarker may correlate with disease severity or outcome, this correlation may not be sufficient to justify its use as a clinical endpoint in a trial. For example, reduction in proteinuria/albuminuria has long been of interest for use as a surrogate endpoint in therapeutic trials for renal diseases. However, more recently, treatment effects on proteinuria have not reliably predicted renal outcomes or disease progression. Thus, combination treatment of Type-2 diabetes patients with aliskiren, a direct renin-inhibitor, and losartan, an angiotensin receptor blocker, led to a reduction of mean urinary albumin-to-creatinine ratio of 20% ($p<0.001$) [7]. However, the Aliskiren Trial in Type-2

Diabetes Using Cardiorenal Endpoints (ALTITUDE), which evaluated cardiovascular and renal outcomes in patients receiving combined therapy with Aliskiren and losartan, demonstrated an increased number of cardiovascular and renal adverse events compared to placebo. The authors noted that the results of this study “underscore the need go beyond surrogate biomarkers and obtain risk-benefit data from clinical-endpoint trials to better inform clinical decisions.” [8]

In selected instances, products also may be approved using an non-validated surrogate endpoint under *Accelerated Approval* regulations [9]. Such an endpoint is one that is *reasonably likely*, based on epidemiologic, therapeutic, pathophysiologic or other evidence, to predict benefit on clinical endpoints that include but are not limited to survival or irreversible morbidity. Accelerated approval is intended to provide a path for products that provide benefit over available therapy for serious or life-threatening diseases. Following accelerated approval, pharmaceutical companies are required to conduct post-approval clinical trials to confirm that the drug provides clinical benefit, as predicted by the surrogate endpoint [10].

The goal of the Baltimore meeting was to discuss the evidence in support of the use of a biomarker--in this case, the percentage change in GFR over time, as estimated using serum creatinine-based equations-- as a validated *surrogate* endpoint for the *clinically meaningful* endpoint of development of end-stage renal disease (ESRD) or as a replacement for the accepted surrogate of doubling of creatinine.

Approach to analyzing GFR as a surrogate endpoint

In the analyses presented at the conference [1], data were combined from the cohort studies participating in the Chronic Kidney Disease Prognosis Consortium (CKD-PC), as well as from clinical trials data collected by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI), to assess possible alternative endpoints of estimated GFR (eGFR) decline and CKD progression, compared to the more standard, FDA-accepted surrogate endpoint of doubling of serum creatinine concentration (57% decline in eGFR). The potential association of alternative surrogate endpoints with established surrogate endpoints in clinical trials was analyzed to determine whether the alternatives yielded outcomes similar to the initial cohort findings. The method that was used allowed evaluation across different types of interventions and types of kidney disease. Pooled data from the previous trials were used to perform simulations to test whether the new surrogates were as effective as the previous standards in predicting treatment effects. The rationale for the studies was to establish the degree of association between declines that were thought to be clinically important, but less than a 57% reduction, and risk of ESRD and mortality in the cohorts. Since the established endpoint of doubling of serum creatinine is a relatively late event in CKD progression, only subjects at later stages of CKD could be included in prior studies. If the proposed alternative levels of eGFR change were sufficiently strongly associated with the clinically meaningful outcomes of doubling of serum creatinine, ESRD and mortality, their utilization as surrogate endpoints would offer a substantially increased opportunity to test new interventions to slow CKD progression earlier in the disease course, with shorter duration of follow-up and fewer enrolled subjects, at lower cost.

The CKD-PC consists of over 50 cohorts with at least 1000 participants each. The cohorts that were included in the meta-analysis needed to have recorded, at a minimum, data on serum creatinine concentration and albuminuria, and to have 50 or more outcome events, specifically mortality or reaching pre-defined kidney disease endpoints. *Risk of CKD progression* was assessed in 22 cohorts: 4 were general population cohorts, 5 cohorts included subjects at high-risk for cardiovascular disease, and 13 were CKD cohorts. All cohorts had repeated measures of serum creatinine. *Mortality* was assessed by analysis of 35 cohorts: 15 general population cohorts, 7 high-risk CVD cohorts, and 13 CKD cohorts. A total of 37 trials were included from CKD-EPI. These had tested renin angiotensin system (RAS) blockade vs. control, RAS blockade vs. calcium channel blocker (CCB), intensive vs. usual blood pressure control, low protein vs. usual protein diet, and immunosuppressive vs. other therapy. All cohorts and trials included participants aged 18 years or older; therefore, progression of CKD in pediatric populations was not specifically assessed, so the generalizability of these findings to pediatric patients has not yet been established.

In the analysis of the cohort studies, as a doubling of serum creatinine corresponds to a 57% change in eGFR, percentage change in eGFR $((\text{last eGFR} - \text{first eGFR}) / (\text{first eGFR}) \times 100\%)$ was assessed in the primary analysis. The primary outcome of interest was time to ESRD, defined as initiation of renal replacement therapy or death due to kidney disease. All-cause mortality as well as cardiovascular mortality, defined as death due to myocardial infarction, heart failure, stroke, or sudden cardiac death, was also assessed. Analyses were stratified by eGFR being less than or greater than 60 mL/min/1.73 m² at baseline. In the clinical trial data analysis, the authors compared the number of endpoints for lesser eGFR declines vs. the established endpoint of 57% decline during the full duration of follow up and during shorter intervals of 12, 18 and 24 months.

In the cohort analysis, the authors assessed the risk of ESRD and death associated with variable percentage change in eGFR. They adjusted for age, sex, race, blood pressure, total cholesterol, diabetes, history of cardiovascular disease and first eGFR. The adjusted hazard ratios (HR) from the meta-analysis were translated from percentage change in eGFR to absolute risk of ESRD or mortality at 1, 3, 5, and 10 years after the baseline period. The meta-analysis for kidney disease progression risk included data on change in eGFR in more than 1.5 million participants. There were over 12,000 subsequent ESRD events during a mean follow-up period of 3.1 years. Mortality analysis evaluated more than 1.7 million participants with over 220,000 deaths. In the analysis of clinical trial data, re-analysis using alternative declines in eGFR than the accepted 57% decline resulted in a 10–50% increase in the number of events in the trials.

Identification of new surrogate markers of CKD progression in adults

The authors determined that in the cohort studies, eGFR declines from baseline that were less than 57% were consistently associated with risk of ESRD and mortality. Declines of more than 30% were associated with greater than 5-fold risk of ESRD for individuals with an eGFR <60 mL/min/1.73m² and a 7-fold risk for those with eGFR >60 mL/min/1.73m². This was a strong and consistent effect, though smaller than the 10-fold and 30-fold risk of ESRD associated with a 40% and 57% decline, respectively. The risk of mortality associated

with these GFR declines was weaker, but overall the trend was similar and a similar dose response was demonstrated. The analysis showed a 50% mortality risk in 10 years associated with a decline of 30% in eGFR, compared to a 32% mortality risk with stable eGFR in individuals of similar age and clinical characteristics and a similar baseline eGFR of 35 mL/min/1.73 m².

In the analysis of clinical trial data, the association of percentage eGFR decline during a 1-year initial trial period with subsequent risk of accepted GFR change outcomes was examined using an analysis that was similar to that described above for the cohorts. The adjusted HRs for a 30% or 40% eGFR decline with the established endpoint were almost 10 and over 20 fold, respectively. Simulation data showed that for interventions that may have moderate or large acute treatment effects, either increasing or decreasing GFR acutely, there was the possibility of a false conclusion about a treatments' effectiveness (Type I error) for interventions with moderate-to-large acute effects for a 40% eGFR decline and for small acute effects for a 30% eGFR decline compared to the 57% eGFR decline. Based on these data, the authors suggested that a 30% or 40% decline in eGFR over 2 years could be considered as an alternative outcome for clinical trials in CKD, with the important caveat that a treatment's potential acute effects should be taken into consideration in making this decision. For both endpoints, the authors recommended a second measure of serum creatinine at baseline and after reaching the endpoint to confirm the eGFR decline. They also recommended a follow-up duration of at least 2–3 years to allow for assessment of benefits and harms. Even if these alternative endpoints were used, the authors acknowledge that large sample sizes (n>1000) and >3 year duration of follow up would be necessary in clinical trials, especially if individuals with only mild decrements in eGFR are enrolled.

Relevance of these findings to pediatric patients

The reports from the CKD Prognosis Consortium establish several important principles for the evaluation of CKD, ones that will facilitate conducting large-scale trials of therapeutic efficacy. It is important to note that the Consortium's meta-analysis examined available data from adult patients and did not specifically address pediatric patients. Even if the evidence is sufficient to validate a specific change in GFR as a surrogate endpoint for the clinically meaningful endpoint of developing ESRD in adults, there may not be sufficient evidence to support its use as a validated surrogate endpoint for ESRD in children. Indeed, since the primary cause of CKD may be a critical determinant of rates and patterns of progression [11], differences in CKD causes between adult and pediatric patients might explain differences in progression rates. The great majority of adult patients have CKD secondary to diabetes or hypertension. In contrast, these two conditions are very rare causes of pediatric CKD. Studies from NAPRTCS [12], ItalKid [13] and CKiD [11] indicate that the most common causes of CKD and ESRD are diseases related to congenital anomalies of the kidney and urinary tract (CAKUT), followed by glomerular disease, neurogenic bladder and other disorders. Importantly, the ItalKid study [13] reported an incidence of hypodysplasia in 57.5% of children with CKD, but only 39.6% of children with ESRD. In contrast, patients with underlying chronic glomerulonephritis or focal segmental glomerulosclerosis comprised 4.4% of CKD patients but 10.7% of ESRD patients. Thus, patients with glomerular lesions appear to be progressing to ESRD more rapidly. Indeed, the need for

renal replacement therapy may not occur until well into adulthood for CAKUT-related CKD [14]. Together, these observations indicate that children may show significant differences from the adult population in both the cause and trajectory of CKD, and emphasize the difficulty in accepting the adult-based evidence to support the use of the proposed decline in eGFR as a surrogate or validated endpoint for pediatric clinical trials. Nonetheless, it may be possible to apply approaches similar to those used by the Consortium to children and, if certain changes in GFR over 2–3 years are highly correlated with ESRD in longer-term follow-up, a pediatric-specific validated or surrogate endpoint could be established.

Limitations of the new criteria for adults and children

A second, related concern, uniformity of progression rates, is relevant to both adult and pediatric populations but is particularly important in children, given the heterogeneity of childhood causes of CKD. The progression of CKD to ESRD often describes an inexorable path from nephron loss to ESRD, where the rate of loss of function is at first linear over time [15] and then accelerates beginning in late stage III CKD [16, 17]. Further, the slope and uniformity of progression rate may vary greatly for individual patients [18]. Steady loss of function over time, via a final common pathway, is a relatively late manifestation that reflects physiological factors in remnant nephrons (described in more detail in [19]). Progressive renal disease actually occurs in three phases. First, injury and response to that injury occur in a disease-specific manner. In the second phase, misdirected repair generates fibrosis and dysfunction. The third and final stage is that of relatively steady, progressive loss of remnant nephrons. Different lesions will enter into this cascade at different points. Hypoplasia manifests some characteristics of fibrosis but may involve more physiological nephron loss. In contrast, glomerulosclerosis presents with entry into the cascade at the level of misdirected repair. The nature of progressive kidney damage, and therefore the reliability of predicting the course toward renal replacement therapy, is thus greatly affected by the primary renal disease. The approach taken by the Consortium suggests that the clinical problem being addressed is the inexorable rate of progression during the final common pathway of kidney failure. While the large number of patients evaluated by the Consortium permits assumption of a generally homogeneous rate of decline of renal function, sufficient data from a smaller, more heterogeneous pediatric population are lacking and will be difficult to obtain.

The Consortium's findings provide an important step that will enhance the medical community's ability to evaluate new treatments more quickly and at less expense. However, their approach does not identify true cessation of disease, but rather demonstrates delaying the final stage of progression. If a study were to be carried out indefinitely, all of the patients would be likely to eventually develop ESRD. Of course, for many patients—especially adults—if the slope is flattened sufficiently, ESRD care might be avoided entirely over a normal lifespan. However, given the high rates of progression in some cases of primary glomerular disease, it is unlikely that decreasing the downward slope of renal function sufficiently to prevent the need for ESRD can be achieved solely by efforts to delay progression in those diseases. Thus, while even delaying progression would be a major accomplishment, there remains an impetus to find a true “cure” for the causes of such progression.

Next steps toward understanding CKD progression

Thus, continued research into the causes and treatment of the response-to-injury and misdirected-repair phases of CKD is essential. But significant difficulties remain inherent to such studies. While basic science evaluations are important for establishing disease causality, in many cases there are no relevant animal models of specific human diseases. This is particularly true of the major diseases that affect pediatric patients, although recent advances have been made in modeling human disorders as different as FSGS [20] and cystinosis [21]. A second problem is the lack of effective biomarkers for disease status. Ideally, these would permit us to determine what specific phase of the disease is present in our patients. The problem is doubly challenging because, in many of the disorders that we treat, the renal tissue itself may be heterogeneous, with some portions in the response-to-injury phase, some manifesting misdirected repair, and others already entered into inexorable functional decline. Finally, the importance of surrogate endpoints cannot be overstated. The great advances of the Consortium were to more fully validate a previously accepted surrogate endpoint (halving of creatinine, equal to 57% loss of renal function), and to propose and validate additional, time-determined end points of 30% and 40% loss of function in two years. At present, the mostly widely studied potential surrogate marker for progression in earlier phases of CKD is proteinuria. More focus on validating proteinuria as a surrogate marker, and identifying other surrogates through novel imaging approaches or molecular analysis of biopsy material, must be a major part of improving patient outcomes.

In the meantime, how might pediatric nephrology benefit from the studies by the Consortium defining potential alternate endpoints for trials in CKD? One possible approach is the application of *pediatric extrapolation* [22]. In certain cases, as outlined by the FDA, effectiveness of a product (e.g., for a new indication or a new population) may be adequately demonstrated without additional, well-controlled clinical efficacy trials. In such cases, other types of data that establish effectiveness for a specific indication or in a specific population may be applied to a new population or to a different dose, dosing regimen, or dosage form [5]. In pediatric extrapolation, available information from adult clinical trials may be used to support efficacy in pediatric populations. The ability to utilize pediatric extrapolation would be based on two fundamental assumptions: 1) that the pathophysiology and progression of the disease are similar in adult and pediatric populations, and 2) that the response to intervention is expected to be similar between adult and pediatric populations. In addition, similar exposure-response relationships (e.g., dose-response curves) of the intervention should be present between adult and pediatric populations. Importantly, pediatric extrapolation cannot be used to establish dosing or the safety of the product because pediatric populations often have different dosing requirements compared to adults, as well as unique safety concerns. Therefore, adequate dosing and safety information must be obtained in order to address these issues in children. Thus, confirming the adult data in carefully designed studies of selected pediatric patients may accelerate our ability to use or adapt specific surrogate endpoints established in adults.

For example, in CAKUT-related CKD, the prolonged course after infancy [14, 23, 24] may reflect a steady rate of decline comparable to that seen in most adult patients. If so, those CAKUT patients who do not require end-stage care in early life might be studied

appropriately using the methods promulgated by the Consortium, by combining data from existing cohorts and examining the association between rates of decline over a specified period and subsequent risk of ESRD. Detailed analysis of the natural course of CKD in these children will assess the validity of both the original doubling of creatinine and the new “adult” paradigms for evaluating progression in at least a subset of pediatric patients. Given the challenges of high patient heterogeneity and low patient numbers, even such limited assessments will require the collaboration of the entire pediatric nephrology community.

Acknowledgments

We appreciate thoughtful comments on the manuscript by Aliza Thompson.

Supported in part by grants R01-DK049362 (to H.W.S.), and K24-DK078737 and U01-DK066174 (to S.L.F.) from the National Institute of Diabetes, Digestive and Kidney Diseases.

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