Clinical Trial Considerations in Developing Treatments for Early Stages of Common, Chronic Kidney Diseases: A Scientific Workshop Cosponsored by the National Kidney Foundation and the US Food and Drug Administration

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In the past decade, advances in the validation of surrogate end points for chronic kidney disease (CKD) progression have heightened interest in evaluating therapies in early CKD. In December 2020, the National Kidney Foundation sponsored a scientific workshop in collaboration with the US Food and Drug Administration (FDA) to explore patient, provider, and payor perceptions of the value of treating early CKD. The workshop reviewed challenges for trials in early CKD, including trial designs, identification of high-risk populations, and cost-benefit and safety considerations. Over 90 people representing a range of stakeholders including experts in clinical trials, nephrology, cardiology and endocrinology, patient advocacy organizations, patients, payors, health economists, regulators and policy makers attended a virtual meeting. There was consensus among the attendees that there is value to preventing the development and treating the progression of early CKD in people who are at high risk for progression, and that surrogate end points should be used to establish efficacy. Attendees also concluded that cost analyses should be holistic and include aspects beyond direct savings for treatment of kidney failure; and that safety data should be collected outside/beyond the duration of a clinical trial. Successful drug development and implementation of effective therapies will require collaboration across sponsors, patients, patient advocacy organizations, medical community, regulators, and payors.

Introduction

Chronic kidney disease (CKD) is a significant global public health problem. There are approximately 30 million people in the United States living with CKD; globally, this number is estimated to be 700 million people. Kidney failure is the most serious manifestation of CKD, but at earlier CKD stages before kidney failure people with CKD are at greater risk of other adverse outcomes such as cardiovascular disease and death than progression to kidney failure. The care for CKD and its complications is costly, with estimated costs in the United States of approximately $120 billion per year.

Kidney failure is the most important complication of CKD and its most visible manifestation. In the past decade, significant progress has been made in validating surrogate end points that can be used to evaluate the efficacy of therapies for CKD progression. This work, together with other scientific advances, has heightened interest in the development of treatments for early stages of CKD (Fig 1). More people have earlier stages of CKD than later stages of CKD. Introduction of treatments at earlier stages of disease could, in principle, reduce progression to kidney failure for a greater number of people than treatments only used at later stages of disease. However, earlier treatments would also increase the total expenditure related to CKD treatments and the total number of people who experience harm from interventions.

The National Kidney Foundation (NKF) cosponsored a scientific workshop with the US Food and Drug Administration (FDA). A central aim of the workshop was to explore patients’, providers’, and payors’ perceptions of the value of treating early CKD. The planning committee included multiple stakeholders, including a patient representative, and spent time framing the workshop discussion points to be reflective of the wide set of stakeholder issues and concerns. The workshop focused specifically on common causes of CKD, given that other forums have discussed strategies for drug development in rare diseases. To aid in the attendees’ discussion of the central aim, the workshop reviewed challenges for trials in and treatments of early CKD, including trial designs, the identification of high-risk populations, and cost-benefit and safety considerations.

Over 90 people representing a range of stakeholders including faculty experts in clinical trials, nephrology, cardiology and endocrinology, patient advocacy organizations, patients, payors, health economists, regulators, and policy makers were invited for a virtual meeting held December 14–17, 2020. Additional information about the workshop is included in Item S1. The purpose of this report is to summarize the science presented in the
workshop, the subsequent discussions, and the conclusions reached by participants on 5 questions.

**Background and Context**

**Natural History of CKD**

CKD is generally a progressive disease that results in loss of glomerular filtration rate (GFR) over time and in some patients progression to kidney failure.\(^\text{14}\) CKD is defined by either GFR less than 60 mL/min/1.73 m\(^2\) or presence of a marker of kidney damage (most commonly albuminuria) for at least 3 months, and is staged for severity by both GFR and albuminuria. Albuminuria is recommended in clinical practice rather than proteinuria, but both are used in drug development. Herein we use the term albuminuria to refer to endpoints using either.

CKD progression is heterogeneous. In some people GFR declines rapidly; in others, GFR declines intermittently with periods of GFR decline or stability; and in still others GFR declines slowly and later stages of kidney disease are unlikely to occur. Increases in albuminuria may occur before GFR decline, and elevated albuminuria is among the strongest risk factors for subsequent GFR decline. Although there are many causes of CKD, the cause is not always known. There are common mechanisms of kidney disease progression, which enables some therapies to treat progressive CKD, regardless of cause.\(^\text{15}\) In this report, we speak of CKD in general but acknowledge there are many factors related to specific causes of kidney disease or specific treatments that will be relevant for an individual specific drug development program or specific patient subgroups.

People with CKD are at increased risk for cardiovascular disease and death not due to kidney failure as well as a myriad of complications, such as cognitive impairment and infections. Decreased GFR and elevated albuminuria are strongly associated with cardiovascular disease, heart failure, hospitalizations, and mortality; more than half of deaths in CKD are attributable to cardiovascular causes.\(^\text{4,16}\)

The converse is also true: cardiovascular disease can precipitate GFR decline.\(^\text{17,18}\) The increased availability of effective treatments for early CKD will provide opportunities to explore whether some treatments that slow CKD progression also reduce cardiovascular morbidity and mortality as well as other complications.

**Identification of Individuals at High Risk for Progressive CKD for Inclusion in Trials and to Guide Treatment Decisions in Clinical Practice**

Risk stratification tools for individual patients that incorporate GFR and albuminuria together with additional risk factors could be used to inform treatment decisions for individual patients and inclusion in trials.

**Key Factors to Consider in Assessing Risk for CKD Progression**

Specific parameters are important to consider when estimating risk for both inclusion in clinical trials and clinical decision-making (Table 1). The risk estimation most relevant to patients is that of absolute risk, or the probability of an event occurring over a specific period. The optimal time frame over which risk should be estimated may differ based on the goal of risk estimation. For patients with CKD, the relevant time frame for

![Figure 1. Goals of the scientific workshop.](image-url)
development of a serious adverse outcome may be a lifetime. By contrast, for sponsors or investigators designing clinical trials, the relevant time frame is often the length of time needed to demonstrate the efficacy of an intervention. Another key parameter in assessing risk for CKD progression is identifying the specific end point of interest. Studies used to develop risk tools for CKD progression have generally used the outcome of kidney failure treated with kidney replacement therapy (KFRT). This has 2 major limitations. First, particularly among older adults and in resource-limited settings, many individuals with kidney failure may not receive kidney replacement therapy, either as a function of choice or resource availability. Second, kidney failure does not capture progression of CKD in the relevant time horizon; accordingly, GFR slope, 30% and 40% declines in GFR, and reaching CKD GFR category 4 (G4; GFR <30 mL/min/1.73 m²) may be more appropriate end points. In addition, because of the importance of cardiovascular disease as a complication and potential contributing factor to CKD progression, cardiovascular disease itself could be an end point of interest in CKD trials or conversely incidence or progression of CKD could be an outcome in cardiovascular trials.19

### Table 1. Elements of Risk Prediction

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Considerations</th>
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<tr>
<td>Type of risk</td>
<td>Absolute risk is the probability of an event happening over a specific time period and can be estimated by observed risks within a population and excess risks based on patient-specific characteristics</td>
</tr>
<tr>
<td>Time horizon</td>
<td>Short-term for estimating power in clinical trials and long-term for determining risks vs benefits in clinical practice</td>
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<tr>
<td>End points</td>
<td>KFRT; kidney failure without replacement therapy; CKD progression (30% GFR decline, 40% GFR decline, CKD stage 4, GFR slope); CVD; all-cause mortality; composite end points</td>
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<tr>
<td>Risk factors</td>
<td>GFR and albuminuria, the presence of hypertension, diabetes, CVD, smoking, and variably obesity; other genetic or molecular biomarkers may also be important in prognosis but have not been adequately studied</td>
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### Risk Stratification Tools

- **Kidney Failure Risk Equation (KFRE)**: Estimates the 2- and 5-year risk of initiating dialysis in individuals with GFR < 60
- **Timing of clinical outcomes in CKD with severely decreased GFR**: Estimates the 2- and 4-year risk of KFRT, cardiovascular events, and all-cause mortality in individuals with GFR < 30
- **KFRT risk tool for kidney donor candidates**: Estimates the 15-year and lifetime risk of kidney failure in potential kidney donor candidates in the absence of donation
- **Early CKD progression**: Estimates the 2- to 3-year risk for 40% GFR decline in individuals with GFR > 60
- **Incident GFR < 60 calculator**: Estimates the 5-year risk of GFR < 60 in individuals with GFR > 60
- **SCORE + kidney variables calculator**: Estimates the 10-year risk of cardiovascular mortality with updates to the original SCORE equation by including eGFR and, if available, albuminuria
- **Pooled cohort equation + kidney variables calculator**: Estimates the 10-year risk of atherosclerotic CVD with updates to the original pooled cohort equation by including estimated GFR and, if available, albuminuria and recalibrating if desired

**Abbreviations**: CKD, chronic kidney disease; CVD, cardiovascular disease; GFR, glomerular filtration rate (in mL/min/1.73 m²); KFRT, kidney failure with replacement therapy; SCORE, CVD mortality by Systematic Coronary Risk Evaluation.

### Traditional Risk Factors and Tools

Traditional potentially modifiable risk factors for CKD progression include level of GFR and albuminuria, the presence of hypertension, diabetes, hyperlipidemia, smoking, and, variably, obesity. Table 1 lists the validated risk tools exist to predict CKD progression. The most widely used calculator, the Kidney Failure Risk Equation (KFRE), predicts risk of KFRT over 2-year and 5-year periods in people with GFR <60 mL/min/1.73 m².20 Risk estimates derived from these tools can be used in patient counseling as well as to guide referral to nephrology, multidisciplinary care, transplant evaluation, and vascular access placement.

For people with higher GFR there are 3 tools are available: estimated risk of KFRT over 15 years and the lifetime, 5-year risk of developing GFR <60 mL/min/1.73 m², and 2- to 3-year risk of developing 40% decline in GFR.21-23 The first model was developed for potential kidney donors and thus is not applicable to persons many people with CKD (eg, GFR <45 mL/min/1.73 m²), severe albuminuria [ie, albumin-creatinine ratio > 300 mg/g], or diabetes requiring insulin therapy), which may preclude use in some trials evaluating therapies in early CKD. The
second and third models are most applicable in the identification of high-risk populations for trials evaluating efficacy of therapies for development or prevention of CKD progression in early CKD, respectively. More data are needed to evaluate their implementation in clinical settings.

Assessment of End Points for CKD Progression Trials

Historically, drug development for CKD has focused on patients with later stages of disease because they are at high risk of CKD progression. This is in part because the commonly used outcomes in clinical trials—kidney failure or the accepted surrogate, doubling of serum creatinine—occur only after a prolonged disease course that may extend 10 to 20 years, a time frame that is not feasible for trials of early CKD. Nevertheless, it is widely recognized that implementing treatments in early stages of CKD could have a greater impact on delaying the time to progression to kidney failure and reducing the risk of progression than interventions applied at later stages of disease (Fig 2).

In the past decade, there have been several advances in trial design that have expanded the population that can be enrolled in CKD progression trials. To date, attention has focused on albuminuria and GFR as candidate surrogate end points because they are the most widely studied biomarkers in CKD. Elevated albuminuria is generally caused by increased permeability of the glomerular capillary wall to macromolecules. Experimental studies showed that increased tubular exposure to albumin promotes activation of inflammatory mediators causing tubulointerstitial injury and further kidney damage. The GFR is the product of the number of functioning nephrons and the single-nephron GFR. GFR decline is on the causal pathway to kidney failure and can be considered an intermediate end point.

Previous workshops cosponsored by the NKF, FDA, and the European Medicines Agency evaluated the validity of changes in albuminuria and GFR as surrogate end points for clinical trials in CKD (Table 2). The 2012 workshop focused on the evidence supporting the validity of 30% and 40% declines in GFR as acceptable alternative end points in clinical trials in some circumstances. Since then, a 40% GFR decline has been used in several pivotal clinical trials. The 2018 workshop focused on the evidence supporting treatment effects on the mean change in albuminuria over 6 and 12 months and the mean rate of GFR decline (GFR slope) as surrogate end points. Strength of associations was substantially stronger for mean GFR slope than mean change in albuminuria. Changes in albuminuria are being used in phase 2 and dose-finding studies to demonstrate proof of concept in prevalent CKD or as an end point for conditional approval and accelerated approval in some rare glomerular kidney diseases. In some settings, GFR slope is being used as an end point to support full approval. When applying these data to the design of a future trial, the most appropriate end point for the new trial needs to be considered in the context of the trial phase, specific population, treatment, and design.

Assessment of Safety and Adverse Events

Before approval, the sponsors must demonstrate that a drug is effective for the proposed use and that the benefits outweigh the risks, with the risks viewed in the context of both the condition being treated as well as other available therapies. For example, a drug that carries a risk of significant toxicity could still be considered to have a favorable benefit-risk profile if it is effective for treatment of a late-stage, life-threatening condition with no other treatment options. By contrast, such a toxicity profile might not be acceptable for a drug intended to treat an early stage of a disease with uncertain progression.

Drug development programs are generally designed to assess efficacy more robustly than safety. Nevertheless, characterizing the risks of a therapy in the target population is a key objective of all drug development programs. The most readily interpretable safety data are obtained from randomized controlled trials that are well designed to evaluate toxicities of interest based on preclinical findings, the experience with the larger pharmacologic class, and data obtained from other trials of the drug.

International regulatory consensus guidelines provide general recommendations on the size of the safety database and duration of exposure needed to assess the safety of drugs that are intended for the long-term treatment of non–life-threatening conditions. However, it is widely recognized that what constitutes an adequate safety database depends on multiple factors. In general, studies conducted to support a marketing application are adequately sized to provide insight into common

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**Figure 2.** Effect of early versus late intervention on development of KFRT. GFR is higher in earlier intervention compared with later intervention. As a result, there are more KFRT-free years among people who undergo earlier intervention compared with those who have a later intervention. Abbreviations: GFR, glomerular filtration rate; KFRT, kidney failure with replacement therapy. Adapted with permission from Inker and Chaudhari; original graphic ©2020 Wolters Kluwer Health, Inc.
<table>
<thead>
<tr>
<th>Table 2. Considerations for End Point Selection</th>
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<tr>
<td><strong>End point</strong></td>
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<tr>
<td>Definition (computation)</td>
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<td>Confidence in end point as valid surrogate</td>
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<td>Population</td>
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<tr>
<td>GFR range</td>
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<tr>
<td>ACR range</td>
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<tr>
<td>Rate of GFR decline</td>
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<tr>
<td>Considerations of acute effect</td>
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<tr>
<td>Other considerations</td>
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<table>
<thead>
<tr>
<th>Assessment</th>
<th>GFR Slope</th>
<th>Time to Sustained Decline in GFR&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Kidney Failure&lt;sup&gt;b&lt;/sup&gt;</th>
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<tbody>
<tr>
<td></td>
<td>Albuminuria</td>
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<td></td>
<td>Chronic Slope</td>
<td>Total Slope</td>
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<td></td>
<td>Multiple baseline and on-treatment measurements to account for biological variation; first morning void urine samples preferred to daytime samples</td>
<td>Multiple measurements at important time points to improve precision and assessment of acute effect</td>
<td>Requires confirmatory measurement</td>
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<td>Multiple measurements at important time points to improve precision</td>
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<td>Requires confirmatory measurement</td>
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<td>Untreated kidney failure may be missed</td>
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</table>

**Abbreviations:** ACR, albumin-creatinine ratio; ΔACR, change in albumin-creatinine ratio; GFR, glomerular filtration rate; Scr, serum creatinine.

<sup>a</sup>In analyses evaluating these end points, sustained decline was defined as change in GFR observed at next visit if not the last visit.<sup>50</sup>

<sup>b</sup>Kidney failure is often defined as composite end point; see the International Society of Nephrology consensus report<sup>1,24</sup> for details.

<sup>c</sup>Treatment effect on chronic slope defined from an initial on-treatment measurement to end of treatment.

<sup>d</sup>Treatment effect on total slope defined as total slope from randomization to end of treatment. The length of the follow-up period to estimate slopes that reliably predict a treatment effect on longer term clinical outcomes is dependent upon the direction and magnitude of the acute effects.

<sup>e</sup>Indicates + reasonably likely; ++ valid surrogate; +++ approaching clinical end point. Strength of the association for treatment effects on the surrogate vs clinical end point (R²) was 72%, 96%, 97% 66%, 91% for albuminuria, chronic slope, total slope over 3 years, 30% decline, 40% decline, respectively, based on CKD-EPI analyses<sup>5-7,26,50,51</sup>. Key limitations are that the results reflect studies included in these analyses and may not be generalizable to populations, diseases, and treatments not included in those set of studies.<sup>2,31</sup>

<sup>f</sup>For albuminuria, treatment effect in range of ~30% is required to have high confidence for a treatment effect in the clinical end point in a future trial. For chronic and total slope, estimated treatment effects would be 0.5-1.0 mL/min/1.73 m² per year.<sup>51</sup>

<sup>g</sup>Slow progression is defined as decline of <3 mL/min/1.73 m² per year; fast progression is defined as decline of ≥3 mL/min/1.73 m² per year.

<sup>h</sup>Acute effect is the immediate effect of an intervention that differs from the longer-term slope. This can be related to changes on the true GFR or on the endogenous filtration marker used to estimate the GFR. Small risk of false conclusions with very large acute effect and very short time line.
adverse reactions that are caused by a drug. By contrast, because of their limited size and duration, they do not provide information on rare adverse reactions or adverse reactions that develop after many years of treatment.

After approval, data from various sources are used to characterize further the risks of a product when used in a real-world setting and to identify adverse reactions that did not appear during the drug approval process. Sources of data may include adverse events reported to regulatory agencies by health care providers, consumers, and the pharmaceutical industry, national medical product safety surveillance systems, postmarketing studies (eg, observational pharmacovigilance studies, comparative efficacy research), and new clinical trials. Such postmarketing studies and clinical trials may be required by regulatory agencies to assess a known serious risk related to the use of the drug, to further evaluate a signal for such a risk, or to identify an unexpected serious risk when available data indicate the potential for a serious risk. The information obtained from these sources may lead to revisions to the label, such as the addition of a new warning, and, on rare occasions, withdrawal of a drug from the market.

Assessing the Safety of Therapies Intended to Treat Early Stages of CKD
To date, there has not been significant discussion of what constitutes a sufficient characterization of safety for use of treatments in people with early stages of CKD, who are at lower risk for developing kidney failure than people with late-stage CKD and in whom side effects may be less acceptable. In addition, some people may be at greater risk of developing adverse cardiovascular outcomes or dying than progressing to late-stage CKD. As such, depending upon the specific drug and population, development programs may need to be designed to characterize cardiovascular safety.

The Cost Versus Benefit for Treating Early CKD
The true cost of any drug encompasses the total of investment in drug development, individual expense, and costs to the health care system minus the financial benefit from preventing impactful illnesses, including all the costs associated with lack of employment and societal expenditures due to the presence of this illness. Assessments of cost-effectiveness of any drug thus require consideration of a broad perspective of value, not only that which is present in the immediate time frame but also anticipated costs and savings (Fig 3). For treatment of early-stage CKD, it is important to explicitly discuss the potential costs and cost savings because benefits of treatment are likely to be achieved after years, the large number of people possibly eligible for treatment, and not all people treated will derive benefit due to uncertainties in clinical course.

There are 2 main sources of costs: direct and indirect. Direct costs are those incurred by the health care system and include those related to prescriptions, outpatient appointments, emergency department visits, and inpatient episodes.37 In the US Medicare CKD population, after adjusting for age, sex, and relevant comorbid conditions, the annual direct spending cost per patient increases with worsening CKD stages ($8,091 for stage 2; $46,128 for stage 4/5, and $87,399 for KFRT37). Indirect costs are those incurred by the patients and their caregivers that may also have substantial societal impacts. These are costs related to absenteeism, presenteeism (reduced productivity at work), unemployment, and lost productivity due to premature mortality or early retirement. All may impact care partners, who may struggle to balance other demands with the care needs of an individual with advanced CKD. For people with autosomal dominant polycystic kidney disease (ADPKD), total indirect costs were estimated to be approximately 20% ($1.4 billion) of the total annual health care burden attributed to ADPKD.38 The higher direct cost in early-stage CKD should be balanced by lower direct and indirect costs associated with late-stage disease.37

Quality of life is also an important driver of value. Within economic evaluations, health utility, measured on
a scale of 1 (perfect health) to 0 (death), is used to adjust 
life expectancy for quality. For example, the health utility 
of a person with CKD stage 2 is estimated to be 0.8 
(representing a 20% decrease in health utility from perfect 
health); this decreases to 0.47 in KFRT. 

Consequently, in line with the concept of value, avoiding CKD progression 
to kidney failure will maximize health gain.

Recently, examples of significant cost benefits associated 
with delaying or preventing CKD progression have become 
available. Examples include a Medicare-funded multidisci-
plinary care program that demonstrated reduced dialysis 
requirement and increased life expectancy; use of tolvap-
tan in ADPKD estimated to delay time to KFRT; and use of 
dapagliflozin for CKD. The later example is of key 
interest as it is expected that sodium/glucose cotransporter 2 
inhibitors will be used broadly in early CKD and will impact 
CKD progression as well vascular disease. In this analysis, 
dapagliflozin was estimated to increase quality-adjusted life 
years by 0.06 and to reduce lifetime total costs by £2,552. For 
both quality-adjusted life years gains and costs, the savings 
largely reflected differences in kidney disease progression, 
including stages of CKD before kidney failure.

Patient Perspectives

To inform discussions in the workshop, NKF surveyed their 
patient community in November 2020 and conducted a 
patient panel session within the workshop to expand on 
findings of the survey. A total of 1,029 participants 
responded to the survey; full results of the survey are pub-
lished elsewhere, along with a perspective from the patient 
member of the planning committee. Three people 
participated in the panel, which is described in Item S2.

Survey respondents and panelists were willing to 
consider taking a medication that reduces their risk of 
kidney disease progression. One panelist with CKD stage 
3b stated, “Anything to help … slow [the] progress of the 
kidney disease—I’m all for it.” The panelist with the 
highest GFR, CKD stage 3a, was more risk averse: “Where I 
am right now, honestly I wouldn’t. However, what would 
alter that—if I did see an appreciable decrease in my 
kidney health then I’m sure I would be much more open 
to trying some things.” The majority of survey respondents 
also indicated that they would be willing to take a medi-
cation to prevent kidney failure, with the stated willingness 
increasing as the proximity to developing kidney failure

Patient responses to question asking about the likelihood of taking a new medication to prevent kidney failure:

![Bar chart showing patient responses to question asking about the likelihood of taking a new medication to prevent kidney failure.](chart1.png)

Patient responses to question asking about willingness to take medication despite symptoms/inconveniences:

![Table showing patient responses to question asking about willingness to take medication despite symptoms/inconveniences.](table1.csv)

Figure 4. Example patient responses from survey about attitudes toward treatment in early CKD. Top panel: Responses to scenario 1: “Your doctor says that there is a new medication which can reduce your chance of developing kidney failure. Please tell us your likelihood of taking this medication under the following circumstances.” Bottom panel: Responses to scenario 2: “If your doctor told you that you have a 20% chance of developing kidney failure over 5 years, how likely would you be to take a drug that has the following side effects or concerns?” Abbreviations: Appts, appointments; CKD, chronic kidney disease; UTI, urinary tract infection. Adapted with permission from Damron et al; original graphics ©2022 Damron et al.
shortened (Fig 4). Survey participants were overwhelmingly willing to continue taking a medication even if side effects occurred (93.6%), but for most (57.7%) this willingness was contingent on their doctor working with them to try to reduce side effects. The panelists agreed that going to the doctor or having blood tests was “just the way of life now” and would not be a major factor in their decision to take a new medication. For one panelist, an amputee, frequent urination and occasional dizziness would be burdensome side effects, highlighting the need to assess individual circumstances and lifestyle considerations. The panelists felt their nephrologists were important drivers in their education about treatment options, effects of CKD, and prognosis. For all 3 panelists, GFR slope was a new concept and one they felt would be helpful in advancing their own understanding of their disease progression. Contrasting with other conditions, where improvement in numbers typically indicates successful treatment, one panelist noted that “understanding that maintaining [kidney function] is actually a miracle” is critical for patients to understand how kidney disease is treated. Panelists also noted the need for all care providers to coordinate both care and messaging: “It’s important to have all your doctors … communicating effectively. They all need to know what is going on with the patients—dealing with the heart, the kidney, the diabetes.”

Collectively, the panelists felt strongly that prior lifestyle changes, particularly with diet, exercise, and medication use, had positively impacted their kidney function and their quality of life. However, these changes happened at various points in their disease course for each panelist; for some, there was a decisive and often catastrophic event like critical illness or dialysis that motivated these changes. Panelists acknowledged they would have benefited from lifestyle changes sooner; however, they also noted they were not ready to engage with these changes any earlier than they had done. One panelist reflected, “I wasn’t as intentional with my health 20 years ago. I’m a lot different [now] than I was 20 years ago.”

The survey participants and panelists underscored the perceived value of early treatment for CKD. We recognize that the conference included only 3 patient panelists, and they and the survey participants were most likely not representative of the entire CKD population. Nevertheless,

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<th>Box 1. Research Recommendations</th>
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**Trial design/drug development program considerations for early CKD**
- Further validation of existing surrogates across different diseases, treatment types, and population characteristics
- Development of data and methods to support the application of seamless adaptive phase 2/phase 3 trial designs that improve the rigor and efficiency of efficacy evaluation of a new treatment by integrating accumulating information on the treatment’s effect on albuminuria, GFR slope, and clinical end points
- Continued discovery and validation of new biomarkers that can be used for pharmacodynamic or treatment response
- Continued evaluation of mechanisms underlying specific causes of CKD progression and whether they are unique to specific etiologies or common across all diseases
- Adoption of pragmatic designs and decentralized trials potentially using point-of-care testing
- Additional work on patient-reported outcomes appropriate for early-stage CKD
- Development of tools to help patient and health care professional assessment of patient values and preferences regarding potential benefits and harms of therapies beginning at earlier stages of kidney disease
- Evaluation of impact of CVD morbidity and mortality reduction by treatments that slow CKD progression
- Development of systems to include patient perspective in a more representative way in all steps of the drug development pathway

**Identifying populations for treatment of early CKD**
- Education of at-risk populations to increase awareness of CKD and its complications
- Optimization of currently available risk scores
  - Evaluation of these tools within the time frame of the RCT
  - Evaluation of these scores for identification of high-risk populations for treatment trials, and evaluation of their consistency across specific causes, if known
  - Evaluation of the utility of including current medications in prediction models
- Further exploration of novel risk models that include biomarkers, social determinants, or genomic information; examples include biomarkers of common injury pathways such as KIM-1, UMOD, sTNFR, genetic variants such as the APOL1 risk alleles, and histological scores
- Development of novel health care delivery structures that identify patients regardless of location of care and enhanced communication across health care professionals

**Assessment of safety of treatments for early-stage CKD**
- Continued evaluation of the role of real-world evidence and registries to augment the understanding of the safety profile of a drug following approval
- Continued evaluation of the size and duration of trials needed to obtain adequate information on a drug’s risks before approval as a treatment for early-stage CKD

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**Abbreviations:** APOL1, apolipoprotein L1; CKD, chronic kidney disease; CVD, cardiovascular disease; GFR, glomerular filtration rate; KIM-1, kidney injury molecule 1; RCT, randomized control trial; sTNFR, soluble tumor necrosis factor receptor; UMOD, uromodulin.
we think the perspectives of these engaged individuals can provide guidance as to patients’ values.47,48 The variation in responses among both groups highlights the importance of individualizing benefit-risk discussions and for increased education and activation of patients earlier in the disease course. These discussions should recur over time to keep up with changes in health and life goals.

Report From the Conference

At the conference, breakout groups discussed the issues reviewed in the preceding sections in formulating the response to 5 questions. The summary of each is shown below and suggested research topics are listed in Box 1.

1. How do patients, providers, and payors perceive the value of treating early CKD? There was a consensus that there is value in evaluating therapies for early CKD, but the details matter as to who, what, when, and how. All participants agreed that the remaining questions (2–5) help provide the details by which these decisions can be made. Specific considerations included risk, patient preferences, costs of the treatments, side effects or additional benefits of treatments, other adverse events related to CKD, tools for monitoring response to therapy, and duration of therapy.

2. What are the trial design/drug development program considerations for early CKD? There was a consensus that validated surrogate end points can be used to evaluate the effects of treatments among individuals with early-stage CKD.

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**Figure 5.** Classification for chronic kidney disease with considerations for treatment and end points for trials. Top panel: Current staging system for CKD and treatment considerations. Middle panel: Proposed scheme for treatments at early stages of CKD. Hatched cells indicate proposed treatment of those at minimal and moderate risk based on additional risk factors. Bottom panel: Simplified scheme for CKD progression end points across CKD GFR and albuminuria stages. Decisions for specific study to be implemented with consideration of the phase and design of the trial, and characteristics of treatment and study population. For all panels, green indicates no CKD; yellow, orange, and red indicate CKD patients who are at minimal and moderate or high and very high increased risk for progression to kidney failure and other outcomes related to CKD, respectively. Abbreviations: A, treatment effect on change in albuminuria; ACR, albumin-creatinine ratio (in mg/g); CE, treatment effect on the clinical end point; CKD, chronic kidney disease; GD, treatment effect on GFR decline (30%, 40%, or 57% decline); GFR, glomerular filtration rate (in mL/min/1.73 m²); GS, treatment effect on GFR slope.
Use of a surrogate end point requires a thorough understanding of the performance of the end point for the population, treatment, and trial being evaluated. Some suggested that drug development programs that use surrogate end points to demonstrate efficacy should be followed by observational studies or registries to obtain further information on treatment effects over time, patient-reported outcomes, and/or impacts on complications of CKD such as cardiovascular disease.

3. Can we identify optimal populations to be treated for early-stage CKD? There was consensus that treatment trials should focus on people with CKD who are at high risk for progression to advanced disease. There was recognition that the tools used to evaluate risk might vary among populations and over time. At present, risk scores based on traditional models can be applied. Future directions might include risk scores based on mechanisms of disease and genetics as our knowledge of these increases, or on other factors relevant to progression such as social determinants of health.

For drugs designed to slow progression of kidney disease, it is appropriate to identify people who are at high risk of progressive kidney disease. From the patient perspective, people with CKD suffer due to kidney disease and its complications even if they do not have kidney failure because they are at high risk for complications of CKD such as cardiovascular disease.

4. What are the cost–benefit considerations for treatment of early-stage CKD? There was general consensus that cost analysis for treatments in early-stage CKD should use a holistic perspective. Savings on short-term and longer-term health care delivery may include savings on the overall burden of kidney disease and kidney disease progression including mental health, quality of life, and cardiovascular disease. Cost effectiveness varies based on multiple factors, including geographic region, health care system, affordability for the country/region (which may be high, middle, or low income), and the relative value the societies place on different priorities. In many systems, payors are not incentivized to prevent longer-term outcomes; rather, they have a short-term focus on established disease, which does not present an avenue for consideration of cost savings in CKD.

5. What constitutes adequate assessment of adverse events for treatments evaluated in early-stage CKD? There was general agreement that it may be important to obtain additional information on the safety of a drug following its approval, possibly via observational data or registries. Considerations in the design of studies to characterize a drug’s safety may include the relative health of the population and any existing knowledge of safety from studies in later kidney disease and/or other diseases.

Summary
Among the conference attendees, there was a consensus that there is value to preventing the development or treating the progression of early-stage CKD in people who are at high risk for progression. The end points for trials to determine the efficacy of such interventions are likely to be intermediate or surrogate end points (Fig 5). Cost analysis for treatments in early-stage CKD should incorporate a holistic perspective that incorporates more than costs of the drug and should consider savings on health care delivery and on treatment of kidney failure. Safety of treatment for early-stage CKD is important and will require additional assessments beyond what is available from time frames available during trials.

Supplementary Material

Supplementary File (PDF)

Item S1: Conference details.
Item S2: Patient perspective.

Article Information

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References


21. Grams ME, Brunskill NJ, Ballew SH, et al. Development and validation of prediction models of adverse kidney outcomes in...
the population with and without diabetes mellitus. *Diabetes Care*. Published online July 20, 2022. doi:10.2337/dc22-0698


50. Inker LA, Heerspink HJL, Mondal H, et al. GFR decline as an alternative end point to kidney failure in clinical trials: a meta-
