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Research in the CKD Clinic: Highs and Lows

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Abstract

Despite rates of chronic kidney disease (CKD) continuing to increase, the current evidence base used to guide CKD management is smaller than that for many other chronic diseases. Clinical investigators face multiple barriers to conducting research in patients with CKD. CKD patients have multiple comorbidities making them a risky intervention target and are often excluded from trials as a result. The lack of approved surrogate endpoints for kidney disease progression makes testing therapies to slow progression very challenging and expensive. Patients with CKD have higher rates of disability and lower educational status than the general population which further complicates their participation in clinical trials. In spite of these barriers, it is imperative that scientific progress be made in this patient population. Increasing education and information regarding CKD clinical trials through brochures and public awareness campaigns may increase trial participation. The FDA needs to approve the new definition of GFR decline as this will result in a decrease in the cost of clinical trials and make industry more likely to invest in trials in patients with CKD. Successful research in this patient population is possible but it requires collaboration between investigators, healthcare providers, patients, industry and the NIH.

Keywords

chronic kidney disease; clinical trials; clinical research; barriers; cardiovascular disease

Introduction

Prevalence rates for chronic kidney disease (CKD) continue to rise, with a reported 13.1% of the US population having the disease in 2004. (1) CKD is associated with extraordinarily high rates of cardiovascular events and mortality. (2) Despite the increasing prevalence and morbidity and mortality of CKD, the current evidence base used to guide CKD management is smaller than that for many other chronic diseases. (3) This is evidenced by the 879 active

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trials currently being conducted in CKD patients in comparison to the 2,485 active cardiovascular disease trials in US adults. (4) The few number of trials conducted in CKD patients has led to many of the treatment and prevention guidelines for CKD to be established from extrapolation of data from randomized controlled trials done in the general population or from subgroup analyses of people with CKD enrolled in such trials. (3) Growing evidence suggests that standard treatment strategies may act differently in patients with and without kidney disease. Hence, funding agencies should make studies in CKD patients a priority, so why aren't they being performed? This review focuses on issues that may complicate the conduction of research in the CKD patient population and potential solutions to overcome them (Table 1).

Patients with CKD are often excluded from interventional trials

The complexity of CKD makes these patients a risky intervention target. More specifically, patients with CKD have multiple comorbid conditions and complications related to their kidney disease such as anemia, malnutrition and abnormalities of mineral metabolism. (5) As a result, CKD patients are often excluded from research trials. Large cardiovascular disease trials exclude nearly 75% of patients with moderate chronic kidney disease whereas subjects with other common risk factors for cardiovascular disease are only rarely excluded. (6) Another reason many CKD patients are excluded from studies is that the reduced glomerular filtration rate (GFR) may alter the safety profile of some drugs and devices. The exclusion of CKD patients for this reason may make sense for Phase I and Phase II trials but not for larger interventional trials. Furthermore, most studies that exclude patients with CKD not yet on dialysis are using drugs such as beta-blockers and statins that have been used safely in studies of dialysis patients. (7) Since patients with CKD may respond differently or not at all to standard therapies, then the inclusion of patients with CKD in trials may result in a decrease in the observed treatment effect and bias towards the null hypothesis. However, this hypothesis has never been proven and should at a minimum be tested in clinical trials before patients with CKD are excluded. The intricate nature of managing care in CKD patients may also result in some physicians neglecting to refer their patients to research studies as a result of not wanting to give up control of their complex care regimens. (8) This may be especially true in the case of CKD patients since they are often taking a plethora of medications for their various comorbidities and altering these medications can require careful titration.

Lack of approved surrogate endpoints for kidney disease progression

Another challenge for researchers conducting trials in CKD is the lack of clinically defined and FDA approved surrogate endpoints for kidney disease progression. Since CKD is often asymptomatic until it reaches late stages, testing therapies to slow the progression of CKD has been challenging. Currently, the FDA accepts a large change in estimated glomerular filtration rate (eGFR) (e.g. doubling of the serum creatinine level) as an endpoint for the development of kidney failure in clinical trials. While a doubling of serum creatinine certainly may be highly predictive of development of kidney failure, it is often a late event in CKD and takes a long time to develop. Consequently, trials must be conducted for a long period of time and the therapies may not be successful in the later stages of CKD. Hence, industry has been very reluctant to engage in drug development for the CKD population

because of the amount of time it takes patients to reach the endpoint required for FDA approval. This has focused attention on considering alternate endpoints for kidney disease progression to shorten the trial time and extend their application to patients in earlier stages of CKD. In 2012, members of the FDA and the National Kidney Foundation held a scientific workshop to examine data supporting new definitions of eGFR decline. The workshop planning committee recommended a 30-40% decline in eGFR as a new surrogate endpoint for clinical trials in CKD and the FDA is now currently considering this definition. This new definition could be used for both drugs and devices and could potentially make new therapies available to patients sooner.

Institutional Review Boards

Federal regulations govern research involving human subjects. Many investigators may view institutional review boards (IRBs) as a substantial obstacle for conducting research in the CKD population, but they are essential to ensure participant safety. Due to the complexity of CKD, especially in the advanced stages, close medical monitoring and adverse events require extra time for reporting as well as follow-up. Adverse events can both interrupt and interfere with study treatment procedures and outcomes, which may lead to participant withdrawal from a project. The numerous requirements of review boards and institutions can significantly delay trial initiation and such delays only increase the time cost of a trial as well as decrease the overall efficiency. (9) Multiple IRBs are often involved in large multi-center trials and IRBs reviewing the same protocol may impose different requirements. For example, IRB requirements for contacting potential research subjects at different sites can affect participation rates. An IRB at one institution may allow release of subject information without the subject's advanced permission whereas other IRBs require advance written permission from the subject. Hence, the response rate for the study may vary widely by contact mode which poses a threat to study validity. (10)

While the IRB process may be frustrating it is necessary for the protection of the human participants. Investigators need to be familiar with research regulations and the responsibilities of the IRB. IRBs and investigators need to work together and have open communication. IRBs should engage in outreach to the investigators through an "open door policy" and educate investigators about the underlying ethics and regulations of the research. Increased awareness of issues can help IRBs and investigators work together, enhance cooperation and compliance and improve human subject protection. (11)

Cost of Clinical Trials

The cost of conducting clinical trials is another hurdle facing current and potential CKD investigators. The average award given by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) in 2012 was \$403,790. (12) Unfortunately, it has been estimated that the NIH institutes pay research sites 20 to 40% less than the actual cost of conducting the trial. (9) While the cost varies depending on the study (length, intervention being tested, etc.) one study found that the average cost of conducting a clinical trial in an academic medical center was \$12,233 per patient. (13) Data from the NIH website indicates that there is currently less money available for CKD trials. The success rate for the percentage of new NIDDK grants has declined from 21.1% in 2010 to 15.7% in 2012. (14)

Furthermore, the success rate for NIDDK R01 grants has dropped from 27% in 2010 to 19.4% in 2012, with the total amount awarded going from \$243,996,350 to \$150,866,822 (Figure 1). Additionally, the 2013 sequester resulted in the budget for the NIH being cut by \$1.71 billion in comparison to 2012 which equates to a 5% reduction in funding. (15) This resulted in NIDDK's appropriation for 2013 decreasing by \$1.69 billion or 5.68%. (16) With such a high price tag for conducting trials, undertaking a research investigation can appear to be a very daunting task to an already busy clinician.

Patient Barriers to Participation in Trials

In addition to the challenges faced by investigators and study personnel, there are numerous barriers for patients with CKD to participate in clinical trials. Firstly, the percentage of US adults with CKD that are disabled was estimated at 18.3% after adjustments for education, income, and race/ethnicity. (17) In the general population, only 9.9% of US adults aged 16-64 were reported as being disabled in 2009. (18) Even in the presence of other comorbidities that can cause disability, CKD confers a higher likelihood of disability especially among people with lower education levels. (17) Many patients do not drive as a result of their disability and thus the burden of transportation to study visits often falls on the research investigator. If trials are not able to provide free transportation or travel reimbursement of some form, they risk limiting their potential participant pool. Furthermore, patients may need to take time off work to accommodate appointments which may not be economically feasible if they are already reduced to working part time as a result of their disability.

The large quantity of medications taken by the majority of CKD patients may serve as another deterrent to participating in clinical research. It is estimated that the average patient will take 10-12 medications by the time they reach stage 5 CKD. (19) Many medications require multiple doses each day and some patients may be instructed to take medications at each meal. Investigators may face issues with study drug compliance in CKD patients as the study drug may simply be viewed as an unnecessary or avoidable increase to the daily pill burden. In addition to increasing medications, participating in a study increases the number of clinic visits for CKD patients. Many CKD patients are seen by nephrologists on a regular basis and likely also have standing appointments with endocrinology, cardiology, urology, etc. to manage other conditions. More appointments may also be seen as an unwelcome burden to take on in addition to managing the already complex nature of CKD.

Another barrier for CKD patients is language and/or illiteracy which can both lead to lack of understanding research study purposes and materials. (8) The complexity of required study documents such as the informed consent can be a deterrent to study participation, especially if the forms are not in the patient's native language and translation is required. While some patients may have family members who are willing to attend study visits and aid in translating, those who do not may feel uncomfortable asking questions of the interpreter with whom they are provided. In turn, this may prevent such patients from enrolling at all or lead to future withdrawal from a study due to confusion or misunderstanding. The percentage of US adults with CKD who have obtained a high school education was 26.7% from the 1999-2008 NHANES data, (17) which is just below the national average of 28.4%.

(20) Lower educational status may lead to patients not having a clear understanding of a research study or procedures which in turn could result in feelings of fear, distrust, or suspicions toward a project. Unfortunately, distrust and suspicions about research have been perpetuated by the media as the public is often given information regarding accidental exposures of patient information. (8) The general public is likely to remember those cases and never be made aware that the vast majority of research studies are conducted up to high ethical standards.

Many CKD patients are asymptomatic in the earlier stages and may not be aware of their condition. This prevents them from being able to understand the importance of delaying the progression of their disease. As a result, not knowing about their condition also makes them unreachable by advertisement for research participation. Once enrolled, participating in a clinical trial requires patience as outcomes and/or benefits are often not immediate and participants may lose interest if they do not feel they are benefiting. This can lead to issues with study compliance as it is often difficult to motivate individuals to follow a treatment regimen when the regimen is inconvenient, may have side effects, and may not result in a direct benefit to the study participant. (5) From an investigator standpoint, aiming to assess kidney disease progression as an outcome presents the challenge of conducting multi-year studies due to the slow development of the disease.

Solutions

Considering the numerous barriers to conducting CKD research, it is imperative that potential solutions be identified in order for scientific progress to continue in this patient population. The need is further illustrated by the fact that CKD patients account for only 9.8% of the Medicare population but make up 27.6% of total Medicare costs. (21) Various barriers for CKD patients participating in clinical trials could be reduced through increased education of patients and healthcare providers. One approach would be to provide informational study brochures at kidney clinics that highlight the main details of a given project and may be less overwhelming than a study consent form. Patients could take the brochures home to read over with family and then contact the study coordinator for more information. Ensuring that the content avoided complex wording and was also available in common foreign languages (such as Spanish in many areas) would be essential to the success of this technique. Conducting informational sessions with clinic nephrologists and primary care physicians may be helpful to increase participant recruitment as studies have shown one of the most common reasons patients participate in studies is due to the influence of their healthcare provider. (22) Having the principal investigator or research coordinator lay out the purpose of a given project and explain how it may benefit potential participants may enhance the likelihood of clinicians referring their patients to a project. If the provider feels that the study team understands the importance of communicating with them in regards to how participation may impact their patients' care, they may be less hesitant to recommend the project to their patients. Additionally, the current classification system and staging of CKD is helpful in providing a means of communication between providers and investigators. The current system allows investigators to specify a given stage (or stages) of CKD when recruiting which helps providers identify and refer appropriate patients for a project.

Public awareness programs on current CKD trials may also be a way to increase participation in clinical trials. Many physicians and patients are unaware of trials that are currently ongoing. This approach is currently being used in cancer research. The Cancer Trials Support Unit (CTSU) is designed to make enrollment into clinical trials easier. It provides physicians with a single access point to the National Cancer Institutes entire phase III clinical trials system and helps with access to protocols, training and educational information. Another public awareness program, Project IMPACT, is a program of the National Medical Association whose goal is to encourage greater participation of African Americans in clinical trials. Project IMPACT provides educational materials to patients and physicians regarding biomedical research and clinical trials. Similar public awareness programs for CKD research may be useful for increasing patient recruitment. Researchers should also consider starting CKD registries of patients willing to participate in clinical trials. This has proven to be successful in other fields including cancer research. Researchers are also turning to social media sites to educate patients about the value of clinical research and encouraging them to participate in studies.

Increasing convenience to study participants will not only assist in recruitment but also in retainment of study participants. Providing transportation or travel reimbursement of some form to participants in CKD research projects could help increase participation in disabled or low income patients who would not have means of getting to and from study visits. Providing free parking and providing flexible appointment times will also result in greater patient participation. Additionally, online, written or telephone medication schedules with reminders could be used to help mitigate the increasing pill burden on CKD patients.

It is essential that investigators find ways to cut costs for both current and future projects to address the reduced funding opportunities and lower award amounts of recent years. If the FDA accepts the new definition of GFR decline this may result in a 25% reduction in the cost of clinical trials. Furthermore, industry may be more likely to invest in clinical trials in patients with CKD. Working to integrate bench-top and bedside research is another important goal for advancing CKD research. The NIH has started the Clinical and Translational Science Awards program to accelerate the process of translating laboratory discoveries into treatments for patients. The program aims to provide resources and infrastructure to support the entire spectrum of translational research and increase communication between basic and clinical researchers. Additionally, providing incentives for individuals to pursue and maintain careers in clinical research should be an aim of organizations and academic institutions. Data from the NIH indicate that resources have become more equitable between basic and applied research from 2002-2014 but trends still favor basic science research. (23) Janet Woodcock, director of the FDA's Center for Drug Evaluation and Research, envisions a future where a permanent network of resources including investigators, support staff and research sites would be available to anyone conducting scientific inquiries in health care. (24) She goes on to state that such a network of resources would be provided with constant funding through contracts as opposed to grants and would be permanent. For such a future to be possible, partnerships between various industry and government agencies would need to be formed.

Conclusion

The CKD population continues to grow and patients with CKD have an incredibly high rate of cardiovascular morbidity and mortality. Many therapies in this group of patients remain unproven and more clinical trials are desperately needed. Successful research in this patient population requires collaboration between investigators, healthcare providers, patients, industry and the NIH. Research in this important patient population is possible and we as healthcare providers should feel an ethical responsibility to establish the efficacy of available therapies in these patients.

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Clinical summary

- Conducting research in CKD patients involves facing numerous barriers on both the investigator and patient's behalf.
- Providing informational study brochures and administering informational sessions at kidney clinics can help educate CKD patients about current research opportunities.
- Organizing public awareness programs and creating a CKD research participant registry for interested patients are two potential means of increasing enrollment into CKD trials.

Figure 1.
Total Amount Awarded for NIDDK R01 Grants from 2010-2012

Table 1

Barriers to research in CKD patients

Investigator barriers	Patient barriers
CKD patients have multiple comorbidities making them a risky target	CKD patients have greater prevalence of disability
Lack of approved surrogate endpoints for kidney disease progression	High pill and clinic visit burden to manage CKD
Low GFR may alter the safety profile of some drugs and devices	Language or illiteracy complicate understanding of research purposes and study materials
Requirements of Institutional Review Boards	Asymptomatic nature of CKD in early stages
Cost of conducting clinical trials	Transportation barriers
Difficulties with patient recruitment	