Advancing Treatments for Chronic Kidney Disease and Rare Renal Disorders in Adults and Children: Trends and Opportunities

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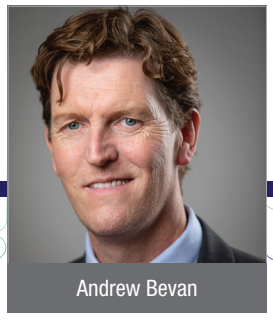
Introduction

Chronic Kidney Disease (CKD) awareness dates to 400 BC when the Greek physician Hippocrates, considered the "Father of Medicine," reported *"When bubbles settle on the surface of the urine, they indicate disease of the kidneys, and that the complaint will be protracted."*

CKD is defined as abnormalities of kidney structure or function present for greater than three months.[1] The etiology of CKD is varied and complex, with diabetes and hypertension responsible for two-thirds of adult cases, and other conditions such as glomerulonephritis, inherited diseases (e.g., polycystic kidney disease), congenital anomalies of the kidney and urinary tract (CAKUT), and certain autoimmune diseases (e.g., lupus nephritis) making up the remaining third. In children, congenital disorders, including CAKUT and hereditary nephropathies, are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responsible for about two thirds of all cases of CKD in developed countries, while acquired causes predominate in developing countries.[2]

CKD is common in adults, with approximately 700 million people affected worldwide in 2017 (9.1% of the population). CKD prevalence has increased 29.3% since 1990.[3] In countries with a low to middle socio-demographic index (SDI), where renal replacement therapy (RRT) is not available or dialysis is inadequate, patients typically die during CKD progression to end stage renal disease (ESRD) due to cardiovascular comorbidities such as coronary artery disease, or within months of reaching ESRD.[3]

In children, the prevalence of kidney disease ranges from 15 to 74.7 cases per one million children[2] making it extremely rare. Kidney disease can affect children in several ways, ranging from treatable disorders without long-term sequelae to life-threatening conditions. Data from the North American Pediatric Renal Trials and Collaborative Studies (NAPRTCS) shows a progression rate from CKD stage II to IV to ESRD of 17% at one year and 39% at three years, with the median time to ESRD of four and a half years. Furthermore, age-specific mortality in children with ESRD is about 30 times greater than children without ESRD.[4]

Children with CKD face many challenges, such as negative self-image, behavior and learning problems, delayed language and motor skills development and delayed growth rate compared to their healthy peers. Kidney disease in children can be caused by birth defects, hereditary disease, infection, nephrotic syndrome, systemic disease, trauma and urine blockage or reflux. The causes of ESRD in children are correlated to age range. For example, birth defects and hereditary disease are the leading causes of ESRD from birth to the age of 4. Hereditary disease, nephrotic syndrome and systemic disease are the leading causes between the ages of 5 through 14. Glomerular disease is the most common cause between the ages of 15 and 19.

A recent Guidehouse[5] analysis of the nephrology market identified several key factors, including high unmet need, ongoing evolution (simplification) of endpoints and faster approval tracks, that make nephrology an interesting development opportunity for the pharmaceutical industry. These factors have contributed to a general increase in clinical development activities in nephrology, as evidenced by a doubling in the number of Phase I and II nephrology studies from 2017 to 2020. The industry's sparked interest in nephrology studies could lead to a surge in new treatments in the coming years.

Given the renewed interest, we assessed metadata from Clinicaltrials.gov and publications from Pubmed.gov to characterize clinical research trends in CKD over the last 20 years, and possibilities for future trajectories for treatment. We compared two 10-year time periods (2002 to 2011 and 2012 to 2021) in terms of numbers of studies, study phases, study populations, type of interventions, endpoints investigated, and research published.

Methods

We searched Clinicaltrials.gov for interventional or observational studies of drugs or biologicals containing the terms "Chronic Renal Failure,""Chronic Renal Disease,"r "Chronic Kidney Disease," or "Chronic Renal Insufficiency" with a first posted date between 01-Jan-2002 and 31-Jan-2021. Our search criteria excluded expanded access studies, medical device studies, and studies containing the terms "End Stage Renal Disease," "End Stage Renal Failure," "End Stage Kidney Disease," "Renal Replacement," "Acute Kidney Failure," "Acute Kidney Injury," "Acute Renal Disease," or "Acute Renal Failure, which were topics outside of the scope of this paper."

Our search resulted in 1038 total records, of which 194 were excluded due the primary study intervention being either behavioral, procedural, diagnostic, a dietary supplement or "other." The 844 studies that were included in the analysis were divided into two time periods. Period one (P1) contained all studies with a first post date from 2002 to 2011. Period two (P2) contained all studies with a first post date from 2012 to 2021. Studies in the two groups were analyzed by study phase, population type, type of intervention and funding to identify potential differences and trends between the two periods.

In addition, we searched Pubmed.gov for published clinical trials containing the Medical Subject Headings (MeSH) Major Topic "Chronic Kidney Disease" over the same period as above. This returned 5,158 records, which were also divided into two time periods and evaluated by population type.

Results

Development Phase and Population Type

There was a 54% increase in the number of studies in P2 (512) compared to P1 (332). The most marked increase was in early phase studies (Phase I-II), which increased by 132% (209 vs. 90) (see Figure 1A), representing a more than two-fold increase in the average number of studies per year (see Figure 2). This was double the increase in the total number of Phase I-II studies registered in Clinicaltrials.gov across in the same period, which increased by 62%. The overwhelming majority of studies were in adult CKD populations (P1 - 88%, P2 - 91%). The absolute increase in studies that included pediatric populations between the two periods was small (P1 - 39, P2 - 47) (see Figure 1B).

Figure 1. Clinical Study Distribution by A) Development Phase and B) Population Type

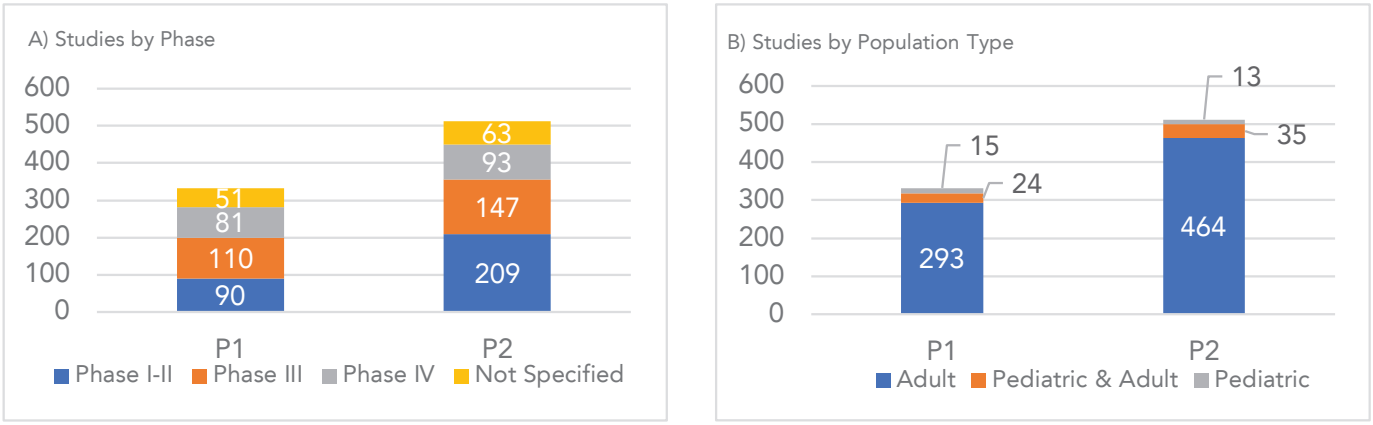
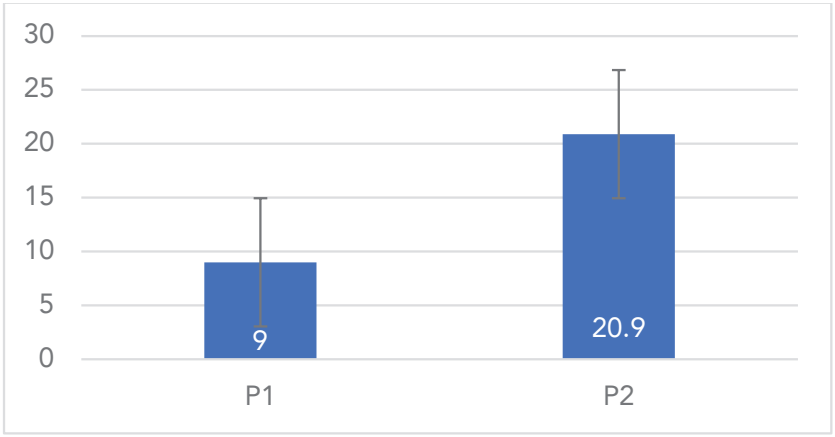


Figure 2. Average Number of Early Phase Studies



Error bars represent the Standard error of the mean (SEM)

Funding and Interventions

The number of industry funded studies increased by 32% in P2 vs. P1; however, there was a marked increase in the number of non-industry funded studies, which doubled (see Figure 3A). This finding may be an indicator of an increase in basic science conducted in academia that may translate into a further increase in future industry sponsored research. We evaluated studies by intervention type (drug or biological) (see Figure 3B) and found that drugs represented 99% of study interventions in P1, with only two studies of biologicals during that period. In comparison, although the number of studies investigating drug intervention was >90% in P2, there was a 19-fold increase in the number of studies investigating biological interventions (39). This is consistent with the growing number of investments and development of biological medications, which are forecasted to overcome sales of "standard technology" products in the next five years and are best designed to precisely target complex biological pathways in disease pathophysiology.[6]

Figure 3. Clinical Study Distribution by A) Funding Source and B) Intervention Types

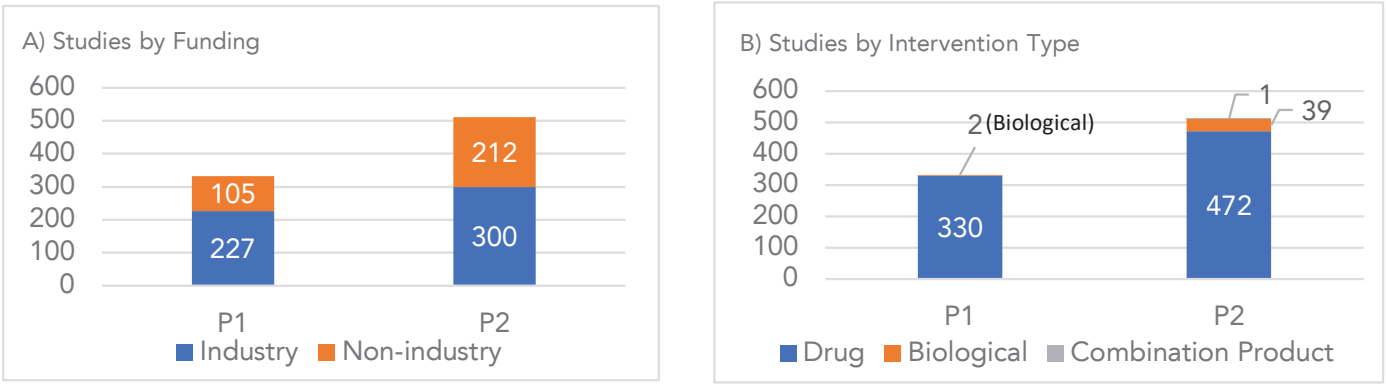
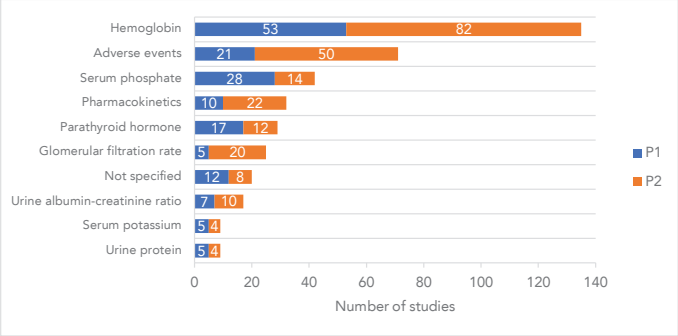


Figure 4. Top 10 Primary Outcome Measures – Industry Sponsored Studies



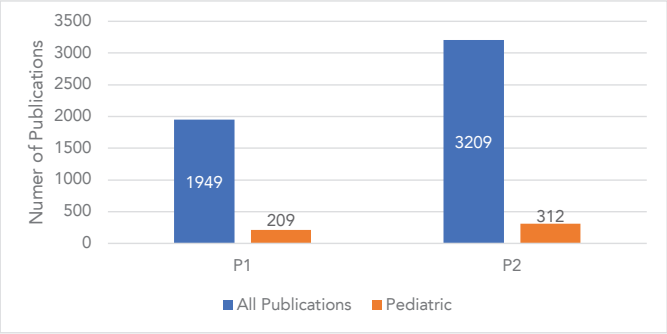
Primary Endpoint Measures

We evaluated the top 10 primary outcome measures in industry-sponsored studies (see Figure 4) and found that hemoglobin (Hb) was the most frequently evaluated measure over the last 20 years. There was a 55% increase in the number of studies investigating the effects of interventions on Hb in P2 compared to P1, which reflects the increased interest in the study of CKD-associated anemia. There was also a 72% increase in the number of studies evaluating adverse events as the primary outcome measure, which reflects an increase in the number of interventional open-label extension studies to primarily assess safety.

Clinical Trial Publications

The number of clinical trial publications increased by 65% in P2 (3,209) compared to P1 (1,949) (see Figure 5). The number of clinical trial publications involving pediatric populations also increased in P2; however, as a proportion of the whole, they were slightly reduced from 11% to 10%.

Figure 5. Distribution of Clinical Trial Publications in CKD



Discussion

Until very recently there had been no significant changes to the treatment of CKD for more than two decades. Antihypertensives, specifically renin-angiotensin-aldosterone system inhibitors (RAASis), have formed the cornerstones of treatment and although these drugs can slow disease progression, they do not prevent many individuals from progressing to ESRD. This highlights the need for more varied and effective treatments to better manage CKD and potentially halt its progression. Our data provides clear evidence of increased clinical research activity in CKD in the last 10 years, which ushered a new era in treatment (as evidenced by recent approvals by the FDA and other regulatory bodies) of drugs such as the sodium-glucose co-transporter-2 (SGLT2) inhibitor dapagliflozin[7] and mineralocorticoid receptor antagonist (MRA) finerenone.[8]

Furthermore, there have been intensive efforts to develop new treatments for common complications associated with CKD. One example is the development of hypoxia-inducible factor prolyl hydroxylase inhibitors (HIF-PHIs) for the treatment of CKD-associated anemia, such as roxadustat, which has been approved in Japan and the European Union (EU), and daprodustat, which has been approved in Japan and is currently under review by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA). The marked increase we found in studies evaluating Hb as the primary endpoint reflects this effort. However, the development of drugs in this class have not been without challenges. For example, the FDA declined marketing authorization for two drugs in the past year on safety grounds, underscoring the fact that the path to commercialization is by no means certain. There are also several biologics emerging that are under investigation or recently approved for the treatment of specific glomerulonephritis or CKD associated conditions, including:

- **Belilumab (Benlista®):** recently approved for the treatment of lupus nephritis[9]
- **Obinutuzumab (Gavaza®/Gazyvaro®):** under investigation in Phase III for the treatment of membranous nephropathy and lupus nephritis[10]
- **Ziltivekimab:** has shown the ability to markedly reduce inflammatory biomarkers of atherosclerosis in patients with chronic kidney disease and high cardiovascular risk[11]
- **Narsoplimab:** has been granted Breakthrough Therapy and Orphan Drug designations by the FDA, and Orphan Medicinal Product designation by the EMA for the treatment of IgA nephropathy (IgAN)[12]

In addition, there are novel small molecule therapies under development. Atrasentan, a potent and selective inhibitor of the endothelin type A (ETA) receptor, is under investigation for the treatment of IgAN and other proteinuric glomerular diseases. Advanced therapy medicinal products (ATMPs) such as stem cell therapies[13] are also being explored. If these products are successful, they will add to the arsenal of options available for nephrologists to more effectively treat autoimmune and rare renal diseases with high unmet needs.

While it is encouraging to see the increase in the development of new treatments to help the inflating population of CKD patients, this increase also brings new considerations for drug developers. Expanded exploration of new therapies means expanded competition. Companies will need a strong evidence generation plan based on answers to these questions:

- What does the competitive landscape look like in this development area?
- Where is the unmet need that we can address to differentiate our product from others on the market or in development?
- How do we design our studies to be patient-focused to increase patient recruitment and retention?
- If pursuing a cell and gene or other advanced therapeutic, what unique challenges might we face that we should consider in our planning?
- What real-world evidence will we need for regulatory approval? For health technology assessment (HTA) bodies and payers?
- Are there ways to optimize our evidence generation to avoid costly delays in approval or access?

Identifying and answering questions like these in early planning can be instrumental in moving your product forward faster and increasing your competitive edge. Experienced experts in CKD can provide guidance on the right scientific methodology needed, how to address specific challenges that renal patients face that could make participation in trials challenging, and global recruitment strategies to engage the right patients needed for your study. Established relationships with large dialysis organizations who can provide support in accessing real-world data resources, as well as identifying patients and sites, is also helpful and can greatly accelerate start-up timelines.

Pediatric CKD

The development of more targeted therapies has the potential to transform the treatment of CKD in children. However, our results did not reveal an increase in research activity in pediatric CKD over the last 10 years. The approach to the treatment of CKD in children broadly follows the same approaches used in adults i.e., RAASis and diuretics to treat kidney disease resulting in high blood pressure, and corticosteroids and immunosuppressive agents to treat nephrotic syndrome and systemic diseases that affect the kidneys (e.g., vasculitis). However, these traditional approaches have limited use and may be restricted in children due to different etiology and/or insufficient data. Therefore, it is imperative that we start to see efforts to expand treatment for children. There is some evidence that this is occurring for hereditary kidney diseases such as autosomal dominant polycystic kidney disease (ADPKD), where a Phase III trial of Tolvaptan (Samsca®), approved for the treatment of in adults, has just completed in a pediatric population,[14] and a Phase II trial of sparsentan, a first-in-class, dual-acting antagonist of endothelin type A (ETA) and angiotensin II subtype 1 (AT1) receptors, which is starting in Phase II in pediatric patients with proteinuric glomerular diseases.[15] These efforts are encouraging and represent a much-needed step forward in the advancement treatment of pediatric CKD, where the level of unmet need is high.

There are, however, inherent challenges with pediatric studies, so engaging with a partner who understands those unique needs across all stages of development. For more information on pediatric drug development, please see "Pediatric Drug Development: Trends and Perspectives in the European Union".

Finally, understanding the requirements and challenges presented by studying novel therapies in children, who commonly suffer with rare disease conditions, is essential for the successful label expansion to pediatric populations. For additional insights on this topic, please read our white paper "Advancing Rare Disease Treatments in the COVID-19 Era and Beyond: Challenges and Opportunities."

Conclusions

CKD has reached epidemic proportions in adults and although rare in children, the causes of CKD can be severely life-limiting. Traditional treatment options do not adequately cover the wide spectrum of diseases that cause CKD. Over the past 20 years there have been increased efforts to expand treatment options, which is reflected in a more than 50% increase in the number of CKD clinical studies in. However, these efforts have been primarily focused on adult CKD, where novel drugs and biologics are entering the market. The level of unmet medical need is arguably the greatest among pediatric CKD. However, there are some glimmers of hope on the horizon with the development of some existing adult therapies in children and some first-in-class molecules and stem cell therapies that may help to treat children with rare renal disease.

As new opportunities arise and new therapies enter development, those glimmers of hope will expand. Early planning, engagement with experienced partners in the CKD space, and consideration of pediatric options in conjunction with adult therapies can all play a role in illuminating new options for patients suffering with CKD.

For more information, please contact us.

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