Improving the Involvement of People with Kidney Disease in Cardiovascular Trials

By Meaghan Allain and Zach Cahill

People with kidney disease are medically complex, and kidney disease may have an impact on the development of therapies to treat the many comorbidities affecting this population. Cardiovascular disease is a common and significant comorbidity among these patients, and individuals with kidney disease make up a sizeable proportion (30% to 60%) of patients with cardiovascular disease (1, 2). Yet, patients with kidney disease have often been excluded from cardiovascular clinical trials (1–4), thus limiting the evidence to guide treatment recommendations of cardiovascular disease for these patients.

The Kidney Health Initiative (KHI) is a public–private partnership between the American Society of Nephrology and the US Food and Drug Administration that focuses on catalyzing innovation and the development of safe and effective patient-centered therapies for people living with kidney diseases.

A KHI workgroup investigated the underrepresentation of people with kidney disease in cardiovascular clinical trials, with a particular focus on those with advanced kidney disease (stage 4 chronic kidney disease and kidney failure), and it identified potential solutions to addressing the barriers to their involvement.

"The project was executed by a diverse, international workgroup representing each stakeholder group involved in the issue," said Charles Herzog, MD, KHI project co-chair. "We used a polling mechanism and a workshop to compile recommendations on the conduct of cardiovascular clinical trials from experts in clinical trials and people with cardiovascular disease and kidney disease, and their care partners."

The workgroup discovered several challenges with involving people with advanced kidney disease in cardiovascular clinical trials, some of which may be more specific to cardiovascular clinical trials (e.g., lack of patient awareness of cardiovascular disease, need for additional work on appropriate cardiovascular endpoints), whereas others may apply more generally to clinical trials involving this population.

Given the safety risks and concerns that involving people with advanced kidney disease may potentially affect the efficacy results, a compelling business case must be made to justify their involvement, and the use of regulatory and financial incentives may help to mitigate risk. Additionally, the design and implementation of clinical trials can be adapted to address the safety and efficacy concerns about including this population.

More broadly, the workgroup highlighted the need for closer collaboration between nephrologists and cardiologists and the need for more systemic change within the nephrology community to prioritize the engagement and enrollment of patients with kidney disease into clinical trials. Despite the inherent advantages of the kidney disease population for clinical trials, such as a data-rich environment and regular contact with clinicians, nephrology lacks an "on-study" culture in which discussing clinical trial participation with people receiving dialysis or experiencing progression to kidney failure is the norm.

"Kidney care professionals need to lead the way in transforming the culture of kidney care into one that prioritizes clinical trials," said Julie H. Ishida, MD, MAS, KHI project co-chair. "It will take leadership from nephrologists, collaboration with other specialties, and engagement with our patients to elevate the importance of clinical trials within our community."

Today, the kidney community is experiencing a new level of investment in novel therapies from pharmaceutical companies. Nephrologists need to take the lead in educating themselves and communicating the value of cardiovascular and other clinical trials to their patients and colleagues. There are many concrete actions the kidney community can take to empower nephrologists to lead in this area. Institutions, societies, and government can provide funding for trials, training in trial design and conduct, and educational resources about clinical trials for patients and care partners. Specifically, for cardiovascular trials, cross-specialty collaborations between cardiologists and nephrologists should be encouraged to improve patient enrollment and trial design and implementation. It will take all the players in the kidney community, including patient organizations, subspecialty societies, healthcare organizations, research sponsors, and dialysis providers, working together to change the culture and create an environment that prioritizes clinical trials.

There are many contributors to the underrepresentation of people with advanced kidney disease in cardiovascular clinical trials, and building a compelling business case and adapting the design and conduct of clinical trials to facilitate their involvement are important. More fundamentally, cultivating an "on-study" mindset within the nephrology community and prioritizing the participation of both physicians and patients in clinical trials will help ensure that the appropriate treatment recommendations can be made for people with kidney disease for cardiovascular and other indications. ■

Meaghan Allain is a senior project associate at the Kidney Health Initiative. Zach Cahill is a marketing and communications specialist at the Kidney Health Initiative. niversity of Rochester, Rochester, New York.

References

1. Coca SG, et al. *JAMA* 2006; 296:1377–1384.
2. Charytan D, Kuntz RE. *Kidney Int* 2006; 70:2021–2030.
3. Konstantinidis I, et al. *JAMA Intern Med* 2016; 176:121–124.
4. Maini R, et al. *JASN* 2018; 29:2782–2786.

Transplant Care Transformed in the Face of COVID-19

By Bridget M. Kuehn

As New York City hospitals braced for a potentially overwhelming surge of COVID-19 cases, Columbia University Medical Center nephrologist Sumit Mohan, MD, MPH, and his colleagues had to transform the way they provided kidney transplant care.

"We put a pause on nearly all kidney transplants," said Mohan, an associate professor of epidemiology and medicine at Columbia University. All elective procedures were put on hold to free up space and ventilators for a surge of COVID-19 patients. For kidney transplant patients with living donors, they decided it was safer to postpone surgeries to prevent donors or immune-suppressed recipients from becoming infected with SARS-CoV-2 in hospitals with large numbers of COVID-19 patients. They concluded that the risks were also too high for most recipients of deceased donors' kidneys, who in addition to being at risk of infection while immunosuppressed could also experience infection transmission from a donor organ, particularly given the severe shortage of tests for the virus in the early days of the pandemic.

"We inactivated the majority of patients on our kidney transplant list," he said. Only a small subset of patients who are highly sensitized and unable to accept 99% of donor organs were kept active in case a rare compatible organ became available.

"Our clinics were essentially emptied out except for a small set of urgent visits, Mohan said. "Whatever didn't need an in-person visit became a telemedicine visit."

Drawing from experience

To care for kidney transplant patients who became infected with SARS-CoV-2, Mohan and colleagues drew on the experience of collaborators from Northern Italy. Their Italian colleagues were seeing large numbers for transplant recipients hospitalized, a high rate of acute kidney injury, and an influx of kidney failure.

"That conversation alerted us to the need to start preparing," Mohan said.

Infectious disease specialists also helped by tapping their past experiences with respiratory infections and previous coronavirus outbreaks. Jay Fishman, MD, director of the Transplant Infectious Disease & Compromised Host Program at Massachusetts General Hospital, explained that transplant patients typically have more severe, prolonged symptoms of respiratory infections like pneumonia. Such patients also experienced more severe disease during outbreaks of the Severe Acute Respiratory Syndrome and Middle East Respiratory Syndrome, which are also caused by coronaviruses.

To help transplant patients fight COVID-19, Mohan and colleagues developed a standardized approach, the cornerstone of which included reducing patients' immunosuppression (1). This is a common tactic in helping transplant patients fight infection, Fishman noted.

"We are always balancing immunosuppression against the risk of infection," Fishman said. "That's where we live."

But COVID-19 can trigger an excessive immune response, and inflammation has added a challenge. Fishman noted that there is some question about whether immunosuppressive drugs may protect transplant patients against COVID-19–linked inflammation, but no one knows for sure. "We've taken a middle ground where we turned down immune suppression, but we don't want rebound inflammation to occur," he said.

With all our decision-making, "we were trying to be as systematic and data-driven as we could be in the chaos, and everyone understood that this was an all-hands-on-deck approach," Fishman said.

Fishman said he hopes programs will be able to take what they have learned from COVID-19 to help improve transplant patient care even after the pandemic ends. As examples, he cited greater use of telehealth, reductions in unnecessary testing, more rapid testing therapies through collaborations across the country, and better use of electronic medical record data.

"All of these things are things that we've learned, it would be a shame not to build on them for our patients in the future," Fishman said. ■

Reference

1. The Columbia University Kidney Transplant Program *JASN*. April 2020. https://doi.org/10.1681/ASN.2020030375