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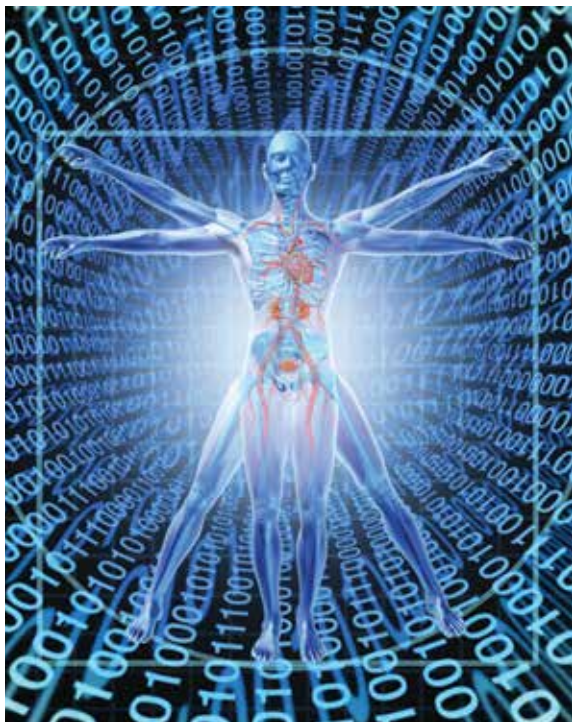
FDA Looks to Increase Role of Real-World Evidence in Regulatory Decisions

By Eric Seaborg



As the COVID-19 pandemic shows no sign of abating and healthcare providers struggle to find effective treatments, valuable information is accumulating in electronic health records (EHRs). Researchers used this information—in observational studies—early in the pandemic when an alarm was raised that blood pressure medications based on renin-angiotensin system inhibition posed a theoretic threat to COVID-19 patients. Studies that mined EHRs found no signal of harm to patients who continued to take these medications. Expert guidelines quickly reflected this.

Clinical trials are difficult to run during a pandemic, making the information from EHRs and other forms of real-world data (RWD) poised to play a more prominent role in the age of COVID-19.

Could this kind of information even be used to create virtual clinical trials? That's a question the US Food and Drug Administration (FDA) has been grappling with since the passage of the 21st Century Cures Act in 2016.

That law requires the FDA to use real-world evidence (RWE) in its regulatory decisions, including approval of new indications for previously approved drugs. These new indications can gain approval through a more streamlined process because the agency assumes that the clinical trials for the original approval established the drug's safety.

From data to evidence

In December 2018, the agency published a "Framework for FDA's Real-World Evidence Program" that distinguishes between RWD and RWE: "RWD are data relating to patient health status and/or the delivery of health care routinely collected from a variety of sources. RWE is the clinical evidence about the usage and potential benefits or risks of a medical product derived from analysis of RWD."

The framework says that RWD can come from a variety of sources, including EHRs, claims and billing activities, product and disease registries, patient-generated data, and data from sources such as mobile devices.

Randomized clinical trials (RCTs) remain the criterion standard for evaluating new drugs and treatments, but

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Challenges Revealed by Pandemic May Drive Innovation in Medicine, Kidney Care

By Bridget M. Kuehn

As former assistant secretary for preparedness and response at the US Department of Health and Human Services, Nicole Lurie, MD, MSPH, has learned that the key to a successful crisis response is having a plan and strong day-to-day systems in place before disaster strikes.

"If your day-to-day system is strong, you are going to do better than if it is not—coronavirus 2019 (COVID-19) is no exception," Lurie said during the Kidney Week 2020 Reimagined session "Policy in a Post-COVID World." Lurie gave the Christopher Blagg, MD, endowed lecture in Kidney Diseases and Public Policy during the session. She co-chairs the ASN's Emergency Partnership Initiative.

Although the lack of a national plan has hindered the COVID-19 response, Lurie said disaster planning for dialysis patients by dialysis organizations and the American Society of Nephrology (ASN) has helped the nephrology community rapidly respond to the high rates of acute kidney injury in COVID-19 patients. Some governors and local leaders have provided "exemplary leadership," and frontline caregivers and institutions like academic medical

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Inside

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Real-World Evidence

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they have limitations:

1. Because of their necessarily small size, they can miss rare side effects. If a side effect occurs in only one patient in a thousand, there might be only two or three reports in an RCT with 3000 participants. But if the drug is approved and used widely, there may be hundreds of reports of the side effect. The analysis of EHRs or insurance claims can often identify the association.
2. Clinical trials take place under idealized conditions, with patients supervised to ensure they not only take the drug but do so at the correct dosage and on schedule. Patients left to themselves have lots of reasons for not taking their drugs as prescribed. RCTs can show how well a drug can work, but RWD can show how likely it is to work in the hands of the average patient.
3. RCTs lack diversity in enrollment, with people of color often underrepresented, which could be particularly insidious given the demographics of kidney diseases. RWD can certainly overcome this.

Testing virtual RCTs

RCTs are also very expensive to conduct, so one first step the FDA is studying is whether RWE can be used to facilitate approvals of new uses for approved drugs. Obviously, a brand-new drug candidate has no track record, but after approval, can researchers sift through thousands, even millions, of patient records to find well-matched participants to run a virtual clinical trial?

The FDA has launched a pair of ambitious projects to test this possibility, according to David Martin, MD, associate director for RWE analytics at the FDA's Center for Drug Evaluation and Research: "One such project, RCT Duplicate, is attempting to duplicate the results of recently completed clinical trials using RWE studies. Approximately 40 trials have been identified for potential duplication. Another 10 ongoing trials will be duplicated before the clinical trial results are reported. A separate project with the Yale-Mayo CERSI will attempt to duplicate several more trials using medical claims and electronic health record data. This work may increase or decrease confidence in the validity of noninterventional RWE, and it may also suggest which techniques are best aligned with different types of drug effectiveness questions."

For the RCT Duplicate (https://www.rctduplicate.org/) project, the FDA has contracted with Boston's Brigham and Women's Hospital and with Aetion, an RWE analysis company founded in 2013, according to company cofounder Sebastian Schneeweiss, MD, ScD. Schneeweiss is also professor of medicine and epidemiology at Harvard Medical School and chief of the division of pharmacoepidemiology at Brigham and Women's Hospital.

The first of the ongoing trials projects was to predict the outcome of the CAROLINA trial, an RCT to compare major adverse cardiovascular outcomes in patients with type 2 diabetes taking the dipeptidyl peptidase-4 inhibitor linagliptin versus patients taking the established sulfonylurea glimepiride. The challenge for Schneeweiss' team was to mine insurance claims data to predict the outcome of the CAROLINA trial before its results were published.

Schneeweiss and his team registered a protocol at clinicaltrials.gov, submitted their article to *Diabetes Care* months before the CAROLINA trial findings were published, and presented their predictions at the American Diabetes Association shortly before the CAROLINA findings were unveiled.

The RWE findings were "spot on" to the RCT findings, Schneeweiss said. "We came to the conclusion that there is no difference in the cardiovascular risk between linagliptin and glimepiride, but we also found that there is a substantial benefit of linagliptin with regard to avoiding hypoglycemic events, he said." So that is the exciting example of how real-world evidence may work at its best."

Dangers of misuse

It is not difficult, however, to find examples of RWE not at its best, when researchers use RWD to come to questionable conclusions. For example, the goal of the CVD-REAL study was to use RWD to extend the findings of the clinical trials of sodium-glucose cotransporter-2 (SGLT2) inhibitors in patients with type 2 diabetes, comparing them with "other glucose-lowering drugs." The CVD-REAL study claimed that SGLT2 inhibitors were associated with a decrease in all-cause mortality that was inconsistent with the findings of the RCTs and so large as to be "unrealistic," Schneeweiss said. An outside analysis of the results contended that the mortality discrepancy could have arisen from researchers miscounting the SGLT2 patients' survival time in an effect known as immortal time bias (also known as survivor treatment selection bias).

One of the RAS blood pressure medication studies illustrates an even more insidious potential danger. The *New England Journal of Medicine* retracted a study that claimed to be an analysis of a large database when the company that provided the alleged dataset would not release the raw data to third-party auditors. Schneeweiss said the situation "is an illustration of what happens if nonexperts who don't understand how you check whether data are real or fake" are involved and of the need for transparency. Aetion's contracts with the FDA allow the agency to check Aetion's data, reproduce Aetion's findings, and do its own repeated analyses with different assumptions.

Well suited for nephrology

In a recent Perspective article in *CJASN* on "EHR-Based Clinical Trials" (1) Khaled Abdel-Kader, MD, of Vanderbilt University, and Manisha Jhamb, MD, MPH, of the University of Pittsburgh, state that "the field of nephrology is uniquely well suited to conduct EHR-based research" because so much relevant information is available in EHRs. They point to the high prevalence of kidney disease, the use of routinely collected biomarkers to detect acute kidney disease and chronic kidney disease, the routine capture of kidney disease risk factors in EHRs, and the use of a common EHR product by the organizations that provide dialysis services.

The authors write that the "nephrology community has been vexed by the dearth of RCTs" but that RWD could be used to overcome this deficit. They note that the Isotonic Solutions and Major Adverse Renal Events Trial used EHR-based enrollment to include nearly 16,000 patients in under 2 years. "EHRs can provide a powerful platform to enroll and randomize patients and deliver interventions, thus lowering the cost and enhancing the feasibility of conducting a clinical trial," they write.

Abdel-Kader told *Kidney News* that the study by Schneeweiss' team represents a cardiovascular disease "safety study, not a study to examine the effectiveness of a medication. It is an observational, cohort study that hopes through rigorous methods to create results that are akin to a trial. I'm skeptical that observational data will be useful for providing FDA-worthy data on effectiveness (i.e., not just noninferiority or safety) in the near term. My opinion is we are many years from fruition re: using observational data to 'recreate virtual RCTs' and for FDA labels of effectiveness (with the exception of rare diseases)." Another example of RWD in kidney care comes from a *Nature Medicine* article by researchers who mined the records of more than 400,000 patients with type 1 and type 2 diabetes in the IBM Explorys database to produce a better model for predicting diabetes-related chronic kidney disease. The authors contend that their model based on seven factors (age, body mass index, GFR, and concentrations of creatinine, albumin, glucose, and hemoglobin A1c) "outperforms published algorithms, which were derived from clinical study data."

The actual utility of the model remains to be seen, but the huge dataset used and the incorporation of seven measurements easily found in EHRs to create it illustrate the point that nephrology is particularly well suited for the application of RWD.

The FDA is hoping for more engagement from nephrologists in this effort. "It is incumbent that the nephrology community participate in the discussion on the use of real-world evidence and real-world data in drug development, learn from the experiences in other disease areas, and continue to conduct and learn from its own pilot projects," Aliza M. Thompson, MD, MS, and Mary Ross Southworth, PharmD, of the FDA's Center for Drug Evaluation and Research, wrote in a *CJASN* Perspective article (2). "There is widespread recognition that there will be a learning curve and that demonstration projects will play a critical role in defining how and when real-world data and real-world evidence can be used."

That learning process is clearly under way. ■

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Challenges

Continued from page 1

centers also have heroically stepped up to lead, she said.

"Crises can bring out the best in people," she said. "One of the things I've seen with the kidney response and with ASN and frankly in many of our communities is just how much it has brought out the best in people."

Lurie and her fellow panelists say now is the time to start addressing policy challenges like systemic racism, a weakened public health system, and immigration policies that harm international medical graduates who have played an essential role in delivering care during the pandemic.

"Never let a good crisis go to waste," Lurie said. "This is really the time for us to be thinking about the way we want the world to look and the way we want kidney care to look going forward."

Stepping into the void

Panelist Paul Klotman, MD, president and chief executive officer at Baylor College of Medicine in Houston, Texas, and other leaders of academic medical centers have found themselves and their institutions having to step in to fill gaps in COVID-19 information, testing, and policy. "We have had a failure of public health leadership in the country with this pandemic; it's exposed a lot of problems, and as a result many of the academic medical centers have had to step up in ways we never intended," he said.

At Duke University, panelist Mary Klotman, MD, dean of the School of Medicine and vice chancellor for health affairs and chief academic officer for Duke Health, and her colleagues have also stepped in to provide expertise and resources at the local, state, and national levels. Duke's physician's assistant program developed a contact tracing curriculum that allowed students to help support local contact tracing efforts while earning credit. Faculty members have contributed their expertise in science and policy to task forces developing plans to distribute vaccines. They've also created The ABC Science Collaborative (1) to guide schools on reopening, and the Latinx Advocacy Team and Interdisciplinary Network for COVID-19 to share information, educational materials, and resources in Latino communities.

"This type of work is not our normal daily operational work, but it has been so critical to advising our communities on how to move forward and how to do things safely," Klotman said.

Experts from academic medical centers have also stepped up to advise the public, business leaders, and policymakers.

"In the media, many of our faculty have become trusted sources of truth," Mary Klotman said. For example, Mark McClellan, MD, PhD, director of the Duke-Margolis Center for Health Policy, regularly shares his policy expertise on news programs, and Baylor's Peter Hotez, MD, PhD, a leading infectious disease expert, makes frequent appearances to talk about COVID-19 and the national response to it.

Baylor stepped in to make COVID-19 tests, and the chief executive officer of the Texas Medical Center led an effort to pool COVID-19 data from area hospital systems and share it with the public and area leaders to guide local decision-making, Paul Klotman said.

"The biggest failure of the public health systems for this particular pandemic is we did not have access to actionable data," Paul Klotman said. "We started sharing data in real time, and because we were developing all the tests we actually could follow the pandemic and the local effects of the pandemic."

Stepping into these roles has led to some good things as well. Mary Klotman noted that institutions learned they could be much more efficient in getting research and partnerships under way, and they have built trust in their surrounding communities. For example, they opened clinical trial centers in communities hard hit by COVID-19, making it easier for people to participate in studies, and the university plans to keep them open going forward.

"Hopefully, we will use this opportunity to learn and be prepared for the next crisis, which undoubtedly is going to happen," she said.

Envisioning an equitable future

The disproportionate effects of the COVID-19 pandemic on Black and brown communities, and civil unrest over police brutality against Black people have also brought renewed attention to the need to address all forms of racism in the United States, in healthcare and kidney care, panelists said.

"The COVID-19 pandemic has pulled the curtain back on the far-reaching effects of structural racism in this country," said Keisha Gibson, MD, MPH, associate professor and chief of pediatric nephrology at the University of North Carolina, Chapel Hill.

The role clinicians' biases play in contributing to race-based disparities in patient outcomes needs to be addressed, Gibson said. "Every last one of us harbors bias," she said. "It is often unconscious and doesn't necessarily align with intent. We owe it to our patients to not only acknowledge that, but to take steps to measure [our biases] and work hard to prevent their impact on our decision-making and conversations with our patients."

To provide truly antiracist kidney care, Gibson said, research focused on race-based health disparities needs to be held to higher standards. She said that studies focusing on race as a biologic factor should be discouraged and that more research should be done on the role racism plays. For example, the LUMINA study, looking at the role of ancestry in lupus outcomes, found that Latinx patients in the United States fare more poorly than individuals with similar ancestry living in Latin America (2). Similarly, other studies have shown that adjustment for poverty and socioeconomic factors eliminates differences in lupus outcomes in white and Black patients receiving comparable treatment.

"We know that race is a social construct," she said. "Despite this, we continue to conduct, publish, and fund studies that apply significant weight on what is likely a minimal biologic influence of race and that consistently fail to address the impact of what this social construct does enable, and that is racism and bias."

Gibson said it is important to interrogate the origins of the science behind the inclusion of race in estimated GFR equations and other clinical algorithms. She noted that although the intent of such algorithms was to streamline care, that intent may have overshadowed biased assertions, tainting some of the research it was based on.

"All kidney health algorithms and policies that include race need to be reevaluated to interrogate the validity and the potential consequences of perpetuating disparities—largely unintended—and changed accordingly," she said.

She noted that policies that hinder the use of unconscious bias training among federal contractors and at federal agencies may disrupt efforts to address implicit bias in care and research.

Greater efforts are needed to boost diversity in the kidney care workforce, both Gibson and Lurie argued. Immigration and travel policies that harm international students and medical graduates must also be addressed, they said.

"As bad as things are now, imagine how much more devastating our fight against COVID-19 would be if we did not have the critical mass of international medical graduates," Gibson said. "Policies that threaten the ability of these colleagues to train and practice in the United States run the risk of absolutely crippling our critical nephrology workforce."

Regarding the policy challenges that have come into stark relief during the pandemic, Gibson stated: "If we are bold and deliberate in our actions to push these policies, we may find ourselves much closer to solving race-based health disparities, rather than just describing them," she said. ■

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ASN during an UNPRECEDENTED YEAR

The year 2020 brought unprecedented challenges to our nation and world. The emergence of the first pandemic in over 100 years and the social unrest following police killings of Black people required action from many quarters of society—including nephrology.

ASN responded on all fronts, advocating for resources for patients and professionals to improve kidney care during a global crisis and committing to dismantle systemic racism in nephrology and to overcome the barriers social determinants of health impose on kidney care.

ASN pivoted the world's premier nephrology meeting to a fully online environment in order to continue to disseminate vital advances in care, research, and education despite the ongoing COVID-19 crisis.

And throughout 2020, ASN continued to honor the dedication and commitment of the kidney care team by supporting ongoing initiatives and programs.

Expanding ASN Efforts on Diversity and Inclusion

In 2020, ASN organized its efforts related to workforce and training, career advancement, and diversity and inclusion into one staff team: Leadership Development and Culture Change. Additionally, the society expanded its efforts related to diversity and inclusion to include equity, health disparities, and social determinants of health.

ASN's current efforts to support diversity, equity, and inclusion focus on five signature initiatives:

1. Partnering with the Robert Wood Johnson Foundation to fund two ASN–Harold Amos Medical Faculty Development Program Scholars. For nearly 40 years, this program has increased diversity among future leaders in medicine, including nephrology, supporting the research and career development of scholars and future health care leaders from a historically disadvantaged background.
2. Providing travel support for ASN members to attend the National Institutes of Health's National Institute of Diabetes and Digestive and Kidney Diseases' (NIDDK) Network of Minority Health Investigators Annual Workshop. In the past five years, ASN has supported nearly 100 members to attend this valuable program.
3. Exhibiting at the Latino Medical Student Association, Student National Medical Association, American Medical Student Association, and American Physician Scientists Association Annual Meetings.
4. Initiating efforts to support the LGBTQ community through an annual LGBTQ and Allies Members Reception at ASN Kidney Week, sessions at ASN Kidney Week on caring for LGBTQ patients, and editorials on caring for diverse patient populations (such as LGBTQ communities).
5. Expanding demographic data collection for ASN members to include sex and ethnicity. By better understanding its members, ASN will strengthen, target, and increase the likely success of its initiatives to increase diversity, equity, and inclusion as well as address systemic racism.

While ASN is proud of its efforts to date, this commitment is hollow if the society fails to oppose and address racism. ASN must intensify its efforts to achieve equality to reduce the adverse impact of racism, especially on health, health care and innovation, and the health workforce.

During the summer of 2020, the ASN Council unanimously approved a plan for how the society can address systemic racism in nephrology. In 2021, ASN will:

1. Launch the ASN Health Disparities Committee to improve the overall health of the entire population and identify opportunities to address health disparities and influence social determinants of health, particularly in populations at risk for and overburdened with kidney diseases. Additionally, the society will expand the ASN Diversity and Inclusion Committee to include equity.
2. Initiate the ASN Loan Mitigation Pilot Program. In 2021, ASN will fund six applicants, reducing the loan burden for each applicant by $50,000 over three years. Year 1 awards will center on individuals racially underrepresented in medicine.
3. Partner with the National Kidney Foundation (NKF) to reassess the inclusion of race in diagnosing kidney diseases. At press time, NKF and ASN were beginning to draft the task force's initial recommendations.
4. Reevaluate every aspect of the annual process for identifying, nominating, and selecting candidates to run for the ASN Council and be nominated for ASN Lifetime Achievement and Midcareer Awards to ensure diversity, equity, and inclusion.
5. Increase engagement with Historically Black Colleges and Universities to reach potential health professionals, researchers, and scientists who are currently underrepresented in medicine.

To learn more about these efforts and ASN's commitment to antiracism, please contact ASN Workforce and Training Associate Riley Hoffman at rhoffman@asn-online.org.

Responding to the COVID-19 Pandemic

In February, ASN launched the ASN COVID-19 Response Team. The team collaborates on COVID-19 education, recommendations, and support for dialysis facilities and the greater kidney community. The Response Team includes nephrologists, nurse administrators, and a patient representative.

Through the work of four subcommittees (Outpatient Dialysis, In-Hospital Dialysis, Home Dialysis, and Transplant), the Response Team has created a website, presented 14 webinars, published key recommendations, launched a COVID-19 toolkit, and expanded collaborations with key partners outside of nephrology to support professionals and improve patient care.

Partners have included the Department of Health and Human Services (HHS), Office of the HHS Assistant Secretary for Preparedness and Response, the Centers for Medicare & Medicaid Services (CMS), the Food and Drug Administration (FDA), the Department of Defense, the Centers for Disease Control and Prevention (CDC), the American Association of Kidney Patients, NKF, and the ASN Policy and Advocacy Committee.

As the COVID-19 pandemic continues, the Response Team will maintain its commitment to providing the best evidence-based resources and recommendations to the kidney community.

Advocating for Kidney Health

In March, ASN members quickly banded together to identify, advocate for, and implement policies to ensure health professionals have the flexibility and resources to meet the needs of the communities they serve during the COVID-19 pandemic. The murder of George Floyd in May brought the public health crisis of racism into sharp focus. ASN members testified before the US Congress about the intersection of racism and COVID-19 on kidney health, advocated for the Health Equity and Accountability Act, and developed a roadmap for action to address these deep-rooted ills.

ASN's initial 2020 policy priorities continue to be advanced, with ASN members working together to help build a better future for kidney health by:

1. Expanding telehealth services in response to COVID-19 to protect all patients—especially those with kidney failure.
2. Persuading CMS to issue a statement clarifying that vascular access placement and organ transplantation are defined as "essential" during the pandemic.
3. Developing kidney-based COVID-19 recommendations for the federal government, including prioritizing access to testing and personal protective equipment, funding for KidneyX, and equipping dialysis centers for telehealth to allow for transplant evaluations.
4. Opposing White House policies that would have negatively impacted immigration policy, the nephrology workforce, patients, and the nation's research capacity. Ensuring the highest-quality care possible requires a well-trained and diverse workforce, including foreign trained physicians.
5. Increasing home dialysis payments after years of advocacy, with CMS agreeing to use payment policy to support home dialysis as well as overall increases in the monthly capitation payment for 2021.
6. Leading efforts to reform and improve organ procurement procedures and expand the ability of transplant centers to open access to transplantation without undue barriers and penalties.
7. Engaging in refining US payment models to support and help nephrologists succeed in them.
8. Advancing immunosuppressive drug coverage legislation.
9. Supporting the launch of the national "Are You The 33%?" campaign in partnership with NKF and HHS.
10. Securing funding increases for research and innovation to advance the state of kidney care. NIDDK received $2.11 billion in Fiscal Year (FY) 2020. ASN secured $5 million in federal appropriations in FY 2020 for KidneyX.

Transforming Dialysis Safety

NTDS Transforming Dialysis Safety

ASN's partnership with the CDC, Nephrologists Transforming Dialysis Safety (NTDS), encourages nephrologists to take the lead in the cultural change necessary to transform infection prevention in dialysis facilities. Key accomplishments include webinars and recommendations for standardization of blood culture collection for patients receiving in-center hemodialysis, as well as launch of a dialysis care checklist pilot.

In late 2019, NTDS partnered with the leadership of Northwest Kidney Centers to present a Pop-up Kidney Leadership Academy aimed at fostering strong, effective leadership skills for the dialysis facility medical director–nurse manager dyad. In 2020, this Academy was enhanced with a series of six podinars on core leadership concepts.

Collaborating on Diabetic Kidney Disease

Release of the CREDENCE trial results in 2019 ushered in a new era of investigation and discovery in the treatment of patients with type 2 diabetes and diabetic kidney disease (DKD). ASN launched the Diabetic Kidney Disease Collaborative (DKD-C) to educate the nephrology community about the new therapies and foster collaboration across specialties regarding their use.

Led by incoming ASN President Susan E. Quaggin, MD, FASN, the DKD-C Task Force has issued calls to action encouraging SGLT2 inhibitor therapy in patients with type 2 diabetes using the inclusion criteria of CREDENCE. The task force hosted in-person and remote conferences bringing together experts from nephrology, industry, and allied fields to help transform patient outcomes in this key area.

Improving AKI Care through AKI!Now

ASN partnered with Baxter Healthcare to help transform how acute kidney injury (AKI) care is delivered, reduce its morbidity and mortality, and improve long-term outcomes, thus promoting recovery and reducing the incidence of kidney disease and failure. The Steering Committee has produced "AKI!Now: From Recognition to Recovery" (*ASN Kidney News*, April 2020), "AKI!Now Initiative: Recommendations for Awareness, Recognition, and Management of AKI" (*CJASN*, October 2020), and a webinar on "COVID-19 Associated AKI Recognition and Management" (April 21, 2020).

In early fall 2020, the Steering Committee released a web-based compendium (https://aki.asn-online.org/home) of the most up-to-date content about AKI.

Focusing on Fellows and Workforce

To measure how the pandemic has changed training and the experiences for the next generation of nephrologists, ASN conducted the COVID-19 Nephrology Fellow Survey in August. ASN's annual Nephrology Fellow Survey, which captures key leading indicators on the job market and demographics of the incoming workforce, was deferred in 2020.

Extramural research published through the ASN Data Analytics Program included a paper that examined how rounding during training may influence fellows' educational experiences, core competencies, and improve patient care (*CJASN*, https://doi.org/10.2215/CJN.10190819).

ASN also launched the Data Resource Center, an online platform for communicating data-driven insights and sharing data resources developed for—and of interest to—the kidney community. Accessible at https://data.asn-online.org/, the site serves as a dedicated home for the society's workforce research products and output.

Achieving the Vision of KidneyX

KidneyX, the public–private partnership of ASN and HHS, completed two prize competitions that awarded $70,000 to 25 winners of the Patient Innovator Challenge and $3 million to six winners of Redesign Dialysis Phase 2. The virtual KidneyX Summit convened representatives from government, investors, industry, academia, and people with kidney diseases to hear pitches by award winners and learn how KidneyX accelerates transformative advances in kidney care.

In October 2020, KidneyX announced the Artificial Kidney Prize competition. To highlight the innovations kidney care clinicians have made to ensure continuity and safety of care during the COVID-19 pandemic, KidneyX launched the COVID-19 Kidney Care Challenge in November. Learn more at www.kidneyx.org.

Advancing Research and Discovery through the Kidney Health Initiative

The Kidney Health Initiative (KHI) expanded its efforts to emphasize the importance of technology development in bringing more people with kidney failure home for dialysis treatment, encouraged the inclusion of people with kidney diseases in clinical trials for COVID-19 vaccines and therapies, and coordinated with the kidney community to ensure the resiliency of kidney clinical trials through the pandemic. In 2020, KHI completed three projects and published four papers, as well as launching a roadmap for AKI biomarkers and producing a clinical trials supplement to the Technology Roadmap for Innovative Approaches to Renal Replacement Therapy. KHI continues to be the largest consortium in the kidney community, with 115 member organizations. To learn more, visit www.kidneyhealthinitiative.org.

Granting $3 Million for Kidney Research

KidneyCure (the ASN Foundation) awarded more than $3 million to support 47 leading kidney researchers in 2020, funding 25 new projects and 22 continuing projects. The foundation funds the Transition to Independence Grants Program, the Ben J. Lipps Research Fellowship Program, the William and Sandra Bennett Clinical Scholars Program, the American Society of Nephrology–Harold Amos Medical Faculty Development Program, and the ASN Pre-Doctoral Fellowship Program.

KidneyCure provided $50,000 in emergency support to grant recipients whose research was affected by COVID-19 lab closures.

Launching *Kidney360*, Prioritizing COVID-19 and Beyond

JASN, *CJASN*, and *Kidney360* received a massive influx of COVID-19–related submissions, resulting in over 80 freely available articles published on the topic. All three journals prioritized peer review and production for these submissions, while maintaining the journals' rigorous peer review standards.

Launched in January 2020, *Kidney360* is a global, peer-reviewed, open access, online-only, general kidney journal with an outstanding editorial team helmed by Editor-in-Chief Michael Allon, MD. Kidney360 is the first nephrology journal to provide readers with commenting at the article level through Disqus, direct transfer from medRxiv and bioRxiv, and publication of articles within 48 hours of acceptance.

CJASN's special article series, Genomics of Kidney Disease, recognizes that genetics and genomics have moved beyond geneticists and basic science researchers. The complete compendium of 17 articles will be available via pdf after series completion. *CJASN* continued to offer its *CJASN* Trainee of the Year prize competition and the *CJASN* Trainee Peer Review Program.

JASN was cited more than any other original research journal in the field. Topic highlights in 2020 include lifestyle factors' influence on CKD and a genome-wide analysis that has advanced the biologic understanding of IgAN. Participants in the *JASN* Editorial Fellowship Program brought valuable expertise to peer review. *JASN's* new podcast program successfully launched with nearly 23,000 users in the initial 3 months.

In 2021, new article series and features will be added to the journals, enhancing the print and online platforms—and the reading experience.

Reimagining Kidney Week 2020

A signature achievement of ASN was pivoting from an in-person Kidney Week in Denver, Colo., to the first digital annual meeting in its history, ASN Kidney Week 2020 Reimagined. More than 10,200 individuals participated, with nearly 27,000 ePoster views, more than 12,000 Chat postings, and record participation in Early Programs. The Digital Exhibit Hall included 81 exhibits. Women represented 45% of speakers and moderators, and the meeting stayed true to its international reach, with 42% participation from outside the US. Top international representation came from Mexico, Canada, Japan, the United Kingdom, Germany, and China.

Kidney Week's educational programming included cutting-edge science and patient care, including sessions on COVID-19, race, ethnicity, and diversity:

- Critical Illness and AKI in COVID-19: What Have We Learned?
- Policy in a Post-COVID World
- Race and Ethnicity Considerations in CKD
- A Slice of Humble Pie: Enhancing Socioeconomic Humility in Nephrology

Growing ASN Communities, Social Media

With over 1000 new discussions each month, ASN Communities engages members from around the world. Popular topics include AKI in COVID-19 and CRRT, Hyponatremia, and Calciphylaxis in PD patients. ASN Communities was recently recognized by Higher Logic for top performance in activity, value, and reach.

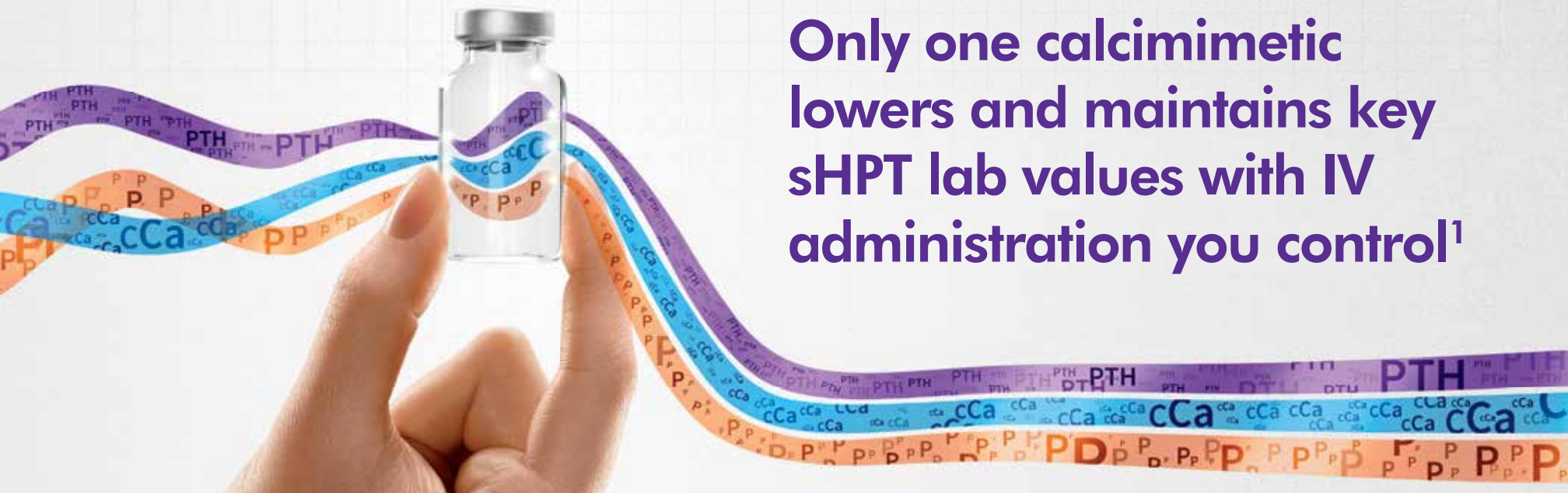
A fully online Kidney Week meant Twitter took center stage in communicating with meeting participants. Impressions of ASN's tweets rose by 37% during Kidney Week 2020 Reimagined, with a 7% increase in engagement. ASN added over 4600 followers from January through October. ASN rebuilt the society's Instagram page, prompting a 37% increase in its Instagram following since January.

Addressing Ethics in Kidney Care

A kidney ethics webinar in November outlined 10 areas of ethical concern as priority challenges requiring collaborative action by ASN, the European Renal Association–European Dialysis and Transplant Association, and the International Society of Nephrology Joint Working Group on Ethical Issues in Nephrology. The publication "Ethical challenges in nephrology: a call to action" also outlines these challenges.

Contributing to #FirstRespondersFirst

"This year, facing the challenges, stress, and ongoing burden of a global pandemic, kidney professionals have demonstrated the resolve and focus on excellence that exemplifies our profession," stated ASN President Anupam Agarwal, MD, FASN, in October. In December, ASN contributed $50,000 to #FirstRespondersFirst to benefit Direct Relief. #FirstRespondersFirst provides essential supplies, personal protective equipment, medicines, and other resources for protecting frontline health care workers worldwide.



Only one calcimimetic lowers and maintains key sHPT lab values with IV administration you control[1]

Not an actual Parsabiv™ vial.
The displayed vial is for illustrative purposes only.

Measure corrected serum calcium prior to initiation of Parsabiv™. Do not initiate in patients if the corrected serum calcium is less than the lower limit of normal. Monitor corrected serum calcium within 1 week after initiation or dose adjustment and every 4 weeks during treatment with Parsabiv™. Measure PTH 4 weeks after initiation or dose adjustment of Parsabiv™. Once the maintenance dose has been established, measure PTH per clinical practice.

Indication

Parsabiv™ (etelcalcetide) is indicated for the treatment of secondary hyperparathyroidism (HPT) in adult patients with chronic kidney disease (CKD) on hemodialysis.

Limitations of Use:

Parsabiv™ has not been studied in adult patients with parathyroid carcinoma, primary hyperparathyroidism, or with CKD who are not on hemodialysis and is not recommended for use in these populations.

Important Safety Information

Contraindication: Parsabiv™ is contraindicated in patients with known hypersensitivity to etelcalcetide or any of its excipients. Hypersensitivity reactions, including pruritic rash, urticaria, and face edema, have occurred.

Hypocalcemia: Parsabiv™ lowers serum calcium and can lead to hypocalcemia, sometimes severe. Significant lowering of serum calcium can cause QT interval prolongation and ventricular arrhythmia. Patients with conditions that predispose to QT interval prolongation and ventricular arrhythmia may be at increased risk for QT interval prolongation and ventricular arrhythmias if they develop hypocalcemia due to Parsabiv™. Closely monitor corrected serum calcium and QT interval in patients at risk on Parsabiv™.

Significant reductions in corrected serum calcium may lower the threshold for seizures. Patients with a history of seizure disorder may be at increased risk for seizures if they develop hypocalcemia due to Parsabiv™. Monitor corrected serum calcium in patients with seizure disorders on Parsabiv™.

Concurrent administration of Parsabiv™ with another oral calcimimetic could result in severe, life-threatening hypocalcemia. Patients switching from cinacalcet to Parsabiv™ should discontinue cinacalcet for at least 7 days prior to initiating Parsabiv™. Closely monitor corrected serum calcium in patients receiving Parsabiv™ and concomitant therapies known to lower serum calcium.

Worsening Heart Failure: In Parsabiv™ clinical studies, cases of hypotension, congestive heart failure, and decreased myocardial performance have been reported. Closely monitor patients treated with Parsabiv™ for worsening signs and symptoms of heart failure.

Upper Gastrointestinal Bleeding: In clinical studies, 2 patients treated with Parsabiv™ in 1253 patient years of exposure had upper gastrointestinal (GI) bleeding at the time of death. The exact cause of GI bleeding in these patients is unknown and there were too few cases to determine whether these cases were related to Parsabiv™.

Patients with risk factors for upper GI bleeding, such as known gastritis, esophagitis, ulcers or severe vomiting, may be at increased risk for GI bleeding with Parsabiv™. Monitor patients for worsening of common Parsabiv™ GI adverse reactions and for signs and symptoms of GI bleeding and ulcerations during Parsabiv™ therapy.

Adynamic Bone: Adynamic bone may develop if PTH levels are chronically suppressed.

Adverse Reactions: In clinical trials of patients with secondary HPT comparing Parsabiv™ to placebo, the most common adverse reactions were blood calcium decreased (64% vs. 10%), muscle spasms (12% vs. 7%), diarrhea (11% vs. 9%), nausea (11% vs. 6%), vomiting (9% vs. 5%), headache (8% vs. 6%), hypocalcemia (7% vs. 0.2%), and paresthesia (6% vs. 1%).

Please see Brief Summary of full Prescribing Information on adjacent page.

IV = intravenous; sHPT = secondary hyperparathyroidism; PTH = parathyroid hormone; P = phosphate; cCa = corrected calcium.

Reference: 1. Parsabiv™ (etelcalcetide) prescribing information, Amgen.

Parsabiv™
(etelcalcetide) Injection for intravenous use
2.5mg/0.5mL | 5mg/1mL | 10mg/2mL

Visit **ParsabivHCP.com** for more information.

BRIEF SUMMARY OF PRESCRIBING INFORMATION

Parsabiv™
(etelcalcetide) Injection for intravenous use
2.5mg/0.5mL | 5mg/1mL | 10mg/2mL

Please see package insert for full Prescribing Information.

INDICATIONS AND USAGE

PARSABIV is indicated for the treatment of secondary hyperparathyroidism (HPT) in adult patients with chronic kidney disease (CKD) on hemodialysis.

Limitations of Use:

PARSABIV has not been studied in adult patients with parathyroid carcinoma, primary hyperparathyroidism, or with chronic kidney disease who are not on hemodialysis and is not recommended for use in these populations.

CONTRAINDICATIONS

Hypersensitivity

PARSABIV is contraindicated in patients with known hypersensitivity to etelcalcetide or any of its excipients. Hypersensitivity reactions, including pruritic rash, urticaria, and face edema, have occurred with PARSABIV *[see Adverse Reactions (6.1) in PARSABIV full prescribing information]*.

WARNINGS AND PRECAUTIONS

Hypocalcemia

PARSABIV lowers serum calcium *[see Adverse Reactions (6.1) in PARSABIV full prescribing information]* and can lead to hypocalcemia, sometimes severe. Significant lowering of serum calcium can cause paresthesias, myalgias, muscle spasms, seizures, QT interval prolongation, and ventricular arrhythmia.

QT Interval Prolongation and Ventricular Arrhythmia

In the combined placebo-controlled studies, more patients treated with PARSABIV experienced a maximum increase from baseline of greater than 60 msec in the QTcF interval (0% placebo versus 1.2% PARSABIV). In these studies, the incidence of a maximum post-baseline predialysis QTcF > 500 msec in the placebo and PARSABIV groups was 1.9% and 4.8%, respectively *[see Adverse Reactions (6.1) in PARSABIV full prescribing information]*. Patients with congenital long QT syndrome, history of QT interval prolongation, family history of long QT syndrome or sudden cardiac death, and other conditions that predispose to QT interval prolongation and ventricular arrhythmia may be at increased risk for QT interval prolongation and ventricular arrhythmias if they develop hypocalcemia due to PARSABIV. Closely monitor corrected serum calcium and QT interval in patients at risk receiving PARSABIV.

Seizures

Significant reductions in corrected serum calcium may lower the threshold for seizures. Patients with a history of seizure disorder may be at increased risk for seizures if they develop hypocalcemia due to PARSABIV. Monitor corrected serum calcium in patients with seizure disorders receiving PARSABIV.

Concurrent administration of PARSABIV with another oral calcium-sensing receptor agonist could result in severe, life-threatening hypocalcemia. Patients switching from cinacalcet to PARSABIV should discontinue cinacalcet for at least 7 days prior to initiating PARSABIV *[see Dosage and Administration (2.4) in PARSABIV full prescribing information]*. Closely monitor corrected serum calcium in patients receiving PARSABIV and concomitant therapies known to lower serum calcium.

Measure corrected serum calcium prior to initiation of PARSABIV. Do not initiate in patients if the corrected serum calcium is less than the lower limit of normal. Monitor corrected serum calcium within 1 week after initiation or dose adjustment and every 4 weeks during treatment with PARSABIV *[see Dosage and Administration (2.2) in PARSABIV full prescribing information]*. Educate patients on the symptoms of hypocalcemia, and advise them to contact a healthcare provider if they occur.

If corrected serum calcium falls below the lower limit of normal or symptoms of hypocalcemia develop, start or increase calcium supplementation (including calcium, calcium-containing phosphate binders, and/or vitamin D sterols or increases in dialysate calcium concentration). PARSABIV dose reduction or discontinuation of PARSABIV may be necessary *[see Dosage and Administration (2.2) in PARSABIV full prescribing information]*.

Worsening Heart Failure

In clinical studies with PARSABIV, cases of hypotension, congestive heart failure, and decreased myocardial performance have been reported. In clinical studies, heart failure requiring hospitalization occurred in 2% of PARSABIV-treated patients and 1% of placebo-treated patients. Reductions in corrected serum calcium may be associated with congestive heart failure, however, a causal relationship to PARSABIV could not be completely excluded. Closely monitor patients treated with PARSABIV for worsening signs and symptoms of heart failure.

Upper Gastrointestinal Bleeding

In clinical studies, two patients treated with PARSABIV in 1253 patient-years of exposure had upper gastrointestinal (GI) bleeding noted at the time of death while no patient in the control groups in 384 patient-years of exposure had upper GI bleeding noted at the time of death. The exact cause of GI bleeding in these patients is unknown, and there were too few cases to determine whether these cases were related to PARSABIV.

Patients with risk factors for upper GI bleeding (such as known gastritis, esophagitis, ulcers, or severe vomiting) may be at increased risk for GI bleeding while receiving PARSABIV treatment. Monitor patients for worsening of common GI adverse reactions of nausea and vomiting associated with PARSABIV *[see Adverse Reactions (6.1) in PARSABIV full prescribing information]* and for signs and symptoms of GI bleeding and ulcerations during PARSABIV therapy. Promptly evaluate and treat any suspected GI bleeding.

Adynamic Bone

Adynamic bone may develop if PTH levels are chronically suppressed. If PTH levels decrease below the recommended target range, the dose of vitamin D sterols and/or PARSABIV should be reduced or therapy discontinued. After discontinuation, resume therapy at a lower dose to maintain PTH levels in the target range *[see Dosage and Administration (2.1) in PARSABIV full prescribing information]*.

ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in other sections of the labeling:

- Hypocalcemia *[see Warnings and Precautions (5.1) in PARSABIV full prescribing information]*
- Worsening Heart Failure *[see Warnings and Precautions (5.2) in PARSABIV full prescribing information]*
- Upper Gastrointestinal Bleeding *[see Warnings and Precautions (5.3) in PARSABIV full prescribing information]*
- Adynamic Bone *[see Warnings and Precautions (5.4) in PARSABIV full prescribing information]*

Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared with rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

The data in Table 2 are derived from two placebo-controlled clinical studies in patients with chronic kidney disease and secondary hyperparathyroidism on hemodialysis. The data reflect exposure of 503 patients to PARSABIV with a mean duration of exposure to PARSABIV of 23.6 weeks. The mean age of patients was approximately 58 years, and 60% of the patients were male. Of the total patients, 67% were Caucasian, 28% were Black or African American, 2.6% were Asian, 1.2% were Native Hawaiian or Other Pacific Islander, and 1.6% were categorized as Other.

Table 2 shows common adverse reactions associated with the use of PARSABIV in the pool of placebo-controlled studies. These adverse reactions occurred more commonly on PARSABIV than on placebo and were reported in at least 5% of patients treated with PARSABIV.

Table 2: Adverse Reactions Reported in ≥ 5% of PARSABIV-Treated Patients

Adverse Reaction*	Placebo (N = 513)	PARSABIV (N = 503)
Blood calcium decreased[a]	10%	64%
Muscle spasms	7%	12%
Diarrhea	9%	11%
Nausea	6%	11%
Vomiting	5%	9%
Headache	6%	8%
Hypocalcemia[b]	0.2%	7%
Paresthesia[c]	1%	6%

*Included adverse reactions reported with at least 1% greater incidence in the PARSABIV group compared to the placebo group

[a] Asymptomatic reductions in calcium below 7.5 mg/dL or clinically significant asymptomatic reductions in corrected serum calcium between 7.5 and < 8.3 mg/dL (that required medical management)

[b] Symptomatic reductions in corrected serum calcium < 8.3 mg/dL

[c] Paresthesia includes preferred terms of paresthesia and hypoesthesia

Other adverse reactions associated with the use of PARSABIV but reported in < 5% of patients in the PARSABIV group in the two placebo-controlled clinical studies were:

- Hyperkalemia: 3% and 4% for placebo and PARSABIV, respectively.
- Hospitalization for Heart Failure: 1% and 2% for placebo and PARSABIV, respectively.
- Myalgia: 0.2% and 2% for placebo and PARSABIV, respectively.
- Hypophosphatemia: 0.2% and 1% for placebo and PARSABIV, respectively.

Description of Selected Adverse Reactions

Hypocalcemia

In the combined placebo-controlled studies, a higher proportion of patients on PARSABIV developed at least one corrected serum calcium value below 7.0 mg/dL (7.6% PARSABIV, 3.1% placebo), below 7.5 mg/dL (27% PARSABIV, 5.5% placebo), and below 8.3 mg/dL (79% PARSABIV, 19% placebo). In the combined placebo-controlled studies, 1% of patients in the PARSABIV group and 0% of patients in the placebo group discontinued treatment due to an adverse reaction attributed to a low corrected serum calcium.

Hypophosphatemia

In the combined placebo-controlled studies, 18% of patients treated with PARSABIV and 8.2% of patients treated with placebo had at least one measured phosphorus level below the lower normal limit (i.e., 2.2 mg/dL).

QTc Interval Prolongation Secondary to Hypocalcemia

In the combined placebo-controlled studies, more patients treated with PARSABIV experienced a maximum increase from baseline of greater than 60 msec in the QTcF interval (0% placebo versus 1.2% PARSABIV). The patient incidence of maximum post-baseline predialysis QTcF > 500 msec in the placebo and PARSABIV groups was 1.9% and 4.8%, respectively.

Hypersensitivity

In the combined placebo-controlled studies, the subject incidence of adverse reactions potentially related to hypersensitivity was 4.4% in the PARSABIV group and 3.7% in the placebo group. Hypersensitivity reactions in the PARSABIV group were pruritic rash, urticaria, and face edema.

Immunogenicity

As with all peptide therapeutics, there is potential for immunogenicity. The detection of anti-drug binding antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody positivity in an assay may be influenced by several factors, including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to etelcalcetide with the incidence of antibodies to other products may be misleading.

In clinical studies, 7.1% (71 out of 995) of patients with secondary hyperparathyroidism treated with PARSABIV for up to 6 months tested positive for binding anti-etelcalcetide antibodies. Fifty-seven out of 71 had pre-existing anti-etelcalcetide antibodies.

No evidence of altered pharmacokinetic profile, clinical response, or safety profile was associated with pre-existing or developing anti-etelcalcetide antibodies. If formation of anti-etelcalcetide binding antibodies with a clinically significant effect is suspected, contact Amgen at 1-800-77-AMGEN (1-800-772-6436) to discuss antibody testing.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

There are no available data on the use of PARSABIV in pregnant women. In animal reproduction studies, effects were seen at doses associated with maternal toxicity that included hypocalcemia. In a pre- and post-natal study in rats administered etelcalcetide during organogenesis through delivery and weaning, there was a slight increase in perinatal pup mortality, delay in parturition, and transient effects on pup growth at exposures 1.8 times the human exposure for the clinical dose of 15 mg three times per week. There was no effect on sexual maturation, neurobehavioral, or reproductive function in the rat offspring. In embryo-fetal studies, when rats and rabbits were administered etelcalcetide during organogenesis, reduced fetal growth was observed at exposures 2.7 and 7 times exposures for the clinical dose, respectively.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Data

Animal Data

There were no effects on embryo-fetal development in Sprague-Dawley rats when etelcalcetide was dosed at 0.75, 1.5, and 3 mg/kg/day by the intravenous route during organogenesis (pre-mating to gestation day 17) at exposures up to 1.8 times human exposures at the clinical dose of 15 mg three times per week based on AUC. No effects on embryo-fetal development were observed in New Zealand White rabbits at doses of etelcalcetide of 0.375, 0.75, and 1.5 mg/kg by the intravenous route (gestation day 7 to 19), representing up to 4.3 times human exposures based on AUC. In separate studies at higher doses of 4.5 mg/kg in rats (gestation days 6 to 17) and 2.25 mg/kg in rabbits (gestation days 7 to 20), representing 2.7 and 7 fold clinical exposures, respectively, there was reduced fetal growth associated with maternal toxicities of hypocalcemia, tremoring, and reductions in body weight and food consumption.

In a pre- and post-natal development study in Sprague-Dawley rats administered etelcalcetide at 0.75, 1.5, and 3 mg/kg/day by the intravenous route (gestation day 7 to lactation day 20), there was a slight increase in perinatal pup mortality, delay in parturition, and transient reductions in post-natal growth at 3 mg/kg/day (representing 1.8-fold human exposures at the clinical dose of 15 mg three times per week based on AUC), associated with maternal toxicities of hypocalcemia, tremoring, and reductions in body weight and food consumption. There were no effects on sexual maturation, neurobehavioral, or reproductive function at up to 3 mg/kg/day, representing exposures up to 1.8-fold human exposure based on AUC.

Lactation

Risk Summary

There are no data regarding the presence of PARSABIV in human milk or effects on the breastfed infant or on milk production. Studies in rats showed [^{14}C]-etelcalcetide was present in the milk at concentrations similar to plasma. Because of the potential for PARSABIV to cause adverse effects in breastfed infants including hypocalcemia, advise women that use of PARSABIV is not recommended while breastfeeding.

Data

Presence in milk was assessed following a single intravenous dose of [^{14}C]-etelcalcetide in lactating rats at maternal exposures similar to the exposure at the human clinical dose of 15 mg three times per week. [^{14}C]-etelcalcetide-derived radioactivity was present in milk at levels similar to plasma.

Pediatric Use

The safety and efficacy of PARSABIV have not been established in pediatric patients.

Geriatric Use

Of the 503 patients in placebo-controlled studies who received PARSABIV, 177 patients (35.2%) were ≥ 65 years old and 72 patients (14%) were ≥ 75 years old.

No clinically significant differences in safety or efficacy were observed between patients ≥ 65 years and younger patients (≥ 18 and < 65 years old). No differences in plasma concentrations of etelcalcetide were observed between patients ≥ 65 years and younger patients (≥ 18 and < 65 years old).

OVERDOSAGE

There is no clinical experience with PARSABIV overdosage. Overdosage of PARSABIV may lead to hypocalcemia with or without clinical symptoms and may require treatment. Although PARSABIV is cleared by dialysis, hemodialysis has not been studied as a treatment for PARSABIV overdosage. In the event of overdosage, corrected serum calcium should be checked and patients should be monitored for symptoms of hypocalcemia, and appropriate measures should be taken *[see Warnings and Precautions (5.1) in PARSABIV full prescribing information]*.

AMGEN®

PARSABIV™ (etelcalcetide)

Manufactured for:
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Patent: http://pat.amgen.com/Parsabiv/

This article is the second in a series about peritoneal dialysis. Additional articles will be published in upcoming issues.

Quality of Life and Mortality in Peritoneal Dialysis

By Ankur Shah and Natasha Dave

The Kidney Disease Outcomes Quality Initiative recommends discussing kidney replacement therapy options when patients reach chronic kidney disease (CKD) stage 4 or have an estimated GFR <30 mL/min per 1.73 m^2 (1). Preparing patients and vetting the options for renal replacement therapy remain pivotal to providing excellent CKD care, which ultimately leads to better patient outcomes. During these conversations, it is crucial that patients fully examine the quality of life, morbidity, and mortality associated with each therapy. For years, researchers have dedicated their time to examining the effects of these modalities in hopes of better facilitating these discussions. With the 2019 executive order on Advancing American Kidney Health, the number of patients choosing home dialysis therapies is likely to increase in the upcoming years. Given this, we believe it is imperative for all clinicians to review and be well versed in the literature on the quality of life, morbidity, and mortality of peritoneal dialysis (PD) before initiating therapy.

Quality of life

The various domains of life are affected when any type of renal replacement therapy is initiated. Dialysis treatments are associated with several limitations, including time commitment, symptoms associated with treatment, and dietary restrictions. These factors, coupled with other social changes, including loss of occupation and hobbies, can significantly affect the quality of life of patients with kidney failure (2).

The Centers for Medicare & Medicaid Services has mandated that health-related quality of life (HrQoL) assessments must be made annually. With significant operational differences between PD and hemodialysis (HD), multiple studies have attempted to evaluate whether HrQoL scores vary on the basis of modality. A 2018 systematic review and meta-analysis of 15 studies with a pooled sample size of 4318 patients found no difference in physical, psychologic, or general domains between the modalities (3). Furthermore, that study evaluated the advancements in both modalities over time. Studies published before 2006 showed no difference in modality, whereas studies published after 2006 showed PD to benefit quality of life. Recently, Eneanya et al. (4) sought to evaluate longitudinal trends in HrQoL using a Fresenius database. Their study compared 880 home modality patients with 4234 in-center patients. The results showed that in-center patients had a significantly lower mean HrQoL at baseline, but irrespective of dialysis type, there was no change of HrQoL in patients who continued to use the same modality. Interestingly, patients who switched from home dialysis to in-center dialysis were found to have a decrease in physical functioning.

Morbidity

Complications specific to PD fall into two major categories: issues with dialysis treatment and complications related to PD. Issues with dialysis treatment include flow dysfunction, infusion pain, drain pain, leak, and ultrafiltration failure. Whereas these obstacles may occur at any time during treatment, physicians must be vigilant and troubleshoot for them as soon as symptoms occur. Complications related to PD include peritonitis, exit site infection, hydrothorax, chyloperitoneum, and encapsulating peritoneal sclerosis. Conversations about morbidity should be included in discussions of PD as a potential modality. The morbidity of PD will be discussed in more detail in a future *ASN Kidney News* article.

Mortality

When examining the association of PD with mortality, nephrologists rely on several observational studies because there are no successful randomized controlled trials. One randomized controlled trial in the Netherlands was attempted in 2003 but was limited for enrollment and therefore underpowered (5). Some of these observational studies examining mortality have often compared PD with HD because researchers have long questioned whether either modality provides a slight advantage over the other.

The United States Renal Data System (USRDS), which collects, analyzes, and distributes information on ESRD patients, found that the adjusted mortality rates in 2016 for HD patients and PD patients were 166 and 154, respectively, per 1000 patient-years (6). This finding added to the perception that there is a clinically significant difference in mortality among dialysis modalities.

A review of the trend over time shows an improvement in unadjusted mortality in PD patients; in those starting peritoneal dialysis in 2003, the 5-year survival was only 42.9%, whereas in those starting PD in 2011, the 5-year survival was 52.1%. Unfortunately, comparing PD and HD patients at face value is problematic. The heterogeneity of PD and HD patients is a major limitation in these studies because PD patients are on average younger, healthier, and more likely to have cystic or glomerular disease, according to the USRDS (6). Wong et al. (7) attempted to control for this by using a standardized assessment of outcomes in patients eligible for both modalities as determined by a multidisciplinary team. They found that among all incident kidney failure patients, PD was associated with a lower risk of death in those <65 years of age. Interestingly, when excluding patients ineligible for PD, they also found that some who were eligible for both modalities had a similar mortality risk that did not vary over time.

With conflicting study results, researchers sought to examine whether perhaps survival benefit changed over time. A large analysis by Yeates et al. (8) compared incident PD and HD patients from 1991 to 2004 from the Canadian Organ Replacement Registry. The results from that study also showed variability in survival, with a favorable risk in PD patients for the first 18 months followed by a favorable risk in HD patients after 36 months. A subgroup analysis between 2001 and 2004 showed that PD was superior for the first 24 months; afterward, both modalities had similar outcomes. That study reaffirms the variations in survival over time and highlights the early benefit for PD patients. Later, Kumar et al. (9) compared the outcomes in matched incident PD and HD patients in the Kaiser Permanente registry. Excluding patients who received dialysis through a central venous catheter during the first 90 days of dialysis, they found that the cumulative risk of death favored PD for the first 3 years, with no difference after that time. This finding led to some clinicians advocating for a transitional kidney failure plan with PD as the primary modality and transition to home HD when residual kidney function is lost (10). However, whereas studies attempt to control heterogenicity among HD and PD patients, it is likely that some residual confounding variables remain. It is difficult to provide an overarching recommendation, especially given the number of conflicting studies.

In conclusion, a true luminary in the field of home dialysis, Joanne Bargman, MD (11), helps capture the essence of this topic with the following statement: "In light of the recent emphasis on patient-centered outcomes and quality of life for patients with kidney disease, we contend that the nephrology community should no longer fund, perform, or publish studies that compare survival by dialysis modality. These studies have become redundant; they are methodologically limited, unhelpful in practice, and therefore a waste of resources."

Conclusion

Several attempts have been made to compare quality of life and patient survival as associated with dialysis modalities. A large meta-analysis spanning >17 years found no difference in HrQoL between dialysis types; however, a recent longitudinal study found decreased scores when patients switched from home to in-center dialysis (3). With no randomized controlled trials and with limited and conflicting observational data, mortality differences between dialysis modalities likely vary over time and should not affect conversations about selecting a dialysis modality. It is important for clinicians to understand and convey findings on the quality of life, morbidity, and mortality associated with each type of dialysis. Discussing these topics with patients can strengthen the provider–patient bond and also help determine the best dialysis modality for each patient. ■

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As of September 21, 2020

ASN PRESIDENT CALLS ON NEPHROLOGISTS TO TAKE THE LEAD IN BUILDING KIDNEY CARE

ASN President Anupam Agarwal, MD, FASN, issued a call to arms to nephrologists to reimagine their profession by 2030.

"Today nephrology stands at a critical crossroads," Agarwal said. "The COVID-19 pandemic and sweeping movements to advocate for racial equality have brought into focus the need for us, all of us, to take the lead and shape our future."

Agarwal made the remarks during the President's Address at Kidney Week Reimagined 2020.

He urged nephrologists to take the lead in building a kidney care workforce; advancing diversity, inclusion, and equity in the field; and expanding innovation and collaboration. He set an ambitious goal of addressing these challenges by 2030.

For 30 years nephrology has had difficulty recruiting, Agarwal said, because nephrology for too long has been undervalued compared with other lifesaving specialties, dampening interest in the field. But he said the ongoing increase in nephrology consultations and dialysis among COVID-19 patients may change the field's image.

"The COVID-19 pandemic has dispelled this misperception and demonstrated the indispensable value of our specialty," he said. But more work is needed to build a fair compensation structure for nephrologists who provide complex 24-hour care to a very vulnerable population. Without improved compensation, many talented medical graduates can't afford to pursue nephrology because of staggering student loan debt. To help, ASN is launching a loan mitigation program for trainees who are currently underrepresented in the field. The society has also asked former ASN President Sharon Moe to lead a task force that will develop nephrology subspecialties and compensation benchmarks.

To attract young people to the profession, Agarwal urged nephrologists to create local programs like the Kidney Disease Screening and Awareness Program that will help inspire future nephrologists.

"Students who witness the dedication and commitment you bring to your work and the lives you change will be inspired to pursue nephrology," he said.

Part of those recruitment efforts should focus on increasing diversity and ensuring that all feel welcome and valued. Agarwal pledged that ASN will advance this goal in all of its programs. He noted that during Kidney Week 2020, 45% of the speakers and moderators were women.

"Each of us must commit to diversity and inclusion, otherwise, nephrology will not reflect the full range and depth of talent needed to deliver exceptional care, educate the next generation, and transform patients' lives through research and innovation," he said. "Without diversity we cannot take the lead."

Addressing policies that limit the practice of international medical graduates is also critical, Agarwal urged. These graduates currently make up half of the US nephrology workforce, but they may be prohibited from taking shifts at more than one hospital, despite the desperate need for nephrology care made clear by the pandemic. To address these concerns, ASN is urging the US Congress to enact the Healthcare Workforce Resilience Act of 2020, which will recapture 25,000 visas for nurses and 15,000 visas for physicians and eliminate restrictions that currently harm immigrants from countries with high immigration rates.

> **Determine how best you can make a difference. Workforce, innovation, diversity, collaboration, all of these will help create positive, inspiring change by 2030.**
>
> -ASN President Anupam Agarwal, MD, FASN

Agarwal also promoted the need to fuel further innovation in the field through research and development. He urged nephrologists to develop collaborations, pursue grant funding, and publish their work. "Determine how best you can make a difference," he said. "Workforce, innovation, diversity, collaboration, all of these will help create positive, inspiring change by 2030." ■

COVID-19 Shines Spotlight on Need for Action on Inequalities in Kidney Care

By Karen Blum

The COVID-19 pandemic has shed light on issues of racial inequality, said Nicole Lurie, MD, MSPH, former Assistant Secretary for Preparedness and Response at the US Department of Health and Human Services. "The excess mortality in Black, Latinx, and Native American populations has been absolutely staggering compared to white populations," she said. "This has coincided with a very challenging and emotional national dialogue about race and racial injustice, structural inequality, and racism."

Lurie gave the Christopher R. Blagg, MD, Endowed Lectureship in Kidney Diseases and Public Policy as part of the "Policy in a Post-COVID World" session.

Race-based patient disparities have been described frequently, with Blacks, Hispanics, and indigenous people having poorer outcomes than other groups in most chronic diseases. About 200 studies in the PubMed database report on race-based disparities and COVID-19, said Kiesha Gibson, MD, FASN, chief of pediatric nephrology at the University of North Carolina School of Medicine. Yet many of these studies fail to address the extent to which outcomes may be explained or driven by structural racism leading to poverty, poor access to care, and other factors.

Structural inequalities in society have put many people of color in the path of COVID-19 exposure, including frontline workers, those who need to take public transportation to work or cannot work from home, and those who may not have good access to testing or live in crowded, multigenerational households. This has pointed to "some real underinvestment in the science of how structural racism and inequality make you sick," Lurie said. Institutional biases, or assumptions that race differences are just differences people cannot change, are now causing people to question whether that's true, Lurie said.

"The kidney community is at the leading edge of this dialogue in medicine, and it has the opportunity to continue to lead and think [about] how to prevent conditions that cause renal failure, and how to get to equity in transportation, home dialysis, and access to new technologies," she said.

Role of nephrology workforce, innovation

People of color are underrepresented among physicians in the nephrology caregiving workforce, Lurie said, but many more people of color are working as dialysis technicians. This presents an opportunity for interprofessional learning about the kinds of conditions and communities that predispose people to illness.

The kidney and healthcare communities need to support efforts that increase workforce diversity, Gibson said. She noted that more than half of African Americans in the healthcare field are trained in historically Black colleges and universities, which should be seen as partners to enhance the workforce pipeline. Physicians also need to support policies that allow international medical graduates to train and practice in the United States.

COVID-19 has required physicians to innovate in ways they never have before, Lurie emphasized. This innovation presents opportunities to think about how to leverage existing systems, such as using emPOWER data to urge dialysis patients to get vaccinated for COVID-19 once a vaccine is approved.

Likewise, the quick adoption of telemedicine during the COVID-19 pandemic became a lifeline for many patients, Gibson said. However, a large segment of society, particularly in rural America, has been left behind by the digital divide, which hinders access to healthcare and keeps people from working safely at home, Gibson said.

"As healthcare professionals, we have a responsibility to advocate for policies that will directly address social and structural factors that affect health, like transportation, housing, food insecurity, and the digital divide," she said. "If we are bold in delivering our actions to push these policies, we may find ourselves much closer to solving race-based health disparities rather than simply describing them." ■

SOCIAL MEDIA BECOMES DRIVING FORCE IN NEPHROLOGY EDUCATION AND NETWORKING

By Bridget M. Kuehn

When she joined Twitter in 2010, Kimberly Manning, MD, professor of medicine and associate vice chair of Diversity, Equity, and Inclusion at Emory University in Atlanta, said she didn't quite understand how it worked, so at first she mostly observed what others were sharing. Then, in 2018, she began sharing some of the 8-minute bite-sized teaching modules (BST Mode) she created for her students, and it helped put her work on the radar.

First came an invitation to discuss the curriculum at Johns Hopkins School of Medicine. During that talk, attendees tweeted about her talk; that led to new collaborators and later an invitation to give a lecture as a visiting professor at the University of California, San Francisco. Over the past year, Manning has focused on mission-based tweeting about topics she is passionate about, including medical education, diversity, equity, inclusion, humanism in medicine, physician–patient communication, and fighting anti-Black racism. This mission-based tweeting has led to more opportunities to speak or serve on editorial boards or in advisory roles for some of her favorite journals. Those opportunities helped raise her national reputation and helped her achieve her dream of reaching a senior rank this year.

"I firmly believe much of it had to do with mission-based tweeting," said Manning during a panel discussion on the power of social media and other technologies at Kidney Week 2020 Reimagined. During the panel, she and other nephrologists shared how social media and other online platforms have become essential tools for networking, teaching, and medical education. In fact, panelist Aisha Shaikh, MD, chief of renal at the James J. Peters VA Medical Center in New York, cited a 2012 survey of physicians that found that 73% of them reported using social media to find medical information at least once a month, and 60% said they thought social media use improved their patient care (1).

"Nephrology has come to the forefront of this movement," said panel co-moderator Samira Farouk, MD, MS, assistant professor of nephrology at the Icahn School of Medicine at Mount Sinai Hospital.

Lifelong learning

In addition to its value in professional and social networking, social media and other online platforms have become important tools for supplementing or amplifying more traditional medical education tools like textbooks and journal clubs.

"Social media in its most basic sense is the democratization of media," said Timothy Yau, MD, associate professor of medicine in the division of nephrology at Washington University in St. Louis. He explained that anyone can create, share, and comment on content on social media. For example, the Renal Fellow Network was founded by the late Nate Hellman, MD, PhD, in 2008 "for fellows, by fellows" as on online forum for sharing interesting case studies and other clinical information (2). It has since formed a partnership with the American Society of Nephrology, and @RenalFellowNetwork boasts about 15,000 followers.

> "Social media in its most basic sense is the democratization of media.
>
> —Timothy Yau, MD, associate professor of medicine, Washington University in St. Louis

Tweets are free and publicly available, and anyone can interact with them in real time, Shaikh said. "There are no geographical, institutional, or academic hierarchical barriers, which I think is fairly critical for trainees and younger consultants because they can access or approach leaders or experts in the field without any barriers," she said

The online journal club #NephJC hosts a twice-monthly journal club for its more than 20,000 followers through Twitter @NephJC as well as a blog and podcast (3). The journal club discussions are a rare opportunity for nephrologists to participate in a live discussion with leading colleagues from around the world and to query the authors directly, in real-time, Yau said. In fact, a recent Perspective article traced how journal clubs evolved beyond the walls of academic centers to Twitter (4).

"As a busy private practice nephrologist, I only had access to journal clubs when I was in medical school," said Arvind Conjeevaram, MD, consultant nephrologist and transplant physician at The Bangalore and Trustwell Hospitals in India. "NephJC is bringing me back to that atmosphere."

Gamefication has also become a popular way to engage nephrologists by using quizzes or other competitions to engage people in learning. For example, #NephMadness is a bracket-based game modeled after college basketball's March Madness tournament: nephrology topics, instead of basketball teams, are pitted against one another (5), Conjeevaram said. Another example is the International Society of Nephrology's Nephrology World Cup, which was played by 2400 people in 53 countries in 2019, he said.

"Gamefication is extremely new," said panel co-moderator Tejas Desai, MD, a nephrologist who created the Nephrology On-Demand online educational platform (6). "It has tremendous potential, and nephrology is already on the cutting edge."

Getting started

Shaikh acknowledged that social media sites like Twitter can be overwhelming for those starting out, but she recommends that nephrologists start by creating an account and following others to learn how it works.

"Once you feel confident, start sharing and posting information," she said. "Then as your confidence level grows and your comfort level goes up you can start participating in discussions and analyzing posts." She suggested eventually working up to creating original content.

Following or tweeting from meetings like Kidney Week (#kidneyWk) is also a valuable way to use Twitter. "When I'm at a national meeting or when I've missed a national meeting, I'm so grateful for people tweeting in real time sharing about those talks going on that I'm missing," Manning said. Investigators may also want to tweet about their publications. Shaikh noted that highly tweeted articles are about 11 times more likely to

be highly cited (7). Manning recommended that nephrologists think about what their mission is while using Twitter and focus on that to help avoid burnout. She recommends starting by following five to 10 accounts that share your mission and being sure to amplify the work of others.

"Ultimately, all the things that you share should be things that fit your mission because they will draw in those individuals who will work with you: potential collaborators," she said. ■

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Exercise Is Good for All Stages of Kidney Disease

By Karen Blum

Loss of muscle mass is a common early complication of chronic kidney disease (CKD), but exercise and lifestyle interventions can help stave off that process.

"Encouraging people with CKD to be less sedentary is absolutely crucial," said James Burton, MBChB, MD, a professor in renal medicine and honorary consultant nephrologist with the University of Leicester, in England.

Expert supervision of structured exercise programs results in greater compliance and potentially better outcomes for patients with kidney disease, he said. "But it's really important that we appreciate that a one size [program] does not fit all," he added. "Really, we should be thinking about a combination of self-management, home-based and center-based exercise, and a mixture of aerobic, resistance, and potentially balance training as well to get the very most out of the interventions to improve outcomes for our patients."

Skeletal muscle wasting, and muscle dysfunction, starts earlier than when most nephrologists think about it as they're sitting with people in clinic, Burton said. Such sarcopenia is associated with lower levels of physical functioning, lower exercise capacity, and increased morbidity and mortality.

Maintenance of muscle mass is a balance between protein synthesis and protein degradation, he said. An imbalance can lead to loss of muscle mass or atrophy of individual muscle fibers. Individual processes contributing to a reduction in protein synthesis include a loss of amino acids through dialysis and hormonal derangements, as well as a sedentary lifestyle that starts the cycle of increased muscle wasting (1). Factors contributing to an increase in protein degradation include insulin resistance, metabolic acidosis, vitamin D deficiency, and increases in oxidative stress. Once a person reaches that state, muscle loss and wasting can lead to weakness, a reduction in muscle strength, and ultimately to low physical performance and potentially to disability and frailty, Burton said.

The good news for CKD patients is that exercise can improve muscle mass and physical functioning, he said. Among CKD patients not using dialysis, a 12-week study that combined resistance and aerobic training for three 30-minute sessions a week found that the exercises led to improvements in muscle strength, muscle volume, and exercise capacity (2). Another 4-month study measured the results from endurance training plus either balance or strength training (3). Sarcopenia did not progress over 12 months in either group. Both groups experienced reductions in fat mass, and the participants who did balance training had an increase in lean mass.

Our knowledge of how dialysis affects the muscles is fairly limited, Burton said, but the process does have a significant impact on physical function, and people using dialysis traditionally become more sedentary, which also can have an impact on mortality. Exercise can help with these patients as well.

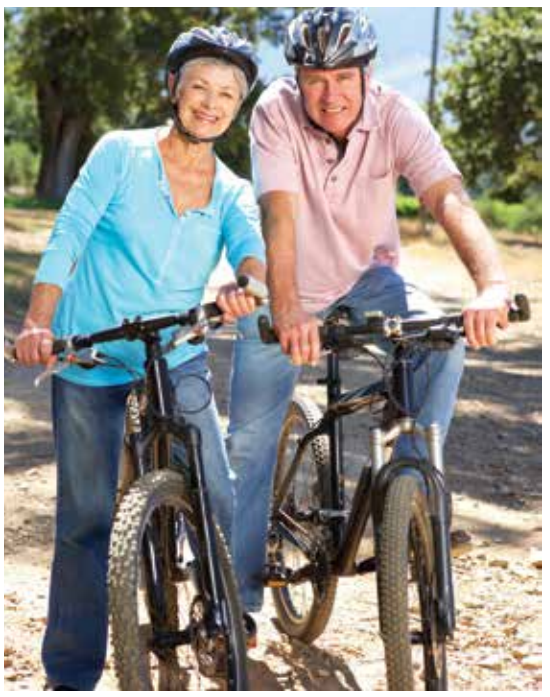
One study found a 30% reduction in mortality among patients undergoing dialysis who exercised either two to three, or four to five, times per week (4). Another trial, presented last year at UK Kidney Week, found that patients randomized to exercise for half an hour between dialysis sessions for 6 months had a mean 11.1-g reduction in left ventricular mass (5)—"a good surrogate outcome for cardiovascular events and mortality," Burton said.

Exercise even can help patients with kidney failure. A 2002 study split patients into three groups for 6 months. One group was assigned to a center-based exercise program delivered by specialists three times a week on nondialysis days, one received an exercise program delivered by specialists on dialysis days, and one was asked to complete a moderate-intensity home-based program 5 days a week and was provided with individual instruction (6). Although more participants (24%) dropped out of the first group compared with the others (17%), those who completed the study had increased measures of peak oxygen consumption and exercise time.

Groups such as Kidney Disease: Improving Global Outcomes (KDIGO) have guidelines recommending that people with CKD be encouraged to exercise at least 30 minutes five times a week to achieve a healthy weight, and other groups suggest exercising three times a week or between dialysis sessions as a person is able. Overall, there is a lack of robust randomized trials for this, Burton said, and getting patients to be more active remains a challenge.

"I think we all know that exercise is good for people, but it's only good for people if they actually take part," he said.

It's important to explain to patients that they can get exercise in many ways, from walking to other social activities, not just by going to a gym, Burton said. Looking at barriers to exercise, he said, "People with CKD are worried about comorbidities and poor health. It's up to us as their healthcare professionals to



highlight to them the importance of exercise in abrogating some of those things that we know are going to make their multimorbidity and outcomes potentially worse." ■

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IMPORTANT SAFETY INFORMATION FOR LOKELMA® (sodium zirconium cyclosilicate)

WARNINGS AND PRECAUTIONS:

- **Gastrointestinal Adverse Events in Patients with Motility Disorders:** Avoid LOKELMA in patients with severe constipation, bowel obstruction or impaction, including abnormal post-operative bowel motility disorders. LOKELMA has not been studied in patients with these conditions and it may be ineffective and may worsen gastrointestinal conditions.
- **Edema:** Each 5-g dose of LOKELMA contains approximately 400 mg of sodium, but the extent of absorption by the patient is unknown. In clinical trials of LOKELMA in patients who were not on dialysis, edema was observed and was generally mild to moderate in severity and was more commonly seen in patients treated with 15 g once daily. Monitor for signs of edema, particularly in patients who should restrict their sodium intake or are prone to fluid overload (eg, heart failure or renal disease). Advise patients to adjust dietary sodium, if appropriate. Increase the dose of diuretics as needed.

  In a clinical trial of LOKELMA in patients on chronic hemodialysis in which most patients were treated with doses of 5 g to 10 g once daily on non-dialysis days, there was no difference in the mean change from baseline in interdialytic weight gain (a measure of fluid retention) between the LOKELMA and placebo groups.
- **Hypokalemia in Patients on Hemodialysis:** Patients on hemodialysis may be prone to acute illness that can increase the risk of hypokalemia on LOKELMA (eg, illnesses associated with decreased oral intake, diarrhea). Consider adjusting LOKELMA dose based on potassium levels in these settings.

ADVERSE REACTIONS: The most common adverse reaction in non-dialysis patients with LOKELMA was mild to moderate edema. In placebo-controlled trials up to 28 days, edema was reported in 4.4%, 5.9%, 16.1% of non-dialysis patients treated with 5 g, 10 g, and 15 g of LOKELMA once daily, respectively vs 2.4% of non-dialysis patients receiving placebo.

DRUG INTERACTIONS: LOKELMA can transiently increase gastric pH. In general, oral medications with pH-dependent solubility should be administered at least 2 hours before or 2 hours after LOKELMA. Spacing is not needed if it has been determined the concomitant medication does not exhibit pH-dependent solubility.

INDICATION AND LIMITATION OF USE

LOKELMA is indicated for the treatment of hyperkalemia in adults.

LOKELMA should not be used as an emergency treatment for life-threatening hyperkalemia because of its delayed onset of action.

LOKELMA IS THE ONLY FDA-APPROVED K^+ BINDER

with efficacy and safety results in the label for adult patients with hyperkalemia on chronic hemodialysis[1]

SIGNIFICANT RESPONSE[1]

41% of patients treated with LOKELMA achieved the primary endpoint* compared to 1% of patients in the placebo group ($P<0.001$)[1]

SUSTAINED†[1]

LOKELMA sustained lower pre-dialysis K^+ levels in patients on hemodialysis with continued treatment[1]

GENERALLY WELL TOLERATED[1]

Safety profile is comparable to placebo‡[1]

Learn more about the K^+ binder for patients on dialysis at LOKELMA-HCP.com

DOSING:

- **Non-hemodialysis Patients:** For initial treatment of hyperkalemia, the recommended starting dose is 10 g administered three times a day up to 48 hours. For maintenance treatment, the recommended starting dose is 10 g once daily. Monitor serum potassium and adjust dose of LOKELMA at 1-week intervals or longer in increments of 5 g based on serum potassium and desired target range. The recommended maintenance dose range is from 5 g every other day to 15 g daily. Discontinue or decrease the dose of LOKELMA if serum potassium is below the desired target range.
- **Hemodialysis Patients:** For patients on chronic hemodialysis, administer LOKELMA only on non-dialysis days. The recommended starting dose is 5 g once daily on non-dialysis days. Consider a starting dose of 10 g once daily on non-dialysis days in patients with serum potassium greater than 6.5 mEq/L. Monitor serum potassium and adjust the dose of LOKELMA based on the pre-dialysis serum potassium value after the long interdialytic interval and desired target range. During initiation and after dose adjustment, assess serum potassium after one week. Discontinue or decrease the dose of LOKELMA if serum potassium falls below the desired target range based on pre-dialysis value after the long interdialytic interval or the patient develops clinically significant hypokalemia. The recommended maintenance dose range is from 5 g to 15 g once daily, on non-dialysis days.

Please read Brief Summary of Prescribing Information on adjacent page.

*Study 4† met its primary endpoint of a proportion of patients classified as responders, defined as patients who maintained a pre-dialysis serum K^+ between 4.0-5.0 mEq/L on at least 3 out of 4 dialysis treatments after the long interdialytic interval and who did not receive rescue therapy during the evaluation period. Rescue therapy was defined as any urgent therapeutic intervention considered necessary to reduce serum K^+ in the setting of severe hyperkalemia (defined as >6.0 mEq/L).[2]

†Study 4 was a double-blind, placebo-controlled trial in patients with end-stage renal disease on chronic hemodialysis (≥ 3 months) and persistent hyperkalemia* (N=196) who were randomized to receive LOKELMA 5 g or placebo once daily on non-dialysis days. In the initial 4-week period the dose could be adjusted weekly in 5 g increments up to 15 g once daily on non-dialysis days to achieve pre-dialysis serum K^+ levels between 4.0 and 5.0 mEq/L after the long interdialytic interval. The dose at the end of the dose-adjustment period was maintained throughout the 4-week evaluation period.[1,2]

‡In Study 4,† 40 patients in the LOKELMA group (41.7%) reported adverse events, compared to 46 patients in the placebo group (46.5%).[2] While 5% of patients developed pre-dialysis hypokalemia (serum K^+ < 3.5mEq/L) in both the LOKELMA and placebo groups, 3% and 1% of patients developed a serum K^+ < 3.0 mEq/L in the LOKELMA and placebo groups, respectively.[1] There was no difference in the mean change from baseline in interdialytic weight gain (a measure of fluid retention) between LOKELMA and the placebo groups.

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AstraZeneca

LOKELMA®
(sodium zirconium cyclosilicate)
5 g | 10 g for oral suspension

LOKELMA® (sodium zirconium cyclosilicate) for oral suspension

Brief Summary of Prescribing Information.
For complete prescribing information consult official package insert.

INDICATIONS AND USAGE

LOKELMA is indicated for the treatment of hyperkalemia in adults.

Limitation of Use

LOKELMA should not be used as an emergency treatment for life-threatening hyperkalemia because of its delayed onset of action *[see Clinical Pharmacology (12.2) and Clinical Studies (14) in the full Prescribing Information]*.

DOSAGE AND ADMINISTRATION

Recommended Dosage

For initial treatment of hyperkalemia, the recommended dose of LOKELMA is 10 g administered three times a day for up to 48 hours. Administer LOKELMA orally as a suspension in water *[see Dosage and Administration (2.3) in the full Prescribing Information]*.

For continued treatment, the recommended dose is 10 g once daily. Monitor serum potassium and adjust the dose of LOKELMA based on the serum potassium level and desired target range. During maintenance treatment, up-titrate based on the serum potassium level at intervals of 1-week or longer and in increments of 5 g. Decrease the dose of LOKELMA or discontinue if the serum potassium is below the desired target range. The recommended maintenance dose range is from 5 g every other day to 15 g daily.

Dosage Adjustment for Patients on Chronic Hemodialysis

For patients on chronic hemodialysis, administer LOKELMA only on non-dialysis days.

The recommended starting dose is 5 g once daily on non-dialysis days. Consider a starting dose of 10 g once daily on non-dialysis days in patients with serum potassium greater than 6.5 mEq/L. Monitor serum potassium and adjust the dose of LOKELMA based on the pre-dialysis serum potassium value after the long inter-dialytic interval and desired target range.

During initiation and after a dose adjustment, assess serum potassium after one week. The recommended maintenance dose range is from 5 g to 15 g once daily, on non-dialysis days.

Discontinue or decrease the dose of LOKELMA if:

- serum potassium falls below the desired target range based on the pre-dialysis value after the long interdialytic interval, or;
- the patient develops clinically significant hypokalemia

Reconstitution and Administration

In general, other oral medications should be administered at least 2 hours before or 2 hours after LOKELMA *[see Drug Interactions (7) in the full Prescribing Information]*.

Instruct patients to empty the entire contents of the packet(s) into a drinking glass containing approximately 3 tablespoons of water or more if desired. Stir well and drink immediately. If powder remains in the drinking glass, add water, stir and drink immediately. Repeat until no powder remains to ensure the entire dose is taken.

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

Gastrointestinal Adverse Events in Patients with Motility Disorders

Avoid use of LOKELMA in patients with severe constipation, bowel obstruction or impaction, including abnormal post-operative bowel motility disorders, because LOKELMA has not been studied in patients with these conditions and may be ineffective and may worsen gastrointestinal conditions.

Edema

Each 5 g dose of LOKELMA contains approximately 400 mg of sodium, but the extent of absorption by the patient is unknown. In clinical trials of LOKELMA in patients who were not on dialysis, edema was observed and was generally mild to moderate in severity and was more commonly seen in patients treated with 15 g once daily. Monitor for signs of edema, particularly in patients who should restrict their sodium intake or are prone to fluid overload (e.g., heart failure or renal disease). Advise patients to adjust dietary sodium, if appropriate. Increase the dose of diuretics as needed *[see Adverse Reactions (6) in the full Prescribing Information]*.

In a clinical trial of LOKELMA in patients on chronic hemodialysis in which most patients were treated with doses of 5 to 10 g once daily on non-dialysis days, there was no difference in the mean change from baseline in interdialytic weight gain (a measure of fluid retention) between the LOKELMA and placebo groups.

Hypokalemia in Patients on Hemodialysis

Patients on hemodialysis may be prone to acute illness that can increase the risk of hypokalemia on LOKELMA (e.g., illnesses associated with decreased oral intake, diarrhea). Consider adjusting Lokelma dose based on potassium levels in these settings.

ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail elsewhere in the label:

- Edema *[see Warnings and Precautions (5.2) in the full Prescribing Information]*.

Clinical Studies Experience

Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in practice.

The total exposure to LOKELMA in the safety and efficacy clinical trials of patients not on dialysis with hyperkalemia was 1,760 patients with 652 patients exposed to LOKELMA for at least 6 months and 507 patients exposed for at least one year.

The population (n=1,009) in the placebo-controlled trials included patients aged 22 to 96 years, females (n=454), Caucasians (n=859) and Blacks (n=130). Patients had hyperkalemia in association with comorbid diseases such as chronic kidney disease, heart failure, and diabetes mellitus.

In placebo-controlled trials in which patients who were not on dialysis were treated with once daily doses of LOKELMA for up to 28 days, edema was reported in 4.4% of patients receiving 5 g, 5.9% of patients receiving 10 g and 16.1% of patients receiving 15 g LOKELMA compared to 2.4% of patients receiving placebo. In longer-term uncontrolled trials in which most patients were maintained on doses <15 g once daily, adverse reactions of edema (edema, generalized edema and peripheral edema) were reported in 8% to 11% of patients.

Laboratory Abnormalities

In clinical trials in patients who were not on dialysis, 4.1% of LOKELMA-treated patients developed hypokalemia with a serum potassium value less than 3.5 mEq/L, which resolved with dosage reduction or discontinuation of LOKELMA. In a clinical trial of LOKELMA in patients on chronic hemodialysis, 5% of patients developed pre-dialysis hypokalemia (serum potassium <3.5 mEq/L) in both the LOKELMA and placebo groups; 3% and 1% of patients developed a serum potassium < 3.0 mEq/L in the LOKELMA and placebo groups, respectively.

DRUG INTERACTIONS

LOKELMA can transiently increase gastric pH. As a result, LOKELMA can change the absorption of co-administered drugs that exhibit pH-dependent solubility, potentially leading to altered efficacy or safety of these drugs when taken close to the time LOKELMA is administered. In general, other oral medications should be administered at least 2 hours before or 2 hours after LOKELMA *[see Dosage and Administration (2.3) and Clinical Pharmacology (12.3) in the full Prescribing Information]*. LOKELMA is not expected to impact systemic exposure of drugs that do not exhibit pH-dependent solubility and so spacing is not needed if it has been determined that the concomitant medication does not exhibit pH-dependent solubility.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

LOKELMA is not absorbed systemically following oral administration and maternal use is not expected to result in fetal exposure to the drug.

Lactation

Risk Summary

LOKELMA is not absorbed systemically following oral administration, and breastfeeding is not expected to result in exposure of the child to LOKELMA.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Geriatric Use

Of the total number of subjects in clinical studies of LOKELMA, 58% were age 65 and over, while 25% were 75 and over. No overall differences in safety or effectiveness were observed between these patients and younger patients.

PATIENT COUNSELING INFORMATION

Dosing

Instruct the patient how to reconstitute LOKELMA for administration. Inform the patient that it is necessary to drink the full dose *[see Dosage and Administration (2.3) in the full Prescribing Information]*.

Instruct dialysis patients who experience acute illness (e.g., decreased oral intake of food or fluids, diarrhea) to contact the health care provider. The dose of Lokelma may need to be adjusted. *[see Warnings and Precautions (5.3) in the full Prescribing Information]*.

Drug Interactions

Advise patients who are taking other oral medications to separate dosing of LOKELMA by at least 2 hours (before or after) *[see Drug Interactions (7) in the full Prescribing Information]*.

Diet

Advise patients to adjust dietary sodium, if appropriate *[see Warnings and Precautions (5.2) in the full Prescribing Information]*.

U.S. Patent No: 6332985, 8808750, 8877255, 8802152, 9592253

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4/20 US-45478 9/20

Practice Self-Compassion and Forge Connections to Overcome Burnout

By Karen Blum

Increasing clinical demands, regulatory issues, and documentation requirements have contributed to physicians' burnout over the past decade, and the COVID-19 pandemic has created additional strain, speakers said during Kidney Week 2020 Reimagined. Now more than ever, they said, clinicians need to practice self-compassion, forge connections, and find ways to alleviate stress.

About 44% of physicians had already experienced at least one manifestation of burnout (1), said Tait Shanafelt, MD, chief wellness officer for Stanford Medicine and associate dean for the Stanford School of Medicine. Then the pandemic changed all aspects of physicians' personal and professional lives. Traditional sources of physicians' distress, including challenges with work-life integration and feelings of decreased control over work, have now been joined by concerns about being exposed to the SARS-CoV-2 virus or bringing it home to family members, Shanafelt said. People are feeling isolated and disconnected from their support networks and extended family.

Nephrology itself is a high-burnout field, said Karen Warburton, MD, FASN, FACP, a transplantation nephrologist and associate director of the Clinician Wellness Program at the University of Virginia School of Medicine.

In a Medscape survey (2) ranking burnout by specialty, nephrology ranked third behind urology and neurology, with 49% of those surveyed reporting burnout, Warburton said. Several factors contribute to these feelings, she said. The clinical workload is intense, with nephrologists working long hours treating complex patients. Nephrologists also have considerable administrative burdens, especially in dialysis care. Many work in a highly protocol-driven environment and feel beholden to regulatory agencies. There are numerous quality metrics and requirements for public reporting, and nephrologists may lack control and flexibility at work. On top of that, the specialty is in the midst of a fellowship recruitment crisis.

"Many of us grew up in families where 'work hard' or 'work now, play later' were either a spoken or an unspoken value," Warburton said. "These values often drive us to work to the point of burnout without being aware that we're even doing this."

There also are personality traits that contribute to burnout (3), she said, such as feelings of doubt or guilt or an exaggerated sense of responsibility. "This leads us to blame ourselves for things that are out of our control," she said. Physicians also tend to be independent to a fault and have difficulty saying no or asking for help. Additionally, many are perfectionists. Pessimism can cause physicians to give more weight to negative experiences over neutral or positive ones. Family stressors and work–home interference also can contribute to burnout.

Physicians may not be able to change some of these factors, Warburton said, "but we can be mindful of them and how they impact how we look at things and the choices we make."

Strategies to reduce burnout

There are strategies that both organizations and individuals can adopt to reduce burnout, the speakers said. During the pandemic, employers can listen and create feedback channels that enable physicians and other healthcare workers to share what they need (4, 5), Shanafelt said. They can provide support for tangible needs like child care, and they can relax some career milestones, like extending the promotion clock while workers care for their families. They can provide emotional support for employees, especially those who quarantine, and they can recognize that people deal with stress differently and encourage people to work together.

In the longer term, they can commit to mitigating burnout through actions like establishing leaders to drive improvement. They can develop strategies and infrastructures to change the work environment and measure their initiatives to assess progress.

On the personal side, physicians can be most effective by focusing their energy on things they can control, Warburton said. Problem-focused coping skills include actions like better time management, delegating tasks or saying no, and developing a mentorship network, even if it is virtual. Seek adequate administrative support, she said, and find meaning at work.

Finding meaning at work can be healing, Warburton said. Studies by Shanafelt and others have shown this can contribute to lower burnout, higher well-being, and a better quality of life. Physicians should consider what they most enjoy about work so they can better cope with activities that may be less enjoyable. A Mayo Clinic study (6) found that those spending less than 20% of their time on activities they found most meaningful had higher rates of burnout, Warburton noted. Making sure they spend at least 20% of their time doing rewarding work can get physicians through the rest of the week, she said.

There also are emotion-focused coping skills clinicians can use to better handle things outside of their control, Warburton said. This includes accepting things they cannot change and allowing for mindfulness and self-care. Many people have narrow views of self-care, thinking that it's limited to going to yoga or coloring, she said, but there are many ways to practice self-care, such as spending time with family and friends, exercising, or taking a few minutes in the day for guided meditation.

Embracing a culture of positivity also can help, Warburton said. Write down three things you are grateful for each day, take time to write thank-you notes or emails, and post thank-you letters from patients and families in work areas for all to see.

Finally, she said, practice self-compassion.

"This practice is one of the most important parts of achieving well-being and can be really hard for us," Warburton said. "Self-compassion is not about ignoring our mistakes or shortcomings, or ruminating on them, but rather using them to grow….It's about recognizing that life is hard and we're doing our best, and beating ourselves up or shifting the blame to others doesn't help anyone."

Self-compassion is critically important during this challenging time, Shanafelt said. Prioritize taking care of yourself and calibrating your stress level (7).

Embracing the mindset of "good enough"

"We have to embrace the mindset of good enough right now," Shanafelt said. "There are things in the world that we can't fix….We can't replace everything [children] are not getting at school and in relationships, and we need to just accept that, do the best we can, recognize that this season will pass, and not hold ourselves to unrealistic expectations."

There are predictable chapters to experiencing a disaster (8). The healthcare community went through initial stress and was inspired by the heroism of colleagues. Now we're in a long chapter of "post-honeymoon disillusionment," he said.

"It can take more than a year to go through recovery, even in short emotional disasters, and recovery is nonlinear," he said. "We often make progress, then take steps back. Be patient with yourself, your colleagues, and your organization as we go through this seesaw." ■

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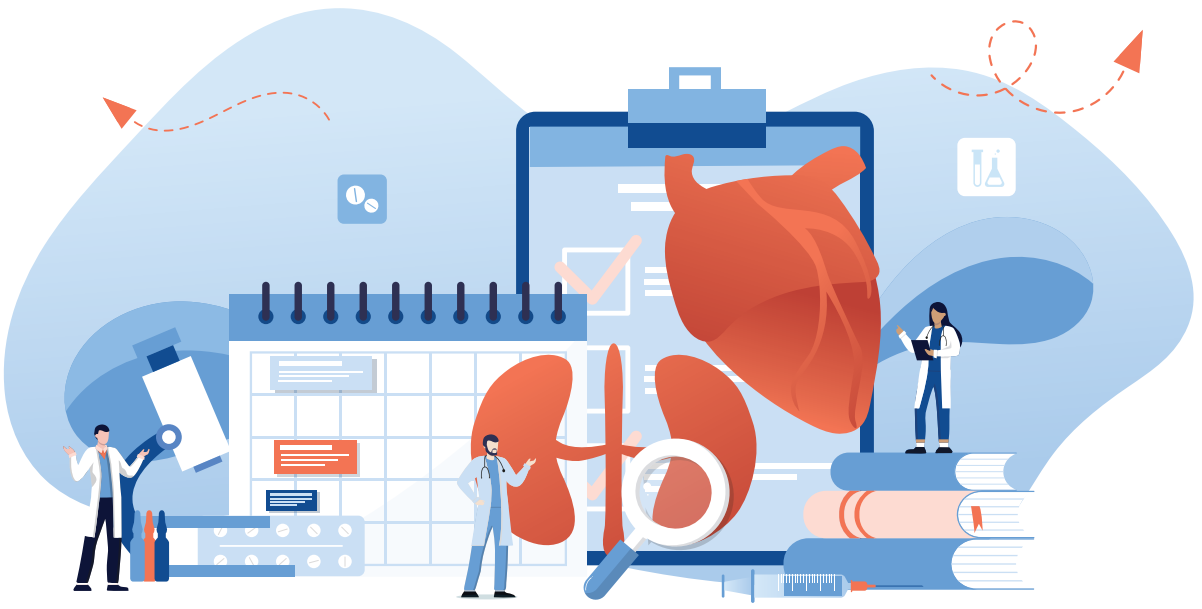
SGLT2 Inhibitors Continue to Show Kidney, Heart Benefits

By Bridget M. Kuehn



Results from two major trials of sodium-glucose cotransporter-2 (SGLT2) inhibitors, a class of drugs initially developed as a treatment for type 2 diabetes mellitus, add to evidence that the drugs may offer kidney-protecting benefits. The results were presented during the High Impact Clinical Trials session at Kidney Week 2020 Reimagined.

The Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease (DAPA-CKD) Trial found that the SGLT2 inhibitor dapagliflozin provided heart and kidney benefits regardless of the cause of underlying kidney disease. Results from the Empagliflozin Outcome Trial in Patients with Chronic Heart Failure with Reduced Ejection Fraction (EMPEROR-Reduced) of the SGLT2 inhibitor empagliflozin showed that the drug reduced serious complications from heart failure and kidney disease in patients with and without chronic kidney disease. Results from the Efficacy and Safety of Finerenone in Subjects With Type 2 Diabetes Mellitus and Diabetic Kidney Disease (FIDELIO-DKD) (FIDELIO-DKD) Trial were also presented during the session and suggested that finerenone, a nonsteroidal mineralocorticoid receptor antagonist, may reduce kidney and heart harm in patients with chronic kidney disease and diabetes, adding to the potential options for this often hard-to-treat group.

"It's an extremely exciting time in nephrology to finally have additional options for the treatment of our patients," said session co-moderator Linda Awdishu, PharmD, a professor of clinical pharmacy at the University of California, San Diego.

SGLT2s shine

Results from DAPA-CKD (1) showed that dapagliflozin improved cardiovascular and kidney outcomes for patients with type 2 diabetes mellitus and chronic kidney disease, but whether the results extended to other types of chronic kidney disease was not clear, said David Wheeler, MD, professor of kidney medicine at University College London.

At Kidney Week, Wheeler presented results of a prespecified secondary analysis including 4304 participants of the DAPA-CKD Trial who showed that the heart and kidney benefits of dapagliflozin were consistent across all types of kidney disease. Patients with polycystic kidney disease and immune system disease requiring immunosuppressant therapy were excluded.

"We've shown that these renal and cardiovascular mortality benefits are present regardless of the underlying cause of chronic kidney disease and regardless of the presence or absence of type 2 diabetes," Wheeler said. "Dapagliflozin was well tolerated with a safety profile that was consistent with that seen in other populations."

Wheeler noted that "importantly, none of the nondiabetic patients developed ketoacidosis or hyperglycemia in the study." He also reported during a press briefing that they did not see an excess of amputations in patients taking the drug compared with placebo. The US Food and Drug Administration (FDA) had initially warned of a potential risk of foot and leg amputation with the SGLT2 inhibitor canagliflozin, but that warning was later removed based on newer data (2).

"Safety information from recent clinical trials also suggests that the risk of amputation, while still increased with canagliflozin, is lower than previously described, particularly when appropriately monitored," according to the FDA statement.

Rajiv Agarwal, MBBS, professor of medicine at the Indiana University School of Medicine, said he believes SGLT2 inhibitors do not increase the risk of amputation.

"Anybody who has had a previous amputation will be at risk of a future amputation," Agarwal said. "These drugs don't enhance that risk."

Daniel Weiner, MD, associate medical director of dialysis and associate professor at Tufts University, said that during the Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE) Trial of canagliflozin (3), he and his colleagues paid a lot of attention to diabetic foot wounds, something he said should be a standard of care in vulnerable patient populations. "In these vulnerable populations with diabetes and kidney diseases, we should be looking at feet regularly," Weiner said. Weiner added in a follow-up interview by email that he believes agents in this class of drugs have similar risk and benefit profiles.

The EMPEROR-Reduced Trial (4) has previously shown that empagliflozin reduces cardiovascular death and heart failure hospitalization and slows kidney function decline in patients with heart failure with reduced ejection fraction. Now, data presented at Kidney Week and published (5) in *Circulation* show that the benefits extend to patients with chronic kidney disease. The study found that empagliflozin reduced the risk of cardiovascular death and heart failure hospitalization by one-quarter; reduced total heart failure hospitalizations by 30%; and reduced a composite of dialysis, transplant, and kidney death by one-half.

"Empagliflozin slows kidney function decline in patients with and without chronic kidney disease across the spectrum," said Faiez Zannad, MD, PhD, a cardiologist and professor of therapeutics at the University of Lorraine in France, during the High Impact Clinical Trials session. Additionally, Zannad et al. (5) found that the treatment was well tolerated by patients with and without chronic kidney disease.

Diabetes options

Treatment options for patients with kidney disease and diabetes have long been limited, but the growing data on the benefits of SGLT2 inhibitors are promising. The results from FIDELIO-DKD suggest that finerenone may be another promising option—if it is approved by the FDA.

In the FIDELIO-DKD Trial, which was published in *The New England Journal of Medicine* (6), 5734 patients with chronic kidney disease and type 2 diabetes mellitus from 48 countries were randomized to receive either finerenone or placebo. All of the patients were treated with renin-angiotensin system blockade prior to randomization. The investigators found that finerenone reduced a composite of kidney failure, a sustained 40% decrease in the estimated glomerular filtration rate from baseline, or death by 18%, said Agarwal, a study co-author, during a press briefing. The drug also reduced a composite of death from cardiovascular causes, nonfatal cardiac events, and hospitalization for heart failure by 14%.

"This is an exciting discovery because we've had many other [failures] in this high-risk population of patients with diabetes and chronic kidney disease," Agarwal said.

As expected, patients in the finerenone group had a higher rate of hyperkalemia compared with the placebo group (18.3% vs. 9%), but only 2.3% of patients in the finerenone group permanently discontinued this drug because of hyperkalemia compared with 0.9% in the placebo group, he said. He noted that the rate of discontinuation because of hyperkalemia was much higher with spironolactone in the AMBER Trial (7).

"An ideal drug would cause no hyperkalemia, but if you look at absolute risk, it's a fraction of what we saw when we used spironolactone in this vulnerable population," Agarwal said.

Too small a proportion of patients in the FIDELIO-DKD Trial (4% in the placebo and 5% in the treatment group) were taking an SGLT2 inhibitor to determine what role SGLT2 inhibitors might play in combination with finerenone, Agarwal said. Wheeler noted during the press briefing that he and his colleagues saw benefits in the small proportion of patients in the DAPA-CKD Trial who were taking a mineralocorticoid receptor antagonist along with dapagliflozin.

Agarwal said dual therapy with an SGLT2 inhibitor and renin-angiotensin-aldosterone system (RAAS) inhibitors is a well-established clinical practice. If finerenone were to be approved by the FDA, then it might become part of a stepwise approach or part of a triple therapy for high-risk patients.

"If we were to be [FDA] approved then, definitely you're going to individualize therapy," he said.

Among the other trials presented during the High Impact Clinical Trials session were the following:

- A trial showing that using citrate for anticoagulation during continuous kidney replacement therapy extended filter life compared with heparin was inconclusive regarding a mortality benefit. Heparin was associated with more bleeds, and citrate was associated with more infections. (Abstract FR-OR75)
- Results from the Reducing the Burden of Dialysis Catheter Complications: a National Approach (REDUCCTION) Trial found that a safety bundle designed to reduce catheter-related bloodstream infections did not significantly reduce these infections. (Abstract FR-OR56)
- A cluster randomized trial of oral protein supplementation during dialysis for patients with normal serum albumin did not find a mortality benefit for patients with normal serum albumin. (Abstract-FR-OR55)

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Researchers Hope to Move Ahead with Artificial Kidney

By Karen Blum

Plans to develop an implantable artificial kidney have been waylaid by fundraising challenges and the COVID-19 pandemic, but researchers hope to soon have a business case to move the work forward in clinical trials, the project's co-director said during Kidney Week 2020 Reimagined.

"This is envisioned to be a device that provides the key functions of a kidney transplant," said Shuvo Roy, PhD, technical director of The Kidney Project, an effort housed at the University of California, San Francisco, and Vanderbilt University Medical Center, to develop an implantable device to provide kidney replacement therapy.

Designed to be inserted in the abdomen, the device will combine two features: a mechanical ultrafiltration unit called a hemofilter, which can remove toxins from the blood by passing it through silicon membranes fabricated with nanometer-scale pores; and a bioreactor, which will contain cultured human kidney cells to perform kidney functions such as maintaining adequate fluid volume and producing hormones. It will not require electrical power, instead operating off the body's blood pressure. Unlike a transplant, no immunosuppression will be necessary.

According to Roy, the basis for a bioartificial kidney can be traced back to pioneering work conducted at the University of Michigan in the 1990s and early 2000s by nephrologist H. David Humes, MD. Humes used one dialyzer for clearance in his model and a second dialyzer lined with kidney cells. A bioreactor connected to a hemofilter is similar to how the tubule is connected to the glomerulus in the natural kidney. Preclinical experiments demonstrated that renal cell therapy through this Renal Assist Device (RAD) could provide physiological treatment for acute kidney injury.

A later clinical trial (1) in acute kidney injury patients demonstrated that survival among patients treated by RAD was 50% better than among those receiving standard continuous renal replacement therapy. The improvement in survival could be attributed to kidney cells in the bioreactor, Roy said.

"The work was notable in that it was the first-ever demonstration of cell therapy to treat kidney failure in patients," he said, but it was a large, complex system with at least two dialysis machines, lots of tubing and multiple pumps. Roy partnered with nephrologist William H. Fissell, MD, now at Vanderbilt, and set out to make a smaller, implantable version of the RAD system.

The team took an engineering approach to designing a miniaturized system, Roy explained. Although in cardiology, engineering helped the cardioverter defibrillator go from "a bulky bedside machine" to an implantable device, the fundamental workhorse of dialysis machines—the hollow fiber membrane dialyzer—"has not changed much since being introduced over 50 years ago," he said. "While there have been some material improvements, it still requires high-driving pressure to drive blood through them, they do not remove toxins efficiently…and they clot and stop functioning after some time of use."

The Kidney Project investigators used semiconductor silicon wafers to build a new nanopore membrane engineered to be thin and robust, Roy said: "They are precisely machined with pores that mimic the natural kidney's microstructure." The team can modify the surface of the membranes by adding thin-film polymer chemistries to prevent fouling and reduce the likelihood of clots. They also can add to the surface different extracellular matrix materials that provide a more physiologic environment to support the growth of kidney cells.

Investigators have tested the prototype hemofilters and bioreactors in pigs. The hemofilter design has been refined such that blood flow is successfully maintained through the device for as long as 30 days using only antiplatelet therapy, not systemic anticoagulation, Roy said. Additional studies have shown the hemofilter can provide urea and creatinine clearance after implantation in pigs for at least three consecutive days without blood thinners.

The initial bioreactor prototype, about the size of a deck of cards, contains human kidney cells behind precisely sized pores that prevent the transport of immunogenic components and provide immunoprotection, he said. The team has tested the device implanted in the neck of pigs, with no immunosuppression or systemic anticoagulation used. After three days, investigators removed the device and studied the kidney cells for signs of rejection. The human kidney cells remained in place within the bioreactor and remained healthy despite being exposed to a foreign immune system, with no clots. Roy presented some of this work during Kidney Week 2019. Both parts of the system could work just using the body's own blood pressure without the need for local/battery power or external electrical connections.

"The next steps are to scale this up, integrate the two components and show function in an appropriate model of kidney failure," he said. "This is not without its risks as an ambitious project."

Roy said he envisioned the device being about 300–600 mL in size, "akin to a large coffee cup," with a weight of "hundreds of grams." The devices should last many years, he said, although in a patient preference survey conducted with the American Association of Kidney Patients, many patients reported they would find a maintenance period of two years acceptable.

For more information, see https://pharm.ucsf.edu/kidney.

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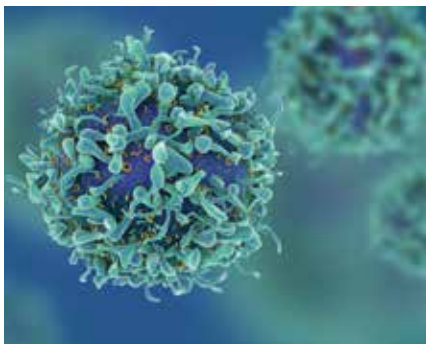


Can nTregs Minimize Immunosuppression after Kidney Transplant?

An approach using autologous natural regulatory T cells (nTregs) appears safe and feasible for minimizing immune suppression after kidney transplantation, according to a phase I/IIa clinical trial in *The British Medical Journal*.

The researchers report an initial experience with their "in-house" autologous CD4+CD25+FoxP3+ nTreg product in 11 living kidney donor transplant recipients. The nTreg product was administered 7 days posttransplant in a single intravenous dose of 0.5, 1.0, or 2.5 to 3.0 × 10^6 cells/kg. After treatment, the investigators attempted stepwise tapering of standard triple immunosuppression to low-dose tacrolimus monotherapy up to week 48.

A composite clinical and safety outcome (biopsy-confirmed acute rejection, nTreg infusion-related adverse effects, and signs of overimmunosuppression) was assessed at 60 weeks, plus an additional 3 years' follow-up. Outcomes were compared with those of nine recipients enrolled in a previous reference trial. The study also assessed allograft functioning and an exploratory biomarker portfolio.

For all 11 enrolled patients, a 40- to 50-mL sample of peripheral blood obtained 2 weeks pretransplant yielded nTregs of sufficient yield, purity, and functionality. There were no dose-limiting toxic effects. All recipients in both trials had a functioning allograft at 3 years with similar clinical and safety outcomes.

Ten of the 11 patients receiving nTregs were successfully weaned to low-dose tacrolimus monotherapy. Two patients were switched back to standard immunosuppression due to clinical events; thus, 8 patients achieved stable monotherapy immunosuppression. Mechanistic studies suggested that nTregs reduced activation of conventional T cells, with an in vivo shift from a polyclonal to an oligoclonal T cell receptor repertoire.

Preclinical trials have suggested that adoptive transfer of nTregs might be a promising approach for tapering immunosuppression after organ transplantation. The new study adds further evidence of good clinical and safety outcomes with nTregs. The investigators conclude, "These data show stable minimisation of immunosuppression in most patients receiving nTreg treatment after kidney transplantation" [Roemhild A, et al. Regulatory T cells for minimising immune suppression in kidney transplantation: Phase I/IIa clinical trial. *BMJ* 2020; 371:m3734. doi: 10.1136/bmj.m3734].

Intensive Urate Lowering in Diabetic Kidney Disease

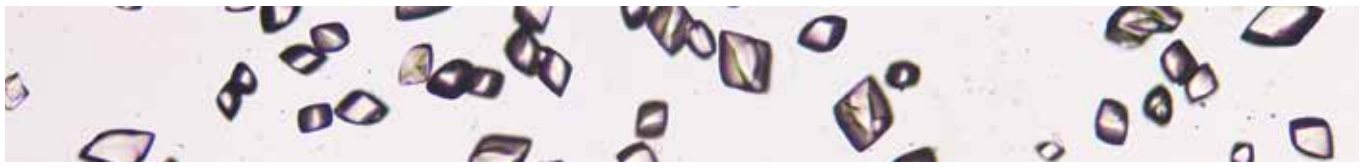
An intensive urate-lowering strategy consisting of verinurad and febuxostat reduces albuminuria in patients with type 2 diabetes and hyperuricemia, reports a phase 2 trial in the *American Journal of Kidney Diseases*.

The multicenter trial enrolled 60 adult patients with type 2 diabetes; albuminuria, urine albumin-to-creatinine ratio (UACR) 30 to 3500 mg/g; and hyperuricemia, serum urate (sUA) concentration 6.0 mg/dL or greater. Mean age was 61.5 years, 70% of patients were men, and about one-half had an estimated glomerular filtration rate (eGFR) of less than 60 mL/min/1.73 m^2. The study excluded patients with stage 4 or 5 chronic kidney disease (CKD).

Patients were randomly assigned to intensive urate-lowering therapy with the specific urate reabsorption inhibitor verinurad (9 mg) plus the xanthine oxidase inhibitor febuxostat (80 mg) or placebo. Treatment lasted for 24 weeks. The primary outcome was change in UACR from baseline to 12 weeks.

Intensive urate lowering was associated with significant reductions in UACR compared to placebo: by 38.6% at 1 week, 39.4% at 12 weeks, and 49.3% at 24 weeks. The verinurad/febuxostat combination also lowered sUA levels: by 59.6% at 12 weeks and 63.7% at 24 weeks.

There were no significant differences in eGFR, serum creatinine, or cystatin C. The urate-lowering combination was well tolerated, with safety outcomes similar to



those of placebo.

Hyperuricemia is associated with the presence and development of CKD and is an independent predictor of the development of microalbuminuria. Experimental and clinical evidence suggests that treatment to lower sUA may slow CKD progression, while reducing kidney and cardiovascular events.

This proof-of-concept study shows that the combination of verinurad and febuxostat, which reduces uric acid via different mechanisms, can lower albuminuria in patients with type 2 diabetes and hyperuricemia. Although noting that their study shows a "true pharmacologic effect," the authors emphasize the need for larger clinical trials to determine whether intensive urate lowering can help to preserve kidney function [Stack AG, et al. Effect of intensive urate lowering with combined verinurad and febuxostat on albuminuria in patients with type 2 diabetes: A randomized trial. *Am J Kidney Dis*, published online ahead of print Oct. 29, 2020. doi: 10.1053/j.ajkd.2020.09.009; https://www.ajkd.org/article/S0272-6386(20)31072-6/fulltext].

High Rate of AKI in Hospitalized COVID-19 Patients

More than one-fourth of patients with COVID-19 admitted to a New York City hospital in the early weeks of the pandemic had acute kidney injury (AKI), reports a study in the *American Journal of Nephrology*.

The retrospective analysis included 469 patients with COVID-19 admitted to the study hospital over a five-week period in March–April 2020. The hospital, which served a high-poverty area of Brooklyn, was among the centers with the most COVID-19 admissions. The study focused on the incidence of in-hospital AKI among COVID-19 patients, defined by The Kidney Disease: Improving Global Outcomes (KDIGO) criteria. Baseline characteristics and laboratory findings associated with this diagnosis were analyzed as well.

Mortality associated with AKI among COVID-19 patients was analyzed as a secondary outcome. The study excluded patients on maintenance hemodialysis or kidney transplant recipients.

The study's patients had a mean age of 64 years and were 57% male and 73% African American. About 15% of patients were in a hemodynamically unstable condition at presentation, and 21% received mechanical ventilation during their hospital stay.

At admission, 44.1% of the patients had an estimated glomerular filtration rate (eGFR) of less than 60 mL/min/1.73 m^2. During hospitalization, 27.1% of COVID-19 patients developed AKI; this included 39.1% of patients with a low eGFR compared to 17.9% of those with an eGFR of 60 mL/min/1.73 m^2 or higher. Stage 3 AKI was present in about one-half of the cases.

Patients with low eGFR were more likely to develop AKI within 48 hours after admission: 53.1% versus 23.4%. Risk factors for AKI included male sex; hypertension; angiotensin-converting enzyme inhibitor or nonsteroidal anti-inflammatory drug use; hemodynamic instability; mechanical ventilation; acute respiratory distress syndrome; and elevated ferritin, creatinine kinase, brain natriuretic peptide, and troponin 1 levels.

Mortality was 71.1% among patients with AKI versus 28.45% in those without AKI. On adjusted analysis, independent risk factors for death were elevated blood urea nitrogen, hazard ratio (HR) 1.75; low eGFR, HR 1.43; AKI stage 2, HR 1.86; and AKI stage 3, HR 2.1. For patients with stage 3 AKI, kidney replacement therapy did not improve survival.

As has become clear, COVID-19 is associated with a significant risk of AKI in hospitalized patients. These data from early in the pandemic show a high incidence of AKI at a hospital serving a low-income, racial/ethnic minority population in New York.

The experience shows "extremely high" mortality, particularly in patients with stage 3 AKI [Zahid U, et al. Acute kidney injury in COVID-19 patients: An inner city hospital experience and policy implications. *Am J Nephrol* 2020; 51:786–796. doi: 10.1159/000511160].

Fellows Corner

Healthcare Transition from Pediatric- to Adult-Focused Care: A Former Pediatric Nephrology Fellow's Perspective

By Sai Sudha Mannemuddh

Sai Sudha Mannemuddhu

One thought that stood out during the first year of my fellowship was "healthcare transition from pediatric- to adult-focused care." When the chart and age indicated readiness for patients' transitions, I was not prepared. There were a lot of questions. Are they ready? Are they going to do well? Will they be able to fulfill their dreams and goals? Are these feelings similar to what one encounters when dropping their child off at college? I wondered. I wasn't sure.

What does transition mean? To understand this better, I decided to make a note of the words that pop into the minds of healthcare professionals when we consider transition. I also asked what was going on in the minds of parents and family members. Most important of all, what was in the minds of patients? Were we all on the same page? If we were, then that would have been great. I was taken by surprise when I saw the results. Take a look at the word clouds in Figure 2 representing what each of us would think. Can you tell which word cloud belongs to whom?

It is easy to recognize the owners of each word cloud. Personally, I felt as if we were talking in different languages. This potential (or real) communication barrier could make the process of healthcare transition challenging. I felt that there was only one way to address this: Have a conversation. Learn the patients' and their families' language. The process of healthcare transition involves patients, families, healthcare providers, healthcare systems, and the community.

We have learned that the process of transition of care should begin early, around 12 to 14 years (1), continuing until ages 24 to 26. This might seem very early, but once patients reach the core teenage years, they get busier with their personal lives and education, not to mention peer pressure. Starting the process by helping them understand their disease and medications can be the first step. Once the fear of the unknown disappears, it can lead to the emergence of more responsible and independent behaviors. Encouraging patients to ask questions will allow us to know them as individuals and could also help them when they meet their new care providers during and after transition. Involving patients and families in every step of the process can mitigate their anxiety and improve accountability.

There are six core elements of transition: developing a transition policy, transition tracking and monitoring, assessing readiness for transition, transition planning, transfer of care, and transition completion (2). An algorithm for transition of care, tailored from McPherson et al. (3), can be adapted for any patient with a chronic medical condition (Figure 1).

With this knowledge, we made a few changes in our program. We started providing chronic kidney disease education flash cards during initial visits and quizzing the patients (>12 years old) during subsequent visits. We also encouraged patients to consider "kidneys" as a topic of choice for their school science projects. A quality improvement project called "Do you know your medications?" directed toward >12 year olds is under way. Other things to consider are developing a transition clinic and giving out a transition passport. Although there are many ways to ensure a smooth transition, I believe this is a start and hope to make improvements as time goes on.

Last, I have a request. Dear adult specialists, whenever you encounter newly transitioned patients, please understand that they are survivors of complex health conditions who may have cognitive impairment and must deal with the challenges associated with a difficult age in life. Also, please be patient, and direct "helicopter parents" to let go, honoring their efforts in helping their children survive.

Acknowledgment

I thank Maria Diaz-Gonzalez de Ferris, MD, MPH, PhD, director of the UNC Chapel Hill Transition Program, for encouraging me to write this article. Her website and free tools for healthcare transition preparation are at https://www.med.unc.edu/transition/.

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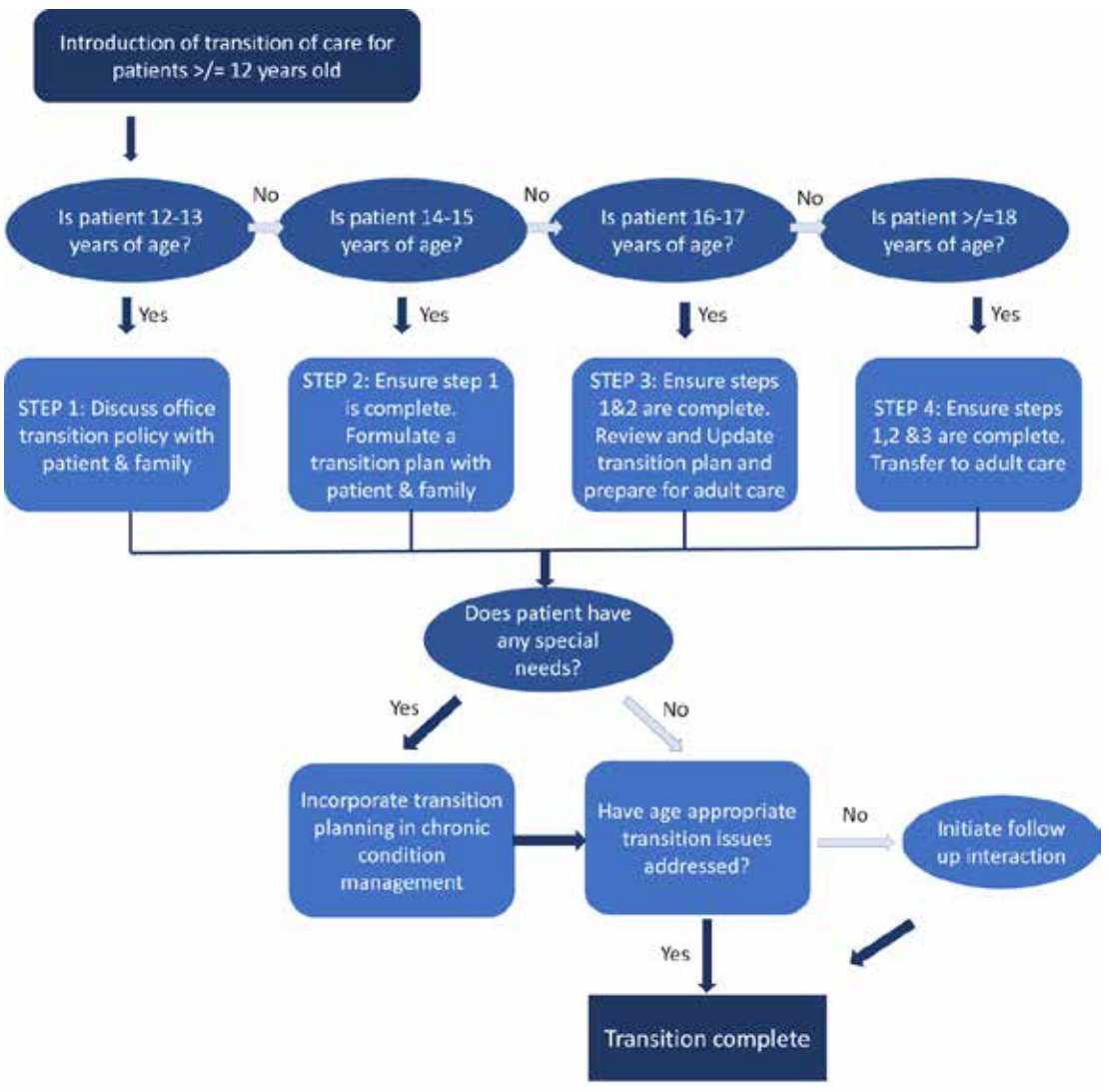
Figure 1. Six core elements of transition



Adapted with permission from McPherson et al. (3)

Figure 2. Word clouds of young patients, their parents, and their healthcare providers as patients approach transition to adult care

Are you a fellow and have a tip or idea you'd like to share with your fellow peers and the broader kidney community?

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