ASN American Society of Nephrology

KidneyNews

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Kidney Risks of Climate Change: A Growing Concern

By Bridget M. Kuehn

An epidemic of CKD among agricultural workers in different parts of the world has scientists searching for the potential cause. Among the chief suspects—although not the only one—is climate change–related heat stress.

As scientists work to verify whether climate change is contributing to the epidemic, concern about the potential health impacts of climate change around the world is growing. A 2017 report from the United Nations outlined the health risks associated with climate change, including increases in vector-borne diseases and extreme weather events, both of which can contribute to new kidney disease and put patients with existing kidney disease at risk (1). There is also growing evidence that rising temperatures increase the risk of kidney stones and AKI.

"Temperatures are increasing throughout the world, and whether or not we think it's manmade, everyone acknowledges that temperatures have been increasing," said Richard Johnson, MD, Tomas Berl Professor in the Division of Renal Diseases and Hypertension at the University of Colorado in Aurora. He noted that temperatures have increased about 1 degree Centigrade over the past 50 to 100 years, and although that may not sound like much, it's contributing to heat waves and other extreme weather events.

Canary in a coal mine?

When alarming numbers of young agricultural workers without traditional risk factors like diabetes, hypertension, or glomerular disease started showing up in Central American hospitals in the 1990s with ESKD, clinicians were concerned, noted Johnson and colleagues in a recent review in the *New England Journal of Medicine* (2). Johnson explained that the cases were clustered among laborers likely exposed to heat stress, which is a known risk factor for AKI. The initial reports led to the identification of clusters of CKD in Honduras, Nicaragua, El Salvador, and Guatemala, he said.

"The thing that was striking was that there are so many people developing this condition, and it looks like it's been increasing," Johnson said. "These countries now have some of the highest rates of kidney failure in the world. It's partly because of this."

Similar clusters of CKD have since been identified in agricultural workers in Sri Lanka and India. But not

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Expediting Transplant with Technology

Drone Delivery, Organ Tracking and Matching Technologies Put to the Test

By Bridget M. Kuehn

You can order just about anything online and track it every step of the way until it reaches your doorstep thanks to modern logistics and technology. Now, those same technologies are being applied to kidney transplants to speed the process and enable more transplants.

It currently takes on average about 18 to 20 hours to get a kidney from the donor to the transplant patient, explained Joseph Scalea, MD, assistant professor of surgery at the University of Maryland Medical Center in Baltimore. During that time the organ is chilled and kept in a solution to protect it from injury, but each hour it spends this way increases the risk of poor outcomes like delayed graft function after transplant or failure of the transplanted organ.

"You can get a pizza on-demand and figure out exactly when it's going to arrive at your house," Scalea said. "For

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Kidney Risks of Climate Change

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all areas where agricultural workers log long hours in hot conditions have seen an uptick in CKD, Johnson noted. Scientists are exploring several potential culprits that might contribute to kidney damage, including toxic agricultural chemicals, heavy metal exposure, silica inhalation, infectious diseases that may cause kidney injury, genetic vulnerabilities, repeated heat stress, or some combination of these risk factors.

"The jury is still very much out on whether heat is the primary driver," said Katherine Barraclough, MD, a consultant nephrologist at the Royal Melbourne Hospital and associate professor at the University of Melbourne in Australia. "It is reasonable to assume, though, that even if heat turns out to not be the primary driver, it has the potential to contribute to or exacerbate kidney dysfunction from any cause, and therefore needs to be treated as a risk factor and managed."

Johnson and his colleagues are testing their hypothesis that repeated heat stress and dehydration in the workers are contributing to low-grade kidney injury by comparing the weather and climate maps with the clinical data they are collecting in workers in Central America. Johnson doesn't rule out other potential contributing factors, but he believes that heat is playing a substantial role.

"If I'm right, we're going to continue to see these outbreaks occurring in more and more places as climate change occurs," Johnson said.

Already, scientists in the United States have identified high rates of AKI among agricultural workers in California (3) and Florida (4), who may also be exposed to extreme heat and poor hydration. Poor working conditions likely are contributing to the kidney harms documented among agricultural workers and have led to some prevention efforts such as promoting better hydration, Johnson noted.

Roberto Lucchini, MD, a professor at the Icahn School of Medicine at Mount Sinai in New York, who studies the health effects of occupational exposures, spoke recently at an event held by the El Programa Salud, Trabajo y Ambiente (SALTRA) in Panama about climate-related health concerns. He said both companies and ministries of health throughout Central America are concerned and are looking for ways to prevent this unexplained form of CKD. He noted that the associated costs for dialysis and other end stage renal care for the countries are substantial.

"They want to put some resources into understanding the ways to target the disease, to prevent the disease," Luchini said. For now, he said there is a need to get a better handle on the epidemiology of the disease. Additionally, he noted, nephrologists in the region are working to develop uniform diagnostic criteria that may help improve the ability to pool their data.

Prevention emphasized

Whereas climate-related CKD risks continue to be investigated, the growing risk of kidney stones and AKI linked to rising temperatures and extreme weather events has been well established, noted Barraclough in a recent review in *Kidney International* (5). For example, in the United States, scientists have linked rising temperatures to an increased risk of kidney stones (6), and scientists in Australia have linked heat waves to increased emergency department admissions for AKI and kidney stones (7).

"There is an increased risk of both AKI and [kidney stones] with rising temperatures—this is clear and well documented," she emphasized. She noted that the elderly, patients with CKD or existing kidney stones, and those taking certain medications like diuretics, β-blockers, and angiotensin-converting enzyme inhibitors are at increased risk for those heat-related harms. Barraclough emphasized the importance of nephrologists advising their patients to stay well hydrated and cool, to avoid strenuous activity, and to follow their physician's recommendations about medication adjustments during extreme heat events.

In addition to rising temperatures, climate change is contributing to extreme weather events like hurricanes, which pose considerable risks to patients with ESKD who rely on dialysis. When Hurricanes Irma and Maria clobbered the Caribbean in 2017, emergency personnel and clinicians scrambled to evacuate dialysis patients or to piece together care for them in the absence of electricity and with medications hard to access (8). In the aftermath of Hurricane Katrina in 2005, the Kidney Community Emergency Response Coalition developed recommendations for dialysis centers and their patients (9). Barraclough highlighted the report's recommendations that both facilities and patients have emergency plans in advance.

"Nephrologists need to be involved at all stages, either doing the work [by] educating patients about what they are able to eat and drink when in the midst of a disaster and unable to access dialysis or providing input into higher-level preparedness planning," she said.

There have been growing efforts among physicians and medical institutions to draw attention to the need to address climate change. For example, the Lancet Countdown was established to monitor the health effects and response to climate change (10). Peter Blankestijn, MD, a nephrologist at the University Medical Center in Utrecht, The Netherlands, argued in a recent commentary that the countdown should be a call to action for nephrologists (11). He explained in an interview that not only does climate change impact health, but also healthcare contributes to climate change—for example, through the production of waste, carbon emissions, and energy use.

"[This] is very much in conflict with the basic principle in medicine of 'first do no harm,'" he said. The first step to reducing that harm, he said, is becoming aware of it and helping to alert others. He noted that the European Renal Association—European Dialysis and Transplant Association will be featuring sessions on climate change at its next meeting in Milan, Italy.

Barraclough also recommended that kidney patients and nephrologists get involved in efforts to help curb climate change. She noted in her review that it may not be possible to stop climate change in the near term, but a concerted global effort may be able to limit warming to 2 degrees Centigrade. Additionally, many interventions to combat climate change may have other health benefits as well, she noted. For example, adopting a plant-based diet or walking or bicycling instead of driving may contribute to improved overall health and well-being in addition to reducing emissions that contribute to climate change. Barraclough noted that clinicians in particular can be powerful advocates.

"I personally think speaking out is our responsibility—it is our job to protect health, and we must speak on behalf of those with less of a voice—this includes those vulnerable populations who will be most impacted by the health effects of climate change and future generations," she said. ■

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Expediting Transplant with Technology

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life-saving organs, nah, that takes 20 hours and you have no idea when it's going to happen."

But Scalea and his colleagues aim to change that by enabling "on demand" delivery of donor kidneys using drones and other technology. In April 2019, he and his team celebrated the first transplantation of a kidney delivered by an unmanned drone. It's just the first step for drone-facilitated delivery. More testing of better, larger, and faster drones lies ahead before this technology will be widely available. But Scalea is hopeful.

"If we can make a more efficient system, I think we could do more transplants," he said.

Scalea is not alone in his effort to leverage technology to streamline kidney transplants. Donor kidneys are now labeled and tracked using a United Parcel Service (UPS)-like bar-code system. And the technology team at the United Network for Organ Sharing (UNOS) has two pilot projects underway that could expedite the process of matching a donor kidney with a patient in need of a transplant.

Taking flight

Trina Glispy of Baltimore, a 44-year-old who had been on dialysis since 2011, received the first drone-delivered kidney on April 19, according to the University of Maryland Medical Center. The roughly 10-minute delivery flight across 2.8 miles marked a major achievement for Scalea and his 100-person team of clinicians, scientists, and engineers who worked for three years to make it happen.

"The whole thing was amazing," Glispy said. "Years ago, this was not something that you would think about."

The current system for organ transport is logistically complicated, using a mix of ground-based carriers, commercial airlines, chartered jets, or helicopters, said David Klassen, a nephrologist and chief medical officer at UNOS. The safety of transplant teams who may accompany the organ on late night flights is also a concern, Klassen noted. It can also be expensive, noted Scalea, who said the average transport cost is about $40,000 per organ.

"Drone technology has the potential to be faster," Klassen said. "It is potentially less logistically complicated."

But developing the drone technology necessary to safely transport an organ is no small feat. Scalea and his team designed and developed a box that would maintain the organ's temperature and system for providing real-time updates to clinicians about the organ's status and location though an app on their phone. He has since patented the technology.

He partnered with engineers from the University of Maryland, who designed and built a custom drone that could manage the 10-pound package. The engineers also helped navigate the logistical and technical challenges of the project.

"It's a systems engineering problem because it's not just one brand of engineering or one type of technology," said Matt Scassero, director of the University of Maryland's Unmanned Aircraft Systems Test Site and a member of the team. "You have to get them all to work together."

The drone was designed with redundant systems to ensure that if one part of the machine failed, the organ was protected and could still be safely delivered, Scassero noted. This included a parachute in case of an emergency landing, dual battery systems, as well as back-up power train, power distribution, and communications systems. The team had 2 drone pilots ready to take over if the automated system failed—but that wasn't necessary, Scalea said.

The team also worked with the Federal Aviation Administration (FAA) to get permission to fly over an urban space near an airport at night, Scassero said. They worked with the city of Baltimore and its first responders to close off a few busy streets while the drone was passing over them to minimize any risks to those below.

Before flying an actual organ intended for transplant, they tested the drone for seven and a half hours over 44 different trips, Scalea said. They also tested the effects of the trip on a donor kidney that wasn't accepted for transplant. They found that the system kept the organ at a steady temperature, although some pressure changes occurred at changing altitudes. The organ experienced less vibration on the drone flight than on an airplane, and biopsies taken before and after the flight revealed no harm.

"It's a triumph of teamwork and leadership and vision, and it's very, very cool," Scalea said.

To achieve the goal of transporting organs over longer distances, Scassero said the team will have to create a larger drone that can navigate long distances out of sight from the engineering team. This will require getting FAA approvals for a different class of drone. The next steps will be continued testing of the technology in both urban and rural areas.

Although he cautioned that this exciting development is just a first step, Klassen noted the technology may one day have the potential to help transport organs to more geographically distant patients and potentially cut transport costs.

If you can get organs potentially within the same timeframe to a broader group of patients, that can potentially address issues of geographic equity.

"If you can get organs potentially within the same timeframe to a broader group of patients, that can potentially address issues of geographic equity," he said. "There's a lot of potential."

Faster matching

When a donor kidney becomes available, a patient's transplant team gets an offer and must quickly decide whether it's a good option for the patient. If it's not a good fit and they decline it, it will be offered to the next patient in line.

Each hour that goes by in this process reduces the quality of the donor kidney and decreases the likelihood of transplant success. Some organs that are less optimal to begin with—for example those from older donors that are expected to function for shorter time periods—may be declined multiple times, Klassen noted. By the time these less optimal kidneys reach a center willing to accept it, it may be too late.

In fact, about 19% of donor kidneys are discarded and never used, said Rob McTier, a business architect at UNOS. Some of these organs may not meet increasingly high standards for transplantation, he explained, but UNOS also hears from centers that say they would have used a less optimal kidney if it had gotten to them sooner.

"We're trying to devise systems of facilitated allocation to really get the organs most quickly to the centers that are most likely to use them," said David Klassen, chief medical officer at UNOS.

One UNOS project is allowing 7 organ procurement organizations (OPOs) to directly upload images of the donor organ into UNOS's DonorNet system to provide centers with the information they need to evaluate an offer as quickly as possible. Currently, some OPOs use external services to share images of donor organs with prospective transplant teams, which may add time to the process, McTier said. Other OPOs may upload images as lower quality attachments or may not provide images at all. The pilot will allow any transplant center receiving an offer from one of the participating OPOs to directly access an interactive image.

Another pilot project will allow centers to filter out kidney offers they are unlikely to accept. It will allow transplant centers to set multiple limits on the offers they receive, McTier said. For example, they may say they don't want offers of kidneys from deceased donors more than 100 miles away. The pilot launched in May 2019 with 29 participating transplant centers.

In the first phase of the pilot project, the centers will establish filters. They may use their existing criteria for donor organs or may use potential criteria suggested by a UNOS analysis of their past choices. UNOS will then analyze how applying those filters would have affected UNOS offers to the centers over the previous 2 to 5 years. In the second phase, the filters will be applied to real donor offers the centers receive. In a third phase, the centers may be able to establish specific filters for individual recipients.

"We're really paying close attention to whether this will have an effect on the kidney discard rate and decrease that," McTier said.

Ninety-six percent of donor organs across the country are currently tracked using a UPS-like bar code system. The program called TransNet started in 2012. It was designed by Department of Health and Human Services Entrepreneur-in-Residence David Cartier, who formerly worked at UPS and used his logistics expertise to create a standardized process that would help streamline organ procurement and reduce errors associated with hand-written labels.

The effort helped eliminate the need for repeated label checks by OPO coordinators, who have the challenging job of working with deceased donors families, said Chris McLaughlin, chief of the Organ Transplantation Branch at the Health Resources and Services Administration.

"It makes their job a little bit easier," McLaughlin said. "It was a tremendous success from our perspective."

Klassen noted UNOS is currently looking at ways to use machine learning and big data analytics techniques to make better use of the data the organization has. The goal of all these projects is "to help get the right organ to the right person as effectively as we can," he said. ■

Suggested Reading

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AKI!NOW

Promoting Excellence in the Prevention and Treatment of Acute Kidney Injury

By Jorge Cerdá, MD, MS, FASN, Chair, AKI!Now Steering Committee

Acute kidney injury (AKI) does not discriminate in its impact. From the very young to the elderly, it can strike at any time, stems from a wide variety of causes, and demonstrates a complex variety of symptoms. The resulting kidney damage is often severe and life-threatening. Those who recover from AKI have a greater likelihood of important health consequences including recurrent AKI, progression to chronic kidney disease or end stage kidney disease, disability, and death.

Given the current state, in addition to developing newer paradigms and treatments, improvement in AKI outcomes will require a very large discussion involving all the disparate members of the healthcare team involved in AKI care, with the goal of promoting education, awareness, early recognition, and thorough understanding of this complex syndrome.

Recognizing these obstacles, through a partnership with Baxter, the American Society of Nephrology has established a new initiative, *AKI!Now*, with the goal of promoting excellence in AKI prevention and treatment by building a foundational program that transforms education and delivery of AKI care, contributes to reducing morbidity and associated mortality, and improves long-term outcomes. This is the first of a series of communications on the planned activities of the AKI!Now Steering Committee.

Multiple factors conspire against efforts to improve AKI outcomes. These include unreliable and late AKI recognition. In particular, first-contact practitioners may be unaware of the problem and may not recognize it in its early stages, when timely intervention is most effective. In addition, once the possibility of AKI is recognized, traditional markers of kidney function are late to change, and are confounded by patient characteristics and fluid status. Despite recent discovery of multiple sensitive and specific biomarkers, their incorporation into routine practice has been inconsistent.

A growing evidence body suggests that widely held paradigms, such as the distinction between "*prerenal*" and "*intrinsic*" kidney injury are not consistently appropriate, and may lead to reflex fluid administration, which is often not only unnecessary, but can cause fluid overload, which is associated with worse outcomes. Newer concepts, largely based on the development of novel biomarkers, increasingly permit the detection of "subclinical" AKI when injury biomarkers indicate absence of damage, and to predict the likelihood of a patient developing AKI even before injury occurs.

Furthermore, AKI is not solely a kidney problem. Developing evidence demonstrates that via "organ crosstalk," AKI is associated with key changes in the function of distant organs such as increased risk of brain and pulmonary edema and cardiac dysfunction, which then complicate treatment and become important determinants of patient outcome.

Part of the reason for our inability to design effective AKI treatments may stem from the heterogeneity of the syndrome; subjects widely differ in their susceptibility, mechanism of injury, and likelihood of recovery. Utilization of a variety of AKI prediction scores, development of context-heightened awareness, enhanced estimation of the probability of AKI development, and use of functional maneuvers such as a protocolized diuretic challenge and "renal angina" detection, will make the application of biomarkers efficient and permit an accurate description of the individual and his or her disease, which should in turn allow for the development of a highly individualized, personalized treatment.

Until recently, the role of the protagonist of the problem—the patient and his/her family—has been virtually absent from consideration. Emerging evidence shows we need to learn in-depth about the patient experience and leverage the potentially powerful healing contribution patients and family can provide.

Finally, the medical community has been slow to recognize that AKI does not end upon patient hospital discharge, but that it continues to impact the patient during the long-term recovery process. Recent evidence highlights that late complications including cardiovascular disease, recurrent AKI episodes, and progressive kidney failure are much more common than usually assumed.

Scope of the AKI!NOW Initiative

Assessing existing knowledge and resources

Early work will focus on a comprehensive review of current AKI-focused initiatives, an examination of the academic body of work housed on multiple ASN platforms, and a needs assessment.

First, the Steering Committee will assess AKI initiatives including the *Acute Kidney Injury Programme: Think Kidneys* (U.K.), the International Society of Nephrology (ISN) 0x25 *AKI Initiative*, and the multiple products of the Acute Dialysis Quality Initiative, as well as the results of the recent KDIGO AKI Controversies Conference. Review of these programs will allow the committee to identify knowledge gaps and potential areas of collaboration.

Second, the landscape analysis will extend to a wide scan of ASN resources, with the goal of developing a web-based clinical compendium of the most up-to-date AKI-focused content. This analysis will include ASN Kidney Week, the ASN Board Review Course and Update, *JASN, CJASN, Kidney News*, and *Kidney News Online*.

Acknowledging the breadth of practitioners who care for and often first encounter AKI, the Steering Committee will conduct a needs assessment among the medical community where this first encounter occurs, including primary care providers, intensivists, nurses, advanced practice providers, and emergency room personnel, as well as better understand the importance of the role of the patient in the healing process. Focus groups of heterogeneous composition will be implemented to better understand the needs and give a voice to all main stakeholders.

This foundational work—review of AKI initiatives, ASN resource review, and needs assessment—will allow the Steering Committee to identify, catalogue, and describe available data concerning:

- Identification of AKI high-risk populations,
- Prevention of AKI in high-risk populations,
- Timely management of AKI in high-risk populations, and
- Current best AKI treatment pathways and practices.

Resource development

With this background on current resources and identified needs, the Steering Committee plans to release a White Paper on "Identification and Management of AKI in High-Risk Populations."

Simultaneously, a web-based compendium will point researchers to abstracts, publications, and news items available through ASN. This online resource will allow users to search, save, review, and mark articles as favorites, to form a periodically updated library of key AKI knowledge.

The Steering Committee will assess the need for educational tools focused on early recognition, treatment pathways, and best demonstrated practices that nephrologists should pursue to optimize patient outcomes, covering the continuum of care and including :

- Early recognition and management: recognition tools including risk scores, e-alerts,
- Use of AKI biomarkers,
- Management of non-dialysis–requiring AKI,
- The pharmacology of AKI: avoiding kidney injury and optimizing drug management,
- Management of severe, dialysis-requiring AKI (AKI-D),
- Management of AKI-D among patients discharged to outpatient dialysis units,
- Promotion of AKI recovery,
- Establishment of appropriate post-AKI follow-up criteria, and
- The patient perspective: learning from the experience of undergoing AKI.

Utilizing insight gained from the needs assessment, these educational tools may include, for example, fact sheets, materials targeted to non-nephrology healthcare providers, a series of Perspective articles published in the ASN core journals, and webinars/podcasts focused on AKI identification and treatment best practices.

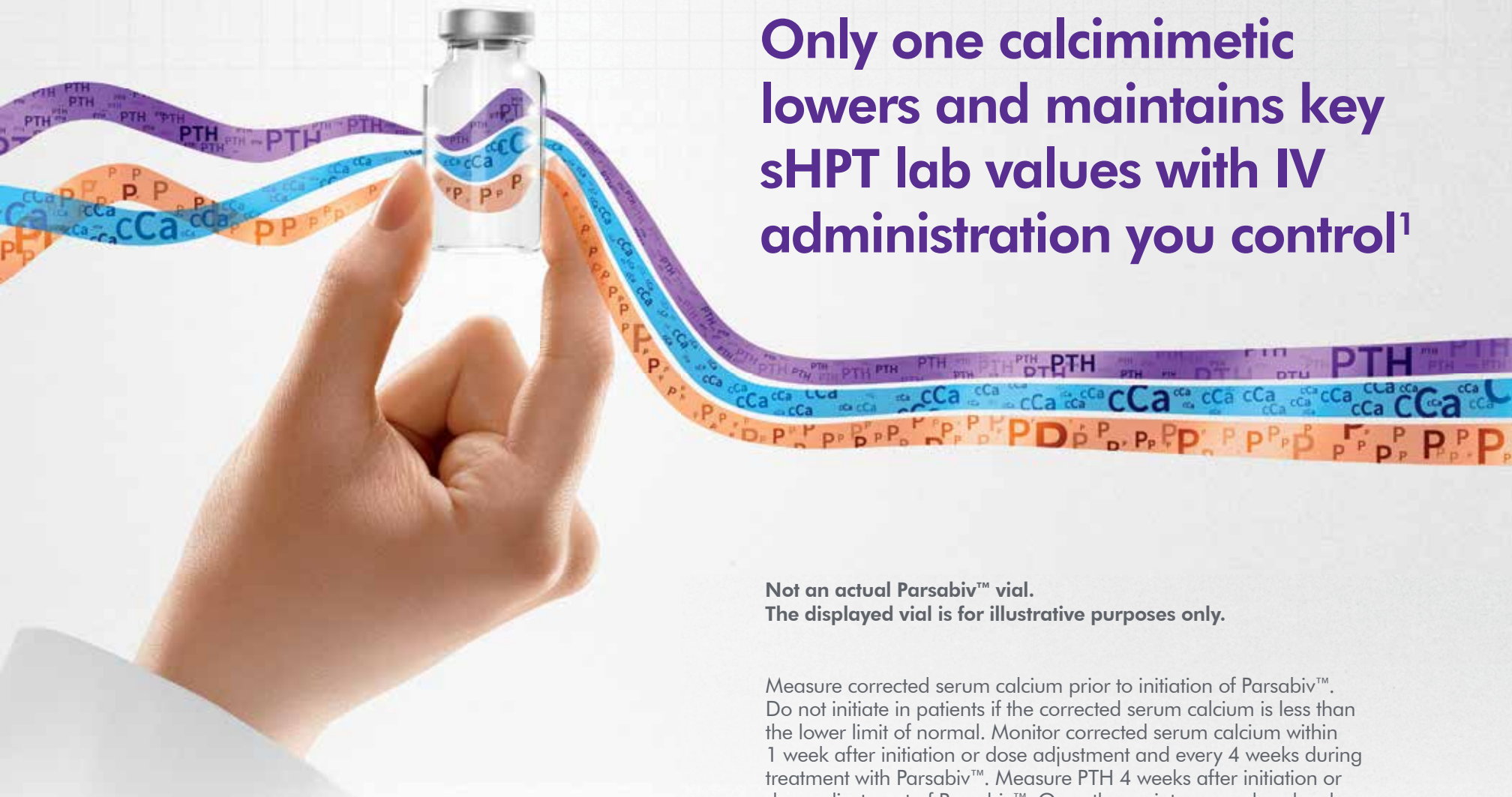
During Kidney Week 2019, we will conduct the first of a series of focus groups to test our approach and perspectives in a heterogeneous group of persons, representative of the actual individuals who are involved in the day-to-day recognition and management of AKI. Results of that discussion will then be disseminated among ASN members for discussion and critique.

Further, members of the AKI!Now group will continue to actively participate in the online Open Forums, which have been so successful in involving a large number of participants from around the world.

More information will be upcoming in the weeks preceding and during ASN Kidney Week, to ensure wide ASN membership participation and feedback. ■

Jorge Cerdá, MD, FASN, is chair of the AKI!Now Steering Committee and is affiliated with Capital District Renal Physicians Albany Medical College in Albany, NY.

The other Steering Committee members are Anupam Agarwal, MD, FASN, Mark Okusa, MD, FASN, Kathleen Liu, MD, PhD, FASN, Anitha Vijayan, MD, FASN, and Stuart Goldstein, MD, FASN.



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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:
KAI Pharmaceuticals, Inc., a wholly owned subsidiary of Amgen, Inc.
One Amgen Center Drive
Thousand Oaks, California 91320-1799

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

Vascular Graft and Fistula News

New reports on the markets for vascular grafts, including hemodialysis grafts, provide insights into this growing industry.

Grand View Research, based in San Francisco, reports that the global vascular grafts market was valued at $2.01 billion in 2019 and is expected to see a compound annual growth rate (CAGR) of 6.4% from 2019 to 2026. One caveat posits the estimate may be lower owing to "low reimbursement and high out-of-pocket expenditure in emerging economies."

Overall the marketplace is divided into hemodialysis access grafts, peripheral vascular grafts, and endovascular stent grafts, the lattermost of which led the overall market in 2018. The peripheral vascular market is set to lead in 2019, Grand View notes.

That leaves hemodialysis access grafts. A report from a different source, Market Insights Reports of Harrisburg, NC, states that the global hemodialysis vascular grafts market is "likely to expand at a CAGR of 4.1%" over the period from 2019 to 2024. The global market size for hemodialysis vascular grafts was valued at $209.1 million in 2018, Grand View reports.

Grand View breaks down regional snapshots, with the United States accounting for more than 27% of global market revenue for hemodialysis vascular grafts. Europe represented about 24% of the total revenue in 2017. In the US, acceptance of synthetic hemodialysis vascular access grafts plus higher numbers of patients with kidney disease are boosting market growth.

Asia and other emerging markets will be key for hemodialysis vascular grafts, notes a report from OG Analysis, based in Manchester, CT.

The reports list several large players in the field: W.L. Gore & Associates (Newark DE); C.R. Bard, Inc. (Murray Hill, NJ); Terumo Medical Corporation (Somerset, NJ); LeMaitre Vascular, Inc. (Burlington, MA); and Getinge AB (Gothenburg, Sweden, with U.S. sales offices in Wayne, NJ, and Rochester, NY).

In addition to hemodialysis vascular grafts, arteriovenous fistulas also are in the news. Fistula innovations aim to make dialysis as streamlined and smooth as possible for patients. Recently a nephrologist created a minimally invasive fistula using two systems newly approved by the FDA—the Ellipsys System developed by Avenu Medical (San Juan Capistrano, CA) and the BD WavelinQ system developed by Becton Dickinson and Company (Franklin Lakes, NJ).

The BD WavelinQ nonsurgical procedure is performed by inserting flexible magnetic catheters into an artery and vein, according to Neghae Mawla, MD, an interventional nephrologist based in Plano, TX. The magnets align and the artery–vein connection is made via a burst of radiofrequency energy. With the BD WavelinQ, the physician can choose between two possible anatomical locations for the endoAVF. In the Ellipsys system, the connection is made via a single catheter inserted through the vein into the artery, followed by a fusion of the two vessels. The location of this connection provides a third access site, potentially allowing for another useable fistula and better outcomes.

CVS Health Clinical Trial for Home Hemodialysis

A week after President Donald J. Trump signed an executive order directing improvement in diagnosis and treatment of patients with kidney diseases and emphasizing increased use of home dialysis, CVS Health announced the start of a clinical trial into the safety and efficacy of a new home system, the HemoCare Hemodialysis System.

The trial is expected to enroll 70 patients at 10 U.S. sites.

In April 2018, CVS, the chain pharmacy giant cum healthcare company based in Woonsocket, RI, announced it would initiate a clinical trial "to demonstrate the safety and efficacy of a new home hemodialysis device in support of a planned FDA submission to obtain market clearance." At that time, the company said the device was designed to make home hemodialysis "simple and safe for patients, in order to facilitate longer, more frequent treatments."

Now CVS has announced that DEKA Research and Development Corp. (Manchester, NH), headed by Segway innovator Dean Kamen, designed the home-use device.

Earlier in his career, Kamen invented the Homechoice peritoneal dialysis system (Baxter Healthcare still offers the Homechoice Claria PD system) and the first wearable insulin pump for people with diabetes. Kamen sold his first

company, AutoSyringe, in 1982.

"CVS Health is uniquely positioned to redefine identification, education, and treatment for chronic kidney disease, making them our ideal partner," Kamen said.

Alan Lotvin, MD, executive vice president and chief transformation officer at CVS Health says, "For those patients who do progress to dialysis, we are working to bring a new solution to the consumer that addresses the current barriers to and limitations of existing dialysis options, and we are working closely with the U.S. Food and Drug Administration as we evaluate this device.

"We have been working to fundamentally disrupt the kidney care market and rapidly innovate in an area that has stagnated for decades, and we applaud the administration for taking bold steps toward advancing kidney care as they are helping to rethink how to make kidney transplant and home dialysis mainstays of therapy," Lotvin said.

The CVS chronic kidney disease (CKD) management program will work with patients to identify and better manage CKD earlier. Once a diagnosis has been made, CVS Kidney Care, in collaboration with healthcare providers, will engage with the patient to educate them about their disease and treatment options, and help them manage their condition, monitor risk factors, and meet their health goals, according to the CVS website. ■

Remote Dialysis Monitoring Competition Grows

Remote dialysis monitoring services are vying for new customers, as dialysis usage in differing settings continues to grow, spurred by the recent U.S. executive order under the Advancing American Kidney Health initiative, which aims to encourage home-based dialysis,.

One of the most recent announcements about a remote-monitoring opportunity comes from Graftworx in San Francisco. The technology company has begun a service evaluation collaborating in northeast England with the Academic Health Science Network and the National Health Service (NHS) Hospital Foundation Trust. That evaluation could result in studies that use the company's technology "to assess patients on dialysis and those with heart failure," *Vascular News* reports.

According to Jonathan Murray, consultant nephrologist at South Tees Hospitals NHS Foundation Trust in Middlesbrough, "The range of assessments that we are planning with GraftWorx is based upon the premise that remotely and continuously capturing early clinical signals will enable our clinical teams to more promptly identify potential problems. Ultimately we are keen to evaluate if digital health–enabled data will improve efficiency and effectiveness of patient care and thereby optimise our care pathways."

As noted in the item above, CVS would like to establish dialysis patient monitoring as well, as it embarks on its clinical trial with a new dialysis device from DEKA. Such collaborations could result in further competition for the large dialysis companies.

Reuters reports that DaVita is "accelerating its home dialysis growth by investing in home remote monitoring and a telehealth platform that make the process easier."

In February, Fresenius received permission from US antitrust authorities to acquire NxStage's dialysis and other medical devices. NxStage System One works with the Nx2me app for iPad to collect treatment information from the dialysis cycler at a patient's home, allowing the patient to easily send it to a clinic and care team, NxStage says. ■

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Kewalramani Takes Helm at Vertex

In the spring of 2020, nephrologist Reshma Kewalramani, MD, FASN, will assume the mantle of president and CEO of Vertex (Boston), a biotechnology company with revenues of $3.04 billion for fiscal year 2018. She will move up from her current position as executive vice president for global medicines development and medical affairs and chief medical officer at the company.

Kewalramani will follow Jeffrey Leiden, MD, PhD, who served in these roles for seven years and who oversaw hearty growth. According to Statnews.com, Vertex's share price rose 360% and its sales doubled to just over $3 billion annually in fiscal year 2018. Revenues for 2018 increased 40% compared with fiscal year 2017.

Pharma and biotechnology reporters, including those at the *Boston Globe, Medpage Today*, and BioPharmaDive, issued headlines that noted Kewalramani is the first woman to head a top biotechnology company. She is also a founding member of the Kidney Health Initiative, a joint partnership between ASN and the U.S. Food and Drug Administration. Kewalramani received her MD from Boston University and trained at Brigham & Women's Hospital in Boston.

Leiden will stay on in the role of executive chairman through the first quarter of 2023, the company reported, working closely with Kewalramani as projects develop.

While Leiden presided over the expansion of cystic fibrosis treatments, Kewalramani will continue to oversee expansion into the biology of rare diseases, including:

- Focal segmental glomerulosclerosis,
- Alpha-1 antitrypsin (AAT) deficiency (NIH.gov's rare diseases site notes that 5% to 29% of people with the AAT deficiency have nephrotic syndrome and/or cirrhosis),
- Sickle cell disease and β-thalassemia, and
- Pain.

FDA Puts CKD Drug on Fast Track

The U.S. Food and Drug Administration (FDA) has given type 2 diabetes drug Farxiga (dapagliflozin) a fast track designation that aims to help chronic kidney disease (CKD) patients. AstraZeneca (Cambridge, UK) announced that the drug was fast tracked for development as a treatment to delay the progression of kidney failure and prevent cardiovascular and renal death in patients with CKD.

The company noted, however, the drug is contraindicated for patients with severe kidney impairment (with an eGFR <30 mL/min/1.73 m^2), with end stage kidney disease, or who are on dialysis.

The drug is also not recommended for patients with type 1 diabetes. In July, the FDA rejected approval of Farxiga as "an add-on treatment for type 1 adults whose insulin therapy isn't enough to control their blood sugar levels," reported FiercePharma.com.

The drug is now on the fast track for CKD treatment. Results from a phase 3 trial showed that the drug reduced "the combined risk of kidney function decline, end-stage renal disease and renal death in Type 2 diabetes patients by 47%," according to FiercePharma.

The company and the FDA await results from the current phase 3 DAPA-CKD clinical trial to evaluate the effect of Farxiga on kidney outcomes and cardiovascular mortality. The trial is for CKD patients both with and without type 2 diabetes, versus placebo.

The FDA defines fast tracking as a process designed to facilitate the development and expedite the review of drugs to treat serious conditions and fill an unmet medical need. "Serious conditions" are roughly defined as those needing a drug treatment that will have an impact on such factors as survival, day-to-day functioning, or the likelihood that the condition, if left untreated, will progress to a more serious one.

Farxiga is a sodium-glucose co-transporter 2 (SGLT-2) inhibitor. Type 2 diabetes patients have a renal threshold for glucose that is increased beyond the typical level. The general mechanism of the drug is to reduce the renal reabsorption of glucose by inhibiting SGLT-2 and clear more glucose from the patient. The drug increases renal urinary glucose excretion, and can be associated with hypotension, according to the farxiga.com website.

Addressing Frailty in the ESKD Population through Professionally Guided In-Center Exercise Programs

By Dyer Diskin, Graham Abra, Wael Hussein, and Brigitte Schiller

Case presentation

A 71-year-old woman began using three-times-weekly hemodialysis (HD) 8 months ago and reports worsening fatigue, along with increasing difficulty with her activities of daily living. She is fearful that loss of independence will require her to move to a nursing facility. As her renal failure progressed over the past year she experienced complications that required repeated hospitalizations. After each discharge, she has reported feeling even weaker. She has declined prior offers of inpatient rehabilitation and has struggled with coordinating in-home physical therapy. She wants to exercise and improve her physical function, but she has a fear of falling. In addition, she is no longer certain about what exercises would be best for her or what her body is capable of doing.

Prevalence of frailty in the ESKD population

Whereas frailty is something that patients and clinicians may broadly discuss, many have tried to detail the various components that define the condition. The current standard measurement was developed by Fried et al. (1), focusing on four domains of frailty: unintended weight loss, low physical activity, weakness, and poor endurance. Patients with ESKD receiving in-center HD experience high rates of frailty, physical inactivity, and mortality. Whereas the prevalence of frailty in older adults (>65 years old) in the community-dwelling population has been measured around 7% (1), in those undergoing in-center HD the prevalence has been found to be as high as 73% (2). The younger (<65 years old) HD population also has a very high prevalence of frailty, measured in prior studies at 36% (3).

Frailty and mortality in the ESKD population

In a study that defined frailty using the Fried Frailty Index for the HD population, frailty was associated with a 40% 3-year mortality compared with the rate of 16% in a similar nonfrail ESKD population (3). Overall, this correlated with a hazard ratio of 2.7 for greater risk of death independent of age, sex, comorbidity, and disability. The various components of frailty (weight loss, exhaustion, low physical activity, weak grip strength, and slow gait speed) individually have shown to be a negative predictive factor for patient health. This risk increased more than fivefold for patients with all five components (4). Exercise has been promoted as a way to combat or slow the progression of frailty across many diseases and age groups. However, achieving exercise in the ESKD patient population remains challenging.

The history of exercise and dialysis

Intradialytic exercise has been the subject of several investigative studies over the past several decades. A Cochrane systematic review in 2011 found significant benefit in patients' aerobic capacity, resting blood pressure, and health-related quality of life from exercising three times per week for longer than 30 minutes per HD session (5). There have been several examples in the literature of exercise studies and subsequent meta-analysis that have shown improvement in many of the physical fitness tests used to measure frailty. These tests include the 6-minute walk test, the Timed Get Up and Go Test, the Maximum Walking Speed Test, the Sit to Stand Test, and overall metabolic equivalents achieved (6–9). These exercise routines usually involve either aerobic exercise, resistance exercise, or a combination of the two for at least 30 minutes during the first 2 hours of each HD session. Even the use of resistance exercise with elastic bands alone has been shown to improve the patient's 30-second Sit to Stand Test and 8-foot Timed Get Up and Go Test (10).

Considerations for intradialytic exercise in the modern HD center

Despite these reported benefits of exercise, there do not appear to be any formal intradialytic exercise protocols in the United States. The main barriers in this country are thought to be interference with the workflow of an outpatient dialysis center and also concern for high rates of patient nonadherence and dropout.

A recent study of an intradialytic exercise biking program in the United Kingdom noted an adherence of 78% at 3 months that decreased to 63% by 12 months (11). One of the only papers to evaluate longer-term adherence was a German single-center study involving exercise professionals that measured 1-year and 5-year adherence at 78% and 43%, respectively (12).

Unfortunately, data on exercise adherence and efficacy in the United States are lacking. This remains a challenge across the world, given that nephrologists and dialysis center staff are thought to lack the personnel and resources needed to advise dialysis patients on individualized exercise regimens (13). A recent study in *CJASN* evaluated the perceived barriers and desired outcomes in 280 in-center HD patients. Improved energy, strength, and maintenance of independence were the top goals for in-center patients, and younger patients were very motivated by the potential for kidney transplantation. In this survey, the top perceived barriers to exercise were mostly related to physical symptoms such as shortness of breath, tiredness, and weakness. Secondary barriers included not knowing how to construct an exercise program, not knowing what exercises are safe, affordability, and lack of travel and time (14). It is these secondary barriers that we hope can be addressed and mitigated by a sponsored in-center program that provides individualized exercise programs under the guidance of exercise professionals.

Successful programs

Prior efforts at intradialytic exercise studies have been successful in using both aerobic and resistance exercises. Some highlights from those selected studies are as follows:

- **Beneficial effects of intradialytic cardiopulmonary rehabilitation, Guio et al. (7)**
  - Prospective trial with 18 patients in Brazil
  - Treated for 8 months with intradialytic cycle ergometer
  - Showed improvement in 6-minute walk test and left ventricle ejection fraction
  - No change in baseline heart rate and BP determinations; improvement in bodily pain and vitality noted by patients

- **Effects of an intradialytic exercise resistance training program on physical function, Bennett et al. (10)**
  - Recruited 171 participants across 15 dialysis units in Australia
  - Treated with progressive resistance band exercises under guidance of an accredited exercise professional for 12 to 48 weeks
  - Patients showed improvement in Sit to Stand Test and Timed Get Up and Go Test

More research is needed to demonstrate the effects of an exercise program over a longer period to examine endpoints such as hospitalizations,

Continued on page 14 >

Addressing Frailty

Continued from page 13

falls, and mortality. If improved functional status and quality of life are among the highest priorities for patients, a value-based performance healthcare system in addition seeks to reduce hospitalizations. If this can be demonstrated, then the introduction and permanent presence of an exercise program in a dialysis center would likely be part of care delivery in the future, providing benefits to patients and including economic gains. ■

Dyer Diskin, MD, is a nephrology fellow at Stanford University, and Graham Abra, MD, is medical director, WellBound San Jose, clinical assistant professor, Stanford University, and director, Medical Clinical Affairs, Satellite Healthcare. Wael Hussein, MBBS, MSc, MRCPI, is director, Clinical Research, and Brigitte Schiller, MD, FASN, is chief medical officer, Satellite Healthcare.

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With PEAK Program, Artificial Intelligence Helps Build Smooth Transition to Dialysis, Encouraging Home Modalities

By Ollie Fielding

There is no denying that machine learning and artificial intelligence (AI) are very much in vogue across the healthcare landscape. AI was a key topic in the president's address by Mark Okusa, MD, FASN, at last year's ASN Kidney Week in San Diego. As more healthcare information becomes digital, it is tempting to get excited about the potential for data-backed tools despite the limited deployment of AI in the clinic. Creating risk models in healthcare takes more than just computing power and advanced algorithms; it requires a deep knowledge of the underlying medical problems and a tight integration with clinical teams and their workflows. Clinicians must understand the models to effectively and seamlessly integrate them into their everyday practice.

The Rogosin Institute is affiliated with New York-Presbyterian Weill Cornell Medical Center and specializes in the care of chronic kidney disease (CKD). In 2015, Rogosin created the Program for Education in Advanced Kidney Disease (PEAK), a multidisciplinary care team that assists patients in making a smooth transition to renal replacement therapy (RRT). The PEAK program educates patients about all their options for dialysis and encourages a higher adoption of home dialysis modalities.

Healthcare AI startup pulseData specializes in creating predictive models that provide insight into the clinical domain. Rogosin and pulseData have been collaborating for over a year to effectively deploy machine learning models in a clinical setting. Through this partnership, we discovered that a deep integration of human intelligence and AI methodology matched to customized workflows is a powerful aid to delivering preventive care.

Rogosin referred patients into the PEAK program when they were at CKD stage 4, but with an increasing number of patients and limited resources, PEAK sought a better way to identify high-risk patients who would best benefit from the transition program. Perhaps machine learning was the answer.

Machine learning

Machine learning might sound complicated, but at its core it is fairly straightforward; it is just labeling with a probability. For example, when you search online for a picture of a cat, the resulting images you see have been labeled by an algorithm as probably being a cat. To create the algorithm, many images that are labeled "cat" or "not cat" are fed into the algorithm, and eventually a machine learns how to label an image as "cat" or "not cat" by creating rules and testing how well those rules work by using the examples it has been shown. Once the algorithm has trained itself in this way, it can then label images it has never seen before.

Often ignored is how much human work went into teaching that algorithm what a cat looks like. This was done by feeding the machine thousands of human-labeled cat photos (a dream job for someone). To create an algorithm that would be useful for the PEAK team, we must use the same general principles and teach an algorithm what the ideal PEAK program patient looks like.

There have been previous efforts to stratify patients for risk of kidney failure; the most highly regarded and used is the Kidney Failure Risk Equation (KFRE) (1). The KFRE assigns a probability that a patient will progress to eGFR <15 mL/min per 1.73 m^2 in the next 2 years. Rogosin and pulseData wanted to more precisely define the optimal PEAK program candidate, focusing on patients likely to experience progression in a very short period of time (the next 6 months) and to have a lower eGFR threshold (<10 mL/min per 1.73 m^2). The PEAK team clinicians thought this represented a renal function level at which there would be a reasonable indication to prepare for RRT and that 6 months allowed sufficient time to arrange for venous access placement and maturation, for workup for transplantation, or both. Using eGFR <10 mL/min per 1.73 m^2 as the outcome also meant the model was not subject to a patient's or physician's choice about when to start dialysis but could provide a more objective score for the patient and provider to interpret.

The model was built using longitudinal patient data collected from the Rogosin's electronic health record (EHR) system, and features were created across patient demographics, vital signs, comorbidities, laboratory values, and medication use. For those interested in the statistical aspects, the model has an area under the curve (AUC) of 0.93, a sensitivity of 0.81, and a specificity of 0.89 at the top quintile of risk. We designed the model to emphasize clinical discrimination rather than AUC, and the AI model reached a positive predictive value of 0.55 in the top quintile of risk, whereas the KFRE had a positive predictive value of 0.33 with an AUC of 0.92.

Model performance in clinical practice

Model performance statistics alone do not determine how well a model will fare in actual clinical practice. We examined the hazard decline curves for patients at various levels of risk to select a risk level where the vast majority of patients (nearly all) would experience the outcome (eGFR declining to <10 mL/min per 1.73 m^2) within a 2-year period. We then set this threshold as the point at which we would refer the patient to the PEAK team.

We examine all the data held within the EHR system once a week and calculate a fresh score for all patients with an eGFR <30 mL/min per 1.73 m^2 who have not yet started dialysis. For patients who are scored over the high-risk threshold level defined by the clinical team (identified with the red line on the hazard curve in Figure 1), an alert is sent to the patient's primary nephrologist to prompt referral to the PEAK program to help the patient make a smooth transition to dialysis. The multidisciplinary team then meets each week to review the patients at high risk, ensure that the patient's treatment plan is documented, and discuss any issues with moving the patient forward.

The PEAK team has achieved increased rates of preemptive transplantations and optimal outcomes. Compared with the New York rate of 2.5% for preemptive transplantations, the PEAK team sees 12.5%. Sixty-eight percent of PEAK patients began dialysis as outpatients compared with only 27% nationally (2), and 57% began with venous access in place compared to only 20% nationally (3). The PEAK team is well on the way to reaching their 25% home dialysis goal, and it currently achieves 20% home modality adoption—a significant lift over the New York City average, which is only 3.6%.

Whereas AI and machine learning are at the forefront of research and transformation in medicine, healthcare is a uniquely human effort, and the knowledge and actions of the multidisciplinary team are pivotal to ensuring better patient outcomes. Purpose-built AI tools can be a powerful partner in this effort: amplifying our human intelligence, precisely directing care, and deepening our understanding of patients.

Ollie Fielding is Head of Product at pulseData.

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Figure 1. Kaplan-Meier curve of high-risk versus non–high-risk groups over time

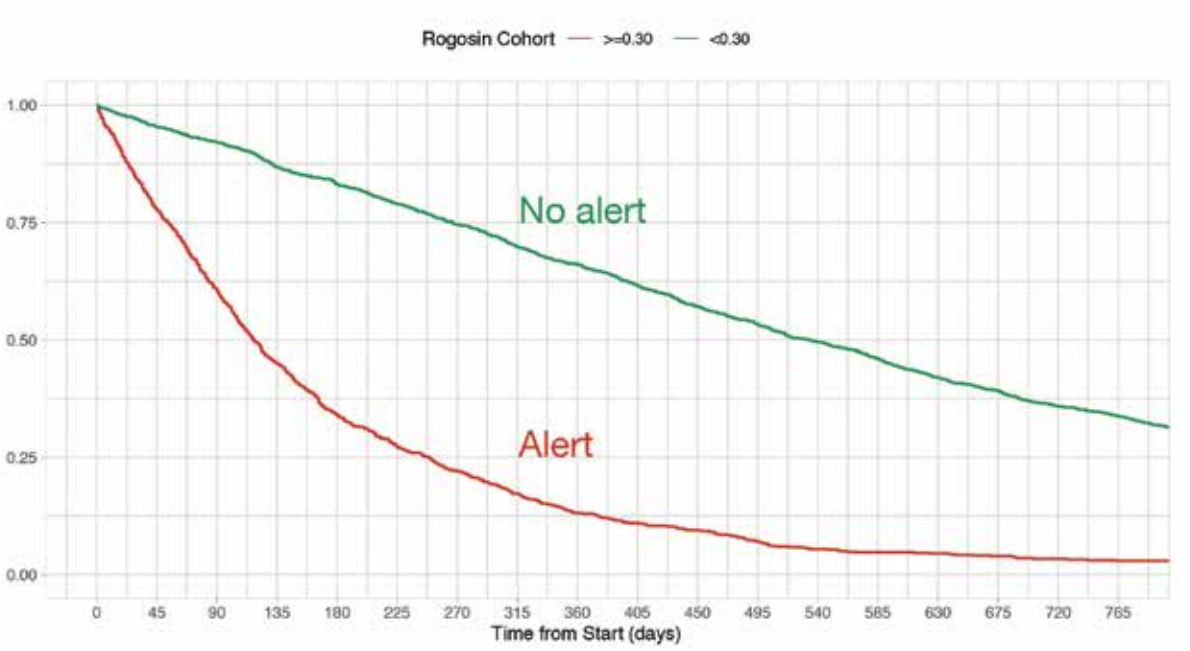


Figure derived from retrospective electronic health record data at Rogosin Institute. Outcome was defined as estimated GFR <10 mL/min per 1.73 m^2 or renal replacement therapy. Time 0 indicates time of calculation of risk score. "No alert" curve indicates cohort with pulseData risk score <0.30. "Alert curve" indicates cohort pulseData risk score >0.30.

POCUS-Enhanced Physical Examination Is the Future, and the Future Is Now

By Harini Bejjanki and Abhilash Koratala

Harini Bejjanki

Abhilash Koratala

What is POCUS?

POCUS, or point-of-care ultrasonography, is a limited ultrasound examination performed by the clinician at the patient's bedside. As opposed to a radiographic examination of an anatomic area, POCUS is intended to answer focused questions, mostly "yes" or "no" questions, and is performed by the same physician examining the patient. It is a valuable adjunct to physical examination, and some authors describe POCUS as a fifth pillar to bedside physical examination in addition to inspection, palpation, percussion, and auscultation (1). In specialties such as emergency medicine, POCUS training has been well established, and the Accreditation Council for Graduate Medical Education recognizes bedside ultrasonography as one of the key index procedures essential for independent practice. More recently, POCUS has spread throughout all levels of medical education and is being integrated into medical school and postgraduate training curricula (2–4).

Why should nephrologists perform POCUS?

Once confined to procedural guidance, the scope of POCUS in nephrology practice is quickly expanding. There are several clinical scenarios where it can guide patient management (Figure 1). For example, one can quickly exclude hydronephrosis using POCUS at the time of history taking, which reduces fragmentation of care and enhances the treatment of patients with acute kidney injury. Determination of volume status is another challenging area of nephrology practice. POCUS, being noninvasive and a dynamic parameter, not only guides therapy but also allows monitoring of response to an intervention such as ultrafiltration or diuretic therapy.

Similarly, maturation of the arteriovenous fistula can be assessed at the time of regular nephrology clinic visits, thereby avoiding the trip to vascular surgery. Moreover, it can enhance our interactions with patients by showing them the imaging findings in real time. In addition to improving clinical care, it enhances the attractiveness of the nephrology fellowship training. Last but not least, if we do not learn this skill, we will soon lag behind other specialties and may be looked upon as not having an essential physical examination skill such as auscultation.

We need to wake up, and the time to do so is now.

Where do we start?

The scope of nephrology-oriented POCUS is still emerging, and there are no well-defined training guidelines or educational approaches. Only a handful of nephrology fellowship programs offer formal training in POCUS (3).

For practicing physicians and trainees from other programs, short-term training opportunities exist in the form of workshops and courses such as those offered by the Emory University Renal Division. Emory is the only ultrasound program accredited by the American Society of Diagnostic and Interventional Nephrology (5). Nonetheless, it is focused on comprehensive kidney and bladder imaging and does not cover other POCUS applications pertinent to nephrology.

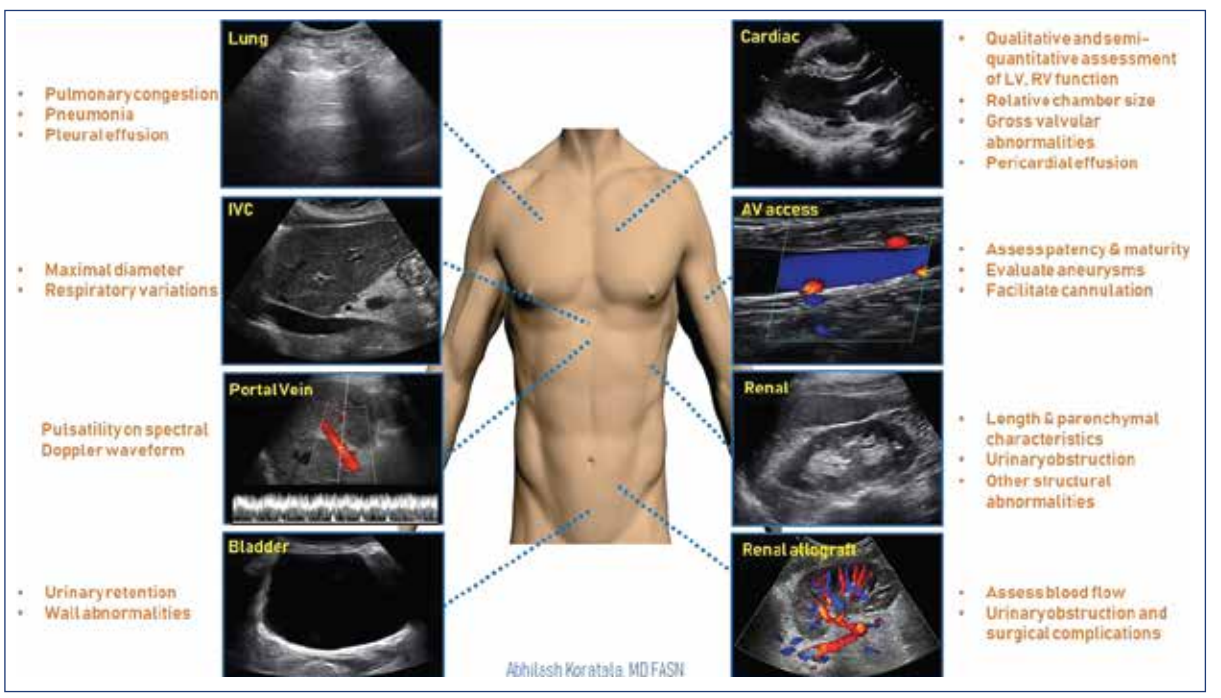
POCUS workshops, typically offered as a "precourse" before national meetings, are a good starting point for novice users to learn the basics of image acquisition and "get a feel" for the technique. However, residency-based or fellowship-based longitudinal training provides an opportunity for long-term skill retention. Nobody masters the skill of auscultation in 1 day, and the same is true with POCUS; we cannot expect to learn everything about it from a half-day workshop.

The best way to gain competence and confidence is to scan at every possible opportunity and to review ultrasound technician–performed formal studies while trying to interpret your own. Until every nephrology fellowship program has a faculty "champion" who leads the POCUS training, a multidisciplinary approach in collaboration with other specialties such as emergency and critical care medicine can be greatly beneficial. In addition, teaching colleagues and students is the best way to learn and practice further. Apart from the ultrasound machine, no expensive resources are required to establish a training room, and at the University of Florida, we use a regular office room with a computer and a foldable bed to scan faculty and trainee volunteers (Figure 2).

What is our POCUS video curriculum?

Recognizing the gaps in training and the scarcity of nephrology-oriented POCUS teaching resources, Dr. Koratala has designed and developed a series of instructional videos covering the common diagnostic POCUS applications relevant to nephrology practice, which fellows and residents at our institution have found immensely helpful (Table 1, Figure 3). The

Figure 1. Infographic demonstrating common diagnostic point-of-care ultrasonography applications and clinical questions and pathologic conditions pertinent to nephrology practice



curriculum is a set of 10 videos available for free on YouTube by typing in the key words "nephrology ultrasound Florida."

The advantage of having a video curriculum is that trainees can review the online material at their own pace, in a low-stress environment that is not impeded by patient care obligations. This flipped classroom model allows more time for interactive demonstrations and hands-on learning. Moreover, with more medical students being trained in POCUS, it is likely that we will have trainees with varying levels of knowledge and skill sets in the future. The availability of a structured video curriculum gives them the opportunity for targeted review of the topics they are less familiar with.

Are there any additional online resources?

In addition to several POCUS educational websites and videos primarily intended for emergency physicians (6), the "Focus on POCUN" series on the Renal Fellow Network authored by Dr. Koratala addresses key concepts in renal-relevant POCUS (7). He also contributes to a POCUS gallery on the Renal Fellow Network, along with hosting the blog nephropocus.com. Those who use Twitter can follow Dr. Koratala's POCUS-specific handle @NephroP for interesting images and discussions. As more programs start incorporating POCUS, more educational material will become available. Until then, do not stop practicing, and do not hesitate to request a formal scan when you are not sure about the diagnosis. ■

Harini Bejjanki, MD, is a nephrology fellow and internist at the University of Florida in Gainesville. Abhilash Koratala, MD, FASN, is assistant professor of medicine in the division of Nephrology, Hypertension & Renal Transplantation at the University of Florida in Gainesville.

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Figure 2. POCUS training room for nephrology fellows at the University of Florida

Figure 3. Representative slides from the University of Florida video curriculum

Table 1. University of Florida YouTube POCUS nephrology curriculum

Lesson 1	Fundamental physics and instrumentation of ultrasonography	**Lesson 6**	Case-based learning and quiz
Lesson 2	Sonographic technique and anatomy of kidney and bladder	**Lesson 7**	Lung ultrasound (B-lines and common pathologies)
Lesson 3	Sonographic volume status assessment: technique and interpretation	**Lesson 8**	Basics of echocardiography
Lesson 4	Case-based learning	**Lesson 9**	Intro to Doppler (arteriovenous access, resistive index, and venous waveforms)
Lesson 5	Kidney stones	**Lesson 10**	Common artifacts

Findings

Differences in Patient Characteristics Affect Generalizability of Dialysis Clinical Trials

Patients enrolled in major clinical trials of end stage kidney disease (ESKD) differ in key demographic and clinical characteristics, compared to the general population of dialysis patients, concludes a meta-analysis in *JAMA Internal Medicine*.

A systematic review identified 189 randomized clinical trials enrolling dialysis-dependent adults with ESKD. The studies, which enrolled at least 100 patients from 2 or more sites, included a total of 80,104 participants. Meta-analysis compared prespecified characteristics of the RCT participants to patients in the US Renal Data System (USRDS) registry. Study characteristics associated with measures of generalizability were analyzed as well.

Patient age was the primary outcome: RCT participants were significantly younger than the USRDS patients, 58.9 versus 61.2 years. The clinical trial patients were also more likely to be male, 58.8% versus 55.7%, and less likely to have diabetes, 40.4% versus 44.2%. The RCT cohort was also much less likely to have diabetes as the cause of renal failure, 29.9% versus 44.2%, or hypertension as the cause of renal failure, 20.7% versus 29.0%. Based on 187 studies, mortality was 8.9 per 100 patient-years in the RCT cohort versus 18.6 per 100 patient-years in the USRDS cohort.

Most of the differences in patient characteristics were similar on analysis of studies recruiting from the United States, although diabetes was more common among RCT participants: 54.6% versus 44.2%. On analysis of study characteristics, mortality was lower in trials with commercial sponsorship or those published more recently.

Differing patient characteristics may affect the generalizability of clinical trial results. Previous studies have described differences in RCT cohorts versus the general population of patients undergoing kidney transplantation, but this issue has not been addressed in the ESKD population.

Dialysis patients enrolled in RCTs are younger, have differing patterns of comorbidity, and have lower mortality than the general population of ESKD patients. The researchers emphasize the need for caution in generalizing RCT results to older, frailer patients, and call for efforts to increase the generalizability of ESKD trials [Smyth B, et al. Representativeness of randomized clinical trial cohorts in end-stage kidney disease: A meta-analysis. *JAMA Intern Med* 2019; DOI: 10.1001/jamainternmed.2019.1501]. ■

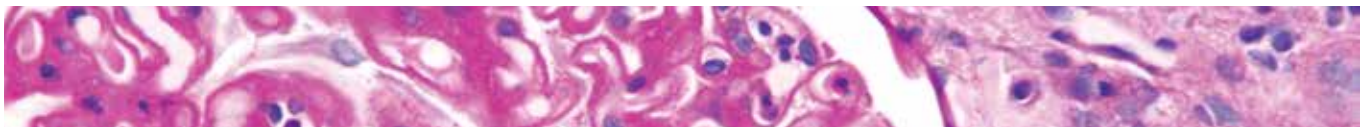
Rituximab versus Cyclosporine for Membranous Nephropathy

In patients with membranous nephropathy, rituximab is noninferior to cyclosporine in inducing remission, and superior in terms of maintaining proteinuria remission up to 2 years, reports a trial in *The New England Journal of Medicine*.

The randomized, open-label "Membranous Nephropathy Trial of Rituximab" (MENTOR) included 130 patients with membranous nephropathy enrolled at 22 North American centers. All had stable quantified creatinine clearance of 40 mL/min/1.73 m^2 or higher and at least 3 months on angiotensin-system blockade. Patients were assigned to rituximab, two 1000 mg IV infusions given 14 days apart; or oral cyclosporine, starting dose 3.5 mg/kg/d for 12 months. In the rituximab group, treatment could be repeated at 6 months in case of partial response.

The complete or partial response rate was 60% with rituximab and 52% with cyclosporine; the 8% difference was within the limit of noninferiority. At 24 months' follow-up, 60% of patients in the rituximab group were still in complete or partial remission for proteinuria compared to 20% in the cyclosporine group; the 40% difference was significant.

Among patients in remission who were positive for anti-phospholipase A2-receptor antibodies, the decline in antibodies was faster, larger, and lasted longer with rituxi-



mab. Adverse event rates were 17% with rituximab and 31% with cyclosporine.

For patients with membranous nephropathy requiring immunosuppressive therapy, the calcineurin inhibitor cyclosporine is effective, but has a high relapse rate after discontinuation. Since B-cell dysfunction plays a pathogenetic role in this condition, selective B-cell suppression with rituximab is a promising alternative.

This study finds no difference in the rate of complete or partial remission with rituximab compared to cyclosporine for patients with membranous nephropathy. Rituximab is superior in terms of long-term proteinuria remission up to 24 months in patients at high risk of progressive disease. The researchers note that intravenous rituximab may improve adherence compared to oral cyclosporine; its higher cost may be offset by its prolonged benefits [Fervenza FC, et al. Rituximab or cyclosporine in the treatment of membranous nephropathy. *N Engl J Med* 2019; 381:36–46]. ■

Canagliflozin as Primary Prevention: Findings from CREDENCE

The sodium-glucose co-transporter 2 (SGLT2) inhibitor canagliflozin reduces cardiovascular and renal events in diabetic patients with chronic kidney disease—even those with no previous history of cardiovascular disease, according to a clinical trial report in *Circulation*.

The analysis included 4401 individuals from the phase 3 CREDENCE trial (Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation) with type 2 diabetes and CKD but no previous cardiovascular disease. In CREDENCE, patients were randomly assigned to canagliflozin or placebo, while continuing optimized standard therapy.

Compared to 2220 secondary prevention patients, those in the primary prevention group were younger, 61 versus 65 years; more likely to be women, 37% versus 31%; and had a shorter duration of diabetes, 15 versus 16 years. Estimated glomerular filtration rate and urine albumin-to-creatinine ratio were similar between groups.

On analysis of the primary outcome, canagliflozin was associated with a lower risk of cardiovascular events overall, hazard ratio (HR) 0.80; in the primary prevention group, HR 0.68; and in the secondary prevention group, HR 0.85. All of the component outcomes were also lower with canagliflozin: HR 0.78 for cardiovascular death, 0.81 for nonfatal myocardial infarction, and 0.80 for nonfatal stroke.

Rates of the primary composite renal outcome (end stage kidney disease, doubling of serum creatinine, or renal or cardiovascular death) were also lower with canagliflozin: HR 0.70 overall, 0.69 in the primary prevention group, and 0.70 in the secondary prevention group. Heart failure hospitalization was significantly reduced, with no increase in fractures or amputations. Numbers needed to treat for the primary composite renal outcome were 19 in the primary prevention group and 26 in the secondary prevention group.

It has been uncertain whether the benefits of SGLT2 inhibition in patients with type 2 diabetes and CKD extend to those without a history of previous cardiovascular disease. This analysis of CREDENCE data shows "robust and consistent" reductions in major cardiovascular and renal outcomes in this group of primary prevention patients.

The investigators conclude: "These data support the initiation of canagliflozin in a much broader patient population with type 2 diabetes including those with glycated hemoglobin as low as 6.5% and in patients with estimated glomerular filtration rate between 30 to 45 mL/min/1.73 m^2 with expected reductions in renal and cardiovascular outcomes" [Mahaffey KW, et al. Canagliflozin and cardiovascular and renal outcomes in type 2 diabetes and chronic kidney disease in primary and secondary cardiovascular prevention groups: results from the randomized CREDENCE trial. *Circulation* 2019; DOI: 10.1161/CIRCULATIONAHA.119.042007]. ■

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Thursday, November 7
Jennifer A. Doudna, PhD,
University of California, Berkeley
Rewriting the Code of Life: The Future of Genome Editing

Friday, November 8
Michael W. Young, PhD, The Rockefeller University
Genes Controlling Sleep and Circadian Rhythms

Saturday, November 9
Dean L. Kamen, DEKA Research & Development Corporation
Bruce Culleton, MD, CVS Health
Perspectives on Innovation and Transformation in Kidney Care

Sunday, November 10
Danielle Ofri, MD, PhD, New York University; Author
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An Interview with Kerry Cooper, MD, Vice President, U.S. Medical Affairs, Renal, AstraZeneca

THE "R" FOR RENAL WAS RECENTLY ADDED TO ONE OF ASTRAZENECA'S THERAPEUTIC AREAS. WHAT LED TO THIS ADDITION OF "RENAL" TO THE CARDIO PLUS METABOLIC AREA?

As a global organization, we show up as one therapeutic area—cardiovascular, renal, and metabolism or "CVRM." With our expertise over time in this space, we recognize that science has uncovered commonalities between cardiovascular, renal, and metabolic diseases and their associated complications. Yet in many cases, each condition is managed in isolation.

Our portfolio approach allows us to uncover the interconnectedness of these diseases and additional comorbidities to treat the patient as a whole. We believe that our existing portfolio and scientific approach position us to tackle multiple unmet needs for patients and treat them along the spectrum of their disease overall.

We do recognize that while globally we are positioned this way, we know there is a need to prioritize bringing new medicines to patients in the renal space swiftly to address some of the gaps that exist today in parallel with our overall CVRM approach. We are proud to continue to advance science and elevate the discussion around making a meaningful difference to innovate in the renal space. We feel as an organization we have a responsibility to prioritize these efforts to shift the dialogue on the way CKD is treated today and the possibility for greater advancements today and in the future.

TALK ABOUT THE PATIENTS WHO WILL BE THE INTENDED GROUP FOR YOUR RENAL-CARDIO PRODUCTS.

As an organization, we believe in building a portfolio that can make a meaningful difference for all patients living with CKD. With an estimated 30 million Americans affected by this disease, we recognize an obligation to advance science and innovate to help fill substantial gaps in unmet needs that exist today.

This includes looking at the full treatment scope of CKD and its associated complications. It is our perception that these patients need and deserve more to help them navigate the vast complexities that fill their everyday lives. We know that the majority of patients managing their CKD are not managing it alone and that their lives are confounded by multiple comorbidities, such as diabetes and heart disease as well as complications from CKD, including hyperkalemia and anemia, that have a tremendous impact.

As a result, patients lead complex lives filled with making daily tradeoffs for their health, which affects their quality of life and ultimately increases risk for further complications. We must continue to deliver research in new drug therapies that can tackle the significant unmet needs that exist for these patients today. This is truly what drives us in everything we do.

WHAT IS THE HIERARCHY OF IMPORTANCE OF THE ASTRAZENECA RENAL PORTFOLIO OF PRODUCTS NOW AND IN THE COMING YEAR?

It is our ambition to deliver across three core areas in renal disease over time. We first aim to address unmet needs that exist today in managing complications that impact CKD patients—in particular, with hyperkalemia and anemia. In parallel, we are investing in research that can intervene earlier and potentially slow progression of the disease—for which there are no treatments today. Ultimately our goal is to continue to innovate in CKD and address residual risks and prevent organ damage in CKD while targeting specific patient populations to consider further advancements.

Approved for the treatment of hyperkalemia in adults, LOKELMA is an innovative, highly selective potassium binder with a unique structure that is designed to be highly selective and works in the gastrointestinal tract (GI) tract, resulting in early capture of potassium, providing rapid and sustained results for patients. In the US, only about 10% of patients are treated for their high potassium today, and recognizing the substantial consequences that can be associated with uncontrolled potassium levels, we believe that increased awareness and diagnosis of high potassium, coupled with the availability of LOKELMA, will help to shed light on hyperkalemia as a chronic condition and options to treat it in the long term.

Through a joint partnership with FibroGen Inc., we continue to research and develop roxadustat, a potential first-in-class hypoxia inducible factor prolyl hydroxylase inhibitor (HIF-PHI), which is in phase 3 trials for the treatment of anemia associated with CKD in dialysis-dependent (DD) and non-dialysis–dependent (NDD) patients. In December 2018, FibroGen and AstraZeneca both disclosed positive topline efficacy data from several phase 3 trials, and we anticipate further updates from the phase 3 pivotal program for roxadustat upon final review of the totality of evidence in the first half of 2019.

While both of these examples provide details into our portfolio and pipeline today, we have robust plans for continued research in the future so we can continue to innovate

> "I am more encouraged than I have ever been that now is the time to innovate and raise awareness of how we can tackle CKD . . . ."

in the renal space to identify potential solutions that can change how we understand and treat across the paradigm.

Another example of this is within the sodium glucose co-transporter (SGLT-2) class of medicines that is indicated to treat type II diabetes. We recently communicated results from DECLARE-TIMI 58, the largest SGLT-2 inhibitor cardiovascular outcomes trial conducted to date, which showed that FARXIGA (dapagliflozin) significantly reduced the risk of hospitalization for heart failure or cardiovascular death composite vs. placebo by 17%. And, although nominally significant, the renal composite endpoint showed that FARXIGA reduced the rate of new or worsening nephropathy by 24% vs. placebo across the broad patient population studied.

To further understand the impact FARXIGA may have on the estimated 200 million people worldwide living with CKD, we look forward to completing the DAPA-CKD Outcomes Trial, a study in CKD patients both with and without diabetes, in 2020.

LOOKING AT THE ENTIRE PHARMACEUTICAL SPECTRUM, IS KIDNEY MEDICINE A CONCERN ACROSS THE BOARD IN THE PHARMA INDUSTRY?

I believe there is no greater time than now to bring research and medicines to the forefront for kidney disease, and that this is truly an opportunity vs. a concern. We continue to see more and more energy put forth toward navigating this treatment paradigm.

Further, we are pleased to see that this space continues to be recognized by government bodies, in particular with the Advancing American Kidney Health initiative, and additional efforts by the Centers for Medicare & Medicaid Services and the U.S. Department of Health and Human Services, which have specifically called out the need for greater innovations in the advancement of therapy for kidney disease. The agencies have begun to identify opportunities to recognize and reward those innovations and ensure patients have access to them. As an organization committed to this space, it is our belief that we must continue to support and encourage all research that can ultimately make a difference for the millions of patients living with chronic kidney disease.

WHEN YOU SAY THERE HAS BEEN LITTLE INNOVATION IN THE RENAL AREA, ARE YOU REFERENCING CKD SPECIFICALLY OR RENAL CONDITIONS OR PATHOLOGY IN GENERAL?

As you are aware, renal disease is a highly complex, specialized area. As a nephrologist, I had the opportunity to practice at a time when we saw some significant advancements in managing complications for chronic kidney disease patients.

However, I also recognize that given the complexity of this space, the investment it takes and at times, much trial and error in research, the progress for which we should be serving such an urgent medical need has lagged in comparison to advancements in other disease areas.

I am more encouraged than I have ever been that now is the time to innovate and raise awareness of how we can tackle CKD as a whole and ultimately work to slow the progression of CKD for patients. We are innovating across many facets of the scope of renal, whether it be tackling complications through approved products and in our late-stage pipeline, continuing life-cycle management for our inline products to understand potential in slowing progression of disease, or as a robust early stage pipeline, which will aim to uncover further research in targeting chronic kidney disease and its associated complications.

DO YOU THINK SOMEDAY—EVEN IN THE NEAR FUTURE—KIDNEYS WILL BE CONSIDERED AS VITAL AS THE HEART AND LUNGS ARE TODAY?

As a former practicing nephrologist and with over 20 years in the industry, I certainly hope so. I joined this company because of its belief in emphasizing the criticality of treating the kidney. With the expected advancements and research on the horizon alone from our pipeline, I do believe it will put forth greater awareness for the importance of innovating to advance treatments for kidney disease.

We must continue to hold ourselves accountable to make this a reality and drive positive change in the industry, working with our partners and allies to advocate for the importance of continued science and awareness in renal disease. We are all in to make this ambition a reality. It is our hope that we can rewrite the story behind kidney disease and the way it's managed today, revolutionize care with significant scientific advancements, and ultimately shift the dialogue to deliver a greater future for those we serve. ■

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