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Exposure to Wildfire Smoke Linked to Higher Death Rates in Patients with Kidney Failure

By Tracy Hampton

Individuals with kidney failure may face a higher risk of dying prematurely if they are exposed to air pollution from wildfires, according to new research published in the *Journal of the American Society of Nephrology*.

Large wildfires are occurring more frequently, and smoke generated from these fires contains high concentrations of fine particulate matter and other forms of pollution. When inhaled, fine particulate matter can travel into the respiratory tract and bloodstream and trigger oxidative stress and inflammation that may contribute to poor health, especially in sensitive populations including the elderly and individuals with chronic health conditions.

Studies have found that air pollution is one of various different environmental factors that can contribute to the development of kidney disease.

Because patients with kidney failure requiring dialysis are a fragile population, often with multiple illnesses such as hypertension and diabetes, investigators examined whether they are especially vulnerable to the health effects of wildfire smoke exposure.

For the study, the team assessed daily exposure of wildfire small particulate matter and mortality rates, both on the day of exposure and up to 30 days following exposure, drawing on information from 253 US counties near a major wildfire between 2008 and 2012.

"This study was possible because the US Renal Data System, a registry of patients with kidney failure, included vital records on almost all US patients receiving in-center hemodialysis, as well as the counties of the dialysis clinics," said lead author Yuzhi Xi, MSPH, of the University of North Carolina at Chapel Hill. "Secondly, we utilized an air quality model to estimate daily exposure to wildfire fine particulate matter across the country at the counties of the dialysis units."

Among the 268,399 US in-center hemodialysis patient deaths in the five-year period of 2008 to 2012, a total of 48,454 deaths were among patients who were receiving dialysis in the 253 counties. Each 10 μg/m^3 increase in the concentration of wildfire fine particulate matter in the air was associated with a 4% higher death rate on the same day and a 7% higher rate over the next month. On days with wildfire fine particulate matter greater than 10 μg/

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Innovators in Bioengineering, Infection Control, and Home Hemodialysis Awarded KidneyX Prizes

By Ruth Jessen Hickman

Bioengineering innovations to decrease failure rates of arteriovenous fistulas and grafts, improved infection control measures in catheter-based and peritoneal dialysis, and a new hemodialysis system designed for home use were the prize-winning "Redesign Dialysis Phase 2" innovations announced at the recent virtual KidneyX Summit.

KidneyX (the Kidney Innovation Accelerator) is a partnership between the American Society of Nephrology and the US Department of Health and Human Services (HHS) to promote innovations in kidney disease prevention, diagnostics, and treatment. Through a series of monetary prize competitions, KidneyX helps speed the development of new medical products by fostering collaboration among patients, health professionals, industry, innovators, and government experts.

This year's summit continued the emphasis of the 2019 Redesign Dialysis Phase 1 competition, awarding grants of $500,000 to each prize winner. The competition received

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Innovators Awarded at KidneyX Summit

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70 submissions, which were reviewed under a rigorous two-phase process.

The need for true, patient-centered innovations in dialysis care is profound. Dialysis itself has changed relatively little in the past several decades, with huge financial impacts on the US healthcare system and on kidney patients' quality of life.

"It will take collaboration across industries and disciplines to truly redesign dialysis and transform the status quo of kidney treatment, and that is what KidneyX is delivering," said Eric Hargan, JD, HHS Deputy Secretary. "You have the chance to change not just the face of kidney care in America, but across the whole world." Kidney health innovation is a top priority for HHS and will help achieve goals outlined in the *Advancing American Kidney Health initiative*.

Serial entrepreneur Dean Kamen, of DEKA Research & Development Corporation, gave the summit's keynote address, noting that true innovations are so compelling that people are willing to change the way they do things. "An innovation actually solves a real human need," he said. "It can be scaled practically. In the medical space, that not only means it has to be safe and reliable, but it has to be affordable."

"What frustrated me about the kidney health innovation landscape was that everybody was talking in different rooms," said panelist Sandeep Patel, PhD, the former HHS open innovation manager who played an integral role in establishing KidneyX. "And that doesn't even get to all the engineers and scientists that don't even know there is a problem to be solved. To me, that's the power of KidneyX." Patel is currently Director of the HHS BARDA Division of Research, Innovation, and Ventures.

KidneyX incorporates patient input at every step of evaluation, and the panelists and award winners highlighted the critical role of such perspectives in their innovations.

Redesign Dialysis Phase 2 award winners

Fistula and graft innovations

The preferred form of dialysis vascular access is an arteriovenous (AV) fistula, which provides lower infection rates and longer functioning lifetime compared to grafts. But not all patients can get AV fistulas. They cannot be utilized as quickly, and sometimes the fistulas never mature. Although less prone to failure than AV grafts, AV fistulas have a 30–40% failure rate at one year. With repeat failures, some patients are forced into catheter-based access, an approach that significantly increases the chances of mortality.

Buddy Ratner, PhD (previous Phase 1 winner), for creation of a new type of AV graft

Ratner is co-director of the Center for Dialysis Innovation at the University of Washington. He and his colleagues created a tubular AV graft with similar mechanical compliance to a native artery. The graft is designed to perform better than those currently available and to reduce the rate of failure.

Although standard Teflon grafts are not toxic, they initiate an inflammatory response, Ratner said, leading to scarring and out-of-control cell growth. This, in turn, leads to partial occlusion of the vessel, and the resultant reduced blood flow leads to clotting. "The scar-like sheath also inhibits the pulsation of the graft with each beat of the heart," Ratner said. "Teflon grafts do not flex, which disturbs blood flow and further enhances the inflammatory reaction."

Ratner and his team invented a porous biomaterial where all the pores are 40 microns in diameter and interconnected. Although not bioresorbable, the material heals inside the body without stimulating a chronic inflammatory reaction or creating a scarring sheath. Over time, blood vessels grow into the tiny pores, providing a path to seed the luminal region with protective endothelium. These blood vessels can also allow phagocytic cells to access bacteria, potentially reducing complications from infection.

The team has studied the new graft type, which they call "pro-regenerative access graft" (PRIDE), in sheep models, where they have demonstrated much reduced thrombotic deposition.

"We believe the PRIDE would reduce expensive and painful surgeries while performing as well or better for blood access than the fistula," Ratner said. They speculate that the grafts might be used to address lower limb complications, as a critical need exists for synthetic vascular conduits for diseased leg vessels less than 5 mm in diameter.

Aijun Wang, PhD, for a product that could modify existing grafts to reduce graft failure

Wang is associate professor of surgery and biomedical engineering at the University of California, Davis, and cofounder of VasoBio, a medical device startup company. He and his team focused on improving vascular grafts for hemodialysis.

Wang's group targeted endothelial cells, cells critical for anti-platelet adhesion, anti-inflammatory responses, and other key properties. "Establishment and maintenance of a healthy endothelium is crucial for the prevention of clotting and narrowing of blood vessels," he said.

Using high-throughput screening technology, the team identified a peptide ligand, LXW7, that possesses high affinity and specificity for endothelial cells and their progenitor cells. They then developed a method to coat grafts already on the market with the ligand. The idea is that the graft would become lined with living endothelial cells that could perform a protective function.

> **"An innovation actually solves a real human need. It can be scaled practically. In the medical space, that not only means it has to be safe and reliable, but it has to be affordable."**
> **—Dean Kamen**

The team verified that endothelial cells do grow and spread more easily on the modified graft. In small and large animal models, the grafts modified with LXW7 maintained significantly higher patency compared to untreated grafts. Those coated with LXW7 displayed a smooth layer of endothelial cells lining the luminal surface, without red blood cell adhesion or platelet clumping.

Although these grafts coated with LXW7 appear identical to uncoated grafts to the naked eye, they work significantly differently at the molecular level, Wang said. They also could be integrated seamlessly into existing surgical protocols. The team posits that the technology might one day successfully be used for such applications as stents, catheters, and chemotherapy ports.

Timothy Boire, PhD, for SelfWrap to reduce AV graft and fistula failure

Boire is the president and CEO of VenoStent. His team developed SelfWrap, a slowly bioresorbable shape memory polymer wrap that provides personalized fit and support at the site of vein-artery or vein-graft junction, the areas most prone to failure as they adapt to an increased blood pressure.

"The main culprit of access failures is inward collapse of the vein through neointimal hyperplasia," Boire said. "Providing durable but flexible mechanical support reduces the

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Take Action to Accelerate Artificial Kidney Development

KIDNEY X
INNOVATION ACCELERATOR

We need your help to secure the $200 million KidneyX Artificial Kidney Prize to address challenges facing people with kidney diseases during the pandemic.

According to Medicare claims data, kidney patients are the most at-risk group among beneficiaries for COVID-19. COVID-19 patients with kidney diseases are 2.5-times more likely to be hospitalized or face other adverse outcomes, including death, from the virus.

Growing evidence suggests that COVID-19 causes kidney injury in patients with otherwise healthy kidney function, further stressing the kidney health system.

COVID-19 has created a new sense of urgency to accelerate the development of an artificial kidney—work that is already underway through KidneyX—and deliver it to patients as quickly as possible, much as the US is investing in bringing a COVID-19 vaccine to market rapidly.

An artificial kidney would enable more patients to safely receive the care they need at home while maintaining a higher quality of life. An artificial kidney would mitigate challenges posed by the current pandemic and make our kidney health system more resilient to future crises such as pandemics or natural disasters.

With appropriate support, multiple artificial kidney technologies could be ready for human in-person clinical trials within 4 years.

Your legislators need to hear from you as a constituent about the risks COVID-19 poses to kidney patients and that investing $200 million to develop an artificial kidney is critical for the health of this vulnerable population.

Click the link below to send a pre-composed email to your members of Congress. https://www.asn-online.org/policy/lac.aspx?ID=24

Innovators Awarded at KidneyX Summit

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deformation of the vein and provides for more effective outward vein growth." The support also mitigates hyperplasia and turbulence within the vessel.

SelfWrap is designed to slide up the graft or vein before surgically securing the connection between the artery and vein or the graft and vein. After this connection is secured, the SelfWrap is slid down over the junction. The material becomes slightly sticky and viscous at body temperature, allowing it to close without the need for sutures and in a manner that provides a custom fit to the patient's specific vessel anatomy.

"The wrap provides mechanical support similar in compliance to that of an artery, and is slowly degraded to improve usability and durability, or maturation and patency," Boire said. Results from sheep studies showed that use of SelfWrap significantly reduced neointimal hyperplasia while promoting outward remodeling of the vessel or graft, potentially leading to reduced infection, thrombosis, and stenosis.

The team is focusing its preclinical development on use in AV fistulas but hopes to receive FDA approval for use in AV grafts as well.

Reducing infection

Two of the KidneyX winners tackled infection prevention as their primary focus, in two quite different contexts: peritoneal dialysis and catheter-based hemodialysis.

Sarah Lee (previous winner, KidneyX Patient Innovator Challenge)

Sarah Lee is CEO of Relavo, a medical device company founded by students at Johns Hopkins University. She and her colleagues created PeritoneX to help prevent infection due to touch contamination in peritoneal dialysis.

Peritoneal dialysis provides better health outcomes, higher patient satisfaction, and improved patient lifestyle, but only 10% of patients needing dialysis are on it because of the inherent risk of peritonitis, which occurs in 30% of patients annually and necessitates hospitalization in 50% of cases, Lee noted. The Advancing American Kidney Health Initiative aims to dramatically increase the percentage of kidney failure patients on home dialysis. This only increases the need to make peritoneal dialysis safer.

PeritoneX is a two-part connection device consisting of a reusable injection-retraction component and a disposable fluid component containing sodium hypochlorite (an established disinfectant in dialysis catheters.)

"Rather than connecting tubes directly, patients will connect them to our device," Lee said. "They'll then push a button to release the antimicrobial solution into the connection space, where it will kill any bacteria on the tube surfaces before being automatically retracted." This maintains a closed system between disinfection and dialysis treatment. In proof-of-concept studies, the device has been shown to exceed industry standards for catheter disinfection.

PeritoneX is compatible with Baxter International peritoneal dialysis supplies, where it can slip seamlessly into the existing setup. Currently no other products on the market aim to reduce risk of peritonitis from peritoneal dialysis, and educational efforts about best practices only slightly decrease rates.

Alexander Yevzlin, MD (previous Phase 1 winner), for NitriCap to reduce catheter infections

Over 110,000 patients in the US use a catheter for vascular access each year, resulting in about 30,000 infections.

In response to this need, Yevzlin, a professor of medicine and director of interventional nephrology at the University of Michigan, and his colleagues developed NitriCap, a disposable hemodialysis cap that secretes nitric oxide gas. The nitric oxide is contained in a stable donor molecule that elutes the gas over three days.

"It's a very simple, unique extension of a regular cap that fits into the hub of a dialysis catheter that can reduce microbial growth," Yevzlin said.

Nitric oxide is well known to be a potent antimicrobial and antifungal, but it has a half-life of only seconds, eliminating potential systemic effects. Added Yevzlin, "Nitric oxide is produced as a gas, never enters the body, and disinfects the inside and outside of the catheter as it diffuses harmlessly into the air."

Studies in sheep demonstrated a more than 100,000-fold reduction in bacteria compared to a control cap. Animal studies also showed that the product prevented the formation of biofilm in all four regions of the catheter. In contrast, commercially available antimicrobial caps using chlorhexidine did not.

"Our patients are constantly living in fear of catheter infection and catheter dysfunction," Yevzlin said. "We think this device can have a huge impact on our patients' lives

Shuvo Roy, PhD (previous Phase 1 winner), for a new hemodialysis system for home care

Roy is a professor in the department of bioengineering and therapeutic sciences at the University of California, San Francisco, and technical director of The Kidney Project, an effort focused on creating a small, surgically implanted, bioartificial kidney to treat kidney failure.

Unlike the other awardees, who are producing products that can merge into and improve existing dialysis setups, Roy and colleagues are developing the iHemo Dialysis System to provide frequent, prolonged hemodialysis sessions with much greater patient ease.

Roy pointed to evidence that patients receiving more frequent and prolonged hemodialysis treatments have better survival rates, better overall health, and fewer dietary restrictions. Currently only about 2% of people on dialysis receive such treatment. Existing bulky hemodialysis systems approved for home use require complex tasks such as vascular cannulation, and they pose risks such as exsanguination.

With iHemo, a compact hemodialyzer (HemoCartridge) is surgically implanted inside the patient's abdomen. It is constructed from silicon nanopore membranes that allow it to work under normal cardiac perfusion pressures, without the need of a mechanical blood pump or systemic anticoagulation therapy. The hemodialyzer connects to the blood vessels on one side, creating a permanent blood circuit inside the patient's body. On the other side, it connects to catheters leading to an external pump.

"From the viewpoint of patients, iHemo fundamentally simplifies the procedure of hemodialysis," said Roy. "The only external component is a compact pump to recirculate dialysate. No blood ever leaves the body, and patients never have to insert needles into a fistula or graft. Instead, they connect dialysis tubing to a catheter to conduct their treatments."

Looking ahead

All the recipients emphasized how important these prizes are for furthering their work. The money allows the teams to push their development forward while they raise additional funds from investors.

"This award will help us advance our prototypes to clinically relevant devices that we can test in preclinical disease models and ultimately in clinical trials," Roy said. "We also hope that the KidneyX award will garner more interest from industry and the investor community to support new innovations to treat kidney failure and kidney disease, because such interest has been significantly lacking for quite some time. It has taken the vision of HHS and ASN to step up."

KidneyX will soon open two more prize competitions: an artificial kidney prize and a competition for solutions to address challenges caused by the COVID-19 pandemic.

"I hope that KidneyX plays a catalytic function, that we'll get a self-sustaining innovation ecosystem where we are getting new products on the market constantly and are constantly improving patient care," Patel said. "Ultimately the measurement of success of KidneyX is not in the programs we create . . . it's whether we create health and wellness for the people for whom we are innovating." ■

Exposure to Wildfire Smoke

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m^3, exposure to the pollution accounted for 8.4% of daily mortality, but this percentage varied from 3.0% to 20.5% across counties depending on the exposure level.

The investigators did not find a significant association with specific causes of death, including cardiac-, vascular-, or infection-related mortality, but they did observe a strong association with deaths related to "other" causes (listed as other, unknown, un-listed other, and missing), which accounted for over 40% of deaths.

"The findings highlight the impact of air pollution exposure in individuals receiving hemodialysis, and they support the need for more research to develop and implement interventions to manage exposure during wildfire smoke episodes in this population," said senior author Ana Rappold, PhD, of the US Environmental Protection Agency.

Ziyad Al-Aly, MD, FASN, who is chief of research and education for the Department of Veterans Affairs Health Care System in St. Louis and was not involved with the study, noted that the findings lend support to results from previous research. "This paper is yet another piece of evidence that air pollution is an important driver of poor health outcomes, and the study's link between exposure to wildfire smoke and death is alarming," he said.

Al-Aly and his colleagues recently integrated all available epidemiological evidence to characterize an exposure–response model of ambient fine particulate matter and the risk of chronic kidney disease, uncovering an increase in risk with increasing air pollution concentrations. The authors of the *BMJ Global Health* study estimated that in 2017, there were 3,284,358 incident and 122,409,460 prevalent cases of chronic kidney disease in the world that were attributable to fine particulate matter, as well as 211,019 deaths due to chronic kidney disease from this form of air pollution. The burden varied by geography and was disproportionally borne by disadvantaged countries.

"Patients and clinicians should be cognizant that poor air quality, especially spikes in levels of fine particulate matter in the setting of wildfires, may be deleterious to human health and especially for our patients with end stage kidney disease on dialysis," Al-Aly said. "The wider policy implications of this body of research are clear: poor air is hazardous to human health, and it tends to disproportionately affect the sick and the poor. Effort to halt climate change and improve air quality is important to the health and well-being of all of us, and especially the most vulnerable among us." ■

The article, titled "Mortality in US Hemodialysis Patients Following Exposure to Wildfire Smoke," appeared online at https://jasn.asnjournals.org/content/early/2020/07/15/ASN.2019101066 on July 16, 2020, doi: 10.1681/ASN.2019101066

COVID-19 Placed Kidney Disease in the Limelight.

Will That Attract More Physicians to the Specialty?

By Nicole Fauteux

Nephrologists have been challenged in recent years to attract young physicians to the specialty. Many attribute this difficulty to the field's complexity, the younger generation's focus on work–life balance, the vulnerability of the patients nephrologists serve, and limited exposure to the field during medical school and residency. Now that kidney disease has been thrust into the limelight by COVID-19, some observers are asking whether the specialty might be more attractive to young physicians in the future.

Such a change would be welcome. In 2019, only 62% of nephrology resident positions were filled during the annual match. That's a slight increase from the lowest point in 2016 but a major drop from 94% a decade earlier.

"The fact that all slots are unfilled during the match clearly highlights the need for better recruitment," said Stephen Sozio, MD, MHS, MEHP, associate professor at Johns Hopkins School of Medicine and associate director of the school's nephrology fellowship program. "How can we care for patients that are critically ill from COVID-19 and other conditions without a stronger pipeline of nephrologists?"

This shortage is part of a larger trend in medicine generally. According to Michael Dill, director of workforce studies at the Association of American Medical Colleges, the growing physician shortage is largely a matter of demographics. As a significant portion of the population enters older adulthood, their need for medical care increases at the same time many physicians are aging out of the workforce.

"We cannot yet know what impact COVID-19 is going to have on physician retirement patterns," Dill said. "Although the numbers are very small, some physicians are coming out of retirement to help out during the pandemic. At the same time, the burnout of caring for COVID-19 patients could result in more early retirements." If it does, this could be problematic, with COVID-19 adding to the disease burden generally and, in some cases, increasing the need for physicians who can treat acute kidney injury.

The somewhat better news?

"The number of folks going into internal medicine and then subspecializing continues to run high," Dill said, "but we're still expecting future shortages because demand is growing even faster."

"One of the things we've seen over the past several years is the emergence of subspecialization in nephrology," Sozio said. "Critical care nephrology is one field that's been blossoming, and we may see even more interest now with COVID-19."

According to Sozio, nephrologists have proved invaluable in some hospitals hard hit during the pandemic. He has heard from colleagues who have been asked to spend more time in general internal medicine wards or intensive care units. "We see patients across the hospital, and we know how to care for patients with complex diseases," he said. "That really does allow us to be flexible when it comes to internal medicine and critical care needs."

A call to arms: "Yes, I belong in this field"

How does Sozio think COVID-19 may affect the future nephrology workforce?

"COVID-19 highlights some of the vulnerabilities that our population has in regard to infectious disease," he said. "Our trainees have seen the COVID era as a call to arms to say, 'Yes, I belong in this field to provide care to everyone that's vulnerable.' At the same time, we are seeing the exhaustion that comes with COVID-19 care, so I am unsure which way our trainees will go."

To encourage more physicians to enter the specialty, ASN has instituted two programs to expose students and residents to nephrology early on: Kidney STARS, which funds participation by students and residents in the ASN annual meeting, and Kidney TREKS, which provides students with a mentored nephrology experience. Sozio said he believes these programs are effective in getting beyond students' preconceptions of kidney care. "They see how one can be effective as a patient advocate and communicator," he said, "and they see the value of research and using data. That's the bright side of nephrology. Making a difference for your patient, and also making a difference for many patients with kidney disease." ■

Nicole Fauteux is the founder of Propensity LLC and a member of the Association of Health Care Journalists.

Bringing Kidney Failure Patients Home

By Nicole Fauteux

To mitigate the risk of COVID-19 infection, a recent white paper released by the Kidney Health Initiative (KHI) Board of Directors urges KHI stakeholders to accelerate the development of home-based technologies for people with kidney failure (1).

"The COVID-19 pandemic is unmasking the shortcomings of in-center hemodialysis for people with kidney failure," the paper states, noting that people who rely on in-center dialysis do not have "the luxury of social distancing during a pandemic," exposing them and those working in dialysis centers to potential infection.

"The global medical device development community needs to collaborate and overcome barriers to bringing more people with kidney failure home for treatment," Raymond C. Harris, MD, FASN, co-chair of KHI, told the press when the paper was released.

The white paper describes the benefits of home therapies and lays out a long list of challenges that are ripe for technological innovation. These include the efficient use of water, point-of-care infection detection, pump and filter miniaturization, vascular access, clotting avoidance, toxin removal, fluid regulation, filtrate transport, and the use of sensors and remote monitoring.

"It's very exciting to see that people are interested and motivated in finding technological solutions to be able to facilitate more dialysis at home, but we have to make sure that we are prepared for the education and support that go along with those advances," said Jeffrey Perl, MD, SM FRCP, an associate professor of medicine at the University of Toronto and staff nephrologist at St. Michael's Hospital UnityHealth. "Technology will be one piece of a whole strategy to empower patients to be able to do dialysis at home."

The white paper's authors also emphasize the need to remain focused on the patient experience as technologies evolve. One current KHI project aims to build the capacity of innovators to incorporate patient perspectives and preferences as they iterate new designs and approaches to kidney replacement therapy (2). The paper states, "KHI has provided tools that innovators can use to integrate patient preferences and patient-reported outcomes throughout their product's lifecycles so that the innovative solutions match what people with kidney disease need."

The paper also stresses that vulnerable and underserved populations must receive equal access to any new technologies that are developed. "Now is the time to bring technologies to market that have the potential to reduce disparities and improve the lives of all individuals with kidney failure," the authors conclude.

The Kidney Health Initiative is a collaborative partnership with the U.S. Food and Drug Administration and more than 100 organizations and companies. The ASN Alliance for Kidney Health created KHI in 2012 to realize ASN's vision of a world without kidney diseases. ■

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Detective Nephron

Detective Nephron, world-renowned for his expert analytic skills, trains budding physician-detectives in the diagnosis and treatment of kidney diseases. L. O. Henle, a budding nephrologist, presents a new case to the master consultant.

Nephron What do you have for us today, my dear apprentice?

Henle I have a 77-year-old white woman with a history of type 2 diabetes mellitus and recently diagnosed metastatic ovarian cancer and now acute kidney injury (AKI).

Nephron Stop… let's see what we can dissect from that.

Henle You will be all over this!

Nephron Not another onconephrology case, Henle; let's do some basic nephrology.

Henle Hmmm. Actually, it really isn't. She hasn't yet received any chemotherapy or immunotherapy. Not even radiation. She was in the process of starting but hasn't yet. Her serum creatinine is 7 mg/dL, and her BUN is 110 mg/dL.

Nephron (*with awe*): What?

Henle Yes, and her serum creatinine was 0.7 mg/dL 1 year ago and 1.2 mg/dL 6 months ago, and just 1.3 mg/dL 2 weeks ago.

Nephron (*angry*): What?

Henle (*surprised*): There you go again—you are stealing my thunder. Yes, and a Foley catheter was placed, but with no urine output.

Nephron Is there any hematuria?

Henle (*rolling his eyes*): Not really; she is not making any urine, so we can't assess for proteinuria or hematuria.

Nephron I am sure they did serologies before they called you.

Henle Yes, so far: antinuclear antibody (ANA), C3, C4, ANCA, double-stranded DNA, and anti–glomerular basement membrane all are negative. She has a negative serum immunofixation, and her serum free light chain ratio was 2.

Nephron Stop right there. Before we go any further, let me summarize this. You have an older lady with recently diagnosed ovarian cancer with a rapidly rising serum creatinine.

Henle (*wondering to himself about quick decision by Nephron*): Yes; correct. By the way, she is not on any medications. No herbal agents, no proton pump inhibitors or nonsteroidal anti-inflammatory drugs—and her complete blood count is normal, making your favorite diagnosis of thrombotic microangiopathy less likely.

Nephron Oh! Oh! No! This is a good one! Glad you brought this one to me. Anuric kidney failure has very few causes. The top three are usually hydronephrosis, hydronephrosis, and hydronephrosis!

Henle (*trying to remember*): Haha… perhaps not. The renal sonogram—sorry, kidney sonogram—was negative for hydronephrosis.

Nephron (*jumping in*): Really….

Henle Hmmm. You are too much! Stop interrupting. I even did a CT scan to see if there was something I was missing. There is significant retroperitoneal metastatic disease, and it seems worse than the prior scan 1 month ago.

Nephron (*shocked*): This is impressive! What are her electrolytes?

Henle Serum sodium is low at 125 mmol/L, and serum potassium is high at 5.8 mmol/L. And she has acidemia, with CO_2 at 18 mm Hg.

Nephron Of course, they are…

Henle (*not sure*): This is probably acute tubular injury or acute interstitial nephritis. What else could this be?

Nephron Hmmm. From what? Was there any hypotension, new medications… contrast material…any other insults?

Henle (*confused*): No to all.

Nephron (*interrupting*): Is there anything on her physical examination?

Henle Some abdominal distention, and 1+ edema in her lower extremities.

Nephron (*confident*): This is hydronephrosis.

Henle No, the sonogram and CT scan were negative for hydronephrosis.

Nephron Smells like a hydronephrosis to me. This is hydronephrosis.

Henle (*puzzled*): OK… but how can you have hydronephrosis without imaging findings?

Nephron The sonogram reads no hydronephrosis and/or dilation. But clinically, the only thing that makes sense to me is obstruction. Especially with the electrolyte findings and this sudden rise of serum creatinine in the setting of a retroperitoneal mass. Nondilated obstruction is not uncommon, especially in patients with cancer that affects the retroperitoneal regions. There is so much disease that there is no room for the kidney to expand. But that does not mean that hydronephrosis is not present. The syndrome of nondilated obstructive uropathy and AKI is well reported in that setting, although the literature suggests that this syndrome is rare, accounting for fewer than 5% of cases of urinary obstruction.

Henle's eyes respond with shock.

Henle Really? You must be kidding!

Nephron One of the earlier studies looked at a series of patients at a single center and found that the most common cause of nondilated hydronephrosis was cancer (likely related to retroperitoneal disease): prostate, colon, bladder, cervical, ovarian, lymphomas. Antegrade urography can help. The first-ever case of this was described in 1948 in someone with retroperitoneal fibrosis.

Henle, puzzled, leaves the room but returns in 2 days.

Nephron And?

Henle (*with a smile*): We asked radiology to place percutaneous nephrostomy tubes, and there was significant bilateral obstruction. The patient's serum creatinine is improving. Her electrolytes have improved as well.

Nephron (*jumping in*): Despite the absence of dilation on renal imaging, a strong suspicion for nondilated obstructive uropathy led to decompression procedures with prompt recovery of kidney function in your patient. This has been reported in the radiology literature. It is an important differential diagnosis to consider. Treatment is usually diagnostic. Given the pathologic features, the ureteral stents sometimes get restenosed and are unable to adequately decompress the collecting system. Percutaneous nephrostomy is usually the best procedure in such situations. Educating our urology and radiology colleagues about this entity is extremely important.

Henle (*surprised*): This is just fascinating and so refreshing. I love nephrology.

Nephron Hyponatremia and hyperkalemia have been reported with hydronephrosis as a result of the effect on the Na+-2Cl-K+ channels and Na+-K+ATPase pump being downregulated. The AKI itself can be responsible for these rapid electrolyte disorders from the hydronephrosis.

Nephron Well done, apprentice. Keep an open mind. Again, never assume. Anuric AKI has very few causes: hydronephrosis, hydronephrosis, and then perhaps acute tubular injury, acute interstitial nephritis, and then cortical necrosis. Again, a quick diagnosis here and a therapeutic procedure saved this patient's kidneys!

Henle (*laughing*): I need some coffee—the super New York style.

Detective Nephron was developed by Kenar D. Jhaveri, MD, professor of medicine at Donald and Barbara Zucker School of Medicine at Hofstra/Northwell. *Thanks to Rimda Wanchoo, MD, associate professor of medicine at Zucker School of Medicine at Hofstra/Northwell, for her editorial assistance.* *Send correspondence regarding this section to kjhaveri@northwell.edu or kdj200@gmail.com*

Fluid Management Key to Protecting Kidneys in COVID-19 Patients

By Bridget M. Kuehn

The dilemma of how to best manage fluid levels in critically ill patients receiving mechanical ventilation is a familiar one to nephrologists who may frequently encounter this challenge in patients with sepsis. But managing fluid balance in patients with coronavirus disease 2019 (COVID-19) poses a whole new set of challenges.

There is bi-directional crosstalk between the lung and kidney in critically ill patients with acute respiratory distress syndrome (ARDS), said Kathleen Liu, MD, PhD, professor of medicine at the University of California, San Francisco. Patients with COVID-19 frequently experience severe and prolonged ARDS, but whether there are COVID-19–specific pathogenic mechanisms that may affect these interrelationships is unknown, she said. However, previous research on ARDS in patients with other conditions suggests managing fluid levels is essential.

Further complicating care for these patients is the need to reduce the risk of clinicians becoming infected with the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) that causes COVID-19. A shortage of personal protective equipment (PPE) that helps reduce the risk of clinician infection has forced hospitals to ration their use. This makes use of many fluid monitoring techniques that require direct contact with COVID-19 patients more challenging.

"We're trying to minimize physical contact with these patients [to reduce spread of the infection] and to reduce the use of PPEs," said Michael Heung, MD, MS, professor of medicine at the University of Michigan in Ann Arbor.

Liu and Heung were part of a panel of expert nephrologists who spoke during a recent ASN webinar on AKI: The Kidney/Lung Connection and Fluid Management in COVID-19 (1).

Age-old quandary

Fluid management in patients with ARDS is an "age-old quandary" nephrologists have struggled with even before COVID-19, Heung said. Fluid overload can contribute to cardiopulmonary edema, acute kidney injury, sepsis, or death. But removing too much fluid can also exacerbate shock, contributing to a lack of perfusion to organs and potentially kidney injury.

"The key concept is really trying to identify fluid responsiveness," Heung said. He noted there are many tools available to help, including physical exams, vital signs, diagnostic maneuvers, intravenous fluid challenges, or noninvasive approaches like ultrasound. But he said clinicians providing direct care to COVID-19 patients in the intensive care unit may not be familiar with these techniques.

Heung and Liu both cited the Fluids and Catheters Treatments Trial (FACTT) results published in 2006 as a reason nephrologists should consider a conservative approach to fluid management in COVID-19 patients (2). The trial compared a liberal and a more conservative approach, which favors a drier lung in patients with ARDS. The trial did not find a mortality benefit for the more conservative fluid management approach, but it did find that this approach resulted in patients having more ventilator-free days than those in the group with the more liberal approach. Patients receiving the more conservative approach also trended toward needing less dialysis than those receiving the more liberal approach, with 10% needing dialysis compared to 14% in the liberal group, although this result did not meet statistical significance.

"This has really moved the field toward being more conservative with fluid management in the ARDS setting," Heung said.

Heung also cited a small, retrospective trial he and his colleagues conducted in pediatric patients receiving ECMO (extracorporeal membrane oxygenation), which suggested avoiding fluid overload was associated with better survival than trying to correct fluid overload after it occurs (3). Based on data he and his colleagues have collected on COVID-19 patients to date, they have not seen an immediate benefit of fluid removal, but they anticipate one based on the FACTT results and will continue to collect data, he said. The Surviving Sepsis COVID-19 guidelines also promote a conservative approach to fluid management for COVID-19 patients (4).

Sumit Mohan, MD, MPH, raised a potential need for caution with the conservative approach, noting that COVID-19 patients who have gastrointestinal symptoms like severe diarrhea or reduced food intake may be coming in with low fluid volume. "You do have to use some clinical judgment," he cautioned. Mohan is associate professor of medicine and epidemiology at Columbia University Medical Center in New York.

The need for close communications with the interdisciplinary team caring for COVID-19 patients is also important, said Juan Carlos Velez, MD, chair of nephrology at the Ochsner Health System at the University of Queensland in Brisbane, Australia. With limited access to some tools for monitoring fluid status like ultrasound during the pandemic, interdisciplinary collaboration is even more important.

Mohan agreed that better multidisciplinary collaboration is essential. "It forced us to communicate better with the intensivist teams and the nursing staff to figure out [patients' fluid status]," Mohan said. "It's a challenge." ■

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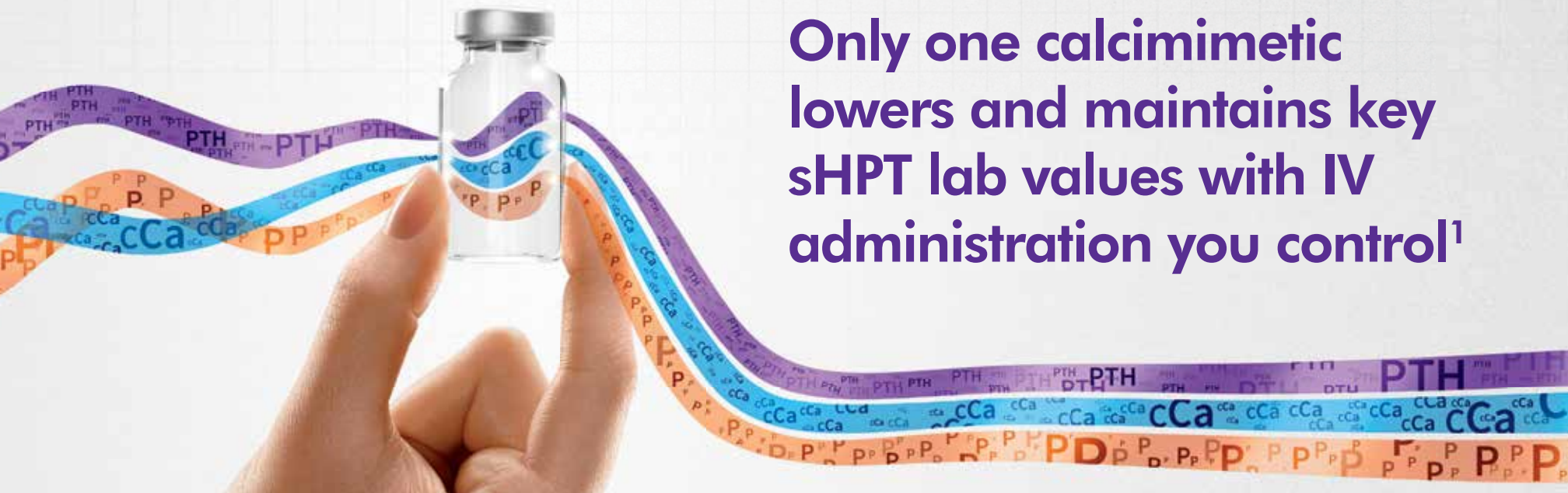

Only one calcimimetic lowers and maintains key sHPT lab values with IV administration you control[1]

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

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

Indication

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

Limitations of Use:

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

Important Safety Information

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

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

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

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

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

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

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

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

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

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

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

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

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BRIEF SUMMARY OF PRESCRIBING INFORMATION

Parsabiv™
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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®

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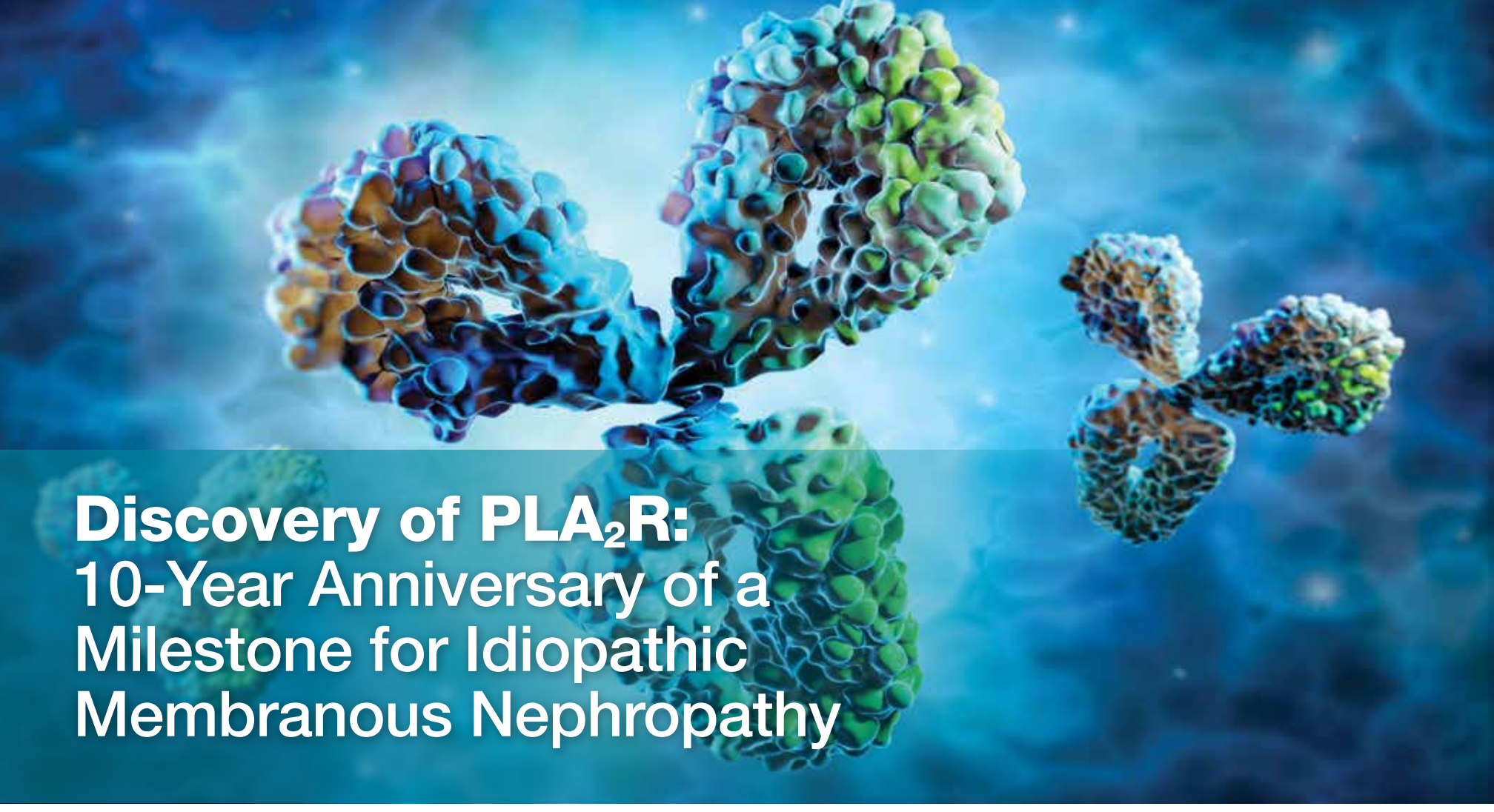

Discovery of PLA_2R: 10-Year Anniversary of a Milestone for Idiopathic Membranous Nephropathy

As a research fellow in the laboratory of Professor David Salant, MB, BCh, at Boston University, Laurence Beck, MD, PhD, spent several frustrating years trying to identify the targets of the autoantibodies that cause idiopathic membranous nephropathy (IMN). Finding these targets was critical to understanding why the immune system attacks the body's own cells in that disease. Then, in 2009, he and his colleagues identified the M-type phospholipase A2 receptor PLA_2R as a prime target (1). At the time, they didn't know how pivotal their discovery would be.

"When we finally identified PLA_2R, that was certainly a time of excitement," said Beck, now an associate professor of medicine at Boston University School of Medicine. "I don't think we really realized how big a story it would be 10 years later. It really has changed this one small area of nephrology and has allowed us to make big steps forward in this disease."

Recently, Dr. Beck spoke with *Kidney News* about the 10-year anniversary of PLA_2R and what has happened in the field since then.

Kidney News: ***How has our understanding of the role of PLA_2R in IMN evolved since your initial discovery?***

Dr. Beck: I don't think we've advanced as much as we had hoped for. There is no good animal model to study the effect of human antibodies on human PLA_2R. A group from Hamburg, Germany, has created a mouse that expresses PLA_2R in podocytes, and you can give it rabbit antibodies against PLA_2R to observe the disease (2). Unfortunately, we can't study human antibodies in that mouse model. So, we're still trying to figure out exactly how these antibodies lead to membranous nephropathy.

We have learned more about the genetics and the immune response against PLA_2R. Soon after the 2009 article describing PLA_2R, another article in the *New England Journal of Medicine* in 2011 talked about the genetic risk factors of IMN (3). It identified two spots in the DNA that are linked with a higher risk of IMN. One is in the *PLA_2R1* gene itself. The other was in the HLA region, which has been linked to other diseases in which the immune system attacks the body. Very precise mapping of this HLA region by two Chinese groups has shown that the risk genes are in the part of the HLA molecule that binds the peptide (4). This suggests that patients with these HLA-associated genetic risk factors are better able to present PLA_2R to the immune system, which may stimulate the pathogenic immune response. A very large genome-wide association study summarized at Kidney Week 2019 by Krzysztof Kiryluk, MD, assistant professor of medicine at Columbia University Medical Center in New York, recently located two more risk alleles associated with the immune response in IMN. It's a fascinating area that will continue to evolve.

Kidney News: ***What have you learned about the immune response in this disease?***

Dr. Beck: A group of scientists at the University of Manchester in England were the first to identify what we call the immunodominant epitope in the N-terminal region of the PLA_2R protein (5). Then, a group in Nice, France, identified that there are actually three distinct epitopes in the PLA_2R extracellular domain: one in the CysR region (confirming the study by Fresquet et al. from Manchester) and two others, one in CTLD1 and one in CTLD7 (C-type lectin-like domains of PLA_2R) (6). Patients who have an immune reaction to multiple epitopes, a process called epitope spreading, tend to have more severe disease. But a new article by the group from Hamburg suggests there is a fourth epitope and that overall antibody titers may be more predictive of disease severity than epitope spreading (7).

Kidney News: ***How has clinical care for patients with IMN changed since your 2009 discovery?***

Dr. Beck: The treatment options that were available in 2009 are still the recommended treatment options now, as the 2012 KDIGO guidelines state. The Ponticelli regimen, which combines corticosteroids and alkylating agents, remains the first-line therapy. Calcineurin inhibitors, like cyclosporine, are an alternative first-line therapy, according to the guidelines. The B cell–depleting agent rituximab was just starting to show some promise and has since become a common option. What has changed is that we now do not guess at who needs the treatment.

When we measured antibodies to PLA_2R in our study (8), using samples provided by the Mayo's Fernando Fervenza, PhD, director of the Nephrology Collaborative Group at the Mayo Clinic, in Rochester, Minnesota, we realized that the antibodies decline and disappear months to years before a clinical response occurs. Now, we monitor the disease course by measuring whether circulating antibodies to PLA_2R are going up and down, and we use that information to guide therapy.

Kidney News: ***More recently you and your colleagues (9) have identified another protein targeted by autoantibodies in patients with IMN who don't have antibodies to PLA_2R. What has been the impact of that discovery?***

Dr. Beck: Only about 3% of patients with IMN or primary membranous nephropathy have antibodies to thrombospondin type-1 domain–containing 7A (THSD7A). There is some limited evidence that you can monitor THSD7A antibody levels to guide treatment decisions. You can use kidney biopsy staining for THSD7A to tell whether a patient has that specific form of membranous nephropathy.

When we first found THSD7A, we had no idea what it was doing in the podocyte. But work from the Hamburg group has beautifully shown that THSD7A sits at the

bottom of the podocyte immediately under the slit diaphragm, which suggests that maybe it has some biologic role in the cell that we don't yet understand (10). The other good thing about that protein is that it is expressed in the mouse and rat podocyte, unlike PLA_2R. This allowed the Hamburg group to create the first mouse model, in which they injected a human anti-THSD7A in rodents and showed that it would localize in the mouse glomeruli and cause proteinuria.

Kidney News: *What makes THSD7A-linked IMN different from PLA2R-linked IMN?*

Dr. Beck: Some of THSD7A's unique features are really interesting. Initially, there was a suggestion that patients who had THSD7A were more likely to have underlying cancer that causes membranous nephropathy. This is supported by case reports from the Hamburg group showing that tumors in two different patients overexpressed THSD7A (11, 12). This suggests that the immune response to the tumor actually triggered the kidney disease by making THSD7A antibodies. Now, when someone receives a diagnosis of THSD7A-type membranous nephropathy, we look very closely to see whether they have any undetected cancers.

Kidney News: *What do you think the future holds in terms of treatments for IMN?*

Dr. Beck: In the future, treatments for autoimmune diseases like IMN will be more specific. Right now, we wipe out broad aspects of the immune system by targeting B cells or the bone marrow precursors. But there is a possibility you could create therapies targeting only the B cells that make antibodies to PLA_2R or THSD7A. Several groups are looking at ways to use CAR-T cell therapy, which is currently being used to treat certain forms of cancer, to destroy PLA_2R-targeting B cells. Another possibility would help a patient develop tolerance to PLA_2R or THSD7A.

Kidney News: *What are some of the key questions that remain to be answered about IMN?*

Dr. Beck: Have we found all the antigens? In the past year, workers at the Mayo Clinic have found two more antigens or biomarkers in certain types of membranous nephropathy. One is exostosin, which is also found in patients who have a systemic autoimmune disease, like lupus. Another is NELL-1. Those workers used new, less labor-intensive techniques that may help identify even more antigens in IMN. We need to learn more about each of the subtypes of the disease.

We also need to learn more about how environmental insults interact with genetic risk. Most cases of IMN emerge in middle age, and we don't know why. There's some evidence from China that air pollution is linked to an increased incidence of membranous nephropathy (13). So, one suspicion is that the increased PLA_2R expression in the lungs in response to air pollution could trigger IMN in susceptible individuals. We also need to learn more about why patients with IMN often experience a relapse.

Kidney News: *In the meantime, what can clinicians do to improve care for patients with IMN?*

Dr. Beck: A lot of people at academic centers are using antigen and autoantibody testing to guide patient care, but it is sometimes more difficult for community practitioners to access these tests. I'm hoping that even more nephrologists will gain familiarity with, and have access to, antibody testing for PLA_2R and THSD7A so they can better guide patient care. ■

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No Increase in COVID-19 Risks With ACE/ARB Use

Among patients with hypertension, previous treatment with angiotensin-converting enzyme inhibitors/angiotensin receptor blockers (ACEI/ARBs) does not increase the risk of severe or fatal COVID-19, concludes a study in *The Journal of the American Medical Association*.

The retrospective analysis included data on 4480 patients with COVID-19, median age 54.7 years, drawn from Danish national registries. Patients were followed up from diagnosis until they reached a study outcome, or until early May 2020.

Twenty percent of patients had been using ACEI/ARBs, based on prescription fills within the previous 6 months. The primary outcome was death; secondary outcome was a composite of death or severe COVID-19, defined as severe acute respiratory syndrome or ICU admission.

COVID-19 patients with a history of ACEI/ARB use were older (mean age 72.8 versus 50.1 years) and more likely to be men (55.1% versus 46.1%), compared to non-ACEI/ARB users. The ACEI/ARB users also had higher rates of comorbid cardiovascular disease, including previous myocardial infarction and heart failure. About half of patients (49.6%) were hospitalized at the time of COVID-19 diagnosis.

Thirty-day mortality was 18.1% in patients with previous ACE/ARB use, compared to 7.3% in nonusers. On unadjusted analysis, mortality risk was more than twice as high in ACEI/ARB users with COVID-19, hazard ratio (HR) 2.65. However, the association became nonsignificant (HR 0.83) after adjustment for age and medical history. Standardized mortality was 8.8% in ACE/ARB users and 10.2% in nonusers.

Thirty-day rates of the composite outcome were 31.9% in ACEI/ARB users versus 14.2% in nonusers. Again, the association was not significant after adjustment for age and comorbidity. The same was true on analysis of severe COVID-19 (with 30-day rates of 22.6% and 10.4%, respectively).

A nested case-control analysis examined susceptibility in 571 COVID-19 patients with previous hypertension, compared to an age- and sex-matched group of 5710 hypertensive patients without COVID-19. Rates of ACEI/ARB use were approximately 85% in both groups.

Because angiotensin-converting enzyme 2 is the receptor for cell entry for SARS-CoV2, there have been concerns that ACE/ARB users might be more susceptible to infection, or might have worse outcomes of COVID-19. These registry data show no increase in the risk of death

or severe disease in COVID-19 patients with a history or ACEI/ARB use, nor any increase in the rate of COVID-19 diagnosis associated with these widely used antihypertensive drugs.

The investigators conclude: "These findings do not support discontinuation of ACEI/ARB medications that are clinically indicated in the context of the COVID-19 pandemic" [Fosbøl EL, et al. Association of angiotensin-converting enzyme inhibitor or angiotensin receptor blocker use with COVID-19 diagnosis and mortality. *JAMA*. 2020; doi: 10.1001/jama.2020.11301]. ■

Industry Spotlight

Diabetic Kidney Disease Drugs Show Promise

Two recent studies show promise for people with type 2 diabetes with kidney disease.

Bayer announced that results of the phase 3 FIDELIO-DKD study of the drug finerenone met its primary endpoint of delaying progression of chronic kidney disease (CKD) in type 2 diabetes patients. CKD progression was delayed through reduction of the combined risk of time to first occurrence of kidney failure, a sustained decrease of estimated glomerular filtration rate (eGFR) greater than or equal to 40% from baseline over a period of at least four weeks, or renal death.

The drug is the first investigational non-steroidal, selective mineralocorticoid receptor antagonist that demonstrates risk reduction in kidney and cardiovascular events, according to Bayer, a worldwide pharmaceutical company based in Leverkusen, Germany, with Bayer US located in Whippany, NJ.

FIDELIO-DKD is a randomized, double-blind, placebo-controlled, parallel-group, multicenter phase 3 study and includes 5700 patients from more than 1000 sites across 48 countries. Patients were randomized to receive either finerenone 10 mg or 20 mg orally once daily or placebo when added to standard of care, which included blood glucose–lowering therapies and maximum tolerated dose of renin–angiotensin system (RAS)-blocking therapy.

Second, AstraZeneca's dapagliflozin (brand name Farxiga, Cambridge, UK) is again showing usefulness for CKD patients with type 2 diabetes. As the company awaits an FDA decision on its application to use the drug as a treatment for patients who have CKD but not diabetes, the firm announced that the drug could reduce the proportion of patients with declining eGFR. The DECLARE-TIMI 58 trial showed that among patients taking dapagliflozin—both type 2 diabetes patients and those with an established or increased risk of cardiovascular disease—eGFR levels declined rapidly in 26.8% versus 37.1% of patients taking a placebo, according to MDMag.com

Terlipressen Makes it Out of FDA Advisory Committee

The drug Terlipressin (Mallinckrodt, Staines-upon-Thames, UK) made it out of an FDA advisory committee with an 8-7 vote for approval. At the recent Cardiovascular and Renal Drugs Advisory Committee meeting, participants pointed out benefits, but also some weaknesses of the drug, which was evaluated for its use in the treatment of hepatorenal syndrome type 1 (HRS-1). This kidney condition can develop in patients with acute or chronic liver disease with advanced liver failure and portal hypertension, and patients have poor survival rates.

Among other data, the FDA panel looked at data from a phase 3 trial of 300 patients, which showed a risk of respiratory failure that affected 10% of patients taking Terlipressin, but only 3% of those on placebo. Deaths from sepsis and septic shock were also more prevalent in the Terlipressin arm when compared with the placebo arm.

Regarding the drug's risks, Daniel Bonner, the advisory committee's patient representative, said the choice to take such risks should be up to the patients, who should be able to weigh a medicine's complications with the possibility of having more time to live.

AKI Algorithm Gets FDA Breakthrough Designation

Dascena (Oakland, CA) received FDA breakthrough device designation for its Previse machine-learning algorithm to predict acute kidney injury (AKI). The Breakthrough Devices Program provides a prioritized review of a device submission to the FDA and lets manufacturers interact with agency experts to address topics as they arise during the premarket review phase.

The algorithm uses values of various heart rates, respiratory rate, temperature, serum creatinine, Glasgow Coma Scale score, and patient age to predict likelihood of AKI. The company demonstrated that its algorithm predicted AKI more than one day before patients would meet the clinical criteria for diagnosis, which is based on changes in serum creatinine, urine output, or both, according to the National Center for Biotechnology information. In validation studies, Previse demonstrated higher sensitivity and predictive value than a clinician's assessment based on clinical criteria.

Diabetic Kidney Disease Collaborative Plans Free Roundtable Discussions

By Karen Blum

The ASN's Diabetic Kidney Disease Collaborative (DKD-C) has organized a series of three virtual roundtable discussions on the management of diabetic kidney disease to occur this summer and fall. Registration is free and open to all ASN members and partner organizations.

The first session, "Management of Diabetes and Kidney Disease Through COVID-19," will be held on Tuesday, Aug. 18, from noon to 1:30 p.m. EDT. The discussion will detail the care needs and patient experience managing diabetes and kidney disease during the COVID-19 pandemic, outline frequent patient concerns, and provide strategies for maintaining health. The conversation will touch on population susceptibility to diabetes, a personal journey of COVID-19 and DKD management, patient access to new therapies, and coordinating DKD care.

The second session, "Goal-Directed Medical Therapies for Patients with Diabetic Kidney Disease," will be held on Tuesday, Sept. 29, from noon to1:30 p.m. EDT. During this event, leading experts in the care of individuals with diabetic kidney disease will describe the new standard of care for DKD, discuss the clinical indications for SGLT2 (sodium-glucose cotransporter-2) inhibitors, and consider payment issues associated with new therapies. The session will address topics such as paying for new therapies and will conclude with a roundtable discussion.

"New Approaches to Transform Outcomes for Kidney Disease and Heart Disease in Diabetes," is the topic of the final webinar, which will be held Thursday, Dec. 10, from 4 p.m. to 5:30 p.m. EST. Clinical experts in this session will review the latest guidelines for both kidney and heart disease, discussing the evolving landscape for diabetic kidney disease as well as the most recent trials and promising therapies. A roundtable of experts from nephrology, cardiology and endocrinology will note the implications for diabetes, kidney, and heart disease treatment as we head into 2021.

The events are sponsored by Bayer, AstraZeneca, Janssen, Eli Lilly, and Baxter International.

"After decades of waiting, we have entered an exciting new era where nephrologists have powerful new treatments to dramatically slow and even halt the progression of kidney disease in patients," said Susan Quaggin, MD, FASN, chair of the DKD-C Task Force. "The DKD-C Task Force has a goal to make sure these treatments reach the patients who need them."

The DKD-C was launched by ASN in July 2019 in response to the recent development of new therapies for people with diabetic kidney disease. The collaborative works to increase coordination among primary care physicians, nephrologists, and other specialists to deliver appropriate therapies to people living with DKD. It also aims to provide educational information to help nephrologists and other health professionals provide high-quality care to people with DKD and to address legislative, regulatory, and policy issues that affect the ability of nephrologists and other health professionals to provide high-quality care to people with DKD. DKD remains one of the most common and serious complications of type 2 diabetes.

Diet and Lifestyle Are Key in Preventing and Managing Kidney Disease

By Bridget M. Kuehn

As a chef and instructor at a culinary school Duane Sunwold knows a lot about food. But when he received a diagnosis of chronic kidney disease (CKD) in 2000, he discovered he still had a lot to learn.

During the first 2 years after his diagnosis, Sunwold gained 60 pounds because of the medications he was taking, and his creatinine level reached 4.9 mg/dL, just shy of the requirement for dialysis. He tried three different nephrologists. Finally, his current doctor recommended that he try a plant-based diet. It wasn't easy, but within 2 weeks, he began to feel better. And that helped him stick with it.

"Today, I'm in complete remission and have been there for about 10 years," said Sunwold, who is a department chair at the Inland Northwest Culinary Academy.

Sunwold said he is living proof that diet and lifestyle can play a role in helping to manage CKD. The plant-based diet is just one of several diet and lifestyle interventions that may help patients with CKD or diabetic kidney disease (DKD) and individuals at risk for the development of those conditions, according to experts. Increasing exercise is also highly recommended. But some other approaches to lifestyle change, such as a low-carbohydrate diet or a low-protein diet, are still hotly debated.

Dietary darlings and dilemmas

Sunwold chose to adopt a plant-based diet, replacing proteins from animal products with plant-based proteins, but there was a substantial learning curve to ensure he was getting all the amino acids his body needed. He said he had to learn about where he could get complete plant-based proteins, such as quinoa, chia, or hemp seed, and to pair legumes and grains together.

"Even as a professional chef I needed to know what plants I should be eating, and I needed some education on plant-based proteins," he said. "I was amazed at how little I knew going into this."

Kam Kalantar-Zadeh, MD, MPH, PhD, professor of medicine and chief of nephrology at the University of California—Irvine School of Medicine, recommends that kidney disease patients try to get 50% or more of their protein from plants. How much protein patients eat is also important because too much protein can put a strain on the kidneys, he emphasized. The typical American diet is high in total protein and animal-based protein, he noted: on average, 1.2 to 1.4 grams per kilogram body weight per day compared with the 0.8 grams per kilogram currently recommended for healthy people. Kalantar-Zadeh recommended that those at risk for kidney disease should avoid high-protein diets involving more than 1 gram per kilogram per day and that those with kidney disease adopt lower-protein diets in the range of 0.6 to 0.8 gram per kilogram per day.

"We need to avoid high-protein diets so that we can avoid overusing and abusing the remainder of kidney function," he said.

But there is some debate about the benefits of a low-protein diet. Srinivasan Beddhu, MD, professor of internal medicine at the University of Utah School of Medicine, explained that some studies testing very-low-protein diets (0.3–0.4 grams/kilogram per day) haven't shown a benefit in terms of kidney function, but there was some evidence of harm in long-term follow-up. Beddhu noted some of his colleagues are very excited about low-protein diets, but he urged caution. Instead, he recommends a moderate-protein diet of no more than 0.8 gram per day for patients.

"A very-high-protein diet should be avoided in people with CKD," he said.

In terms of diets, Beddhu suggested that the Mediterranean diet or the Dietary Approaches to Stop Hypertension (DASH) diet, the latter of which emphasizes low sodium intake to reduce hypertension, are probably the best choices for patients with DKD.

One major dietary debate raging right now is about the use of low-carbohydrate diets in patients with kidney disease or those at risk. There is evidence that low-carbohydrate diets may help patients with diabetes or obesity lose weight, reduce blood pressure, and improve glycemic function, but clinicians have concerns about the effect of these higher-protein diets on kidney function, noted Nia Mitchell, MD, assistant professor of medicine at the Duke University School of Medicine in Durham, North Carolina. Mitchell recently published a review of the evidence on the safety of low-carbohydrate diets on patients with kidney disease with and without diabetes.

"The evidence is inconclusive, because there have been no randomized controlled trials," Mitchell said. She explained that there have been numerous studies of low-carbohydrate diets but that patients with CKD or DKD have been excluded. She said clinical trials of low-carbohydrate diets in patients with DKD and CKD are needed that carefully track what they eat, their weight, and their kidney function.

Mitchell frequently recommends low-carbohydrate diets for patients with obesity at the Duke Diet and Fitness Center. For patients with kidney disease or DKD, she offers a menu of options that include low-carbohydrate diets. A patient with kidney disease who chooses a low-carbohydrate diet receives extra monitoring for kidney function, and she collaborates with the patient's nephrologist. She may also liberalize carbohydrate intake for patients with kidney disease. Patients who stick with it can lose substantial amounts of weight, Mitchell noted, so she cautioned against throwing it out as an option.

"Treating obesity is so difficult," she said. "We need to have a bunch of things that we can offer. Not being able to offer people with CKD or DKD a low-carb diet because of what we think might happen is not really an option."

Kalantar-Zadeh, who has criticized low-carbohydrate diets because of their potential to harm the kidney, acknowledged that it can be hard to argue with patients with diabetes or obesity who have seen substantial weight loss on low-carbohydrate diets. He suggested that perhaps such diets could be used for a shorter duration, with close supervision of kidney function.

"The ultimate compromise would be that if someone has DKD, we can use high-protein diets in short-term phases with supervised and tailored plans to lose weight," he said. In the longer term, he suggested that it is wise to increase carbohydrate levels after the patient's weight loss goals have been met.

Getting moving

Increased activity can be a helpful lifestyle change for patients with kidney disease or those at risk. Many patients with CKD or diabetes have poor muscle tone and function, in part because of their condition, noted Beddhu. They may also struggle with fatigue. Both of these conditions can make starting an exercise regimen difficult.

"If we ask our patients to walk a couple of miles a day, they're going to find it difficult because of those issues," he said. "We need to address the underlying problem—the muscle dysfunction—before we can improve physical activity."

Beddhu suggests that patients start with muscle-strengthening activities and try to do them at least 5 to 10 minutes a day. That doesn't require expensive equipment; individuals can just use elastic bands and ankle weights, he said. This can help them build up the strength they need for other types of physical activities. He said it is also important to decrease sedentary activities and to be as active as possible, which has been shown to reduce the risk of mortality in both CKD patients and the general population.

"They should choose a routine, whatever best fits their lifestyle that they enjoy doing," he said. Sunwold said he has made swimming a part of his routine.

Sunwold acknowledged that making lasting dietary and exercise changes is hard. He noted that he still occasionally eats meat and will have a few bites of things he really enjoys, but that envisioning his "kidneys on crutches" helps him to stick with his diet and exercise routine. "I give myself a 30-second pity party," Sunwold said. "But after 30 seconds, the pity party has got to stop. We've got to move on."

Beddhu said the work Sunwold is doing to educate other patients is great. And he encourages physicians to educate their patients about beneficial lifestyle and dietary changes as well, even though not everyone may be able to make lasting changes.

"With lifestyle, I understand that not everybody will be successful," Beddhu said. "It's like asking people to stop smoking: if only 10% or 20% eventually do, that's still a significant number, and that can still impact outcomes for those people."

The most important thing, Kalantar-Zadeh said, is to customize lifestyle and diet to fit an individual patient's needs and preferences. This includes taking into account their condition, preferences, and goals.

"No one size fits all," he said. "We can't do that any more; it has to be a highly patient-centered approach." ■

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In Peritoneal Dialysis, Substantial Variations in Peritonitis Rates

Rates of peritonitis related to peritoneal dialysis (PD) vary significantly between countries, and between facilities within countries, reports a study in the *American Journal of Kidney Diseases*.

The researchers analyzed data on 7051 adult PD patients at 209 facilities in seven countries, drawn from the prospective, observational Peritoneal Dialysis Outcomes and Practice Patterns Study (PDOPPS). Peritonitis rates were assessed at the country and facility levels, and associations with selected facility practices were assessed.

The data included 2272 episodes of peritonitis: crude rate 0.28 episodes per patient-year. Peritonitis rates varied within countries, exceeding 0.50 per patient-year at 10% of facilities. By country, peritonitis rates (per patient-year) were 0.40 in Thailand, 0.38 in the United Kingdom, 0.35 in Australia/New Zealand, 0.29 in Canada, 0.27 in Japan, and 0.26 in the United States. Larger center size, based on number of patients, was associated with higher peritonitis risk only in Japan. More than two-thirds of peritonitis episodes led to hospitalization.

Certain facility practices were associated with lower peritonitis rates: greater use of automated PD, rate ratio (RR) 0.95 per 10-percentage point increase; antibiotic use at catheter insertion, RR 0.83; and at least 6 days of PD training, RR 0.81. Data also suggested lower peritonitis risk at facilities using muciprocin or aminoglycoside ointment at the exit site, although this fell short of statistical significance.

Peritonitis is the main cause of permanent transition to hemodialysis in PD patients. Current information on the occurrence of PD-related peritonitis and the factors associated with it are needed to develop effective prevention strategies.

The PDOPPS data show substantial international variations in the risk of peritonitis. The study also identifies potentially modifiable facility practices associated with lower rates of peritonitis, including automated PD use, antibiotic practices, and PD training. "[T]he present findings should inform future guidelines in potentially setting lower maximally acceptable peritonitis rates," the researchers write [Perl J, et al. Peritoneal dialysis–related infection rates and outcomes: Results from the Peritoneal Dialysis Outcomes and Practice Patterns Study (PDOPPS). *Am J Kidney Dis* 2020; 76:42–53]. doi: 10.1053/j.ajkd.2019.09.016 ■

Fruits, Vegetables and Whole Grains Reduce Type 2 Diabetes Risk

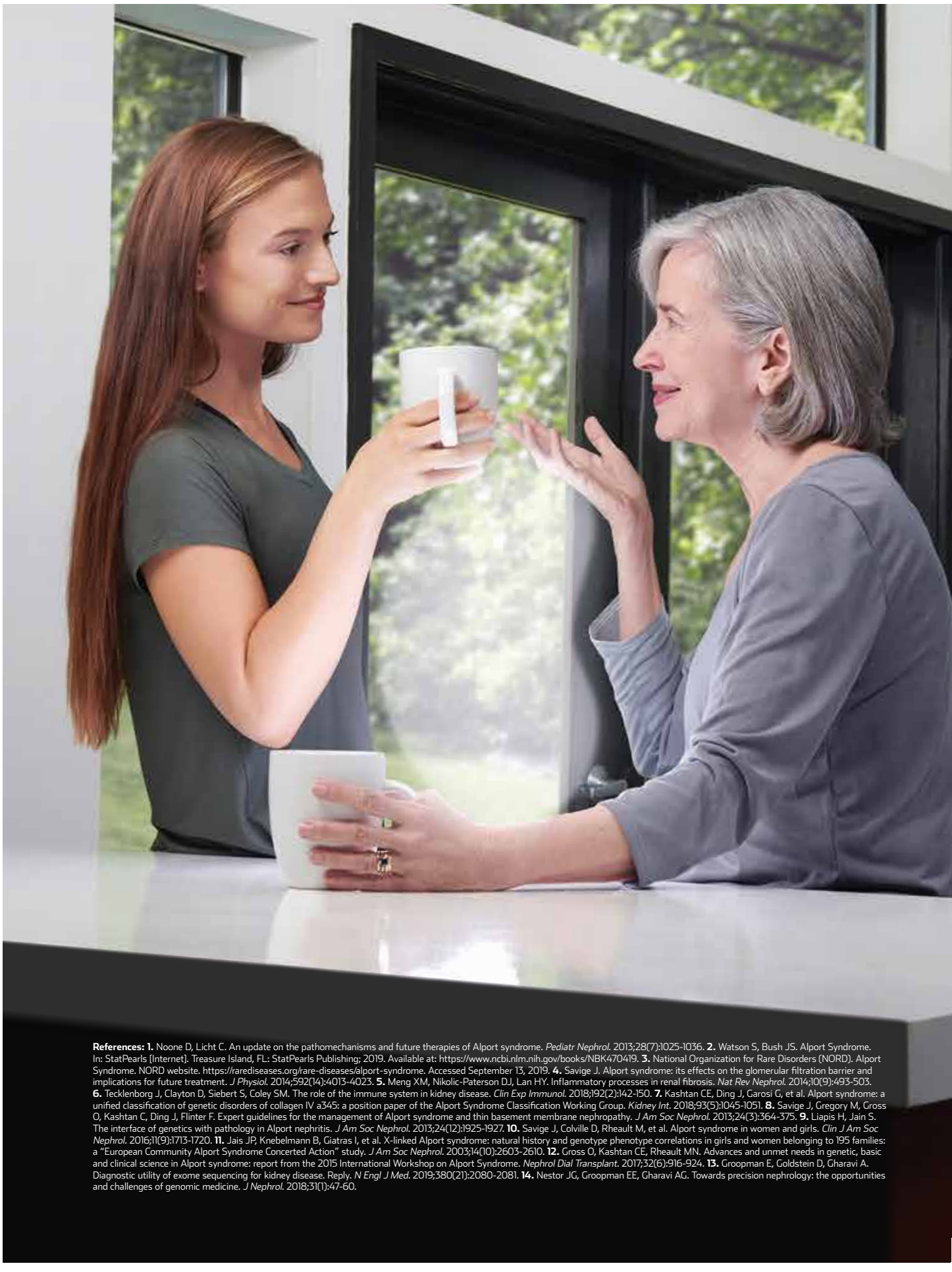
Higher consumption of fruit and vegetables and whole-grain foods is associated with a lower risk of type 2 diabetes, according to a pair of studies in the *British Medical Journal*.

A prospective study of fruit and vegetable intake included 9754 individuals with incident type 2 diabetes, as well as a subcohort of 13,662 participants from the European Prospective Investigation into Cancer and Nutrition (EPIC)-InterAct study. The study included measurement of plasma biomarkers—vitamin C and carotenoids—of fruit and vegetable intake.

In a multivariable adjusted model, participants with higher plasma vitamin C had a lower risk of type 2 diabetes: hazard ratio (HR) 0.82 per standard deviation. Higher total carotenoids were also associated with a lower risk of type 2 diabetes: HR 0.75 per SD. For a composite biomarker including vitamin C plus individual carotenoids, risk of type 2 diabetes was reduced by half (HR 0.50) for participants in the highest versus lowest quintile.

One SD difference in the composite biomarker score was associated with a 66 g/d difference in self-reported total fruit and vegetable consumption, along with a one-fourth reduction (HR 0.75) in type 2 diabetes. From a public health standpoint, the investigators conclude, "[C]onsumption of even a moderately increased amount of fruit and vegetables among populations who typically consume low levels could help to prevent type 2 diabetes."

The second study included data on 158,259 women and 36,525 men from two Nurses' Health Study cohorts and



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from the Health Professionals' Follow-Up Study. Consumption of whole-grain foods was assessed using food frequency questionnaires. In more than 4.6 million years of follow-up, 18,629 incident cases of type 2 diabetes were identified.

With adjustment for lifestyle and dietary risk factors, participants with higher total whole-grain consumption had a consistently lower risk of type 2 diabetes. On pooled analysis, the HR for type 2 diabetes was 0.71 for participants with the highest intake of whole-grain foods, compared to the lowest level. For those consuming one or more servings of whole-grain breakfast cereal per day, the HR was 0.81. For other whole-grain foods at two or more servings per week, HRs were 0.79 for oatmeal, 0.88 for brown rice, 0.85 for added bran, and 0.88 for wheat germ.

The protective effects of whole-grain consumption were greater in participants who were lean, rather than overweight or obese. "These findings provide further support for the current recommendations that promote increased consumption of whole grain as part of a healthy diet for the prevention of type 2 diabetes," the researchers write [Zheng J-S, et al. Association of plasma biomarkers of fruit and vegetable intake with incident type 2 diabetes: EPIC-InterAct case-cohort study in eight European countries. *BMJ*. 2020; 370:m2194, doi: 10.1136/bmj.m2194;; Hu Y, et al. Intake of whole grain foods and risk of type 2 diabetes: results from three prospective cohort studies. *BMJ*. 2020; 370: m2206, doi: 10.1136/bmj.m2206]. ■

Medical and Social Factors Do Not Explain Racial Disparities in Kidney Transplant

Disparities in waitlisting for kidney transplantation among African American patients are independent of medical factors, and even of social determinants of health, reports a study in *Transplantation*.

The prospective cohort study included 1055 white or African American patients referred for kidney transplant evaluation in 2013 and followed up to 2018. At baseline, a wide range of potential predictors of transplant outcomes were assessed: demographic, medical/health, culturally related, and psychosocial factors, along with transplant-related knowledge, concerns, and preferences. All of these factors were evaluated for association with waitlisting for kidney transplantation.

At initial evaluation, African American patients were younger, of lower socioeconomic status, more likely to be on public insurance, and less likely to be married than white patients. African American patients also had more comorbid conditions, longer dialysis vintage, and more potential donors.

On initial analyses, African American patients were nearly one-half less likely to be waitlisted, compared to white patients: hazard ratio (HR) 0.56. The association was weaker but remained significant after adjustment for demographic and medical factors, HR 0.69; and after further adjustment for psychosocial factors, HR 0.75. Older age, lower income, public insurance, increased comorbidity, and being on dialysis at the time of evaluation were associated with a lower likelihood of waitlisting.

The study adds to previous evidence of racial disparities in kidney transplant waitlisting between African American and white patients. The disparities persist even after adjustment for cultural and psychosocial factors, such as perceived racism and experience of discrimination in healthcare. "Efforts to identify novel factors that continue to contribute to racial disparity are needed," the researchers write [Ng Y-H, et al. Does racial disparity in kidney transplant waitlisting persist after accounting for social determinants of health? *Transplantation* 2020; 104:1445–1455, doi: 10.1097/TP.0000000000003002]. ■

ASN Policy Team Interviews Expert on Transplant and Organ Procurement Policy

In late 2019, the Centers for Medicare & Medicaid Services (CMS) issued a proposed rule for Organ Procurement Organizations (OPOs) Conditions for Coverage. The proposed rule intends to require transparent, verifiable, and uniform metrics by which CMS can evaluate OPO performance. The American Society of Nephrology (ASN) provided comments of support and recommendations for improvement in February 2020.

The proposed rule would replace the existing outcome measures for OPO recertification with two new outcome measures that would be used to assess an OPO's performance: "donation rate" and "organ transplantation rate," effective beginning in 2022. The "donation rate" would be measured as the number of actual deceased donors as a percentage of total inpatient deaths in the donation service area (DSA) among patients 75 years of age or younger with any cause of death that would not be an absolute contraindication to organ donation. The "organ transplantation rate" would be measured as the number of organs procured within the DSA and transplanted as a percentage of total inpatient deaths in the DSA among patients 75 years of age or younger with any cause of death that would not be an absolute contraindication to organ donation. These important changes to evaluating OPO performance are expected to be finalized in rulemaking in the near future.

The ASN Policy team interviewed Jennifer Erickson, who served in the White House Office of Science and Technology Policy in the Obama administration, about the changes. Erickson's portfolio included organ policy and innovation efforts. She has been a strong advocate for changing OPO regulations inside and outside of government.

You have played a major role in guiding transplant policy for the foreseeable future. What drew you to this issue? Do you agree with the characterization that we are on the cusp of major change?

I've seen the horrors of organ failure firsthand. I've spent far too much time sitting next to a dialysis chair and talking to people desperate for a call about an available organ transplant. When I learned that thousands more patients each year could receive organ transplants if government contractors were more efficient, I was committed to being part of reform efforts.

Thanks to the leadership of the Department of Health and Human Services (HHS), we are on the verge of changing what's possible for patients and saving tens of thousands of lives. I am hugely heartened by Secretary Azar's promise that "We're going to stop looking the other way while lives are lost and hold OPOs accountable." That's what patients deserve.

In your view, what should the future of organ procurement look like?

It should be efficient and driven by data and accountability, and there needs to be a lot more oversight, both from HHS and from Congress. I have a huge respect for the importance of coordinating organ donation and the work it takes to do that. After all, the vast majority of Americans support it—it's something we agree on as a country. So learning that there is a 400% variation for organ recovery across the country and that no OPO has ever lost a government contract due to poor performance—not even in cases of fraud, waste and abuse or criminality—is mind-boggling. OPOs that are performing this sacred public trust at a high standard should keep their contracts. As Baylor College of Medicine stated: " [O]nly the best performing OPOs should be surviving, while those underperforming centers are subject to consolidation or closure." It's a life and death issue, and patients can't wait.

What does the future hold for individuals in need of a kidney transplant?

That depends on when the proposed regulatory changes from HHS are finalized and how they are implemented. Keep in mind: HHS said the majority of OPOs are failing. If HHS moves to hold OPOs accountable right away by decertifying underperformers and giving those territories to higher performers, then a lot more kidney patients will get transplants. That goes for patients with other types of organ failure too. So hearing that some OPOs are arguing for delay or for unworkable metrics is deeply concerning. As former NAACP President Ben Jealous recently wrote: "Astoundingly [OPOs] are also asking that the new standards not be implemented until 2026, during which time tens of thousands more patients—disproportionately people of color—would die." That is unconscionable. And I agree with Reps. Katie Porter and Karen Bass, who wrote to Secretary Azar and CMS Administrator Verma: "We cannot consign 20,000 or more patients to die waiting for organ transplants while federal contractors are not held accountable, and therefore urge you to use the new standards in the next recertification cycle."

In your view, why are new rules for OPOs needed?

Patients are dying, every day and unnecessarily, because of massive underperformance by some OPOs. It's like the Wild West, and in all of my years in government I've never seen anything else like it. No one should be able to write their own report card—and that's the current system we have. Not only is it unreliable, it makes the current standards unenforceable.

Consider this: In my home state of Virginia, research shows the OPO recovered the organs of only 34% of potential donors. OPOs including Los Angeles, New York City, northern New Jersey, South Carolina, and Kentucky had even lower recovery rates. Transplant centers can't perform surgeries with organs that were never recovered. And the story earlier this year from *Kaiser Health News* that showed "UNOS is approximately 15 times as likely to lose, damage. or mishandle an organ as the airline industry is your luggage" was shocking. So we need rules that hold government contractors accountable at every step of the process. The government has to step in on behalf of patients. That's also why it's been great to see bipartisan oversight efforts from Sens. Chuck Grassley and Ron Wyden on the Senate Finance Committee, and calls for reform from Reps. Katie Porter and Karen Bass, chair of the Congressional Black Caucus, in the House.

What are the major changes proposed by the Department of Health and Human Services? How will they benefit patients? What role do you see for nephrologists—both transplant and nontransplant?

HHS is proposing accountability based on objective data, and while it's truly alarming that we haven't done this before, it's a big deal that HHS is doing it now. Ted Kennedy asked about underperformance in the nation's organ donation system in 1997, and since then, more than 200,000 Americans have died waiting for organ transplants. Patients do not need more studies or consensus conferences, they need action. Nephrologists know that patients deserve better. Hopefully increased accountability means they will be able to help more of their patients access transplants soon.

If the proposed rule is finalized and successfully implemented, what do you anticipate the effects could be on the organ shortage?

Simple: thousands more patients will live each year. Right now, 33 patients are removed from the organ waiting list every day because they have died or become too sick to transplant, and even that number likely grossly understates what the true demand is, given that so many patients who would benefit from transplant are never even listed in the first place. HHS' own proposed rule suggests that OPOs just hitting minimum compliance standards would translate to 5000 more transplants per year. Seth Karp, MD, the transplant chief at Vanderbilt, says data suggest that reforming the system could end the waiting lists for livers, lungs, and hearts within 3 years and dramatically decrease waiting times for kidney transplants.

Besides working to optimize organ procurement, what are other steps the kidney community can take, now or in the future, to increase patient access to transplantation?

Be impatient. Kidney patients deserve better than they are getting in terms of treatments, technology, and the whole system of care. The Advancing American Kidney Health Executive Order lays the groundwork for transformation, but rules still need to be finalized and implemented to reform deceased donation and support living donors, and Congress needs to invest in research and innovation via KidneyX and other mechanisms. And, as I've written about in the past, along with co-authors from the Trump administration and ASN leadership, we need to make sure there is real accountability and oversight.

ASN Continues Advocacy for International Medical Graduates

A robust and diverse group of health professionals and researchers serves as an asset to the nation's healthcare system, provides a sound foundation of scientific and medical expertise, and ensures the highest quality of patient care.

ASN and its members have long tracked federal policies that impact international medical graduates who are citizens of other nations (non-US IMGs) given their strong representation in the nephrology workforce. In 2017, the US nephrology workforce had the second highest percentage among medical specialties of active physicians who were international medical graduates at 49% (1). Non-US IMGs are necessary to maintain a strong healthcare workforce that is able to protect the health of all Americans as the nation battles the COVID-19 pandemic and prepares for future health challenges. ASN has recently taken steps to address concerns about federal policies related to non-US IMGs on both the legislative and executive fronts.

First, ASN endorsed the Healthcare Workforce Resilience Act (S. 3599, H.R. 6788), bipartisan, bicameral legislation that aims to strengthen the healthcare workforce and increase healthcare access during the COVID-19 pandemic.

The Healthcare Workforce Resilience Act directs the U.S. Citizenship and Immigration Services (USCIS) to "recapture" up to 40,000 previously unused immigrant visas and to reserve 25,000 of these visas for nurses and 15,000 for physicians. Previously unused immigrant visas can also be used for the families of these medical professionals and will not be counted toward the 40,000 cap. Visas recaptured as a result of the Healthcare Workforce Resilience Act will not be subject to country caps. To qualify, medical professionals will need to meet licensing requirements, pay required filing fees, maintain a clean criminal background, and clear a national security check. ASN will continue to track and advocate for passage of this legislation.

Second, ASN, recognizing that a collaborative approach is necessary to make significant progress in this policy area, has worked closely with partners across the medical and scientific communities. Most recently, in response to the administration's Proclamation Suspending Entry of Aliens Who Present a Risk to the U.S. Labor Market Following

the Coronavirus Outbreak issued on June 22, 2020, ASN collaborated with the Council of Medical Specialty Societies and 20 other specialty societies to express grave concerns to the administration over its suspension of certain immigration visas (including H-1B and some J-1 visas) for the remainder of 2020.

In a letter to the heads of the Department of Labor, Department of Homeland Security, Department of State, and the Department of Health and Human Services, the group stressed that it was not in the nation's best interest to further close its borders to skilled health and science professionals. The Executive Order will limit the nation's ability to attract the world's most talented clinicians, researchers, and educators, impacting the healthcare workforce and harming public health. The letter further urged the administration to "clarify that all healthcare professionals and researchers—not only those who are involved in COVID-19 research and practice—are critical to our nation's interest, and therefore exempt from the executive order" (2).

To provide optimal healthcare for all Americans, ASN will continue to advocate for federal policies that maintain the nation's robust healthcare workforce, advance patient care, and protect our research enterprise. Future articles in *Kidney News* and *Kidney News Online* will include continued coverage of ASN's advocacy efforts on this and other policy priorities. For the most up to date information, follow @ASNAdvocacy on Twitter.

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Persistent Kidney Health Disparities Require New Approaches

By Bridget M. Kuehn

Patients receiving dialysis in predominantly black neighborhoods have higher rates of hospitalization, and Black and Hispanic women have higher rates of hypertension after preeclampsia, according to a pair of studies.

The studies are the latest in a growing body of evidence to suggest that substantial disparities in kidney care exist among patients who are Black and Hispanic, and they highlight the need for improved care to reduce preventable complications.

While the studies identify disparities, they fail to explicitly address the role that both structural racism and implicit biases in care may play in causing them, said Vanessa Grubbs, MD, associate professor in the Division of Nephrology at the University of California–San Francisco and author of "Hundreds of Interlaced Fingers: A Kidney Doctor's Search for the Perfect Match."

"We keep trying to find the reason within the group rather than looking at the common denominator of who takes care of these groups," Grubbs said. "There's a consistent push, it seems, to call race a risk factor rather than racism. Until we are willing to really acknowledge that there is no biologic meaning to race and rather how we attribute meaning to it, that affects our clinical judgment and therefore patient outcomes and we're always going to see these disparities."

Hospitalizations and hypertension

Research by Ladan Golestaneh, MD, a professor of medicine in the Department of Nephrology at Montefiore Medical Center in the Bronx, New York, assessed hospitalization rates among 4567 patients on hemodialysis in 154 facilities in 127 zip codes to assess what causes extreme variability in dialysis patient outcomes from community to community. The analysis found that patients in majority Black neighborhoods had high hospitalization rates.

This trend occurred even though patients receiving care in majority Black communities were younger and healthier. Patients receiving care in these communities also received dialysis care that was of comparable quality to care in other areas in terms of the medications and duration of dialysis they received and the urea reduction ratio. But they were more likely to receive dialysis in for-profit facilities with higher patient ratios.

Golestaneh could not pinpoint the exact cause of these higher hospitalization rates among those living in majority Black communities but she did rule out race itself as the explanation. She said she would like to see fine grained data on the health systems that serve these patients or whether other services fall short in their communities. Examples might include a lack of culturally sensitive education materials or poor access to healthy foods.

"Hospitalization may or may not reflect a need for acute care," Golestaneh said. "A lot of times, hospitalization really reflects failures of outpatient care coordination, or outpatient care provision, such that a lot of unnecessary hospitalizations occur."

Golestaneh acknowledged her analysis could not definitively provide an answer about what is driving higher hospitalization rates but suggested "that maybe hospitalizations in this case are really just a surrogate for not getting the outpatient care coordination and outpatient care intensity that that you need in communities."

A second analysis by Jessica Sheehan Tangren, MD, a nephrologist and instructor in medicine at Massachusetts General Hospital in Boston, looked at a cohort of 20,864 women with a pregnancy between 1998 and 2014, including 524 who developed preeclampsia: 23% were Hispanic and 6% were Black. The risk of hypertension after pregnancy was elevated in women of all races and ethnicities, but it was particularly high among Hispanic women, who had an adjusted hazard ratio of 2.8, and Black women, who had an adjusted hazard ratio of 2.7. Non-Hispanic white women had an adjusted hazard ratio of 1.8.

Root causes

Golestaneh suggested it would be important to consider how socioeconomic and other factors contribute to these disparities.

"It's something significant that needs to be explored if we want those disparities to go away, or if we want to have health equity in our society," she said.

She acknowledged that physicians don't do a good job of understanding their patients' experiences with the health system. For example, are patients able to get in touch with primary care physicians or get prescriptions filled?

"We need to do a better job of looking at the patient more holistically, and really going after those details in their lives," she said.

But Grubbs, whose book details her husband's kidney failure, her decision to donate a kidney to him, and their experiences with the health system, would like physicians to pay more attention to both structural racism and racism in medicine as potential contributors to persistent disparities.

"Most of us believe that we are coming from a really positive place, and that we're trying to do the best for our patients," she said. "But I don't think, in general, we're willing to consider the role that unconscious bias has, that we're not willing to question the assumptions that we make about the person in front of us."

She noted that unconscious bias can contribute to a lack of trust or cause stress among patients. For example, if a woman experiences a complicated pregnancy and feels she's not being heard or listened to, that could increase her level of stress, which could contribute to higher blood pressure later on.

"The structure of our entire society for centuries has led to where we are now, so that certain groups have always been treated inequitably," she said. "If no one is going to address those structural systemwide issues, or even acknowledge them, then you don't have to do anything outright to be blatantly racist."

Fellows Corner

Acute Respiratory Distress Syndrome from a Kidney Perspective

By Camilo Cortesi

Camilo Cortesi

The coronavirus 2019 (COVID-19) pandemic has brought the interaction of the lung and kidney to the fore. Nephrologists have worked in tandem with critical care to manage the acute kidney injury (AKI) that has increasingly occurred in patients with acute respiratory distress syndrome (ARDS) as a result of COVID-19.

Nephrologists and renal fellows are often asked to evaluate patients with acute respiratory distress syndrome (ARDS) for acute kidney injury (AKI), electrolyte or acid–base disturbances, or volume overload. ARDS is associated with high mortality rates and is present in ≤10.4% of patients in critical care units (1). Evidence has shown that ARDS is an independent risk factor for AKI, which is prevalent in up to a third of ARDS patients (2).

Decisions about the initiation of renal replacement therapy (RRT) in patients with ARDS require special attention from nephrologists because there are considerations beyond traditional indications. Determining whether or not ARDS patients meet the criteria for RRT is a common challenge, which is quite difficult to decipher in patients with preserved kidney function. This article provides a concise review of the lung–kidney crosstalk and highlights key points for treating patients with AKI and ARDS.

ARDS is a life-threatening condition and is frequently encountered in the intensive care unit. It is characterized by an alveolo-capillary barrier insult from an ARDS trigger. This insult causes acute pulmonary inflammation and increased vascular permeability, leading to noncardiogenic pulmonary edema, often followed by respiratory failure. Many ARDS triggers should be taken into consideration when evaluating a patient, most commonly but not limited to sepsis, pneumonia, pancreatitis, trauma, extensive burns, pulmonary inhalation injury, aspiration of gastric contents, thoracic surgery, transfusion, and administration of chemotherapy. Treating the underlying cause is the most crucial first step in the management of this condition. ARDS-like conditions such as acute cardiogenic pulmonary edema, vasculitis, and bilateral pneumonia, among others, should also be considered during the evaluation.

ARDS should be suspected in the presence of a known ARDS trigger and the development of acute-onset (<7 days) respiratory symptoms, increased oxygen requirement, and radiologic evidence of bilateral lung infiltrates not solely attributed to acute heart failure or volume overload. The Berlin definition provides a severity stratification for prognosis and therapy guidelines based on PaO_2/FiO_2 levels in patients using ventilatory support with settings delivering ≥5 cm H_2O of peak end-expiratory pressures in moderate and severe forms or delivering ≥5 cm H_2O of continuous positive airway pressure in mild forms of ARDS. Mild ARDS is defined as PaO_2/FiO_2 >200 mm Hg and ≤300 mm Hg, moderate ARDS as PaO_2/FiO_2 >100 mm Hg and ≤200 mm Hg, and severe ARDS as PaO_2/FiO_2 ≤100 mm Hg (3).

Healthcare providers, especially nephrologists and critical care practitioners, should be aware of the lung and kidney crosstalk in ARDS and its implications when evaluating a patient afflicted by this process (Figures 1 and 2). Five factors are crucial for the nephrologist to consider when evaluating ARDS patients; they include: 1) volume overload, 2) mechanical ventilation, 3) hypoxemia, 4) hypercarbia, and 5) acidosis.

Volume overload

Volume overload can increase right-sided heart pressures, worsen venous congestion, and aggravate pulmonary hypertension. Subsequently, this can lead to right ventricular dysfunction and renal interstitial edema from worsening venous congestion. Elevated interstitial and intratubular pressures decrease kidney perfusion pressures and oxygen delivery, which may result in AKI.

At the level of the pulmonary microvasculature, increased hydrostatic pressure from volume overload disproportionately affects the lungs as compared with other organs because of the increased vascular permeability of pulmonary capillaries, which in turn promotes pulmonary interstitial edema and worsens respiratory failure. Increasing ventilator requirements increase the risk of biotrauma and barotrauma and worsen respiratory status, leading to a vicious cycle. A fluid conservative therapy approach has been shown to be associated with improvement in lung function, an increase in ventilator-free days, and a decreased stay in the intensive care unit (4). Positive fluid balance in ARDS is known to be associated with adverse outcomes (5); when management with diuretics is ineffective, RRT should be considered to manage volume overload to offset or prevent its detrimental effects in ARDS.

Mechanical ventilation

Kidney function is impaired in patients with ARDS receiving mechanical ventilation as a result of hemodynamic and neurohormonal changes with a subsequent inflammatory response. Mechanical ventilation reduces preload, which can lead to decreased cardiac output and neurohormonal activation, both of which can affect renal blood flow and thus decrease estimated GFR (eGFR). This seems to be especially exacerbated when the peak end-expiratory pressure is >10 cm H_2O. Moreover, mechanical ventilation can increase intrathoracic pressure and pulmonary vascular resistance, which can worsen pulmonary hypertension, right ventricular dysfunction, and venous congestion, and, as a result, worsen kidney function by way of the mechanism explained in the above paragraph.

Barotrauma and biotrauma from mechanical ventilation result in the release of proinflammatory cytokines, leading to a systemic inflammatory state that can itself trigger AKI or in general exert noxious effects on distal organs. The mechanism by which inflammatory mediators induce injury in distal organs is not completely understood. Elevated levels of plasminogen activator inhibitor-1, interleukin-6, and tumor necrosis factor receptor I and II have been associated with the development of AKI in ARDS patients (6). This observation can elucidate why a lung-protective ventilation strategy with a low tidal volume of 4 to 6 mL/kg of ideal body weight and plateau pressure ≤30 cm H_2O is associated with reduced mortality and improved outcomes (7). In summary, lung protective ventilation strategies decrease serum cytokine levels, i.e., systemic inflammation, thereby decreasing multiorgan failure, which in turn reduces mortality.

Hypoxemia, hypercarbia, and acidemia

Hypoxemia, hypercarbia, and acidemia from ARDS inflict deleterious effects on kidney parenchyma. Severe hypoxemia impairs the nitric oxide, angiotensin II, endothelin, and bradykinin pathways in the kidneys and activates the sympathetic system, with a subsequent reduction in kidney blood flow and eGFR. In addition, severe hypoxia produces pulmonary arterial vasoconstriction, pulmonary hypertension, and venous congestion, which can contribute to kidney dysfunction (8). Hypercarbia, like severe hypoxemia, causes pulmonary vasoconstriction; in the kidneys, it produces renal arterial vasoconstriction, sympathetic activation, and activation of the renin-angiotensin-aldosterone system, which causes a reduction in kidney blood flow and eGFR (9). Severe hypoxemia and hypercarbia have a synergistic effect on kidney blood flow reduction and can also lead to apoptosis of renal tubular cells, as opposed to permissive hypercapnia without hypoxemia, which seems to have an anti-inflammatory effect and reduces apoptosis in both kidneys and lungs (10, 11). Finally, moderate levels of acidemia can result in renal vasodilation, whereas severe acidemia can cause renal vasoconstriction.

In addition to lung-protective ventilation and conservative fluid therapy, supportive therapies that have been shown to improve outcomes in ARDS include prone ventilation, neuromuscular blockade, and extracorporeal membrane oxygenation (12–14). The evidence for early initiation of RRT in ARDS patients remains controversial. The known indications for RRT in ARDS include 1) prevention of volume overload, 2) diuretic-resistant volume, 3) AKI, and 4) electrolyte and acid-base derangements refractory to medical management. A recent post hoc analysis of the AKIKI randomized clinical trial showed no significant difference in 60-day mortality nor

in the time to successful extubation based on the initiation time of RRT in ARDS patients. In fact, recovery of kidney function occurred earlier in the delayed RRT group (15).

In conclusion, it is essential to understand the lung–kidney crosstalk because it elucidates the importance of promptly addressing hypoxia, hypercarbia, acidemia, and volume overload in the evaluation of ARDS patients. Larger clinical trials to evaluate this specific population are needed to determine the most appropriate strategy and indications for RRT. On the other hand, research efforts are ongoing to evaluate the therapeutic implications of biomarkers in ARDS and AKI, aiming to ultimately improve decision-making and, in turn, patient care and outcomes. ■

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Figure 1. The lung kidney axis: interaction of various deleterious effects as a result of AKI and ARDS

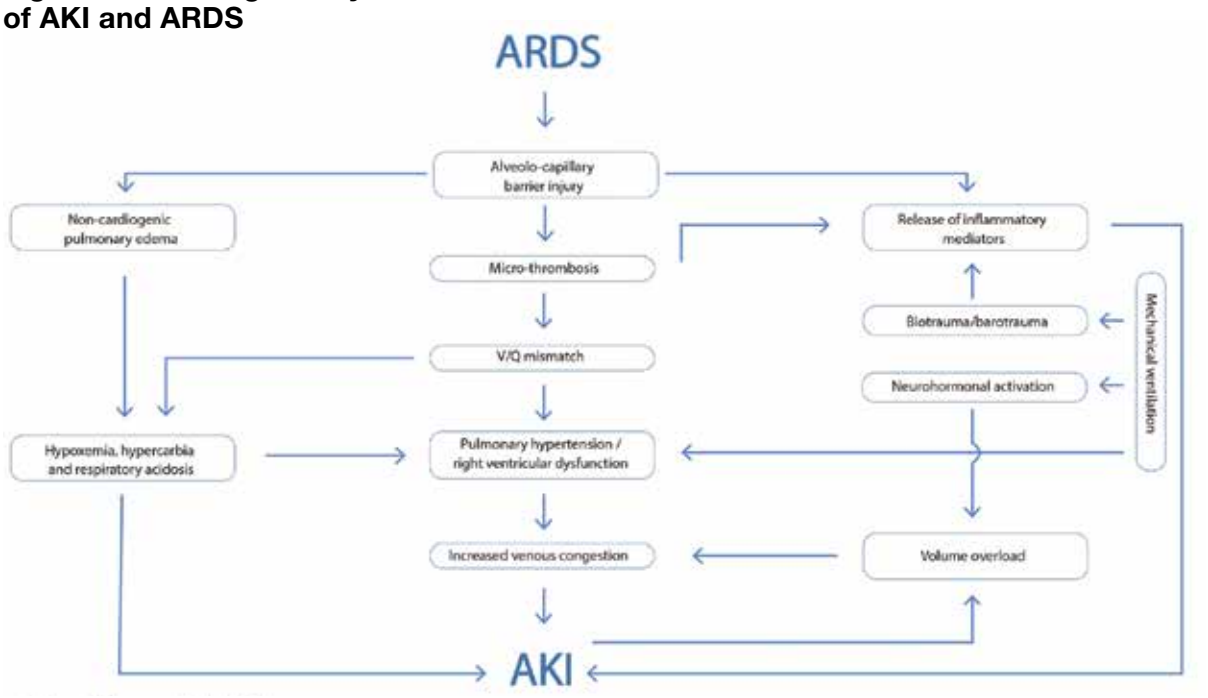
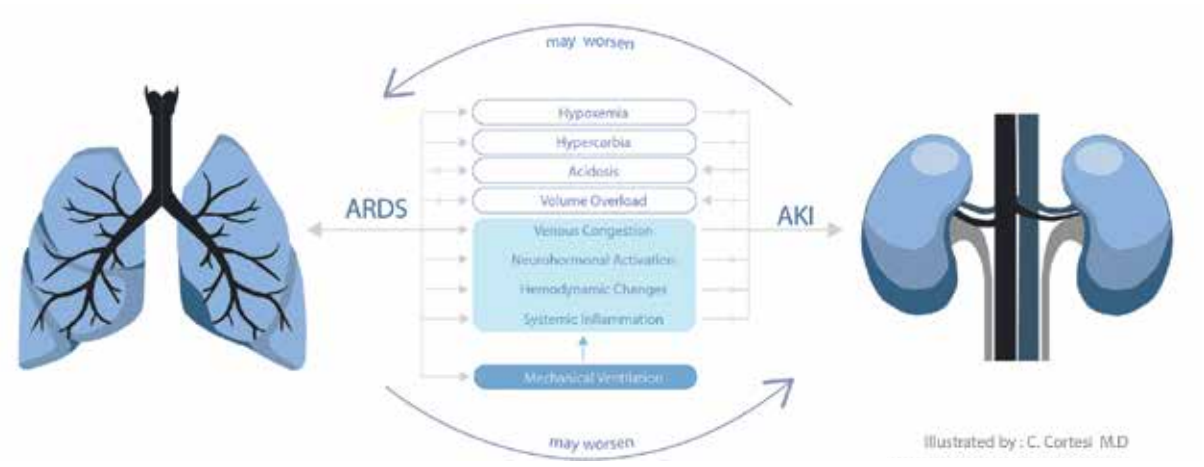


Figure 2. The vicious cycle of ARDS and AKI: conditions created by dysfunction of one system lead to worsening of the other.



Allopurinol Does Not Reduce CKD Progression

Urate-lowering therapy does not reduce the risk of progression in patients with chronic kidney disease (CKD), reports *The New England Journal of Medicine*.

The "Controlled Trial of Slowing of Kidney Disease Progression from the Inhibition of Xanthine Oxidase" (CKD-FIX) enrolled adults with stage 3 or 4 CKD (urinary albumin:creatinine ratio of 265 or higher or estimated glomerular filtration rate [eGFR] at least 3.0 mL/min/1.73 m^2) and no history of gout. Patients were assigned to allopurinol, 100 to 300 mg/d, or placebo. The main outcome of interest was change in eGFR from baseline to 104 weeks.

Planned sample size was 620, but enrollment was stopped after 369 patients due to slow recruitment. On analysis of 363 patients, mean change in eGFR was –3.33 mL/min/1.73 m^2/y in the allopurinol group and –3.23 mL/min/1.73 m^2/y in the placebo group. Rates of serious adverse events were 46% and 44%, respectively.

Secondary outcomes were also similar, including a composite of 40% decrease in eGFR, end stage kidney disease, or death from any cause. After dose escalation, mean serum rate level was 5.3 mg/dL in the allopurinol group and 8.2 mg/dL in the placebo group.

High serum urate levels are a risk factor for progression of chronic kidney disease (CKD), but it is unclear whether there is any causal association. Evidence on the use of urate-lowering medications to slow the progression of CKD is limited.

The CKD-FIX results find no benefit of allopurinol

in slowing CKD progression in high-risk patients. The lack of effect is despite a sustained 35% reduction of serum urate levels with allopurinol, compared to placebo [Badver SV, et al. Effects of allopurinol on the progression of chronic kidney disease. *N Engl J Med* 2020; 382:2504–2513]. ■

American Kidney Fund Announces Two Clinical Scientist Awards

The American Kidney Fund recently awarded research funding from its Clinical Scientist in Nephrology Program to two promising emerging clinical researchers in nephrology: Anika Lucas, MD, a nephrology fellow at Duke University, and Maria Clarissa Tio, MD, a fellow at Brigham and Women's Hospital/ Massachusetts General Hospital's Joint Nephrology Program. *Kidney News* Editorial Board member Edgar Lerma, MD, FASN, interviewed them about the award and their interest in nephrology.

Maria Clarissa Tio, MD

Tell us about yourself.

I am originally from the Philippines, and I majored in biology at the University of the Philippines Manila. Thereafter, I moved to Singapore to take up medicine at the Duke—National University of Singapore Graduate Medical School. Because it is a joint program with Duke University, I had an opportunity to go to Duke during my third and fourth years to do research in the Duke Molecular Physiology Institute and to complete several clinical rotations and a sub-internship at the Duke University Medical Center. After 5 years of medical education, which included some back-and-forth travel between Singapore and Durham, I moved to Dallas, Texas, for my residency training at the University of Texas Southwestern. The time I spent in residency represented some of the most formative years of my education and training. After that, I moved here to Boston to train in nephrology, in the combined Massachusetts General Hospital and Brigham nephrology fellowship program.

How did you get into nephrology?

As a medical student I did a renal consults rotation at Duke. Going in, I felt that the field was very intimidating, and really my goal was just to learn more about this black box that is renal physiology. But I was fortunate enough to have worked with several amazing attendings then, and that month transformed an intimidating field into a very exciting one for me. Our residency training really exposed us to a wide range of kidney patients in Dallas, from the transplantation success stories to patients who have lifelong tunneled catheters and receive hemodialysis only on an "emergency" basis. It was really challenging to care for some of them as their primary care provider, but I also knew that we (as residents and soon-to-be fellows in nephrology) were in a unique position to give them the best care possible, and to find ways to improve their care through research. At UT Southwestern, I was also surrounded by inspirational and aspirational nephrologists who are giants in their field but are also excellent physicians in both nephrology and internal medicine. All those exposures inspired me to get into the field.

What made you decide to apply for the award?

AKF's mission to "fight kidney disease and help people live healthier lives" resonates with my values and career goals. I support the work the AKF does, which includes sponsoring important advocacies like community screening for kidney disease, patient education, financial support for kidney patients, and lobbying for kidney patients in Washington, DC, to name a few. Additionally, as a J-1 visa holder I can apply for only a limited number of fellowship grants. Thankfully, the AKF has an established history of supporting young clinician-scientists regardless of their citizenship status.

What does the "American Kidney Fund Clinical Scientist" designation mean to you?

To me, an AKF clinical scientist is someone who is committed to excellent patient care, rigorous scientific research, and effective public advocacy that can improve the lives of and our care delivery to patients with kidney disease. It's an honor to be part of the AKF family.

What is your research about?

My research is about crystalline nephropathies and how they associate with more common forms of chronic kidney disease. I will be using the Safety of Urate Elevation in Parkinson's Disease (SURE-PD) trial and Chronic Renal Insufficiency Cohort (CRIC) for my studies. In the SURE-PD trial, patients with early Parkinson's disease had their serum uric acid pharmacologically elevated to test whether this can delay progression of Parkinson's disease. It presents a unique opportunity to study whether hyperuricemia, even in persons with normal kidney function, is associated with biomarkers of kidney injury and inflammation. In CRIC, I plan to study how urinary oxalate excretion in persons with chronic kidney disease is associated with biomarkers of kidney injury and assess whether these biomarkers modify the association of urinary oxalate excretion with renal outcomes.

What is your advice to our younger colleagues who may be interested in following in your footsteps?

Hard work is very important, of course. Seize opportunities that come your way. Find a mentor and a division that has your back. Collaboration is key—this is not a solo journey!

Anika Lucas, MD

Tell us about yourself.

I am a research fellow in the division of nephrology at Duke University focused on women's health and health disparities. I grew up in New York City and witnessed the burden of chronic diseases in my minority neighborhood, with many barriers to care. This experience shaped my decision to pursue a career in medicine. Before attending medical school, I attended Harvard Divinity School, where I studied how different religious traditions grapple with the concept of human suffering. I graduated from Temple University School of Medicine and completed residency at the University of Connecticut, where I continued to observe health disparities. During my first year of nephrology fellowship I served as an intern on ASN's Diversity and Inclusion Committee, working toward promoting diversity and inclusion in the workforce and field of nephrology

How did you get into nephrology?

I decided to become a nephrologist in my second year of residency. Although I enjoyed learning renal physiology in medical school and completed a nephrology elective as a fourth-year medical student, I originally decided to become a primary care physician because of my interest in eliminating health disparities and establishing longitudinal relationships with patients. I even joined the primary care track in my residency program. I met Scherly Leon, MD, a nephrologist in New York City and a member of ASN's Media and Communications Committee, who encouraged me to consider a career in nephrology. She also invited me to apply to the Kidney STARS Program. Through the generous support of ASN I was able to attend ASN Kidney Week 2016 in Chicago. The excitement at Kidney Week was palpable. I reunited with faculty from medical school and attended a talk by Deidre Crews, MD, FASN, on the impact of dietary factors on decline in kidney function among urban African Americans. I soon realized that as a nephrologist I could still maintain longitudinal relationships with my patients and work toward combating health disparities. I received further mentorship from Ruchir Trivedi, MD, a nephrologist at the University of Connecticut. Participating in the Kidney STARs program transformed the trajectory of my medical career.

What made you decide to apply for the award?

I first learned about the American Kidney Fund Clinical Scientist in Nephrology program from my assistant program director, Matthew Sparks, MD. I was further encouraged by my mentor, Christina Wyatt, MD, to apply for the award.

What does the "American Kidney Fund Clinical Scientist" designation mean to you?

The American Kidney Fund's vision is a "world without kidney disease." Through patient education and financial support, support of clinical research, and advocacy, the AKF has diligently worked toward making that vision a reality. Many leaders in our field were former recipients of this award. It is clear that participation in the AKF's Clinical Scientist in Nephrology program helped to launch their early careers. I am humbled to be one of the recipients of this prestigious award. This award will provide me with the opportunity to perform clinical research and receive the support of many successful researchers in our field.

What is your research about?

My research project aims to determine whether kidney hyperfiltration and/or failure to hyperfilter in pregnancy predicts, and possibly even contributes to, adverse pregnancy and kidney outcomes. I am currently evaluating the relationship between maternal second-trimester estimated GFR and likelihood of adverse pregnancy outcomes in women with a history of lupus. I will also evaluate the impact of race on both adverse pregnancy and kidney outcomes. The goal of this work is to facilitate early identification of women at risk for the development and progression of kidney disease.

What would be your advice to our younger colleagues who may be interested in following in your footsteps?

I would advise fellows to establish clear professional and personal goals. Fellows who desire to pursue a career in research should identify areas of interest as early as possible. Most importantly, everyone should find mentors. Strong mentorship is integral to success. Although choosing mentors may seem daunting at the start of a fellowship, I have found that many nephrologists are very approachable. Seek out individuals with whom you share common interests and individuals you would like to emulate. ■

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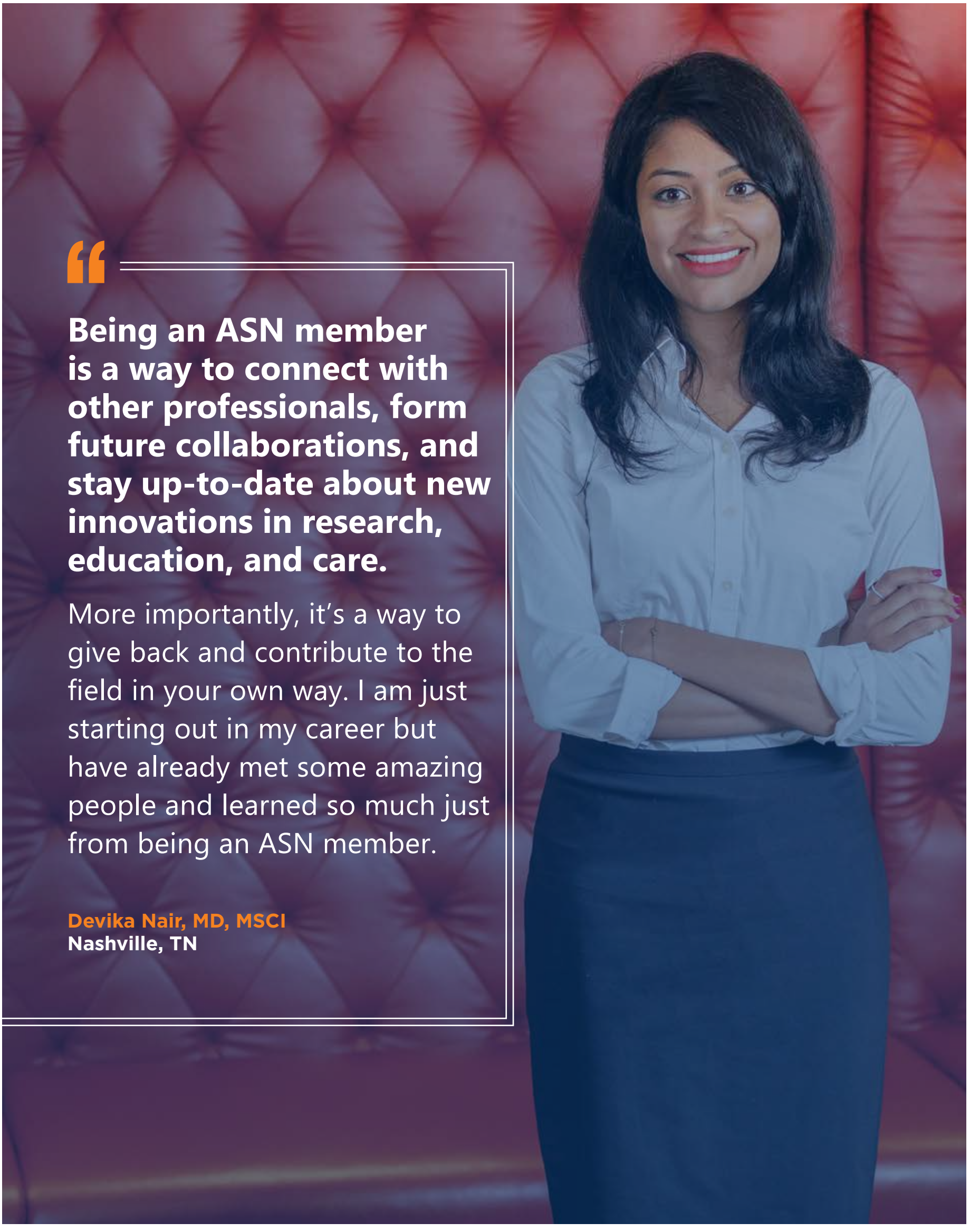

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