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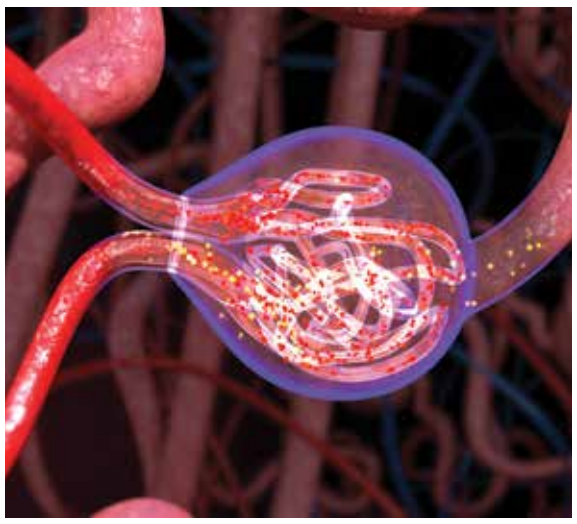
Emerging Work on Boosting Nephron Number Could Aid Kidney Function Preservation in Preemies, Adults

By Bridget M. Kuehn



Advances in neonatal care are boosting survival rates of those born prematurely, but these survivors may later face kidney complications. New insights on how the kidney forms early in life and new tools to help monitor kidney development may one day help improve their health.

As the basic working units of the kidney, nephrons filter the blood, remove and eliminate urine, and help keep nutrients in the body. People have on average about 1 million nephrons per kidney, although the numbers may vary between individuals from 200,000 to about 2 million, said Marva Moxey-Mims, MD, chief of the division of nephrology at Children's National Health System in Washington, DC.

Because nephron formation typically stops by 36 weeks of gestation, babies born earlier may not have a full complement of nephrons, said Moxey-Mims. Some nephrons may still be formed after birth, she noted, but far fewer than if gestation continued. Life-saving treatments, such as certain antibiotics, also may damage the nephrons these premature infants have, she noted.

"We can keep very, very early birth babies alive, but at a cost," said Raphael Kopan, PhD, director of the division of developmental biology at Cincinnati Children's. "The cost will be exacted when they are adults. They are at great risk for end stage renal disease."

Recent findings from a study by Kopan and his colleagues suggest it may be possible to extend the production of nephrons early in life. These findings, along with emerging technologies to help clinicians count nephrons, may lead to new kidney-preserving strategies for both preemies and individuals with other forms of kidney disease.

Extending the clock

Nephrons are under a lot of pressure, and it is normal for some to die over the course of a life. But most people have enough that they can lose some and still eliminate urine effectively. Those born early may not have enough to spare.

"One of the advantages of having so many is that you can lose some of them," said Kevin Bennett, PhD, associate professor of radiology at Washington University in St. Louis.

Pioneering work by nephrologist Barry Brenner showed that those born with fewer nephrons were more likely to develop high blood pressure as adults, eventually leading to kidney failure, Bennett noted.

Understanding why nephrogenesis ends so early in life and what lever turns it off might allow scientists to extend nephron production and boost the number of

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Racial Disparities in Diabetes Complications Are Reduced by Delivering Standardized Care

By Tracy Hampton

Type 2 diabetes and associated chronic kidney disease (CKD) disproportionately affect blacks. Yet when black and white individuals received comparable diabetes care within the context of a clinical trial, black race was not associated with faster development or progression of CKD. The findings are published in the *Clinical Journal of the American Society of Nephrology (CJASN)*.

The prevalence of type 2 diabetes is higher in non-Hispanic blacks than in non-Hispanic whites, and blacks have an elevated risk of diabetes-related complications. In addition, after development of CKD, blacks with type 2 diabetes are more likely to progress to kidney failure.

It has been unclear whether these burdens may be explained by biological factors that influence propensity to CKD and its severity or by differences in type 2 diabetes care.

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Inside

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Boosting Nephron Number

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nephrons in premature infants.

Kopan and his colleagues started with two distinct ideas about how the process might work. One was that nephrogenesis could occur only during a set time period, much like the story of Cinderella, Kopan explained.

"When the clock struck 12, just like in the legend, the whole process ended," he said.

The other idea was that a special niche in the kidney where nephron stem cells live disintegrates soon after birth, forcing all stem cells to differentiate, he said.

To test these ideas, he and his colleagues studied young and old kidney stem cells in the laboratory. It turned out both ideas were wrong. So, they took a closer look at what was happening in the cells.

"As often happens in science, it turned out something even more exciting was going on, which we did not anticipate," Kopan said.

In a study they published in the *Proceedings of the National Academy of Sciences*, they manipulated genetic switches in the nephron-producing stem cells of mice to see how they affected nephrogenesis. If they completely eliminated the gene for the protein Mtor, which controls the metabolism and growth of cells, in mice, the animals died within 2 days of birth and didn't have normal kidneys.

Mice with just one copy of the gene for Mtor lived, but had smaller kidneys with fewer nephrons. If they completely eliminated the Mtor regulator Tsc1 gene, which makes a protein called hamartin, the mice also died within 2 days of birth, likely owing to kidney failure. But mice with only one copy of the Tsc1 gene had about 25% more nephrons than expected because they produced nephrons through the 4th day of life, instead of ending nephrogenesis by the second day, which is normal for mice, Kopan said.

"It suggested there could be a molecular handle with which we can manipulate how long the period of nephron generation is in mice and then hopefully in [humans]," Kopan said.

Moxey-Mims called the findings "exciting," but cautioned much more work would be needed to translate the findings into humans. These types of genetic manipulations would be difficult to do in humans because of ethical and technical constraints. Instead, they would likely have to find drugs that extend nephrogenesis by targeting specific molecular pathways.

"It's a nice step in trying to help us learn a little bit more on a molecular level about what's happening when nephrons are being formed and what types of things can impact how nephrons are formed," she said.

Safer target needed

Drugs targeting hamartin are likely to be too risky because the protein is a tumor suppressor. Mutations in the Tsc1 gene that alter harmartin cause tuberous sclerosis, a condition in which benign tumors form in the brains, kidneys, and other organs. But Kopan is hopeful it will be possible to find alternative nephrogenesis-extending targets that don't interfere with hamartin's tumor suppression. He also thinks there may be other strategies for extending nephrogenesis.

"Having found one, I'm absolutely certain there will be more genetic pathways that can have the same effect," Kopan said. "There might be several different pathways that alone or synergistically will give you the desired effect."

He and his colleagues are currently looking at all the proteins that hamartin may be acting on. They are also using large-scale genetic screening techniques to look for other nephrogenesis-extending genes.

"We are trying to use big data as well as classical mouse genetics and some elbow grease to try and figure out how to identify candidate pathways that are drugable, which we could use to intervene," he said.

Kopan cautioned that while the idea of extending nephrogenesis is very appealing, it is at least 30 years away from the clinic.

By the numbers

To target nephron-boosting therapies to the people who need them and to test whether such therapies work, clinicians need to be able to count nephrons in patients.

Being able to use imaging to count nephrons would help practitioners provide better care for [patients . . . and] also could aid the development of drugs that are safer for the kidney.

Several groups are working on creating such tools.

For example, Bennett and his colleagues are working on a kidney-safe contrast agent that would allow clinicians to see individual nephrons in three dimensions in patients using magnetic resonance imaging (MRI). They've tested it in animals, as well as human organs not suitable for transplant, and are beginning the process of gaining U.S. Food and Drug Administration approval. This technique could be useful for many kidney diseases.

"Pretty much every possible type of chronic kidney disease involves some type of nephron loss, and the extent of that is really important to assess," Bennett said.

It's currently very difficult to assess the kidney health of those born prematurely, noted Jennifer Charlton, MD, MS, professor in the department of pediatrics at the University of Virginia in Charlottesville and Bennett's collaborator. The size of the kidney is not a good indicator of nephron numbers, and the kidney is so good at compensating for low nephron numbers that problems often aren't detected until they are severe, she said. For example, the kidney health prospects of a child with just one kidney may vary greatly.

"If that single kidney has 2.7 million nephrons in it, you're fine," she said. "You're probably going to be good to go for the rest of your life. But if that kidney is less well endowed, and only has 500,000 nephrons in it, then you may be in trouble as you get to mid-adulthood."

Matching kidney life with recipient life

Being able to use imaging to count nephrons would help practitioners provide better care for these patients. It also could aid the development of drugs that are safer for the kidney by allowing researchers to monitor drugs' effects on nephrons, Charlton said. It might also be used to match donor kidneys with the best patients. For example, Charlton explained, a kidney from a 70-year-old with 2.7 million nephrons could be matched with a patient with a longer lifespan.

"Matching up nephron number with the recipient could reduce the [number] of organs that we need over a lifetime, because you're matching up kidney life with recipient life," she said. "You wouldn't have recipients dying with a graft that's still functioning, or a recipient needing two or three transplants, because they didn't have a good enough nephron endowment to begin with."

Moxey-Mims cautioned that these nephron-counting tools aren't yet ready for use in babies. If they do become available, they might allow neonatologists to monitor whether treatments are harming nephrons.

"The more we can understand about this and try to look at ways that we can mitigate the impact of prematurity, I think it's helpful just in adding to our general knowledge down the road." ■

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A Hidden Epidemic: More than 850 Million Suffer from Kidney Diseases Worldwide, Organizations Report

The global burden of kidney diseases is much higher than commonly reported, according to a notice recently issued by the American Society of Nephrology (ASN), European Renal Association—European Dialysis and Transplant Association (ERA-EDTA), and International Society of Nephrology (ISN).

"We estimate that over 850 million people worldwide have some form of kidney disease, which is roughly double the number of people who live with diabetes (422 million [1]) and 20 times more than the prevalence of cancer worldwide (42 million [2]) or people living with AIDS/HIV (36.7 million [3])," the groups stated.

The three organizations are collaborating to raise awareness of kidney diseases worldwide and to improve prevention efforts.

"It is high time to put the global spread of kidney diseases into focus," said Professor David Harris, current president of the ISN and Professor Adeera Levin, Past-President of the ISN.

Although kidney diseases are one of the most common health problems worldwide, many people are unaware of their impaired kidney function, and the public at large is not aware of the extent of this health issue.

Chronic kidney diseases—abnormalities of kidney structure or function that persist for more than 3 months—account for most current prevalence estimates, at 10.4% among men and 11.8% among women (4).

Between 5.3 and 10.5 million people need dialysis or transplantation, yet many do not receive either treatment owing to financial barriers or lack of resources. Acute kidney injury, which may resolve or lead to chronic kidney diseases or kidney failure at a later time, affects 13.3 million people each year.

"Using all these sources of data, and existing estimates of acute and chronic kidney diseases, we estimate approximately 850 million kidney patients . . . a number which surely signifies an 'epidemic' worldwide," Levin said.

Kidney diseases' effects on other health outcomes

According to a Global Burden of Disease study that looked at mortality and health outcomes data from 1990 to 2013, people with kidney diseases have a much higher age-standardized mortality rate owing to low kidney function, at 21 deaths per 100,000 people.

Prof. Carmine Zoccali, president of the ERA-EDTA, noted that the cardiovascular death toll from chronic kidney diseases is especially large: In 2013, 1.2 million cardiovascular deaths were attributed to kidney diseases [5].

"The death rate among people with kidney diseases is incredibly high. AIDS, for example, accounts for only 1.9 deaths per 100,000 [6], but think about all the campaigning with celebrities and the resulting recognition of HIV as a priority health issue," Zocalli said. "There is only little active campaigning on behalf of people with kidney diseases, even though the number of people who die from kidney deterioration is 11 times higher."

"It is time for constructive change in kidney care policy," said Mark D. Okusa, MD, FASN, ASN president. "The number of people with kidney diseases is alarmingly high, but the public is not aware of this reality. These patients have outcomes and kidney diseases impose a heavy financial burden on healthcare budgets." ■

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Racial Disparities

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To investigate, a team led by Claire Gerber, PhD, MPH, and Tamara Isakova, MD, MMSc, of the Feinberg School of Medicine at Northwestern University, in Chicago, performed a post hoc analysis of a subset of 1937 black and 6372 white middle-aged and older patients with type 2 diabetes who were participating in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial. All patients received comparable type 2 diabetes care.

Although people who self-identify as black or African American are underrepresented in pivotal clinical trials for new drug approvals, blacks were adequately represented in the ACCORD trial, comprising 19% of participants. (Blacks constitute 7% of overall clinical trial participants, although they make up 13% of the US population.)

The researchers hypothesized that compared with white participants, black participants with type 2 diabetes who received standardized multifactorial type 2 diabetes care within the context of a randomized controlled trial would have faster kidney function decline and be at greater risk of development and progression of CKD during follow-up. During a median follow-up period of 4 to 5 years, however, black race was not associated with accelerated kidney function decline, and fewer black participants than white participants developed CKD. Specifically, blacks had a 27% lower risk of incident CKD defined by new onset eGFR <60 mL/min/1.73 m^2, eGFR decline by >25%, and slope of eGFR decline faster than -1.6 mL/min/1.73 m^2.

"In spite of blacks having more risk factors for adverse kidney outcomes in our study, we found that comprehensive type 2 diabetes care within the context of a clinical trial eradicated racial disparities in the development and progression of CKD," Gerber said.

At the start of the trial, blacks had higher levels of systolic blood pressure and hemoglobin A1c, as well as more frequent macro- and microalbuminuria. During follow-up, however, there were no racial differences in the development of albuminuria.

Isakova noted that the findings are similar to recent results from the Indian Health Service's first Diabetes Standards of Care implementation effort that delivered comprehensive diabetes care to American Indians and Alaska Natives and eliminated disparities in kidney outcomes in these high-risk populations.

"Taken together, our results and the findings from the Indian Health Service demonstrate that delivery of comparable diabetes care has the potential to achieve equitable health outcomes for all patients with diabetes."

Nilka Ríos Burrows, MPH, MT, of the Division of Diabetes Translation at the Centers for Disease Control and Prevention, in Atlanta, who was a co-investigator in the American Indians and Alaska Natives study, noted that integrating kidney disease prevention and education into routine diabetes care can help prevent or delay kidney problems.

"The diabetes care team can help patients avoid kidney failure by keeping blood pressure and blood sugar under control, using medicines that lower blood pressure and protect the kidneys, and monitoring kidney function," she said. "These and other strategies used successfully by the Indian Health Service contributed to reducing kidney failure from diabetes among American Indians and Alaska Natives and can serve as a model to reduce disparities in other populations."

In an editorial accompanying the *CJASN* study, Katherine Tuttle, MD, FASN, FACP, of Providence Medical Research Center, in Spokane, WA, called for action. She pointed to numerous areas in which blacks in the United States are disadvantaged across social determinants of health: socioeconomic status, psychosocial factors, healthcare access, neighborhood, and environment. She also pointed to barriers to CKD screening among blacks, including lack of knowledge, mistrust, and financial burden. Key facilitators to screening include CKD education, culturally sensitive communication, and better access by convenient screening.

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Kidney News Online interviewed Edwin Simcox, Acting Chief Technology Officer, Department of Health and Human Services (HHS), and HHS liaison to KidneyX.

KIDNEY INNOVATION ACCELERATOR

Edwin Simcox

Tell us about your background. How long have you been with HHS?

I've spent the bulk of my career working to create a better healthcare system with the goals of reducing cost and increasing quality and patient satisfaction. Much of my focus has been on health IT and innovative technologies dealing with challenges like EHR usability and interoperability. But I also have experience using innovation to improve healthcare operations.

During the past year or so of my time at HHS, the Office of the Chief Technology Officer (CTO) has worked on a number of important initiatives including open data, innovation, and increasing the ability of startups to access such a huge bureaucracy as HHS.

The KidneyX initiative epitomizes what we are trying to do because it combines innovation and greater access to improve healthcare for the more than 40 million Americans living with kidney diseases.

Why is the Office of the HHS CTO interested in kidney diseases?

That's a great question. Since the creation of dialysis 60+ years ago, there has been little to no innovation in the treatment of kidney diseases. Plus, chronic kidney disease is the only disease state that can qualify people for Medicare regardless of age. Of those Americans facing kidney diseases, 661,000 have kidney failure requiring dialysis or transplantation.

According to a 2017 GAO report, Medicare annually spends $34 billion treating kidney failure, which is more than the entire budget of the National Institutes of Health (NIH) or NASA, and the costs continue to increase. We at HHS are the largest payer for kidney care, but we haven't traditionally asked for innovation. This is what we are trying to do with KidneyX. We are trying to create a sense of urgency to develop new therapies to treat kidney diseases.

KidneyX says to innovators across the world that this is an area we care about at HHS and for which we want to see innovation. The Food and Drug Administration (FDA), Centers for Medicare & Medicaid Services (CMS) and NIH are key partners at HHS in supporting the pipeline of innovation. With KidneyX, FDA and CMS have signaled to the world that this is an area they care about and that they are committed to clarifying the pathway to commercialization for innovators.

While the pilot KidneyX prize will focus on developing alternative treatment options to dialysis, we will then launch additional prizes that will focus on other areas, such as improving prevention and diagnostics of kidney diseases. We have to move upstream to help patients earlier so that we can reduce the occurrence of kidney failure. Chronic kidney disease is debilitating to millions of Americans, so we must focus also on prevention and diagnosis to really improve quality of life.

What is the first goal you hope to achieve through KidneyX?

We aim to "de-risk" innovation by streamlining processes, reducing regulatory barriers, and modernizing the way we pay for treatment. This is going to require innovation from outside the government. We plan to stimulate and accelerate innovation through a series of cash prize competitions.

We are getting ready to kick off the first pilot prize competition, which will focus on fostering the development of technologies for next-generation renal replacement therapy. Dialysis is the initial focus because we understand the problems there and we know what approaches have limited upside. We also intend to address the lack of innovation in the areas of diagnostics and prevention. We are working on defining where those future opportunities are and plan to launch prizes that will address those areas.

What are the biggest challenges and opportunities for KidneyX moving forward?

We are confident in our plan. We have robust support from HHS Secretary Alex Azar and widespread support within the relevant HHS agencies. That said, we understand we are creatively disrupting a large, complex, bureaucratic system, and we know this presents a challenge.

Another challenge is lack of a mature innovation pipeline in the development of medical products for kidney diseases. We have to do a better job attracting innovators who may have never worked in the kidney disease space and address any real or perceived barriers keeping them from getting new products to patients. There is a learning curve innovators who are new to this space and HHS may experience. One way the Office of the Chief Technology Officer is helping to partially address this learning curve is by doing outreach across the United States at "startup days," which aim to demystify HHS and the regulatory processes as a first step.

Regarding opportunities, I can tell you that our team is super excited about KidneyX because we have the potential opportunity to foster innovation that brings hope to the millions of Americans with kidney diseases. We think the future is bright and we really hope we can make a positive impact in people's lives.

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

Send your idea to the *Kidney News* Fellows Corner column at kidneynews@asn-online.org

Patients with ESRD Put a High Priority on Alleviating Symptoms That Interfere with Daily Life

By Bridget M. Kuehn

As a dialysis patient and peer coach, Caroline Wilkie knows how postdialysis fatigue and cramping can get in the way of socializing, work, or other responsibilities.

"A lot of us don't plan things in advance because we never know how tired we're going to be," Wilkie said.

Her views and those of other patients with ESRD took center stage recently in a project led by ASN's Kidney Health Initiative (KHI), a public–private partnership between ASN and the U.S. Food and Drug Administration (FDA), aimed at understanding which symptoms patients find most troubling. The project found that insomnia, fatigue, and cramping were the top-ranked physical symptoms, according to results published in the *Clinical Journal of the American Society of Nephrology (CJASN)*. The top-ranked mood symptoms were anxiety, depression, and frustration.

The ultimate goal of the project is to spur the development of therapies that help address these symptoms and improve patients' quality of life, said Jennifer E. Flythe, MD, MPH, assistant professor of medicine at the University of North Carolina at Chapel Hill and co-chair of the project. She noted that currently there are no FDA-approved treatments specifically for treating ESRD-related symptoms. This often leaves patients experimenting with non–evidence-based ways to manage symptoms. For example, Wilkie noted, some try pickle juice or mustard for cramps.

"A lot of people just try a lot of different things until they find relief, or some people don't ever find relief," Wilkie said.

Prioritizing symptoms

Previous research had documented symptoms that affect ESRD patients, but the KHI project is the first to document how patients rank them, said Steven Weisbord, MD, MSC, associate professor of medicine in the Renal-Electrolyte Division at the University of Pittsburgh School of Medicine.

The KHI study included 32 participants in focus groups in North Carolina, Arizona, and Washington state, along with 87 patients who responded to an online survey. The high frequency of fatigue (94%), cramping (79%), and body aches (76%), along with depression (66%), worry (64%), and frustration (63%), confirmed the results of previous studies by Weisbord and colleagues that used a tool to assess symptoms.

The highest-priority symptoms were consistent across the focus and survey groups in the KHI study. Patients rated symptoms with the greatest impact on day-to-day activities, quality of life, and their family's finances as the most burdensome. For example, one focus group participant reported in the study, "Sometimes I think I am a burden to my family because I cannot work [because of my symptoms] . . . Sometimes I get real depressed."

"What was concerning to them was how frequently these symptoms occurred, the duration, and how unpredictable they were," said Wendy St. Peter, PharmD, a professor in the College of Pharmacy at the University of Minnesota and the KHI board liaison to the ESRD symptom project. "Those are things that oftentimes as healthcare providers we don't think about."

Patients also gave their views about the types of symptom-targeted therapies they might find helpful. Participants reported that their physical symptoms were often interrelated with their mood symptoms. For example, Flythe noted that postdialysis-related fatigue might leave patients so tired they can't play with their grandchildren or work, which might contribute to a depressed mood. By treating fatigue, physicians might be able to address both problems without having to use pharmacotherapy to treat the mood symptoms, Flythe said.

Additionally, study participants expressed a desire for behavioral therapies that might address their symptoms, such as peer support groups or cognitive behavioral therapy. Given that the average dialysis patient is already taking 19 pills a day and is aware that medications may come with side effects, it is not surprising that patients weren't eager to add to their pill burden, St. Peter said.

"It was a really good reminder that they are interested in other therapies," Flythe said.

Symptom strategies

The hope is that these insights into patients' preferences will drive the development of new symptom-directed therapies or the repurposing of existing medications to ease symptoms in patients with ESRD.

Numerous medications are available to treat insomnia, but there hasn't been much study about whether they are effective for patients with ESRD, noted St. Peter. A few small studies have looked at the effects of antidepressant medications in patients with ESRD, but some results have been disappointing.

"We just don't know what's going to be most effective or whether the medications will be effective at all in dialysis patients," St. Peter said. She noted it is particularly important to assess whether drugs that are eliminated through the kidneys

will be safe in ESRD patients, whose kidneys are compromised.

There was also discussion about behavioral or other therapies that might be helpful. For example, Wilkie suggested that cognitive behavioral therapy or exercise might ease some symptoms. So far, there are limited data on cognitive behavioral therapies in ESRD patients, noted Flythe. A few small studies have looked at the potential benefits of exercise for patients receiving dialysis. She noted the key challenge is finding interventions that are accessible and easy for patients to stick with.

"It's figuring out what types of exercise programs are sustainable," Flythe said. "It's less of a question of whether they can be helpful."

Another approach to reducing symptoms like cramping and fatigue might be to adjust dialysis itself, noted St. Peter. She explained that rapid removal of fluids and shifts in electrolyte levels during traditional in-center dialysis, which is usually delivered three times a week for 4 hours, might contribute to cramps or fatigue. Slowing the process or using more frequent home dialysis might help, but more study is needed.

"Patients who are getting daily dialysis or longer dialysis oftentimes feel better overall," St. Peter said. "These therapies haven't been investigated yet for symptoms such as cramping or fatigue, so those are really important considerations."

To help drive such research and the development of new therapies, KHI held a workshop with patients, clinicians, industry representatives, and the FDA in January 2018 to develop plans for each of the top-rated symptoms. Those plans will be published later this year. Weisbord cautioned that the process of translating the findings of the KHI project into practice will be challenging and may take a long time.

In the meantime, Flythe hopes the KHI project will help raise awareness among physicians about the importance of symptoms to patients' quality of life. A study by Weisbord and colleagues found that physicians often weren't aware of their patients' symptoms. Weisbord attributed this in part to a focus by nephrologists on adjusting medications or dialysis prescriptions, along with potential discomfort or unfamiliarity with treating conditions like pain or depression.

"When you have a limited time to talk to a patient, oftentimes conversations get focused on numbers," Flythe said.

But it is important for physicians to ask, Flythe and Weisbord said.

"We need to be very cognizant of patients' symptoms and what is very important to each patient," St. Peter said. "They want to feel their care providers are listening to them, that if they're having symptoms they are taken seriously."

Wilkie also urged patients to speak up and share their symptoms with their physicians.

"It helps, even if there's nothing that can be done; it helps for your doctors to know what you're going through," Wilkie said. ■

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Measuring Fatigue Is Key to Knowing How to Manage It

By Bridget M. Kuehn

Fatigue is one of the most common symptoms reported by patients on dialysis, but there is little data to guide clinicians about how to manage it. A new initiative aims to change that by helping researchers routinely and consistently measure fatigue in their studies of dialysis-related care.

The Standardized Outcomes in Nephrology–Hemodialysis (SONG-HD) project was created to establish a standard set of measures that should be used in all studies enrolling patients receiving dialysis. Having such a standard set of measures used across clinical trials makes it easier to compare the results of different studies, explained Angela Ju, BSc, of the University of Sydney in Australia. To identify which measures were most important to patients and clinicians, SONG-HD did a rigorous, three-round online survey of patients and clinicians.

"Fatigue was the top patient-reported outcome that health professionals and patients both picked," said Ju, who is the project coordinator of the SONG-HD fatigue project. So, Ju and her colleagues began assessing how fatigue is currently measured in clinical trials, with the hope of identifying an existing questionnaire they could recommend for use across trials. Their results were published in a review that found many different measures were being used ranging from 20 questions to only 4 questions, Ju noted. Some questions ask only about physical fatigue while other questions address other dimensions of fatigue, for example, how it affects mental capacity.

"There's a whole lot out there, but it became clear that it wasn't really standardized," Ju said.

Shared values

To assess what is most important to patients and other stakeholders when measuring fatigue, Mark Unruh, MD, professor of medicine at the University of New Mexico and chair of the SONG-HD fatigue project, led a workshop in Chicago in November 2016. The workshop brought together 15 patients or caregivers and 42 other stakeholders, including clinicians, researchers, policymakers, and industry representatives.

The participants confirmed that fatigue is seen as a key measure that should be measured consistently across studies.

"The patients and stakeholders felt that fatigue was important enough to include as a measure in basically every trial looking at dialysis outcomes," Unruh said.

For patients, the most important aspect of dialysis-related fatigue was how it affected their day-to-day life. One patient participant said: "When I got off [dialysis] I was wasted. I couldn't do anything. It was hard to walk a block to get to my car."

> *One patient . . . said that she and her fellow patients often discuss symptoms like fatigue in the waiting room rather than talking with their physician.*

In discussions with patients, Ju learned that such crippling fatigue was manageable if patients could go home and sleep, but it becomes a serious problem when it prevents patients from completing essential tasks like working or picking up their children from school or activities. "That's when it becomes important," Ju said.

The workshop also provided valuable insights regarding how patients and physicians feel about talking about fatigue during visits.

Some patients expressed concern about wasting their physician's time by asking about their fatigue, Ju said. One patient she spoke with told Ju that she and her fellow patients often discuss symptoms like fatigue in the waiting room rather than talking with their physician.

Patients also suggested physicians place more "emphasis on how the patient is feeling, less on what the doctor thinks," by asking the patient their views on how to best manage fatigue. But clinicians noted they were worried about burdening patients with repetitive questions.

"They don't want to tire them out by asking them the same questions all the time," Ju said.

Researchers on the project also expressed a need for short, meaningful questionnaires that can fit into the workload of research teams.

A better measure

The workshop and surveys by the SONG-HD team revealed three key dimensions of fatigue that should be measured: fatigue's impact on the patient's life, patient's energy level, and their degree of tiredness. None of the existing measures Ju and her colleagues identified in her review looked at all three of these dimensions.

"There wasn't one measure that maps out these dimensions that we could just take and validate," Ju said.

So, they created a short questionnaire of their own that addresses these three dimensions, and they have already begun the process of validating it.

Once that process is complete, Unruh said he hopes this new measure will become a tool that is used routinely in studies in the same way that estimated glomerular filtration rate is used as a routine measure of kidney function. This will allow researchers to track how the treatments they are studying affect fatigue, even if reducing fatigue is not the primary goal of the treatment being studied, Unruh explained.

"We all kind of know what fatigue is, but being able to measure it and reproduce it is what has been missing because everybody kind of chooses their own fatigue questionnaire," Unruh said. "Measuring fatigue in a careful way and being able to reproduce that I think would be helpful toward improving that outcome." ■

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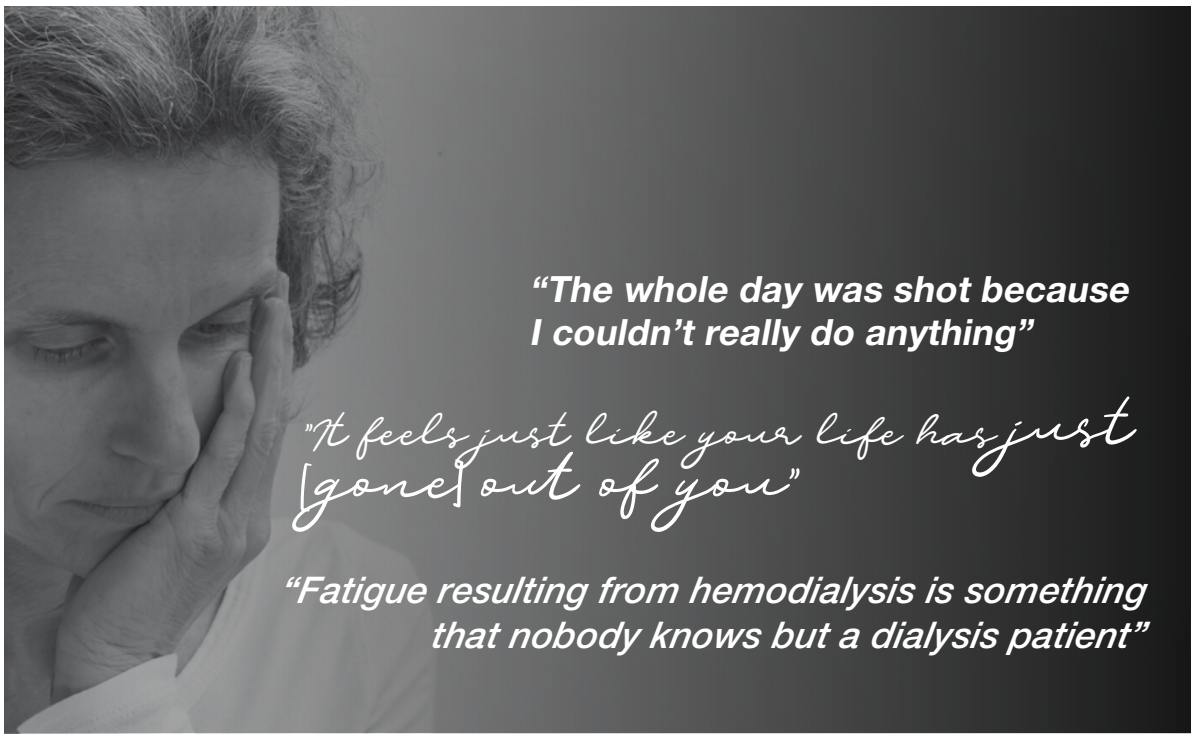
Postdialysis Fatigue

By Vishal Duggal, Wael Hussein, and Graham Abra



A 65-year-old woman who has undergone hemodialysis (HD) three times per week for 10 years notes that she "has no energy" after her treatments. After dialysis, she goes home, sleeps for 2 hours, and still feels tired for several more hours. Sometimes she does not feel "back to [her] normal self" until the next day. She asks her provider why she feels so fatigued and what can be done to help.

Postdialysis fatigue

Fatigue is commonly reported by HD patients. Although there is no widely accepted definition of postdialysis fatigue, patients often express feeling exhausted or drained soon after dialysis. Patients lose their ability to "experience life" as a result of both the physical and emotional impact of HD. Postdialysis fatigue is associated with hard outcomes such as hospitalization and mortality (1). As such, fatigue has been identified by clinicians and patients as a research priority (2).

The time required by patients to recuperate from dialysis is often quantified in minutes or hours and is typically referred to as dialysis recovery time (3). The patients most likely to experience longer recovery times include those with advanced age, greater number of years receiving dialysis, and multiple comorbidities (4). The dialysis routine, which involves travel, waiting, and changes to rest times and mealtimes, contributes to recovery time. The buildup of fluid and uremic waste before dialysis and the rapid shifts during dialysis, particularly after longer interdialytic intervals with traditional three-times-per-week in-center dialysis, is also associated with fatigue. High ultrafiltration rates, particularly when associated with hypotension, are also associated with postdialysis fatigue (5).

A significant proportion of HD patients experience fatigue after dialysis, often requiring several hours of restful inactivity or sleep before recovery (6), which they describe as unique to dialysis days.

How to measure fatigue

One of the difficulties facing researchers in this area is the lack of a suitable measurement tool. Available tools include the four-item Vitality section of the 36-item Short Form Health Survey, among several others (8). The length of surveys is prohibitive for their use, particularly in patients with severe fatigue. In addition, most if not all of these tools have limited or no validation in the HD population. To complicate things further, fatigue itself is difficult to define, with several dimensions to capture. For example, a measurement tool needs to differentiate between a nagging, ongoing, and prolonged fatigue compared with a short, yet severe, drop in energy. A current initiative is being undertaken by the Standardized Outcomes in Nephrology–Hemodialysis group to develop a tool that addresses these issues (8).

The minutes-to-recovery question (dialysis recovery time)

Answers to the question "How long does it take you to recover from a dialysis session?" can be used to obtain information about fatigue (3). Shorter recovery times reported with this question correlate with higher quality of life survey scores. Sixty-eight percent of patients report more than 2 hours of recovery time, whereas 27% of patients report more than 6 hours (4). However, the recovery time question also has limitations (4, 5). For example, this question does not capture the severity of symptoms, nor does it differentiate between recovery from fatigue and recovery from other common complaints such as headaches, cramps, and back pain. The open-ended nature of the question allows for a wide range of interpretation, with patients' answers referring to the last treatment or an average experience over different periods of time.

How to manage postdialysis fatigue

Management strategies must be individualized. Various approaches have been suggested:

- Physical factors: Optimal treatment of comorbid conditions such as heart failure, malnutrition, and anemia.
- Adjustments to the dialysis prescription:
  - Consider whether inadequate dialysis is contributing to fatigue.
  - Measures to address intradialytic hypotension: One study observed shorter recovery times with lower ultrafiltration rates (5), but this was not the case in other studies (4). No interventional studies have been conducted to evaluate this discrepancy.
  - Consider longer or more frequent dialysis: The Frequent Hemodialysis Network trials have shown benefits from more frequent dialysis. The time taken to recover from dialysis decreased significantly when patients on three-times-per-week dialysis were changed to frequent daily or frequent nocturnal dialysis (9).
- Social support: Anxiety and depression can contribute to fatigue (6, 10).
- Exercise: A trial of low-intensity core strengthening, range of motion, and stretching/flexibility exercises for 30 minutes per week during dialysis found a decrease in postdialysis recovery time (11).

The most important step in treating postdialysis fatigue is to recognize and validate it. Successful management should be interdisciplinary, involving not only nephrologists and dialysis unit staff but also patients and family. Although the causes of postdialysis fatigue may be multifactorial, there are often modifiable factors at play, such as excessive ultrafiltration, depression, and physical deconditioning. Applied pragmatic clinical research to address this issue is urgently needed.

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Big changes afoot with CMS Evaluation and Management Coding

By David L. White

Every summer, the Centers for Medicare & Medicaid Services (CMS) propose rules that govern physician reimbursement, the Medicare End-Stage Renal Disease (ESRD) program, and the newer Quality Payment Program (QPP), which is entering its third year in calendar year 2019. This summer has been no exception, with some proposed changes that benignly refine programs around the edges, and others that mark significant changes in course.

In July 2018, CMS released the ESRD PPS and QIP proposed rules. In what is expected to be a permanent change, the proposed rule for the first time combines the QPP and the Physician Fee Schedule (PFS).

The American Society of Nephrology (ASN) Quality Committee and ASN Council each year review and comment on these recommendations as they relate to nephrology and best practices in medicine. The committee and Council are currently reviewing the 2000 pages of proposed regulations, some of which are far-reaching in nature, in advance of the deadline for comment submission on September 10, 2018.

Following are highlights of the proposed changes.

Physician Fee Schedule/Quality Payment Program

Reducing Evaluation and Management (E&M) coding documentation

CMS Administrator Seema Verma discussed the E&M changes in a Health and Human Services (HHS) Department video.

"Evaluation and Management or E&M visits make up around 40% of all Medicare payments under the Physician Fee Schedule, and guidelines have not been updated since 1997–21 years ago," according to Verma, who added that nearly 750,000 clinicians use these codes. "The requirements often mean that doctors have to cut or paste chunks of information across medical records strictly for billing purposes." Verma said this documentation process is a "poor use" of clinician time that detracts from direct patient care. "Time spent at the computer documenting and coding for visits is time doctors could be spending with their patients." In addition, she said that E&M codes "pack the medical records with information that isn't useful for patient care."

In the proposed rule, CMS states: "We propose to allow practitioners to choose, as an alternative to the current framework specified under the 1995 or 1997 guidelines, either medical decision making (MDM) or time as a basis to determine the appropriate level of E/M visit."

"If you add up the amount of time saved for clinicians across America, in one year from our proposal it would constitute more than 500 years of additional time available for patient care," Seema noted in the video.

However, CMS has coupled this paperwork reduction with a reimbursement policy that is sure to be far more controversial.

Creating a compressed single payment for E&M levels 2–5 (one for new patients and one for established patients)

CMS has proposed creating a single, flat payment for the compressed E&M levels 2–5 with one payment for new patients at a slightly higher rate due to CMS' expectations that a new patient will require more time on the clinician's part. The established patient's rate would be slightly less for the expected slight reduction in the time required with the clinician. This proposal has already drawn criticism from different parts of the medical community and was discussed in-depth at the ASN Quality Committee's in-person meeting in late July 2018.

Some are concerned that the new proposal will penalize clinicians who serve largely complex patients and who more commonly bill at levels 4 and 5. CMS is somewhat concerned about that effect and wants to create an adjuster to be used by some specialties; however, ASN Quality Committee members are concerned that the adjuster is not robust enough and CMS does not apply it to nephrology.

Allowing the scoring methodology for the End-Stage Renal Disease QIP to be used for clinicians who spend the majority of their time in the dialysis facility

This move is still being considered, and CMS has been signaling it for at least a year. CMS writes in the proposed rule on PFS/QPP: "We seek comment on the extent to which the quality measures of dialysis centers reflect clinician performance. Additionally, we seek comments on whether we might be able to attribute the performance of a specific facility to an individual clinician."

Creating new telehealth opportunities

Several provisions affecting telehealth are included in the proposed rule. One allows a clinician to bill for a non-face-to-face service that avoids an office visit and thereby benefits the patient and saves CMS money. CMS is seeking comment on what level of technical functionality clinicians believe is necessary for this service.

Second, CMS is proposing to pay clinicians for evaluating "store and forward" videos or images provided by a patient. As with the first provision, if the telehealth service leads to a patient visit, it would be bundled into that office visit reimbursement. The payment would occur when the service allows a patient to avoid coming in for an office visit.

ESRD PPS/QIP

Changing, expanding Transitional Drug Add-on Payment Adjustment (TDAPA)

CMS is proposing modifications to the designation process and expansion of TDAPA to all new drugs, not just those in new functional categories, for a period of two years.

The proposed rule revises the drug designation policy in TDAPA "to reflect that the process applies for all new renal dialysis drugs and biologicals that are approved regardless of the form or the route of administration, that is, new injectable, intravenous, oral, or other routes of administration or dosage form."

The proposed rule also removes four measures from the QIP: Healthcare Personnel Influenza Vaccination, Pain Assessment and Follow-Up, Anemia Management, and Serum Phosphorus, and adds transplant metrics.

These are just some of the more notable recommendations for these rules. ■

To read more about the QPP/PFS proposed rule, visit the ASN website at https://www.asn-online.org/policy/webdocs/QPP_PFS_Proposed_rule_2018-14985.pdf

To read more about the ESRD PPS QIP proposed rule, visit the ASN website at https://www.asn-online.org/policy/webdocs/2019_Proposed_Rule_Highlights.pdf

ASN Scores Wins in Appropriations Process

By Zachary Kribs, ASN Government Affairs Specialist

In July 2018, the House Appropriations Committee approved the annual Labor, Health and Human Services, and Education spending bill (LHHS), passing it to the House floor for consideration.

The bill, and its Senate counterpart, contain multiple priorities of the American Society of Nephrology (ASN), a direct result of the countless emails, meetings, and phone calls made by members to their legislators.

Chief among these priorities is a sizable increase for the National Institutes of Health (NIH). Working with peer organizations, ASN and its members were able to build on the momentum of previous years and advocate for a consistent, sustained increase for the NIH in Fiscal Year 2019—including in a letter signed by a record 37 patient, physician, and provider groups across the kidney and transplant community.

The Senate version of the LHHS bill proposes a $2 billion increase for the NIH, while the House version of the bill proposes a $1.25 billion increase. In addition to the topline NIH funding level, both bills also propose sizable increases for the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), $60 million in the Senate and $24 million in the House.

Another fixture of ASN's congressional advocacy has been the dissemination of a 2017 Government Accountability Office (GAO) report on the state of funding for kidney diseases research. The report found a significant discrepancy between the burden created by kidney diseases and investment in research of the diseases. At the time it was written the government spent more on treating kidney failure than on the entire NIH or NASA budget, while allocating less than 1% of that amount on kidney research.

The House bill includes language encouraging "NIDDK to continue working with stakeholders to disseminate critical information and discuss new opportunities for research," a clear acknowledgment of the report's findings and the work done by ASN and peer organizations to draw attention to the need for greater investment in kidney diseases research.

Immunosuppressive drug coverage; living donor provisions

The House bill also includes language encouraging CMS to address current policy surrounding the coverage of immunosuppressive medications after kidney transplantation. Currently, Medicare pays for costly immunosuppressive medications for only 3 years after receiving a transplant, leaving many recipients who cannot afford the medications at risk of transplant failure and in need of a new transplant.

In the proposed legislation, the House Appropriations Committee encouraged CMS to commission a study of

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The Dialysis PATIENTS Demonstration Act

The Dialysis PATIENTS Demonstration Act (DPDA) has been the subject of considerable enthusiasm and controversy within the kidney and transplant communities since its introduction in September 2016. The most recent iteration of the legislation, introduced in the U.S. House of Representatives and Senate by a bipartisan group of lawmakers, has garnered substantial support in both chambers, with 185 House cosponsors and 8 Senate cosponsors at press time. Yet the legislation remains a focal point of division within the broader kidney and transplant communities.

At the most basic level, DPDA proposes a Medicare demonstration project that would test a dialysis-focused integrated care model. In the model, dialysis providers and potentially others would assume the full risk of administering all care to dialysis patients enrolled in the model in an open or preferred network setting. By providing integrated care for dialysis patients centered on the dialysis organization, the model seeks to either improve care or generate savings by reducing hospitalizations.

Proponents of the legislation point to the success of integrated care models—such as Accountable Care Organizations (ACO) and ESRD Seamless Care Organizations (ESCO)—in streamlining care and improving outcomes. According to proponents, this legislation would let dialysis centers serve as the primary point of care for dialysis patients, increasing access to comprehensive care for the hundreds of thousands of dialysis patients already receiving care in these settings.

Opponents of the bill have raised concerns about the possibility of increased consolidation in the dialysis market and establishment of perverse incentives that would reduce access to transplantation.

In one provision of the bill, dialysis providers with adequate capitalization can provide plans that resemble Medicare Advantage (MA) for dialysis patients. Some critics maintain that, unlike other MA plans, these plans for dialysis patients would start at dialysis initiation and end at dialysis termination, potentially reinforcing existing silos of care, reducing emphasis on prevention, and providing potential financial disincentives for patients to be referred for transplantation.

Opponents have suggested that only two dialysis organizations would likely be financially capable of assuming the full risk of insuring dialysis patients and claim this would prohibit smaller organizations from participation in the model, further reducing patient choice.

ASN Scores Wins

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the "cost-effectiveness of the current payment policy of restrictive coverage for these lifesaving immunosuppressive medications," as well as consider "all possible payment models for dialysis patients considering the immense amount of data showing the benefits of greater care management for this population." ASN and peer organizations have advocated for CMS and Congress to revisit this policy for many years, and the inclusion of this language represents a major win.

Finally, ASN and peer organizations have long advocated for living organ donation to be covered under the Family and Medical Leave Act, which would provide job security for individuals recovering from a life-saving kidney donation surgery—a period of typically 4 weeks. In their bill, the House Appropriations Committee stated their support for "efforts that seek to remove impediments to live organ donation for those willing to give the gift of life to others" and requested that the Department of Labor clarify in public communications the eligibility of living organ donors for coverage under the Family and Medical Leave Act.

The inclusion of these priorities in the House and Senate LHHS bills represents a major victory for ASN members after years of advocacy. Both bills are now waiting for a vote in their respective chambers, after which the bills will be combined in a process called conferencing. ASN and its members will continue to advocate for the inclusion of language supporting the GAO report, the study of immunosuppressive drug coverage, job security for living donors, and an increase in funding for the NIH and NIDDK in the final version of the bill.

The move toward a value-based comprehensive care system from the current fee-for-service system is in line with broader trends in healthcare, and similar efforts are supported by ASN. However, as outlined in a letter sent by ASN and the American Association of Kidney Patients (AAKP) to the bill's cosponsors, several provisions of potential concern in the legislation outweigh the potential benefits patients would receive were the bill to be enacted. As described in the letter (see excerpts below), these potential risks include: restriction of patient choice, exacerbation of existing silos of care, exclusion of transplanted patients from the model, and an infringement on the patient-physician relationship and disruption of care.

In a January 31, 2018, statement supporting the legislation, the Renal Physicians Association (RPA) asserted the PATIENTS Act "builds on RPA's commitment to the use of integrated care models in kidney disease. . . . RPA has supported the ESRD Seamless Care Organization (ESCO) payment model and developed an Incident ESRD Payment Model proposal recently recommended for implementation by the Physician Focused Payment Model Technical Advisory Committee (PTAC)." These integrated care models "offer tremendous potential to improve patient care via reduced hospitalizations, enhanced care coordination, increased availability to social support and nutritional staff, and transportation to care when necessary," RPA added in its statement.

"With integrated care, patients undergo fewer duplicative and wasteful tests, and they receive holistic care that focuses on the whole patient, not just their disease," wrote Dialysis Patient Citizens CEO Hrant Jamgochian, JD, on December 3, 2017, in a Real Clear Politics article urging Congress to advance the legislation. "The Dialysis PATIENTS Act seeks to build on the successes of the Comprehensive ESRD Care Model and Medicare Advantage ESRD Chronic Special Needs Plans, while expanding dialysis patients' access to integrated care," Jamgochian stated.

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Policy Update

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DPDA has received significant bipartisan support in the House. Some in Washington, DC, believe the legislation may be included in a package of member-priority health bills after the chamber's August recess. In the Senate, procedural rules dictate that legislation must receive a score by the Congressional Budget Office (CBO) before being put to a vote on the Senate floor. At press time, CBO had not given the bill a score, likely delaying consideration of the legislation until after the November 2018 election. Every member of the House and one-third of the Senate are up for reelection this fall.

The following are excerpts of a joint letter from AAKP and ASN opposing the legislation that was sent February 28, 2018, to the sponsors of DPDA in the House and Senate. The full text of the letter is available at www.asn-online.org/policy.

"ASN and AAKP appreciate your [cosponsors of the bill] recognition of the significant challenges facing individuals with kidney diseases and kidney failure as well as your commitment to improving their lives. Our organizations were both grateful for the opportunity to provide input on the draft Dialysis PATIENTS Demonstration Act of 2017 (S. 2065), and we commend your efforts to collaborate with our organizations and the rest of the kidney community to refine and further improve the legislation. However, as described below, ASN and AAKP are unable to support the legislation.

"We appreciate the emphasis in the bill on creating a demonstration project to test an integrated care model to increase care coordination. As staunch proponents of the move towards value-based care, we believe that increasing care coordination for patients with kidney diseases—including those with kidney failure—is essential to provide better care for people with these complex needs. ASN and AAKP believe the model proposed in S. 2065 offers elements with the potential for:

- **Improving patient care via reduced hospitalizations,** a serious event from patients' perspective and one of the costliest aspects of the Medicare ESRD program.
- **Enhancing care coordination** by requiring a range of integrated care strategies.
- **Increasing access to social workers and dieticians,** which current research shows improves long-term patient outcomes.
- **Improving access to transportation services,** a current challenge for many patients that, if resolved, could help improve adherence, outcomes, and quality of life.

"However, ASN and AAKP remain concerned about the possibility of unintended consequences and risks associated with foundational aspects of the PATIENTS Act. These potential risks include:

- **Restricting patient choice** by automatically enrolling patients in the model and not permitting them to move from an ESRD Integrated Care Organization's preferred network to its open network after a 75-day period. Additionally, patients must wait a full year to make any of the permitted changes, regardless of their care experience.
- **Exacerbating existing silos of care** by excluding patients with earlier kidney diseases and missing critical opportunities to slow or prevent progression to kidney failure as well as improve patients' lives and avoid more costly care.
- **Excluding transplanted patients from the model.** Not including the optimal therapy for most patients as a treatment option within the model runs contrary to national efforts to encourage more transplantation as a means of improving patient health outcomes and lowering overall costs to taxpayers.
- **Infringing on the patient-physician relationship and disrupting care** by prohibiting nephrologists who are not part of preferred networks from caring for their patients receiving care in units owned by an ESRD Integrated Care Organization participating in the model.

"ASN and AAKP believe that the potential beneficial elements for patients receiving dialysis in the PATIENTS Act could be achieved in more effective ways that minimize or eliminate the potential risks and unintended consequences described above. As such, ASN and AAKP are unable to support S. 2065 at this time."

Apixaban Said to Lower Bleeding Risk in Dialysis Patients with Atrial Fibrillation

In dialysis patients with atrial fibrillation, the factor Xa inhibitor apixaban reduced the risk of major bleeding compared to warfarin in a nationwide sample, reports a study in *Circulation*.

Standard-dose apixaban is also associated with lower risks of thromboembolism and death compared to warfarin.

The introduction of direct oral anticoagulants has changed the approach to management of stroke risk in patients with atrial fibrillation. But the pivotal trials of these agents excluded atrial fibrillation patients with kidney failure. Some studies have reported adverse outcomes with dabigatran and rivaroxaban in this patient population. Standard-dose apixaban is approved for use in hemodialysis patients, but little has been known about the clinical outcomes.

The retrospective cohort study in *Circulation* included 25,523 Medicaid beneficiaries with atrial fibrillation who were receiving dialysis and were included in the U.S. Renal Data System from 2010 to 2015. The mean age of those studied was 68.2 years, and 54.3% of the patients were men. All the patients initiated treatment with an oral anticoagulant, and the 2351 patients taking apixaban were matched for prognostic score to 23,172 patients taking warfarin.

The apixaban and warfarin groups were compared for efficacy and safety outcomes: survival free of stroke or systemic embolism, major bleeding including gastrointestinal or intracranial bleeding, and death. Trends in apixaban prescribing were also analyzed.

Rates of apixaban treatment increased after its approval in 2013, and use of warfarin showed a corresponding decrease. By 2015, apixaban accounted for 26.6% of new oral anticoagulant prescriptions.

Survival free of stroke or systemic embolism was not significantly different between the groups in the *Circulation* study. Incidence of these events was 12.4 per 100 patient-years with apixaban and 11.8 per 100 patient-years with warfarin. However, the incidence of major bleeding was significantly lower in the apixaban group: 19.7 versus 22.9 per 100 patient-years, with a hazard ratio (HR) of 0.72.

There were trends toward lower rates of gastrointestinal bleeding and death in patients receiving apixaban, but they were not significant. There were no significant differences in intracranial bleeding. Analysis of 580 patients who were originally prescribed warfarin but later switched to apixaban yielded similar results.

Within the apixaban group, 44% of patients received the standard dose of 5 mg twice daily, while 56% were prescribed the reduced dose of 2.5 mg twice daily. Compared to warfarin, standard-dose apixaban was associated with significant reductions in stroke/systemic embolism, HR 0.64; major bleeding, HR 0.71; and death, HR 0.63.

The only significant reduction was in major bleeding for patients receiving reduced-dose apixaban, HR 0.71. When apixaban-treated patients were analyzed with dose as a predictor variable, the standard dose was associated with reductions in stroke/systemic embolism, HR 0.61; and death, HR 0.64.

With apixaban accounting for more than one-fourth of anticoagulant prescriptions in kidney failure patients with atrial fibrillation, randomized trials are needed to confirm these findings, the authors noted.

Siontis KC, et al. Outcomes associated with apixaban use in end-stage kidney disease patients with atrial fibrillation in the United States. Circulation 2018. http://doi.org/10.1161/CIRCULATIONAHA.118.035418].

Promoting productive relationships between nephrologists and public health professionals

By Anitha Vijayan, MD, on behalf of Nephrologists Transforming Dialysis Patient Safety

Imagine this scenario as a nephrologist.

Your patient with ESRD undergoing hemodialysis has newly diagnosed hepatitis C virus (HCV) infection. In addition to addressing the immediate medical issue, what is the next course of action? What are the reporting requirements for a new case of HCV infection? Are you required to report this case to state and federal public health agencies? How do you ensure your patient did not acquire the infection due to lapses in infection prevention and control measures at the dialysis facility?

This series of questions may not be at the forefront in the minds of nephrologists during their day-to-day clinical practice. However, reporting of HCV infections is a requirement at both state and federal levels, and it is important that nephrologists understand the importance of partnering with state health departments in preventing healthcare-associated infections in dialysis facilities.

Infections—either individual cases or clusters—are quite frequent in hemodialysis facilities and are associated with high morbidity and mortality. Infections can vary from acute HCV, to influenza outbreaks in winter, to bloodstream infections (BSIs) related to vascular access or other factors. Between 2008 and 2017, 57% of the 37 healthcare-related HCV outbreaks reported nationwide occurred in hemodialysis facilities and resulted in 102 new cases of HCV. An additional 11 single cases, confirmed as likely patient-to-patient healthcare-associated transmission, were reported in the same time period.

Bloodstream infections are usually related to vascular access, and 70% of these are related to use of central venous catheters. The Centers for Disease Control and Prevention (CDC) strongly encourages the tracking of BSIs through the National Healthcare Safety Network (NHSN) surveillance program, and the Centers for Medicare & Medicaid Services (CMS) has mandated that all ESRD facilities use the NHSN reporting system to track BSIs as a quality indicator.

In addition to the CDC, local and state level programs play a major role in promoting healthy and safe practices in a variety of healthcare settings (Figure 1). Surveillance of infections in hemodialysis facilities also falls under the purview of the state Healthcare-Associated Infection (HAI) programs. The structure and role of HAI programs vary from state to state, depending on their laws and policies. Local and state health departments monitor trends in healthcare-acquired infections, recognize emerging pathogens, and help identify unsafe medical practices. They promote implementation of known prevention strategies, use data to recognize unmet needs in infection prevention, and support and coordinate collaborative prevention activities. The Infection Control Assessment and Response (ICAR) tool created by the CDC is widely used by local and state HAI personnel to assess infection prevention practices and guide quality improvement activities (https://www.cdc.gov/hai/prevent/infection-control-assessment-tools.html) (Figure 2). In some states (e.g., Massachusetts), HAI personnel offer teaching sessions for hemodialysis staff, using didactic presentations and simulation exercises in hand hygiene, safe injection, and cannulation practices.

What are some of the lapses in infection prevention and control practices that have resulted in the transmission of infections in hemodialysis facilities?

A collaborative effort between CDC and state health departments in four different states identified potential gaps in infection prevention and control practices when new HCV cases were identified at one hemodialysis center in each of the states (1).

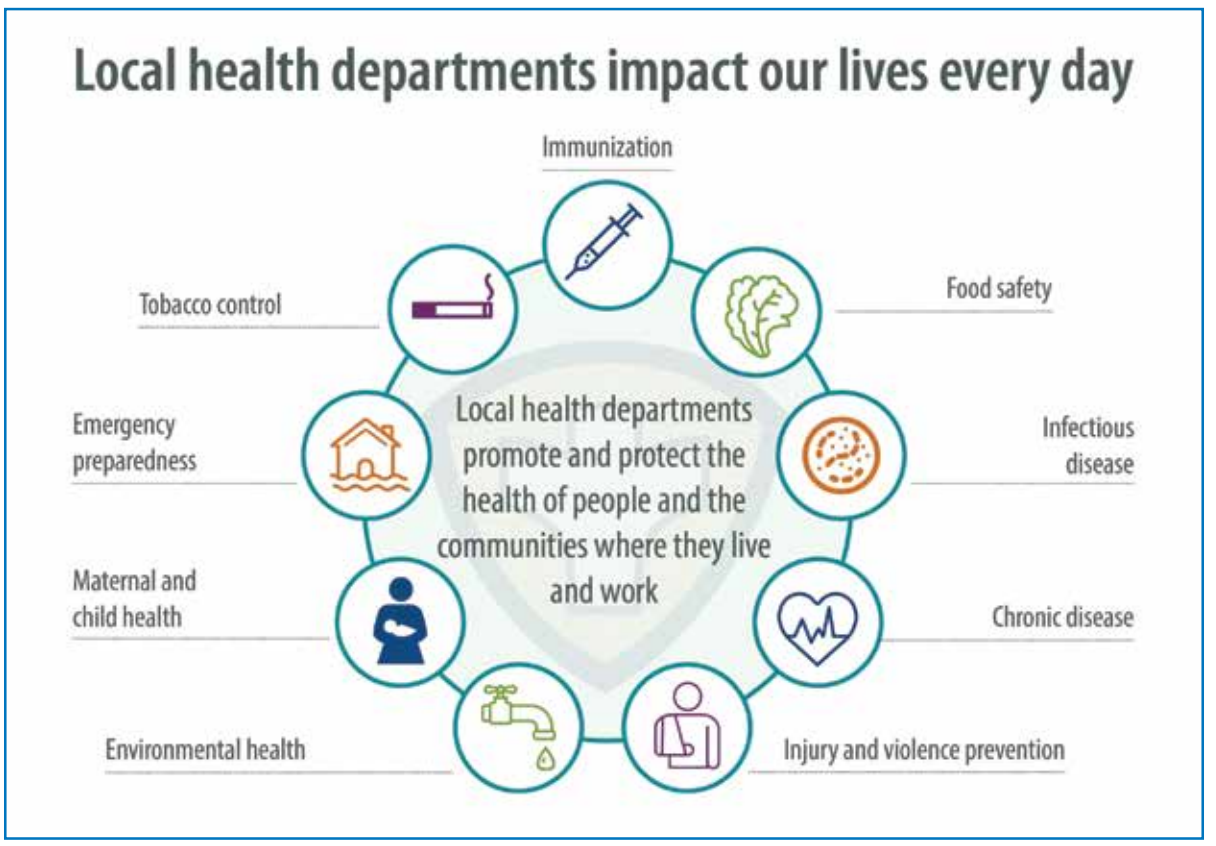
The investigation identified the following lapses in infection prevention and control practices at the facilities: 1) preparation of an intravenous medication from a multidose vial performed at the dialysis station; 2) failure to routinely clean and disinfect the dialysis station and machine surfaces and empty priming buckets between patients; 3) use of a mobile cart to take medications from station to station; and 4) administration of intravenous medication from a single-dose vial to multiple patients.

Investigations such as this one have resulted in specific infection prevention and control recommendations: 1) single use of a single-dose vial; 2) preparation of medications at a clean central area away from dialysis stations; 3) transport of syringes by hand to individual stations instead of using supply carts; and 4) careful cleaning and disinfection of chairs and stations after patients have left the dialysis treatment area. Frequent audits, and feedback of results to frontline staff, of these and other infection control practices, such as hand hygiene, are essential to prevent transmission of pathogens.

Public health officials rely on healthcare providers to report the occurrence of reportable diseases. Timely and accurate reporting of communicable diseases is important to ensure patients receive appropriate medical treatment, to detect common sources, and to prevent transmission.

There are some perceived barriers that may prevent reporting of infections and impede collaborative efforts between state health departments and nephrologists. Hemodialysis-specific reporting requirements, such as the

Figure 1. General role of local and state health departments



Courtesy National Association of County and City Health Officials https://www.naccho.org/about

Figure 2. Infection Control Assessment and Response (ICAR) process used by HAI programs to identify gaps in infection prevention and control practices

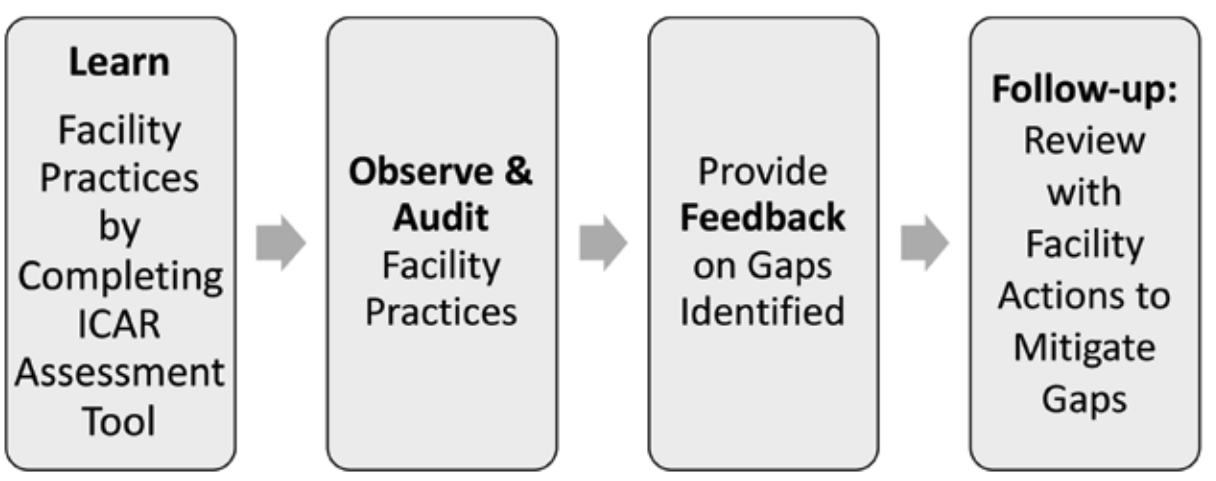
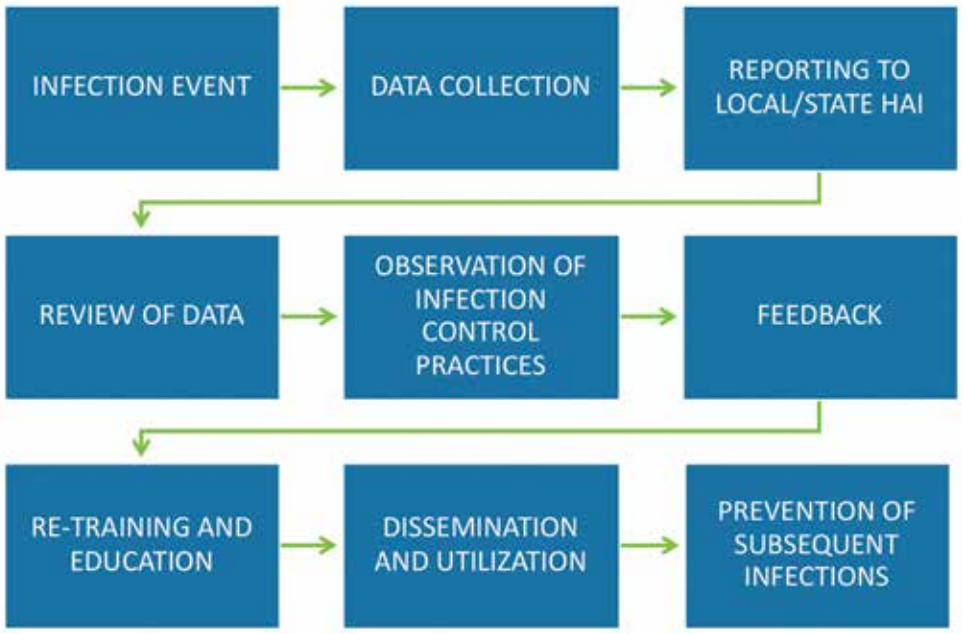


Figure 3. Possible scenario whereby an infection event at a hemodialysis facility can trigger a series of responses, resulting in prevention of subsequent infections



Infection control and prevention is a collaborative effort between hemodialysis facilities and local and state Healthcare-Associated Infection (HAI) programs.

type of reportable infections, vary by state and may be difficult to find on state health department websites. In some states, infections must be reported at the local as well as the state level.

Physicians and dialysis staff may have misconceptions that paperwork required for reporting of infections is cumbersome. The biggest barrier, however, may be the concern among nephrologists and dialysis staff that the reporting of infection will trigger a visit by state inspectors and result in citations for the hemodialysis facility. On the other side, state HAI personnel, when contacted, may not have sufficient knowledge about ESRD facilities, and infections occurring in the dialysis setting, to conduct a comprehensive investigation of the reported issue. They may find it difficult to obtain information from hemodialysis facilities. Education on both sides is required to improve the partnership between dialysis personnel and state and local HAI programs.

In addition to reporting barriers, the services provided by state HAI professionals are often unfamiliar to the dialysis staff and nephrologists. One of the major goals of the American Society of Nephrology (ASN) Nephrologists Transforming Dialysis Safety (NTDS) initiative is to improve communication and collaboration between nephrologists and dialysis professionals and their local and state HAI personnel. We should keep in mind that the best resource to determine state-specific requirements is our local and state Department of Public Health. It is important for the dialysis staff to recognize that the relationship with state HAI staff is collaborative and not punitive in nature. The survey and certification section is a separate department from the HAI prevention and education section in most state health agencies. The resources and feedback from state HAI programs can be an invaluable collaborative tool in implementing and promoting infection control practices in the dialysis facility (Figure 3).

In summary, local and state-level HAI programs serve as a major resource for healthcare facilities, including hemodialysis centers. They can provide technical assistance about HAI surveillance, expertise on topics such as antibiotic stewardship, and information on infection control breaches. Local and state HAI experts offer assistance to facilities dealing with new infections or outbreaks, such as a patient with newly diagnosed HCV infection. Nephrologists can assist HAI personnel by providing education on the complexities of dialysis, ensuring ongoing infection surveillance at their dialysis facilities, helping to identify staff educational needs, and promoting the use of CDC infection prevention tools (https://www.cdc.gov/dialysis/prevention-tools/index.html). With a collaborative relationship among nephrologists, dialysis staff, and local and state HAI programs, we can be one step closer to our goal to "target zero infections" in the hemodialysis facility.

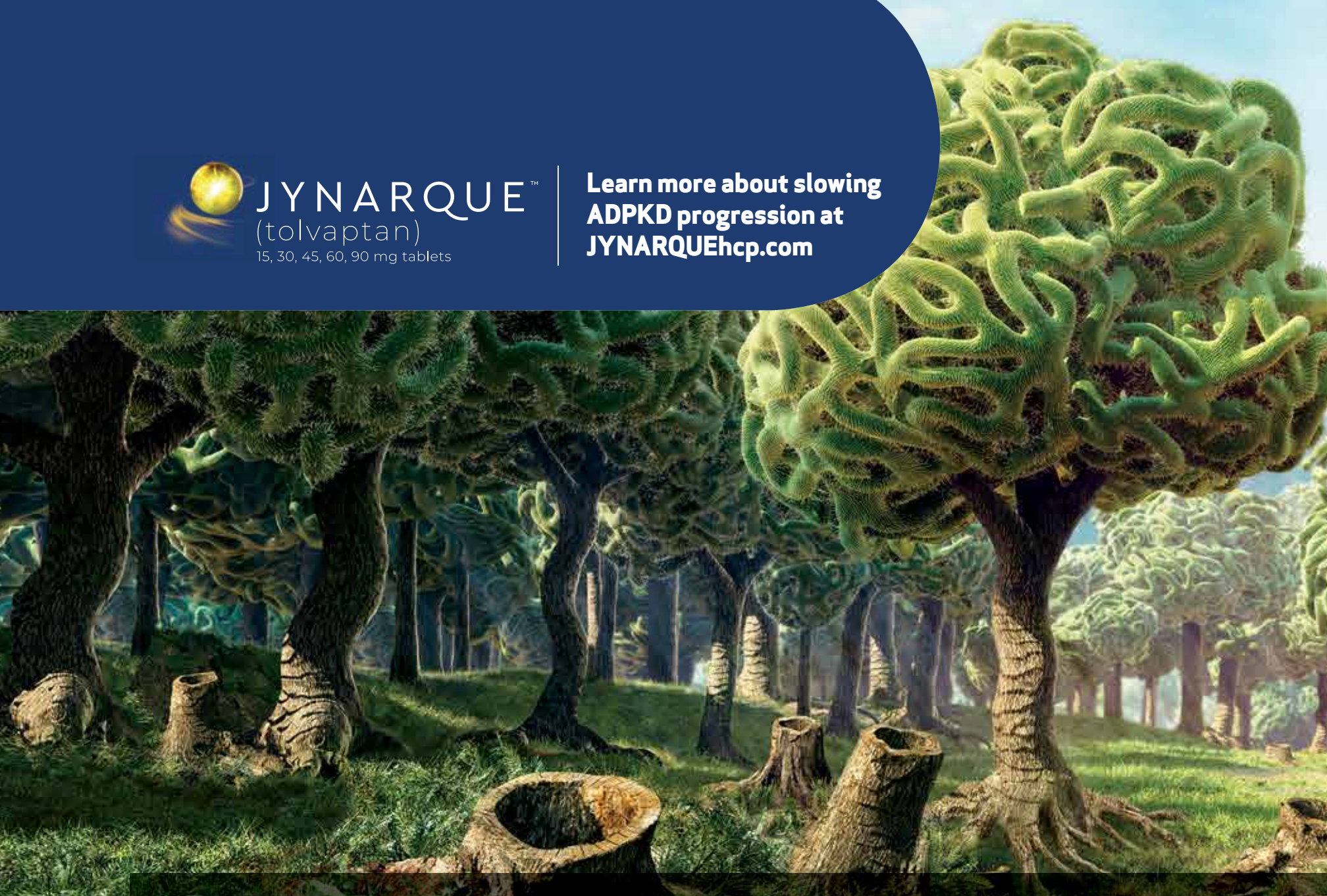
Anitha Vijayan, MD, is affiliated with the Division of Nephrology, Department of Medicine, Washington University, St. Louis, MO.

Reference

1. Thompson ND, et al. Hepatitis C virus transmission in hemodialysis units: importance of infection control practices and aseptic technique. *Infect Control Hosp Epidemiol* 2009; 30:900–903.

JYNARQUE™
(tolvaptan)
15, 30, 45, 60, 90 mg tablets

Learn more about slowing ADPKD progression at JYNARQUEhcp.com



INDICATION and IMPORTANT SAFETY INFORMATION for JYNARQUE™ (tolvaptan)

INDICATION:
JYNARQUE is indicated to slow kidney function decline in adults at risk of rapidly progressing autosomal dominant polycystic kidney disease (ADPKD).

IMPORTANT SAFETY INFORMATION:

WARNING: RISK OF SERIOUS LIVER INJURY

- **JYNARQUE (tolvaptan) can cause serious and potentially fatal liver injury. Acute liver failure requiring liver transplantation has been reported**
- **Measure transaminases (ALT, AST) and bilirubin before initiating treatment, at 2 weeks and 4 weeks after initiation, then monthly for the first 18 months and every 3 months thereafter. Prompt action in response to laboratory abnormalities, signs, or symptoms indicative of hepatic injury can mitigate, but not eliminate, the risk of serious hepatotoxicity.**
- **Because of the risks of serious liver injury, JYNARQUE is available only through a Risk Evaluation and Mitigation Strategy program called the JYNARQUE REMS Program**

CONTRAINDICATIONS:

- History, signs or symptoms of significant liver impairment or injury. This contraindication does not apply to uncomplicated polycystic liver disease
- Taking strong CYP3A inhibitors
- With uncorrected abnormal blood sodium concentrations
- Unable to sense or respond to thirst
- Hypovolemia
- Hypersensitivity (e.g., anaphylaxis, rash) to JYNARQUE or any component of the product
- Uncorrected urinary outflow obstruction
- Anuria

Serious Liver Injury: JYNARQUE can cause serious and potentially fatal liver injury. Acute liver failure requiring liver transplantation has been reported in the post-marketing ADPKD experience. Discontinuation in response to laboratory abnormalities or signs or symptoms of liver injury (such as fatigue, anorexia, nausea, right upper abdominal discomfort, vomiting, fever, rash, pruritus, icterus, dark urine or jaundice) can reduce the risk of severe hepatotoxicity. To reduce the risk of significant or irreversible liver injury, assess ALT, AST and bilirubin prior to initiating JYNARQUE, at 2 weeks and 4 weeks after initiation, then monthly for 18 months and every 3 months thereafter.

Hypernatremia, Dehydration and Hypovolemia: JYNARQUE therapy increases free water clearance which can lead to dehydration, hypovolemia and hypernatremia. Instruct patients to drink water when thirsty, and throughout the day and night if awake. Monitor for weight loss, tachycardia and hypotension because they may signal dehydration. Ensure abnormalities in sodium concentrations are corrected before initiating therapy. If serum sodium increases above normal or the patient becomes hypovolemic or dehydrated and fluid intake cannot be increased, suspend JYNARQUE until serum sodium, hydration status and volume status parameters are within the normal range.

HELP CONSERVE NEPHRON FUNCTION BY SLOWING THE DECLINE OF KIDNEY FUNCTION WITH THE FIRST AND ONLY FDA-APPROVED TREATMENT FOR ADPKD

JYNARQUE™ (tolvaptan) slows disease progression, so you can finally take a stand against ADPKD

ADPKD=autosomal dominant polycystic kidney disease.

Inhibitors of CYP3A: Concomitant use of JYNARQUE with drugs that are moderate or strong CYP3A inhibitors (e.g., ketoconazole, itraconazole, lopinavir/ritonavir, indinavir/ritonavir, ritonavir, and conivaptan) increases tolvaptan exposure. Use with strong CYP3A inhibitors is contraindicated; dose reduction of JYNARQUE is recommended for patients taking moderate CYP3A inhibitors. Patients should avoid grapefruit juice beverages while taking JYNARQUE.

Adverse Reactions: Most common observed adverse reactions with JYNARQUE (incidence >10% and at least twice that for placebo) were thirst, polyuria, nocturia, pollakiuria and polydipsia.

Other Drug Interactions:

- **Strong CYP3A Inducers:** Co-administration with strong CYP3A inducers reduces exposure to JYNARQUE. Avoid concomitant use of JYNARQUE with strong CYP3A inducers
- **OATP1B1/3 and OAT3 Transporter Substrates:** Patients who take JYNARQUE should avoid concomitant use with OATP1B1/B3 and OAT3 substrates (e.g., statins, bosentan, glyburide, nateglinide, repaglinide, methotrexate, furosemide), as the plasma concentrations of these substrates may be increased.
- **BCRP Transporter Substrates:** Tolvaptan is an inhibitor of BCRP. Patients who take JYNARQUE, should avoid concomitant use with BCRP substrates (e.g., rosuvastatin)
- **V_2-Receptor Agonist:** Tolvaptan interferes with the V_2-agonist activity of desmopressin (dDAVP). Avoid concomitant use of JYNARQUE with a V_2-agonist.

Pregnancy and Lactation: Based on animal data, JYNARQUE may cause fetal harm. In general, JYNARQUE should be discontinued during pregnancy. Advise women not to breastfeed during treatment with JYNARQUE.

To report SUSPECTED ADVERSE REACTIONS, contact Otsuka America Pharmaceutical, Inc. at 1-800-438-9927 or FDA at 1-800-FDA-1088 (www.fda.gov/medwatch).

Please see Brief Summary of FULL PRESCRIBING INFORMATION, including **BOXED WARNING**, on the following pages.

Otsuka

Otsuka America Pharmaceutical, Inc.

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June 2018 10US18EBP0160

FDA Approves Two New AV Fistula Devices

The U.S. Food and Drug Administration (FDA) has granted marketing approval for two catheter devices used in dialysis. Both the everlinQ endoAVF System, which uses two catheters, and the Ellipsys Vascular Access System with a single catheter are designed to create arteriovenous (AV) fistulas, using an energy source to forge the connection between blood vessels in a patient's arm. Traditionally a central venous catheter for dialysis patients is created through a surgical process. An AV graft uses a tube or cadaveric blood vessel to create a bridge between artery and vein.

The FDA reviewed data for the everlinQ endoAVF System from a non-randomized, multi-center study of 60 patients, and also considered supporting data from three other studies. The device has been used by clinicians outside the United States.

TVA Medical (Austin, TX) manufactures the everlinQ system, which works as a series of spaced magnets in each catheter, one venous and one arterial, that are designed to attract and align. The patient is then ready for a radiofrequency pulse deployed at the desired spot between the close brachial (arm) blood vessels.

In the main study of the everlinQ endoAVF System, 52 patients (86.7%) met the criteria for a usable AV fistula within three months after the procedure. Almost all patients (96.7%) required an additional procedure at the time the fistula was created, and 28.3% of patients required an additional procedure (such as balloon angioplasty) in the first 12 months to maintain the fistula, the FDA noted.

The Ellipsys Vascular Access System is a product of Avenu Medical, based in San Juan Capistrano, CA. The single catheter delivers a small amount of thermal energy that fuses a permanent connection between the vein and artery.

The FDA reviewed data from a non-randomized, U.S. multicenter study of 103 patients, of whom 92 patients (89.3%) met the criteria for a usable AV fistula within three months. Almost all patients (96.1%) required an additional procedure (such as balloon angioplasty) in the first 12 months, the FDA reported.

Both systems were reviewed through the De Novo premarket review pathway for low-to-moderate risk devices of a new type.

Akebia and Keryx to Merge by Year's End

A new company is forming to produce treatments for patients with chronic kidney disease (CKD). Subject to antitrust considerations, the merger of Akebia Therapeutics (Cambridge, MA) and Keryx Biopharmaceuticals (Boston, MA) is expected to be complete by the end of the year. The new company will be called Akebia Therapeutics.

The merger is valued at $1.3 billion, notes Pitchbook, a financial newsletter. Under terms of the merger, Akebia shareholders will own a bit more than half of the combined firm, the website FierceBiotech reported.

The strategy behind the merger is severalfold. First, the merger establishes a renal company with an enhanced market position that neither company has alone. The combined company will open a larger marketplace, including Akebia's product candidate, Vadadustat (for anemia treatment) and Keryx's Auryxia, which is FDA approved for the control of serum phosphorus levels in adults with CKD who are on dialysis. According to a joint news release about the merger, the combined company will "provide nephrologists with a portfolio of renal products." Vadadustat is up for FDA approval.

The merging companies said they will have the potential to help patients across all stages of CKD, including both those who need and those who don't need dialysis, and could become a partner for the renal patient community as well as for companies developing renal products.

The merger will result in a new management team that has been developing and commercializing products for patients with kidney disease. John P. Butler, current CEO of Akebia, will lead as CEO. He formerly led Genzyme Corporation's renal business.

Keryx will appoint the chairperson of the Board of Directors of the combined company.

The new company will have $453 million in cash plus the potential for increasing revenues from Auryxia sales and cost synergies expected to be in the neighborhood of more than $250 million, according to Keryx and Akebia.

Up and Comer in Progressive Kidney Disease

XORTX Therapeutics, a company founded to focus on developing therapies to treat progressive kidney disease, has filed a pre-IND (Investigational New Drug) meeting request with the FDA. The company, based in Calgary, Alberta, filed pre-IND documents and secured a September 2018 meeting with the FDA to discuss development of its compound, XRx-008, for the treatment of autosomal dominant polycystic kidney disease (ADPKD). The company currently plans to advance XRx-008 through phase 2 clinical trials.

Said XORTX's CEO Allen Davidoff, MD: "We are excited to take this important first regulatory step in the development of the XRx-008 program for ADPKD. This request initiates the process of establishing communication and discussion with the FDA regarding our phase 2 clinical trial plans and defining the critical path for clinical development and marketing approval of this therapy for PKD patients."

In 2018 the company has been advancing its two key programs: the ADPKD program and the diabetic nephropathy program through phase 2 proof-of-concept clinical trials.

The company's stated aim is to identify and assess acquisition opportunities of companies that "have products for unmet needs and a higher than average probability of success."

XORTX is continuing to partner with emerging and large pharma companies through opportunities to co-develop drugs and is in-licensing as a way to pursue corporate partnerships. In-licensing occurs when a company takes on some of the financial or technological work of developing a product, in return for a share of sales revenue.

Expanding its outlook in the renal community, XORTX has also paired with the Polycystic Kidney Disease Foundation to support patients, the company announced.

Diabetes Drug Roundup

Manufacturers of two different diabetes drugs have reported positive results recently.

Jardiance (empagliflozin) consistently reduced the risk of new or worsening kidney disease versus placebo, reported a two-member diabetes pharmaceutical alliance.

Boehringer Ingelheim (Ridgefield, CT) and Eli Lilly (Indianapolis) joined forces in 2011 to form an alliance that centers on compounds in "several of the largest diabetes treatment classes," the companies noted.

The companies shared findings from two new analyses from the long-term EMPA-REG OUTCOME trial of empagliflozin. One analysis showed that patients taking the drug consistently reduced the risk of new or worsening kidney disease when compared with patients taking placebo. This finding held regardless of level of control over blood pressure, level of low-density lipoprotein cholesterol or HbA1C levels, individually or combined, and other factors, Nasdaq.com reported.

A separate analysis showed a consistent reduction in the risk of cardiovascular death compared with placebo in patients stratified to low, intermediate, high, and highest cardiovascular risk groups, MD magazine reported. Likewise, there were similar reductions in the risk of hospitalization for heart failure among the patient groups taking empagliflozin.

At the 2018 American Diabetes Association (ADA) 78th Scientific Sessions in Orlando, FL, Rogelio Braceras, MD, therapeutic area head of Clinical Development and Medical Affairs (Metabolism) for Boehringer Ingelheim, said the results on Jardiance are "very reassuring, very informative, because we are doing the CVD outcome studies for heart failure and also for kidney programs through the EMPA-REG," a trial in 42 countries, MD magazine reported.

In a study published online in Lancet *Diabetes & Endocrinology* (1), researchers from the United States and Australia found that canagliflozin, marketed as Invokana by Janssen Pharmaceuticals (Johnson & Johnson, J&J) reduced kidney decline and albuminuria more than a placebo treatment.The research team assessed a number of kidney markers including end stage renal disease, with results from two studies taken between November 2009 and March 2011 and between January 2014 and May 2015.

Reference

1. Perkovic V, et al. Canagliflozin and renal outcomes in type 2 diabetes: results from the CANVAS Program randomised clinical trials. *Lancet Diabetes Endocrinol* 2018; DOI: https://doi.org/10.1016/S2213-8587(18)30141-4

Findings

New Model Predicts Time to ESRD in Pediatric CKD

A new "six-risk-stage model" provides useful prognostic information for estimating time to end stage renal disease (ESRD) in children with chronic kidney disease (CKD), reports a study in the *American Journal of Kidney Diseases*.

The analysis included data on 1169 children and adolescents enrolled in North American and European multicenter study cohorts: the Chronic Kidney Disease in Children (CKiD) study and the Effect of Strict Blood Pressure Control and ACE Inhibition on the Progression of CRF in Pediatric Patients (ESCAPE) trial. Patients were classified according to three variables: glomerular filtration rate (GFR), estimated using the CKiD "beside" equation; proteinuria, measured as first-morning urine protein-creatinine ratio (UPCR); and glomerular versus nonglomerular CKD diagnosis.

The investigators used these characteristics to define unique categories of CKD progression risk, along with estimated timelines to progression. The study definition of CKD progression was a composite of a 50% reduction in baseline GFR, decrease in eGFR to less than 15 mL/min/1.73 m^2, and/or dialysis or transplantation.

The patients were 707 males and 462 females, median age 12 years. All had a baseline eGFR of greater than 15 mL/min/1.73 m^2, with a median value of 47 mL/min/1.73 m^2. Initial UPCR was greater than 2.0 mg/mg in 13% of patients; 75% had nonglomerular diagnoses.

Median time to CKD progression exceeded 10 years for children with an eGFR of 45 to 90 mL/min/1.73 m^2 and UPCR less than 0.5 mg/mg. In contrast, for those with an eGFR of 15 to 30 mL/min/1.73 m^2 with a UPCR of greater than 2 mg/mg, median time to progression was 0.8 years. Within the various risk stages, time to progression was 43% shorter for children with nonglomerular CKD.

Pediatric CKD is an uncommon problem associated with reduced life expectancy and high costs. The Kidney Disease: Improving Global Outcomes (KDIGO) classification system was developed to predict the risk of adverse outcomes and guide management strategies for adults with CKD. The researchers sought to develop a modified KDIGO classification system for pediatric CKD.

Their model provides useful prognostic information and "excellent discrimination" for predicting CKD progression in children with CKD. They call for further studies, including external validation (rather than cross-validation) of the pediatric CKD classification system.

"This classification system can be used as an adjunct to clinical judgment in planning for timing of transplantation evaluation or dialysis access placement," the researchers write. The online version of their article includes a printable page summarizing the six risk groups and their associated times to CKD progression events [Furth SL, et al. Estimating time to ESRD in children with CKD. *Am J Kidney Dis* 2018; 71:783–792].

Sunitinib without Nephrectomy for Metastatic Renal Cell Carcinoma

For patients receiving targeted therapies for metastatic renal cell carcinoma, outcomes are similar with sunitinib alone versus nephrectomy followed by sunitinib, concludes a trial in *The New England Journal of Medicine*.

The phase 3 randomized Clinical Trial to Assess the Importance of Nephrectomy (CARMENA) included 450 patients with biopsy-confirmed metastatic renal cell carcinoma, enrolled at 79 centers in France and other European countries. All were suitable candidates for nephrectomy followed by sunitinib. Memorial Sloan Kettering Cancer Center risk category was intermediate risk in about 58% of patients and poor risk in 42%.

After risk stratification, patients were assigned in a 1:1 ratio to nephrectomy followed by sunitinib (standard treatment) or sunitinib alone. Sunitinib dose schedule was 50 mg daily in cycles of 28 days on and 14 days off every 6 weeks. The main study endpoint was overall survival.

At planned interim analysis, with a median follow-up of 50.9 months, 326 patients had died. There was no significant difference in overall survival—the stratified hazard ratio for death fell below the specified boundary for noninferiority. Median overall survival was longer with sunitinib alone versus nephrectomy followed by sunitinib: 23.4 versus 19.0 months in the intermediate-risk group and 13.3 versus 10.2 months in the poor-risk group.

Response rate and progression-free survival were similar with or without nephrectomy. There was evidence of clinical benefit in 47.9% of patients in the sunitinib-alone group versus 36.6% in the nephrectomy-sunitinib group. Adverse events were as expected; dose reduction occurred in about 30% of both groups.

Cytoreductive nephrectomy has long been the standard of care for metastatic renal cell carcinoma. In recent years, new targeted therapies have emerged, including the vascular endothelial growth factor receptor inhibitor sunitinib. Few previous studies have directly compared the benefits of nephrectomy versus targeted therapy.

This randomized trial finds sunitinib alone noninferior to nephrectomy followed by sunitinib in patients with intermediate- or poor-risk metastatic renal cell carcinoma. The findings contrast with those of retrospective studies reporting a survival benefit of nephrectomy in patients receiving targeted therapies.

"Although nephrectomy may have a role in controlling symptoms in some patients…there is no 'one size fits all' approach," the investigators conclude [Méjean A, et al. Sunitinib alone or after nephrectomy in metastatic renal cell carcinoma. *N Engl J Med* 2018; DOI: 10.1056/NEJMoa1803675].

"Emergency-Only Dialysis" Policy Puts Burdens on Clinicians

Following emergency-only hemodialysis (EOHD) policies for undocumented immigrants causes moral distress and may contribute to burnout among healthcare professionals at safety-net hospitals, reports a qualitative study in *Annals of Internal Medicine*.

The researchers interviewed 50 physicians, nurses, and other clinicians at safety-net hospitals/systems in two cities (Denver and Houston) that provided a high volume of EOHD for undocumented patients. Thematic analysis was performed to describe the experiences and perspectives of clinicians providing this type of care.

Four major themes were identified. Emergency-only dialysis policies contributed to drivers of professional burnout, with healthcare professionals experiencing emotional exhaustion related to patients' "needless suffering" and high mortality. Clinicians felt they had to "emotionally dissociate" themselves due to a policy that was not under their control. They also reported mortal distress related to EOHD policies. All participants felt that it was unethical to make care decisions based on nonmedical factors, and felt justified in "bending the rules."

Clinicians were frustrated over the "confusing and perverse" financial incentives associated with EOHD, which they viewed as an inefficient and unsustainable use of hospital and system resources. Despite their distress and frustrations, the healthcare professionals felt inspired by their patients' resilience, kindness, and gratitude. Clinicians felt that working with these patients provided them an opportunity to act according to their best instincts and "motivated them to advocacy."

In many states, undocumented immigrants with ESRD do not receive dialysis until they develop life-threatening renal failure. This EOHD policy leads to high mortality and distress for patients, but little is known about its impact on clinicians.

"The burden on clinicians of providing EOHD should inform policy discussions and systemic approaches to support provision of an adequate standard of care to all patients with ESKD," the investigators said. [Cervantes L, et al. Clinicians' perspectives on providing emergency-only hemodialysis to undocumented immigrants: a qualitative study. *Ann Intern Med* 2018; DOI: 10.7326/M18-0400].

FGF-23 Does Not Predict Renal Function Decline in Older Adults

Fibroblast growth factor 23 (FGF-23) does not consistently predict declining kidney function or development of CKD in healthy older adults, reports a study in *Kidney International*.

The analysis included 2496 well-functioning older adults, aged 70 to 79 years at baseline, enrolled in the prospective Healthy Aging and Body Composition study. Fifty-two percent of participants were women and 38% were black. Levels of FGF-23, measured using a commercial assay, were analyzed as a predictor of subsequent decline in kidney function and incident CKD (based on repeated measurements of cystatin C).

The median FGF-23 value was 46 pg/mL; participants with higher FGF-23 levels were more likely to have comorbid conditions including diabetes, hypertension, coronary artery disease, and heart failure. About 28% of older adults had an eGFR decline of greater than 3 mL/min/year, 16% had a 30% decline in kidney function, and 21% had incident CKD.

With adjustment for baseline kidney function and a wide range of other variables, doubling of FGF-23 was not related to any of the three measures of kidney function decline. Participants in the highest quartile of FGF-23 were more likely to develop CKD, compared to those in the lowest quartile: incident rate ratio 1.27. There were no significant interactions between FGF-23 and incident CKD.

Previous studies have reported that FGF-23 is a risk factor for the development of ESRD. Less is known about this hormone's association with earlier signs of progressive kidney disease.

The new study suggests that FGF-23 is not a strong independent risk factor for declining kidney function or incident CKD in community-dwelling older adults. Initial associations are weakened by adjustment for comorbid conditions, kidney disease risk factors, and indicators of mineral metabolism. The results "suggest that FGF-23 may be a marker of kidney health or function, rather than a mediator of kidney damage, the researchers write [Drew DA, et al. Fibroblast growth factor 23: a biomarker of kidney function decline. *Am J Nephrol* 2018; 47:242–250].

High Risk of Complications with Urethral Catheters

Close to 60% of patients undergoing placement of an indwelling urethral catheter experience complications—mainly noninfectious—within 30 days, reports a study in *JAMA Internal Medicine*.

The prospective cohort study included 2967 patients undergoing new insertion of an indwelling urethral catheter at four US hospitals (including two VA medical centers) over a 2-year period. All were enrolled within 3 days after catheter placement. Patients underwent a baseline examination, with follow-up contacts at 14 and 30 days after insertion. In addition to catheter-related infectious and noninfectious complications, the study assessed impact on activities of daily living, social activities, and general comfort.

About three-fourths of patients agreed to participate. Of the 2076 patients included in the analysis, 71.4% were male; the mean age was 68 years. Catheters were placed before surgical procedures in 79.6% of patients. In 76.0% of patients, catheters were removed within 3 days.

Overall, 57.0% of patients reported at least one complication during the 30 days after catheter insertion. Noninfectious complications such as pain/discomfort, blood in urine, or a sense of urinary urgency occurred in 55.4% of patients, while the rate of infectious complications was 10.5%.

Women were more likely to report infectious complications, 15.5% versus 8.6%; but men were more likely to report noninfectious complications, 58.6% versus 47.3%. Of 124 patients with a catheter still in place, 39.5% reported restrictions in activities of daily living while 43.9% reported social limitations.

Sexual problems after catheter removal were reported by 4.9% of patients. Both infectious and noninfectious complications were more likely to be reported by patients with moderate and severe American Urological Association symptom scores at baseline and in those with urinary catheter duration of longer than 3 days.

Indwelling urethral (Foley) catheters are widely used in the care of hospitalized patients. Infectious complications related to urethral catheters are well recognized; however, relatively little is known about the noninfectious complications that may occur with these invasive devices.

This prospective cohort study finds a 57% rate of complications in patients undergoing indwelling urethral catheter placement. Noninfectious complications are five times more frequent than noninfectious complications. Patients with catheters in place report high rates of restrictions in activities of daily living and social activities.

The authors note that their active follow-up study identified complications of concern to patients that occur outside the hospital setting. The investigators conclude:

"In light of the frequency with which urethral catheters are used, we should consider not only infectious complications but also the noninfectious complications associated with these catheters as key areas of possible harms and thus vital targets for future prevention efforts" [Saint S, et al. A multicenter study of patient-reported infectious and noninfectious complications associated with indwelling urethral catheters. *JAMA Intern Med* 2018 doi:10.1001/jamainternmed.2018.2417].

'TAKE-IT' Improves Adherence in Young Kidney Recipients

A teen adherence intervention improves the use of prescribed immunosuppressive medications in adolescent and young adult kidney transplant recipients, reports a randomized trial in the *American Journal of Kidney Diseases*.

The "Teen Adherence in Kidney Transplant Effectiveness of Intervention Trial" (TAKE-IT) included 169 prevalent kidney transplant recipients, aged 11 to 24 years. Patients were enrolled at least 3 months after transplantation at eight North American transplant centers between 2012 and 2016. One group was assigned to the TAKE-IT intervention, which included text, e-mail, and/or visual cue dose reminders. Every 3 months, patients met with a coach for review of adherence data. The intervention included an "Action-Focused Problem Solving" approach to address barriers to adherence identified by the patient.

Control patients met with coaches every 3 months but did not receive feedback on adherence. Males accounted for 57% of patients in the TAKE-IT group and 61% in the control group; median ages were 15.5 and 15.8 years, respectively. Adherence was electronically measured in terms of the proportion of prescribed doses taken as well as the timing of medication doses (between 1 hour before and 2 hours after the recommended time).

The analysis included electronic adherence data on 64 intervention patients and 74 control patients. Both adherence measures were better in the TAKE-IT group: odds ratio 1.66 for taking prescribed medications and 1.74 for taking doses at or near the prescribed time.

Self-reported adherence was high and similar between groups. There was no difference in the standard deviation of tacrolimus trough concentrations. No graft failures occurred. There were nonsignificantly fewer episodes of acute rejection in the intervention group. Statistical power for clinical outcomes was low.

Among kidney transplant recipients, graft failure rates are highest between the ages of 17 and 24 years. Low adherence to immunosuppressive drugs is thought to be an important contributor to graft failure in this age group.

The TAKE-IT intervention leads to improved adherence in adolescent and young adult kidney transplant recipients. Larger studies will be needed to show that interventions to improve medication adherence will lead to better graft outcomes [Foster BJ, et al. A randomized trial of a multicomponent intervention to promote medication adherence: The Teen Adherence in Kidney Transplant Effectiveness of Intervention Trial (TAKE-IT). *Am J Kidney Dis* 2018; 72:30–41].

ure-Na™

*Oral Urea **Made Palatable***

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Real world experience on the use of ure-Na was presented independently at the 2018 annual meeting of the National Kidney Foundation.

The team from University of Pittsburgh reported the following primary findings:

UREA IN THE TREATMENT OF HYPONATREMIA: THE FIRST REPORTED U.S. INPATIENT EXPERIENCE

- 58 patients received ure-Na for hyponatremia. 14 patients received ure-Na as monotherapy.
- 57 of 58 patients tolerated ure-Na.
- SIADH was the most common cause of hyponatremia.
- Dose of urea ranged from 7.5 to 90 g per day, with a median duration of treatment of 4.5 days.
- Ure-Na therapy was associated with a median increase in plasma sodium from 124 mEq/L to 130.5 mEq/L ($p<0.001$) with no over-correction.
- No adverse effects were reported.
- Overall, treatment with ure-Na was found to be well tolerated, safe and effective for the treatment of inpatient hyponatremia.
- Nephcentric, the developer of ure-Na did not sponsor or have prior knowledge of this presentation.

Please see the Physicians section of ure-na.com for a link to the poster that was presented.

*The European Clinical Practice Guideline on the management of hyponatremia recommend the use of oral urea as a treatment option in SIADH for moderate to profound hyponatremia. UpToDate also reviews the use of urea as a management option for hyponatremia.

Learn more about the use of urea and ure-Na for hyponatremia at ure-na.com

For samples of ure-Na please see the sample order section of nephcentric.com.

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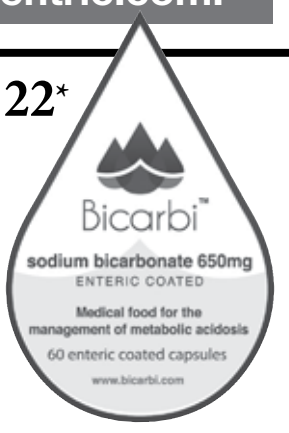

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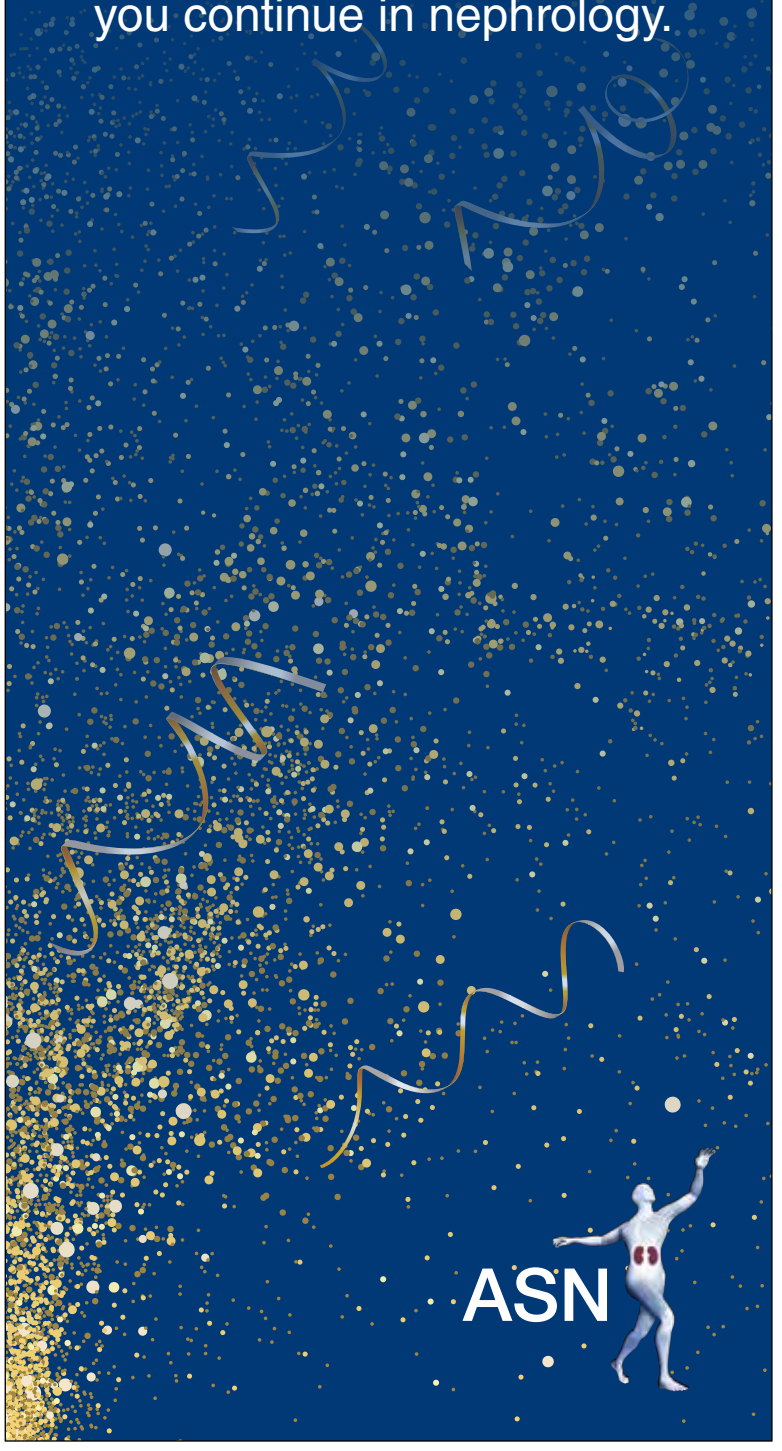
Congrats to FELLOWS

The American Society of Nephrology (ASN) would like to congratulate this year's Fellow members for completing their fellowship membership.

We thank you for your participation with ASN and look forward to serving you as you continue in nephrology.



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Index to Advertisers

BRIEF SUMMARY OF PRESCRIBING INFORMATION

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

Please see package insert for full Prescribing Information.

INDICATIONS AND USAGE

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

Limitations of Use:

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

CONTRAINDICATIONS

Hypersensitivity

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

WARNINGS AND PRECAUTIONS

Hypocalcemia

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

QT Interval Prolongation and Ventricular Arrhythmia

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

Seizures

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

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

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

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

Worsening Heart Failure

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

Upper Gastrointestinal Bleeding

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

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

Adynamic Bone

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

ADVERSE REACTIONS

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

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

Clinical Trials Experience

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

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

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

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

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

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

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

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

[c] Paresthesia includes preferred terms of paresthesia and hypoesthesia

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

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

Description of Selected Adverse Reactions

Hypocalcemia

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

Hypophosphatemia

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

QTc Interval Prolongation Secondary to Hypocalcemia

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

Hypersensitivity

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

Immunogenicity

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

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

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

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

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

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

Data

Animal Data

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

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

Lactation

Risk Summary

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

Data

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

Pediatric Use

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

Geriatric Use

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

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

OVERDOSAGE

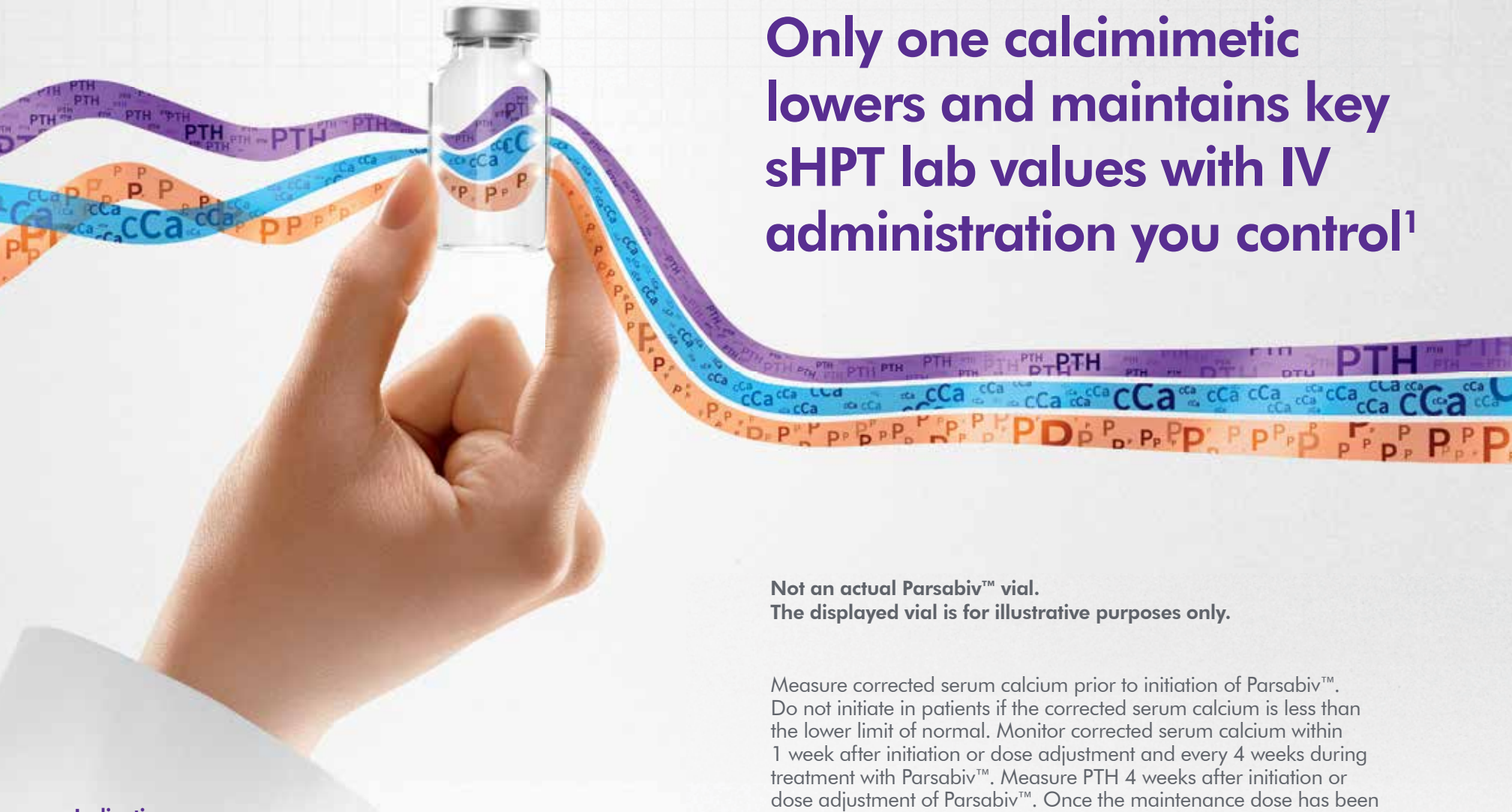
There is no clinical experience with PARSABIV overdosage. Overdosage of PARSABIV may lead to hypocalcemia with or without clinical symptoms and may require treatment. Although PARSABIV is cleared by dialysis, hemodialysis has not been studied as a treatment for PARSABIV overdosage. In the event of overdosage,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

AMGEN®

PARSABIV™ (etelcalcetide)

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

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



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.

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.

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.

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

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

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

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

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

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

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

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

Parsabiv™
(etelcalcetide) Injection for intravenous use
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Visit **ParsabivHCP.com** for more information.