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Health Institutions At Risk From Repeat Ransomware Attacks

By Bridget M. Kuehn

The high profile WannaCry and Petya ransomware attacks in 2017 brought institutions—including major health systems—around the world to a screeching halt and drew attention to the rising cybersecurity threats facing healthcare.

In fact, the nonprofit ECRI Institute named ransomware and other malicious software its top health technology hazard for 2018. Hackers use these computer programs to infiltrate an organization's network and prevent the organization from accessing its electronic medical records or online systems. The attackers then demand a ransom to stop the attack. These attacks can bring normal hospital operations to a halt causing delays in patient care that could threaten patient safety, said Juuso Leinonen, senior project engineer in the ECRI Institute's Health Devices Group.

"This is a problem and there's probably no hospital that's completely immune to it," Leinonen said.

Healthcare has become the top target for such attacks, according to a survey of 2700 Internet Technology (IT) managers by network security company Sophos. Three-quarters of healthcare institutions that responded to the survey had been victims of ransomware attacks, even though more than half had systems in place to prevent them. Across sectors, the average cost of an attack was $133,000 and affected organizations often face repeat attacks.

Vulnerable systems

Healthcare organizations often are easier targets than organizations in other industries that have worked to harden their defenses, explained James Scott, senior fellow at the nonprofit Institute for Critical Infrastructure Technology (ICIT) in Washington, DC. Hospitals may not have leaders who are well versed in cybersecurity and their frontline information technology staff may not have the right expertise and training to ward off attacks, he said.

"The nature of 24/7 patient care also makes routine IT maintenance tasks more difficult to achieve," said Andrew Mundell, a security architect at Sophos.

Growing use of networked medical devices is another challenge, Leinonen noted. These expensive devices may have lifespans that stretch for a decade, he said. Some hospital devices may still require manual updates; others may be so old new security patches are no longer available.

"The reality is that there are thousands of medical devices in most healthcare institutions from hundreds of different vendors and potentially each one of those devices

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KidneyX Accelerator Holds Promise for Fostering, Speeding Innovations in Kidney Care

A new effort to foster the development of innovative technologies and therapeutics in the kidney space is on the horizon.

A signed Memorandum of Understanding between ASN and the U.S. Department of Health and Human Services (HHS) established the Kidney Innovation Accelerator (KidneyX), a public-private partnership. KidneyX aims to prevent kidney diseases while improving the lives of the 850,000,000 people worldwide who are currently affected by accelerating innovation in the prevention, diagnosis, and treatment of kidney diseases. KidneyX will award prize funding to promising companies, enabling and accelerating the commercialization of more products to benefit people with and at risk for kidney diseases. Building off the success of similar public-private accelerators, KidneyX will engage a community of researchers, innovators, and investors to bring breakthrough therapies to patients.

With KidneyX, "HHS sends an important message to investors and innovators regarding the desire and demand for new therapies," said HHS Chief Technology Officer Bruce D. Greenstein, who announced HHS's commit-

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Inside

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Speeding Innovations

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ment to launching KidneyX in partnership with ASN and the broader medical community at ASN Kidney Week 2017.

KidneyX will use a three-pronged approach to address the barriers innovators commonly identify as they look to bring new drugs and technologies in kidney care to market, bridging the gap between research and market-ready products.

First, the Accelerator will provide merit-based, non-dilutive funding to promising innovators selected through a competitive process. This funding will incentivize the accelerated development and commercialization of disruptive technologies in kidney care, such as a next-generation kidney.

Second, KidneyX will encourage better coordination across HHS with the National Institutes of Health (NIH), Food and Drug Administration (FDA), and Centers for Medicare & Medicaid Services (CMS) in order to help clarify the path toward commercialization.

The third prong of KidneyX's approach to accelerate innovation in kidney care is to create a sense of urgency to develop new therapies, much like the sense of urgency associated with other areas of healthcare including oncology, neuroscience, heart disease, and diabetes. An important part of this effort will be increasing interactions with the venture capital community and other investors who have previously shied away from the kidney space.

By opening pathways of collaboration among science, engineering, finance, and other disciplines, KidneyX aims to bring that same sense of urgency to innovators and investors.

"The urgency to develop better therapies and, ultimately, cures, is palpable to patients and their families on a daily basis. ASN applauds the commitment of HHS to fight kidney diseases, and is proud to partner with them in launching KidneyX and generating real change within the kidney community," noted Mark D. Okusa, MD, FASN, ASN President.

The Kidney Health Initiative's (KHI) *Development of a Roadmap for Innovation in Renal Replacement Therapy* project will serve as a resource for KidneyX. The KHI project aims to describe scientific, technical, and regulatory milestones needed to achieve the goal of creating a bioartificial or bioengineered alternative to dialysis as renal replacement therapy.

KidneyX's first round of prize funding will focus on accelerating the commercialization of next-generation dialysis products and will begin accepting applications in late summer 2018. Individuals who are interested in learning more about KidneyX are encouraged to visit www.kidneyx.org and join our mailing list.

What is the Kidney Innovation Accelerator?

Mission: Accelerate innovation in the prevention, diagnosis, and treatment of kidney diseases

KidneyX Principles

- **Patient-Centered** Ensure all product development is patient-centered
- **Urgent** Create a sense of urgency to meet the needs of people with kidney diseases
- **Achievable** Ground in scientifically driven technology development
- **Catalytic** Reduce regulatory and financial risks to catalyze investment in the kidney space
- **Collaborative** Foster multidisciplinary collaboration including innovators throughout science and technology, the business community, patients, care partners, and other stakeholders
- **Additive** Address barriers to innovation public/private sectors do not otherwise address
- **Sustainable** Invest in a diverse portfolio to balance risk and sustain KidneyX

Ransomware Attacks

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could have their own security requirements or patching requirements so that definitely makes it a significant problem and very difficult to manage," Leinonen said.

Smaller healthcare organizations like physicians' offices or dialysis centers may be at even greater risk, said Mundell.

"[Small organizations] are likely to have smaller IT and security teams working to combat the latest threat," he said.

Once an organization has been compromised, they are likely to face repeated attacks, according to the Sophos report. They may be re-infected by the same malicious software if the organization fails to properly remove it from the system, Mundell said. After an organization pays a ransom, attackers may increase the number or sophistication of their attacks in the hopes of securing another ransom.

Very sophisticated hackers may use a ransomware attack as distraction, so they can establish remote access to medical records or other data that they can later extract undetected, Scott said. Patient information such as Social Security numbers, credit card numbers, or health insurance credentials can be sold to would-be identity thieves for $20-$1300 depending on how much information is offered, according to an ICIT report.

"The fact that there is a lot of sensitive data in a healthcare institution makes it inherently risky and appropriate controls need to be in place to make sure that data is protected both on your medical devices as well as in your other systems," Leinonen said.

The reality is that there are thousands of medical devices in most healthcare institutions from hundreds of different vendors and potentially each one of those devices could have their own security requirements.
—Juuso Leinonen

Data defenses

There are many steps that healthcare organizations of all sizes should be taking to protect against ransomware and other online threats. Some may require substantial time and financial resources, but experts say they are essential.

"You are investing for the future," said Michelle De Mooy, director of the Privacy & Data Project at the Center for Democracy and Technology. "You are protecting your patients' privacy and the integrity of your data."

Organizations should do a risk or security audit to help them identify their vulnerabilities, De Mooy recommended. Institutions should encrypt their data and have backup systems in place, she said. They should also ensure that all employees are adequately trained to recognize potential threats, such as suspicious links in e-mails or files ending in .exe.

They should also have a complete inventory of all networked medical devices, the software they use, and records of system updates, Leinonen said. He and his ECRI colleagues frequently field questions from hospitals hit by ransomware attacks about which devices may be vulnerable. Too often these facilities don't have the information they need to quickly identify devices at risk.

"Knowing what you have is almost a requirement to protecting them effectively," he said.

They should consider security when they purchase new medical devices, Leinonen said. These decisions should be made with input from frontline medical staff, IT staff, and the Chief Information Officer.

Facilities should aim to have a multi-layered defense against attacks, Scott said, so that attackers "give up and move on." He emphasized the importance of investing in qualified IT staff and hiring an in-house or outsourced threat-hunting team that can proactively test for weaknesses, seek out hackers in the system, and patch vulnerabilities.

Leinonen emphasized the need to adequately budget for data and systems security in order to preserve smooth operations.

"The reality today is that things are going to get more and more connected and this is going to be more of a significant concern as time goes on," he said. "This is not solely an IT problem, this is something where anybody, everybody from C-Suite to frontend clinicians can and should have a role to positively contribute overall to managing the security risks that may exist within the organization."

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

The Role of the Community in Improving Care for Chronic Kidney Disease

By Reverend Kimberly Headley

The Rogosin Institute hosted its annual symposium and follow-up roundtable on the topic "New Models for the Prevention and Better Management of Kidney Disease: Saving Lives, Improving Quality, Reducing Costs" in late 2017. The speakers at the symposium and the participants in the roundtable represented a cross-section of patients, payers, providers, and community representatives, all of whom were concerned with both the prevention and the better care of kidney disease.

A critical question addressed at these sessions was the role of the community itself in realizing these objectives. Whereas the tendency has been to regard the community's role as that of passive recipients of healthcare information and services, the following article by a representative of the Brownsville/East New York (Brooklyn) New York City communities and a roundtable participant demonstrates that the community can, and should, have an important role in models designed to prevent and improve the management of kidney disease, and in the reduction of health disparities more generally.

—Glenda Payne, series editor

Am I my brother's or my sister's keeper?

I live in a community with minimal services offered to those residents who struggle with unemployment and inadequate healthcare. I live in a community where the life expectancy is 10 years less than in other parts of Brooklyn and Manhattan. I live in a community where the infant mortality rate is twice that of Brooklyn as a whole and eight times that of Manhattan's Upper East Side. Here the premature mortality rate is twice that of Brooklyn and New York City as a whole and five times that of Manhattan's financial district.

In my community, one in every six adults has type 2 diabetes, and the top 10 causes of death are higher in every category than in New York City as a whole (NYC Department of Mental Health and Hygiene Vital Statistics, 2015).

Yet, this is Brooklyn, the "New Manhattan." This is "*New York, concrete jungle where dreams are made of; there's nothing you can't do. Now you're in New York.*" This may be the dream many aspire to as they hum Alicia Keys's intoxicating refrain to the urban anthem, "Empire State of Mind," but for those who live in Central Brooklyn, where the mortality rate is much less hopeful than that of the entire city, something is very wrong.

The disparities in health statistics are clear. How to reduce them and improve both health and quality of life for everyone is the question. Mobilizing individuals, families, and communities to assume more responsibility for their own well-being and empowering them to become part of the solution to achieving better health, even in the face of limited resources and suboptimal services, is important.

To achieve the aim of better health, community-based organizations in Brownsville and East New York (Brooklyn) came together in 2016 to form the Central Brooklyn Health Movement (CBHM). The Rogosin Institute, the initiating stimulus, and now anchor, for this health movement, tapped existing partnerships with community and faith-based leaders and with other healthcare providers to identify and support a core group composed of volunteers who recognize the health challenges they and their neighbors are facing, and, at the same time, are in the best position to help bring about the improvements in health and healthcare needed in that community.

For the past 2 years, these volunteers have conducted outreach and health education throughout Central Brooklyn as part of the Better Health Movement. They work within their communities to raise awareness of kidney diseases and promote healthy lifestyles for disease prevention. A goal is to continue to grow the number of individuals who are better-health activists and/or champions, progressively engaging more and more of the community in a transformative process that encourages active problem identification and solving in a setting of caring for one's neighbor.

As a specific example of the power of such community action, let me tell you about the CBHM approach to increasing living and deceased kidney donation for transplantation. With the lowest (but improving) rate of organ donation registration in the country, New York has a lot of work to do to educate the public—education that could reduce the average 6- to 8-year waiting time for a kidney transplant in New York City.

Of course, New York state is not alone in the need to increase organ donation. The Obama administration recognized this as a national problem and in 2016 made increasing organ donation a priority by convening a White House Organ Donation Summit that involved dozens of companies, foundations, universities, hospitals, patients, and patient advocacy organizations, including the Rogosin Institute, and announcing new actions and commitments to increase organ donation and transplantation. The Rogosin Institute and the CBHM committed to an effort in Brownsville and East New York.

Understanding attitudes toward kidney disease and organ donation

To catalyze action to increase organ donation and to reduce the unacceptable waiting time for a kidney transplant, the CBHM, led by Strong Power Consulting, Inc., a consulting firm that partners with faith-based organizations and a key CBHM/Rogosin partner, developed an outreach strategy to collect information on community awareness and attitudes around kidney disease and organ donation.

Through outreach at churches, community board meetings, tenant associations, colleges, senior centers, and community events, the Strong Power team collected some 10,000 surveys in Central Brooklyn. Survey analysis revealed that 62.5% of those surveyed were willing to give a living donor kidney, while 50% said they would agree to give one or both kidneys after death. At the same time, almost a third of those surveyed said they knew someone with kidney disease, and just below 30% knew someone who needed a kidney. Clearly, there is a great opportunity here to provide more kidneys for those who need them. The CBHM partners are now working to turn that level of willingness into actions that increase the rate of transplantation for its citizens and to promote kidney health and disease prevention more generally.

Beyond providing baseline data to help direct programming strategies to increase organ donation and also promote kidney health, the process of preparing and conducting the survey has resulted in the activation of a large group of community better-health advocates, including educators, tenant group leaders, elected officials, churches, housing developments, senior citizen directors, colleges, public schools, and community residents. This mobilization of the community is the heart of the CBHM: without this, there is no "movement." In essence, the CBHM is an invitation to the community and individuals to take more responsibility for managing their own health, with particular emphasis on the prevention of chronic illnesses like diabetes and kidney diseases. Through the development of culturally specific grassroots education strategies and materials, as well as creating opportunities for reflection and open discussion about kidney health, chronic disease prevention, disease prevention, and organ donation, we are seeing what can happen when mobilization of local volunteers and multiple grassroots organizations get the word out that "My health matters!"

We are committed to the principle that community involvement, in partnership with professional health services of all types, can improve health and prevent disease. We believe the community must be involved if we are to see fewer of our fellow citizens suffering from end stage renal disease due to a lack of information, interest, or awareness. We have the opportunity through the CBHM and its partners to take charge and see that our communities, which are currently rated poorly with respect to health and life expectancy, become the healthiest communities in Central Brooklyn, especially with regard to kidney disease.

So, is it important to ask whether we, as residents in a given community, are really responsible for one another, especially with respect to health? In other words, "Am I my brother's/sister's keeper?" My answer is "Yes." I believe we have a God-mandated responsibility to help those less fortunate than ourselves, and faith- and community-based settings can serve as vehicles to help us achieve this goal. The community must be at the table and must be part of the solution to achieving better health in Brooklyn. When models for improving kidney healthcare are under consideration, the role of the community as an active participant should always be included in the design.

Reverend Kimberly Headley is affiliated with the Central Brooklyn Health Movement and Chief Operating Officer for Strong Power Consulting, Inc.

Polycystic kidney disease (PKD) is characterized by the progressive enlargement of numerous fluid filled cysts in the kidney. The 2 main types of PKD are ARPKD,* and the most commonly seen ADPKD.†[1,2]

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*Autosomal recessive polycystic kidney disease.
†Autosomal dominant polycystic kidney disease.
‡Estimated glomerular filtration rate.

References: 1. Harris PC, Torres VE. Polycystic kidney disease. *Annu Rev Med*. 2009;60:321-337. **2.** Braun WE. Autosomal dominant polycystic kidney disease: emerging concepts of pathogenesis and new treatments. *Cleve Clin J Med*. 2009;76(2):97-104. **3.** Grantham JJ. Autosomal dominant polycystic kidney disease. *N Engl J Med*. 2008;359(14):1477-1485.

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Industry Spotlight

Acute kidney injury news

Two manufacturers reported on recent results in acute kidney injury (AKI) studies.

Biopharmaceutical company AM-Pharma, based in Bunnik, the Netherlands, announced that its phase II STOP-AKI study demonstrated a noteworthy reduction in mortality in a 28-day period. The company is focused on the development of recombinant human alkaline phosphatase (recAP) for the treatment of AKI, ulcerative colitis, and hypophosphatasia. Pfizer acquired a minority interest in AM-Pharma in May 2015 and may acquire the rest of the company through an option.

The 301-patient study compared a treatment group of sepsis patients with AKI with a similar group receiving placebo. Adding recAP to standard of care did not have an effect during week 1 of the study, which was the study's primary endpoint. However, recAP demonstrated a significant and dose-dependent relative reduction in mortality of more than 40% in the treatment group compared with the placebo group. The researchers also reported a significant, progressive, and sustained improvement in renal function over the entire 28-day study period.

Principal investigator Peter Pikkers, chair of experimental intensive care medicine at Radboud University Medical Center, Nijmegen, the Netherlands, presented the data at the International Conference on Advances in Critical Care Nephrology in San Diego in March 2018. He said that the significant improvement demonstrated in survival and kidney function "are very encouraging and strongly support further development of recAP," BioWorld.com reported.

At the same conference, La Jolla Pharmaceutical presented its work, "Outcomes in Patients with Acute Kidney Injury Receiving Angiotensin II for Vasodilatory Shock."

A La Jolla online Power Point presentation refers to Giapreza as a novel vasopressor that is the "first and only synthetic human angiotensin II."

Researchers analyzed the data from 105 AKI patients requiring renal replacement therapy at the initiation of the drug study. Survival through day 28 was 53% for the Giapreza group compared with 30% for the placebo group ($p = 0.012$). By the end of the first week, 38% of patients treated with Giapreza discontinued renal replacement therapy compared with 15% of patients treated with placebo ($p = 0.007$). The study results were published online in *Critical Care Medicine*.

"Acute kidney injury requiring dialysis associated with distributive shock … represents a significant medical risk for patients and a significant financial burden to the healthcare system," said study presenter James Tumlin, MD, professor of medicine at the University of Tennessee at Chattanooga and director of the NephroNet Clinical Trials Consortium. "These analyses of the effect of angiotensin II on AKI patients requiring dialysis in the ATHOS-3 Study demonstrated angiotensin II is a promising therapy to address this unmet need."

DaVita cuts some clinical research jobs

DaVita has cut 38 positions in a clinical research arm of the company based in Minneapolis. The cuts are "part of a company decision to discontinue one of three segments in its clinical research division," a spokesman said in an e-mail to the *Minneapolis Star Tribune*.

The company will be discontinuing its work in "early clinical research" in Minneapolis and also in Denver, according to the *Star Tribune*.

The cuts are a further indication that DaVita will concentrate on its core business, dialysis services. In December 2017, DaVita sold off, for $4.9 billion, its DaVita Medical Group, which joined Optum, part of UnitedHealth Group.

Late in 2017, DaVita Chief Executive Officer Kent Thiry said the company would use the $4.9 billion to buy back stock in the next 2 years, to pay down obligations, and to fund general corporate initiatives. Thiry said the company would "pursue other investments in health care services outside of kidney care" in addition to "focusing on U.S. and international kidney care businesses."

Merck and Eisai sign deal for renal cancer drug

Merck & Co., in Kenilworth, NJ, and Tokyo-based Eisai Co. Ltd. signed a collaboration to develop and sell Eisai's renal cancer drug Lenvima (lenvatinib), a tyrosine kinase inhibitor.

The drug is already approved in many countries for advanced renal cancer and for locally recurrent or metastatic differentiated thyroid cancer.

The terms specify that Lenvima will be developed for several types of cancer as a standalone treatment and in combination with Merck's anti–PD-1 immunotherapeutic agent, Keytruda (pembrolizumab).

In January, the U.S. Food and Drug Administration granted a breakthrough therapy designation for the combination of the two drugs. The data showed that Lenvima in combination with Keytruda led to tumor shrinkage in 63% of patients with advanced kidney cancer, Reuters reported.

A phase III study, sponsored by Eisai, currently is investigating separate combinations of Lenvima with Keytruda or Lenvima with everolimus versus chemotherapy alone for the treatment of renal cell carcinoma, Eisai noted.

Merck and Eisai will split the gross profits generated by Lenvima, the companies agreed in an announcement.

Merck will be entitled to half of all global Lenvima sales revenue, even for its thyroid cancer and combination drug uses, Reuters said.

Merck will also make one-time payments totaling 80 billion yen ($756 million) to Eisai along with development milestone payments, according to the Asia.nikkei.com site. The total may reach 611 billion yen (about $5.77 billion). The deal specifies that much of that amount would be paid before the end of 2021, and most would be contingent, depending on eventual sales.

Eisai shares surged 10% when the deal was reported. The deal reflects the structure of another oncology collaboration Merck entered with AstraZeneca in July 2017.

Seeking ASN Co-Chair for Kidney Health Initiative

Since its establishment in September 2012, Prabir Roy-Chaudhury, MD, PhD, FASN, has served as the American Society of Nephrology (ASN) co-chair of the Kidney Health Initiative (KHI). KHI is a public-private partnership among the ASN, FDA, and nephrology community that aims to bring together nephrologists, industry partners, patient advocacy groups, and regulatory agencies to foster development of drugs, devices, and biologics for people with kidney diseases. Dr. Roy-Chaudhury will complete his term at the end of 2018, and ASN is looking for his successor.

The ASN Co-Chair for KHI serves a three-year term, renewable for one additional term, and reports to the ASN Council. Successful candidates should possess a wide knowledge of and experience in nephrology as well as have a broad understanding of issues facing development of therapies for kidney diseases. Additionally, broad knowledge of the kidney community is ideal. Candidates should also possess strong leadership qualities, vision, organizational abilities, and experience relevant to managing a program similar in size and scope to KHI.

In this role, the Co-Chair assists the Kidney Health Initiative by identifying the needs of KHI members, specifically in the broad areas of therapeutic product innovation and patient safety. The Co-Chair provides guidance and direction to KHI staff, project workgroups, and the KHI Board of Directors regarding strategic input to achieve KHI's vision, mission, and goals. KHI relies on the Co-Chair to attend regularly scheduled meetings on a weekly, monthly, and annual basis with various members, including the FDA. The Co-Chair assists with recruiting new members to join KHI through internal and external networks.

KHI
KIDNEY HEALTH INITIATIVE

The three-year term will start on Tuesday, January 1, 2019, and ASN will provide a competitive stipend to cover the estimated percent effort for the position. The ASN Co-Chair for KHI is supported with full time administrative staff as well as support from ASN departments, such as meetings, marketing, finance, and operations.

To read more about the full roles and responsibilities of the KHI Co-Chair, as well as to review the timeline of the application and selection process, please visit the KHI website at http://www.kidneyhealthinitiative.org.

If you have any questions about the position, or about KHI, please contact Anupam Agarwal, ASN Council Liaison to KHI at aagarwal@uabmc.edu or Melissa West, KHI Project Director at mwest@asn-online.org.

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In Dialysis Patients, Mortality Differs Between Beta-Blockers

One-year mortality is higher for hemodialysis patients starting carvedilol compared to those starting metoprolol, suggests a study in the *American Journal of Kidney Diseases*.

The retrospective analysis included 27,064 Medicare patients starting hemodialysis in a large US dialysis organization from 2007 through 2012. All included patients who initiated beta-blocker therapy with metoprolol (64.7% of patients) or carvedilol (35.3%). These two groups were compared for the 1-year outcomes of all-cause mortality, cardiovascular mortality, and intradialytic hypotension, with adjustment for demographic, clinical, laboratory, and dialysis treatment covariates.

Propensity score analysis suggested that the two groups were highly comparable. All-cause mortality per 1000 person-years was 225.1 for patients initiating carvedilol versus 195.8 for those initiating metoprolol: adjusted hazard ratio (HR) 1.08. Cardiovascular mortality was also higher with carvedilol: 108.3 versus 85.1 per 1000 person-years, adjusted HR 1.18.

Subgroup analyses suggested similar mortality differences across major indications for beta-blocker therapy: hypertension, atrial fibrillation, heart failure, and recent myocardial infarction. Carvedilol was also associated with a higher rate of intradialytic hypotension: 57.5 versus 55.2 episodes per 1000 person-treatments, adjusted incidence rate ratio 1.10.

About 80% of beta-blocker prescriptions to US dialysis patients are metoprolol and carvedilol. Despite their recognized pharmacologic and pharmacokinetic differences, there are few data on the comparative safety and efficacy of these two medications.

This large retrospective study suggests higher overall and cardiovascular mortality in hemodialysis patients initiating carvedilol versus metoprolol. Pending definitive randomized trials, the authors suggest that possible adverse hemodynamic effects of carvedilol should be considered when starting beta-blockers in hemodialysis patients [Assimon MM, et al. A comparative study of carvedilol versus metoprolol initiation and 1-year mortality among individuals receiving maintenance hemodialysis. *Am J Kidney Dis* 2018; DOI: https://doi.org/10.1053/j.ajkd.2018.02.350].

Caffeine Reduces AKI Risk of Preterm Neonates

Early administration of caffeine citrate can reduce the risk of acute kidney injury (AKI) in preterm newborns, according to a study in *JAMA Pediatrics*.

The researchers analyzed data on a multicenter cohort of 675 preterm neonates enrolled in the "Assessment of Worldwide Acute Kidney Injury Epidemiology in Neonates" (AWAKEN). The infants were admitted to 24 participating level III or IV neonatal intensive care units. About 55% were male; mean gestational age was 28.9 weeks and mean birthweight 1285 g.

Acute kidney injury developed during the first week after birth in 18.1% of infants, based on the modified neonatal Kidney Disease: Improving Global Outcomes definition. The incidence and severity of AKI were compared for 447 infants treated with caffeine during the first week of life versus 228 who did not receive caffeine. Neonates treated with caffeine had younger gestational age and lower birthweight, were more likely to be intubated in the delivery room, and had lower Apgar scores.

Incidence of AKI was 11.2% in infants treated with caffeine, compared to 31.6% in those not treated with caffeine. The reduction in AKI risk remained significant after multivariable adjustment: odds ratio 0.20. Number needed to treat to prevent one case of AKI was 4.3. Among neonates who developed AKI, caffeine was associated with a lower risk of stage 2 or 3 AKI.

Preterm newborns are at high risk of AKI, with associated increases in morbidity and mortality. One single-center study has suggested that caffeine citrate, a methylxanthine, reduces the incidence of AKI in very low-birthweight infants.

This secondary analysis of multicenter cohort data suggests that treatment with caffeine reduces the risk and severity of AKI in preterm neonates. Further studies will be needed to identify the optimal timing and dosage of caffeine citrate therapy as well as the effects on long-term renal outcomes [Harer MW, et al. Association between early caffeine citrate administration and risk of acute kidney injury in preterm neonates: Results from the AWAKEN Study. *JAMA Pediatr* 2018; DOI: 10.1001/jamapediatrics.2018.0322].

What's the US Sodium Intake? New Nationwide Estimates Released

Analysis of 24-hour urine samples from a large sample of US adults provides important baseline data on estimated sodium and potassium intake, reports a study in *The Journal of the American Medical Association*.

The cross-sectional study included 24-hour urine collections from 827 men and women aged 20 to 69 years. The subjects were drawn from the examination component of the National Health and Nutrition Examination Survey (NHANES) in 2014. The researchers estimated 24-hour urinary sodium and potassium excretion and their molar ratios.

Nearly two-thirds of the study population were white; Hispanic, black, and Asian racial/ethnic groups were represented as well. Hypertension was present in 43.5% of individuals, while 10.0% said they had been diagnosed with diabetes.

Mean 24-hour sodium excretion was 3608 mg, with a median of 3320 mg. Mean sodium excretion was higher in men than women, 4205 versus 3039 mg; and somewhat higher in subjects aged 20 to 44 compared to older ages, 3699 versus 3507 mg.

The mean value for 24-hour urine potassium excretion was 2155 mg overall, 2399 mg in men, and 1922 mg in women. Mean potassium excretion was 2155 mg in subjects aged 20 to 44 and 2343 mg in those aged 45 to 69. Overall mean sodium-to-potassium molar ratio was 3.17, with a median of 2.87.

Twenty-four-hour urine collection is recommended for more accurate estimation of US sodium intake. Based on previous studies suggesting that about 90% of consumed sodium is excreted in urine, the cross-sectional data suggest a mean sodium intake of approximately 4000 mg/d in US adults. Mean potassium intake appears to be below currently recommended levels. The authors discuss the cross-sectional findings in light of previous studies and suggest their data will provide a useful benchmark for future research [Cogswell ME, et al. Estimated 24-hour urinary sodium and potassium excretion in US adults. *JAMA* 2018; 319:1209–1220].

New Strategy Prevents HCV Infection from Kidney Donors

Direct-acting antivirals (DAAs) can prevent hepatitis C virus (HCV) transmission from HCV-infected kidney donors to noninfected recipients, according to an initial clinical trial in the *Annals of Internal Medicine*.

The open-label trial included 10 non-HCV–infected patients receiving kidneys from HCV-infected donors at one transplant center. All recipients were over age 50 (median 71 years) and had no available living donor. The deceased donors, median age 30 years, had positive HCV RNA and HCV antibody test results. Six donors had died of drug overdose.

Immediately before transplantation, all patients were treated with grazoprevir (GZR) 100 mg and elbasvir (EBR) 50 mg. Those whose donors were infected with HCV genotype 1 received GZR-EBR for 12 weeks posttransplant; those whose donors had genotype 2 or 3 received triple therapy with sofosbuvir 400 mg added to GZR-EBR.

On safety analysis, none of the 10 recipients had adverse events related to GZR-EBR. At 12 weeks after treatment, none of the patients had detectable HCV RNA. Five patients never had detectable HCV RNA, suggesting that DAA treatment also prevented acute HCV infection.

Now that DAA agents with high cure rates are available, transplantation from HCV-infected deceased donors—a generally young group with few comorbid conditions—may be possible. This nonrandomized trial shows the feasibility of DAA prophylaxis for non-HCV–infected recipients of kidneys from HCV-infected donors.

The researchers conclude, "If confirmed in larger studies, this strategy should markedly expand organ options and reduce mortality for kidney transplant candidates without HCV infection" [Durand CM, et al. Direct-acting antiviral prophylaxis in kidney transplantation from hepatitis C virus–infected donors to noninfected recipients: an open-label nonrandomized trial. *Ann Intern Med* 2018; DOI: 10.7326/M17-2871].

Barbershop Intervention Helps Lower BP in Black Men

A health promotion intervention in black-owned barbershops—incorporating medication management by pharmacists—reduces blood pressure in black men with uncontrolled hypertension, reports a study in *The New England Journal of Medicine*.

The cluster randomized trial included 319 non-Hispanic black men with hypertension (systolic BP 140 mm Hg or higher) who were regular customers at 52 black-owned barbershops in Los Angeles County. One group of barbershops was assigned to a pharmacist-led intervention, in which barbers encouraged men to meet with specialty-trained pharmacists. The pharmacists prescribed and monitored antihypertensive drug therapy in a collaborative practice agreement with the patients' physicians. Barbershops assigned to an active control group promoted lifestyle modification and doctor's office visits.

Six-month outcomes were assessed in 132 men in the intervention group and 171 in the control group. Mean baseline systolic BP was 152.8 and 154.6 mm Hg, respectively; mean age was about 54.

Systolic BP decreased by 27.0 mm Hg (to 125.8 mm Hg) among men participating in the pharmacist-led intervention, compared with 9.3 mm Hg (to 145.4 mm Hg) for those in the active control group. Nearly two-thirds (63.6%) reached a BP target of less than 130/80 mm Hg, compared to 11.7% of the control group.

The intervention cohort had a retention rate of 95%; adverse events were infrequent but included three cases of transient acute kidney injury. Men in the intervention group had greater improvements in self-rated health and patient engagement. Each intervention patient received an average of seven in-person visits and four follow-up calls with the pharmacist.

This health-promotion intervention in black-owned barbershops achieves significant reductions in BP among black men with hypertension. The trial shows a large net intervention effect in a difficult-to-reach population at high risk of hypertension-related death. An ongoing extension phase will assess the sustainability of this community-level intervention [Victor RG, et al. A cluster-randomized trial of blood-pressure reduction in black barbershops. *N Engl J Med* 2018; 378:1291–1301].

Kidney Patients and Physicians Call for Accelerated Innovation at Kidney Health Advocacy Day 2018

By Zachary Kribs

Advocates from the American Association of Kidney Patients and the American Society of Nephrology gathered in Washington, DC, on March 28, 2018, for the 6th Annual Kidney Health Advocacy Day (KHAD) to meet with lawmakers, share their stories, and discuss the need for greater innovation for patients with kidney diseases.

The group of nearly 50 kidney patients and physicians met with more than 60 legislators and their staff. Highlighting the barriers to innovation in kidney care and the consequences of the lack of innovation, advocates urged Congress to support KidneyX, a new public-private partnership to accelerate innovation in the prevention, diagnosis, and treatment of kidney diseases.

"It is difficult to understate the exceptional venue that Kidney Health Advocacy Day provided to speak on behalf of researchers, clinicians, and most important, our patients," said Alejandro Diez, MD, a transplant nephrologist at Ohio State University.

"Sharing narratives with legislative leaders on how our community fights against kidney disease, and particularly the promise of KidneyX, was a powerful experience. We all go into medicine out of a sense of altruism, hoping to become an agent of change," Diez said. "The opportunity to participate in KHAD strengthened my love of nephrology and reaffirmed my commitment to advocate for my patients—the reasons why I became a transplant nephrologist."

In the United States, more than 40 million people are living with kidney disease, and more than 700,000 of those individuals have kidney failure and require either a kidney transplant or dialysis to live. Annually, Medicare pays nearly $34 billion to provide care for individuals with kidney failure, and dialysis, a therapy invented more than 50 years ago, remains the most common therapy for kidney failure despite often poor outcomes for patients. Of all individuals beginning dialysis, 50% die within the first 5 years of treatment.

For Scott Burton, a lifelong kidney patient and founder of the Forever is Tomorrow Foundation, which works to raise awareness about kidney diseases, KHAD was an "educational and inspiring experience."

"With kidney diseases continuing to grow in prevalence, I feel it's crucial that research and innovation be at the top of the list of priorities," Burton said. "Having lived this my entire life, I have observed the lack of advances in treatment options, so it's my hope that KidneyX will be the catalyst to curb the growth of kidney disease, bringing about a positive outlook for future generations."

Despite the immense burden kidney diseases place on patients and society, there has been a dearth of innovation compared to other areas of medicine, and our healthcare system has fostered a sense of complacency with existing therapies. KidneyX aims to accelerate breakthroughs in the development of new products including drugs, devices, biologics, and other therapies for people with kidney diseases.

With a recently signed Memorandum of Understanding between ASN and the U.S. Department of Health and Human Services (HHS), KidneyX has already begun to create a sense of urgency in the kidney community.

"This public-private partnership will stimulate new and exciting research and development in the kidney space," said Andrew Malone, MB, BCh, a professor of transplant nephrology at the University of Washington. KidneyX has made it "an exciting time to be a nephrologist, and I look forward to being in the position to offer better therapies for our patients."

American Association of Kidney Patients advocate Toni Martin (right) and her daughter and caretaker Ashley Martin (center) join ASN advocate Alejandro Diez, MD, FASN (left) to describe the need for KidneyX and the accelerated development of treatments and therapies for people with kidney diseases during a meeting with the staff of Sen. Sherrod Brown (D-OH, not pictured).

On Capitol Hill, advocates noted that their call for support of KidneyX was well received, and that Congress shared their excitement for the accelerator. According to Mukta Baweja, MD, assistant professor at the Ichan School of Medicine at Mount Sinai, advocates at KHAD "grabbed the attention of our congressional leaders, galvanizing support for transforming our otherwise stagnant, inefficient, and costly—nearly $100 billion per year—approach to care." She added, "It was fantastic to see the support our leaders have for our patients."

After meeting with constituents during KHAD, Sen. Chuck Grassley (R-IA) wrote a letter to HHS Secretary Alex Azar voicing his support for accelerating breakthrough innovations for kidney patients, and applauding "the efforts of HHS to prioritize this initiative."

In the House of Representatives, a group of 17 bipartisan lawmakers led by Rep. Brian Babin (R-TX) and Congressional Kidney Caucus Co-Chairs Reps. Tom Marino (R-PA) and Susan DelBene (D-WA) called for Congress to match the $25 million raised by the private sector for KidneyX with equal public funding.

For many lawmakers, the matching public-private partnership created by KidneyX has been key to ensuring their support. At the heart of the partnership is the acknowledgment of shared responsibility between the public and private sector for providing breakthrough innovations to improve the lives of kidney patients.

"Improving care takes many actors: government, communities, health systems, and physicians," said Sri Lekha Tummalapali, MD, MBA, a nephrology fellow at the University of California San Francisco Medical Center, further noting that the private sector sharing responsibility with public institutions can "improve access to care, funding for research, and align incentives … to ultimately create the change our patients need."

Said Baweja, "The time for complacency with suboptimal standards of care is over. We must demand better for nephrology and for our patients."

"All patients and nephrologists experience the problems that face kidney disease patients on a daily basis: poor access to care and transplantation, lack of therapies, and disparities in outcomes. Uniting the voices of patients and physicians on Kidney Health Advocacy Day to call for urgent change was a powerful experience. The personal stories of patients living through the disease matched the studies and statistics to create a narrative to Congress about the need for innovation. Representing the voices of constituents and participating in the democratic process shows that improving care takes many actors: government, communities, health systems, and physicians. Coming together with public institutions can improve access to care, funding for research, and align incentives through well-designed payment models to ultimately create the change our patients need."

—Sri LekhaTummalapali, MD, MBA, nephrology fellow at the University of California San Francisco Medical Center

"I had the great pleasure of representing ASN members and working with patients from AAKP to advocate for kidney research on Capitol Hill on March 28. We had very constructive meetings with members of Congress, all expressing support for the KidneyX project. This public-private partnership will stimulate new and exciting research and development in the kidney space. It is an exciting time to be a nephrologist and I look forward to being in the position to offer better therapies for our patients."

—Andrew Malone, MB, BCh, professor of transplant nephrology at the University of Washington

"ASN's Kidney Health Advocacy Day was an educational and inspiring experience. With kidney disease continuing to grow in prevalence, I feel it is crucial that research and innovation be at the top of the list of priorities. Having lived this my entire life, I have observed the lack of advances in treatment options, so it is my hope that KidneyX will be the catalyst to curb the growth of kidney disease, bringing about a positive outlook for future generations. It was my pleasure to be a part of it and I look forward to becoming even more involved in the future."

—Scott Burton, lifelong kidney patient and founder of the Forever is Tomorrow Foundation

"At KHAD 2018, we grabbed the attention of our congressional leaders, galvanizing support for transforming our otherwise stagnant, inefficient, and costly—nearly $100 billion per year—approach to care. It was fantastic to see the support our leaders have for our patients, but we still have a lot of work to do in order to implement optimal resolutions. We must not only advocate for cost-effective prevention and treatment strategies, but [also for] radical advancements that transcend transplantation and dialysis as our status quo. The time for complacency with suboptimal standards of care is over. We must demand better for nephrology and for our patients."

—Mukta Baweja, MD, assistant professor at the Ichan School of Medicine at Mount Sinai

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Innovative Alternatives to Renal Replacement Therapy: Developing a Roadmap

By Grace Squillaci

Smartphones, iPads, insulin pumps, and pharmacogenomics: these are all technology developments made in the past 50 years.

While the world around us has exploded with technological advancements, the way we provide dialysis has changed very little in 50 years. Most people with kidney failure still endure treatment sessions of 4 to 6 hours three times a week in a dialysis center. The process is intrusive and affects their quality of life as they are tethered to a schedule and a machine. Not only can travel be restrictive, but maintaining a job and family life can be a challenge as well. Additionally, patients undergoing dialysis often undergo numerous surgeries and experience many adverse effects from cramping to clotting and infections.

Beyond the personal and physical toll, there is also the societal and medical burden. In 2016, Medicare spent $34 billion, or 7%, of all expenditures on treatment of end stage renal disease. Despite this large investment in treatment, the US government spends less than 1% of Medicare kidney care costs in kidney research. According to a US Government Accountability Office study, more is spent on treating kidney failure than the entire National Institutes of Health (NIH) budget.

Despite these enormous costs, patient outcomes are poor. The 5-year survival rate for a hemodialysis patient is worse than that of most cancers. There is no cure for kidney failure, and while transplantation is the optimal form of renal replacement therapy (RRT) available, patients face long wait lists and organ shortages.

> **"If we are going to keep patients alive by artificial means, we then incur the responsibility to see that it is a good life and an enjoyable life."**
>
> —Willem Kolff, father of hemodialysis and artificial organs

Can we break this cycle of a lack of innovation, high costs, poor quality, and poor outcomes? The Kidney Health Initiative (KHI) believes we can. Established in 2012 as a public-private partnership between the ASN and the US Food and Drug Administration (FDA), KHI aims to foster innovation and enhance patient safety for kidney diseases. KHI is a collaborative partnership that aims to bring together all the major stakeholders in kidney disease (patients and patient organizations, big pharma and small biotech, dialysis providers, health professional organizations, and federal agencies [FDA, NIH, the Centers for Disease Control, and the Centers for Medicare & Medicaid Services] as well as international partners).

Figure 1. Considerations in developing RRT alternatives

In 2016, KHI submitted a commitment statement to the White House Summit on Organ Donation to "identify the scientific, technical, and regulatory milestones needed to achieve the goal of creating a bioengineered alternative to dialysis as renal replacement therapy"—in other words, to create a roadmap that would serve as a catalyst to develop patient-centered, patient-driven alternatives to RRT (Figure 1). According to Prabir Roy-Chaudhury MD, PhD, FRCP, Professor of Medicine and the Division Director for Nephrology at the University of Arizona and Co-Chair on the KHI Board of Directors of the American Society of Nephrology, "The only way to change the current construct of dialysis is to focus on patient-centered innovation. We need to identify the issues that are important to patients with kidney failure and then harness the multi-disciplinary strengths of all the stakeholders to develop technologies and pathways that *allow patients to live; not just keep them alive*."

KHI's goals are to:

- Convene a diverse group of stakeholders, patients and care partners, academics, industry, and regulators.
- Describe scientific, technical, reimbursement, and regulatory challenges for mechanical, cellular, and hybrid technologies.
- Create a set of design criteria for future alternatives to RRT.
- Identify ways to incorporate patient preferences and feedback on design features.
- Create a roadmap with milestones and opportunities for creating a bioengineered alternative to dialysis.

In March 2017, KHI conducted a workshop of over 100 stakeholders to review the state of the science in RRT and gain input on challenges and potential design criteria for alternatives to RRT. There are numerous initiatives underway to bring advances in technology to a solution that will benefit our patients. These include academic consortia such as NIH's (Re)Building a Kidney Consortium and translational approaches for cellular therapy or wearable/portable devices by start-up companies.

Despite this progress, many challenges remain. There are knowledge gaps in determining what is "necessary" vs. optimal RRT to minimize uremic symptoms and consequences, how cells can repair or replace a damaged kidney's functions, and how to incorporate diverse patient needs. Financial coverage for innovative technologies by the single-payer system for ESRD and parallel review with the FDA are also areas that must be explored. The KHI collaboration started with the ASN and FDA and continues to draw a great deal of strength from the ongoing integral interaction.

KHI has established working groups to focus on mechanical, cellular, and vascular access patient-centered design criteria for components of RRT, and a 12-member Patient Advisory Committee is providing the very important patient perspective to these working groups. The necessary innovations are being positioned along a continuum that ranges from technical innovations needed for portable/wearable devices to implantable devices, including bio-hybrid approaches, to alternative directions including chimeric kidneys, xenotransplantation, and innovative biological repair/rebuilding.

"We are taking a systematic approach and being careful not to predetermine the form of the ultimate products that will accomplish our goal," said Joseph V. Bonventre, MD, PhD, Chief of the Renal Unit and Director of the Bioengineering Division at Brigham and Women's Hospital and Chair of the KHI RRT Roadmap Steering Committee. "Our patients have waited long enough, and we owe it to them to do all we can to bring new innovative solutions to alleviate the burden of loss of kidney function."

The first draft of the RRT Roadmap will be available in late summer 2018. But the process is ongoing and will not only guide product development for industry but also be an important tool for early-stage companies with access to investors, business and manufacturing experts, scientists, engineers, patients, payers, and consumers.

In summary, the KHI RRT roadmap project is complex, but the objective is simple. We aim to serve as a catalyst for industry, academia, and other organizations to invest in RRT alternatives, and to help direct those investments to optimize solutions that will successfully address patient needs.

For more information or to participate in the roadmap project, please contact: khi@asn-online.org or visit our website, www.kidneyhealthinitiative.org.

Grace Squillaci works for the Griff Group and is serving as a project manager for KHI and the RRT Roadmap teams.

Share the Spare:
Nephrologist Donates Kidney to Brother

By Sara Leeds

Brothers Owais and Rizwan Badar, the day after Owais' surgery

A kidney transplant is generally a better option than renal replacement therapy for patients with ESRD who are lucky enough to receive one. A transplant can restore an individual's long-term health and quality of life, and is also cost-effective. Dialysis, whether hemo- or peritoneal, and whether performed in-center or at home, is life preserving and necessary. However, it cannot compete with the benefits of receiving a real organ.

When Rizwan Badar, MD, a nephrologist in southern California, learned that his older brother needed a kidney, he didn't hesitate to offer him one of his own. He and his brother, Owais, underwent surgery in the summer of 2017, and have both made full recoveries. Dr. Badar said the experience was humbling and that it has helped make him a better physician and improved the way he communicates with his patients.

"My brother was basically living out by the beach, enjoying a normal life. He was very social and always liked to go out with friends," Dr. Badar said. "But then when he went into kidney failure and needed dialysis, like many of my patients, it changed everything."

Owais, who lives in Louisiana, worked as a paralegal until he got sick about 5 years ago. Although his doctors weren't sure exactly what caused his kidney failure, they believed it was most likely due to uncontrolled high blood pressure that persisted for many years. He had been on dialysis ever since, feeling more and more like a shadow of himself as treatments continued.

In addition, Owais was experiencing early stage heart failure, and his doctors were concerned that performing a transplant would be extremely dangerous. Thus they did not place him on the transplant waiting list right away. Luckily though, around the beginning of the summer of 2017, his cardiac condition began to improve somewhat. Although his doctors deemed him a high-risk patient, they felt he was just healthy enough to be added to the waiting list.

"His surgeons decided that if Owais ever had the opportunity to get a kidney, it should happen as soon as possible," Dr. Badar said.

He and his younger brother both wanted to help, so they got tested to see if they were a compatible match. When the results came back, Dr. Badar was deemed the better-matched candidate. He didn't think twice about going through with the procedure to save his brother's life.

Since Owais and his team of doctors were in Louisiana, Dr. Badar traveled to Tulane University for the surgery.

"The easiest part of the procedure was for me," he laughed. "I just had to shower with a special antiseptic shampoo for 24 hours prior to the surgery to lessen the amount of bacteria on my body, and then show up." He explained that it was a bit more involved for his brother, the recipient, and his team of doctors. Fortunately, the procedures both went without a hitch, and Owais started producing urine on the surgical table practically as soon as the surgeons connected the kidney. He has not needed dialysis since, and there were no complications from the surgery.

People often ask if Owais's condition inspired him to pursue nephrology, but in fact, Dr. Badar had been practicing nephrology long before his brother became sick.

"To me, it's the best field," Dr. Badar said. "I really like to be involved in all aspects of medicine, and nephrology is that one subspecialty that really covers all the organ systems of the body. After all, most end-stage organ diseases will ultimately affect the kidney. So essentially, you have to have knowledge of all organ systems to be able to practice as a nephrologist. It's challenging and it fascinates me."

Being a kidney donor has also given Dr. Badar a unique opportunity to relate with his patients and their donors on a more personal level.

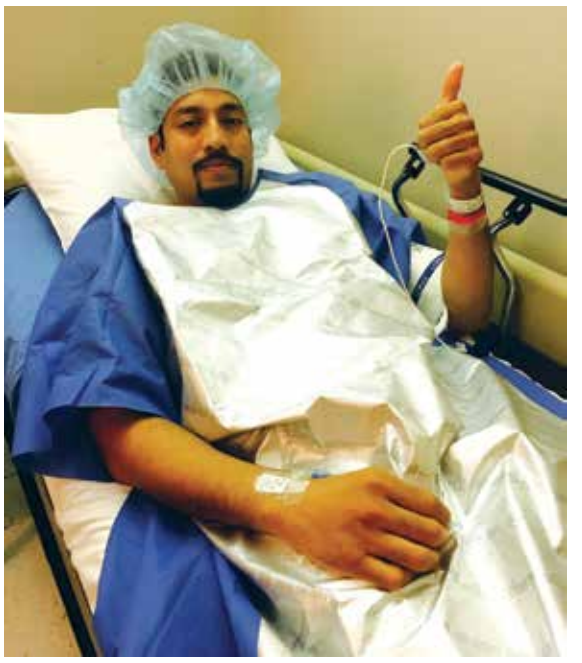
"Before, if someone asked me about kidney donation, I would just say 'oh yeah, it's easy. You just go have the surgery, they take out a kidney, and the next day you go home,'" Dr. Badar said.

But having gone through the surgery himself, Dr. Badar now realizes that there is more to it: "... when it's suddenly you, it makes you think about things a lot more." Although the recovery is a relatively short two weeks, he said he now understands just how painful it can be at times, as well as how the procedure can cause apprehension and tension among families. Even though his wife and parents were worried, they all knew it was the best thing to do and supported his decision. He says he would do it again in a heartbeat if he could.

Now when he speaks with patients and their families, he can tell them about his own firsthand experience and how donation can be scary, but the statistics are in favor of people doing very well afterward.

"The slogan I stand by is 'Share the Spare,'" he said. "Plus, being able to save a life is amazing."

Surgeon Anil Paramesh and Rizwan



Rizwan, minutes before surgery to donate his kidney

Long-term Health of Organ Donors Gets Fresh Look

By Mary Jane Gore

Older kidney recipients can benefit from organs from older donors. But previous cerebrovascular disease may reduce the survival benefits of these kidney transplants, according to a recent study.

Living donors are now getting their due as a medical population of interest that will be officially monitored for health outcomes and other data over time.

A pilot study at 10 transplant centers began enrolling donors for the Living Donor Collective, a living donor registry, in January 2018 and will enroll through September 2019 (Table 1). After that, the registry will begin enrolling at other transplant programs nationwide. A wide variety of medical and other data will be gathered through a questionnaire survey to learn more about health parameters and why people do or do not choose to donate.

By contrast, organ recipients have been tracked carefully for nearly 35 years. Since 1984, when Congress passed the National Organ Transplantation Act, there has been a mandate for a national registry for organ matching, with a scientific registry of the recipients of organ transplants. That act led to the founding of the Scientific Registry of Transplant Recipients (SRTR) and the Organ Procurement and Transplantation Network (OPTN) (1).

It was not until recently, however, that the federal Health Resources and Services Administration (HRSA) that administers the SRTR and OPTN called for the formation of a Living Donor Collective, a similar registry for living donors.

SRTR now is establishing a national registry to address important questions about health outcomes, long-term safety of donation, and why the number of living donors has decreased in recent years for both kidney and liver donors.

According to an article published in the *American Journal of Transplantation* about the formation of the collective, living donor kidney transplant procedures in the United States decreased by 14.3% in an 11-year span (2). The peak was 6572 in 2005, and the number fell to 5629 in 2016. (During the same period, however, the number of deceased donor kidney transplant procedures increased 35.5%, from 9913 in 2005 to 13,431 in 2016.)

Similarly, liver donation among living donors in the United States has dropped off since an annual high of 524 donors in 2001 (2). While just 219 living donor liver transplants were performed in 2009, this number had increased to 345 in 2016. Authors of the Living Donor Collective article conjectured that a report about a living donor death most likely led to the decline after 2001.

Emphasis on living donor health has been gaining attention. A 2018 study published in the *Annals of Internal Medicine* used 52 observational studies to extract medical data and report on the health of 118,426 living kidney donors and a comparison group of 117,656 nondonors (3).

The *Annals* study found that living kidney donors had higher mean diastolic blood pressure, higher mean serum creatinine levels, a lower mean estimated glomerular filtration rate, and lower high-density lipoprotein cholesterol than the nondonors (3).

Living kidney donors had an almost 9-fold greater relative risk (RR) for developing end-stage renal disease (8.83; 95% CI, 1.02–20.93), Medscape reported, calling this finding perhaps the "most striking" of all (4). The health website was quick to note, however, that the "absolute risk for ESRD among donors was very low," with an incidence rate of 0.5 events per 1000 person-years compared with 0.1 event among nondonors.

In female living donors, a higher rate of post-donation preeclampsia, a problematic high blood pressure, emerged as a problem. The *Annals* study noted that previous studies had reported preeclampsia as a more common condition among living kidney donors than in the general population. The authors cautioned that the ability to generalize about living donors in the study was limited by the selected control populations of the studies examined.

Based on articles like the *Annals* observational study and other studies on living donors, the new collective will carefully document medical findings, and, for example, "place a high priority on establishing the risk of kidney donation with regard to pregnancy" and plans to develop a survey instrument for pregnancy complications (2).

Nondonor information also is considered an important part of the Living Donor Collective data gathering. The collective's work will help transplant centers understand the reasons that prevent living donor candidates from donating. "Only by following donor candidates who are turned down or decide not to donate due to concerns that donation would adversely affect their health can we determine whether those concerns are justified," wrote the study authors.

The 10 pilot study sites will work to develop a survey for future sites. The survey will include both medical and psychosocial issues that are important to candidate donors and actual donors.

The pilot program will need to determine the best routes through which to contact participants—mail, email, social media, or phone—about one year after donation or a year after the person decides not to donate, and every one to two years after that. A website for donors will share outcomes and other information that may be helpful.

Transplantation centers will have the ability to ask their own specific questions of donors and potential donors. Through its relationship with the federal agency HRSA, SRTR can help investigators gain access to information to conduct studies that will improve the understanding of living donation outcomes.

Emilio D. Poggio, MD, from Cleveland Clinic, and Peter P. Reese, MD, from the University of Pennsylvania, wrote that the findings by Emanuele Di Angelantonio, MD, of the University of Cambridge in England and colleagues offer insights into the medical risks of living donation.

Until more is known, "we should do our best to protect potential donors with careful selection, candor about harms, open discussion about unknowns, and a commitment to their lifelong health after nephrectomy," they wrote in an accompanying editorial published in the *Annals* (5).

With the information from the pilot program's new data sets, a more focused description of living donors and their health over time will emerge, and challenges faced by the national donation system can better be addressed.

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Table 1
Donor registry pilot sites

The pilot sites for kidney and liver donors in the Living Donor Collective are:
Rochester Methodist Hospital, Mayo Clinic, Minnesota
UCLA Medical Center, California
Mount Sinai Medical Center, New York
University of Minnesota Medical Center
Johns Hopkins Hospital, Maryland
Baylor University Medical Center, Texas
University of Pittsburgh Medical Center, Pennsylvania
Kidney-only donor sites:
Emory University Hospital, Georgia
Hennepin County Medical Center, Minnesota
Saint Louis University Hospital, Missouri

Fellows Corner

Nephrology Business Leadership University
Fellows Learning the Business Aspects of Medicine

By Sapna Shah

Sapna Shah

Rare is the occasion when business training intersects with medical education.

Absent in most medical curricula and nearly taboo in academic residency and fellowship training, understanding the operational aspects of nephrology is imperative in preparing young fellows for practice. Too often, budding nephrologists are ensnared in complicated contracts, beguiled by partner promises, or seduced by transient gains. Unaware and unprepared, young and enthusiastic nephrologists often learn the business as they go, eager to see patients but often without the means or knowledge of how to achieve that goal. This must change.

Throughout training, we have short-term goals. Although we often tell ourselves, "just 4 years of medical school, just 3 years of residency, just 2 years of fellowship before the next step…," entering the workplace becomes a lifetime commitment many are ill-equipped to make. Our focus on short-term goals quickly becomes apparent as we search for our next position. By focusing on salary, weekend calls, and working hours, young physicians often lose sight of long-term plans, potential for growth, and practice philosophy. This lack of insight often results in quick turnover of positions, loss of patient continuity, and overall dissatisfaction. In the end, we are often left with the same series of questions: What questions should I ask? What should I look for in a practice? How do I know this is a good fit?

A theme frequently voiced to fellows by many mentors in both academic and private practice is, "What I wish I had known when I was in your shoes." Too often, young fellows are thrown into an arena equipped with medical knowledge, able to manage hypertension and proteinuria, but uneducated in the business of nephrology. Shielded throughout training, they enter practice encumbered by billing and coding, submerged in Quality Assurance and Performance Improvement (QAPI) and MACRA (Medicare Access and CHIP Reauthorization Act of 2015), and overwhelmed by insurance and investment. Although none would argue that the focus of nephrology education should be on economics, many practicing physicians say they were ill-equipped to handle the challenges thrust upon them in practice.

To address these shortcomings, the Nephrology Business Leadership University (NBLU) was created. This 4.5-day program focuses on transitioning fellows from training to practice, with emphasis on providing the tools needed to interview, to find the right job, and to grasp the economics of nephrology.

I attended the conference not knowing what to expect. I left with a better understanding of how to analyze a practice, assess a market, and screen for red flags. I left with competence, now able to interview with assuredness, tailor my resume with expertise, and parse a contract with awareness. I left with the confidence needed to evaluate programs, screen for overhead, and question my fit in a practice.

While there, I met with nephrologists working in traditional and nontraditional roles as presidents of hospitals, chief executive officers of companies, fellowship program directors, basic science researchers, joint nephrology hospitalists, and consultant nocturnists of large multispecialty groups and solo rural practices. Hearing their perspectives not only has provided me with a cabinet of mentors but also has encouraged me to break the traditional workplace stereotype and apply for more leadership roles in the field. Overall, I found the experience to be valuable, empowering, and eye-opening.

Now more than ever, being a nephrologist requires more than just an understanding of medicine. With a decrease in the number of nephrologists, we must push ourselves further to improve the care of our patients. Before this experience, I was more eager to just find a job rather than try to find one that was the right fit. *NBLU* has condensed lifetimes of learning experiences and provided me with the tools necessary to make this leap and become an independent, satisfied physician.

At the end of the conference, the energy, enthusiasm, and excitement about being a nephrologist were palpable, partly owing to a focus often lost in training programs. Education in the business aspects of nephrology is crucial in preparing the young fellow for future practice.

For more information regarding NBLU, please visit http://nbluniv.com/ or @NBLUniv.

Sapna Shah is a second year fellow at Mt. Sinai in New York.

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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

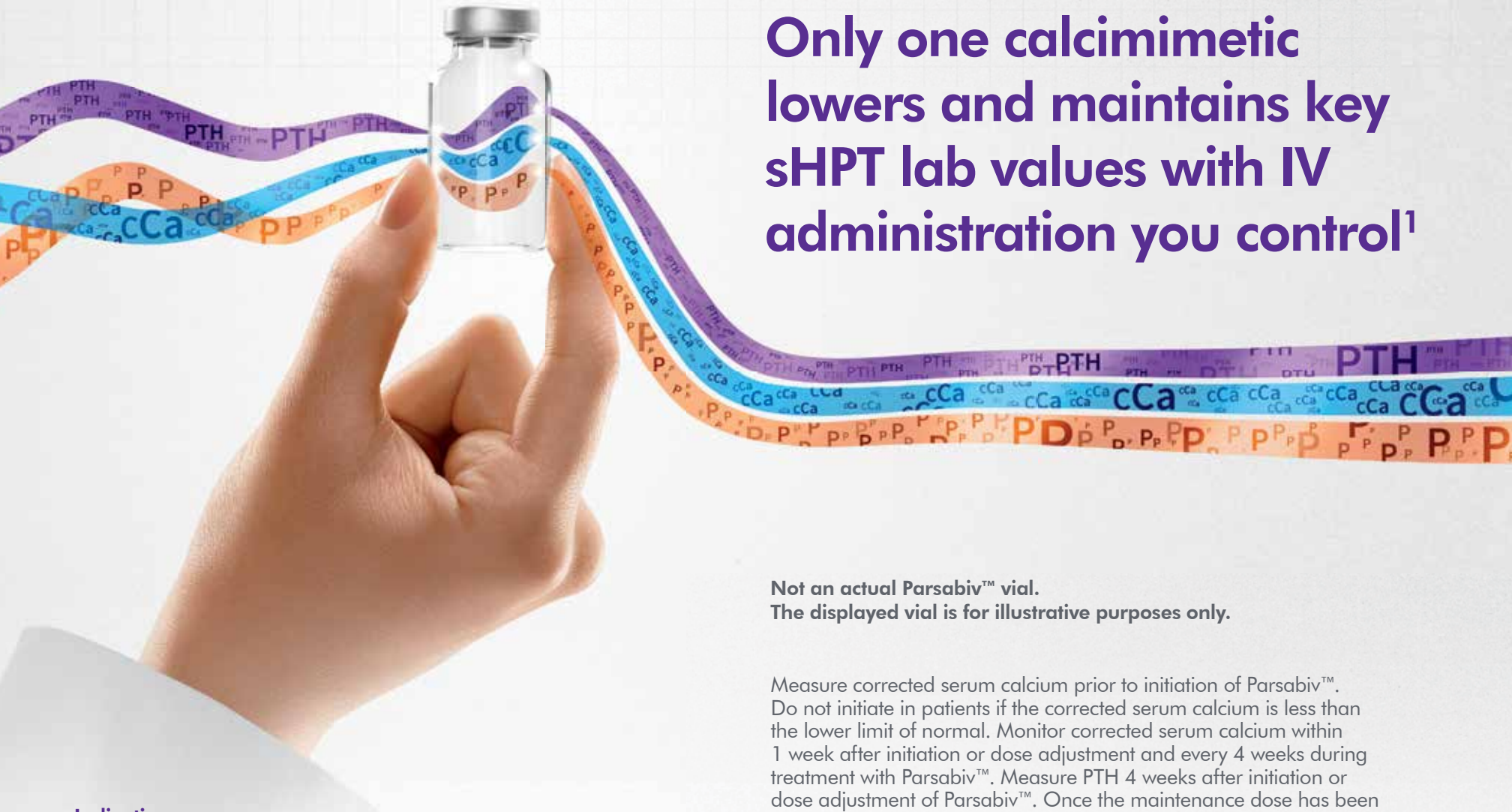
There is no clinical experience with PARSABIV overdosage. Overdosage of PARSABIV may lead to hypocalcemia with or without clinical symptoms and may require treatment. Although PARSABIV is cleared by dialysis, hemodialysis has not been studied as a treatment for PARSABIV overdosage. In the event of overdosage, 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.