



KidneyNews

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The Future is Now for Kidney Care

New Care Model, Potential for Expanded Coverage of Immunosuppressant Drugs on Horizon

By David L. White



Members of Congress and regulators are keenly focused on kidney healthcare and the policies around it. With more than 40 million people in the United States living with kidney diseases and 700,000 Americans with kidney failure, Medicare costs topped more than \$114 billion in managing kidney diseases in 2016, which accounts for 23% of all Medicare spending. With such a growing burden both on patients and their families and on taxpayers, the pressure is on policymakers to realign the incentives and priorities to achieve better outcomes.

A new vision for kidney care

Department of Health and Human Services (HHS) Secretary Alex M. Azar, II, is developing a kidney strategy to realign incentives and cut across silos in kidney care that have defied truly integrated kidney healthcare. In a speech last month, he outlined the approach, indicating it focused on preventing kidney diseases by catalyzing innovation in healthcare delivery and therapeutics, ex-

panding alternatives to in-center dialysis, and increasing the availability of organs for kidney transplantation.

“Today, I want to lay out what it would look like to pay for kidney health, rather than kidney disease—and pay for Americans with kidney disease to actually get good outcomes, rather than the endless, life-consuming procedures that you all know so well,” he said.

ASN leadership and staff have been meeting with HHS to advocate for a comprehensive, cross-cutting care approach for the model currently under development. ASN President Mark E. Rosenberg, MD, FASN, commented that “ASN commends the Secretary and this administration for acknowledging that the current state of care for kidney patients is unacceptable and that complex barriers inhibit innovation—and for developing a visionary strategy to change that reality.”

Secretary Azar’s speech was followed by a public discussion of the yet-to-be-released model with Adam Boehler, Deputy Administrator for CMS and Director at the

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Final Vision Commission Report Addresses MOC Concerns

Transparency, Practice Improvement Still Challenged

By Bridget M. Kuehn

The final report from the American Board of Medical Specialties’ (ABMS) Continuing Board Certification: Vision for the Future Commission recommends shifting the focus of ongoing certification from high-stakes exams while still maintaining a role for ABMS’s 24 specialty boards in determining physicians’ certification status.

The final recommendations address one of the primary concerns ASN and other physicians’ organizations raised about basing a physician’s ability to continue practicing

on a single high-stakes exam. Instead, it recommends ongoing formative assessments be combined with other data on a physician’s professional standing, continuing education, and practice improvement efforts in certification decisions. It also requires that boards provide physicians who fail to initially pass such assessments a pathway to meet the standards before certification is lost.

But the report may not go far enough in recognizing

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Findings

Teen blood pressure predicts future risk of kidney failure



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A rapidly growing modality



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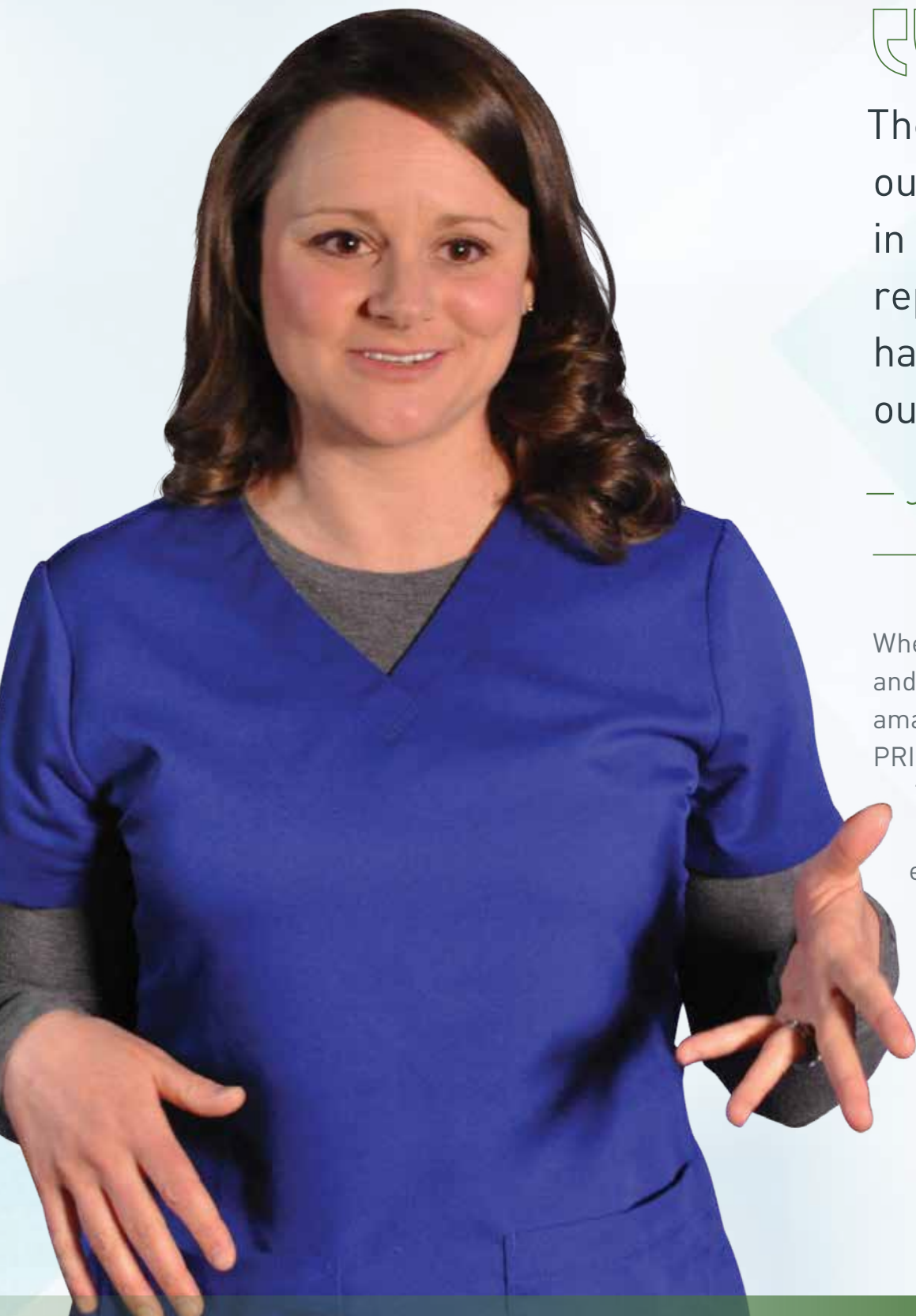
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The Future is Now

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Center for Medicare and Medicaid Innovation (CMMI) which is developing the model and will oversee its testing. Boehler spoke about CMMI's intention to test a kidney model that includes late-stage kidney diseases (stages 4 and 5), kidney failure, and transplantation, saying that the current state of kidney care "is an area that cannot remain static."

He noted that the rate of home dialysis in the United States is 11% while it is around 75% in Hong Kong. He also noted that the transplant rate for kidneys is approximately 20% while laying out ambitious goals for the very near future. Boehler said he would like to see 80% of patients with kidney failure either on home dialysis or receiving a kidney transplant by 2025. Both Secretary Azar and Deputy Administrator Boehler expressed confidence these goals are obtainable with a realignment of the incentives currently in place, especially with regard to payment/reimbursement policies.

A new future for patient data

To realign incentives and follow patients throughout their care, especially for patients with chronic conditions, patients need greater access to their own data to share with the many caregivers they interact with along

their journey. As such, CMS has issued a long-awaited proposed rule aimed at enhancing interoperability and increasing patient access to health information. The rule is one of a set of two rules; the other was issued by the HHS Office of the National Coordinator (ONC). Some of the highlights are:

- **ADTs and Facilities**
Requires hospitals, including psychiatric and critical access hospitals, to send an electronic notification when a patient is admitted, discharged, or transferred (ADT). The CMS proposed rules mention dialysis facilities once in the context of their eligibility to be included in models that will be tested by CMMI.
- **Trusted Exchange Networks**
Requires other private and public payers to participate in a trusted exchange network with the capacity for patients, providers, and insurers to access secure patient records, transmit them across EHRs, and provide a messaging and notification platform.
- **Mobile Apps**
Uses standardized Application Programming Interfaces (APIs) to allow patients and healthcare providers the opportunity to use third-party software (like a mobile app) to access secure information in a standardized format.
- **Information Blocking**
Prohibits "information blocking,"—the practice of

withholding data or intentionally limiting compatibility or interoperability of health information.

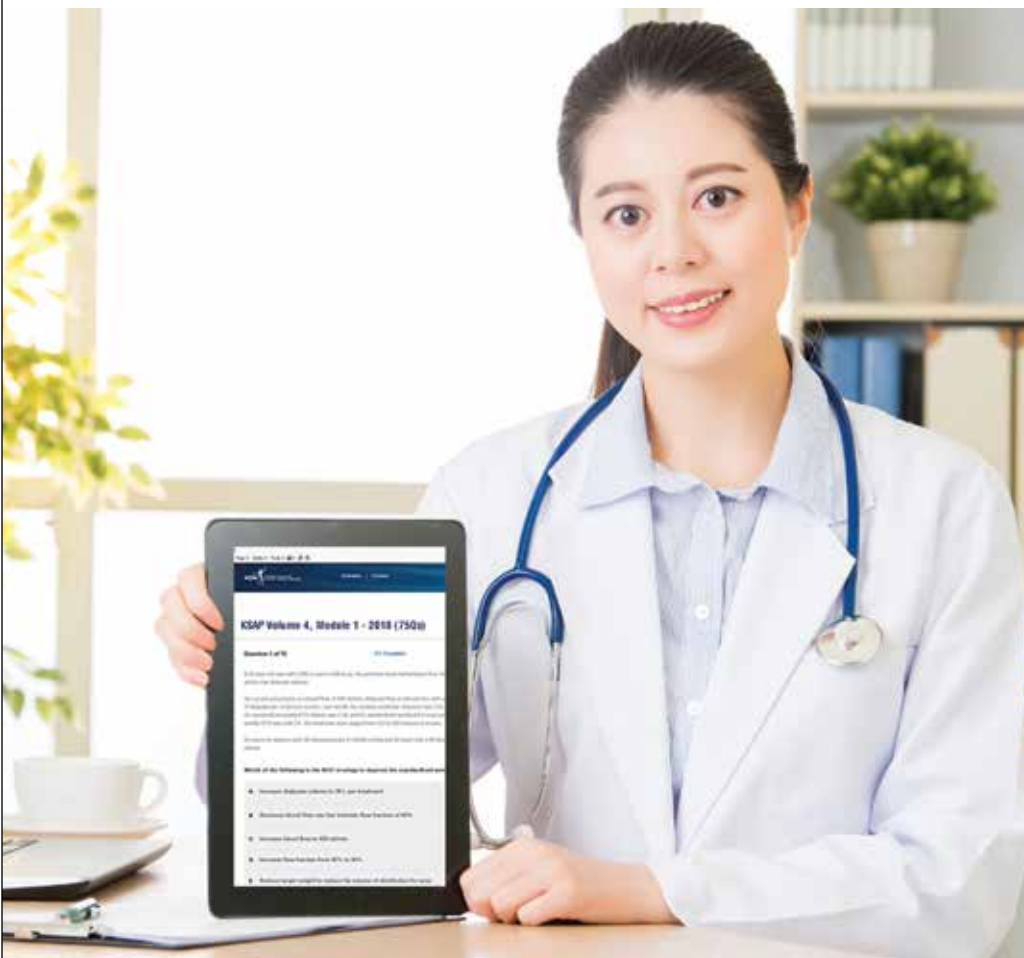
CMS proposes requiring compliance in two stages by January 1, 2020, and by July 1, 2020.

A new day for a long-awaited change for kidney transplant recipients

In keeping with his new look at kidney healthcare, Secretary Azar also signaled a potentially huge change in immunosuppressant drug coverage in March 2019. One week after his keynote speech on kidney healthcare, Secretary Azar revealed that a preliminary HHS Office of the Actuary analysis indicates that the savings generated by averting dialysis would be greater than the cost required to extend coverage for immunosuppressant drugs beyond the current three-year limit. While noting that any potential savings would be "specific to the design of any actual policy," the secretary underscored that HHS is "very focused on ways we can incentivize toward transplantation."

The preliminary analysis from the Office of the Actuary that points toward potential savings is significant news. For years, one of the chief challenges to passing legislation that extends lifetime Medicare coverage of immunosuppressant drugs for kidney transplant patients has been a concern regarding the cost of the legislation. This has been a policy priority for ASN for many years. ■

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MOC Concerns

Continued from page 1

the role of specialty societies in lifelong learning and continuous professional development.

“ASN affirms its position that each nephrologist choose a process of maintaining career excellence that upholds the values of the medical profession and highlights to patients and the public his or her ability to provide high-quality care,” said Suzanne M. Norby, MD, FASN, chair of the ASN Continuous Professional Development Committee and a faculty member at the Mayo Clinic College of Medicine.

On March 12, 2019, ABMS announced plans to implement recommendations from the report, including creation of collaborative task forces on remediation pathways, professionalism, advancing practice, and information and data sharing. The task forces will include representatives from professional and state societies and other external stakeholders, ABMS said in its announcement.

The announcement also noted that ABMS is committed to developing new, integrated standards for continuing certification programs by 2020, and that all 24 member boards agreed to commit to longitudinal or other formative assessment strategies and to offer alternatives to the highly secure, point-in-time examinations of knowledge.

Concerns remain

Opponents of the hotly debated maintenance of certification (MOC) are disappointed with some of the final recommendations, particularly the ongoing use of MOC instead of lifetime certification for physicians and the inclusion of practice improvement data.

Some like Lu Huber, MD, PhD, FASN, of Avera Medical Group Nephrology in Sioux Falls, SD, argue ABMS should issue lifetime certifications and leave ongoing oversight to professional associations.

“The self-regulation or self-policing of our profession should only involve physician organizations,” Huber said.

But proponents say the new recommendations may stimulate innovation and ease the process of maintaining certification for nephrologists with multiple specialties. Nephrologist Jeffrey S. Berns, MD, FASN, chair of the American Board of Internal Medicine Council, said it is important to note the recommendations do not support “continuing certification based solely on continuing medical education (CME) and state licensure.” Berns is associate dean for graduate medical education and nephrology fellowship director at the University of Pennsylvania.

“It should help guide a national dialogue about how best to keep physicians engaged in productive, lifelong learning and maintaining clinical skills over time,” Berns said. “It also stresses that a key function of ABMS boards is making summative decisions about certification status and acknowledges the notion that some diplomates may lose their certification status for failure to meet established certification standards.”

MOC by any other name

Since its creation, MOC has proved divisive, as some physicians have raised concerns about the time, cost, and clinical relevance of the programs.

“Physicians feel like their livelihood is at stake every 10 years,” explained Matthew E. Sparks, MD, FASN, assistant professor and associate program director of the nephrology fellowship program at Duke University. Sparks, who hosted a recent #AskASN Twitter chat on MOC, noted the process doesn’t account for workloads, research responsibilities, or family responsibilities and that it can affect a physician’s well-being. It also doesn’t take into account the work that most physicians do daily to keep up to date, he said.

Earlier versions of the commission’s recommendations also met with some criticism from the Council of Medical Specialty Societies (CMSS) and its 43 member specialty societies, including ASN. CMSS objected to the high-stakes exams and inclusion of practice improvement efforts in MOC. In its January 15, 2019, letter to the co-chairs of the Vision Commission, CMSS stated: “Given the significant role of specialty societies in practice improvement for their members, CMSS would be pleased to work with ABMS and the member boards on a future vision for practice improvement that would be collaborative and meaningful to practicing physicians, including participation in clinical registries.”

Huber argues that ABMS has a conflict of interest, and that the value of MOC versus continuing education has not been demonstrated.

“ABMS is a proprietary organization in the business of credentialing,” Huber said. “They should not speak for educational entities, our scientific or clinical societies, our hospitals or our state medical boards. The legitimacy of ABIM in promoting more credentialing processes such as MOC is therefore questionable, and raises significant issues, including financial conflicts.”

The Vision Commission’s final report acknowledges some concerns about MOC and provides numerous recommendations that aim to address them, starting with renaming MOC.

“A new term that communicates the concept, intent, and expectations of continuing certification programs should be adopted by ABMS in order to reengage disaffected diplomates and assure the public and other stakeholders that the certificate has enduring meaning and value,” the commission wrote.

It recommends that ABMS boards engage their diplomates in practice-relevant activities on an ongoing basis instead of at intervals of every 2, 5, or 10 years. It nixes the use of high-stakes, point-in-time exams in most circumstances.

There are many questions remaining about how these recommendations would be implemented and the effects they would have.

“If the high stakes exams are eliminated, how do we ensure that the burden to physicians in an alternative system is not even more, that it allows for them to continue to take care of patients and to be a productive member of the specialty while advancing clinical medicine and science?” Sparks asked.

Addressing another concern raised by ASN and other groups, the Vision Commission also discourages hospitals, health systems, and payers from using certification status as the sole criterion for credentialing and privileging decisions.

“That’s a good statement to have,” Sparks said, although he said the recommendation could have been stronger. He also questioned what it would mean for subspecialty certifications such as that for dialysis unit directors that are currently used as a job requirement.

The Vision Commission also urges ABMS and its boards to develop “consistent processes and requirements for continuing certification that are fair, equitable, transparent, effective, and efficient. It requires the boards to make public diplomates’ certification histories.”

But the commission’s decision to keep practice improvement in the final recommendations is likely to be controversial. Many physicians were uneasy with the idea of ABMS boards using data from their practices to assess quality improvement efforts, Sparks said, noting it might duplicate other quality improvement efforts required by payers or health systems.

“Being directly involved in extracting data from a physician’s practice is considered to be taking board certification too far,” Sparks said.

Berns countered that including practice improvement as a part of certification requirements rewards the many nephrologists engaged in quality improvement and patient safety efforts, and may expand opportunities for more to participate.

Data-driven innovation

As the recommendations move on to ABMS’s member boards, the debate about the best path forward is likely to continue. Many organizations will likely develop new continuing certification approaches to replace MOC. To help determine what is most effective, the Vision Commission recommends independent research to assess ongoing certification programs.

“It seems likely that new, innovative mechanisms to maintain certification will be developed that rely on assembling information from a variety of sources and depend less on a single test,” Berns said. He noted ABIM’s Knowledge Check-In, a two-year assessment option, is already designed this way. Internal medicine and nephrology are the specialties that have thus far piloted the Knowledge Check-In, and other options are likely to follow.

One recommendation from the Vision Commission that may be particularly helpful to nephrologists states that ABMS boards should streamline the process of maintaining certification in multiple specialties, Berns noted. This would allow clinicians to earn credit for certification in multiple specialties simultaneously. Many nephrologists maintain certifications in internal medicine and nephrology, and a growing number have certifications in critical care and hospice and palliative medicine.

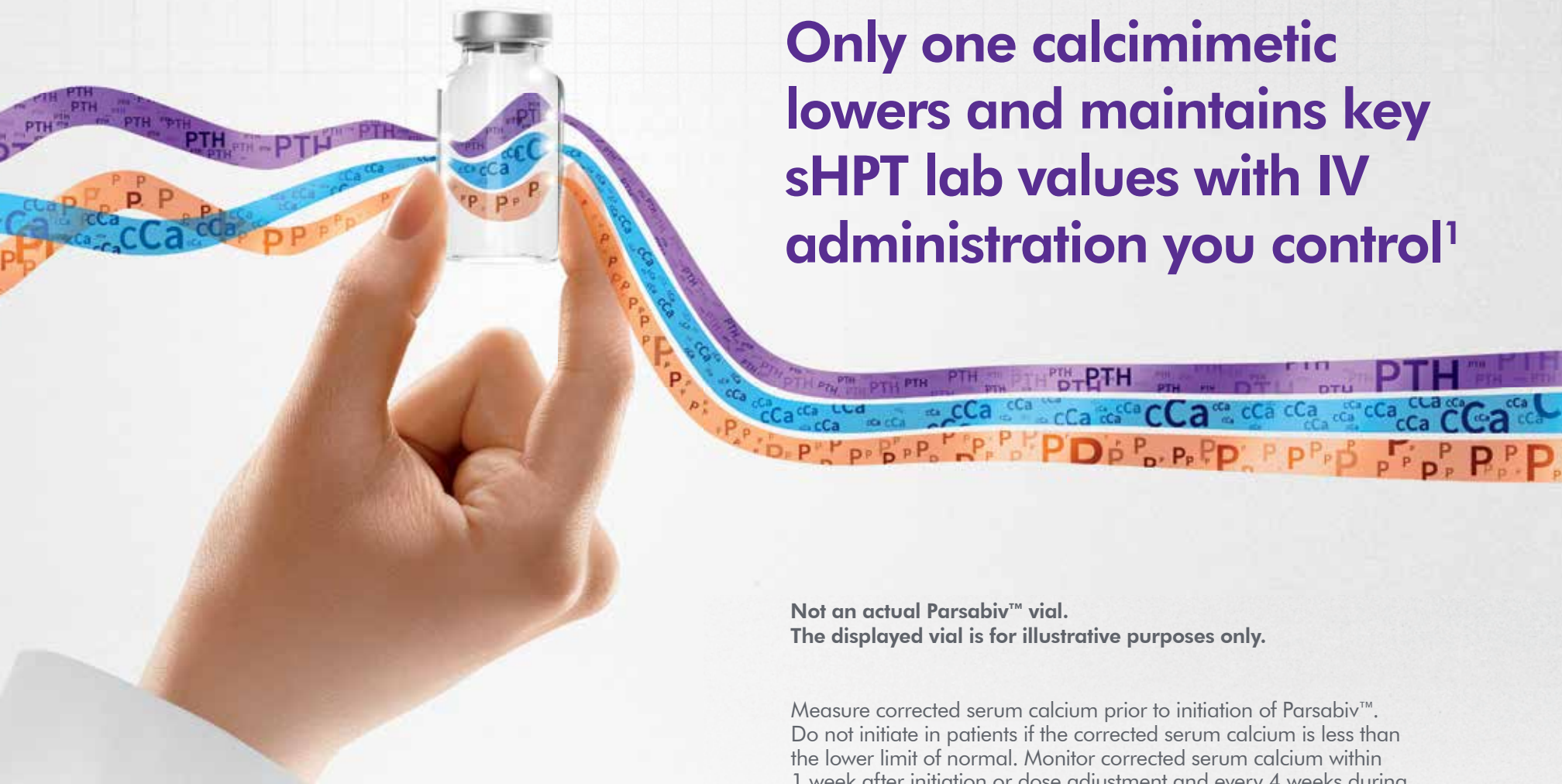
“I see great opportunities for ABIM to work with ASN and other societies to craft creative learning tools that really support continuous learning with regular formative feedback and directed learning targeted at filling in knowledge gaps and keeping current one’s knowledge,” Berns said.

Sparks said he would like to see more creative approaches to certification moving forward, particularly ones that leverage everyday activities physicians are already engaged in and that have data backing their effectiveness. For example, he highlighted the American Board of Anesthesiology’s Maintenance of Certification in Anesthesiology (MOCA) Minute program, which demonstrated success in a recent *New England Journal of Medicine* article. The program asks anesthesiologists to answer 30 multiple-choice questions relevant to their specific scope of practice each quarter. Physicians have one minute to answer each question and receive immediate feedback on incorrect answers as well as information on relevant continuing educational offerings.

“I’d like to see ABMS take these recommendations to heart and make the changes that need to be made,” Sparks said. This should include ending high-stakes exams, implementing a fair remediation process, and developing a more thoughtful process for dual or triple certified physicians, he said. ■

Suggested Reading

1. MOC Returns as a Hot Issue this Winter. *Kidney News* February 2019; 11:2 (www.kidneynews.org/kidneynews/current-issue/moc-returns-hot-issue-this-winter)
2. Bertka K. Continuing Board Certification: Vision for the Future Commission Draft Report for Public Comment. January 15, 2019. (https://www.asn-online.org/education/moc/2019_01_15_ASN_Comment_Letter_Vision_Commission.pdf)
3. Rosenberg M. Continuing Board Certification: Vision for the Future Commission Draft Report for Public Comment. January 15, 2019 (https://www.asn-online.org/education/moc/2019_01_15_ASN_Comment_Letter_Vision_Commission.pdf)
4. American Board of Internal Medicine. Knowledge Check In. <https://www.abim.org/maintenance-of-certification/assessment-information/assessment-options/knowledge-check-in.aspx>
5. Macario A, et al. Evolving board certification—glimpses of success. *N Engl J Med* 2019; 380:115–118; DOI:10.1056/NEJMp1809322



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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.

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™.

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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 [¹⁴C]-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 [¹⁴C]-etelcalcetide in lactating rats at maternal exposures similar to the exposure at the human clinical dose of 15 mg three times per week. [¹⁴C]-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 overdose. 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 overdose. In the event of overdose, 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/>

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Buddy Dialysis Probed as Hemodialysis Alternative

By Bridget M. Kuehn

More than 2 million individuals die worldwide each year because they don't have access to renal replacement therapy, a recent *Lancet* study suggested (1). In many low- and middle-income countries, patients cannot afford or don't have access to dialysis or transplant, said Peter Kotanko, MD, research director at the Renal Research Institute in New York.

"There is clearly a great unmet need," Kotanko said. "The main reason why dialysis is not delivered in these areas is because of the high cost."

Now, mathematical modeling data suggest that it may be possible to use a healthy volunteer's kidneys in lieu of dialysis.

paradigm. Kotanko and his colleagues are currently doing laboratory experiments to determine the best strategies for anticoagulation in allo-hemodialysis. They hope to test allo-hemodialysis in animal studies next year.

"This is an amazingly clever idea," said Roger Rodby, MD, professor of nephrology at Rush University Medical Center in Chicago. Rodby, who was not affiliated with the work, noted that many breakthroughs in medicine come from "out of the box" thinking.

Rodby cautioned, however, that the model focused on urea, the main toxin removed by dialysis. He noted that dialysis also performs other functions such as removing potassium and supplying bicarbonate, and it is not clear

Ethical issues for buddy dialysis

In addition to validating that such a model would work, there are ethical issues that would need to be addressed. These would include the potential risks to the health of the buddy, such as potential exposure to viruses or catheter-related complications.

To address whether it was ethical to further continue the research, Kotanko consulted Nicholas Steneck, PhD, a professor emeritus of history at the University of Michigan and a research integrity consultant. In an e-mail interview, Steneck noted that allo-hemodialysis is still in the development stages, and it is too early to assess many questions about the potential risks and benefits at this point.

"AlloHD does raise ethical questions, but in my view, none would suggest that further research should not be undertaken," Steneck said. "Given the magnitude of the problem being addressed—millions of individuals who do not have access to renal replacement therapy—there would seem to be an ethical mandate to explore other treatment options. Also, given the fact that access to treatment clearly depends on economic status, there would also seem to be an ethical mandate to explore options that will serve developing countries."

Steneck cautioned, however, that final judgments on ethics cannot be made until more research is completed on this intervention.

If the experimental technique is able to clear the next hurdles in research and development, Kotanko envisions that allo-hemodialysis sessions could be done at home using a very simple, inexpensive machine.

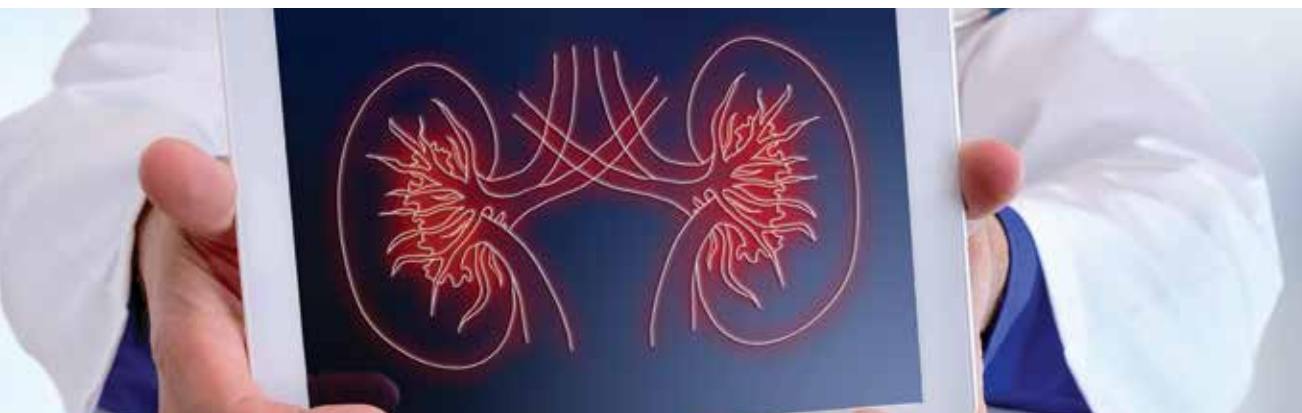
"We're envisioning that the practical challenges will be much less compared to current home dialysis [options]."

So far, Kotanko said that colleagues he has spoken to in several countries including Taiwan, Sudan, and Mexico have been very receptive to the idea given its low cost and simple technology, although he acknowledged not all cultures may be accepting of the idea. He hopes the technology could ultimately provide a treatment option for patients without access to hemodialysis or transplant.

"It's really about increasing choices," he said. ■

Reference

1. Lianage T, et al. Worldwide access to treatment for end-stage kidney disease: a systematic review. *Lancet* 2015; 14:61601-9.



Kotanko and his colleagues are exploring whether it would be possible to replace the need for a dialysis machine by creating a simple machine that would allow a buddy to filter toxins from a kidney patient's blood through a dialysis membrane with their own healthy kidneys, a process they call allo-hemodialysis.

Using mathematical modeling data, the group demonstrated that it would be possible to achieve adequate urea clearance from a 20 kg child through four 4-hour dialysis sessions with a healthy 70 kg adult. For an adult buddy to provide urea clearance for another adult, it would take 6 weekly sessions, the modeling suggested. Kotanko presented some of the group's findings at ASN Kidney Week 2018.

The results are just the first step in many that would be needed to validate such an experimental treatment

whether you could remove enough potassium or supply enough bicarbonate through allo-hemodialysis.

"Modeling should be done for the other ions [like potassium and bicarbonate] that you are affecting with a dialysis treatment to see if an expected balance could be achieved during the same treatment that modeling showed was effective for urea," Rodby suggested.

He noted there may be other practical challenges as well, including potential bloodborne transmission of viruses or transfer of medications from one person to another.

"Putting two people on dialysis simultaneously would not be easy," Rodby said. "The person with normal kidney function would have to sit there for 3 to 4 hours 4 times a week. That is a lot to ask anyone, but might be preferred to death of a loved one."

KIDNEY WEEK ON-DEMAND

Kidney Week *On-Demand* is available and includes access to the following Annual Meeting educational content presented during ASN Kidney Week 2018:

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ASN
American Society
of Nephrology

ASN and CDC's "Nephrologists Transforming Dialysis Safety" Team Up with Human Factors Engineers to Target Zero Infections in Hemodialysis

By Alan S. Kliger and Sarah Henrickson Parker

Each year in the United States, more than 8000 hemodialysis patients die after experiencing sepsis or other serious infectious complications. Of those patients, the highest percentage have infections related to a central venous catheter. Other vascular access sites can also become infected and cause sepsis.

Infections caused by multidrug-resistant organisms are far more common in the dialysis population than in the general population and have a high rate of mortality. Influenza is common and can be deadly in patients receiving dialysis. It has recently been estimated that more than 1000 dialysis patients in the United States die annually of influenza-like illnesses. Healthcare transmission of hepatitis C has occurred frequently among dialysis patients, and *Clostridium difficile* infections have increased in this population. Hospitalizations for infectious diseases now exceed hospitalization for cardiovascular disease in dialysis patients.

The Centers for Disease Control and Prevention (CDC) has recommended practices to prevent and monitor serious infectious disease in dialysis patients, using interventions that have been demonstrated to reduce infections and infectious complications. Despite these recommendations, sepsis and other complications of infection remain leading causes of morbidity and mortality in the dialysis population.

In response to this challenge, the CDC embarked on two major initiatives to raise awareness of the problem and the proven measures to reduce infection. The first initiative established The Making Dialysis Safer for Patients Coalition to bring organizations and individuals together and facilitate the implementation and adoption of tools to reduce infections. For the second initiative, the CDC provided 3 years of funding to the American Society of Nephrology (ASN) to establish Nephrologists Transforming Dialysis Safety (NTDS), a project with a goal to "Target Zero Infections" in dialysis patients. NTDS has reached more than half a million professionals through peer-reviewed and other publications, lectures, seminars, focus groups, and social media to get the word out: infections are the second leading cause of death and the leading cause of hospitalization—and most of these incidents are preventable.

To truly understand how work at the front lines of care is influencing patient safety, the CDC and the NTDS have integrated expertise from the field of human factors engineering. Human factors is a scientific discipline that examines human capabilities and limitations and applies that knowledge to the design of tools, technology, and processes to facilitate safe, efficient, and effective work. The focus of human factors is to integrate the scientific findings from psychology and engineering on human performance and to apply those findings to the design of daily work.

In the dialysis unit, staff members with diverse skill sets interact with one another and with complex patients with multiple comorbidities and with very complicated dialysis machines and other devices, ultimately to safely and efficiently deliver dialysis care. These complex interactions often present both barriers and facilitators to excellent team performance. System issues, such as time pressures, dialysis facility layout and space constraints, and dialysis policies and procedures, alongside variability in individual skill sets and cognition, result in a complex, challenging, and dynamic environment in which long-term care is provided. It can be challenging to bring these components together for best care. A hands-on assessment of how these elements—policies, procedures, machines, caregivers, and the patient—come together can enable an understanding of how and



Stephanie Booth, BSHCA (left), Laurie Wolf, PhD (center), and Alan Kliger, MD (right), discuss observations during a Human Factors visit to a dialysis facility.

why best practice is sometimes not carried out despite best intentions. Human factors engineers, specialists in assessing these complex environments, can help use evidence about human performance to redesign dialysis facility procedures to make them more intuitive and easier to accomplish.

Over a 6-month interval, NTDS is visiting six diverse dialysis facilities with respect to geography, ownership, and adult and pediatric patient populations. At each site, a team consisting of human factors engineers from Virginia Tech and Carilion Clinic in Roanoke, VA; physicians and nurses from the NTDS; and physicians and infection preventionists from the CDC spends two and a half days observing daily operations. The team interviews leadership and staff at each unit, conducts staff focus groups, and uses human factors assessment tools to understand the culture of each facility and the opportunities to improve operations. In each facility, this team specifically examines four domains: techniques of central venous catheter procedures at the onset and completion of dialysis, hand hygiene, medication preparation and administration, and disinfection of the dialysis station after dialysis procedures.

The team collects information on the movement patterns of staff as they go about their routine and urgent care duties, and they speak with staff about the challenges of their work and the need to multitask. They collect approximately 1000 pieces of information at each facility, detailing staff movement, medication administration procedures, catheter accessing, chair and machine cleaning between shifts, and other staff and patient activities. The engineers will often consider questions like these: If everyone understands the need for hand hygiene before and after touching the access site, why is this policy breached in some instances? What factors, such as space restraints, location of sinks and hand gel dispensers, competing priorities, drying effects of the alcohol-based gel on the skin, local practice culture, or other factors, may contribute to observed breaches in best practice? What unique aspects of each dialysis unit facilitate their staff "doing the right thing" every time?

NTDS, CDC, and the human factors engineers are compiling an overview report for each of these dialysis facilities. These reports outline the "facilitators" and "barriers" to delivering best-practice care in each of the four domains examined. After all six visits are completed, the team will then compile a detailed analysis of all data, allowing additional analysis of practices, facilitators, and barriers, and identify ways to improve or redesign processes to reduce infections

and other unintended complications.

The NTDS project, now in its third year, has taught us that three essential components can make care safer in dialysis facilities:

1. *Knowledge of best practice.* Every dialysis facility and all staff members need to understand what evidence-based best practice is, how to deliver it to their patients, and how to provide ongoing monitoring of these practices to sustain best care.
2. *Effective and inspiring leadership.* Nursing and medical leaders who can inspire their staff to better serve patients are the glue that holds a staff together and the vision of where a facility needs to go. By the example of their own practice, these leaders show how good communication, receptivity to feedback, examination of data from the patient cohort, and ability to respond effectively to clinical challenges all lead to happier staff and healthier patients.
3. *Analysis of how facility policies and procedures translate to direct care.* Human factors engineering provides the tools and the analytic techniques to understand the reality of a unit as it operates and to identify what potential system redesigns might provide improved outcomes for staff and patients alike. We might find some procedures that are most successful and can be shared among all dialysis units. We may find barriers that many facilities have in common, and potential solutions with widespread opportunity for improvement.

Our team is working together to target zero infections in dialysis units. These efforts may help change the current reality, whereby more hospital days are caused by infection than cardiovascular disease, or when one in ten dialysis patients dies of complications of infectious disease. We can get to zero preventable infections for our dialysis patients. ■

Alan S. Kliger, MD, is clinical professor of medicine, Yale School of Medicine, and chair, project committee, Nephrologists Transforming Dialysis Safety. Sarah Henrickson Parker, PhD, is senior director, Center for Simulation, Research and Patient Safety, Carilion Clinic; assistant professor, department of biomedical science, Virginia Tech Carilion School of Medicine; and assistant professor of research, Fralin Biomedical Research Institute at Virginia Tech Carilion and department of psychology, Virginia Tech.

FOR YOUR CKD PATIENTS

When you see risk factors of confirmed hyperkalemia...¹



Indication and Usage

VELTASSA is indicated for the treatment of hyperkalemia.

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

ACE=angiotensin-converting enzyme; CKD=chronic kidney disease.

PATIENT PORTRAYAL



Consider once-daily, sodium-free VELTASSA

IMPORTANT INFORMATION

Contraindications: VELTASSA is contraindicated in patients with a history of a hypersensitivity reaction to VELTASSA or any of its components.

Worsening of Gastrointestinal Motility: Avoid use of VELTASSA in patients with severe constipation, bowel obstruction or impaction, including abnormal post-operative bowel motility disorders, because VELTASSA may be ineffective and may worsen gastrointestinal conditions. Patients with a history of bowel obstruction or major gastrointestinal surgery, severe gastrointestinal disorders, or swallowing disorders were not included in clinical studies.

Hypomagnesemia: VELTASSA binds to magnesium in the colon, which can lead to hypomagnesemia. In clinical studies, hypomagnesemia was reported as an adverse reaction in 5.3% of patients treated with VELTASSA. Approximately 9% of patients in clinical trials developed hypomagnesemia with a serum magnesium value <1.4 mg/dL. Monitor serum magnesium. Consider magnesium supplementation in patients who develop low serum magnesium levels.

Adverse Reactions: The most common adverse reactions (incidence $\geq 2\%$) are constipation, hypomagnesemia, diarrhea, nausea, abdominal discomfort and flatulence. Mild to moderate hypersensitivity reactions were reported in 0.3% of patients treated with VELTASSA and included edema of the lips.

Please see Brief Summary of Prescribing Information on following page.



ACCESS TO VELTASSA IS **BROAD AND IMPROVING**²

VELTASSA is covered by **most insurance plans**, including Medicare Part D.



VELTASSA HAS BEEN PRESCRIBED TO OVER **50,000 PATIENTS** SINCE APPROVAL³

Join **thousands of physicians** helping their patients by treating hyperkalemia with VELTASSA.



Industry Spotlight

AKI Research News

Scientists are making strides in predicting occurrence of acute kidney injury (AKI) and in evaluating extensive data on patients who recover from AKI.

The Department of Veterans Affairs (VA) announced a year ago that it had signed a formal agreement with DeepMind to gather and analyze data on kidney disease and other conditions. *Wired* magazine caught up with the project's status recently, and noted that it drew on about 700,000 medical records from veterans. The VA has

been working with DeepMind (owned by Google's parent company, Alphabet) to create software that tries to predict when patients might develop AKI.

The VA's director of predictive analytics, Christopher Nielsen, told *Wired* that the project has "been fairly successful in predicting AKI at an early enough stage to prevent it."

The next step may be to use live data from the VA system to evaluate the accuracy of the AKI predictive factors over time, *Wired* noted. Then it would be possible to

introduce the system for use in a VA clinic to see if it helps improve care, a test that is at least one year away.

Dialysis and kidney care giant Fresenius also is interested in using its extensive patient data to learn more about AKI. Of 9000 patients diagnosed with AKI at Fresenius North America outpatient clinics, about one-third recovered kidney function within 90 days of beginning in-center hemodialysis, according to Fresenius.

Overall, 38% of patients recovered kidney function within 150 days of initiating

outpatient therapy, the company said in a press release.

The preliminary analysis of the Fresenius data included several clinical measures, such as type of vascular access used, ultrafiltration rates, and biochemical measures during the first 90 days of outpatient dialysis therapy.

The data also suggested that 20% of patients who begin outpatient in-center hemodialysis are diagnosed with AKI, and 44% of those patients transition to ESRD within 150 days of starting outpatient hemodialysis.

"This groundbreaking data holds enormous promise for developing further insights into the treatment of acute kidney injury," said Frank Maddux, MD, chief medical officer and executive vice president for clinical and scientific affairs at Fresenius Medical Care North America. ■

VELTASSA® (patiomer) for Oral Suspension

Brief Summary of Prescribing Information. Please see Full Prescribing Information for complete product information.

INDICATION AND USAGE

VELTASSA is indicated for the treatment of hyperkalemia.

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

CONTRAINDICATIONS

VELTASSA is contraindicated in patients with a history of a hypersensitivity reaction to VELTASSA or any of its components [see *Adverse Reactions*].

WARNINGS AND PRECAUTIONS

Worsening of Gastrointestinal Motility Avoid use of VELTASSA in patients with severe constipation, bowel obstruction or impaction, including abnormal post-operative bowel motility disorders, because VELTASSA may be ineffective and may worsen gastrointestinal conditions. Patients with a history of bowel obstruction or major gastrointestinal surgery, severe gastrointestinal disorders, or swallowing disorders were not included in the clinical studies.

Hypomagnesemia VELTASSA binds to magnesium in the colon, which can lead to hypomagnesemia. In clinical studies, hypomagnesemia was reported as an adverse reaction in 5.3% of patients treated with VELTASSA [see *Adverse Reactions*]. Monitor serum magnesium. Consider magnesium supplementation in patients who develop low serum magnesium levels on VELTASSA.

ADVERSE REACTIONS

The following adverse reaction is discussed in greater detail elsewhere in the label:

- Hypomagnesemia [see *Warnings and Precautions*]

Clinical Trials Experience Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of VELTASSA cannot be directly compared to rates in the clinical trials of other drugs and may not reflect the rates observed in practice. In the safety and efficacy clinical trials, 666 adult patients received at least one dose of VELTASSA, including 219 exposed for at least 6 months and 149 exposed for at least one year. Table 1 provides a summary of the most common adverse reactions (occurring in $\geq 2\%$ of patients) in patients treated with VELTASSA in these clinical trials. Most adverse reactions were mild to moderate. Constipation generally resolved during the course of treatment.

Table 1: Adverse Reactions Reported in $\geq 2\%$ of Patients

Adverse Reactions	Patients treated with VELTASSA (N=666)
Constipation	7.2%
Hypomagnesemia	5.3%
Diarrhea	4.8%
Nausea	2.3%
Abdominal discomfort	2.0%
Flatulence	2.0%

During the clinical studies, the most commonly reported adverse reactions leading to discontinuation of VELTASSA were gastrointestinal adverse reactions (2.7%), including vomiting (0.8%), diarrhea (0.6%), constipation (0.5%) and flatulence (0.5%). Mild to moderate hypersensitivity reactions were reported in 0.3% of patients treated with VELTASSA in clinical trials. Reactions have included edema of the lips.

Laboratory Abnormalities Approximately 4.7% of patients in clinical trials developed hypokalemia with a serum potassium value < 3.5 mEq/L. Approximately 9% of patients in clinical trials developed hypomagnesemia with a serum magnesium value < 1.4 mg/dL.

DRUG INTERACTIONS

In clinical studies, VELTASSA decreased systemic exposure of some coadministered oral medications. Binding of VELTASSA to other oral medications could cause decreased gastrointestinal absorption and loss of efficacy when taken close to the time VELTASSA is administered. Administer other oral medications at least 3 hours before or 3 hours after VELTASSA.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

VELTASSA is not absorbed systemically following oral administration and maternal use is not expected to result in fetal risk.

Lactation

Risk Summary

VELTASSA is not absorbed systemically by the mother, so breastfeeding is not expected to result in risk to the infant.

Pediatric Use Safety and efficacy in pediatric patients have not been established.

Geriatric Use Of the 666 patients treated with VELTASSA in clinical studies, 59.8% were age 65 and over, and 19.8% were age 75 and over. No overall differences in effectiveness were observed between these patients and younger patients. Patients age 65 and older reported more gastrointestinal adverse reactions than younger patients.

Renal Impairment Of the 666 patients treated with VELTASSA in clinical studies, 93% had chronic kidney disease (CKD). No special dosing adjustments are needed for patients with renal impairment.

OVERDOSAGE

Doses of VELTASSA in excess of 50.4 grams per day have not been tested. Excessive doses of VELTASSA may result in hypokalemia. Restore serum potassium if hypokalemia occurs.

PATIENT COUNSELING INFORMATION

Drug Interactions Advise patients who are taking other oral medication to separate the dosing of VELTASSA by at least 3 hours (before or after) [see *Drug Interactions*].

Dosing Recommendations Inform patients to take VELTASSA as directed with or without food and adhere to their prescribed diets. Inform patients that VELTASSA should not be heated (e.g., microwaved) or added to heated foods or liquids and should not be taken in its dry form.

Manufactured for:

Relypsa, Inc.
Redwood City, CA 94063
Version 05; May 2018

References: 1. Weir MR, Bakris GL, Bushinsky DA, et al; for OPAL-HK Investigators. Patiomer in patients with kidney disease and hyperkalemia receiving RAAS inhibitors. *N Engl J Med.* 2015;372(3):211-221. 2. Data on file as of December 2017. Relypsa, Inc. 3. Data on file as of March 2018. Relypsa, Inc.

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Different Fates for two RCC Treatments

One manufacturer has decided not to file for FDA approval of its renal cell carcinoma (RCC) treatment, while another manufacturer's combination of RCC drugs has won European approval.

Aveo Oncology, based in Cambridge, MA, decided against filing a new drug application for tivozanib (brand name Fotivda) in the United States. The FDA had informed Aveo that it was unsatisfied with the drug's overall survival data, and that the data failed to improve upon initial concerns the FDA had when it rejected the drug in 2013.

In that year, the FDA questioned the drug's benefits because data showed that tivozanib failed to beat the overall survival rate of Bayer's drug, Nexavar, FierceBiotech reported. An August 2018 analysis of required data will no longer be Aveo's final analysis but rather an interim analysis as the company continues toward FDA approval. Fotivda is approved for first-line treatment of advanced RCC in Europe.

Meanwhile, an RCC treatment that consists of a drug combination was approved for European patients. Bristol-Myers Squibb (Princeton, NJ) announced that the European Commission had approved the combination of its trademarked drugs Opdivo (nivolumab) 3 mg/kg plus Yervoy (ipilimumab) 1 mg/kg ("low-dose").

The combination therapy is a first-line therapy to treat patients with intermediate- and poor-risk advanced RCC. The European approval hinged on results from the CheckMate-214 trial, a phase 3, randomized, open-label study evaluating the combination of Opdivo plus Yervoy versus sunitinib in patients with previously untreated advanced renal cell carcinoma. The FDA has already approved the combination for certain patients whose cancer has metastasized. ■

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NURSING HOME DIALYSIS

Rapidly Growing and Complicated

By Suresh Samson, MD, FASN

On August 10, 2018, the Centers for Medicare & Medicaid Services (CMS) published updated regulations for dialysis facilities (1). The CMS guidance encompasses several modalities, with a focus on the locations where dialysis services are provided.

The new guidance reaffirmed CMS' recognition of dialysis in a nursing home setting, making revisions to the State Operations Manual (Chapter 2, ESRD Facilities), adding section 2271A, titled "Dialysis in Nursing Homes." This action affirmed that Medicare-approved ESRD facilities may provide dialysis services to skilled nursing facility (SNF) residents in the nursing home within an approved home training and support modality. These new requirements include operational, logistical, physical, and staffing guidelines for nursing home dialysis. What follows is a summary of the nursing home dialysis model.

First, let us briefly frame the term "subacute care dialysis" (SACD), which includes dialysis provided in SNFs. Dialysis patients in such facilities may receive hemodialysis or peritoneal dialysis. Hemodialysis in these facilities

in nursing homes is unclear. However, using data from the U.S. Renal Data System and CMS, reliable estimates place the number at about 10% of the broader nationwide dialysis population—at approximately 70,000 (2, 3). With the rapid increase in the number of new ESRD patients in the >65 years age group, this number is sure to increase in the coming years.

SACD: the logistics

The framework under which SACD is provided is simple: The nursing home chooses the space in its building to convert into a hemodialysis unit, and it bears the expense of constructing the unit. If conventional thrice-weekly dialysis is sought, a nursing home dialysis unit has many of the physical characteristics of a standalone outpatient unit—just in miniature form. It will have its own water treatment system, dialysis equipment, and traditional dialysis supplies. The nursing home would contract with a home dialysis provider to provide services. CMS guidelines indicate that the ESRD facility can only provide home dialysis services to a nursing home resident under a written agreement with the home, and that the nursing home is charged with maintaining direct responsibility for the dialysis-related care over that patient. Moreover, the quality of such services must remain consistent with the ESRD Conditions for Coverage requirements, as well as the terms of an applicable agreement with the nursing home. The agreement itself must clearly delineate the responsibilities of the ESRD facility and the nursing home regarding the care of the resident before, during, and after dialysis treatments (1).

The new guidance emphasizes the need for communication and collaboration between the dialysis provider and nursing home. There must be a constant, uninterrupted flow of information between the dialysis unit and the nursing home staff, through systematic processes. Unlike traditional in-center dialysis facilities, a nursing home dialysis provider must establish defined mechanisms to ensure that respective staffs are exchanging information,

As someone overseeing these processes, my recommendation is that the agreement between the two entities clearly set forth each entity's responsibilities and build in weekly and monthly meetings between appropriate members of the respective interdisciplinary teams to address any nonmedical/clinical needs, general medical/clinical needs, and each patient to assess plans of care and potential problems or issues that could hamper treatment goals.

SACD from a patient's perspective

In most states, a hemodialysis patient admitted to a nursing home must be transported to a regular dialysis unit three-times weekly. The provision of dialysis in-house eliminates the need for the patient to endure such travel, which carries multiple risks, particularly in cold-weather states. Receiving in-house dialysis treatment, on the other hand, allows patients to spend more time receiving therapy and working to improve their condition and to work toward discharge home.

More time is also afforded for physician visits and recreational time. Whether in-house dialysis reduces the length of nursing home stay is yet to be seen. This model is a great advantage for the patient and his or her family.

SACD from a physician's perspective

Physicians must be versed with this model to appropriately care for their patients.

First, they will naturally be required to have privileges with the dialysis provider to see patients in the dialysis unit. Because of the need for a significant amount of coordination of care with the nursing home and its staff, however, it would behoove physicians to obtain privileges with the nursing home as well. Given that patients have multiple comorbidities and a higher acuity than the average in-center patient, their medication regimen often changes with more frequency, increasing the utility of having access to both the dialysis provider and nursing home's systems for better control and management of such patients.

Of note, CMS considers SNFs to be the patient's home (4). Therefore, these patients are required to be seen at least once a month as is the case with conventional home dialysis patients. This is an important distinction between SACD and the in-center setting. Although patients can be scheduled to see physicians in their own clinics, my recommendation is to do the monthly physician examination in the nursing home—and not necessarily during dialysis. This offers the physician the opportunity to better coordinate the patient's care and facilitates a discussion of care plans with the interdisciplinary team.

Physicians may also discover opportunities to serve as medical directors with nursing home dialysis providers. Because each dialysis unit has a small capacity, this may include overseeing care at multiple nursing home dialysis units. Physicians may use such opportunities to build relationships with area nursing homes and hospitals, while also assisting nursing homes with the crafting and implementation of their policies and procedures, which are essential for the proper care of dialysis patients.

General pitfalls to avoid

- Ensure that your name is entered on the nursing home patient's chart as the nephrologist, with your contact details.
- Obtain privileges with *both* the dialysis provider and the SNF. You will be unable to provide orders directly if you do not have SNF privileges.
- Familiarize yourself with both electronic medical record (EMR) systems.
- Owing to the high proportion of patients with multi-drug-resistant infections, familiarize yourself with infection control policies of both the dialysis provider and SNF.
- Communicate with the interdisciplinary team for both the dialysis provider and the SNF.
- Evaluate patients monthly. It is not required that you

can be either conventional thrice-weekly treatments or shorter treatments five or six days weekly. As the nursing home peritoneal dialysis population is small and delivery relatively straightforward, this article concentrates on hemodialysis in nursing homes.

While there are nearly 700,000 ESRD patients in the United States (2), the precise number of dialysis patients

which will lead to timely and appropriate medication administration; knowledge of physician/treatment orders; laboratory values and vital signs; nutritional/fluid management; changes and/or decline in condition unrelated to dialysis; the occurrence or risk of falls; dialysis adverse reactions/complications; and/or recommendations for follow-up observations and monitoring.



examine patients while they are receiving dialysis. They may be examined outside the dialysis unit.

- Develop a team of cardiologist, vascular surgeon, and interventionalist to coordinate access placement.
- Ensure communication to the patient's regular dialysis unit about any changes during the nursing home stay.

Physicians must be aware of certain clinical challenges that are unique to this model of dialysis care. Nearly 30% of ESRD patients are admitted to SNFs in the last 90 days of life (5). Preliminary unpublished data on 1800 ESRD patients who underwent dialysis in 2018 by Concerto Renal Services—one of the nation's largest nursing home dialysis providers, which performs thrice-weekly hemodialysis—show the following:

- Only 50% of patients achieved an anemia goal between 9 and 11 g/dL.
- Nearly 25% had phosphorus levels <3 mg/dL.
- Nearly 40% had albumin <3.5 g/dL in spite of adequate protein supplementation.
- 40% of patients had a >90-day catheter rate.
- There was a 35% readmission rate for patients admitted with hemoglobin <8 g/dL compared with <10 g/dL for others.

Multiple variables may account for these findings. First, dialysis patients in nursing homes tend to be sicker, with more comorbidities and ongoing inflammation, mostly in the setting of conditions like decubitus ulcers, urinary catheters, colitis, and diabetic ulcers. Their nu-

tritional status is often poor, reflecting the high proportion of patients with low phosphorus levels. Physicians and medical directors will also face the challenge of getting access placement for this population, mainly due to the shorter length of stay in nursing homes and patients' multiple comorbidities requiring extensive evaluation for surgical clearance.

SACD from a nursing home perspective

On-site dialysis improves the efficiency of nursing homes by reducing the need for transportation arrangements for dialysis. Because of the above-mentioned advantages, it is likely that a nursing home with on-site dialysis will attract more patients.

On-site dialysis also saves on healthcare costs. A study by Stephens et al. estimated the national cost of dialysis transportation for the year 2014 to be nearly \$3.2 billion. The cost per dialysis patient per year was estimated to be about \$8300 (6).

Despite nursing homes' bearing the costs of building the dialysis unit, on-site dialysis can rightfully be seen as a prudent investment. Given the growth in the number of elderly dialysis patients, this is an essential service and will benefit the nursing home in the long run.

This care model is an evolving one, with the prospect of additional clarity from the CMS in the coming years as the number of nursing home dialysis patients rapidly increases. As with any healthcare model, this one must retain quality patient care as the core principle, and all parties will benefit. ■

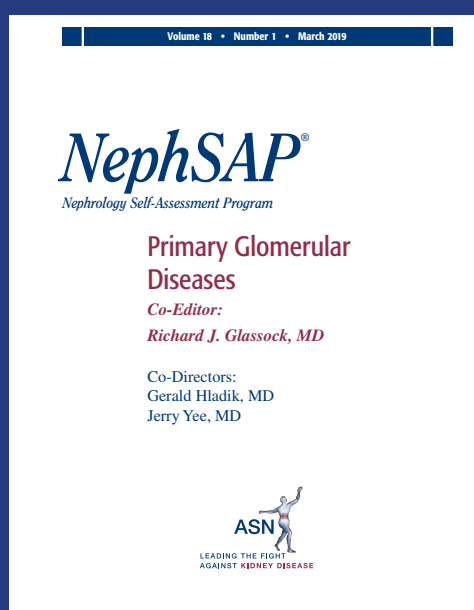
Suresh Samson, MD, FASN, is the Chief Medical Officer for Concerto Renal Services (Concerto), a Chicago-based dialysis provider and one of the nation's largest providers of nursing home dialysis. In 2018, Concerto provided nursing home dialysis to nearly 1800 patients in Illinois, Indiana, and Wisconsin, and is currently working to implement its model in multiple other states by the close of 2019.

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Fellows Corner

Blood Pressure Variability: The Basics and Beyond

By Sriram Sriperumbuduri



Sriram Sriperumbuduri

Blood pressure (BP) is a dynamic entity and, just like many other orders in nature, is affected by variability. Studies have shown variability in an individual's BP over seconds, minutes, and days. This variability has been found to correlate with morbidity and mortality events. This review is intended to highlight some basic concepts of this entity with a focus on measures of variability and outcomes. The types of BP variability are shown in Table 1 (1).

Indices for measurement of short-term variability

Short-term variation is measured by 24-hour ambulatory BP monitoring (ABPM) through the following indices:

The standard deviation (SD) of 24-hour average BP values is used widely, but its main drawback is that it represents the dispersion of values around the mean but does not account for the order in which BP measurements are obtained. It is sensitive to the low sampling frequency of noninvasive BP monitoring.

The weighted mean of daytime and nighttime values is used because the nighttime fall in BP has more effect on an accurate BP variability assessment. In the study by Bilo et al. (2), the weighted 24-hour SD of BP removed the mathematical interference from the nighttime fall in BP and correlated better with end-organ damage.

The coefficient of variation (CoV) is the ratio of the average SD of BP and the mean BP multiplied by 100.

The average real variability (ARV) is a more reliable prognostic indicator than SD because it is sensitive to the order of individual BP measurements. First described by Mena et al. (3) in 2005, ARV represents a reliable index inspired by a total variability concept of real analysis in mathematics. For example, Figure 1 shows that two subjects with different BP measurement sets could have the same SD but different ARVs: clearly, subject b with more variability has a higher ARV than subject a, who has less variability despite a similar SD. Therefore, the SD index may not always reflect data variability.

In their study of 312 subjects, Mena et al. (3) tested the performance of ARV versus SD and showed a statistically significant relative risk of 4.548 for cardiovascular (CV) events in the group with higher BPV with respect to low BPV with ARV. The relative risk for the SD index was not significant statistically. Thus, ARV may be a better measure based on which patients could be treated.

Significance of BP variability

Increased BP variability has been reported to be associated with adverse CV outcomes; hence, there has been a resurgence in studies investigating this area. This is beyond a mere assessment of circadian BP patterns (e.g., nocturnal dipping status, morning surge), which have been known for a while to be associated with adverse outcomes.

In a post hoc analysis of the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) (4), which included 25,814 patients, the higher visit-to-visit variability (VVV) of systolic BP to SBP (defined as the SD of SBP measurements over seven visits) was associated with an increased risk for CV disease and mortality. The hazard ratio for SBP variability in a comparison of study participants in the highest versus the lowest quintile of SD (≥ 14.4 mm Hg vs. < 6.5 mm Hg) was 1.30 (95% confidence interval [CI], 1.06 to 1.59) for fatal coronary heart disease or nonfatal myocardial infarction, 1.58 (CI, 1.32 to 1.90) for all-cause mortality, 1.46 (CI, 1.06 to 2.01) for stroke, and 1.25 (CI, 0.97 to 1.61) for heart failure.

Verdecchia et al. (5) analyzed the association of ambulatory BP variability with mortality and CV events by studying 7112 individuals with untreated hypertension; their mean age was 52 years, and the median follow-up time was 5.5 years. The nighttime systolic BP SD of ≥ 12.2 mm Hg was associated with a 41% greater risk of CV events, a 55% greater risk of CV death, and a 59% increased risk of all-cause mortality in comparison with an SD of < 12.2 mm Hg. The authors suggested that the addition of BP variability to models of long-term outcomes in hypertensive patients would increase the predictive value for long-term outcomes.

Impact of treating BP variability

Inasmuch as both short-term and long-term variability have shown an association with CV events, treating variability might be a beneficial target for CV protection. In the Anglo-Scandinavian Cardiac Outcomes Trial Blood Pressure Lowering Arm (ASCOT-BPLA) trial (6), both VVV and ABPM BP variability were reduced by amlodipine, which likely contributed to the reduced event rate in that group versus atenolol. A study by Hoshimo et al. (7) of 31 patients showed the effect of chronotherapy; the administration of amlodipine and olmesartan at bedtime reduced the morning BP surge, corrected the nocturnal BP fall, and improved urine albumin excretion.

Thus, BP variability represents an interesting entity with a wide scope for review and research. Many questions and avenues are still to be explored in this area. What are the mechanistic explanations for the difference in variability? Would any interventions favorably change this variability, and would these interventions

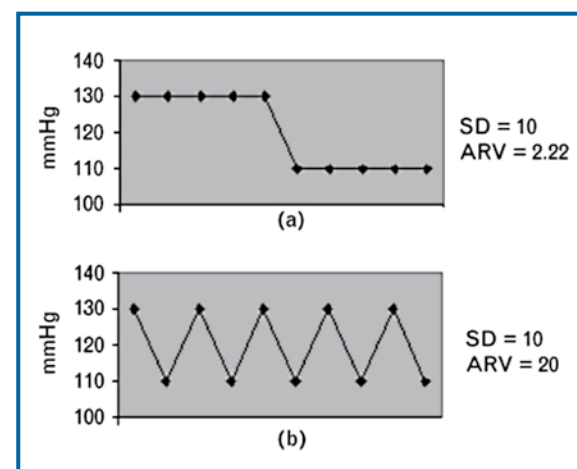
have a beneficial effect on clinical outcomes? More research is needed. ■

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Figure 1. Comparison of the two measures of BP variability



The standard deviation (SD) is similar in the two subjects (a) and (b) but the average real variability (ARV) is variable. The calculation is based on the following computer-based formula, from the 24-hour ambulatory BP monitoring data: $ARV = 1/N-1 \sum_{k=1}^{N-1} |BP_{k+1} - BP_k|$ where N = number of valid BP measurements and K = order of measurements from each subject's monitoring.

Table 1. Types of BP variability

CHARACTERISTIC	TYPE		
	VERY SHORT TERM	SHORT TERM	LONG TERM
What is it?	Beat-to-beat changes in BP	Variation in BP over minutes to hours	Variation over days, office visits, and seasons
What causes it?	Interaction between RAS, vascular myogenic response, and NO release from endothelium	Physical activity, sleep, emotional stimuli, humoral and local vasomotor phenomena	Inadequate treatment, measurement errors, seasonal influences, temperature, daylight hours, behavior
How is it measured?	Specialized finger cuffs	24-hour ABPM	ABPM, OBPM, HBPM

RAS, renin-angiotensin system; NO, nitric oxide; ABPM, ambulatory BP monitoring; OBPM, office BP monitoring; HBPM, home BP monitoring.

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Findings

Teen Blood Pressure Predicts Future ESRD Risk



Otherwise-healthy adolescents with hypertension are at double the risk of developing end stage renal disease (ESRD) as adults, reports a study in *JAMA Internal Medicine*.

The retrospective study included nearly 2.7 million healthy Israeli youth, aged 16 to 19, who underwent medical evaluation before military conscription from 1967 through 2013. Sixty percent of participants were male. The mean age was 17.4 years. The analysis excluded those with evidence of kidney damage or risk factors for kidney disease. Adolescent hypertension was evaluated for association with ESRD diagnosed from 1990 through 2014, based on national registry data.

At examination, 0.3% of adolescents had diagnosed hypertension (higher than 140/90 mm Hg). Approximately 29% of individuals with hypertension were obese and 20% were overweight, compared to 4% and 9% of nonhypertensive adolescents, respectively. About 42% of hypertensive youth were from the United States or Europe and 21% were from the former Soviet Union.

During a median follow-up of 19.6 years, ESRD was diagnosed in 0.5% of participants who had had hypertension as adolescents. This group had a crude ESRD incidence rate of 20.2 per 100,000 person-years, compared to 3.9 per 100,000 for the nonhypertensive group. In a fully adjusted multivariable model, adolescent hypertension was associated with a twofold increase in ESRD risk: odds ratio 1.98. The association remained significant on analysis excluding participants with severe hypertension (higher than 160/100 mm Hg) and on subanalysis of non-overweight adolescents.

The presence of established hypertension during late adolescence is associated with a twofold increase in the risk of developing ESRD later in life.

“This finding may suggest that nonmalignant hypertension, while being a close surrogate and strong promoter of chronic kidney disease progression, is a relatively modest initiator of the disease,” the researchers write [Leiba A, et al. Association of adolescent hypertension with future end-stage renal disease. *JAMA Intern Med* 2019; DOI: 10.1001/jamainternmed.2018.7632]. ■

Higher eGFR Linked to Higher Mortality in Pediatric Dialysis Patients

For children and adolescents with end stage renal disease, a higher estimated glomerular filtration rate (eGFR) at the time of dialysis initiation is associated with an increased risk of death, reports a study in the *American Journal of Kidney Diseases*.

The study used US Renal Data System data on 9963 patients aged 1 to 17 (median 13 years) starting dialysis between 1995 and 2016. Using the pediatric-specific bedside Schwarz equation, initial eGFR was classified as less than 5 mL/min/1.73 m² in 19% of patients, between 5 and 7 mL/min/1.73 m² in 22%, between 7 and 9 mL/min/1.73

m² in 23%, between 9 and 12 mL/min/1.73 m² in 20%, and 12 mL/min/1.73 m² or higher in 17%. Time to death from any cause was compared among eGFR groups, with adjustment for case-mix variables, height, body mass index, and hemoglobin and serum albumin levels.

At a median follow-up of 1.4 years, 696 patients died; the overall mortality rate was 31 per 1000 patient-years. Mortality was incrementally higher for pediatric patients with higher eGFRs: adjusted hazard ratios were 0.57 in the under 5 mL/min/1.73 m² group versus 1.31 in the 12 mL/



min/1.73 m² and higher group (with eGFR between 7 and 9 mL/min/1.73 m² as the reference group). The association between eGFR and mortality was consistent among patients aged 6 years or older but was weaker in the relatively small group (1263 patients) under age 6.

The association between eGFR at dialysis initiation and mortality in adults remains controversial, with some studies reporting no benefit of earlier dialysis. Few studies have looked at the relationship between eGFR and mortality in pediatric dialysis patients.

This retrospective study finds increased mortality among children and adolescents with higher eGFR at dialysis initiation. The association appears to be modified by age, with an attenuated effect in children less than 6 years old. The authors emphasize the need for further studies in this younger age group, as well as studies evaluating the benefits of starting dialysis at lower eGFRs in pediatric kidney disease [Okuda Y, et al. Estimated GFR at dialysis initiation and mortality in children and adolescents. *Am J Kidney Dis* 2019; DOI: 10.1053/j.ajkd.2018.12.038]. ■

New Combination for First-line Therapy of Advanced RCC

Compared to sunitinib, a combination of avelumab plus axitinib improves progression-free survival in patients with advanced clear-cell renal cell carcinoma (RCC), reports a phase 3 randomized trial in *The New England Journal of Medicine*.

The industry-sponsored JAVELIN Renal 101 trial included 886 patients with previously untreated advanced RCC with a clear-cell component—the most common type of kidney cancer. Patients assigned to the intervention group received the immunotherapy drug avelumab plus the highly selective vascular endothelial growth factor (VEGF) receptor inhibitor axitinib. Those in the comparison group received the anti-VEGF agent sunitinib, which has been a standard treatment for advanced clear-cell RCC.

The two primary endpoints were progression-free and overall survival among the 560 patients whose tumors were positive for programmed cell death ligand 1 (PD-L1). Progression-free survival in the overall sample was also assessed, along with objective response and safety outcomes.

In the PD-L1–positive group, median progression-free survival was 13.8 months with the avelumab/axitinib combination compared to 7.2 months with sunitinib: hazard ratio (HR) 0.61 for disease progression or death. Avelumab plus axitinib had a similar advantage in the overall population: progression-free survival 13.8 versus 8.4 months, HR 0.69.

The avelumab/axitinib combination had a 55.2% objective response rate in PD-L1–positive patients, compared to 25.5% with sunitinib. There were 37 deaths in the avelumab/axitinib group (median follow-up 11.6 months) and 44 in the sunitinib group (median follow-up 10.7 months). In both groups, 99% of patients experienced adverse events, with more than 70% of events being grade 3 or higher.

In a previous phase 1b trial in patients with advanced clear-cell RCC, avelumab plus axitinib produced an objective response rate of 58% and a disease control rate of 78%, with better results in PD-L1–positive patients. The JAVELIN Renal 101 results show longer progression-free survival with first-line avelumab plus axitinib, compared to sunitinib.

The efficacy benefit is seen in patients with and without PD-L1–positive tumors and across prognostic risk groups. The researchers believe their findings support “at least additive if not synergistic effects of the VEGF tyrosine kinase inhibitor-immune checkpoint inhibitor combination” [Motzer RJ, et al. Avelumab plus axitinib versus sunitinib for advanced renal-cell carcinoma. *N Engl J Med* 2019; DOI: 10.1056/NEJMoa1816047]. ■

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Findings

Oxalate Excretion Linked to Risk of CKD Progression

Higher urinary oxalate excretion is linked to an increased risk of progressive chronic kidney disease (CKD), reports a study in *JAMA Internal Medicine*.

The analysis included 3123 patients with stage 2 to 4 CKD, drawn from the Chronic Renal Insufficiency Study. Twenty-four-hour urinary oxalate excretion was measured at enrollment in 2003–08. Median oxalate excretion was 18.6 mg/24 hours; this value was inversely correlated with estimated glomerular filtration rate (eGFR) and positively correlated with 24-hour proteinuria.

Progression of CKD was evaluated in 2003–08, with a total follow-up of 22,318 person-years. At follow-up, 752 patients had developed end stage renal disease (ESRD), while 940 patients had reached the composite endpoint of a 50% decline in eGFR or ESRD. Both risks were significantly elevated for patients with higher oxalate excretion. From the highest to the lowest quintile (27.8 versus 11.5 mg/24 hours), hazard ratios were 1.33 for CKD progression and 1.45 for ESRD.

The association was nonlinear, with a threshold effect for patients in the third to fifth quintiles. Using the 40th percentile of oxalate excretion as a cutoff point, hazard ratios were 1.32 for CKD progression and 1.37 for ESRD.

High levels of urinary oxalate—a potentially toxic terminal metabolite—are known to be associated with acute kidney injury and CKD in certain disease states. This prospective cohort study reports that higher urinary oxalate excretion is an independent risk factor for CKD progression and ESRD. If confirmed, the findings may point to future studies evaluating the benefit of treatments to lower oxalate excretion in CKD patients [Waikar SS, et al. Association of urinary oxalate excretion with the risk of chronic kidney disease progression. *JAMA Intern Med* 2019; DOI: 10.1001/jamainternmed.2018.7980]. ■

In Dialysis Patients, Spironolactone Doesn't Reduce LV Mass



Spironolactone does not reduce left ventricular mass (LVM) in hemodialysis patients, concludes a randomized trial in *Kidney International*.

The Mineralocorticoid Receptor Antagonists in End-Stage Renal Disease (MiREnDa) trial included 97 adults receiving maintenance hemodialysis: 75 men and 22 women, mean age 60 years. They were assigned to treatment with spironolactone, 50 mg once daily, or placebo. At 40 weeks, cardiac MRI was performed to assess change in LVM index. Secondary outcomes included the incidence and severity of hyperkalemia and change in residual renal function.

Change in LVM index was not significantly dif-

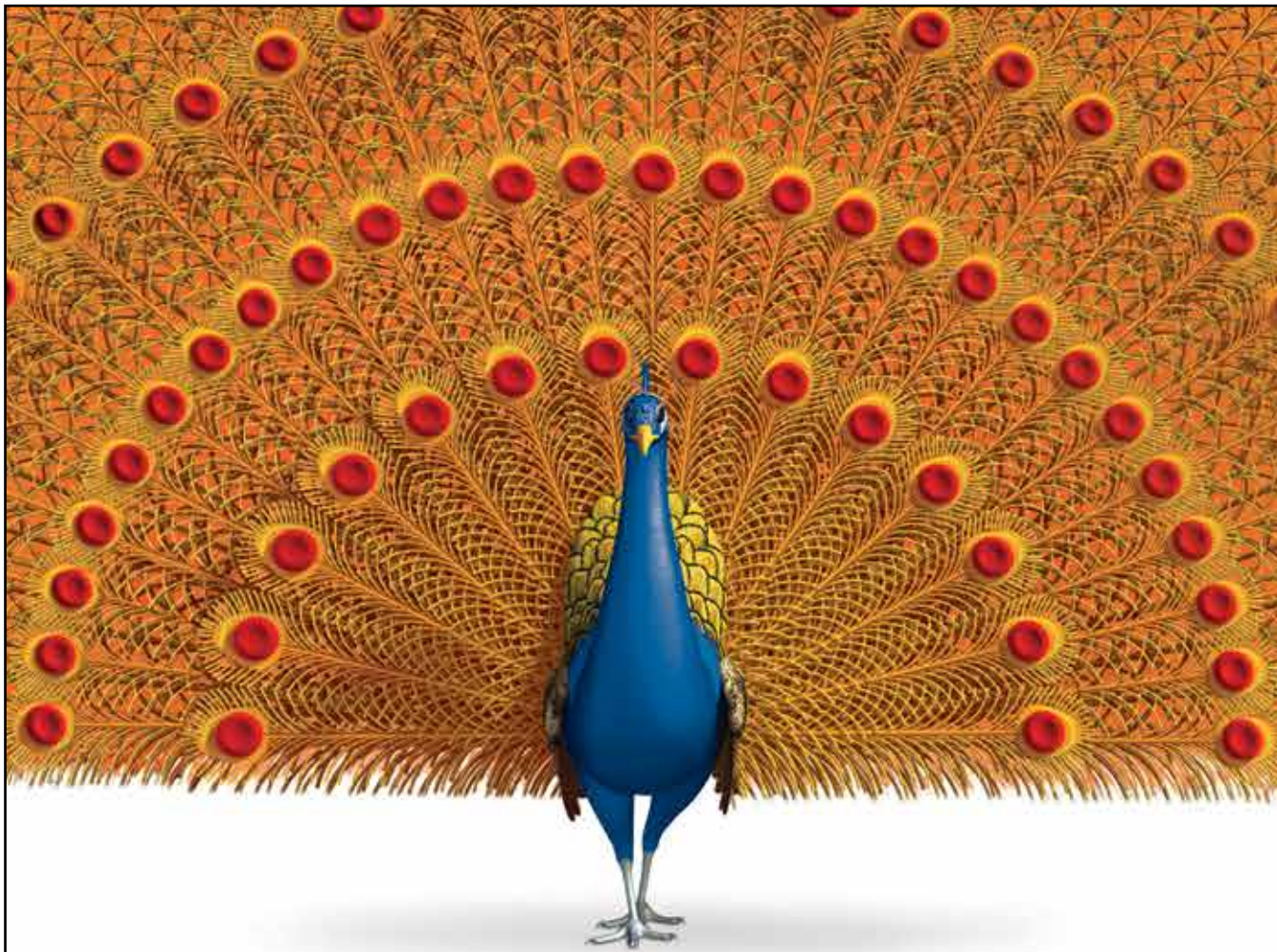
ferent between treatment groups: 2.86 with spironolactone and 0.41 g/m² with placebo. Neither were there any significant changes in left ventricular ejection fraction, blood pressure, or functional capacity.

There were 155 episodes of moderate hyperkalemia (predialysis potassium 6.0 to 6.5 mmol/L) in the spironolactone group versus 80 in the placebo group. However, the incidence of severe hyperkalemia was similar between groups: 14 and 24 events, respectively. There was no significant difference in residual urine volume or measured glomerular filtration rate.

Left ventricular hypertrophy is a key risk factor for sudden cardiac death and all-cause mortality in hemodialysis patients. Mineralocorticoid receptor antagonists such as

spironolactone can favorably affect left ventricular remodeling in patients with heart failure, but there are few data on their safety and efficacy in dialysis patients.

The placebo-controlled MiREnDa trial finds no change in LVM index for hemodialysis patients assigned to spironolactone 50 mg/d. Spironolactone is associated with a higher rate of moderate but not severe hyperkalemia. The study finds no significant effect on surrogate cardiovascular endpoints; the authors note that two trials are underway to evaluate the cardiovascular and survival benefits of spironolactone 25 mg in dialysis patients [Hammer F, et al. A randomized controlled trial of the effect of spironolactone on left ventricular mass in hemodialysis patients. *Kidney Int* 2019; <https://doi.org/10.1016/j.kint.2018.11.025>]. ■



IMPORTANT SAFETY INFORMATION

CONTRAINDICATION: AURYXIA® (ferric citrate) is contraindicated in patients with iron overload syndromes

WARNINGS AND PRECAUTIONS:

- **Iron Overload:** Monitor ferritin and transferrin saturation (TSAT). Patients may require a reduction in dose or discontinuation of concomitant intravenous (IV) iron
- **Risk of Overdosage in Children Due to Accidental Ingestion:** Accidental ingestion and resulting overdose of iron-containing products is a leading cause of fatal poisoning in children under 6 years of age. Advise patients to keep AURYXIA out of the reach of children

PREGNANCY AND LACTATION: Overdosing of iron in pregnant women may carry a risk for spontaneous abortion, gestational diabetes and fetal malformation. Rat studies have shown the transfer of iron into milk. There is possible infant exposure when AURYXIA is taken by a nursing woman

ADVERSE REACTIONS: The most common adverse reactions reported with AURYXIA in clinical trials were:

- **Iron Deficiency Anemia in CKD Not on Dialysis:** Discolored feces (22%), diarrhea (21%), constipation (18%), nausea (10%), abdominal pain (5%) and hyperkalemia (5%)

To report suspected adverse reactions, contact Akebia Therapeutics at 1-844-445-3799

FOR MORE INFORMATION, VISIT [AURYXIA.COM](https://www.akebia.com)



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Depression Treatment in Dialysis Patients—Randomized Trial

Both sertraline and cognitive-behavioral therapy (CBT) improve depression symptoms in hemodialysis patients, but an engagement interview does not increase patient acceptance of depression therapy, reports a two-phase trial in *Annals of Internal Medicine*.

The open-label, randomized trial included 184 maintenance dialysis patients at 31 facilities in three US metropolitan areas. All had been receiving dialysis for at least 3 months and scored 15 or higher on the Beck Depression Inventory-II (BD-II). In an initial sample of nearly 2600 patients completing the BD-II, about one-fourth scored 15 or higher.

In the first phase of the study, patients were assigned to un-

dergo an engagement interview or a control visit. Interviews were conducted by trained therapists, with the goals of increasing patients' willingness to accept the diagnosis of depression and engage in treatment. In phase two, 120 patients were assigned to 12 weeks of CBT, conducted by therapists during outpatient hemodialysis; or treatment with sertraline, with a target dose of 200 mg.

In phase 1, the engagement interview did not significantly affect patient acceptance of depression therapy. In both groups, about two-thirds of patients initiated treatment within 28 days.

In phase 2, both treatments were associated with improvement on the Quick Inventory of Depressive Symptoms scale:

from 12.2 to 8.1 with CBT and from 10.9 to 5.9 with sertraline. The response to sertraline was greater, with an estimated effect of -1.84 . Mild to moderate adverse events were more frequent with sertraline.

Depression is common among dialysis patients, but most patients do not receive therapy. The new study is the first multicenter clinical trial of treatment for depression in maintenance hemodialysis patients.

The results suggest that an engagement interview does not increase patient acceptance of treatment [Mehrotra R, et al. Comparative efficacy of therapies for treatment of depression for patients undergoing maintenance hemodialysis: a randomized clinical trial. *Ann Intern Med* 2019; DOI: 10.7326/M18-2229]. ■

For the treatment of iron deficiency anemia in adult patients with chronic kidney disease (CKD) not on dialysis

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 - Patients in the Phase III pivotal trial achieved results without the use of ESAs or IV iron
 - 52% of patients achieved the primary endpoint of a hemoglobin increase of ≥ 1.0 g/dL at any time point by Week 16
 - Mean TSAT increased from 20.2% at baseline to 35.6% at Week 16^{1,2}
- Discontinuation rates due to adverse reactions were similar between AURYXIA and placebo (10% vs 9%)
- Convenient mealtime dosing
- Each tablet contains 210 mg of elemental iron
- Patients with commercial insurance can pay as little as \$0 per fill of AURYXIA

ESAs=erythropoiesis stimulating agents.

References: 1. Fishbane S, Block GA, Loram L, et al. Effects of ferric citrate in patients with nondialysis-dependent CKD and iron deficiency anemia. *J Am Soc Nephrol*. 2017;28(6):1851-1858. 2. Data on File 14, Keryx Biopharmaceuticals, Inc.

Please see Brief Summary including patient counseling information on following page

Auryxia[®]
(ferric citrate) tablets

Kidney Transplant Improves Survival in Patients with HCV

Hepatitis C virus (HCV)-positive patients with kidney failure may have difficulty accessing kidney transplantation—but when they do, they rapidly achieve a significant survival benefit, reports a study in the *American Journal of Kidney Diseases*.

The retrospective cohort study included more than 442,000 adult dialysis patients, identified from clinical data provided by a large national dialysis provider. Of these patients, 7.2% were reported as HCV-seropositive. The HCV-seropositive group were younger (median age 56 versus 64), more likely to be men (66% versus 54%), and more likely to be African American (54% versus 29%).

After linkage to Organ Procurement and Transplantation Network data, associations between HCV serostatus, mortality, and kidney transplant waitlisting were assessed. The study also estimated the survival benefit from kidney transplant for HCV-seropositive patients, compared to remaining on dialysis.

Dialysis patients who were HCV-seropositive were at modestly increased risk of death, adjusted hazard ratio (HR) 1.09; but were one-third less likely to be placed on the kidney transplant waitlist, HR 0.67. After waitlisting, the chances of kidney transplant were similar for HCV-seropositive versus HCV-seronegative patients. Waiting time was shorter for recipients of HCV-seropositive kidneys.

Kidney transplantation brought a significant survival benefit, achieved within 9 months posttransplant. By 3 years, the HR for death associated with transplantation, compared to continued waiting, was 0.42. The survival benefit of transplantation was unaffected by donor HCV serostatus.

Many ESRD patients are HCV-seropositive, which may create barriers to kidney transplantation. Because registry data lack information on HCV serostatus, little is known about survival on dialysis and the outcomes of kidney transplantation for HCV-seropositive patients.

The new study shows that ESRD patients with HCV are less likely to be waitlisted, despite deriving a substantial survival benefit from kidney transplantation. Patients receiving kidneys from HCV-seropositive donors show a survival advantage at 2 years, compared to those who remain on the waitlist. The researchers conclude, “[R]emoving barriers to waitlisting for this patient group should be a priority for providers” [Sawinski D, et al. Mortality and kidney transplantation outcomes among hepatitis C virus-seropositive maintenance dialysis patients: a retrospective cohort study. *Am J Kidney Dis* 2019; DOI: <https://doi.org/10.1053/j.ajkd.2018.11.009>]. ■

Automated Office BP Beats Routine Readings: Meta-Analysis

Automated office blood pressure (AOBP) readings are more accurate than office measurements and should be the “preferred method” for recording BP in clinical practice, concludes a meta-analysis in *JAMA Internal Medicine*.

A systematic review of the literature identified 31 articles related to AOBP including a total of 9279 patients. All of the studies included at least 30 patients with properly recorded AOBP measurements: patient unattended and sitting in a quiet place. The studies provided data enabling

comparison of AOBP with awake ambulatory BP, research-quality office BP, or routine office BP measurements.

Mean systolic AOBP was 130 mm Hg or higher in about half of the studies, totaling 4892 patients. In these studies, the routine and research office systolic BP readings were significantly higher than the AOBP readings: pooled mean differences were 14.5 and 7.0 mm Hg, respectively.

In contrast, there was little or no difference in systolic awake ambulatory BP or AOBP measurements: pooled mean differ-

ence 0.3 mm Hg. The results were consistent for studies using different devices, and in studies including specialist/referral versus unselected patient populations.

Previous studies have reported that AOBP is more accurate than routine office BP measurement, with no “white coat effect.” The new report is the first comprehensive systematic review and meta-analysis of the evidence comparing AOBP with other measurement techniques.

Recorded properly, AOBP is more accurate than routine or even research-quality

office BP measurements, and similar to awake ambulatory BP readings. The investigators conclude: “Automated office BP should now be the preferred method for recording BP in routine clinical practice to identify patients with possible hypertension, with the diagnosis to be confirmed by 24-hour ABPM or home BP” [Roerecke M, et al. Comparing automated office blood pressure readings with other methods of blood pressure measurement for identifying patients with possible hypertension: a systematic review and meta-analysis. *JAMA Intern Med* 2019; DOI:10.1001/jamainternmed.2018.6551]. ■

Survival Benefit of Kidney Transplant in Lupus Nephritis

Kidney transplantation reduces mortality, mainly due to cardiovascular disease and infection, in patients with lupus nephritis, reports a study in *Annals of Internal Medicine*.

Through the United States Renal Data System, the researchers identified 20,974 individuals with kidney failure due to lupus nephritis (ESRD-LN) between 1995 and 2014. Of 9659 waitlisted patients, 5738 (59%) received a kidney transplant. Eighty-two percent of waitlisted patients were women and 60% were nonwhite.

Analyzed as a time-varying exposure, renal transplantation was associated with lower all-cause mortality among waitlisted patients: adjusted hazard ratio (HR) 0.30. There were also significant reductions in mortality due to cardiovascular disease, HR 0.26; coronary heart disease, HR 0.41; and infection or sepsis, HR 0.41 for each. The survival benefit remained significant for subgroups defined by race/ethnicity, sex, and age and throughout the study period.

Secondary analysis of a Medicare-enrolled subset included matched groups of 2963 patients with and without transplantation. Mortality rates were 21.1 and 77.1 per 1000 person-years, respectively. Adjusted HRs for death were 0.32 for deceased-donor and 0.24 for living-donor recipients.

Patients with ESRD-LN are at high risk of premature death, compared to systemic lupus erythematosus patients without kidney involvement. The survival benefit of renal transplantation in ESRD-LN patients remains unclear.

This study finds a “considerable survival benefit” of kidney transplantation in a nationwide cohort of patients with LN-ESRD. The reduction in mortality results largely from lower risks of deaths due to cardiovascular disease and infections, particularly sepsis. The researchers conclude: “Therefore, timely consideration of renal transplant should be a part of routine care for patients with LN-ESRD, and improved access to renal transplantation for this population may considerably improve outcomes” [Jorge A, et al. Renal transplantation and survival among patients with lupus nephritis: a cohort study. *Ann Intern Med* 2019; DOI: 10.7326/M18-1570]. ■

Auryxia[®] (ferric citrate) tablets

AURYXIA[®] (ferric citrate) tablets for oral use containing 210 mg of ferric iron equivalent to 1 g AURYXIA for oral use.

INDICATION AND USAGE

AURYXIA is indicated for the treatment of iron deficiency anemia in adult patients with chronic kidney disease not on dialysis.

CONTRAINDICATIONS

AURYXIA is contraindicated in patients with iron overload syndromes (e.g., hemochromatosis).

WARNINGS AND PRECAUTIONS

Iron Overload: Iron absorption from AURYXIA may lead to excessive elevations in iron stores. Increases in serum ferritin and transferrin saturation (TSAT) levels were observed in clinical trials. In a 56-week safety and efficacy trial evaluating the control of serum phosphate levels in patients with chronic kidney disease on dialysis in which concomitant use of intravenous iron was permitted, 55 (19%) of patients treated with AURYXIA had a ferritin level >1500 ng/mL as compared with 13 (9%) of patients treated with active control.

Assess iron parameters (e.g., serum ferritin and TSAT) prior to initiating AURYXIA and monitor iron parameters while on therapy. Patients receiving intravenous iron may require a reduction in dose or discontinuation of intravenous iron therapy.

Risk of Overdose in Children Due to Accidental Ingestion: Accidental ingestion and resulting overdose of iron-containing products is a leading cause of fatal poisoning in children under 6 years of age. Advise patients of the risks to children and to keep AURYXIA out of the reach of children.

ADVERSE REACTIONS

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

Iron Deficiency Anemia in Chronic Kidney Disease Not on Dialysis

Across two trials, 190 patients with CKD-NDD were treated with AURYXIA. This included a study of 117 patients treated with AURYXIA and 116 patients treated with placebo in a 16-week, randomized, double-blind period and a study of 75 patients treated with AURYXIA and 73 treated with placebo in a 12-week randomized double-blind period. Dosage regimens in these trials ranged from 210 mg to 2,520 mg of ferric iron per day, equivalent to 1 to 12 tablets of AURYXIA.

Adverse reactions reported in at least 5% of patients treated with AURYXIA in these trials are listed in Table 1.

Table 1: Adverse Reactions Reported in Two Clinical Trials in at least 5% of patients receiving AURYXIA

Body System Adverse Reaction	AURYXIA % (N=190)	Placebo % (N=188)
Any Adverse Reaction	75	62
Metabolism and Nutrition Disorders		
Hyperkalemia	5	3
Gastrointestinal Disorders		
Discolored feces	22	0
Diarrhea	21	12
Constipation	18	10
Nausea	10	4
Abdominal Pain	5	2

During the 16-week, placebo-control trial, 12 patients (10%) on AURYXIA discontinued study drug because of an adverse reaction, as compared to 10 patients (9%) in the placebo control arm. Diarrhea was the most common adverse reaction leading to discontinuation of AURYXIA (2.6%).

DRUG INTERACTIONS

Orally administered doxycycline has to be taken at least 1 hour before AURYXIA. Orally administered ciprofloxacin should be taken at least 2 hours before or after AURYXIA. Oral drugs that can be administered concomitantly with AURYXIA are: amlodipine, aspirin, atorvastatin, calcitriol, clopidogrel, digoxin, diltiazem, doxercalciferol, enalapril, fluvastatin, glimepiride, levofloxacin, losartan, metoprolol, pravastatin, propranolol, sitagliptin, and warfarin.

Oral medications not listed above

There are no empirical data on avoiding drug interactions between AURYXIA and most concomitant oral drugs. For oral medications where a reduction in the bioavailability of that medication would have a clinically significant effect on its safety or efficacy, consider separation of the timing of the administration

of the two drugs. The duration of separation depends upon the absorption characteristics of the medication concomitantly administered, such as the time to reach peak systemic levels and whether the drug is an immediate release or an extended release product. Consider monitoring clinical responses or blood levels of concomitant medications that have a narrow therapeutic range.

USE IN SPECIFIC POPULATIONS

Pregnancy:

Risk Summary

There are no available data on AURYXIA use in pregnant women to inform a drug-associated risk of major birth defects and miscarriage. Animal reproduction studies have not been conducted using AURYXIA. Skeletal and encephalic malformation was observed in neonatal mice when ferric gluconate was administered intraperitoneally to gravid dams on gestation days 7-9. However, oral administration of other ferric or ferrous compounds to gravid CD1-mice and Wistar-rats caused no fetal malformation.

An overdose of iron in pregnant women may carry a risk for spontaneous abortion, gestational diabetes and fetal malformation.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. Adverse outcomes in pregnancy occur regardless of the health of the mother or the use of medications. In the U.S. general population, the estimated background risks of major birth defects and miscarriage in clinically recognized pregnancies are 2 to 4% and 15 to 20% respectively.

Clinical Considerations

The effect of AURYXIA on the absorption of vitamins and other nutrients has not been studied in pregnant women. Requirements for vitamins and other nutrients are increased in pregnancy.

Lactation:

Risk Summary

There are no human data regarding the effect of AURYXIA in human milk, the effects on the breastfed child, or the effects on milk production. Data from rat studies have shown the transfer of iron into milk by divalent metal transporter-1 (DMT-1) and ferroportin-1 (FPN-1). Hence, there is a possibility of infant exposure when AURYXIA is administered to a nursing woman. The development and health benefits of breastfeeding should be considered along with the mother's clinical need for AURYXIA and any potential adverse effects on the breastfed child from AURYXIA or from the underlying maternal condition.

Pediatric Use: The safety and efficacy of AURYXIA have not been established in pediatric patients.

Geriatric Use: Clinical studies of AURYXIA included 292 subjects aged 65 years and older (104 subjects aged 75 years and older). Overall, the clinical study experience has not identified any obvious differences in responses between the elderly and younger patients in the tolerability or efficacy of AURYXIA.

OVERDOSAGE

No data are available regarding overdose of AURYXIA in patients. In patients with chronic kidney disease, the maximum dose studied was 2,520 mg ferric iron (12 tablets of AURYXIA) per day. Iron absorption from AURYXIA may lead to excessive elevations in iron stores, especially when concomitant intravenous iron is used.

In clinical trials, one case of elevated iron in the liver as confirmed by biopsy was reported in a patient on dialysis administered intravenous iron and AURYXIA.

PATIENT COUNSELING INFORMATION

Dosing Recommendations: Instruct patients to take AURYXIA as directed with meals and adhere to their prescribed diets. Instruct patients on concomitant medications that should be dosed apart from AURYXIA. Advise patients not to chew or crush AURYXIA because tablets may cause discoloration of mouth and teeth.

Adverse Reactions: Advise patients that AURYXIA may cause discolored (dark) stools, but this staining of the stool is considered normal with oral medications containing iron.

AURYXIA may cause diarrhea, nausea, constipation, vomiting, hyperkalemia, abdominal pain, and cough. Advise patients to report severe or persistent gastrointestinal symptoms to their physician.

Accidental Ingestion: Advise patients to keep this product out of the reach of children and to seek immediate medical attention in case of accidental ingestion by a child.

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