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New Payment Model Aims to Boost Transplant Access

By Bridget M. Kuehn

The Center for Medicare and Medicaid Innovation (CMMI) will test a new transplant payment model that aims to increase access to kidney transplants, improve transparency and accountability in the transplant system, and provide patients with enhanced care before, during, and after transplant.

The new Increasing Organ Transplant Access (IOTA) model, announced in May, is a 6-year mandatory payment model pilot (1). Eligible transplant centers in half of the donation service areas in the United States will be required to participate, and centers in the other half will serve as a comparison group. Approximately 230 adult kidney transplant programs that perform at least 11 transplants each year will participate in the model, which is currently scheduled to kick off in 2025. The model and its goals received praise from ASN and organizations representing patients with kidney diseases.

"The American Society of Nephrology (ASN) has been advocating for increased investment and reform in the U.S. transplant system for many years," said ASN President Deidra C. Crews, MD, ScM, FASN, in a statement (2). "People with kidney failure deserve to have access to the best therapy—a kidney transplant—maximized at every opportunity. ASN is grateful for the leadership of the Biden-Harris Administration in testing patient-centered changes to how kidney transplant care is delivered, and we welcome the opportunity to review and suggest improvements to the proposed IOTA model released today."

Tackling inequity and transparency

Kidney transplant is widely accepted as the best treatment for kidney failure. Yet many of the 120,000 individuals diagnosed with kidney failure each year will never receive one. There are approximately 90,000 people on the deceased donor kidney transplant list. Still, only approximately 28,000 kidney transplants are performed each year in the United States, and 5000 people die on the waiting list each year, according to data from the national Organ Procurement & Transplantation Network (3).

Despite the dire need for kidney allografts, up to 30% of donor kidneys are unused each year because of system inefficiencies. Kevin Longino, MBA, chief executive officer of the National Kidney Foundation and a kidney transplant recipient, said in a statement that discarding a donor's kidney is a disservice to donors, their families, and people relying on dialysis who could benefit from a transplant (4). "It is fundamentally necessary to reform the transplant ecosystem to one that honors organ donors and their selfless, life-saving gifts," Longino stated. "The IOTA model will also uphold the responsibility of

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Agencies, Practices Grapple With Increased Health Care Cybersecurity Threats

By Karen Blum

Suneel Udani, MD, FASN, said he cannot recall how he first heard about the February 21st cyberattack that took down practices at Change Healthcare, one of the largest clearinghouses for insurance billing and payments in the country, but the effects on numerous medical settings, including his, are hard to forget.

Only about 30% of claims from Udani's practice, Nephrology Associates of Northern Illinois and Indiana (NANI) in Hinsdale, IL, are processed through Change Healthcare. But another clearinghouse that NANI uses became "overflooded" as it worked to make up the difference, he said. Additionally, revenue from a joint venture partnership with Fresenius Medical Care that the practice relies on to lower overhead and help pay for office staff and equipment rentals "essentially went to zero" for 3 months. "Because this was unprecedented, there was no playbook [for what to do]," Udani said. "We're a large practice and had a very longstanding and large partnership with Fresenius, so if we were in this position, I can only imagine what other practices have been going through…. It definitely did leave us in a position [in which] we were kind of in limbo."

Practices of all sizes are at risk for cyberattack, said Brian Mazanec, deputy director of the Office of Preparedness for the U.S. Department of Health and Human Services' Administration for Strategic Preparedness and Response

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Inside

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INDICATION

XPHOZAH (tenapanor) 30 mg BID is indicated to reduce serum phosphorus in adults with chronic kidney disease (CKD) on dialysis as add-on therapy in patients who have an inadequate response to phosphate binders or who are intolerant of any dose of phosphate binder therapy.

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

XPHOZAH is contraindicated in:

- Pediatric patients under 6 years of age
- Patients with known or suspected mechanical gastrointestinal obstruction

WARNINGS AND PRECAUTIONS

Diarrhea

Patients may experience severe diarrhea. Treatment with XPHOZAH should be discontinued in patients who develop severe diarrhea.

MOST COMMON ADVERSE REACTIONS

Diarrhea, which occurred in 43-53% of patients, was the only adverse reaction reported in at least 5% of XPHOZAH-treated patients with CKD on dialysis across trials. The majority of diarrhea events in XPHOZAH-treated patients were reported to be mild-to-moderate in severity and resolved over time, or with dose reduction. Diarrhea was typically reported soon after initiation but could occur at any time during treatment with XPHOZAH. Severe diarrhea was reported in 5% of XPHOZAH-treated patients in these trials.

Please see Brief Summary of full Prescribing Information on the following page.

Reference: XPHOZAH® (tenapanor) full Prescribing Information. Waltham, MA: Ardelyx, Inc.; 2023.

ardelyx®

XPHOZAH (tenapanor) tablets, for oral use
Brief Summary of Prescribing Information

1 INDICATIONS AND USAGE

XPHOZAH is indicated to reduce serum phosphorus in adults with chronic kidney disease (CKD) on dialysis as add-on therapy in patients who have an inadequate response to phosphate binders or who are intolerant of any dose of phosphate binder therapy.

4 CONTRAINDICATIONS

XPHOZAH is contraindicated in patients under 6 years of age because of the risk of diarrhea and serious dehydration *[see Warnings and Precautions (5.1), Use in Specific Populations (8.5)]*.

XPHOZAH is contraindicated in patients with known or suspected mechanical gastrointestinal obstruction.

5 WARNINGS AND PRECAUTIONS

5.1 Diarrhea

Diarrhea was the most common adverse reaction in XPHOZAH-treated patients with CKD on dialysis *[see Dosage and Administration (2) in the full Prescribing Information, Contraindications (4) and Adverse Reactions (6.1)]*. In clinical trials, diarrhea was reported in up to 53% of patients, reported as severe in 5%, and associated with dehydration and hyponatremia in less than 1% of patients. Treatment with XPHOZAH should be discontinued in patients who develop severe diarrhea.

6 ADVERSE REACTIONS

6.1 Clinical Trial 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 practice.

The safety data described below reflect data from 754 adults with CKD on dialysis taking XPHOZAH in clinical trials as monotherapy and in combination with phosphate binders. Among the 754 patients, 258 patients were exposed to tenapanor for at least 26 weeks and 75 were exposed to tenapanor for at least one year. *[see Clinical Studies (14) in the full Prescribing Information]*.

Most Common Adverse Reaction

Diarrhea, which occurred in 43-53% of patients, was the only adverse reaction reported in at least 5% of XPHOZAH-treated patients with CKD on dialysis across trials. The majority of diarrhea events in the XPHOZAH-treated patients were reported to be mild-to-moderate in severity and resolved over time, or with dose reduction. Diarrhea was typically reported soon after initiation but could occur at any time during treatment with XPHOZAH. Severe diarrhea was reported in 5% of XPHOZAH-treated patients in these trials *[see Warnings and Precautions (5.1)]*.

7 DRUG INTERACTIONS

7.1 OATP2B1 Substrates

Tenapanor is an inhibitor of intestinal uptake transporter, OATP2B1 *[see Clinical Pharmacology (12.3) in the full Prescribing Information]*. Drugs which are substrates of OATP2B1 may have reduced exposures when concomitantly taken with XPHOZAH. Monitor for signs related to loss of efficacy and adjust the dose of concomitantly administered drug as needed.

Enalapril is a substrate of OATP2B1. When enalapril was coadministered with XPHOZAH (30 mg twice daily for five days), the peak exposure (Cmax) of enalapril and its active metabolite, enalaprilat, decreased by approximately 70% and total systemic exposures (AUC) decreased by 50 to 65% compared to when enalapril was administered alone *[see Clinical Pharmacology (12.3) in the full Prescribing Information]*. However, the decrease in enalaprilat's exposure with XPHOZAH may be offset by the inherently higher exposures observed in patients with CKD on dialysis due to its reduced renal clearance. Therefore, a lower starting dose of enalapril, which is otherwise recommended in patients with CKD on dialysis is not required when enalapril is coadministered with XPHOZAH.

7.2 Sodium Polystyrene Sulfonate

Separate administration XPHOZAH and sodium polystyrene sulfonate (SPS) by at least 3 hours. SPS binds to many commonly prescribed oral medicines.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Tenapanor is essentially non-absorbed systemically, with plasma concentrations below the limit of quantification (less than 0.5 ng/mL) following oral administration *[see Clinical Pharmacology (12.3) in the full Prescribing Information]*. Therefore, maternal use is not expected to result in fetal exposure to the drug.

The available data on XPHOZAH exposure from a small number of pregnant women have not identified any drug associated risk for major birth defects, miscarriage, or adverse maternal or fetal outcomes. In reproduction studies with tenapanor in pregnant rats and rabbits, no adverse fetal effects were observed in rats at 0.2 times the maximum recommended human dose and in rabbits at doses up to 15 times the maximum recommended human dose (based on body surface area) *[see Nonclinical Toxicology (13.1) in the full Prescribing Information]*.

The estimated background risk of major birth defects and miscarriage for women with CKD on dialysis with hyperphosphatemia is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the United States general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Animal Data

In an embryofetal development study in rats, tenapanor was administered orally to pregnant rats during the period of organogenesis at dose levels of 1, 10 and 30 mg/kg/day. Tenapanor doses of 10 and 30 mg/kg/day were not tolerated by the pregnant rats and was associated with mortality and moribundity with body weight loss. The 10 and 30 mg/kg dose group animals were sacrificed early, and the fetuses were not examined for intrauterine parameters and fetal morphology. No adverse fetal effects were observed in rats at 1 mg/kg/day (approximately 0.2 times the maximum recommended human dose) and in rabbits at doses up to 45 mg/kg/day (approximately 15 times the maximum recommended human dose, based on body surface area). In a pre- and post-natal developmental study in mice, tenapanor at doses up to 200 mg/kg/day (approximately 16.5 times the maximum recommended human dose, based on body surface area) had no effect on pre- and post-natal development.

8.2 Lactation

Risk Summary

There are no data available on the presence of tenapanor in either human or animal milk, its effects on milk production or its effects on the breastfed infant. Tenapanor is essentially non-absorbed systemically, with plasma concentrations below the limit of quantification (less than 0.5 ng/mL) following oral administration *[see Clinical Pharmacology (12.3) in the full Prescribing Information]*. The minimal systemic absorption of tenapanor will not result in a clinically relevant exposure to breastfed infants. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for XPHOZAH and any potential adverse effects on the breastfed infant from XPHOZAH or from the underlying maternal condition.

8.4 Pediatric Use

Risk Summary

XPHOZAH is contraindicated in patients less than 6 years of age. In nonclinical studies, deaths occurred in young juvenile rats (less than 1-week old rats; approximate human age-equivalent of less than 2 years of age) and in older juvenile rats (approximate human age-equivalent of 2 years of age) following oral administration of tenapanor, as described below in Juvenile Animal Toxicity Data.

The safety and effectiveness of XPHOZAH in pediatric patients have not been established.

Juvenile Animal Toxicity Data

In a 21-day oral dose range finding toxicity study in juvenile rats, tenapanor was administered to neonatal rats (post-natal day (PND) 5) at doses of 5 and 10 mg/kg/day. Tenapanor was not tolerated in male and female pups and the study was terminated on PND 16 due to mortalities and decreased body weight (24% to 29% reduction in females at the respective dose groups and 33% reduction in males in the 10 mg/kg/day group, compared to control).

In a second dose range finding study, tenapanor doses of 0.1, 0.5, 2.5, or 5 mg/kg/day were administered to neonatal rats from PND 5 through PND 24. Treatment-related mortalities were observed at 0.5, 2.5, and 5 mg/kg/day doses. These premature deaths were observed as early as PND 8, with majority of deaths occurring between PND 15 and 25. In the 5 mg/kg/day group, mean body weights were 47% lower for males on PND 23 and 35% lower for females on PND 22 when compared to the controls. Slightly lower mean tibial lengths (5% to 11%) were noted in males and females in the 0.5, 2.5, and 5 mg/kg/day dose groups on PND 25 and correlated with the decrements in body weight noted in these groups. Lower spleen, thymus, and/or ovarian weights were noted at the 0.5, 2.5, and 5 mg/kg/day doses. Tenapanor-related gastrointestinal distension and microscopic bone findings of increased osteoclasts, eroded bone, and/or decreased bone in sternum and/or femorotibial joint were noted in males and females in the 0.5, 2.5, and 5 mg/kg/day dose groups.

In juvenile rats administered tenapanor at 0.03, 0.1, or 0.3 mg/kg/day on PND 5 through PND 61, treatment-related mortalities were observed at 0.3 mg/kg/day. Lower mean body weight gains were noted in the 0.3 mg/kg/day group males and females compared to the control group primarily during PND 12–24 but continuing sporadically during the remainder of the dosing period; corresponding lower mean food consumption was noted in this group during PND 21–33. As a result, mean body weights were up to 15.8% and 16.8% lower in males and females, respectively, compared to the control group; the greatest difference was on PND 24 for males and PND 21 for females. Mean body weight in the 0.3 mg/kg/day group males was only 3.9% lower than the control group on PND 61. There were no tenapanor-related effects on mean body weights, body weight gains, or food consumption in the 0.03 and 0.1 mg/kg/day group males and females. A dosage level of 0.1 mg/kg/day was considered to be the no-observed-adverse-effect level (NOAEL) for juvenile toxicity of tenapanor *[see Contraindications (4), Warnings and Precautions (5.1)]*.

In a 21-day oral dose range finding study in older (weaned) juvenile rats administered tenapanor at 0.1, 1, or 5 mg/kg/day on PND 21 through PND 41 (approximate human age-equivalent of 2 to 12 years of age), treatment-related mortalities or moribundities were observed during the first two days of the study in the 1 mg/kg/day males and the 5 mg/kg/day males and females. Watery feces, decreased food consumption, and lower mean body weight were also observed in the 1 and 5 mg/kg/day groups.

In weaned juvenile rats administered tenapanor at 0.1, 0.3, and 0.7 (males) or 1 (females) mg/kg/day on PND 21 through PND 80, no mortalities were observed. Significant decreases in mean body weights were observed in the 0.3 and 0.7 mg/kg/day males throughout the dosing period (up to 20.3% lower than control) and in the 1 mg/kg/day females between PND 23 to 35 (up to 16.7% lower than control), with food consumption notably decreased on PND 21 to 29. There were also reductions in tibia length between PND 76 and 80 in the 0.3 and 0.7 mg/kg/day males, and between PND 36 and 64 in the 0.7 mg/kg/day males, which were not observed during the 14-day recovery period. The NOAEL was considered to be 0.1 mg/kg/day for juvenile toxicity of tenapanor.

8.5 Geriatric Use

Of 1010 adult patients with CKD on dialysis randomized and treated in two randomized, double-blind, placebo-controlled randomized withdrawal clinical trials for XPHOZAH (TEN-02-201 and TEN-02-301) as well as a third randomized, double-blind, placebo-controlled trial (TEN-02-202) for XPHOZAH in combination with phosphate binders, 282 (28%) were 65 years of age and older. Clinical studies of XPHOZAH did not include sufficient numbers of patients aged 65 and older to determine whether they respond differently than younger patients.

10 OVERDOSAGE

No data are available regarding overdosage of XPHOZAH in patients. Based on nonclinical data, overdose of XPHOZAH may result in gastrointestinal adverse effects such as diarrhea, as a result of exaggerated pharmacology with a risk for dehydration if diarrhea is severe or prolonged *[see Warnings and Precautions (5.1)]*.

17 PATIENT COUNSELING INFORMATION

Advise Patients:

Diarrhea

Instruct patients to contact their healthcare provider if they experience severe diarrhea *[see Warnings and Precautions (5.1)]*.

- Instruct patients not to use stool softeners or laxatives with XPHOZAH.

Administration and Handling Instructions

Instruct Patients:

- To take XPHOZAH just prior to the first and last meals of the day *[see Dosage and Administration (2.2) in the full Prescribing Information]*.
- Patients should be counseled not to take XPHOZAH right before a hemodialysis session, and to take XPHOZAH right before the next meal, as some patients may experience diarrhea after taking XPHOZAH.
- If a dose is missed, take the dose just before the next meal. Do not take 2 doses at the same time *[see Dosage and Administration (2.2) in the full Prescribing Information]*.
- To keep XPHOZAH in a dry place. Protect from moisture. Keep in the original bottle. Do not remove desiccant from the bottle. Keep bottles tightly closed *[see How Supplied/Storage and Handling (16) in the full Prescribing Information]*.

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New Payment Model Aims to Boost Transplant Access

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organ procurement and transplant professionals to deliver high-quality care, resulting in better health outcomes that close disparities in access to the life-saving treatment of kidney transplantation that every [patient with kidney diseases] deserves."

Longino also applauded the focus on increasing transparency. Patients on the waiting list and their nephrologists often receive little information about their status, whether they have been offered allografts that were turned down by their transplant team, and why.

"Nephrologists and their patients don't know where things stand sometimes," said Michelle Josephson, MD, FASN, transplant nephrologist at The University of Chicago, IL, and ASN past president. "It's been a black box, and this [model] will open that up."

The model encourages transplant centers to have monthly shared decision-making discussions with waitlisted patients and to keep patients informed when an organ is offered to them and turned down, along with the reason behind the decision. Josephson said that patients are more engaged than ever, and the model will provide valuable information on how much and what type of information patients want. The model will also provide metrics on transplant centers' organ acceptance rates, their transplant criteria, and more information about their waitlists, which may help patients select centers.

Additionally, the model acknowledges racial, ethnic, geographic, and socioeconomic disparities in those offered transplants. For example, patients with private insurance are more likely than those with public insurance to have a living donor transplant, according to the current CMMI plan. Furthermore, some transplant programs use social determinants of health, such as access to transportation or the ability to afford copays for posttransplant immunosuppression regimens, as criteria to determine transplant eligibility, which may contribute to disparities.

The IOTA model aims to address some of these problems. Its goals are to:

- Maximize the use of deceased donor kidneys
- Improve patient care before, during, and after transplant
- Increase transplant access equity by addressing barriers
- Identify more living donors
- Improve care coordination and patient-centeredness

Josephson believes that the randomization of centers in the model and the flexibility that centers will have in meeting the goals will help the field learn the best practices to reach these goals. "I'm very enthusiastic about the goals," Josephson shared. "We'll see what happens. Sometimes things work out better than you expect; sometimes you learn things you didn't expect or find out everything you thought was wrong."

Incentivizing growth and efficiency

Previous payment models from the Centers for Medicare & Medicaid Services (CMS), like the 2021 End-Stage Renal Disease Treatment Choices model and the 2022 Kidney Care Choices model, incentivized nephrologists and dialysis centers to evaluate and refer patients for transplants. But that left a bottleneck at transplant centers that were not receiving incentives to expand transplant access, explained Sumit Mohan, MD, FASN, MPH, professor of medicine and epidemiology at Columbia University in New York City. "If [the transplant center] doesn't have the bandwidth to take the patient, evaluate, waitlist them, or [have them undergo a] transplant, then [the referring physician's] efforts were in vain," he said.

The IOTA model's focus on incentivizing transplant centers to grow is "a massive change," Mohan said. Participating hospitals will receive incentive payments if they reach yearly performance goals. Those that fail to meet their metrics have to pay CMS. Centers may also fall in a neutral performance range without an incentive or penalty. Centers that meet their metrics will receive an additional $8000 per Medicare fee-for-service (FFS) beneficiary who undergoes a transplant. Those that fail to meet goals must pay CMS $2000 per patient. The metrics include the number of adult kidney transplants performed regardless of the payor, the center's organ offer acceptance rate, graft survival, shared-decision making, colorectal cancer screening, and a three-item care transition metric.

Mallika Mendu, MD, MBA, FASN, a nephrologist and vice president of Clinical Operations and Care Continuum at Brigham and Women's Hospital in Boston, MA, said it is the first model focused on kidney transplants and helps align incentives for organ procurement organizations, transplant centers, and hospitals. She also said that the focus on increasing transplant volume was very positive. Mendu explained, "The more transplants [that transplant centers achieve], the more patients are going to live longer and healthier lives because the data [are] very clear that they are superior to dialysis from a clinical outcomes perspective and a quality-of-life perspective."

Mohan said that incentivizing hospitals to improve their organ acceptance rate could help reduce the number of organs discarded and help make the allocation system more efficient. He explained that hospitals will have to provide a good reason for turning down a kidney. It will also encourage hospitals to add filters in the allocation system to ensure that their patients are offered only organs that they will consider or to temporarily inactivate a patient on the waitlist who is unable to receive a transplant at the moment because of a short-term illness or injury. "It allows the allocation system to become more efficient," he said. "The organ gets to where it needs to go sooner and has a lower likelihood of being discarded."

Josephson noted that the incentives may also help transplant surgeons learn more about making the most of the available allografts. "Not every kidney can be used, and we don't know what the sweet spot is," Josephson said. "We may start to get a sense of how far we can go in using these organs and how to do it successfully." Josephson also appreciated the focus on improving long-term transplant patient care. "The goal is for the [organs] to last," she said.

The model also contains features geared to overcome socioeconomic hurdles that stand in the way of transplants for patients with limited income, those with public insurance, or other underserved groups with greater health disparities. Participating hospitals must have health equity plans that identify these populations and devise ways to serve them better. Centers will get extra credit toward their quality metrics for transplants in patients from populations with limited income. They will also receive incentives for providing transplants for patients who are dually eligible for Medicare and Medicaid or whose living donors qualify for the living donor assistance program. Medicare will also cover copays for transplant medications for eligible patients, so a lack of secondary insurance or an inability to afford copays will not stand in the way of a transplant.

Mendu said that including patients with lower incomes and those covered by Medicaid was very positive. But she noted that the model did not include adjustments for potentially greater care needs or higher rates of comorbidity in these populations, which could add to care costs and make it harder for centers caring for these patients to achieve targets. "Early monitoring of the success of the models and particularly the impact on patients from [populations of limited incomes], vulnerable populations, [and] Black and Hispanic patients is going to be critical to ensure [that] there aren't any unintended consequences of the model," she said.

Room for improvement

Many experts praised the overall goals and design of the model but say there may also be room for improvement. "It's a good model," Mohan said. "We could tweak some things and make things better." Mohan noted that the growth goals are ambitious, with a target of 50% growth in the number of transplants. He said that might be doable for a hospital starting with 100 transplants per year but might be more challenging for hospitals already doing several hundred per year.

It is also unclear whether the incentive payments will be large enough to help support growth and improved care. Mohan explained that although the model measures a center's performance based on total transplants, it will only receive incentive payments for Medicare FFS patients. Patients covered by Medicare Advantage plans, who make up a growing share of those covered by Medicare, would not count. For example, a hospital that performs 200 transplants each year, half of which are FFS patients, would receive $800,000 in incentive payments if it meets its performance metrics. Mohan said the payments could help fund a patient outreach coordinator, social worker, or patient navigator but might not go much further and is contingent on reaching all of its metrics. Falling short on some metrics or having a larger proportion of Medicare Advantage patients would reduce its incentive payments.

Mendu agreed that $8000 might not be enough of an incentive. She suggested added incentives geared to increasing transplant access equity or providing upfront payments to help defray the associated care costs. Mohan and Mendu agreed that the model's success will be measured based on its impact on transplant volume and whether it boosts transplants among populations that are underserved. "The bottom line of what IOTA is doing is trying to grow transplant volume across the country," Mohan said. "That will be a key measure of success."

"It is fundamentally necessary to reform the transplant ecosystem to one that honors organ donors and their selfless, life-saving gifts."

Mendu said that she hoped CMMI would use the data it collected from the pilot to improve the model over time. She also applauded CMS's recent focus on kidney care payment models. "I hope that CMS continues to really listen to the clinicians, patients, and patient advocates and really hear the feedback and be open to iterating over time," she said.

At the time of publication, CMMI was seeking feedback on the proposed model and its timeline for implementation, and ASN and its committees were reviewing the plan and submitting feedback. "[CMMI is] being thoughtful and careful about how to do this," Mohan expressed. "[It's] very clear about the goals and [wants] to get it right. That is really refreshing."

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Agencies, Practices Grapple With Increased Health Care Cybersecurity Threats

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(ASPR). "Even for a small clinic, there's generally an opportunity for malicious actors to exploit the fragmented infrastructure, the unwieldy number of applications, the legacy systems, and network-connected devices," he noted, adding that some practices may not have a lot of information technology (IT) support staff. "It's just a very vulnerable, hard-to-defend target."

Nephrology practices are among those that are vulnerable. Hypertension Nephrology Associates, P.C., of Willow Grove, PA, disclosed in May that it had been the target of an extortion attack on February 6th. The discovery came after an extortion note was found on its computer system. The practice took immediate action, including hiring cybersecurity experts and launching an investigation to discover the scope of the breach, according to a local news story (1). A forensic investigation revealed that cybercriminals had infiltrated the firm's computer systems and gained access to data files from January 20th to February 6th, potentially acquiring files containing sensitive information on 39,491 individuals, according to an announcement from the Murphy Law Firm, Oklahoma City, OK, which announced it was evaluating legal options on behalf of patients affected (2). *Kidney News*' calls to the nephrology practice were not returned.

In NANI's case, Udani said that some payors relayed that despite the Change Healthcare cyberattack, they would not extend the deadlines for claims to be submitted. This meant that with the clearinghouse's electronic systems disabled, NANI's revenue-cycle staff had to fill out and send paper claims by regular mail. "Everyone had to either relearn old processes to utilize them now, or had to develop new ones on the fly," he said. "In a time [in which] physician office staffing shortages are sort of the norm, it only increased the burden on those folks."

Heightened preparedness

Following the Change Healthcare cyberattack, the IT staff at NANI made several adaptations, Udani said. Previously, he and other physicians could log onto the system from any location or device. Now, they are required to conduct work only on practice-issued computers from a secure location. If they access patient records from a nonsecure location outside of a hospital, they are required to use a virtual private network, or VPN, to protect data from being intercepted. The practice is also instituting cybersecurity courses for staff to maintain compliance and periodically sending test emails with suspicious links to assess their savvy in recognizing potential spam. Steps like these are among a number of procedures that medical offices can adopt to protect patient data, say experts interviewed for this article. It starts with user education.

Most breaches occur as a result of an employee unwittingly responding to a phishing request (a scam in which attackers deceive people into revealing sensitive information), said Emily Jones, principal practice leader for the Warren Averett Technology Group, an IT consulting firm in Montgomery, AL. "People don't necessarily have ill intent, but they don't realize that what they just clicked on in a phishing email or something they just downloaded actually was malware [malicious software]," she said.

Generative artificial intelligence programs often used by hackers to send phishing emails are getting more sophisticated and more difficult to detect, said Chris Callahan, chief of cybersecurity for the Cybersecurity and Infrastructure Security Agency (CISA) Region 10, which covers the Pacific Northwest. CISA is a federal agency that helps protect the country from cyberattacks and other threats. "We used to say, 'Oh, look at the language,' because it might be a little bit off, but now they're doing a really good job with that," Callahan warns. "Don't click on any attachments or any links within a suspicious-looking email."

ASPR released a list in January of voluntary health care-specific cybersecurity performance goals (https://hphcyber.hhs.gov/performance-goals.html) and a new website (https://hphcyber.hhs.gov/) to help health care organizations prioritize implementation of high-impact cybersecurity practices. It includes 10 essential goals, such as mandating basic cybersecurity training for staff and using strong encryption to share sensitive data, as well as 10 enhanced goals, including establishing processes to discover and respond to known threats, Mazanec explained. "They were developed to try to demystify the multiple, more complicated sets of best practices that exist," he said. "We recognize that small clinics and underresourced rural hospitals don't have dedicated cybersecurity teams."

Jones suggests four key steps that organizations of any size can take:

1. **Educate.** Educate all employees who work for your practice about cybersecurity practices, and repeat it frequently.
2. **Maintain infrastructure.** Keep up to date on all software patches for your devices and servers.
3. **Create a disaster recovery plan and backup procedures to operate in downtime.** "It's not *if* you're breached, it's *when* you're breached," said Jones, "and when you're breached, you definitely don't want to be without some type of plan." Ensure all employees know where to find your plan and are able to work to the best of their abilities.
4. **Test your systems.** Testing should be thorough and frequent. "There are various types: backup and recovery testing, security assessments, vulnerability scanning, and penetration testing that can give you a clear picture of your practice's security footprint," Jones said. CISA and other cybersecurity companies perform such services, looking for vulnerabilities in need of patching.

Additionally, Jones advises that employees use complex passwords and are prohibited from using the same passwords for personal and work-related devices. Organizations should use multifactor authentication to verify users allowed onto the network, and they should establish separate wireless networks for patient versus business use. In testing scenarios, Jones has seen computer-savvy individuals sit in an organization's lobby and gain access to accounting and employee records.

Breach response

Through a free service called the Pre-Ransomware Notification Initiative (3), CISA representatives can monitor networks at small- to medium-sized medical practices and alert them if it finds malware on their system, so the practice can fix the problem. The challenge is that a breach will often occur after hours or on a weekend, Callahan said, and contacting the appropriate IT person or third-party vendor can take time.

If you are impacted by a breach, disconnect your system, and do not panic, he said. Report the breach to CISA by emailing report@cisa.gov, calling 1-844-say-CISA, or filling out an incident report online at https://www.cisa.gov/report. Also, contact your attorney if you have cybersecurity insurance. CISA can keep your identification anonymous while still alerting others about the breach as well as trends that it may observe. There may be other state oversight or Health Insurance Portability and Accountability Act-related regulations that CISA or an attorney can help you understand.

Should you pay a ransom? The federal government advises against it, Callahan said. "But at the end of the day, it's a business decision that has to be made within these organizations." Even if the attackers provide a decryption

Cybersecurity Resources

- The American Medical Association has a website with tools and resources dedicated to physician cybersecurity (https://www.ama-assn.org/practice-management/sustainability/physician-cybersecurity). It also has an eight-part training on cybersecurity in a clinical setting.
- CISA offers several free services for physician and medical practices, including cyber assessments (https://www.cisa.gov/resources-tools/resources/cyber-assessments) and penetration testing (https://www.cisa.gov/resources-tools/services/penetration-testing) to identify potential vulnerabilities in networks and systems and ongoing cyber hygiene services (https://www.cisa.gov/cyber-hygiene-services) to help organizations reduce their exposure to threats.
- The Department of Health and Human Services' ASPR offers its free Risk Identification and Site Criticality Toolkit (https://aspr.hhs.gov/RISC/Pages/default.aspx) to help organizations with risk assessment for multiple areas including cybersecurity. It also releases a weekly cybersecurity bulletin (https://www.phe.gov/Preparedness/planning/cip/Pages/CIPInquiry.aspx), as well as a cyber incident response bulletin as needed to alert readers about cyber incidents impacting the health care and public health sector. ASPR also can support tabletop exercises (an employee collaborative learning situation with suggestions about an organization's emergency plans) with public health departments or hospitals to help practice how to respond to a cyber incident.
- There is good news for rural and critical access hospitals. The White House announced in June that it will be partnering with technology companies Microsoft and Google to offer free or low-cost cybersecurity products. For independent critical access hospitals and rural emergency hospitals, Microsoft is extending its nonprofit program to provide grants and up to a 75% discount on security products optimized for smaller organizations (4). Larger rural hospitals already using Microsoft solutions can add an advanced security suite at no cost for 1 year. Additional benefits include free cybersecurity assessments and training for frontline and IT staff at eligible hospitals. For more information, see https://nonprofits.tsi.microsoft.com/EN-US/security-program-for-rural-hospitals/.
- As part of the same initiative, Google will provide no-cost security advice to rural hospitals and nonprofit organizations as well as discounted pricing for some of its tools and provide funding to support software migration.

key, it is likely that they already have copied patient information like birth dates or Social Security numbers that could be sold on the dark web, Jones cautioned.

Do not be ashamed if a breach occurs, Callahan added. Some organizations do not want to talk about cyberattacks, but by sharing information, they can help protect others. ■

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ASN Executive Vice President's Update

Increasing Access to Home Dialysis to Improve Kidney Care

By Tod Ibrahim

When the Executive Order on Advancing American Kidney Health was signed in 2019, much of the kidney community scoffed at the initiative's bold goals. However, the executive order's audacity served as a call to action, resulting in considerable progress, especially in expanding access to home dialysis and transplantation. One could argue that ASN and the kidney community have accomplished more in the past 5 years—despite the COVID-19 pandemic—than the 1971 "war on cancer's" initial 5-year goal of curing cancer in time for the US Bicentennial (1).

The executive order aspired that by 2025, 80% of patients who were newly experiencing kidney failure would be "receiving dialysis in the home or receiving a transplant" (2). To advance these goals and institute lasting reforms, the executive order resulted in two new payment models for kidney care. Besides helping to shape both models, ASN continues to advocate for additional changes to the US transplant policy to maximize access to kidney transplantation regardless of socioeconomic status, geography, race, ethnicity, sex, or gender.

Efforts to increase home dialysis in the United States have received less publicity than transforming transplant. When the Medicare End-Stage Renal Disease (ESRD) Program started in 1973, "more than 40% of the 11,000 or so [patients on dialysis] in the United States" were receiving "home hemodialysis" (3). By the time of the executive order in 2019, the total number of patients on dialysis in the United States had increased to 566,614, but the percentage dialyzing at home was only 12.7% (4).

The major drivers of the shift away from home dialysis are well-documented. The Medicare ESRD Program included financial incentives that focused dialysis on in-center care. As Paul Starr, PhD, observed in 1982, "Kidney dialysis centers provide a particularly graphic example of the rise of private industry in response to public financing" (5).

This focus on in-center dialysis also stifled innovation in making home dialysis more accessible for people living with kidney failure. Because most patients undergoing dialysis are treated in-center, and home-based technology has failed to keep pace with therapies in other specialties, many nephrology fellows have lacked both appropriate training in home dialysis and mentorship when they enter practice.

Given the overall lack of public awareness about kidney diseases, uneven fellowship training in home dialysis, and a limited pool of nephrologists with expertise in providing such care, it is not surprising that people faced with kidney failure are often unaware that home dialysis is an option. This lack of awareness is further exacerbated by health disparities and inequities in the United States.

To address these obstacles and ensure the ongoing success of the executive order, ASN has used a multipronged approach for increasing home dialysis in the United States. Charged with boosting "awareness and outcomes of home dialysis therapies by enhancing education of kidney care professionals and trainees, addressing disparities in access to home dialysis, and advocating for policies that improve access to all dialysis treatment options in order to promote the highest quality of care," the ASN Home Dialysis Project is the centerpiece of this effort (6).

Reversing more than 50 years of federal policy

ASN helped undo decades of substantially lower payment rates for nephrologists providing home dialysis care as compared with in-center dialysis care by helping make the two rates of payment closer. Taking effect in 2021, this increase in payment for home dialysis occurred at approximately the same time as the two payment models for kidney care were introduced.

ASN also led advocacy efforts to enact legislation permitting nephrologists to use telehealth to interact with patients dialyzing at home. This 2019 change marked the first instance in which the Medicare program allowed physicians to care for patients in their homes via telehealth. ASN also supports assisted home dialysis for limited periods, such as in the beginning or when patients on dialysis (or their care partners) are ill.

Additionally, ASN urged the Agency for Healthcare Research and Quality to conduct a literature review on the benefits of assisted home dialysis. If successful, this request could result in the agency's increased validation of the benefits associated with supporting people who dialyze at home and advance consideration of such policies within Congress and the Centers for Medicare & Medicaid Services.

Spurring innovation

In tandem, the Kidney Health Initiative (KHI) and Kidney Innovation Accelerator (KidneyX) have advanced home dialysis by addressing regulatory barriers and funding innovators, respectively. KHI's workshop, "Stimulating Patient Engagement in Medical Device Development in Kidney Disease," resulted in a comprehensive review by the US Food and Drug Administration to expand the label of a cleared home hemodialysis device, permitting treatment in absence of a qualified care partner (7). This expansion continues to stimulate innovation and investments in home dialysis devices (8).

To further support innovations that will accelerate the adoption of home dialysis, KHI convened the kidney community to publish a "Technology Roadmap for Innovative Approaches to Renal Replacement Therapy" (9). A collaboration with the US Food and Drug Administration, this roadmap aligned different technology-driven approaches spanning in-center and portable dialysis devices to an implanted biomechanical and xenotransplanted artificial kidney.

KidneyX used the roadmap to frame four prize competitions awarding more than $17 million to stimulate innovation. These competitions identified more than 20 winners who are developing technologies to advance safer, more patient-friendly dialysis access; remote monitoring; home dialysis; and portable or wearable dialysis, as well as virtual training, telemonitoring, and telehealth. The KidneyX Patient Innovator Challenge (a partnership with the National Kidney Foundation) produced 11 winners focused on improving home dialysis.

KHI and KidneyX are building on an important legacy and closing a gap that has existed for far too long. As a recent editorial emphasized, "many critical innovations in clinical care delivery and research" in home dialysis—particularly peritoneal dialysis (PD)—originated in the United States (10). "These include the development and introduction of the Tenckhoff PD catheter, the first description of the use of continuous ambulatory PD for patients with kidney failure, the development of the first PD cycler, the first description of the peritoneal equilibration test in 1987, and the first genome-wide association study among patients on PD, to name just a few."

Training the nephrology workforce

The ASN Task Force on the Future of Nephrology issued 10 recommendations in 2022. The task force's third recommendation committed ASN to emphasizing patient-centered care: "Nephrology must emphasize personalized care to optimize kidney health and increase patient choice, including early intervention, transplantation, and dialysis" (11). In recognizing that "home-based modalities for kidney replacement therapy are often preferred options," the task force highlighted that training requirements for nephrology fellows must further highlight home dialysis.

Responding to ASN's recommendation, the Accreditation Council for Graduate Medical Education now requires nephrology fellowship training programs to "deliver effective and patient-centered education regarding options for management of ESRD, including transplant, home dialysis therapies (peritoneal dialysis and home hemodialysis), in-center hemodialysis, and supportive care" (12). ASN has encouraged the American Board of Internal Medicine to revise the "blueprint" for the initial certification examination in nephrology to include more questions about PD and home hemodialysis (13).

To facilitate more training in home dialysis—and with funding from the Centers for Disease Control and Prevention—ASN partnered with the Home Dialysis University (HDU) to provide travel support for nephrology fellows to attend HDU in 2023 (30 fellows) and 2024 (60 fellows). Through an in-person, immersive approach to home dialysis therapies, HDU has been educating nephrology fellows and nephrologists since 1998.

HDU's partnership with ASN has also produced a case-based education series that covers a wide range of topics in home hemodialysis and PD, including dialysis access, complications' management, writing prescriptions, and day-to-day troubleshooting. The program now encourages "mentoring," by creating opportunities for the fellows to network with expert faculty as well as to join a targeted ASN Online Community. The ASN-HDU partnership will continue to help nephrology fellowship training programs comply with the new Accreditation Council for Graduate Medical Education requirements and future fellows to certify through the American Board of Internal Medicine. Ideally, if expanded, the partnership could help all nephrologists who wish to enhance their skills, knowledge, and experience with home dialysis.

In addition to partnering with HDU, ASN is compiling a set of PD core interventions for infection prevention similar to the Centers for Disease Control and Prevention's Core Interventions for Dialysis Bloodstream Infection Prevention. Dialysis facility staff can follow this set of core interventions to minimize risk of infection (such as peritonitis, exit site, or tunnel infection) for people using PD.

Recognizing the central role of dialysis access (vascular access or PD catheters) in the uptake of home dialysis, ASN has also initiated a new program on "Transforming Dialysis Access Together," which is focusing on the innovation, training, and awareness needed for successful home dialysis access care.

Earlier this year, *CJASN* published a 16-article series, "Home Dialysis: Fundamentals and Beyond" (14). This series "curates state-of-the-art, practice-centered reviews on home dialysis to highlight the most cogent issues needed for the nephrologist providing primary or consultative care for patients receiving home dialysis, with a focus on recent advances."

Increasing patient awareness

ASN has long advocated to expand the Kidney Disease Education (KDE) benefit (currently only available for stage 4 chronic kidney disease) to stages 3b and 5. By teaching people how to slow the progression of kidney diseases and explaining modality choice, the KDE benefit provides information essential to promoting home dialysis. Reflecting ASN advocacy, one of the aforementioned payment models expanded KDE to stages 3b and 5 and waived the copay for patients using this benefit.

Overcoming disparities and inequities

Even though Black and Latinx/Hispanic Americans have a greater risk of kidney failure, they "are less likely than non-Latinx White patients to be treated with home dialysis" (15). This difference is "not completely explained by geographic, demographic, and clinical factors," which means that these groups face "other contributing factors, specifically environmental, social, and system-level barriers to home dialysis."

Black and Latinx/Hispanic Americans living with kidney diseases also "experience a disproportionate burden" of hypertension, diabetes, and obesity; are less likely to receive care before their kidneys fail; are referred later to a nephrologist, often requiring "inpatient or urgent dialysis initiation, which in most cases, results in central venous catheter placement and in-center dialysis"; and may face socioeconomic barriers, such as poverty, that are "associated with home dialysis failure, which may influence their likelihood of being offered home therapies in the first place" (16).

Beyond Black and Latinx/Hispanic Americans, communities with disproportionately low rates of access to home dialysis include people "with low educational attainment, limited family support, and Medicaid coverage" as well as people living in rural communities (16). As such, nephrology fellowship training (and beyond) must address potential biases and barriers that could impede offering home dialysis as an option for people from socially marginalized communities.

In addition to leveraging its role in supporting fellowship and continuing education, ASN must focus specifically on overcoming inequities and disparities in home dialysis. Each of these challenges merits a focused intervention by the ASN Home Dialysis Project or Health Care Justice Committee.

Making progress

Galvanized by the Executive Order on Advancing American Kidney Health, ASN has spent the past 5 years trying to increase home dialysis in the United States by reversing more than 50 years of federal policy, spurring innovation, improving training for the nephrology workforce, increasing patient awareness, and overcoming disparities and inequities. Clearly, much more progress is needed, but it is notable that the United States is one of the few countries in which use of home dialysis is increasing (10).

According to the US Renal Data System, the rate of home dialysis utilization increased from 10.2% to 14.1% between 2012 and 2021 (4). An abstract presented at ASN Kidney Week 2023 concludes that "the rate of home dialysis utilization grew from 12.3% to 15.9% across all Medicare FFS [Fee-for-Service] beneficiaries" between the first quarter of 2019 and the second quarter of 2022 (17). Fueled by the executive order, ASN and the kidney community deserve credit for this progress as the United States nears its semiquincentennial.

On November 4, 1971, Shep Glazer testified on behalf of the National Association of Patients on Hemodialysis (for which he was a former vice president and which later became the American Association of Kidney Patients) to the Ways and Means Committee of the House of Representatives while attempting to dialyze. Mr. Glazer's wife stated after his testimony, "The idea of bringing the dialysis machine was not for shock value or for publicity, it was to prove and inform, because there has been so much misconception about dialysis in the country today" (18). She continued, "As you can see, it is not necessarily a hospital procedure. It can be done anywhere if it could be done here in the hearing room." ■

Tod Ibrahim, MLA, is executive vice president, American Society of Nephrology, Washington, DC. You can reach him at tibrahim@asn-online.org.

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INDICATION AND IMPORTANT SAFETY INFORMATION

INDICATION

TAVNEOS (avacopan) is indicated as an adjunctive treatment of adult patients with severe active anti-neutrophil cytoplasmic autoantibody (ANCA)-associated vasculitis (granulomatosis with polyangiitis [GPA] and microscopic polyangiitis [MPA]) in combination with standard therapy including glucocorticoids. TAVNEOS does not eliminate glucocorticoid use.

CONTRAINDICATIONS

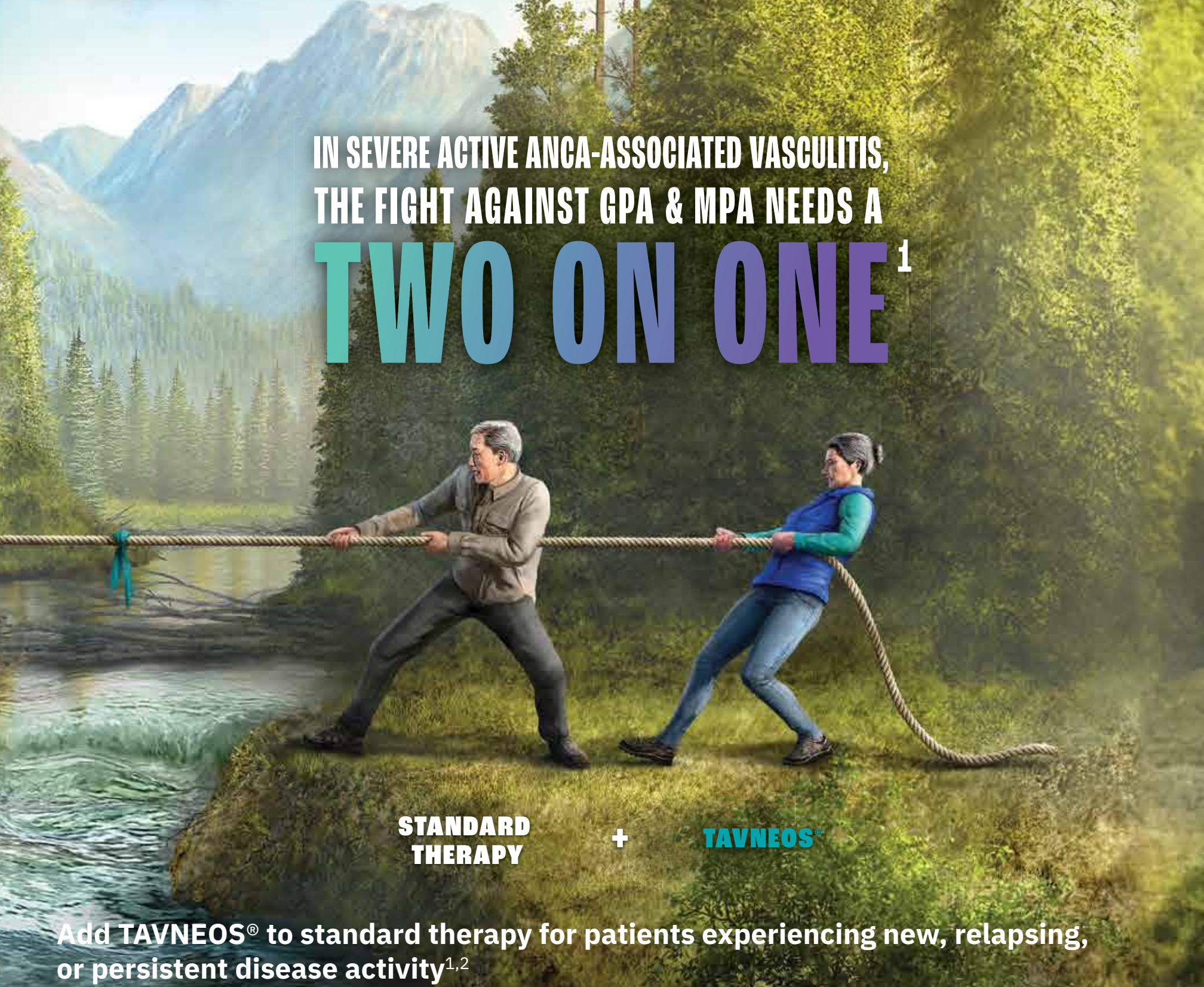
Serious hypersensitivity to avacopan or to any of the excipients.

WARNINGS AND PRECAUTIONS

Hepatotoxicity: Serious cases of hepatic injury have been observed in patients taking TAVNEOS, including life-threatening events. Obtain liver test panel before initiating TAVNEOS, every 4 weeks after start of therapy for 6 months and as clinically indicated thereafter. Monitor patients closely for hepatic adverse reactions, and consider pausing or discontinuing treatment as clinically indicated (refer to section 5.1 of the Prescribing Information). TAVNEOS is not recommended for patients with active, untreated, and/or uncontrolled chronic liver disease (e.g., chronic active hepatitis B, untreated hepatitis C, uncontrolled autoimmune hepatitis) and cirrhosis. Consider the risks and benefits before administering this drug to a patient with liver disease.

Serious Hypersensitivity Reactions: Cases of angioedema occurred in a clinical trial, including 1 serious event requiring hospitalization. Discontinue immediately if angioedema occurs and manage accordingly. TAVNEOS must not be readministered unless another cause has been established.

Hepatitis B Virus (HBV) Reactivation: Hepatitis B reactivation, including life-threatening hepatitis B, was observed in the clinical program. Screen patients for HBV. For patients with evidence of prior infection, consult with physicians with expertise in HBV and monitor during TAVNEOS therapy and for 6 months following. If patients develop HBV reactivation, immediately discontinue TAVNEOS and concomitant therapies associated with HBV reactivation, and consult with experts before resuming.



Add TAVNEOS® to standard therapy for patients experiencing new, relapsing, or persistent disease activity[1,2]

Serious Infections: Serious infections, including fatal infections, have been reported in patients receiving TAVNEOS. The most common serious infections reported in the TAVNEOS group were pneumonia and urinary tract infections. Avoid use of TAVNEOS in patients with active, serious infection, including localized infections. Consider the risks and benefits before initiating TAVNEOS in patients with chronic infection, at increased risk of infection, or who have been to places where certain infections are common.

ADVERSE REACTIONS

The most common adverse reactions (≥5% of patients and higher in the TAVNEOS group vs. prednisone group) were nausea, headache, hypertension, diarrhea, vomiting, rash, fatigue, upper abdominal pain, dizziness, blood creatinine increased, and paresthesia.

DRUG INTERACTIONS

Avoid coadministration of TAVNEOS with strong and moderate CYP3A4 enzyme inducers. Reduce TAVNEOS dose when coadministered with strong CYP3A4 enzyme inhibitors to 30 mg once daily. Monitor for adverse reactions and consider dose reduction of certain sensitive CYP3A4 substrates.

TAVNEOS is available as a 10 mg capsule.

To report a suspected adverse event, call 1-833-828-6367. You may report to the FDA directly by visiting **www.fda.gov/medwatch** or calling 1-800-332-1088.

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Please see Brief Summary of Prescribing Information for TAVNEOS® on the following pages.

12/23 USA-569-80504

AMGEN®

BRIEF SUMMARY OF PRESCRIBING INFORMATION
TAVNEOS® (avacopan) capsules, for oral use
Please see package insert for full Prescribing Information.

INDICATIONS AND USAGE

TAVNEOS is indicated as an adjunctive treatment of adult patients with severe active anti-neutrophil cytoplasmic autoantibody (ANCA)-associated vasculitis (granulomatosis with polyangiitis [GPA] and microscopic polyangiitis [MPA]) in combination with standard therapy including glucocorticoids. TAVNEOS does not eliminate glucocorticoid use.

CONTRAINDICATIONS

TAVNEOS is contraindicated in patients with serious hypersensitivity reactions to avacopan or to any of the excipients *[see Warnings and Precautions (5.2)]*.

WARNINGS AND PRECAUTIONS

Hepatotoxicity

Serious cases of hepatic injury have been observed in patients taking TAVNEOS. During controlled trials, the TAVNEOS treatment group had a higher incidence of transaminase elevations and hepatobiliary events, including serious and life-threatening events *[see Adverse Reactions (6.1)]*.

Obtain liver test panel (serum alanine aminotransferase [ALT], aspartate aminotransferase [AST], alkaline phosphatase, and total bilirubin) before initiating TAVNEOS, every 4 weeks after start of therapy for the first 6 months of treatment and as clinically indicated thereafter.

If a patient receiving treatment with TAVNEOS presents with an elevation in ALT or AST to >3 times the upper limit of normal, evaluate promptly and consider pausing treatment as clinically indicated.

If AST or ALT is >5 times the upper limit of normal, or if a patient develops transaminases >3 times the upper limit of normal with elevation of bilirubin to >2 times the upper limit of normal, discontinue TAVNEOS until TAVNEOS-induced liver injury is ruled out *[see Adverse Reactions (6.1)]*.

TAVNEOS is not recommended for patients with active, untreated and/or uncontrolled chronic liver disease (e.g., chronic active hepatitis B, untreated hepatitis C, uncontrolled autoimmune hepatitis) and cirrhosis. Consider the risk and benefit before administering TAVNEOS to a patient with liver disease. Monitor patients closely for hepatic adverse reactions *[see Use in Specific Populations (8.7)]*.

Hypersensitivity Reactions

TAVNEOS may cause angioedema *[see Adverse Reactions (6.1)]*. In clinical trials, two cases of angioedema occurred, including one serious event requiring hospitalization. If angioedema occurs, discontinue TAVNEOS immediately, provide appropriate therapy, and monitor for airway compromise. TAVNEOS must not be re-administered unless another cause has been established. Educate patients on recognizing the signs and symptoms of a hypersensitivity reaction and to seek immediate medical care should they develop.

Hepatitis B Virus (HBV) Reactivation

Hepatitis B virus (HBV) reactivation, including life threatening hepatitis B, was observed in the clinical program.

HBV reactivation is defined as an abrupt increase in HBV replication, manifesting as a rapid increase in serum HBV DNA levels or detection of HBsAg, in a person who was previously HBsAg negative and anti-HBc positive. Reactivation of HBV replication is often followed by hepatitis, i.e., increase in transaminase levels. In severe cases, increase in bilirubin levels, liver failure, and death can occur.

Screen patients for HBV infection by measuring HBsAg and anti-HBc before initiating treatment with TAVNEOS. For patients who show evidence of prior hepatitis B infection (HBsAg positive [regardless of antibody status] or HBsAg negative but anti-HBc positive), consult physicians with expertise in managing hepatitis B regarding monitoring and consideration for HBV antiviral therapy before and/or during TAVNEOS treatment.

Monitor patients with evidence of current or prior HBV infection for clinical and laboratory signs of hepatitis, or HBV reactivation during and for six months following TAVNEOS therapy.

In patients who develop reactivation of HBV while on TAVNEOS, immediately discontinue TAVNEOS and any concomitant therapy associated with HBV reactivation, and institute appropriate treatment. Insufficient data exist regarding the safety of resuming TAVNEOS treatment in patients who develop HBV reactivation. Resumption of TAVNEOS treatment in patients whose HBV reactivation resolves should be discussed with physicians with expertise in managing HBV.

Serious Infections

Serious infections, including fatal infections, have been reported in patients receiving TAVNEOS. The most common serious infections reported in the TAVNEOS group were pneumonia and urinary tract infections.

Avoid use of TAVNEOS in patients with an active, serious infection, including localized infections. Consider the risks and benefits of treatment prior to initiating TAVNEOS in patients:

- with chronic or recurrent infection
- who have been exposed to tuberculosis
- with a history of a serious or an opportunistic infection
- who have resided or traveled in areas of endemic tuberculosis or endemic mycoses; or
- with underlying conditions that may predispose them to infection.

Closely monitor patients for the development of signs and symptoms of infection during and after treatment with TAVNEOS. Interrupt TAVNEOS if a patient develops a serious or opportunistic infection. A patient who develops a new infection during treatment with TAVNEOS should undergo prompt and complete diagnostic testing appropriate for an immunocompromised patient; appropriate antimicrobial therapy should be initiated, the patient should be closely monitored, and TAVNEOS should be interrupted if the patient is not responding to antimicrobial therapy. TAVNEOS may be resumed once the infection is controlled.

ADVERSE REACTIONS

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

- Hepatotoxicity *[see Warnings and Precautions (5.1)]*
- Hypersensitivity Reactions *[see Warnings and Precautions (5.2)]*
- Hepatitis B Virus (HBV) Reactivation *[see Warnings and Precautions (5.3)]*
- Serious Infections *[see Warnings and Precautions (5.4)]*

Clinical Trials Experience

Because the 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 practice.

The identification of potential adverse drug reactions was based on safety data from the phase 3 clinical trial in which 330 patients with ANCA-associated vasculitis were randomized 1:1 to either TAVNEOS or prednisone *[see Clinical Studies (14)]*. The mean age of patients was 60.9 years (range of 13 to 88 years), with a predominance of men (56.4%) and Caucasians (84.2%). The cumulative exposure to TAVNEOS was 138.7 patient-years. Additionally, two phase 2 trials were conducted in ANCA-associated vasculitis. The cumulative clinical trial exposure from the phase 2 and 3 trials equals 212.3 patient-years.

The most frequent serious adverse reactions reported more frequently in patients treated with TAVNEOS than with prednisone were pneumonia (4.8% TAVNEOS vs. 3.7% prednisone), GPA (3.0% TAVNEOS vs. 0.6% prednisone), acute kidney injury (1.8% TAVNEOS vs. 0.6% prednisone), and urinary tract infection (1.8% TAVNEOS vs. 1.2% prednisone). Within 52 weeks, 4 patients in the prednisone treatment group (2.4%) and 2 patients in the TAVNEOS group (1.2%) died. There were no deaths in the phase 2 trials.

In the phase 3 trial, seven patients (4.2%) in the TAVNEOS treatment group and 2 patients (1.2%) in the prednisone treatment group discontinued treatment due to hepatic-related adverse reactions, including hepatobiliary adverse reactions and liver enzymes abnormalities. The most frequent adverse reaction that led to drug discontinuation reported by > 1 patient and more frequently reported in patients treated with TAVNEOS was hepatic function abnormal (1.8%).

The most common adverse reactions that occurred in ≥5% of patients and higher in the TAVNEOS group as compared with the prednisone group are listed in Table 1.

Table 1: Adverse Reactions Reported in ≥5% of Patients and Higher in TAVNEOS Group vs. Prednisone Group in Phase 3 Trial

Adverse Reaction	Prednisone (N=164) n (%)	TAVNEOS (N=166) n (%)
Nausea	34 (20.7)	39 (23.5)
Headache	23 (14.0)	34 (20.5)
Hypertension	29 (17.7)	30 (18.1)
Diarrhea	24 (14.6)	25 (15.1)
Vomiting	21 (12.8)	25 (15.1)
Rash	13 (7.9)	19 (11.4)
Fatigue	15 (9.1)	17 (10.2)
Upper abdominal pain	10 (6.1)	11 (6.6)
Dizziness	10 (6.1)	11 (6.6)
Blood creatinine increased	8 (4.9)	10 (6.0)
Paresthesia	7 (4.3)	9 (5.4)

N=number of patients randomized to treatment group in the Safety Population; n=number of patients in specified category.

Hepatotoxicity and Elevated Liver Function Tests

In the phase 3 trial, a total of 19 patients (11.6%) in the prednisone group and 22 patients (13.3%) in the TAVNEOS group had hepatic-related adverse reactions, including hepatobiliary adverse reactions and liver enzyme abnormalities. Study medication was paused or discontinued permanently due to hepatic-related adverse reactions in 5 patients (3.0%) in the prednisone group and 9 patients (5.4%) in the TAVNEOS group. Serious hepatic-related adverse reactions were reported in 6 patients (3.7%) in the prednisone group and 9 patients (5.4%) in the TAVNEOS group. A serious hepatic-related adverse reaction was reported in 1 patient in the TAVNEOS group in the phase 2 studies.

Angioedema

In the phase 3 trial, 2 patients (1.2%) in the TAVNEOS group had angioedema; one event was a serious adverse reaction requiring hospitalization.

Elevated Creatine Phosphokinase

In the phase 3 trial, 1 patient (0.6%) in the prednisone group and 6 patients (3.6%) in the TAVNEOS group had increased creatine phosphokinase. One TAVNEOS-treated patient discontinued treatment due to increased creatine phosphokinase.

DRUG INTERACTIONS

CYP3A4 Inducers

Avacopan exposure is decreased when co-administered with strong CYP3A4 enzyme inducers such as rifampin *[see Clinical Pharmacology (12.3)]*. Avoid coadministration of strong and moderate CYP3A4 inducers with TAVNEOS.

CYP3A4 Inhibitors

Avacopan exposure is increased when co-administered with strong CYP3A4 enzyme inhibitors such as itraconazole *[see Clinical Pharmacology (12.3)]*. Administer TAVNEOS 30 mg once daily when coadministered with strong CYP3A4 inhibitors.

CYP3A4 Substrates

Avacopan is a CYP3A4 inhibitor. Closely monitor patients for adverse reactions and consider dose reduction of sensitive CYP3A4 substrates with a narrow therapeutic window when coadministered with TAVNEOS *[see Clinical Pharmacology (12.3)]*.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

There are no adequate and well-controlled studies with TAVNEOS in pregnant women to inform a drug-associated risk. In animal reproduction studies, oral administration of avacopan to pregnant hamsters and rabbits during the period of organogenesis produced no evidence of fetal harm with exposures up to approximately 5 and 0.6 times, respectively, the exposure at the maximum recommended human dose (MRHD) of 30 mg twice daily (on an area under the curve [AUC] basis). Avacopan caused an increase in the number of abortions in rabbits at an exposure 0.6 times the MRHD *(see Animal Data)*.

The background risk of major birth defects and miscarriage for the indicated population are 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

In an embryo-fetal development study with pregnant hamsters dosed by the oral route during the period of organogenesis from gestation days 6 to 12, avacopan produced an increase in the incidence of a skeletal variation, described as supernumerary ribs, at an exposure that was 5 times the MRHD (on an AUC basis with a maternal oral dose of 1000 mg/kg/day). No structural abnormalities were noted with exposures up to 5 times the MRHD (on an AUC basis with maternal oral doses up to 1000 mg/kg/day).

In an embryo-fetal development study with pregnant rabbits dosed by the oral route during the period of organogenesis from gestation days 6 to 18, avacopan caused an increase in the number of abortions at an exposure 0.6 times the MRHD (on an AUC basis with a maternal oral dose of 200 mg/kg/day), however, no evidence of fetal harm was observed with such exposures. Maternal toxicity, as evidenced by decreased body weight gains, was observed at exposures 0.6 times and higher than the MRHD (on an AUC basis with maternal oral doses of 30 mg/kg/day and higher).

In a prenatal and postnatal development study with pregnant hamsters dosed by the oral route during the periods of gestation and lactation from gestation day 6 to lactation day 20, avacopan had no effects on the growth and development of offspring with exposures up to approximately 5 times the MRHD (on an AUC basis with maternal oral doses up to 1000 mg/kg/day).

Lactation

Risk Summary

There are no available data on the effects of avacopan on the breastfed child or on milk production. It is unknown whether avacopan is secreted in human milk. Avacopan was detected in the plasma of undosed hamster pups nursing from drug-treated dams *(see Animal Data)*. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for TAVNEOS and any potential adverse effects on the breast-fed infant from TAVNEOS or from the underlying maternal condition.

Animal Data

Avacopan has not been measured in the milk of lactating animals; however, it was detected in the plasma of nursing offspring in a pre- and post-natal development study with hamsters at a pup to maternal plasma ratio of 0.37. This finding suggests that avacopan is secreted into the milk of lactating hamsters *[see Nonclinical Pharmacology (13.1)]*.

Pediatric Use

The safety and effectiveness of TAVNEOS in pediatric patients have not been established.

Geriatric Use

Of the 86 geriatric patients who received TAVNEOS in the phase 3 randomized clinical trial for ANCA-associated vasculitis *[see Clinical Studies (14)]*, 62 patients were between 65-74 years and 24 were 75 years or older. No overall differences in safety or effectiveness were observed between geriatric patients and younger patients.

Patients With Renal Impairment

No dose adjustment is required for patients with mild, moderate, or severe renal impairment *[see Clinical Pharmacology (12.3)]*. TAVNEOS has not been studied in patients with ANCA-associated vasculitis who are on dialysis.

Patients With Hepatic Impairment

No dosage adjustment is recommended for patients with mild or moderate (as indicated by the Child-Pugh method) hepatic impairment *[see Clinical Pharmacology (12.3)]*. TAVNEOS has not been studied in patients with severe hepatic impairment (Child-Pugh Class C).

The risk information provided here is not comprehensive. The FDA-approved product labeling can be found at www.tavneospro.com or contact Amgen Medical Information at 1-800-772-6436

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Transplant Nephrology Accredited by ACGME: A Solution to the Shortage?

By Pablo Garcia and Christos Argyropoulos

In the United States, transplant nephrology training is a 1-year clinical fellowship after general nephrology training. Over the past 10 years, the number of nephrology and transplant positions filled in the country has declined (1). This decline is concerning given the foreseen increase in the transplant workforce in the United States because the Advancing American Kidney Health Initiative aims to double the number of kidney transplants by 2030 (2). Given the concerns, a group of leaders in the kidney transplant field in the United States recently wrote a thought- and debate-provoking article in *CJASN* asking, "Should Transplant Nephrology Pursue Recognition from the Accreditation Council for Graduate Medical Education (ACGME)?" (3).

There are a few potential benefits in recognizing transplant nephrology by ACGME. Once transplant nephrology is ACGME-accredited, followed by American Medical Association recognition, we can possibly expect recognition from the Centers for Medicare & Medicaid Services (CMS). CMS recognition might add more value to a transplant nephrology practice and better reimbursement. In the educational setting, among other areas highlighted in the Table, we can expect salary support for program directors during nonclinical times. Probably the most crucial benefit of being recognized is the one related to visas; as of July 1, 2023, ACGME-accredited institutions that want to host J-1 trainees in nonstandard training programs are required to obtain ACGME nonstandard training programs' recognition; otherwise, the programs cannot hire transplant fellows on J-1 visas (4).

Although ACGME recognition could increase applicants, protect educational time, and boost reimbursement, it also has potential downsides, such as administrative costs associated with the ACGME certification and maintenance process, costs associated with American Board of Internal Medicine (ABIM) exams, and additional examinations for certification. Therefore, the solution to the present and future shortage may not solely lie in ACGME recognition.

Approximately one-third of US nephrology fellows surveyed reported experiencing burnout and depressive symptoms (5). We as a field should consider expanding the transplant nephrology training options for fellows in general nephrology so that those who choose to can finish their fellowship with enhanced transplant nephrology skills. This could be the proverbial stone that kills two birds: 1) diversify general nephrology training, making it more appealing through increased exposure to organ replacement through transplant and home dialysis; 2) generate a cadre of nephrologists who can take care of transplant recipients, extending the actual scope of practice away from in-center dialysis, which will likely decline due to the novel therapeutic advances such as sodium-glucose cotransporter-2 inhibitors, glucagon-like peptide-1 receptor agonists, and mineralocorticoid receptor antagonists.

In the *CJASN* article (3), the authors discuss the successes of hepatology and gastroenterology and advanced heart failure with transplant cardiology (AHFTC) fellowships. Even though AHFTC is an ACGME-recognized specialty, the field is struggling with recruitment; approximately 43% of the AHFTC positions went unfilled in 2023. A recent survey exploring factors that influence a cardiology subspecialty choice found that AHFTC trainees were less incentivized by certain career characteristics related to work-life balance. Compared with respondents with other career interests, trainees with AHFTC interests were less strongly motivated by work schedules, geographic flexibility, and financial compensation (6). Perhaps, as a field, we need to understand that ACGME recognition will not solve our shortage, and we are training a unique group of people driven by the desire to take care of patients with complex medical issues.

We need more comprehensive data to better understand why nephrology trainees are not showing interest in kidney transplantation training. Are they prioritizing immediate employment to manage debts or to support their families? If so, transplant programs in the United States should consider the Organ Procurement & Transplantation Network/United Network for Organ Sharing clinical experience pathway. We also need data on kidney transplant programs. Are they not filling up because they cannot enroll trainees on a J-1 visa, or is it due to a lack of applicants? If visas are the main issue, then ACGME recognition could be a potential solution.

We must include other transplant practitioners in this discussion on shortage; nurse practitioners (NPs) can successfully care for patients with complex diseases, such as kidney diseases. A recent study in Canada found that care provided independently by NPs was associated with greater guideline-concordant care than with primary care alone or with care by nephrologists, with clinical outcomes that were similar to those achieved with care by nephrologists (7). Can NPs care for patients in the kidney transplant setting? Yes; we can work along with NPs and accept a more supervisory role as a way to solve the issue. Another potential solution to the shortage is to empower general nephrologists to take care of postkidney transplant patients through robust educational resources.

Most recently, the field of transplantation has experienced significant advances, such as expanding the donor pool by implementing the hepatitis C program, developing new diagnostic tests based on cell-free DNA, and most recently, in xenotransplantation (8–10). These advances underscore the need for a set of specific and unique skills to move the field forward. It is our specialized knowledge and expertise that will drive the interest in the field of transplant nephrology, coupled with innovation and an increase in reimbursement. ■

Table. Positives and negatives of ACGME recognition by area

Area	Positives	Negatives
Reimbursement	• Funding for transplant nephrology training through GME • CMS recognition with the potential to increase reimbursement	• Administrative and cost burden due to the accreditation process • ABIM examination fees
Education	• Salary support of nonclinical time for program directors • Potential utilization of the National Resident Matching Program system • Enhancing the quality of transplant training across institutions	• Potential requirement for ABIM or additional examination after finishing transplant training • Reduction of transplant nephrology training among general nephrology trainees
Immigration	• Pathway opening for J-1 fellows • Possibly meeting state licensure requirements for exceptionally qualified candidates	

Pablo Garcia, MD, MS, FASN, is an assistant professor of medicine, and Christos Argyropoulos, MD, MS, PhD, FASN, is division chief and an associate professor of medicine and nephrology at The University of New Mexico School of Medicine, Albuquerque.

The authors report no conflicts of interest.

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A Paradigm Shift in Primary Aldosteronism

By Gregory L. Hundemer, Jade M. Teakell, and Swapnil Hiremath

Primary aldosteronism (PA) was historically considered a niche disease, but modern-day prevalence studies report that 4%–7% of newly diagnosed hypertension in primary care (1) and up to 20% of resistant hypertension are attributed to PA (2). Importantly, PA leads to a disproportionately higher risk for cardiovascular and kidney diseases compared with essential hypertension, even independent of blood pressure (3, 4). Recent literature is also challenging the dogma of simplifying PA to a categorical disease defined by strict biochemical thresholds in patients with severe hypertension, hypokalemia, or an adrenal nodule (5–7). These studies show that PA spans a broader continuum of dysregulated aldosterone secretion, whereby overt PA is merely the "tip of the iceberg." In fact, PA pathophysiology has been clearly demonstrated in individuals with mild hypertension and even normotension—populations that are not historically tested for PA (8)—and is associated with inappropriate mineralocorticoid receptor activation, blood pressure elevation, arterial stiffening, and adverse cardiac remodeling.

The latest addition to the literature showcasing PA as a disease that spans a broad continuum of thresholds comes from the recent Repetition of Aldosterone-to-Renin Ratio (ROARR) study (9). This prospective European cohort study followed 184 individuals with an elevated aldosterone-to-renin ratio but a negative confirmatory test for PA (i.e., not meeting the classical thresholds defining PA). At a mean follow-up time of approximately 5 years, PA confirmatory testing was repeated, and one out of every five study participants did meet criteria for PA at that time. One interpretation of these results could be that they simply reflect the inherent challenges in interpreting existing PA confirmatory tests for which the established thresholds are based on very low-quality evidence, leading to poor accuracy and reproducibility among individuals with elevated aldosterone-to-renin ratios and high-probability PA features (10). However, another important finding from the ROARR study is that those participants who transitioned from having a negative to a positive confirmatory test during follow-up also showed worsening blood pressure control and a higher rate of cardiac damage (concentric remodeling or left ventricular hypertrophy) despite similar use of antihypertensive medications (9). This suggests temporal disease progression in these individuals, both clinically and biochemically, along the PA severity continuum to a point at which aldosterone suppressibility was reduced to a level in which it met the classical definition of PA. This underscores the importance of not treating screening and confirmatory testing as a one-time action, especially given the potential for avoiding end-organ damage.

Overall, the mounting evidence showcasing PA as a disease that stretches well beyond its historical confines has reached a point that can no longer be ignored. We need clinical trials to determine whether more expansive use of aldosterone-targeted therapies throughout the PA continuum will serve to improve health outcomes for a much broader patient population. ■

Gregory L. Hundemer, MD, MPH, is an assistant professor of medicine, and Swapnil Hiremath, MD, FASN, MPH, is an associate professor of medicine at The Ottawa Hospital, Ottawa, Ontario, Canada. Jade M. Teakell, MD, PhD, FASN, is an associate professor, McGovern Medical School at UTHealth Houston, TX.

The authors report no conflicts of interest.

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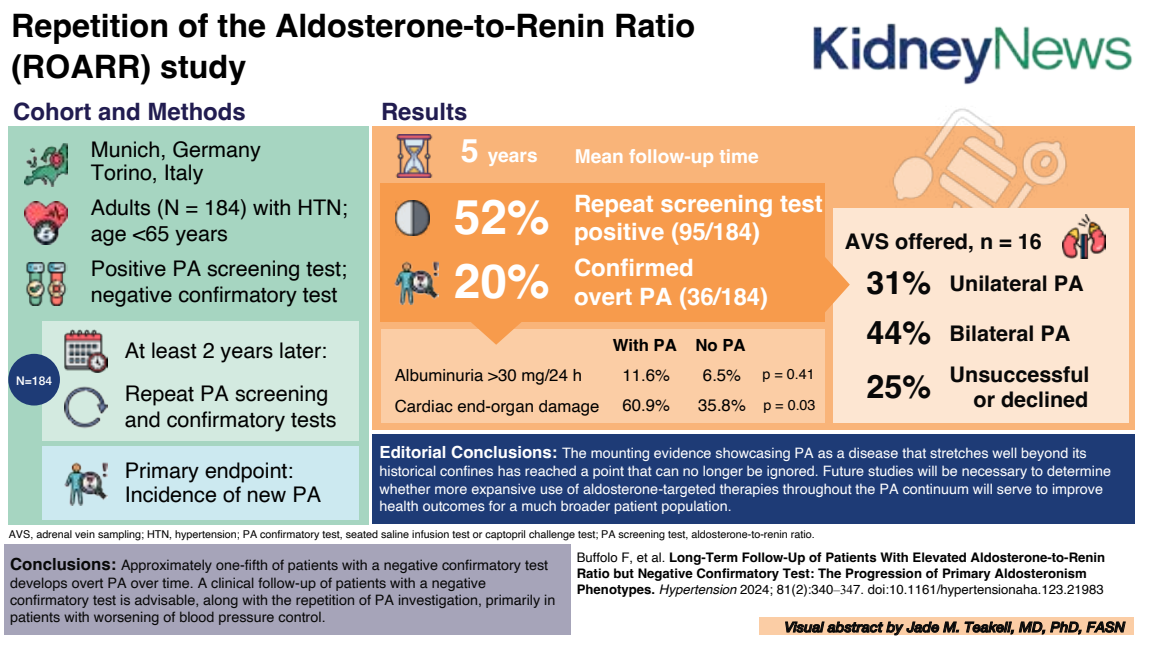


Predicting Renal Relapses in ANCA-GN: Can We Rely on Urinary CD4⁺ T Cells?

By Andreas Kronbichler and Cecilia Barnini

Effective therapies to manage antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis have transformed a fatal disease into a relapsing-remitting disease. Predictors of relapses, identified in numerous studies, include ear, nose, and throat involvement; proteinase 3 (PR3)-ANCA positivity; granulomatosis with polyangiitis as the disease phenotype; preserved kidney function; prior relapse; and the use of maintenance agents other than rituximab (1).

Analyses of patients recruited into the earlier European Vasculitis Society trials, who were followed for over 5 years, indicated that the occurrence of a renal relapse significantly predicted the risk of kidney failure with a subhazard ratio of almost 9 (2). This finding clearly underlines the importance to avoid disease relapses, and especially renal relapses, to limit the loss of nephrons and thus reduce the risk of kidney failure. A candidate biomarker should ideally associate with disease activity and should become detectable or increase in the months before a relapse occurs. Furthermore, it needs to distinguish risk of disease activity of ANCA-glomerulonephritis (GN) from potential differential diagnoses, such as acute kidney injury (AKI) due to infectious complications or drug-induced AKI. In addition, a candidate biomarker would ideally be easily measurable, and its predictive capacity should be confirmed by independent research groups.

Urinary soluble CD163 (sCD163) has emerged as a promising biomarker, with the ability to distinguish between active disease and remission, active ANCA-GN and other glomerular diseases, and AKI and different causes and to predict renal relapse. At a diagnostic cutoff of 253 ng/mmol, a 2021 study by Moran et al. (3) reported an area under the curve of 0.95, with a sensitivity of 96.8% and a specificity of 86.8% to detect renal relapse. In a more recent study by Sonnemann et al. (4), flow cytometry assessment of urinary T cells of 95 patients, of whom 52 had active ANCA-GN, revealed that CD3⁺, CD4⁺, and regulatory T cell counts were significantly higher during phases of active renal disease compared with urine samples obtained during remission. Detection of CD3⁺ T cells and regulatory T cells outperformed other experimental markers such as urinary sCD163, monocyte chemoattractant protein 1, and complement C5a in the urine, whereas a dipstick analysis showed a more robust diagnostic performance. In a follow-up study—the prospective PRE-FLARED (Urinary T Lymphocytes Predict Renal Flares in Patients With Inactive ANCA-Associated Glomerulonephritis) study—the authors investigated whether urinary T lymphocyte assessment would predict renal flares within 6 months of assessment. For this purpose, 102 patients in remission were recruited. Patients with a subsequent renal relapse (n = 10; 9.8%) had higher detectable urinary CD4⁺ lymphocytes (811 cells per 100 mL of urine) compared with those with a stable remission (38 cells per 100 mL of urine) by using a cutoff of over 490 CD4⁺ T cells, a sensitivity of 60%, and a specificity of 97.8%, with an area under the curve of 0.88. Measurement of CD4⁺ T cells predicted renal relapse more accurately as widely available biomarkers, such as ANCA titers, proteinuria/albuminuria, and hematuria. The addition of PR3-ANCA to urinary CD4⁺ T lymphocytes yielded better diagnostic accuracy (5).

The findings of PRE-FLARED are highly relevant, and urinary CD4⁺ T cell analysis might further help to identify patients at risk of subsequent disease relapses. This would have direct implications on management of patients with ANCA-GN, as the analysis might identify a subset of patients who will require longer-term maintenance therapies. In the therapy of ANCA-GN, the ultimate goal must be avoidance of renal relapses, given their impact on kidney failure risk. Independent confirmation of measurement of urinary T lymphocytes to predict relapses and eventually a clinical trial with the aim to stratify patients according to their levels of CD4⁺ T cells in the urine are required to further personalize treatment approaches in ANCA-GN (Figure). ■

Andreas Kronbichler, MD, PhD, and Cecilia Barnini, MD, are with the Department of Internal Medicine IV, Nephrology and Hypertension, Medical University Innsbruck, Innsbruck, Austria.

The authors report no conflicts of interest.

Figure. ANCA-GN: From pathophysiology to clinical implications

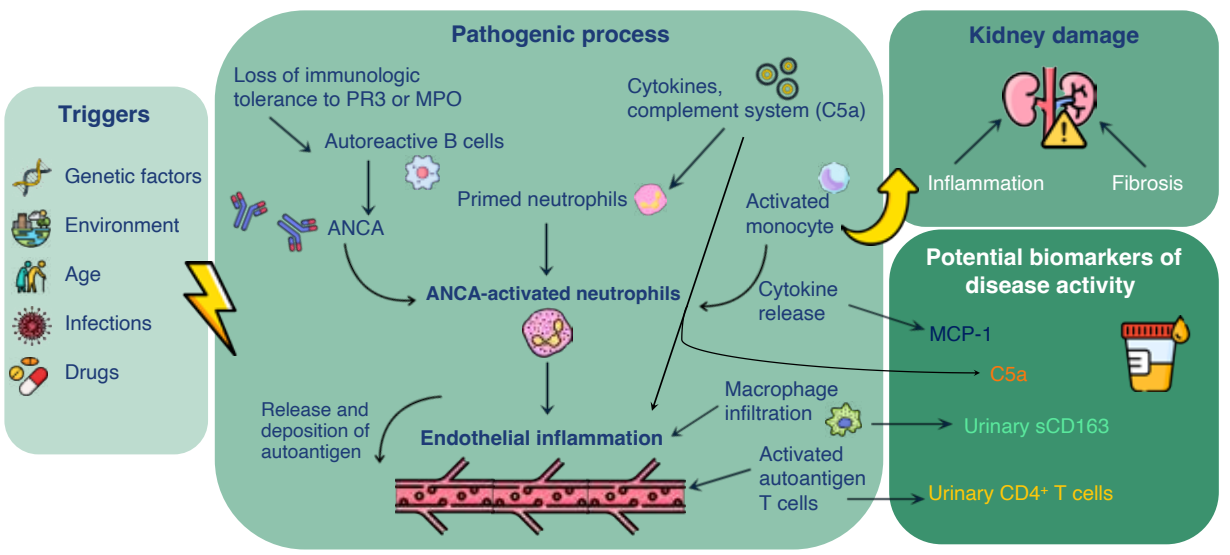
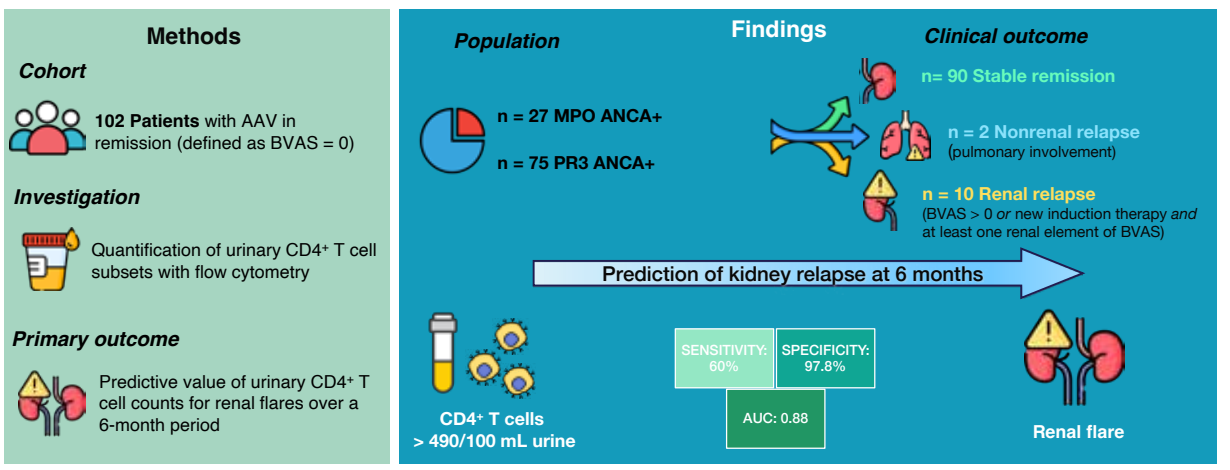


Figure by Cecilia Barnini, MD

A complex interplay of different environmental and genetic factors, infectious complications, and certain drugs can induce ANCA-associated vasculitis. There is an underlying loss of immunologic tolerance, which leads to the production of ANCA, and the increase in inflammatory cells, which reside around areas of inflammation. This eventually leads to endothelial damage and repair mechanisms, and some of the repair mechanisms contribute to fibrosis of kidney tissue. The hunt for promising biomarkers reflecting different disease stages is ongoing and is summarized here. MCP-1, monocyte chemoattractant protein 1; MPO, myeloperoxidase.

Urinary CD4⁺ T cells: A novel predictive biomarker for renal flares in patients with ANCA-associated vasculitis

KidneyNews



Conclusions: Measurement of urinary CD4⁺ T cell counts in patients with ANCA-associated vasculitis (AAV) can identify those at higher risk of subsequent renal relapse within 6 months. These findings may have relevant clinical implications for the management of these patients. AUC, area under the curve; BVAS, Birmingham Vasculitis Activity Score; MPO, myeloperoxidase.

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Visual abstract by Cecilia Barnini, MD

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Patients on Dialysis Advocate for Needleless Access, More Innovation

By Lisa Schwartz

Is a future without needles or pain possible in dialysis? Christina Gilchrist, a person living with kidney disease, hopes so.

At the Dialysis Vascular Access Workshop, held on May 6, 2024, in Washington, DC, Gilchrist emphasized the critical impact of vascular access on her daily life, explaining that patients on dialysis want and need needleless access to reduce pain and improve their quality of life. "For patients, our access affects our lives every single day," she relayed to workshop participants, who included physicians, innovators, and industry leaders, during the patient perspectives panel. "I want something that does not hurt. I am in pain every single day. There's not 1 day that goes by that I feel like a billion bucks. So please, let's get rid of the needles."

Diagnosed with kidney disease at age 12 and facing kidney failure at 22, due in part to severe preeclampsia during her first pregnancy, Gilchrist's future looked starkly different from the one she had planned. In need of immediate dialysis for her failing kidneys after the birth of her child, she underwent a vascular procedure to create a fistula. After years of on- and off-again dialysis and two kidney transplants that resulted in rejection, Gilchrist joined the ranks of patients in need of lifelong dialysis. Along the way, she experienced various types of accesses, from fistulas and peritoneal dialysis catheters to a central venous catheter for home hemodialysis.

The workshop, hosted by the Kidney Health Initiative (KHI), fostered candid discussions with a clear message: Patients do not want to live at the mercy of their vascular accesses or dialysis needs. They need needleless access, durability, and more freedom to live their lives without the constraints of dialysis.

"Our vascular accesses and dialysis are our lifeline and our curse," stated Vanessa Evans, MA, director of patient advocacy at Fresenius Medical Care. Evans brought one of the day's most unique perspectives as both a long-time patient on dialysis and a vocal advocate for innovation. She highlighted the stagnation in vascular access innovation despite substantial national spending on kidney diseases, pointing out that although the nation spends nearly $7 billion each year on kidney diseases, vascular access for dialysis has not changed much in over 60 years.

Meeting of the minds

During her welcome message, Vandana Dua Niyyar, MD, FASN, professor of medicine in the Division of Nephrology at Emory University, Atlanta, GA, and a member of the Devices Committee of the KHI Board of Directors, implored the room of attendees to challenge the status quo. "By bringing this group of like-minded individuals together, we can look forward to innovation that will change and optimize dialysis access care."

Niyyar emphasized the importance of incorporating the patient perspective early in the development process and ensuring that the patient voice is the guiding force for innovation and advancement. She further noted that dialysis access care remains fragmented. There is a tremendous need to convert the existing dialysis access care silos into an integrated multidisciplinary approach to overcome dialysis access-related challenges.

Niyyar, however, remains confident that platforms like KHI and ASN's Transforming Dialysis Access Together initiative will build on their foundational work in this area and bring unique and diverse perspectives together to solve the pressing issues facing patients undergoing dialysis. "I encourage innovators and industry leaders to remain vocal and diligent in pushing innovation forward."

Road to needleless access

Addressing the intricacies of device development that combines patient needs with affordable, accessible, and reimbursable technology, innovators presented promising designs throughout the day aimed at achieving needleless access and solutions for preventing infection, another obstacle patients face with vascular access.

Dialysis-X, for example, highlighted its needle-free access device, a one-time surgical implant designed to reduce complications for patients undergoing hemodialysis. Several other start-up companies, including Healionics Corp.; VenoStent, Inc.; and Kuleana Technology, presented needleless access products and infection-prevention technologies in the very early stages of development.

Although the new technologies differed in scope, the consensus among the innovation teams was similar: the end products must improve patients' quality of life. To get there, they acknowledged the importance of collaborating and involving patient perspectives and feedback early in the development process.

Prabir Roy-Chaudhury, MD, PhD, FASN, ASN president-elect, highlighted the exciting advancements in vascular access therapies, noting the potential for significant clinical paradigm shifts in his keynote presentation on Options and Opportunities for Dialysis Vascular Access. "This is an incredibly exciting time for vascular access. There are many different therapies out there, either in clinical trials or being used clinically that are focused on vascular access. This was not so 10 years ago."

Challenges and roadblocks to overcome

The journey to needleless access involves overcoming challenges such as high-development costs and funding needs, regulatory and reimbursement hurdles, and the diverse needs of patients undergoing hemodialysis.

Agreeing that patients are at the center of everything they do, the panel of innovators also emphasized the importance of enrolling patients in clinical trials, collecting evidence-based information, and the need for a centralized registry for dialysis access outcomes as avenues for securing the investments and reimbursements needed to bring products to market.

Accessibility and usability of new devices and technologies were also highlighted in the day's discussions. Industry leaders and clinicians agreed that with dialysis access being so complex, any device must be usable by the most and least experienced vascular access surgeons. Manisha Dadhania, MBA, vice president of global marketing at Mozarc Medical and member of the Devices Committee of the KHI Board of Directors, explained that with several vascular surgeons and interventional radiologists dedicated to performing vascular access surgery, addressing varying skillsets among surgeons is important as new products are rolled out. "Making sure that we're investing in the initial and ongoing training and education for all clinicians is critical so that these devices are accessible to all patients," she said.

Addressing the fragmentation raised earlier by Niyyar, standardizing training and improving patient education were also noted by patients, industry experts, and care practitioners as solutions to work toward. In breakout focus groups, patients noted that because training varies from clinician to clinician and clinic to clinic, the techniques used in dialysis centers around the country also vary. On the product side, developers acknowledged the requirement for technology that eliminates the need for ongoing training and education and products that are easier to use for patients and practitioners.

Looking at the promising new devices currently in development, Dadhania believes that it is also important to take incremental steps toward future innovations. "Needleless access is where we want to get to as quickly as possible for the patients, but along the way, there are going to be other innovations that will help patient outcomes," she said, noting that identifying technologies that are accessible in other countries that could be brought to market in the United States could be a step in the right direction.

Call to action

Evans urged attendees to create a clear roadmap for action now. She said that the roadmap should include building core teams that collaborate and work together to find solutions to some of the obstacles to innovation, including regulation, reimbursement, and funding, noting that there needs to be a focus on three I's: investment, interest, and innovation.

"There has been dialysis access innovation over the years, but we haven't come as far as we need to because of operational challenges and roadblocks put into place by the payer system. This meeting made it very clear that we have a call to action. We must work together to break down the barriers that exist so that more innovation can take place," Evans stated.

The call to action also emphasized the importance of keeping the patient at the essence of all novel dialysis access developments. For Gilchrist, sharing her journey was a huge step forward to putting the patient experience at the heart of future innovation. She reminded participants that patients need needleless, painless, and discrete vascular accesses. "We want freedom in our lives," she emphasized.

Niyyar concluded the workshop with optimism for the future. Facilitating collaboration between clinicians and innovators and placing the patient at the center of everything will "allow us to ultimately optimize dialysis care and get to the ideal of having an access that is a lifeline that lasts a lifetime. We must provide the right access for the right patient for the right reasons at the right time."

"We can do all of this if we work together," she said. "The more we collaborate, the more we innovate."

Detective Nephron

Detective Nephron, world-renowned for his expert analytic skills, trains budding physician-detectives in the diagnosis and treatment of kidney diseases. Mackenzie Ula Densa, a budding nephrologist, plans to present a new case to the master consultant.

Nephron It's been a while, Mac. What do you have for me?

Mac I have a 58-year-old woman with type 2 diabetes for over 20 years on insulin with worsening proteinuria.

Nephron (*bored*) Whoa! Stop right there. This sounds like diabetic nephropathy. I know people are excited about that diagnosis these days due to the rising pharmaceutical interest with so many new drugs—sodium-glucose cotransporter-2 inhibitor, glucagon-like peptide-1 agonists, and mineralocorticoid receptor antagonists.

Mac Just trust me. You are going to love this one! It's not your typical diabetic nephropathy. Go with the FLOW.

Nephron Well, in that case, we may have to put on my "glomerulonephritis [GN] hat," as we are taking a break from the electrolytes.

Mac Hmm…oh well. I can totally relate to that one.

Pause as Dr. Slit Nephrin enters

S Nephrin Dear Nephron and Mac, please continue to discuss the case. The GN King has arrived. Now let's do the "GN chat." Oh, this is a different forum. My bad!

Mac As I was saying, this 58-year-old woman with type 2 diabetes has worsening proteinuria. She had nonadherence to her medications, resulting in remaining high hemoglobin A_{1c} (HbA_{1c}) (10%–14%) throughout her clinical course. She now presents to the office with worsening proteinuria. She has the usual: hypertension (HTN) hyperlipidemia, diabetic retinopathy, and neuropathy. Her meds include a nifedipine, doxazosin mesylate, trichlormethiazide, spironolactone, rosuvastatin calcium, and insulin regimen.

Nephron Stop! Give us the labs, Mac. This is boring so far.

Mac (*laughing out loud*) Can we move on? The focus is proteinuria.

The following labs apply to the patient: white blood cell count: $4.59 \times 10^3/\mu L$; hemoglobin: 11.2 g/dL; platelet count: $21.3 \times 10^4/\mu L$; urine protein: 12.0 g/gCr; urine red blood cells: 10–19 per high-power field; serum creatinine: 1.20 mg/dL; estimated glomerular filtration rate (using the 2021 Chronic Kidney Disease [CKD] Epidemiology Collaboration creatinine equation): 53.5 mL/min/1.73 m^2; serum albumin: 2.3 g/dL; and HbA_{1c}: 8.0%. No abnormalities were observed in immunoglobulin (Ig)G, IgA, or IgM; C3 or C4 levels; or autoantibodies. Phospholipase A2 receptor neg, antinuclear antibody, double-stranded DNA neg, and antineutrophil cytoplasmic antibody titers were negative. The serum-free light chain ratio was 2, and serum immunofixation electrophoresis was negative.

Nephron (*bored, rolling his eyes*) Well, you just confirmed what I said earlier. This is a boring case of diabetic nephropathy with significant proteinuria.

S Nephrin Interesting. Do you have the trend of the proteinuria?

Nephron (*winking*) Dr. Slit Nephrin, I'm glad you asked.

Mac Let me tell you a little more about this case. A few years ago, proteinuria was 0.3 gm and creatinine, 0.9 mg/dL; 1 year ago, proteinuria was 3 gm and creatinine, 1.2 mg/dL; 5 weeks ago, proteinuria was 10 gm and creatinine, 1.5 mg/dL…. (*fading*)

Nephron (*laughing*) Big deal. Let me guess: You even did a renal biopsy? I mean a kidney biopsy.

S Nephrin Hmm…. Has the blood pressure been harder to control?

Mac (*trying to remember*) Yes. But that's not unusual for people with diabetes with HTN, right?

S Nephrin (*jumping in*) I think you should consider a kidney biopsy to rule out thrombotic microangiopathy (TMA).

Silence

Nephron (*shocked*) Let me guess. It's SARS-CoV-2 or quinine use? Everything cannot be TMA.

Mac (*smirking*) I thought TMA was your favorite diagnosis, Dr. Nephron.

Silence

Mac (*confident*) A kidney biopsy was performed, and the puzzle begins after that. It confirmed early diabetic nephropathy but acute on chronic TMA as well.

S Nephrin Fascinating! But what is causing her TMA?

Mac To me, TMA is a syndromic process showing hemolysis and endothelial injury. HTN, proteinuria, and, in some cases, systemic hemolysis may be the hallmark indicators. She appears to have more of a "renal-limited" TMA. ADAMTS-13-mediated TMA was ruled out, Shiga toxin was negative, and there were no signs of systemic autoimmune diseases. Certain viral and bacterial infections were ruled out as potential causes of TMA. Pregnancy is not a contender here. She is not a solid organ or stem cell transplant recipient. She may have a complement deficiency, but those results of both the factor levels and genetics will take time to validate. I think this is a potential drug-induced process.

Nephron (*smiling*) Nice work flaunting your TMA knowledge. I agree that this is likely a direct endothelial injury or likely an idiosyncratic reaction from the potential culprit drug. What about this just being from the type 2 diabetes?

S Nephrin (*interrupting*) TMA has been reported with diabetic nephropathy. Patients with diabetic nephropathy and TMA usually have higher blood pressure and proteinuria and a lower rate of glomerular filtration at baseline. Vascular endothelial growth factor (VEGF) assessments obtained in such patients showed lower arteriolar and glomerular expression with diabetic nephropathy plus TMA. The VEGF expression levels had an inverse relationship with proteinuria. There is also a higher probability of kidney failure in patients with diabetic nephropathy plus TMA.

Mac (*proclaiming*) Fascinating. But she started intravitreal injection of aflibercept (2 mg every 4 weeks) for the treatment of retinopathy 2 years ago. Fourteen months after the first injection, she reported bilateral leg edema and HTN (159/87 mm Hg) with a urine protein level of 4.9 g/gCr, urine red blood cells of 0–1 per high-power field, and a serum creatinine of 0.65 mg/dL; thus, amlodipine, telmisartan, and furosemide were added to the therapy. Nevertheless, urine protein continued to increase to 10.0 g/gCr at 2 years after the first injection, and she was referred. A total dose of 40 mg of aflibercept was administered in 20 injections during the 2 years following the first injection, which stabilized her retinopathy and vision.

S Nephrin Yes, this is important and the likely culprit. Despite being intravitreal, anti-VEGF therapy has been known to cause TMA (systemic or renal limited). I think we must ask her to stop this agent.

Mac (*nodding*) So, what do we do here…let her go blind and protect the kidney?

Nephron (*puzzled*) Seriously?! I don't believe this! Can you enlighten me regarding this small intravitreal dose and TMA?

Mac So dramatic, you are!

S Nephrin Since the 1990s, systemic inhibition of angiogenesis has revolutionized cancer treatment. The discovery of the VEGF receptor led to bevacizumab's clinical application, effectively targeting various malignancies like lung, renal, breast, and colorectal cancers; gliomas; and retinal neovascularization. Aflibercept and ranibizumab, newer inhibitors, offer increased potency and duration compared with bevacizumab.

Nephron We know this stuff already, and systemic anti-VEGF therapy for cancer can lead to renal-limited TMA. Bevacizumab has been used intravitreally for age-related macular degeneration and proliferative diabetic retinopathy/diabetic macular edema. Many retina specialists also use aflibercept and ranibizumab. Pegaptanib, a multimer nonmonoclonal aptamer anti-VEGF agent, was also approved with an indication for intravitreal use for proliferative diabetic retinopathy.

S Nephrin (*confident*) US Food and Drug Administration data on aflibercept and ranibizumab revealed detectable serum levels after intravitreal injections, with aflibercept levels approximately 200-fold lower than needed for systemic VEGF inhibition. Systemic absorption varied among ocular pathologies. Some studies later found that systemic levels after injections exceeded inhibitory concentrations, persisting for weeks. Aflibercept showed prolonged systemic presence, whereas ranibizumab had quicker clearance. Multiple injections maintained detectable serum levels, with aflibercept displaying potent systemic VEGF inhibition compared with bevacizumab and ranibizumab. Of course, there are several case reports and series showing this association of intravitreal anti-VEGF and renal injury.

Mac (*jumping in*) I also found some retrospective and observational data that patients with CKD and diabetes who received these agents were more likely to progress to kidney failure faster with a higher need for renal replacement therapy.

Nephron Although I am still skeptical, I will go along to see what happens once we hold this agent.

Mac (*surprised*) Well, we may have to wait a few months to see any improvement.

Nephron Fantastic! Let's do that. What about anticomplement therapy?

Mac For now, I am not sure but wouldn't want to do that, as I am confident this is the offending agent.

S Nephrin Good question, Detective Nephron. Of course, as with any rare disease, such as drug-induced TMA, there are no data to support anything.

Silence

Nephron You sound like a true GN doctor, needing more data on GN. IgA nephropathy seems to be gathering some momentum.

Mac winks.

5 Months later

Mac I have an update for you, Detective Nephron and Dr. Slit Nephrin! Intravitreal aflibercept injection was discontinued after the biopsy, and both urinary protein and serum albumin gradually improved. Four months after withdrawal of aflibercept, the patient no longer has nephrotic syndrome. She has improvement in her leg edema with disappearance of the bilateral pleural effusion and ascites. After ceasing aflibercept, her laboratory parameters (serum creatinine: 1.49 mg/dL, serum albumin: 4.0 g/dL, and urine protein: 0.6 g/gCr) and blood pressure (123/54 mm Hg) have improved. Her eyesight has remained stable even after aflibercept discontinuation.

Nephron (*laughing*) There you go again! Fascinating diagnosis and treatment, Mac. Special thanks to our GN specialist, Dr. Slit Nephrin, in helping us with this tough case. I must say, GN nephrologists are truly the best detectives on the planet.

Dr. Slit Nephrin takes a bow and winks. ■

Detective Nephron was developed by Kenar D. Jhaveri, MD, FASN, professor of medicine at the Donald and Barbara Zucker School of Medicine at Hofstra/Northwell, Hempstead, NY. Special thanks are extended to Dr. Rimda Wanchoo, professor of medicine at the Donald and Barbara Zucker School of Medicine at Hofstra/Northwell for editorial assistance. Send correspondence regarding this section to kjhaveri@kidneynews.org.

A Novel Solution: The Key to Un-"lock"ing Catheter Dysfunction?

By Mukesh Sharma and Vandana Dua Niyyar

Central venous catheter (CVC) dysfunction due to infection, thrombosis, or central venous stenosis continues to be a major source of morbidity and mortality in patients undergoing hemodialysis (1). Interdialytic catheter lock solutions, whether antithrombotic, antimicrobial (antiseptic or antibacterial), or a combination thereof, may help minimize these complications (2). Efforts to identify an ideal lock solution that prevents both infection and thrombosis are ongoing, and a multitude of lock solutions has been evaluated in clinical studies with varying results (3, 4).

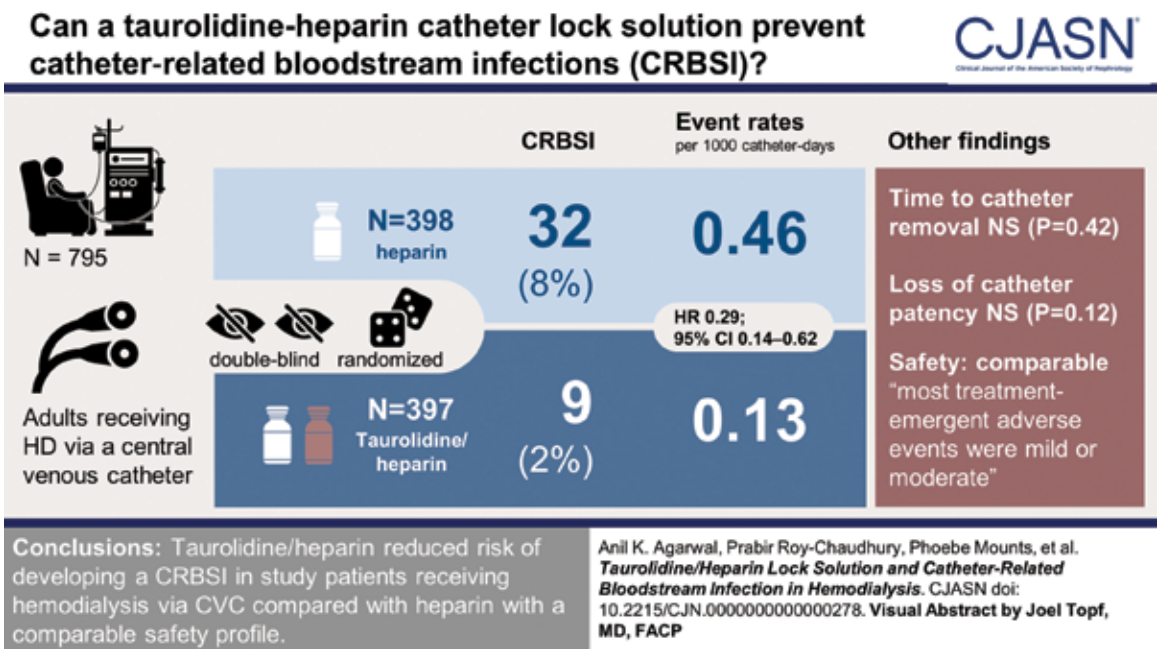
In the recently published randomized, double-blind, multicenter, phase 3 LOCK IT-100 trial (Study Assessing Safety & Effectiveness of a Catheter Lock Solution in Dialysis Patients to Prevent Bloodstream Infection) (5), researchers investigated the efficacy of taurolidine/heparin lock solution in 795 patients undergoing hemodialysis across 70 centers. The primary endpoint was catheter-related bloodstream infection (CRBSI), and the secondary endpoint was catheter patency. Taurolidine is a derivative of the amino acid taurine, with in vitro studies indicating broad antimicrobial activity against gram-positive and gram-negative bacteria, including antibiotic-resistant strains, as well as mycobacteria and clinically relevant fungi, whereas heparin has been the standard of care for preventing catheter-related thrombosis.

A preplanned interim analysis by the Clinical Adjudication Committee led to the Data and Safety Monitoring Board recommendation of terminating the study early due to a highly statistically significant result favoring taurolidine/heparin with no safety concerns or differences in catheter patency between the two groups. In the final analysis, 9 patients (n = 397 [2%]) in the taurolidine/heparin arm developed CRBSI vs. 32 patients (n = 398 [8%]) in the heparin arm—a 71% risk reduction in CRBSI. These findings are consistent with earlier, smaller studies showing significant reduction in CRBSIs in patients undergoing hemodialysis with taurolidine/heparin lock solutions (6).

These promising results led to the US Food and Drug Administration's designation of the solution as a Qualified Infectious Disease Product (7). Furthermore, the Centers for Medicare & Medicaid Services determined that it met the criteria for the Transitional Drug Add-On Payment Adjustment (8), which provides additional payment reimbursement beyond the End-Stage Renal Disease bundled rate to outpatient practitioners for up to 5 years. These measures will help increase the initial uptake of this proprietary lock solution in outpatient hemodialysis units. However, as a considerable proportion of patients undergoing hemodialysis are under the umbrella of large dialysis organizations, their involvement will be critical for widespread adoption.

Additionally, long-term efficacy and safety data are needed before recommendations can be made for specific patient populations, as a caveat that is universally applicable to all lock solutions is their potential for systemic effects due to leakage into the systemic circulation, despite being localized within the catheter lumen (9). It remains to be seen if the taurolidine/heparin catheter lock solution will become the norm for all patients dialyzing with a CVC or if it will be reserved for those vulnerable patients who are solely dependent on their CVC for dialysis access and in whom a CRBSI would be catastrophic. If longitudinal studies demonstrate decreased morbidity and mortality in the long-term, as well as improved economic impacts downstream from decreased hospitalizations and complications, the paradigm for access choice may change. Consequently, CVCs might be used more liberally for those patients who are not ideal candidates for arteriovenous accesses. In the future, indications may well be expanded to patients not undergoing dialysis who require long-term CVCs for chemotherapy, intravenous antibiotics, or total parenteral nutrition.

The adage, "An ounce of prevention is worth a pound of cure," still holds true. The best prophylaxis remains avoidance of CVCs for most patients on dialysis. If necessity mandates catheter placement, irrespective of the "lock" solution used, the "key" to minimizing dysfunction includes education of all dialysis staff and patients on proper catheter care and universal adoption of strict aseptic techniques. These meticulous infection control and hygienic measures may further minimize the morbidity and mortality associated with CVCs (10). ■



CI, confidence interval; HD, hemodialysis; HR, hazard ratio; NS, not significant. Reprinted with permission from Agarwal et al. (5).

Mukesh Sharma, MD, MS, FASN, FACP, FASDIN, is a clinical associate professor, University of Nevada, Reno, School of Medicine, Sierra Nevada Specialty Care, Reno, NV. Vandana Dua Niyyar, MD, FASN, FNKF, FASDIN, is professor of medicine, Emory University School of Medicine, Atlanta, GA.

Dr. Sharma reports no conflicts of interest. Dr. Niyyar reports having an advisory/leadership role in the following organizations: immediate past-president of the American Society of Diagnostic and Interventional Nephrology; Board of Directors member for the Kidney Health Initiative; and chair of the Transforming Dialysis Access Together initiative. She also serves as a consultant for Sonavex and Vexev and as an Editorial Board member for Elsevier ClinicalKey.

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CAR T Cell Therapy for Autoimmune Diseases: Dawn of a New Era Toward a Cure

By Jeffrey A. Sparks and Matthew A. Sparks

Systemic autoimmune diseases, such as systemic lupus erythematosus (SLE), traditionally require long-term immunosuppression to maintain disease control (1). Although treatment options have expanded over the past few decades, a cure remains elusive (1, 2). A recent case series of outcomes after patients received chimeric antigen receptor (CAR) T cell therapy, published in *The New England Journal of Medicine* (3), may usher in a new era toward a cure for systemic autoimmune diseases.

CAR T cell therapies are currently approved by the US Food and Drug Administration to treat some types of lymphoma, leukemia, and multiple myeloma (4). These CAR T cell therapies target one of two antigens on B cells: the CD19 or B cell maturation antigen (4), resulting in death of that specific cell harboring the antigen by the CAR T cell. However, CAR T cell technology could be used to target any antigen, opening up a new platform for targeted therapy.

In the case series (3), investigators in Germany prospectively enrolled 15 patients with refractory systemic autoimmune rheumatic diseases (including SLE, idiopathic inflammatory myositis, and systemic sclerosis) to receive CD19 CAR T cell therapy. CD19 is a transmembrane protein uniquely expressed in both normal and neoplastic B cells, making it an attractive target for immunotherapy. It is expressed on B cell lineages, including plasma cells. The investigators found marked improvements in serologic and clinical markers of disease activity during a median follow-up of 15 months. Most impressively, after the single infusion of CAR T cells, all 15 patients were able to completely discontinue their systemic immunosuppressive medications, an outcome rarely achieved through usual clinical care.

Relevant to nephrologists, among the 8 patients with SLE, all had lupus nephritis, and all resolved proteinuria, normalized complement levels, and had undetectable double-stranded DNA autoantibodies by month 12 (3). Thus, many pharmaceutical companies and rheumatology centers are developing CAR T cell therapy research programs. CAR T cell and other cellular therapies are also being pursued to treat rheumatoid arthritis, inflammatory bowel disease, type 1 diabetes, and multiple sclerosis and to prevent organ rejection and treat BK polyomavirus infection, including for kidney transplant recipients (5, 6).

Although these initial results are impressive, some caveats and logistical considerations are needed. The open-label case series was small, uncontrolled, included several heterogeneous diseases, and had a relatively short follow-up. Whereas drug-free remission is thought to be rare, it is not often attempted. B cell depletion with monoclonal antibodies targeting CD20 has been previously studied for lupus nephritis in placebo-controlled studies (7–9), with less impressive results than the case series (3). It is possible that a deeper but transient B cell depletion by CD19 CAR T cell therapy can "reset" the immune system to restore homeostasis. CAR T cell therapy is expensive and logistically complex, requiring apheresis, cellular engineering, and hospitalization to receive a chemotherapy regimen for lymphodepletion, infuse the CAR T cells, and monitor for potential serious side effects, including cytokine release syndrome, neurotoxicity, and infection (4). Indeed, cytokine release syndrome occurred in 10 out of 15 patients, although nearly all were mild (3). Several infections occurred, including COVID-19, pneumonia, and cellulitis (3). There have been some cases of lymphoma occurring secondary to CAR T cell therapy in patients with cancer (10). Thus, larger controlled studies with a longer follow-up are needed to establish efficacy, safety, and tolerability.

CAR T cell therapy offers a new dawn toward a cure for patients with systemic autoimmune diseases. Other CAR therapies are being investigated that target different antigens and use T regulatory cells that should have less toxicity and do not require conditioning chemotherapy. Nephrologists will be at the forefront of this innovative therapy across myriad indications that will include lupus nephritis, systemic vasculitis, kidney transplant, and glomerulonephritis. ■

Jeffrey A. Sparks, MD, MMSc, is an associate professor of medicine and director of immuno-oncology and autoimmunity in the Division of Rheumatology, Inflammation, and Immunity, Brigham and Women's Hospital and Harvard Medical School, Boston, MA. Matthew A. Sparks, MD, FASN, is an associate professor of medicine and program director of the nephrology fellowship in the Division of Nephrology, Duke University School of Medicine in Durham, NC. He serves on the editorial board of Kidney News *and is the communications editor of ASN journals.*

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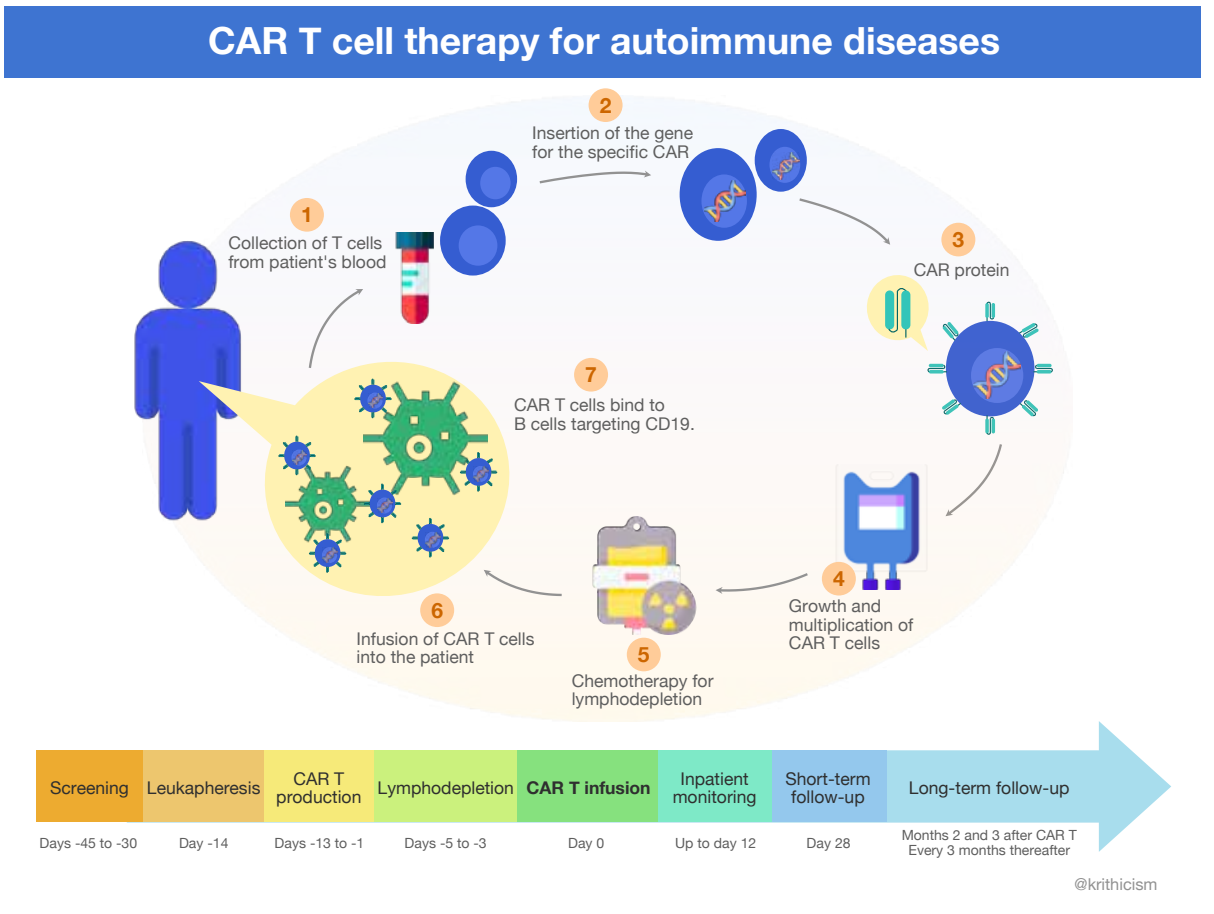

One Social Media Post Changed Two Lives Forever

By Lisa Schwartz

On January 23, 2024, Susan Willner underwent surgery at The Johns Hopkins Hospital in Baltimore, MD, to have a kidney removed. Susan was not sick nor had she been diagnosed with a kidney disease; she was a lifesaving kidney donor. Within hours, Susan's right kidney was functioning in a new body, restoring the life of recipient Dianne Burbank.

Susan (left) stands with Dianne (seated) and Dianne's two daughters the morning after their successful surgeries.

Search for a living donor

A plea for help on social media brought Susan and Dianne together, setting their lives on a path neither woman ever expected.

In May 2014, Dianne's primary care physician noticed that her creatinine was higher than normal and referred her to a nephrologist. The appointment was made for October. Just 2 weeks before her appointment, Dianne suffered a heart attack, which was attributed, in part, to her later diagnosis of stage 3 polycystic kidney disease (PKD). PKD is a form of chronic kidney disease (CKD) causing the growth of fluid-filled cysts in one's kidneys. It can lead to kidney failure among other complications throughout the body. The most common form of genetic kidney disease, PKD is estimated to affect more than 600,000 people and is the fourth leading cause of kidney failure (1).

Worried about the diagnosis, whether it could affect her daughters, and her family's history of CKD and diabetes—her father died at 46 years of age with CKD and diabetes after undergoing dialysis for 8 years—Dianne's disease was followed closely. Over the next 8 years, she significantly modified her diet and limited potassium intake to protect her kidneys, yet by early 2022, Dianne's kidney function had declined. Her nephrologist soon had a candid discussion with her about kidney transplantation.

According to the American Kidney Fund (2), nearly 36 million Americans live with kidney diseases, and more than 800,000 Americans are living with kidney failure. Close to 100,000 people in the United States are awaiting kidney transplant, but in 2023, only 27,332 received the surgery. Just 6290 transplants were performed with allografts from living donors, which provides better outcomes and lowers the risk of rejection. The National Kidney Foundation reports that 12 people die each day waiting for kidney transplant surgery, and every month, 3000 people are added to the transplant waitlist (3).

Dianne had four older sisters as potential kidney matches, but unfortunately, their own health issues precluded them from being candidates for living donation. In April 2022, Dianne was placed on the national kidney transplant waitlist with the hope of finding a donor before dialysis might be needed.

With few other options in sight, one of Dianne's sisters posted an appeal to friends and family on Facebook in November 2022 in an attempt to find a living donor match.

Living donor journey

Heeding her friend's plea for help, Susan called the number listed on the social media post for the Johns Hopkins Medicine Comprehensive Transplant Center (4) to begin the process of determining her eligibility as a living donor and to direct her kidney donation to Dianne. She then began learning all she could about living kidney donation. Susan, a longtime blood donor, knew in her heart that this was something she was meant to do. She was acutely aware of the growing problem of CKD from her work as the associate director of ASN Publications, and she soon discovered that a person could live a long, healthy life with just one kidney.

At 63 years old, Susan was concerned about being healthy enough to be deemed a candidate for living donation as she began the process of getting tested as a potential match. She appreciated her dedicated donor team, who prioritized her health. "Every donor has their own team separate from the recipient's transplant team. They act as advocates for the donor and walked me through every step of the process, which was reassuring," Susan explained.

After what Susan called the most thorough physical of her life, including several extensive blood and tissue tests, computed tomography scans, x-rays, and 6 months of monitoring a lung nodule she had, she received the telephone call that she had been anxiously awaiting: She was a healthy candidate and a match for Dianne.

> **"…donating my kidney gave me something I wasn't expecting—hope and purpose."**

"That social media post saved me," said Dianne, aged 59 years. Dianne recalled meeting Susan at one of her sister's annual parties but was not aware that Susan was her donor until 1 week before the transplant surgery, at Susan's request. "I could not believe someone would do something like this for me," Dianne exclaimed.

"I gave because I could give," said Susan. "But even if I didn't match for Dianne, I learned so much during the process that I decided I would donate a kidney to someone in need. After 4 years of feeling helpless because of the pandemic and the violence in the United States and the world, donating my kidney gave me something I wasn't expecting—hope and purpose."

Go time

The surgery date was scheduled after nearly 9 months of rigorous physical testing and mental and emotional counseling for both Dianne and Susan.

Just before the surgeries began on January 23rd, Dianne paid her donor one last visit. "I remember standing by Susan's hospital bed. We both just started crying. I didn't know what else to say other than thank you. I thanked her over and over," she recalled.

Susan's surgery was first. Her right kidney was removed through four 1-inch incisions and one slightly larger 4-inch incision in the abdomen using a less invasive robotic surgical approach. Robotic surgery allows surgeons to operate with greater precision using enhanced visualization and with control of surgical instruments that offer greater range of motion and dexterity. The benefits to patients include smaller incisions that typically result in less pain, bleeding, and scarring as well as a shorter recovery. Once removed, Susan's kidney was whisked into the next operating room where Dianne's surgical team was ready and waiting to transplant the healthy organ.

The transplant itself entailed a more extensive surgery for Dianne, lasting several hours. Because of the intricacies of transplantation, Dianne's surgery was performed as an open surgical procedure. Placing the new kidney into the lower right side of the abdomen, the surgeon attached the donor kidney's artery and vein to the patient's external iliac artery and vein. The donor ureter was connected to the bladder in preparation for the new kidney to begin producing urine (4). In Dianne's case, she had two drains placed in the surgical site to drain excess fluid and reduce swelling.

One day posttransplant, Susan and Dianne reunited in the hospital. "Seeing her surrounded by her family with my healthy kidney already working was extraordinary," said Susan.

On the road to recovery

Within 1 day of surgery, Susan was walking 2500 steps around the hospital halls. She was discharged 2 days later. Three days after the surgery, she was walking 2 miles around her neighborhood, albeit slowly, and she was grocery shopping by the fourth day. "My recovery was easy, and by the day after surgery, I was able to control any pain with Tylenol and lidocaine patches."

One week after her kidney donation, Susan had little to no pain, was walking a few miles each day, and was feeling good. Just 10 days after surgery, she called into her department staff meeting. "I was bored and ready to get back to work!" she laughed.

Dianne's recovery was more extensive because of the magnitude of the transplant itself. The first 24 hours were focused on controlling pain and emptying the drains while monitoring urine output to ensure the new kidney was

working well. Although the recovery was difficult and slow-going, she was discharged with a new working kidney after 4 days.

"[Thankfully] I had my husband as my caregiver! For the first 2 weeks he helped me shower, emptied my drains three times per day, and documented the output, as well as documented my vitals in a binder. After about 2 weeks, I was doing more myself. It felt good to get back my independence and strength each day," Dianne recalled. She added that although she had pain those first couple of weeks, it was manageable.

Today, Dianne is back to work as an assistant director of an after-school art-enrichment program and summer camp and continues to dabble in freelance graphic design. She has more energy and is regaining her strength each day. Although she still gets tired, she can now do more of what she enjoys, like eating tomatoes, yogurt, and cheese and dining at restaurants without concern, which were all restricted before her transplant. "It sounds trivial, but eating is about quality of life, and I didn't have great quality before the transplant," Dianne said.

Bonded for life

The enormity of the donation and transplant struck Susan at their follow-up appointments 1 week after the transplantation. "Seeing Dianne healthy and hearing her say that she was eating foods she hadn't in years because of the healthy, working kidney made me realize that I helped her get to a better life. That was truly overwhelming."

Both Dianne and Susan praised their care teams for making the experience as smooth as possible. "The entire donor care team at Johns Hopkins was amazing," added Susan. "They answered all my questions and referred me to the National Kidney Foundation peer mentoring program [https://www.kidney.org/peers]. Through the program, I was matched with a wonderful woman for support and guidance who had donated her kidney in 2020." Susan herself was inspired to become a mentor to help other kidney donors through the process.

"I'm telling my story not to ask for praise but to let everyone know how easy it is to donate a kidney," she said. "Being able to make a difference for someone else motivated me to donate. The emotional impact of giving truly feeds the soul. What I got in return for being a kidney donor cannot be put into words."

Susan and Dianne keep in touch. They text often, celebrating Dianne's milestone monthly "kidney-versaries," as they call them.

Dianne and her husband recently celebrated their 29th wedding anniversary, and she is looking forward to her daughter's wedding in October. "I now have a chance at more time. I have a future because of Susan's selfless kidney donation," Dianne reflected. ■

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Renal and Cardiovascular Benefits of Semaglutide in Type 2 Diabetes With CKD

The glucagon-like peptide-1 receptor agonist semaglutide improves renal outcomes and reduces cardiovascular mortality in patients with type 2 diabetes and chronic kidney disease (CKD), reports a clinical trial in *The New England Journal of Medicine*.

A Research Study to See How Semaglutide Works Compared to Placebo in People With Type 2 Diabetes and Chronic Kidney Disease (FLOW), an international, multicenter trial, enrolled 3533 patients (mean age, 67 years) with type 2 diabetes and CKD. Eligible patients had an estimated glomerular filtration rate (eGFR) of 50 to 75 mL/min/1.73 m^2 with a urinary albumin to creatinine ratio of >300 and <5000 or an eGFR of 25 to <50 mL/min/1.73 m^2 with a urinary albumin to creatinine ratio of >100 and <5000.

Participants were randomly assigned to receive subcutaneous semaglutide (1.0 mg weekly) or placebo. Primary outcomes were major kidney disease events, a composite of kidney failure, 50% or greater reduction in eGFR, or death from renal or cardiovascular causes.

The trial was halted at a median follow-up of 3.4 years based on the results of a prespecified interim analysis of efficacy. At that time, the primary outcome event rate was 5.8 per 100 patient-years with semaglutide versus 7.5 per 100 patient-years with placebo (hazard ratio [HR], 0.76). Similar patterns were shown for a composite of kidney-specific components of the primary outcome (HR, 0.79) and for death from cardiovascular causes (HR, 0.71).

Semaglutide also improved secondary outcomes, including a 1.16-mL/min/1.73 m^2 decrease in the mean annual eGFR slope. Major cardiovascular events (HR, 0.82) and all-cause mortality (HR, 0.80) also decreased. Numbers needed to treat were 45 to prevent one major cardiovascular event and 39 to prevent one death.

Patients in the semaglutide group had greater reductions in body weight (mean difference, 4.10 kg), glycated hemoglobin, and systolic blood pressure. Semaglutide was also associated with a lower rate of serious adverse events, mainly reflecting fewer events related to infections or cardiovascular disorders.

Previous studies of glucagon-like peptide-1 receptor agonists in type 2 diabetes have not addressed clinically important kidney outcomes. The FLOW trial "provides confidence that the use of semaglutide in patients with type 2 diabetes and chronic kidney disease will reduce the risk of kidney failure and slow the decline in the eGFR, as well as reduce the risk of cardiovascular events and death," the researchers write. They discuss the mechanisms of semaglutide's kidney-protective effects, which are likely multifactorial [Perkovic V, et al.; FLOW Trial Committees and Investigators. Effects of semaglutide on chronic kidney disease in patients with type 2 diabetes. *N Engl J Med*, published online May 24, 2024. doi: 10.1056/NEJMoa2403347].

Tacrolimus Linked to Long-Term eGFR Decline in Lupus Nephritis

Among patients with lupus nephritis, exposure to the calcineurin inhibitor (CNI) tacrolimus is associated with greater long-term reduction in kidney function, reports a study in *Nephrology Dialysis Transplantation*.

The retrospective cohort study included 219 patients with lupus nephritis treated at the authors' center between 2010 and 2023. Of these, 43 patients were exposed to tacrolimus, and 176 had never been treated with any CNI. Renal outcomes, diabetes status, cardiovascular events, and risk factors were compared between groups at a median follow-up of 7.1 years.

The median follow-up was 80.6 months in the tacrolimus group and 88.9 months in those with no CNI exposure. The median duration of tacrolimus exposure was 17.7 months. Disease flares were the most common indication for tacrolimus therapy, followed by pregnancy and side effects of previous immunosuppression.

Patients receiving tacrolimus had a greater decline in the estimated glomerular filtration rate (eGFR): median, –6.8 mL/min/1.73 m^2 compared with –0.8 mL/min/1.73 m^2 in the nonexposed group. The median annual eGFR slope was 1.1 for the tacrolimus group versus 0.1 mL/min/1.73 m^2 for the group without CNI. The rate of eGFR decline was related to the duration of tacrolimus treatment. Three patients in the tacrolimus group progressed to kidney failure, all during active tacrolimus treatment.

After adjustment for potential confounders, tacrolimus exposure was associated with a –14.7-mL/min/1.73 m^2 decline in eGFR. On the sensitivity analysis, the tacrolimus-associated change in eGFR was greater in patients without a major disease flare: –20.0 mL/min/1.73 m^2.

Tacrolimus exposure was also associated with higher hemoglobin A_{1c}: 37.4 mmol/mol versus 33.6 mmol/mol. Cardiovascular events and cardiovascular risk factors were not significantly different between groups.

Tacrolimus, in combination with mycophenolate and corticosteroids, is an effective treatment option for patients with active lupus nephritis. CNIs have known renal and cardiovascular adverse effects in kidney transplant recipients. However, in the absence of long-term follow-up data, there are persistent concerns about the safety of tacrolimus in lupus nephritis.

The new study shows "clinically meaningful" long-term declines in kidney function associated with tacrolimus treatment in patients with lupus nephritis. The effect on an eGFR decline is greater with longer duration of treatment but appears independent of indications of tacrolimus therapy. The researchers conclude: "[O]ur study supports the need for increased vigilance [toward] tacrolimus treatment, especially in [patients with lupus nephritis] with an increased risk of developing ESKD [end stage kidney disease]" [van Schaik M, et al. Long-term renal and cardiovascular risks of tacrolimus in patients with lupus nephritis. *Nephrol Dial Transpl*, published online May 20, 2024. doi: 10.1093/ndt/gfae113].

Anti-CD38 Shows Safety in Antibody-Mediated Rejection

The investigational CD38 monoclonal antibody felzartamab has a low rate of serious adverse events in the treatment of antibody-mediated kidney transplant rejection, according to a clinical trial report in *The New England Journal of Medicine*.

The phase 2 randomized, double-blind trial included 22 kidney transplant recipients with antibody-mediated rejection occurring after at least 180 days. Median time from transplant to study enrollment was 9 years. In equal numbers, patients were assigned to felzartamab (nine infusions at a dose of 16 mg/kg of body weight) or to placebo. Treatment continued for 6 months, followed by a 6-month observation period.

Safety and side-effect profiles were evaluated as the primary outcome. A range of secondary efficacy outcomes were evaluated as well, including resolution of antibody-mediated rejection.

Eight patients in the felzartamab group

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Anti-CD38 Shows Safety in Antibody-Mediated Rejection

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experienced mild to moderate infusion reactions. Serious adverse events, primarily infection-related, occurred in one patient with felzartamab versus four patients with placebo. Graft loss occurred in one patient in the placebo group; there were no deaths in either group.

Renal biopsy performed at 24 weeks showed resolution of morphologic antibody-mediated rejection in 82% of patients (9 of 11) assigned to felzartamab versus 20% (2 of 10) in the placebo group. Other efficacy outcomes also favored felzartamab: microvascular inflammation, median score of 0 versus 25; a molecular score indicating probability of antibody-mediated rejection, 0.17 versus 0.77; and donor-derived cell-free DNA level, 0.31% versus 0.82%.

At 52 weeks, antibody-mediated rejection occurred in three of the nine patients who responded to felzartamab. Recurrence was associated with rising rejection-related molecular scores and natural killer cell burden.

CD38 is a promising target for depletion of plasma cells producing donor-specific antibodies and natural killer cells, which are believed to contribute to microvascular inflammation. A different anti-CD38 therapy has been approved for depletion of malignant plasma cells in multiple myeloma.

The new phase 2 trial shows "an acceptable safety profile" and "potential therapeutic benefit" of felzartamab for late active or chronic active antibody-mediated rejection after kidney transplantation. "[F]elzartamab may have the potential to effectively and safely reverse ongoing antibody-mediated rejection," the investigators conclude. The study "underscores the potential of felzartamab as a therapeutic option warranting further investigation in the context of late or even early rejection after organ transplantation" [Mayer KA, et al. A randomized phase 2 trial of felzartamab in antibody-mediated rejection. *N Engl J Med,* published online May 25, 2024. doi: 10.1056/NEJMoa2400763]. ■

No Decrease in CKD Admissions With "ICD-Pieces"

A primary care intervention to promote guideline-based care for patients with the "kidney dysfunction triad" does not lead to reduced rates of hospitalization due to chronic kidney disease (CKD), reports a pragmatic trial in *The New England Journal of Medicine*.

The cluster-randomized Improving Chronic Disease Management with Pieces (ICD-Pieces) trial evaluated a multidisciplinary intervention to promote guideline-directed therapy for patients with CKD. The intervention included a personalized algorithm, based on electronic health record data, to identify patients with the triad of CKD, type 2 diabetes, and hypertension, as well as practice facilitators who assisted primary care practitioners in implementing evidence-based interventions.

A total of 11,182 patients at 141 clinics in four large health systems were assigned to intervention or usual-care groups. All-cause hospitalization at 1 year was compared between groups, along with secondary outcomes. Patient characteristics were similar between intervention and usual-care groups.

Rates of hospitalization for any cause were not significantly different between groups: 20.7% for patients assigned to the ICD-Pieces intervention and 21.1% in the usual-care group. Secondary outcomes were similar as well, including emergency department visits, hospital readmissions, cardiovascular events, dialysis, and death from any cause.

The ICD-Pieces intervention was associated with a higher rate of acute kidney injury: 12.7% versus 11.3%. Other adverse events were comparable between groups.

Patients with the kidney dysfunction triad are at high risk for cardiovascular events and kidney failure. Although several guideline-directed therapies targeting these patients have been developed, few studies have evaluated the effects on morbidity and mortality.

The new pragmatic trial shows no significant effect of ICD-Pieces implementation on CKD hospitalization rates. "[T]he use of an EHR [electronic health record]-based algorithm and practice facilitators embedded in primary care clinics did not translate into reduced hospitalization at 1 year," the researchers write. They discuss implications for future clinical trials of multicomponent interventions for patients with multiple chronic diseases [Vazquez MA, et al.; ICD-Pieces Study Group. Pragmatic trial of hospitalization rate in chronic kidney disease. *N Engl J Med* 2024; 390:1196–1206. doi: 10.1056/NEJMoa2311708]. ■

The Role of Peritoneal Dialysis in the Management of Patients Undergoing Cardiac Surgery

By Graham Abra

Patients with kidney failure treated with maintenance dialysis are at high risk for cardiovascular morbidity and mortality (1). As such, they frequently undergo invasive cardiac procedures such as coronary artery bypass grafting (CABG) and valvular surgery. There is conflicting evidence as to whether there are differences in outcomes between patients with kidney failure treated with hemodialysis (HD) versus peritoneal dialysis (PD) after such procedures, and surgeons will commonly request a modality change from PD to HD (2, 3). Although there are valid clinical reasons to convert patients from PD to HD after cardiac surgery, many cases are driven by a lack of understanding of the advantages and disadvantages of the modality in the postoperative setting (Figure).

Bassil et al. (4) recently published the largest retrospective study to date examining mortality and a variety of important secondary outcomes in 590 patients with kidney failure who underwent CABG and/or valvular surgery at the Cleveland Clinic from October 2009 to October 2019 using an intent-to-treat study design. The cohort included 62 patients on PD and 528 on HD with some notable differences in baseline and perioperative characteristics. Patients on PD predictably had lower baseline mean serum albumin given the dialytic albumin losses that occur with PD, higher rates of dyslipidemia, and lower rates of heart failure and prior CABG compared with patients on HD. The HD group had a higher number of days from admittance to surgery, had more cardiopulmonary bypass time, and were more likely to undergo valvular surgery alone versus the PD group.

Over one quarter of patients (16 out of 62) converted from PD to HD postoperatively; among these conversions, 25% (n = 4) were driven by clinician preference. The remaining PD to HD conversions were due to hemodynamic instability (n = 7), catheter malfunction (n = 3), cardiac tamponade (n = 1), and gadolinium exposure (n = 1). Some of these patients might reasonably have remained on PD, highlighting the need for nephrology teams skilled in managing the modality.

There was no difference between PD and HD in the primary outcomes of in-hospital mortality (2% versus 5%; p = 0.51) or 30-day survival (98.2% versus 95.7%; p = 0.30). Patients treated with HD were more likely to experience a composite outcome of death, cardiac arrest, pericardial effusion, or sternal wound infection (odds ratio, 9.5; 95% confidence interval, 1.3–70.1). There was no difference in the number of intraoperative packed red blood cell transfusions between groups. This is a reassuring finding, as patients on PD often have higher blood urea nitrogen concentrations compared with those on HD, raising concerns about an increased risk of bleeding from uremic platelet dysfunction. However, these concerns have not been observed in the outpatient setting (5).

There was no difference between groups in time spent in the intensive care unit, an important clinical and operational finding. Hospital-acquired PD-associated peritonitis is often raised as a concern in discussions surrounding dialysis modalities, but there was no observed difference in rates of postoperative sepsis between patients on PD (4.9%) and HD (2.7%) (p = 0.32). It should be noted that PD-associated peritonitis uncommonly leads to bacteremia in contrast to HD catheter-related bloodstream infections and the possible serious complications of subsequent metastatic infection (6).

Important limitations include residual confounding (given the retrospective study design) and generalizability (given the single-center nature of the data). An ideal study might prospectively randomize patients on PD postoperatively, who could reasonably use either modality, to PD versus HD. As we await higher quality evidence, the study from Bassil and colleagues (4) provides us reassurance that, absent strong clinical contraindications to PD, it is reasonable to continue the modality after cardiac surgery. ■

Graham Abra, MD, is the director of Inpatient Nephrology at Stanford Hospital and a clinical associate professor in the Division of Nephrology, Department of Medicine, Stanford University School of Medicine, Palo Alto, CA.

The author reports no conflicts of interest.

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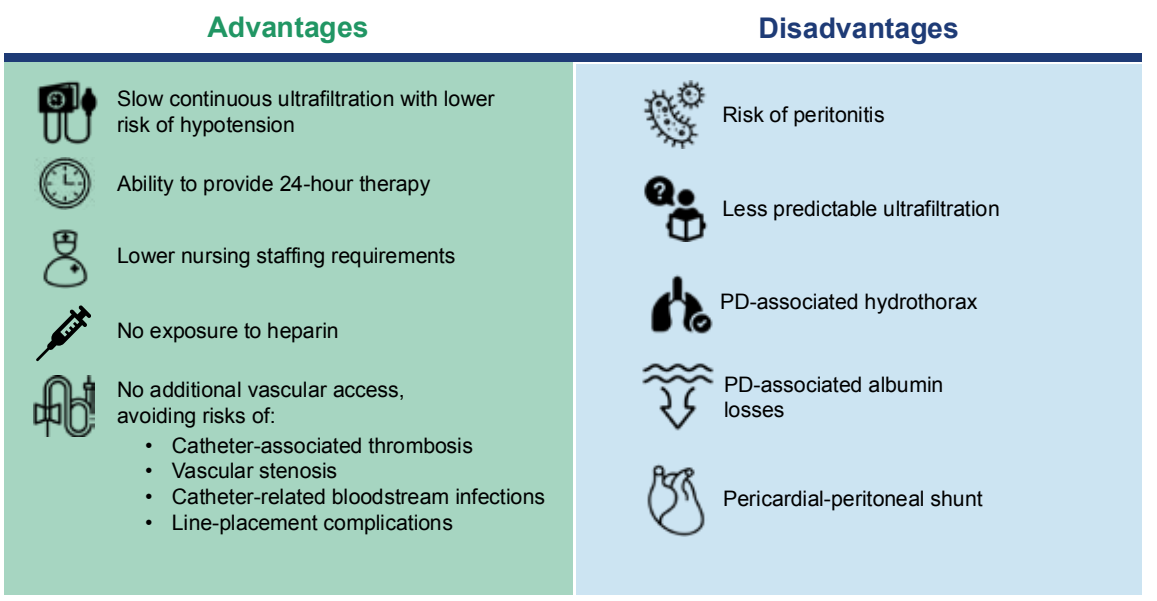
Figure. Potential advantages and disadvantages of PD compared with HD postcardiac surgery



ASN Responds to CMS RFI on Research Data Request and Access Policy Changes

By Ryan Murray

With broad implications for kidney research using data from the Centers for Medicare & Medicaid Services (CMS), the agency issued a Request for Information (RFI) on a proposal on Research Data Request and Access Policy Changes on February 14, 2024, which was later updated on March 1, 2024. In its RFI, CMS announced a decision to discontinue the physical delivery of critical health care data in support of external research projects and to require researchers to use the Chronic Conditions Data Warehouse Virtual Research Data Center to conduct all research using CMS Research Identifiable File data. After soliciting feedback from its members, including those with direct experience with conducting research with data from federal agencies, ASN responded to CMS's RFI on May 15, 2024.

ASN shared how CMS's proposal jeopardizes the future of research on kidney diseases and will likely directly harm Medicare and Medicaid beneficiaries' access to and quality of care and specifically highlighted the following concerns:

- The lack of transparency regarding the future of CMS kidney-related data in light of this proposal
- The unique nature of the federal government's role in kidney care given Medicare's End-Stage Renal Disease program and thus, the potential for jeopardizing the real-time research necessary for policymakers to improve kidney care
- The impact that a future dearth of research will have on disadvantaged populations given the inequities faced by patients with kidney diseases and their families
- The impact of increased costs for researchers and their institutions, especially those at smaller, less financially endowed universities
- The potential to impede the future capacity of researchers across specialties but in particular, in the realm of kidney diseases

CMS data, especially kidney data, are an invaluable resource to policymakers, health care systems, researchers, and the millions of individuals impacted by the contribution of that research through improving outcomes and saving valuable resources. ASN urged CMS to pause the proposal to allow for time to address concerns of the kidney community, those of the broader health care community, and, most importantly, those of individuals living with kidney diseases. ASN will continue to advocate for transparent and open access to federal datasets and keep the kidney research community informed of any updates.

ASN will provide future updates as policy is refined. To read ASN's full response to the RFI, please visit https://www.asn-online.org/policy/webdocs/05.15.24VRDCLetterFinal.pdf or the ASN website at www.asn-online.org/policy.

Ryan Murray is the senior manager of Policy and Government Affairs at ASN.

ASN Responds to CMS Comment Period on Medicare Advantage Data

By Lauren Ahearn

The Centers for Medicare & Medicaid Services (CMS) issued a Request for Information (RFI) on Medicare Advantage (MA) data on January 30, 2024. This RFI is a part of the Biden-Harris Administration's efforts to promote competition in health care, which includes increasing transparency in the MA insurance market and strengthening programmatic MA data. CMS plans to use the information solicited by the RFI to support efforts for MA plans to best meet the needs of people with Medicare, for people with Medicare to have timely access to care, to ensure that MA plans appropriately use taxpayer funds, and for the market to have healthy competition.

ASN addressed the following topics related to MA data in a letter submitted to CMS on May 29, 2024:

- **Missing data on transparency:** Despite estimates of MA enrollment amongst Medicare's End-Stage Renal Disease (ESRD) beneficiaries exceeding 50%, exact data on enrollment from CMS have not been made available. In response to this issue, ASN urged CMS to collect and publish the annual number and percentage of ESRD enrollees who enrolled in an MA plan and the annual number and percentage of those who disenrolled.
- **Questions of transparency:** ASN has raised in previous comment letters concern that MA plans do not provide the same level of transparency as the Medicare Fee-for-Service program, which has a strong history of providing quality data to researchers and policymakers alike. ASN urged CMS to require MA plans to provide the ESRD enrollee data similar to the data collected for Fee-for-Service beneficiaries.
- **Medicare Chronic Condition Special Needs Plan:** Little is known about the impact of Medicare's Chronic Condition Special Needs Plan largely, in part, because MA data have not been made available to researchers and policymakers. ASN urged CMS to publish these data.
- **Network adequacy:** MA network adequacy issues refer to the concerns regarding the sufficiency and accessibility of health care practitioners within the networks of MA plans. Network adequacy issues can have significant implications for patients with kidney failure who require specialized care and frequent access to health care services. Although CMS requires MA plans to submit data on their physician networks, much of these data remain undisclosed to researchers and the public.
- **Equity:** ASN stressed that improving data collection and transparency on MA coverage and enrollees is essential for promoting health equity and ensuring that patients with kidney failure have equitable access to high-quality health care services.
- **Prior authorizations:** Currently, MA insurers are not required to report prior authorization requests, denials, and appeals by types of service, for a specific plan within a contract, or reasons for authorization denials. ASN stressed that improving data collection and transparency regarding prior authorization in MA plans is crucial for ensuring patients with kidney failure receive prompt access to the care and treatments that they need to manage their condition effectively and maintain their health and quality of life.

ASN will provide future updates as policy is refined. To read ASN's full response to the RFI, please visit https://www.asn-online.org/policy/webdocs/05.29.24MedicareAdvantageDataRFI.pdf or the ASN website at www.asn-online.org/policy.

Lauren Ahearn is a quality and regulatory affairs associate at ASN.

Fellows First

Addressing the Silent Epidemic: Urgent Global Action for Chronic Kidney Disease

By Urvashi Khan

Chronic kidney disease (CKD) is not just a medical issue; it is a global crisis demanding immediate attention. The recently published joint statement, Chronic Kidney Disease and the Global Public Health Agenda: An International Consensus, published in *Nature Reviews Nephrology* (1), underscores the severity of this burgeoning problem and advocates for swift action to combat its far-reaching consequences. This article was developed through a consensus among major nephrology societies, including ASN, the European Renal Association, and the International Society of Nephrology, to address the escalating global burden of CKD. Motivated by the rising prevalence of CKD and inconsistent screening practices, these societies aim to standardize guidelines, enhance early detection, and improve health care infrastructure. Their unified effort seeks to raise awareness, advocate for policy support, and ultimately improve CKD management and patient outcomes worldwide.

One of the key messages from the article is the escalating prevalence of CKD worldwide and its devastating impact on mortality, quality of life, and health care expenditures. CKD affects approximately 10% of the global population, with millions remaining undiagnosed and untreated. This should serve as a wake-up call for policymakers, health care practitioners, and society. Ignoring the rising tide of CKD will only exacerbate its toll on individuals and health care systems, particularly in low-income and low- to middle-income countries for which access to diagnosis and treatment is often limited. Moreover, it rightly emphasizes the socioeconomic disparities perpetuating unequal health outcomes among historically disadvantaged populations. Lack of access to optimal therapies further widens the gap, making it imperative to address not only the medical aspects of CKD but also the systemic inequalities that fuel its prevalence.

An essential call to action put forth the inclusion of kidney diseases in the World Health Organization's statement on major noncommunicable disease drivers of premature mortality. Countries face significant challenges in CKD screening and management due to limited awareness, inadequate screening programs, and health system constraints. Economic barriers, technological and infrastructure limitations, and epidemiological factors exacerbate the issue, and cultural, policy, research, and social determinants further complicate efforts. Addressing these challenges requires comprehensive strategies involving education, health care access, system improvements, and robust policy and research initiatives. This recognition would catalyze global efforts to raise awareness, establish guidelines, improve surveillance, and allocate resources for kidney health. By integrating CKD into the global health agenda, we can begin to chip away at the barriers that hinder progress in combating this silent epidemic (2).

Furthermore, the moral imperative to prioritize kidney health cannot be overstated, especially in light of the United Nations' Sustainable Development Goals (SDGs). Addressing CKD aligns with several SDGs, including those related to reducing noncommunicable diseases, ensuring universal health coverage, and achieving health equity. By improving CKD screening and management, we can make significant strides toward these global health objectives, ultimately enhancing quality of life and reducing health care disparities worldwide. Excluding CKD from the global health agenda perpetuates inequities and undermines efforts to achieve health equity for all. Recognizing kidney diseases as major drivers of early mortality is not just a matter of policy; it is a moral obligation to address the needs of the most vulnerable members of society (3).

The article also outlines a roadmap for tackling the grand challenges of kidney health, including improving access to care, enhancing prevention strategies, and investing in research and development (Table). These efforts must be underpinned by a commitment to addressing social determinants of health and ensuring equitable access to resources for all individuals affected by CKD (4).

Urgent action is needed to confront the growing burden of CKD and prevent its catastrophic consequences. The time to act is now, and the stakes could not be higher. By heeding the call to prioritize kidney health, embracing global collaboration, and implementing comprehensive strategies, we can chart a course toward a healthier future for all. The recognition of CKD by the World Health Organization is not just a symbolic gesture; it is a pivotal step toward transforming the landscape of kidney care and safeguarding the well-being of future generations (5). ■

Urvashi Khan, MBBS, MD, DNB Medicine, DrNB, is a nephrology resident at Dharamshila Narayana Superspeciality Hospital, Delhi, India.

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Table. Proposed roadmap for tackling the greatest kidney health challenges

Improving access to care	· **Policy development:** Advocate for the inclusion of CKD in national health agendas and policies. · **Health care infrastructure:** Strengthen health care systems to provide comprehensive CKD care, including dialysis and transplant services. · **Health coverage:** Ensure universal health coverage that includes CKD diagnosis, treatment, and management. · **Telemedicine and remote care:** Expand telehealth services to reach remote and underserved populations.
Enhancing prevention strategies	· **Public awareness campaigns:** Launch educational programs to raise awareness about CKD risk factors, prevention, and early detection. · **Screening programs:** Implement routine CKD screening for high-risk populations, including those with diabetes and hypertension. · **Lifestyle interventions:** Promote healthy lifestyle changes, such as diet and exercise, to prevent the onset and progression of CKD. · **Control of risk factors:** Intensify efforts to control diabetes, hypertension, and other conditions that contribute to CKD.
Investing in research and development	· **Research funding:** Increase funding for CKD research to discover new treatments and improve existing therapies. · **Collaborative research networks:** Establish international collaborations to share data and insights, accelerating the pace of discovery. · **Clinical trials:** Support and expand clinical trials focused on CKD prevention, treatment, and management. · **Innovation in treatment:** Invest in the development of novel therapies and technologies to improve patient outcomes.
Strengthening health systems	· **Workforce training:** Educate and train health care professionals on the latest CKD care practices and guidelines. · **Integrated care models:** Develop integrated care models that coordinate services across different levels of health care. · **Health information systems:** Implement robust health information systems to track CKD prevalence, treatment outcomes, and patient data.
Promoting health equity	· **Address social determinants:** Tackle the social determinants of health that contribute to CKD disparities, such as poverty, education, and access to healthy food. · **Equitable resource distribution:** Ensure equitable distribution of resources and health care services across different population groups. · **Community engagement:** Engage communities in CKD prevention and management efforts to ensure culturally appropriate interventions.
Global collaboration and advocacy	· **International partnerships:** Foster partnerships among governments, nongovernmental organizations, and international organizations to coordinate global CKD efforts. · **Global health initiatives:** Align CKD strategies with global health initiatives, such as SDGs. · **Advocacy campaigns:** Advocate for CKD recognition and prioritization in global health policies and funding allocations.
Monitoring and evaluation	· **Data collection:** Establish robust mechanisms for data collection and analysis to monitor CKD prevalence, risk factors, and outcomes. · **Performance metrics:** Develop and use performance metrics to evaluate the effectiveness of CKD programs and initiatives. · **Continuous improvement:** Implement feedback loops to continuously improve CKD prevention, treatment, and management strategies.

Adapted from Francis et al.; American Society of Nephrology; European Renal Association; International Society of Nephrology (1).

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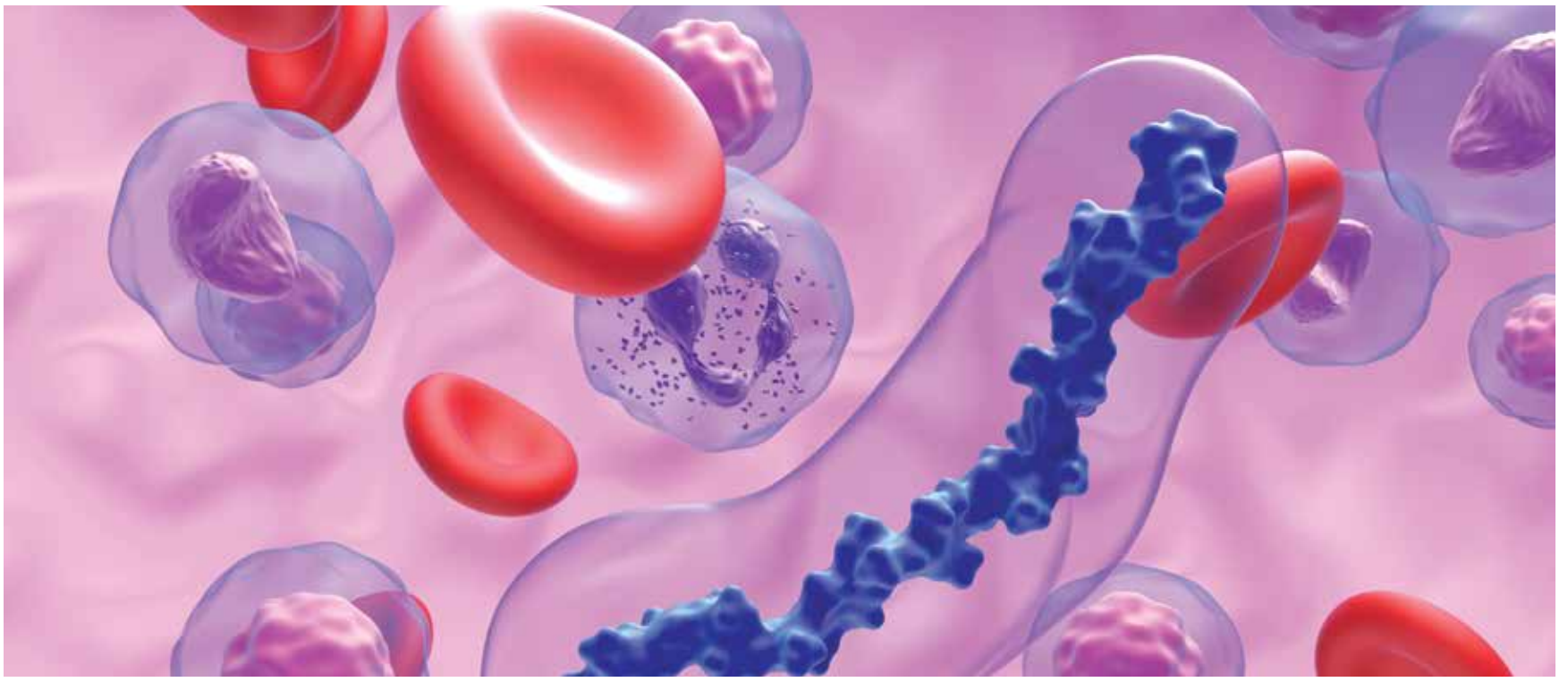

Hope in the 11th Hour: Are New Anticoagulation Options on the Horizon for Patients Undergoing Hemodialysis?

By Karen de Wolski and Nisha Bansal

Anticoagulation in patients undergoing hemodialysis for conditions such as atrial fibrillation has long posed a clinical challenge given competing elevated risks of both thromboembolism and bleeding (1). Even the efficacy and safety of direct oral anticoagulants compared with vitamin K antagonists remain uncertain (2, 3). This has led to ambiguity and thus heterogeneity in prescribing practices for oral anticoagulation in kidney failure. A recent *Kidney International* study of a phase II dose-ranging randomized controlled trial (4) evaluated the safety of the subcutaneously injected novel factor XI inhibitor, fesomersen, in patients undergoing hemodialysis. Factor XI inhibitors have shown promise for prevention of thromboembolic events with relatively low bleeding incidence in some prior phase II trials (5), a pharmacologic approach that could offer a promising avenue for anticoagulation in the population on dialysis. This trial demonstrated a dose-dependent reduction in factor XI levels without an increase in bleeding events among 307 patients undergoing hemodialysis.

In addition to studying an innovative therapy, the trial had numerous strengths. It is commendable that this study specifically enrolled patients undergoing hemodialysis, given frequent exclusion of this highly complex cohort from most cardiovascular trials (6). Participants from 69 sites in 15 countries were enrolled at an impressive pace from a broad international pool, seeming to overcome enrollment challenges seen in other related trials (2, 3). Patient characteristics were well matched across placebo and dosage categories. Pharmacodynamic studies of factor XI levels demonstrated a clear inverse correlation to a fesomersen dose (albeit with wide standard deviation), and these levels were further shown to correspond to the more clinically relatable activated partial thromboplastin time. Endpoints included thrombotic events of hemodialysis accesses, a morbid complication specific to this population that would benefit from further primary and secondary prevention options.

Although results for an impressive array of safety and efficacy endpoints were given, event rates were low with wide confidence intervals. For example, only one major atherothrombotic event per group, including placebo (pooled hazard ratio, 0.92; 95% confidence interval, 0.10–8.81; p = 0.94), was detected in the trial period. Additionally, patients who would seemingly be at highest risk for safety or efficacy events, such as those with a recent bleeding or thromboembolic incident and those already on anticoagulants, were excluded from this trial, which may help explain why these endpoints were seen at such low rates. These analyses were descriptive without a formal sample size calculation prior to enrollment, so the study was not actually powered to detect differences. Finally, the population studied was a general population undergoing hemodialysis in whom anticoagulation may not be indicated; further research of more applicable patients (e.g., those with atrial fibrillation) would be informative.

So where does this leave us? Fesomersen may represent a novel anticoagulant that could confer some advantages over existing options, and further data and therapeutics in this arena are greatly needed for patients on dialysis. This trial demonstrates that factor XI levels respond in a dose-dependent manner to fesomersen. However, due to lack of power, reported results related to efficacy and safety are not conclusive but certainly warrant further investigation. Importantly, this trial gives us hope that it is feasible to enroll patients undergoing hemodialysis in cardiovascular trials. After the success of recent chronic kidney disease trials, the time is now to focus on patients undergoing hemodialysis. We hope that this study (and others) paves a new path forward for investigation of novel cardiovascular therapies in this high-risk population. ■

Karen de Wolski, MD, is an assistant professor, and Nisha Bansal, MD, FASN, MAS, is a professor in the Division of Nephrology, University of Washington, Seattle.

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