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Leveraging Real-World Patient Data Is Key to Kidney Care Innovation

By Bridget Kuehn

Reams of electronic data are generated during day-to-day care of patients with kidney diseases. Some data are entered by clinicians into electronic medical records; other data are collected by monitors or machines used in patient care. Experts who attended the Kidney Innovation Conference in June agree that the often-untapped data trove may hold the key to helping accelerate innovation in kidney health care.

The 2-day conference hosted by the Kidney Health Initiative, KidneyCure, and the Kidney Innovation Accelerator (KidneyX) brought together clinicians, patients, regulators, and industry representatives to discuss the best ways to rapidly improve care and outcomes for patients with kidney diseases. Across all sectors, experts agreed that better leveraging of the available data to discover new insights, personalize care, and make care more proactive is essential to progress. Some participants advocated for "pragmatic trials" conducted in real-world clinical care settings.

"We need to have more innovation; we need to be faster getting care to our patients, generating the evidence for the next step," said Miguel Vazquez, MD, FASN, clinical chief of nephrology and professor in the Department of Internal Medicine at The University of Texas Southwestern Medical Center, Dallas. "Pragmatic trials can offer an opportunity to do that using already available data or generating data with our partners in health systems."

Other speakers described how new technologies like artificial intelligence (AI) or machine learning could extract insights from large amounts of data to help clinicians predict when patients with chronic kidney disease (CKD) might progress, need dialysis, or develop vascular access difficulties and enable early interventions. The devices aim to help nephrologists work more efficiently and effectively by taking on tasks that they might otherwise not have time for, said Mandar Gori, MS, MBA, chief business officer at AWAK Technologies based in Singapore.

"The final decision [about what to do with the data] is still the clinician's," said Gori, whose medical technology company is developing AI-driven patient-monitoring software. "Taking on some of these other tasks frees up [clinicians'] time elsewhere that could lead to more improvement."

Real-world studies

Pragmatic trials are rigorous randomized trials carried out in everyday practice settings with more representative populations than are typically included in traditional randomized trials, which often exclude patients with comorbidities or

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More Research Needed on Menopause and the Kidneys

By Melanie Padgett Powers

Menopause is coming out of the shadows. Every person who has ovaries and lives to a certain age will go through the menopausal transition. And yet, until recently, there has not been much public discussion about perimenopause (the transitional time before menopause) and menopause. But as Generation X (those born between 1965 and 1980) and Millennials (those born between 1981 and 1996) reach the age of perimenopause, they are often baffled and shocked by the spectrum of symptoms, learning that it is not just hot flashes with which they must contend. These generations are more outspoken about the topic, and social media is filled with individuals in their 40s and 50s sharing their symptoms and quests for treatment.

"Menopause is such a normal part of female life, and females make up 51% of the population, so this is something we should be talking about," said nephrologist Sandra Dumanski, MD, MSc. "A lot of female-specific health concerns have been hushed for many years, and it's only lately that we're seeing a wave of renewed interest." Dumanski, an assistant professor in the Department of Medicine at the University of Calgary, Alberta, Canada, studies the impact of sex and gender on kidney and cardiovascular (CV) outcomes.

Not every individual with ovaries will become pregnant, but every individual with ovaries will eventually reach menopause. Yet, there are very little training or

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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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Leveraging Real-World Patient Data Is Key to Kidney Care Innovation

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other conditions, Vazquez explained. The nature of pragmatic trials can make it easier to generalize the results of the studies to typical patient populations, and the studies help demonstrate the feasibility of implementing the intervention in day-to-day practice, he said. "Our patients already go to many, many appointments [whether they are undergoing dialysis or living with CKD or have undergone transplant]," Vazquez said. "[Pragmatic trials] don't add additional follow-ups."

Vazquez and his colleagues conducted a pragmatic trial to test an intervention designed to improve primary care for patients with co-occurring CKD, diabetes, and hypertension (1). The investigators randomized primary care clinics to implement the intervention or continue providing usual care. The study received a waiver of informed consent from the institutional review board overseeing it, but patients could opt out of having their data used by the study. Participating health systems included a local safety net hospital system in Dallas County, TX; a private hospital system in North Texas; the Veterans Affairs North Texas health care system; and an accountable care organization in Connecticut.

Participating practices updated patients' problem lists and implemented a suite of simple, evidence-based practices, including blood pressure and cholesterol management, diabetes care, immunizations, avoidance of medications harmful to the kidney, and education about kidney diseases.

The study yielded a few surprises. One was that many patients at participating institutions were already well-managed for their co-occurring conditions. The intervention also did not reduce hospitalization rates compared with usual care, the primary study endpoint. It also did not improve 30-day readmissions, emergency department visits, or cardiovascular events. However, a manual chart review did find improvements in the care that patients received at clinics implementing the intervention.

The study is ongoing, and although it did not find a reduction in hospitalizations, it did demonstrate that it is possible to implement an intervention with high fidelity across a diverse set of health systems, Vazquez said. He thinks that investigators can replicate this model to study interventions to slow CKD progression, prevent acute kidney injury, improve transplant, or smooth care transitions.

Gary Curhan, MD, ScD, FASN, a professor at Harvard Medical School in Boston, MA, cautioned that real-world studies cannot answer every question but may be more informative or more practical than randomized trials in some situations. For example, if a large sample size is needed, or patients must be followed for years or decades, randomized trials may be too costly or logistically challenging. He noted that real-world datasets like electronic health records' systems may have data on millions of patients over many years.

The real-world studies may also help study rare diseases or unusual disease presentations. For example, Curhan noted an AI study examining Fabry disease, a rare kidney disease with a heterogeneous presentation, in 5000 patients (2). The study provided valuable data on the wide variation in symptom presentation and allowed the team to test a method to identify patients who may be undiagnosed. Similarly, a large study using data in the Geisinger Health System found that patients who have one allele for the recessive genetic condition Alport syndrome were more likely to have blood in their urine and reduced estimated glomerular filtration rates and proteinuria than people with no copies of the syndrome-linked allele (3). But these individuals did not have hearing loss like individuals with two copies of the allele. The study suggested that these individuals may also have Alport syndrome, but clinicians may not diagnose them because they do not have two alleles or hearing loss, Curhan said.

"Many of these real-world studies are opportunistic, but if you can take advantage of the data, [these studies may be the] only way to answer some of these questions." He cited another study that linked elevated 24-hour urine oxalate levels with a higher risk of incident CKD (4).

Big data to solve big problems

Patients on hemodialysis often struggle not knowing when potential complications might arise, said Samit Gupta, PhD, chief scientific officer and cofounder of Alio.ai. He noted that access failures, fluid overload, or cardiac problems caused by potassium abnormalities can all crop up unexpectedly. "There's a whole host of challenges that your care team and your clinic are trying to help you manage as best they can, but you are living in a constant state of existential dread," Gupta said. "That sense of frustration and lack of control also exists on the [practitioner] side."

Gupta and his colleagues at Alio.ai are trying to leverage AI to solve this problem. They have received US Food and Drug Administration (FDA) clearance to use their technology to monitor hemoglobin, hematocrit, and potassium levels and for signs of access failure. Patients wear a peel-and-stick patch that uses sensors to capture acoustic, mechanical, and thermal data. For example, the company uses the sensors to monitor the patient's pulse and for sounds that clinicians would usually capture with a stethoscope that may indicate disruptions in blood flow or stenosis associated with access failure to provide early warnings. Physicians can view their patients' data in a portal that tracks patients' trends and alerts them to signs of trouble. Gupta said some clinicians use the technology to check the portal daily to monitor patients, whereas others rely on notifications. "We are actively working on moving upstream to [monitor patients during] earlier stages of kidney disease[s] and peritoneal dialysis," Gupta said.

Another potential application for AI is identifying patients whose kidney disease is progressing before they "crash into dialysis," said Gori. He noted that more than 60% of patients crash into dialysis, which leads to higher costs, fewer options for patients, and poorer outcomes. He said only about 12% of patients in the United States are on home dialysis, a substantially lower rate than in other countries. AWAK Technologies is currently testing a wearable dialysis device that would provide patients with another option for peritoneal dialysis. "Many patients are going into in-center dialysis when we know that quality of life is much better when the patient is dialyzed at home," he said. "We wanted to go upstream and capture patients [who are progressing toward kidney failure] earlier on."

The company has developed a monitoring device for use with AWAK's wearable dialysis device, which may also help identify patients with later-stage CKD progressing toward kidney failure and predict the need for dialysis. The device can classify patients as low, medium, or high risk of progression or needing dialysis. To do this, the company uses evidence-based guidelines and adds additional patient information to improve its prediction accuracy. "It's a decision support tool, which helps [clinicians] to save time and focus on [the patients who need more attention]," Gori explained.

Alio.ai's technology relies on an artificial neural network to parse the data, but it has designed the program to explain the basis of its predictions to clinicians. The intention is to help avoid problems arising when previous technology was a "black box" for clinicians, preventing them from catching errors. That is part of a trend in the field—to create "explainable AI" to help avoid problems associated with poor transparency.

Gori and his colleagues trained their computer algorithm using data on more than 10,000 patients from five hospitals in Taiwan. Then, 10 nephrologists from another hospital tested the monitoring tool built using the algorithm for about 3 months. AWAK Technologies received a "breakthrough device" designation from FDA based on the data (5).

Pros and cons of AI

Brad Keller, MS, PhD, who leads the clinical development group at Baxter Healthcare, agreed that remote patient monitoring is one promising application for AI in kidney diseases. He noted that effective early management of adverse events could cut costs and improve outcomes. He said that remote cyclers for peritoneal dialysis capture large amounts of data on patients' therapy and adherence that could be paired with other patient data to monitor their condition. But the volume is so great that it would be difficult and time-consuming for a human to parse. AI could potentially help detect emerging problems. However, Keller warned that there are pitfalls that developers and clinicians need to be careful to avoid.

"With big data comes big problems because the more you assess people, the more you might find something that is or is not real," Keller said. He explained that assessing whether such anomalies are a real concern could require additional clinical care and evaluation and tax both the health system and patients, who already have a high care burden. He noted that frequent false positives can also cause patients and clinicians to ignore alerts.

He also noted that having the "right data" up front is vital to troubleshooting downstream. For example, many medical datasets have a survivor bias and may only include patients whose data were suspicious, leading to intervention. Those who did not have adverse events or whose adverse events went undetected may be missing from the data. Using such flawed datasets can lead to flawed tools. For example, recent studies have shown that pulse oximeters inaccurately reported oxygenation—leading to underdiagnosis of low oxygen—in people with dark skin who were under-represented in the datasets used to train the tools (6).

Keller emphasized the importance of using an iterative process to assess and improve the tools and troubleshoot problems. He also said that it is important to work together across sectors to collect data and ensure the right questions are being asked. "It's important to learn from the past so that we can accelerate to the future," he advised.

Ongoing improvement

FDA has authorized more than 500 AI- or machine learning-based devices across a wide range of medical specialties, said Sivakami Venkatachalam, MS, Gastroenterology and Endoscopy technical lead in FDA's Center for Devices and Radiological Health. The agency is working with developers to promote good practices and transparency in the development of devices and ways to make the process more efficient. "We are continuously looking at new ways to evolve the regulatory approach to enable fast-moving innovation," she said.

Gupta noted that beyond devices that require long developmental processes and FDA approval, AI may also be useful in gleaning insights from clinical data. He said there is likely other "low-hanging" fruit in patient care data that could be used to improve patient care. "There are opportunities for learning that are faster and not gated by technology development and approval," he added. ■

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More Research Needed on Menopause and the Kidneys

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studies about this transition, even in obstetrics and gynecology. A 2019 survey reported in *Mayo Clinical Proceedings* found that only 6.8% of family medicine, internal medicine, and obstetrics and gynecology residents reported feeling adequately prepared to manage individuals experiencing menopause (1). Another 2019 study, this time involving nephrologists, found that more than 65% lacked confidence in women's health issues, including menopause (2).

Menopause causes lower levels of estrogen and other hormones, leading to a variety of symptoms, although many females primarily know about the vasomotor symptoms—hot flashes and night sweats. There is no specific clinical test to determine when a person has transitioned from perimenopause to menopause. Instead, menopause is defined as 12 months without a menstrual bleed that is not caused by other conditions. The average age of menopause is 51 years (3). Perimenopause could last for 4 to 8 years.

Menopause may occur at about the same age as some females experience chronic kidney disease (CKD). So, how might menopause affect the kidneys, and, in turn, how might CKD affect menopause? Nephrologists and other scientists are trying to find the answers.

Physiological paths

Menopause and kidney diseases have some commonalities, but it is unclear whether there are physiological linkages. Both come with a higher risk of CV disease and bone disease. In addition, females with CKD can develop early menopause because there is a disruption of the physiological process that results in a normal menstrual cycle. The hypothalamic-pituitary-gonadotropin axis is disrupted due to loss of a pulsatile gonadotropin-releasing hormone, but this loss is not fully understood, said nephrologist Sofia B. Ahmed, MD, MS, MSc, professor in the Faculty of Medicine and Dentistry and research chair in sex and gender at the University of Alberta, Edmonton, Canada.

Most knowledge about perimenopause and menopause and the kidneys comes from studies examining only people with kidney failure, often undergoing conventional hemodialysis, Dumanski said. What is known: CKD is more prevalent in females than in males, and kidney diseases are diseases of accelerated aging, said nephrologist Katharine L. Cheung, MD, MS, PhD, FASN, assistant professor and interim director of the Center on Aging at The University of Vermont Medical Center, Burlington. A 2015 study of 17,891 postmenopausal females in the Women's Health Initiative cohort showed that females with mild CKD went through menopause but had fewer vasomotor symptoms when compared with females without CKD (4). The study compared those with an estimated glomerular filtration rate >60 versus <60 mL/min/1.73 m^2; the mean estimated glomerular filtration rate in the cohort was 50, which is not low for kidney diseases, Cheung said. "I think it's interesting that even in modestly reduced kidney function, you're seeing signs that CKD is impacting menopause," she added.

That females with CKD reported fewer vasomotor symptoms contradicted Cheung's original hypothesis that people with CKD would have more vasomotor symptoms and that they would be more severe. She wonders if the pathophysiology behind the finding could be related to people with kidney diseases having preexisting vascular disease. "Vasomotor symptoms occur because of peripheral vasodilation of the blood vessels that allows heat to be expelled, and then you have that flushing feeling," she explained. But in kidney diseases, the blood vessels are not normal. "Often, there's vascular disease. The blood vessels have calcification, the arteries are stiffer, and there's endothelial dysfunction."

Research findings

One condition that menopause and kidney diseases have in common is weaker bones. But is there any connection? In natural menopause, lower levels of estrogen decrease bone density and can lead to osteoporosis, while people living with kidney diseases can have renal bone disease because of an imbalance in phosphorus and calcium. Furthermore, the use of bisphosphonates to treat osteoporosis in the general population is generally contraindicated in advanced kidney diseases, said Vesna D. Garovic, MD, PhD, FASN, professor of medicine and chair in the Division of Nephrology and Hypertension at the Mayo Clinic, Rochester, MN. "Thus, safer alternatives are needed for treatment of postmenopausal osteoporosis in [females] with kidney disease[s]," she said.

A recent study among postmenopausal females in Korea showed an association between CKD and tooth loss (5). The study evaluated a survey of nearly 65,000 participants, ages 40 to 79 years. They were divided into two groups based on their number of teeth. Adults should have 32 teeth, but the results showed that females with kidney diseases had a higher risk of having fewer than 20 teeth, particularly among postmenopausal females, ages 66 to 79 years.

But what about individuals with healthy kidneys who are going through menopause? "The short answer is we don't know much about menopause in general, let alone what happens in the setting of kidney disease[s] or in a completely healthy individual," Ahmed said. Kidney disease clinics often see older individuals, she continued. "A lot of these individuals are menopausal through normal physiological processes, and then they develop kidney disease[s] later on—and some of the other people in clinic have developed menopause presumably *because* of kidney disease[s]. But we don't know who is who."

For many individuals with CKD who are experiencing menopause and who undergo a successful kidney transplant, their menstrual cycles may return. This demonstrates that they did not undergo a "normal" state of menopause, so maybe their kidney-related menopause should be called "functional menopause," Ahmed said.

In a 2020 study, Ahmed's laboratory hypothesized that a lower level of estrogen over many years might contribute to the higher mortality rates of females with kidney failure compared with males. However, the results were the opposite. They measured estradiol levels of 482 females over 2.9 years. There were 237 deaths, with 31% caused by CV disease. When stratified by age, higher levels of estradiol were associated with greater all-cause mortality and non-CV mortality but not CV mortality in older females.

Another area that calls for more research is hormone therapy (HT). Guidelines from the American College of Obstetricians and Gynecologists and other leading medical societies recommend HT for the management of menopausal symptoms (6). HT (sometimes called "hormone replacement therapy") is typically a combination of estrogen and progestin; those without a uterus can take estrogen alone.

Dumanski said that more research is needed on the different formulations and types of HT for menopausal individuals, which include pills, patches, skin gels, vaginal creams, and more. Clinicians do not have concrete evidence-based guidelines stating which types are safer and more effective in females with certain health characteristics, such as kidney diseases. "Saying you're taking hormone replacement therapy is akin to saying, 'I'm taking antibiotics,'" Ahmed said. "The type of estrogen, the route of delivery—meaning as a tablet, a patch, or vaginally—concomitant progestin use, and the type of progestin all matter. Other factors to consider are the indication for and duration of HT use and age [at] menopause relative to HT initiation, as well as the cause of menopause."

The studies on HT and kidney function have been conflicting. HT use is associated with less albumin in the urine, but oral HT, at least in older populations, may not be as good for kidney function compared with the other routes of HT delivery, Ahmed continued. She added that HT requires more research in general, including any effects on the kidneys with gender-affirming HT, hormonal contraception, androgen deprivation therapy for prostate cancer, or antiestrogen therapy for breast cancer.

A path forward

Women's health has been getting increasingly more attention in recent years. Earlier this year, the federal government's Advanced Research Projects Agency for Health announced the Sprint for Women's Health, a $100 million investment to close the gap in federal funding for research and development into women's health. The program is the first major project of the new White House Initiative on Women's Health Research.

In February 2023, Kidney Disease: Improving Global Outcomes (KDIGO) held its Controversies Conference on Women and Kidney Health, which convened a global, multidisciplinary clinical panel and patients to identify key gender and sex issues in kidney care (7). (At press time, the conference report was not yet available.)

There are many questions and so much research yet to do. "The course of chronic [kidney] disease in postmenopausal [individuals] needs to be better characterized in order to optimize the treatment of these [individuals]," Garovic said. For instance, is there a potential therapeutic role of estrogen in kidney diseases? "At present, due to the lack of specific data [on] the [population with CKD], guidelines for the general population are being followed with recommendation for dose reduction," she said. "Future efforts should focus on developing compounds that mimic the protective role of this hormone but [that] do not have adverse cardiovascular effects."

Dumanski points to several other areas that need more attention: large, well-designed studies that examine how menopause affects CKD and vice versa, studies that ask females about their menopausal symptoms and experiences, and whether—and how—to prescribe HT to females of menopausal age with kidney diseases.

"I think there is a movement within nephrology and an increased recognition that these are important factors," Ahmed said. "Is there work to do? Absolutely. Can we do better? Yes. This is an important area that we can't ignore any longer." ■

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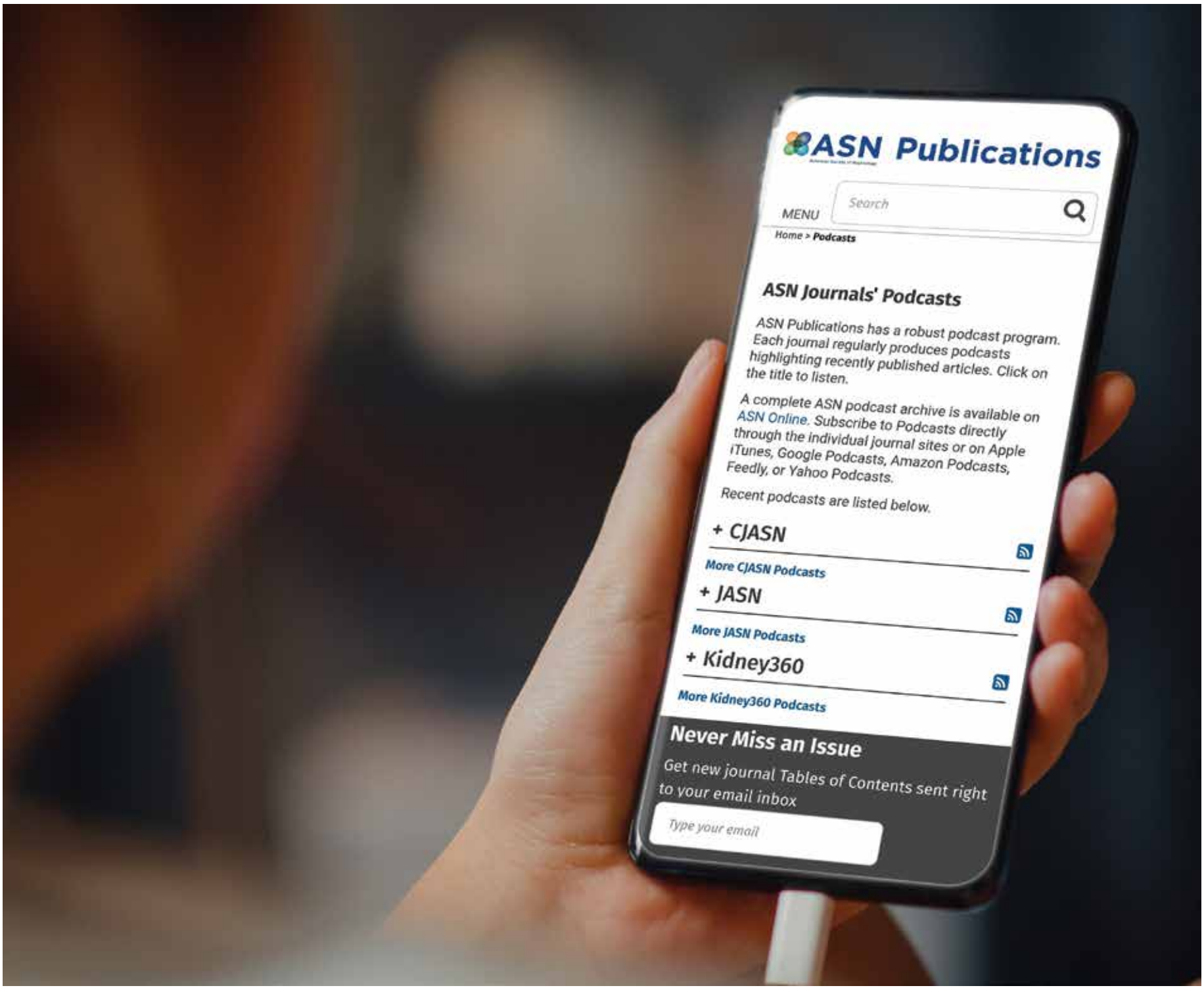

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Business Round-up: Q1–Q2 2024 Activity in the Nephrology Industry

By Melissa West

Understanding the changing landscape in health care and kidney care is an important effort as private equity, artificial intelligence, technology companies' interest, and value-based care influence the direction of patient care and research. Over the past 3 years, a quarterly report has been provided to ASN Council and staff tracking activities in this critical space. The report and analysis are drawn from publicly available data, including news articles, press releases, and investment statements.

The following summaries are generated from over 800 data points collected from January to June 2024 and presented in the first of a twice-a-year update for *Kidney News*.

Health equity and home care

Achieving health equity and approaches to increasing diversity in clinical trials were regularly reported during the first two quarters of 2024. ASN staff continues to track rural health and how innovation can support this population, especially people living with kidney diseases, care partners, nephrologists, and the care team. To this end, the US Food and Drug Administration (FDA) has recently launched a "Home as a Health Care Hub" initiative to enable the safe use of medical devices within one's home. ASN staff will continue to track these efforts closely.

Transplant and reimbursement

It would be remiss in this summary not to mention the recent and regular news around transplant, including the Health Resources and Services Administration's initiative to reform the organ transplant system and the Centers for Medicare & Medicaid Services' proposed mandatory organ transplant payment model. Continuing with payment policy, many of the collected data points' inventory activity are related to the Medicare Advantage and End Stage Renal Disease Prospective Payment System Transitional Drug Add-on Payment Adjustment. Without a mechanism for coverage, it is challenging for patients to access the new therapies that are working their way through the development pipeline or for investors to consider kidneys as a viable market for innovation.

Patient advocacy and public awareness

On a final note, this first half of 2024 has seen many individuals with kidney diseases come forward to share their stories and testimonies. Notably, Suni Lee, US gymnast and Olympic Team member, speaks openly about her health and conditions, including kidney disease. Patient advocacy and involvement are key to health care innovation, and increased sharing of patients' unique experiences can help guide the future of patient-centered kidney care.

This report will be provided again in early 2025 with a focus on Q3 and Q4 2024 activity, including relevant highlights from ASN Kidney Week. ■

Melissa West is the Senior Director, Strategic Relations and Patient Engagement at ASN. She previously was the Project Director for the Kidney Health Initiative. With over 20 years' experience working in the kidney community, Ms. West tracks the trends in business and kidney care for ASN Council and staff. Please contact Ms. West at mwest@asn-online.org to share publicly available information that may have been missed in this article.

Summary: FDA Approvals

Approval	Type	Product	Company	Reference
510K Clearance	Device	5008X Hemodialysis System	Fresenius Medical Care	Fresenius Medical Care Brings Industry-Leading Dialysis Therapy to Kidney Disease Patients in the U.S., Demonstrating Global Leadership in Medical Device and Membrane Engineering Technologies (February 8, 2024). https://www.prnewswire.com/news-releases/fresenius-medical-care-brings-industry-leading-dialysis-therapy-to-kidney-disease-patients-in-the-us-demonstrating-global-leadership-in-medical-device-and-membrane-engineering-technologies-302057603.html
Approval	Drug, new indication	Wegovy (semaglutide) for cardiovascular disease, either obesity or overweight	Novo Nordisk	FDA Receives First Treatment to Reduce Risk of Serious Heart Problems Specifically in Adults With Obesity or Overweight (March 8, 2024). https://www.fda.gov/news-events/press-announcements/fda-approves-first-treatment-reduce-risk-serious-heart-problems-specifically-adults-obesity-or
Approval	Device	Redesigned CVAC™ Aspiration System	Calyxo	Calyxo Announces FDA Clearance for New, Redesigned CVAC System (March 26, 2024). https://calyxoinc.com/calyxo-news/calyxo-fda-approved-cvac-system-kidney-stones/
Approval	Drug	Vafseo (vadadustat)	Akebia	Akebia Receives FDA Approval of Vafseo® (Vadadustat) Tablets for the Treatment of Anemia due to Chronic Kidney Disease in Adult Patients on Dialysis (March 27, 2024). https://ir.akebia.com/news-releases/news-release-details/akebia-receives-fda-approval-vafseor-vadadustat-tablets

Summary: Biologic, Drug, and Device Development

Activity	Category	Product	Company	Reference
Drug FLOW trial	Chronic kidney disease	Semaglutide	Novo Nordisk	Novo Nordisk A/S: Semaglutide 1.0 mg Demonstrates 24% Reduction in the Risk of Kidney Disease-Related Events in People With Type 2 Diabetes and Chronic Kidney Disease in the FLOW Trial (March 5, 2024). https://www.novonordisk.com/content/nncorp/global/en/news-and-media/news-and-ir-materials/news-details.html
Drug 7-Year Orphan Drug exclusivity	IgA nephropathy	Tarpeyo	Calliditas	Calliditas Announces an Additional Seven Year Orphan Drug Exclusivity Period for TARPEYO® (March 6, 2024). https://www.prnewswire.com/news-releases/calliditas-announces-an-additional-seven-year-orphan-drug-exclusivity-period-for-tarpeyo-302081084.html
Solid organ	Xenotransplantation	HuCo Kidney	eGenesis	Surgeons Transplant Pig Kidney Into a Patient, a Medical Milestone (March 21, 2024). https://www.nytimes.com/2024/03/21/health/pig-kidney-organ-transplant.html
Drug	Xenotransplantation	Tegoprubart	Eledon Pharmaceuticals	Eledon Pharmaceuticals Announces Use of Tegoprubart in First-Ever Transplant of Genetically Modified Kidney From a Pig to a Human (March 21, 2024). https://ir.eledon.com/news-releases/news-release-details/eledon-pharmaceuticals-announces-use-tegoprubart-first-ever
Drug Orphan Drug designation	Transplantation	Felzartamab	HI-Bio	HI-Bio Receives FDA Orphan Drug Designation for Felzartamab for the Treatment of Antibody-Mediated Rejection (AMR) in Kidney Transplant Recipients (March 21, 2024). https://hibio.com/news/hi-bio-receives-fda-orphan-drug-designation-for-felzartamab-for-the-treatment-of-antibody-mediated-rejection-amr-in-kidney-transplant-recipients
Drug Orphan Drug designation	Autosomal dominant polycystic kidney disease	AP303	Alebund Pharmaceuticals	Alebund's Innovative Investigational Drug AP303 Receives FDA Orphan Drug Designation (ODD) for the Treatment of Autosomal Dominant Polycystic Kidney Disease (ADPKD) (March 29, 2024). https://www.prnewswire.com/news-releases/alebunds-innovative-investigational-drug-ap303-receives-fda-orphan-drug-designation-odd-for-the-treatment-of-autosomal-dominant-polycystic-kidney-disease-adpkd-302101896.html
Drug Advances to phase 2/3 trial	APOL1-mediated kidney disease	Inaxaplin (VX-147)	Vertex	Vertex Advances Inaxaplin (VX-147) Into Phase 3 Portion of Adaptive Phase 2/3 Clinical Trial for the Treatment of APOL1-Mediated Kidney Disease (April 1, 2024). https://news.vrtx.com/news-releases/news-release-details/vertex-advances-inaxaplin-vx-147-phase-3-portion-adaptive-phase
Drug FDA Priority Review	IgA nephropathy	Fabhalta (iptacopan)	Novartis	Novartis Secures Phase III Fabhalta Win in IgAN as FDA Starts Priority Review (April 16, 2024). https://www.biospace.com/article/novartis-secures-phase-iii-fabhalta-win-in-igan-as-fda-starts-priority-review
Solid organ	Xenotransplantation	HuCo Kidney	eGenesis	Surgeons Perform First Combined Heart Pump and Pig Kidney Transplant (April 25, 2024). https://www.cnn.com/2024/04/24/health/combined-heart-pump-pig-kidney-transplant
Diagnostic FDA Breakthrough designation	Imaging and artificial intelligence	MyKidneyAI	Toku Inc.	Toku Inc. Secures FDA Breakthrough Designation for Technology That Identifies Chronic Kidney Disease Risk Through the Eye (April 30, 2024). https://www.biospace.com/article/releases/toku-inc-secures-fda-breakthrough-designation-for-technology-that-identifies-chronic-kidney-disease-risk-through-the-eye/

APOL1, apolipoprotein L1; IgA, immunoglobulin A.

Summary: Investments

Company	Amount, million $	Type	Reference
HI-Bio	95	Series-B	HI-Bio Announces $95 Million Series B Financing to Advance Targeted Therapies for Immune-Mediated Diseases (January 4, 2024). https://hibio.com/news/hi-bio-announces-95-million-series-b-financing-to-advance-targeted-therapies-for-immune-mediated-diseases
ImmunoFree	Undisclosed	NKF Innovation Fund investment	National Kidney Foundation Innovation Fund Invests in ImmunoFree (January 30, 2024). https://www.kidney.org/news/national-kidney-foundation-innovation-fund-invests-immunofree
Vera Therapeutics	287.5	Public offering (class A common stock)	Vera Therapeutics Announces Closing of Upsized Public Offering and Full Exercise of Underwriters' Option to Purchase Additional Shares in Public Offering of Class A Common Stock (February 6, 2024). https://ir.veratx.com/news-releases/news-release-details/vera-therapeutics-announces-closing-upsized-public-offering-and
Kyverna Therapeutics	366.9	IPO	Kyverna Therapeutics Announces Closing of Initial Public Offering and Full Exercise of Underwriters' Option to Purchase Additional Shares (February 12, 2024). https://ir.kyvernatx.com/news-releases/news-release-details/kyverna-therapeutics-announces-closing-initial-public-offering
Healionics	5.5	Series-A	Healionics Closes $5.5 Million Series A-3 Financing Round (February 22, 2024). https://www.einnews.com/pr_news/690637670/healionics-closes-5-5-million-series-a-3-financing-round
Healionics	1.25	NIH SBIR	Healionics Awarded $1.25M NIH Grant to Support Commercialization of STARgraft Vascular Graft (May 10, 2024). https://www.einpresswire.com/article/710364170/healionics-awarded-1-25m-nih-grant-to-support-commercialization-of-stargraft-vascular-graft
ProKidney	130	Public offering (class A common stock)	ProKidney Announces Pricing of Its Upsized $130 Million Public Offering of Class A Ordinary Shares and Concurrent Registered Direct Offering (June 11, 2024). https://investors.prokidney.com/news-releases/news-release-details/prokidney-announces-pricing-its-upsized-130-million-public

IPO, initial public offering; NIH, National Institutes of Health; NKF, National Kidney Foundation; SBIR, small business innovation research.

Summary: Mergers and Acquisitions[a]

Company	Amount, billion $	Type	Reference
SanReno Therapeutics	N/A; exclusive rights as indirect, wholly owned subsidiary	Novartis	SanReno Therapeutics Announces Acquisition by Novartis in Pivotal Transaction to Bring Forward Transformative Therapeutics in Kidney Disease (January 5, 2024). https://www.prnewswire.com/news-releases/sanreno-therapeutics-announces-acquisition-by-novartis-in-pivotal-transaction-to-bring-forward-transformative-therapeutics-in-kidney-disease-302026982.html
Alpine Immune Sciences	4.9	Vertex	Vertex Enters Into Agreement to Acquire Alpine Immune Sciences (April 10, 2024). https://news.vrtx.com/news-releases/news-release-details/vertex-enters-agreement-acquire-alpine-immune-sciences
HI-Bio	1.15	Biogen	Biogen Bolsters Late-Stage Pipeline, Expands Immunology Portfolio With Agreement to Acquire Human Immunology Biosciences (May 22, 2024). https://investors.biogen.com/news-releases/news-release-details/biogen-bolsters-late-stage-pipeline-expands-immunology-portfolio
Calliditas	1.8	Asahi Kasei	Asahi Kasei to Acquire Calliditas Therapeutics AB to Accelerate Growth as a Global Healthcare Company (May 28, 2024). https://www.asahi-kasei.com/news/2024/e9eg7a00000000a5-att/e240528.pdf

N/A, not applicable.
[a]Data presented are on the first public story and not the current stage of merger or acquisition.

Summary: Value-Based Kidney Care[a]

Organization	Type	VBC relationship	Reference
Allina Health, Aetna, a Minnesota-based health insurance plan	Insurer	Evergreen Nephrology	New Approach to Kidney Care Available to Minnesotans on Allina Health. Aetna Plans With Evergreen Nephrology (January 2, 2024). https://www.allinahealthaetna.com/en/about-us/news/aha-teams-up-with-evergreen-nephrology-kidney-care.html
Millennium Physician Group Partner (Florida)	ACO/physician group	Monogram Health	Monogram Health and Millennium Physician Group Partner to Improve Chronic Kidney Disease Outcomes for Several Thousand Patients Across Florida (January 8, 2024). https://www.monogramhealth.com/press/monogram-health-and-millennium-physician-group-partner-to-improve-chronic-kidney-disease-outcomes-for-several-thousand-patients-across-florida
Blue Cross Blue Shield (Arizona)	Insurer	Monogram Health	Monogram Health and Blue Cross Blue Shield of Arizona Partner to Improve Chronic Kidney Disease Outcomes (January 29, 2024). https://www.monogramhealth.com/press/monogram-health-and-blue-cross-blue-shield-of-arizona-partner-to-improve-chronic-kidney-disease-outcomes
AmeriHealth Administrators	Third-party administrator	Renalogic	Renalogic Partners With AmeriHealth Administrators to Address High-Cost Dialysis Claims for the Marketplace (January 31, 2024). https://renalogic.com/renalogic-partners-with-amerihealth-administrators/
Sun Life	Financial services company	Somatus	Sun Life Partners With Somatus to Provide Comprehensive Services for Late-Stage Kidney Disease and Cardiovascular Care (February 6, 2024). https://www.prnewswire.com/news-releases/sun-life-partners-with-somatus-to-provide-comprehensive-services-for-late-stage-kidney-disease-and-cardiovascular-care-302054040.html
Aetna	Insurer	Monogram Health	CVS' Aetna Expands Into Home Kidney Care (February 14, 2024). https://www.beckerspayer.com/payer/cvs-aetna-expands-into-kidney-care.html
Medical Mutual (Ohio)	Insurer	Strive Health	Fierce Healthcare: Medical Mutual Partners With Strive Health (February 20, 2024). https://strivehealth.com/news/fierce-healthcare-medical-mutual-partners-with-strive-health/
Humana (expansion)	Insurer	Strive Health	Humana and Strive Health Announce Expansion of Holistic, Patient-Centered Care for People with Kidney Disease (March 5, 2024). https://www.businesswire.com/news/home/20240305671765/en/Humana-and-Strive-Health-Announce-Expansion-of-Holistic-Patient-Centered-Care-for-People-with-Kidney-Disease
The Kidney and Hypertension Center (Ohio)	Private practice	Panoramic Health	Panoramic Health and The Kidney and Hypertension Center Join Forces to Elevate Kidney Care in Ohio (March 19, 2024). https://panoramichealth.com/news-and-events/panoramic-health-and-the-kidney-and-hypertension-center-join-forces-to-elevate-kidney-care-in-ohio/
West Virginia University Medicine	Academic practice	Interwell Health	WVU Medicine Joins Interwell Health Network to Bring Value-Based Kidney Care to West Virginia (March 26, 2024). https://wvumedicine.org/news-feed/news-article/WVU-Medicine/Ruby-Memorial-Hospital/wvu-medicine-joins-interwell-health-network-to-bring-value-based-kidney-care-to-west-virginia/
Triple-S Salud (Blue Cross Blue Shield)	Insurer	Healthmap Solutions	Healthmap Solutions Celebrates Puerto Rico Office Grand Opening and Ribbon-Cutting Ceremony (April 8, 2024). https://news.healthmapsolutions.com/blog/healthmap-solutions-celebrates-puerto-rico-office-grand-opening-and-ribbon-cutting-ceremony
Western Nephrology	Private practice	Evergreen	Evergreen Nephrology and Western Nephrology Partner to Raise the Standard of Kidney Care (May 14, 2024). https://www.prnewswire.com/news-releases/evergreen-nephrology-and-western-nephrology-partner-to-raise-the-standard-of-kidney-care-302145062.html
Western Kentucky Kidney Specialists	Private practice	Evergreen	Evergreen Nephrology and Western Kentucky Kidney Specialists Announce Partnership (May 29, 2024). https://www.prnewswire.com/news-releases/evergreen-nephrology-and-western-kentucky-kidney-specialists-announce-partnership-302158180.html
Memorial Hermann Health System	Health system	Monogram Health	Monogram Health and Memorial Hermann Join Forces to Improve Outcomes for Patients Impacted by Polychronic Conditions (June 25, 2024). https://www.monogramhealth.com/press/monogram-health-and-memorial-hermann-join-forces-to-improve-outcomesfor-patients-impacted-by-polychronic-conditions

ACO, accountable care organization; VBC, value-based care; WVU, West Virginia University.
[a]Activity from January to June 2024.

ASN Executive Vice President's Update

Four Potential Scenarios for US Nephrology in the 2030s

By Tod Ibrahim

For decades, corporate executives, military strategists, and policymakers have used scenario planning to help anticipate the future and guide strategic thinking. Rather than assess the probability of each scenario, the purpose of this exercise is to remain open minded about the future and not get caught flatfooted "when events don't develop quite as you'd expected" (1).

Developing scenarios for how US nephrology might look in the 2030s requires an understanding of several drivers. For example, due to an aging population and the Affordable Care Act, government will continue to play a large (if not expanded) role in health care, particularly in kidney care because of the Medicare End-Stage Renal Disease (ESRD) program. At the same time, the federal deficit is expected to top $2.6 trillion in 2034 (and the federal debt will reach its highest level ever as a percentage of the nation's gross domestic product), which likely means cuts to (or flat funding for) entitlement programs (like Medicare) and discretionary programs (like the National Institutes of Health) (2).

Additionally, all aspects of US health care are consolidating—from insurers and health systems to dialysis organizations and physician practices (3). Much of this consolidation is fueled by private equity and venture capital, making it motivated by the bottom line and not altruism or the best interest of patients (4). At the same time, interest by private equity and venture capital often indicates medical specialties that are perceived as more successful in delivering care, developing new therapies, and attracting the next generation of health care professionals.

Augmented and artificial intelligence (AI) are accelerating technological advances that will likely increase patient empowerment and decrease clinician autonomy. The biotechnology, medical device, and pharmaceutical industries are producing new therapies at an astonishing rate, and people living with kidney diseases are starting to have hope for the first time in generations.

Historically, physicians in the United States have led a self-regulating profession. Physicians determine the standards for undergraduate, graduate, and continuing medical education through the Liaison Committee for Medical Education, Accreditation Council for Graduate Medical Education (ACGME), and Accreditation Council for Continuing Medical Education, respectively. Through the American Board of Medical Specialties (ABMS) and its 24 member boards—including the American Board of Internal Medicine (ABIM)—physicians define their specialties, subspecialties, and sub-subspecialities. The American Medical Association works "with national medical specialty societies to provide recommended updates and changes directly" to the Centers for Medicare & Medicaid Services (5).

Due to external and internal forces, however, the dominion of this self-regulation has diminished during the past few decades. Insurers and health systems are dictating standards of care, government is inserting itself between patients and their physicians, some physicians are rebelling against recertification (better known as maintenance of certification), and a few states desperate for clinicians are bypassing established requirements for training and credentialing. This tumult has set the stage for greater frustration, dissatisfaction, and burnout that are exacerbated by shortages among physicians and other health care professionals—particularly nurses—throughout the country but especially in rural communities. These struggles are particularly acute in nephrology, as the specialty faces "difficulties in recruitment, a large number of retiring nephrologists, and a growing population of people who need kidney care" (6).

At least four scenarios exist for US nephrology in the 2030s based on these 10 drivers: the role of government, federal funding, consolidation, private equity and venture capital, AI, patient empowerment, industry and new therapies, self-regulation, burnout, and the workforce shortage (Table). Besides being plausible and developed from the 10 drivers, the four scenarios that follow are intended to start a discussion. This discussion will likely lead to the addition of more drivers—such as addressing inequities and disparities in kidney care—and the identification of other scenarios.

In considering these four scenarios for nephrology's future, ask yourself: What do you like and not like about each scenario? Which strategies will contribute to shaping a positive future for nephrology regardless of scenario? In attempting to answer these questions, it is important to focus on the plausible, consider as many drivers as possible (beyond the 10 included in this exercise), and—most important—attempt to determine which scenarios and strategies are in the best interests of the millions of people living with kidney diseases.

Scenario 1: Centralism. *Nephrology remains an internal medicine specialty, incorporates new therapies that slow (even prevent) kidney failure, and continues as is with occasional "tweaks" (like the focus on critical care nephrology or onconephrology).*

This scenario is the most conservative, which means some optimism around new therapies, the focus on intervening earlier, and advances in transplant policy as well as pessimism about the continuation of myriad challenges that nephrology currently faces. Driven by the Medicare ESRD program, dialysis remains the financial axis around which care is organized. Fewer value-based care companies focus solely on kidney health, slowing investment by private equity and venture capital, while consolidation accelerates, particularly among dialysis organizations and nephrology practices.

The federal government continues to underfund kidney research, which means nephrology cedes more ground to other specialties. Simultaneously, there is less investment in kidney-related AI or biotechnology, medical devices, and pharmaceuticals. The lack of public and private funding for kidney research activates kidney advocates who demand more.

Interest in nephrology careers among medical students and residents continues to wane, exacerbating the workforce shortage and increasing burnout among nephrologists. Under this scenario, cardiology fails in establishing its own board recognized by ABMS and separate from ABIM, so nephrology's "position" within ABIM remains minor (7). (At this time, approximately 10,000 of ABIM's estimated 200,000 diplomates are nephrologists, so nephrology only represents 5% of the board's constituents.)

Scenario 2: Connectivism. *This is similar to centralism, in that nephrology stays within internal medicine, but there is more of an effort to either create new specialties or to partner with other specialties (like cardiology, critical care, endocrinology, and oncology).*

Starting with transplant nephrology, ACGME accredits nephrology subspecialties like interventional nephrology. At the same time, nephrology also emulates hematology-oncology and pulmonary-critical care by partnering with other specialties to establish joint fellowship programs like nephrology-cardiology, nephrology-endocrinology, nephrology-critical care, and onconephrology.

Although less traditional than centralism (scenario 1), this scenario includes some optimism (around new therapies, intervening earlier, and advances in transplant policy) and pessimism (because of myriad challenges that nephrology currently faces). Kidney care still revolves around dialysis (and the Medicare ESRD program), the number of value-based care companies focused solely on kidney health declines, investment by private equity and venture slows, and consolidation accelerates.

The federal government continues to underfund kidney research, but individual investigators benefit from more funding in other areas (such as for interventional nephrology or nephrology-cardiology). Similarly, there is less investment in kidney-specific AI or biotechnology, medical devices, and pharmaceuticals, but the subspecialties and combined specialties attract interest. These subspecialties and combined subspecialties also amplify the voice of people living with kidney diseases.

Interest in nephrology careers varies among medical students and residents. Traditional nephrology continues to struggle, but interest increases for subspecialties and combined specialties. Unfortunately, these positive trends are not enough to overcome the workforce shortage or reduce burnout.

Scenario 3: Complementarism. *Cardiology leaves ABIM and forms its own board under ABMS, US medical graduates (USMGs) start to match directly into cardiology, and nephrology and endocrinology shift from internal medicine specialties to join cardiology and form a new specialty.*

Last fall, the American Heart Association issued a "presidential advisory" on "cardiovascular-kidney-metabolic health" to provide "guidance on the definition, staging, prediction paradigms, and holistic approaches to care for patients with cardiovascular-kidney-metabolic syndrome and details a multicomponent vision for effectively and equitably enhancing cardiovascular-kidney-metabolic health in the population" (8). When paired with a potential American Board of Cardiology (or American Board of Cardiorenalmetabolic Health), the presidential advisory "provides a new opportunity to forge strong partnerships

with other clinicians to advance the care of patients with or at risk of CKD [chronic kidney disease] by integrating care for kidney disease, cardiovascular disease, diabetes, obesity, and other metabolic risk factors" (9).

Although losing its unique identity as a specialty, nephrology benefits from a broader profile, increasing both government interest in—and public funding for research to advance—cardiovascular-kidney-metabolic health. Private equity and venture capital pour into this new specialty by expanding AI, increasing industry research, and producing new therapies. The US Food and Drug Administration (FDA) already aligns cardiology and nephrology as a division within the Office of Cardiology, Hematology, Endocrinology and Nephrology in FDA's Center for Drug Evaluation and Research.

Medical students are interested in this new specialty, USMGs match directly into cardiorenalmetabolic residency programs (that lead to additional fellowship training in nephrology), and the pipeline strengthens dramatically. A stronger pipeline results in less burnout and fewer workforce shortages. Historically, 5% to 8% of graduating USMGs have failed to match (including 6.5% in 2024), so this scenario opens additional first-year residency positions (10).

Initially, patient advocacy remains separate among cardiology, kidney diseases, and endocrinology (especially diabetes), which means patient empowerment continues to vary among these three constituencies. People living with kidney diseases struggle to differentiate themselves, complicating efforts to raise public awareness about kidney health.

Scenario 4: Confederationism. *Nephrology evolves to become a mosaic of all three of the previous scenarios by remaining within internal medicine in a traditional way, joining forces with cardiology and endocrinology, creating new specialties, and partnering with existing ones.*

To paraphrase the poet William Butler Yeats, "Things fall apart," nephrology "cannot hold," the specialty is no longer whole, and it splinters to the point of disappearing (11). The lack of a center means consolidation slows, new therapies vary, and self-regulation by nephrologists becomes unimaginably complicated.

While burnout intensifies, the workforce shortages begin to subside due to the sheer number of physicians involved in kidney care. The quality of this care is quite variable, given the confederated nature of expertise in kidney health. Because of the many specialties involved directly and indirectly, the government plays a larger role in kidney care, federal funding for kidney research increases, private equity and venture capital escalate, and AI expands.

Patient empowerment fluctuates depending on the constituency. Kidney-specific advocates demand more, whereas kidney health struggles to differentiate itself when combined with cardiology and endocrinology, included in a new specialty, or partnered with other specialties like critical care. Overall, this variation means people living with kidney diseases are less empowered.

Shaping the best outcome

In *Thinking in Bets: Making Smarter Decisions When You Don't Have All the Facts*, Annie Duke, PhD—a former professional poker player with an academic background in cognitive psychology—observes, "scenario planning reminds us that the future is inherently uncertain. By making that explicit in our decision-making process, we have a more realistic view of the world" (12). These four scenarios are intended to stimulate thinking about nephrology's future, making ASN and the rest of the kidney community "nimbler because we've considered and are prepared for a wider variety of possible futures," Duke notes.

For example, the gastroenterology and hepatology communities came together in 1999 to plan for the future of digestive health in the United States. This effort resulted in important outcomes, such as increasing the length of fellowship training in gastroenterology from 2 to 3 years (and thus, reducing the number of first-year fellowship positions) and earning ACGME accreditation for hepatology fellowship training. According to an article by Don W. Powell, MD, who led this effort 25 years ago, "The most robust strategies succeed in all of the scenarios, while the most powerful strategies contribute to bringing about preferred scenarios" (13).

Together, ASN and the rest of the kidney community will need to adapt to navigate the future, ideally shaping the best outcome for the millions of people living with kidney diseases. If you would like to comment on these scenarios or suggest additional ones, please email me at tibrahim@asn-online.org.

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Table. Ten drivers of US health care

1. Determining the government's role in patient care, health research, and medical education
2. Considering the level of federal funding for care, research, and education
3. Anticipating consolidation by insurers, health systems, dialysis organizations, and physician practices
4. Forecasting investment by private equity and venture capital
5. Tracking the impact of augmented and artificial intelligence
6. Ensuring patients are empowered and self-directed
7. Anticipating new biotechnology, medical device, and pharmaceutical therapies
8. Moderating self-regulation by physicians
9. Recognizing burnout among health professionals, including physicians
10. Predicting workforce shortages

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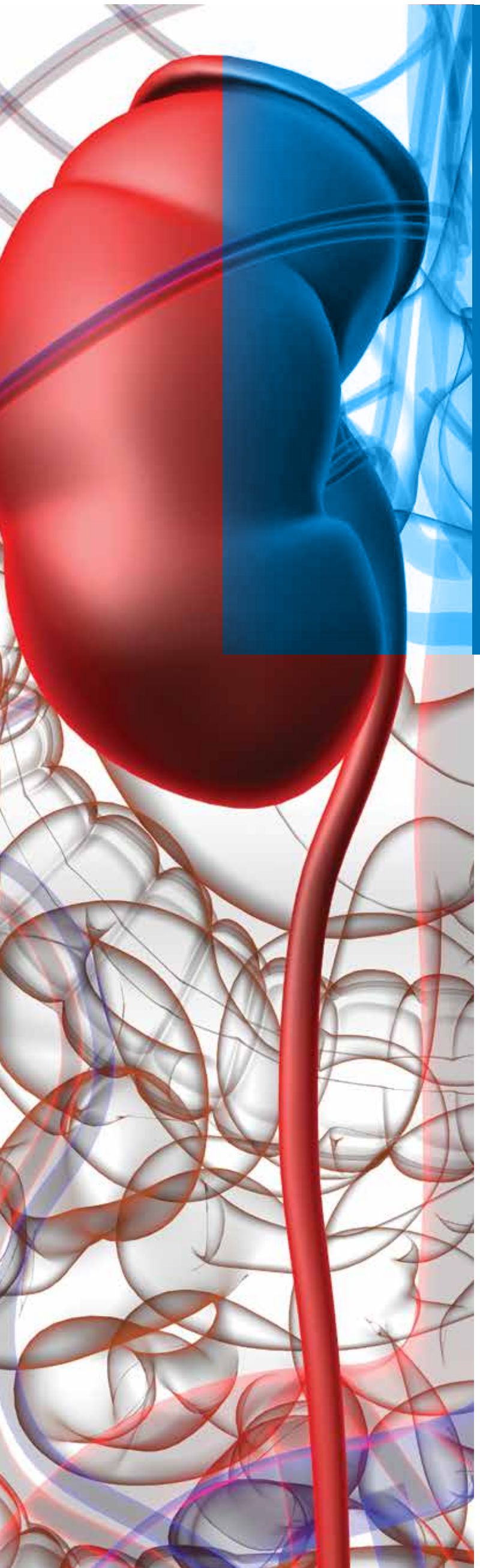

TOXICOLOGY AND KIDNEY HEALTH

The kidneys play a crucial role in filtering waste and toxins from the blood to maintain overall health. Exposure to various environmental and chemical toxins can disrupt kidney development and impair kidney function, leading to severe health consequences. This special section of *Kidney News* explores the complex intersection between toxicology and kidney health, spanning topics from the role of the nephrologist in drug safety to how to treat patients who are poisoned by various agents. *Kidney News* thanks Prakash Gudsoorkar, MD, FASN, for selecting and coediting these articles.

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Pharmacokinetics and Kidney Clearance: A Nephrologist's Role in Drug Safety and Toxicology

By Linda Awdishu

The kidneys play a vital role in eliminating drugs and their metabolites, making it essential for nephrologists to understand pharmacokinetic changes in kidney injury and diseases. Drugs may be excreted by the kidney by glomerular filtration or by tubular secretion via active drug transporters. They may also be reabsorbed from the filtrate across the renal tubular epithelial lining, usually by passive diffusion. Total clearance is the sum of glomerular filtration and tubular secretion minus tubular reabsorption (1). The proximal tubule is the site of elimination for small molecules such as antibiotics, antivirals, diuretics, nonsteroidal anti-inflammatory drugs, and antidiabetic agents (2).

Nephrologists are uniquely positioned to assess kidney function and provide guidance on appropriate drug dosing through daily review of medications and documentation in the problem list (a summary of the patient's relevant clinical information). By evaluating a patient's glomerular filtration rate (GFR) and considering other factors such as age, weight and muscle mass, and comorbidities, nephrologists can recommend the most appropriate biomarkers to order for GFR estimation, provide their estimate of a patient's GFR, and collaborate with pharmacists to optimize the dose to maximize therapeutic efficacy while minimizing toxicity (3). For example, consider a patient with chronic kidney disease (CKD) taking the antiretroviral combination agent dolutegravir/tenofovir alafenamide/emtricitabine, in which dolutegravir interferes with tubular secretion of serum creatinine (SCr) leading to elevations in baseline SCr. In this situation, serum cystatin C may be ordered to better estimate GFR.

In CKD, as GFR declines, changes in pharmacokinetics occur (1). Protein binding may be altered due to conformational changes in albumin-binding sites or occupation of those sites by uremic toxins, impairing binding and increasing the free drug concentration of drugs like phenytoin. Alterations in the drug metabolism have been seen in CKD due to a decreased intrarenal and hepatic metabolism and are generally proportional to the reductions in GFR. In transplant recipients, calcineurin inhibitors are metabolized by cytochrome P450 3A4, and drug–drug interactions can lead to changes in drug exposure. Common interacting drug classes include calcium channel blockers, azole antifungals, rifampin, macrolide antibiotics, and anticonvulsants. Lastly, drugs eliminated by the kidney will require dose adjustment as GFR declines. Drugs

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Pharmacokinetics and Kidney Clearance

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such as gabapentin, baclofen, or cefepime are eliminated by glomerular filtration, necessitating dose adjustment to avoid accumulation and adverse effects such as drowsiness, falls, edema (for gabapentin), and neurotoxicity (for baclofen and cefepime) (4–6). The dose of baclofen should be reduced by 50% for CKD stage 3 and avoided in stages 4–5. Risk of cefepime-associated neurotoxicity increases in CKD stage 4 and is minimized with therapeutic drug monitoring keeping trough concentrations <7.5 mg/L (6).

Acute kidney injury (AKI) can significantly alter drug pharmacokinetics (7). In critical illness, absorption is impaired due to changes in gastrointestinal pH, perfusion, transit time, and intestinal atrophy, resulting in lower drug exposure. Fluid shifts, volume overload, and changes in protein binding can alter drug distribution. In patients who are critically ill, the measured volume of distribution (Vd) can differ from the estimated Vd, as massive hemorrhage, ascites, and other fluctuations in the fluid status commonly occur. Many patient-related factors can alter protein binding, including hypoalbuminemia, systemic pH, hyperbilirubinemia, uremic products, heparin therapy, and other drugs that may act as competitive displacers. In AKI, cytochrome P450 expression is variable, and the degree of reduction in the drug metabolism does not appear to be as great in AKI as in kidney failure (8). Many patients may recover within 48 hours (9), making dose adjustments sometimes unnecessary. Consider temporarily discontinuing certain medications, reducing doses, or switching to alternative therapies until kidney function improves.

Estimating GFR in AKI is challenged by inaccurate estimating equations; nonsteady state equations, measured iohexol clearance, or timed creatinine clearances (CrCls) can be used (10). In critical illness, SCr may be inaccurate, especially in patients with cachexia, muscle wasting, or a prolonged intensive care unit stay; SCr may be lower than expected, leading to an overestimation of kidney function (11). In these cases, nephrologists may need to order cystatin C to identify patients at risk for erroneous dosing, necessitating additional therapeutic drug monitoring. Cystatin C has its own limitations and may be impacted by glucocorticoid use, cancer, thyroid status, inflammation, and obesity (3). Lastly, augmented renal clearance is measured as CrCl > 130 mL/min/1.73 m^2 and is seen in 20%–65% of younger patients who are critically ill with trauma, major surgery, or severe burns. Prompt recognition of augmented renal clearance is paramount to ensuring adequate antimicrobial dosing and avoiding subtherapeutic concentrations (12).

The extent of drug removal by renal replacement therapy (RRT) depends on drug factors such as molecular weight, protein binding, and Vd (7). Most drugs have a molecular weight <500 Da and can be removed by conventional hemofilters with a cutoff of 1500 Da (13). Only the unbound fraction of a drug is cleared by dialysis, and the degree of protein binding is the most important factor to determine whether a drug needs dose adjustment. A drug that is >90% bound to plasma proteins (e.g., ceftriaxone and warfarin) is unlikely to be removed by dialysis; however, it is very likely to be removed by pheresis. The drug sieving coefficient is the capacity of the drug to pass the membrane by convection and can be estimated by the fraction unbound (13). The sieving coefficient is then used to determine the drug clearance (Table). A large Vd reflects distribution outside of the plasma space, resulting in low removal by dialysis and pheresis. Vd is the most important determinant for removal by pheresis therapy. A drug with Vd <1 L/kg is more likely to be removed by RRT; <0.3 L/kg, likely to be removed by pheresis; and >2 L/kg, less likely to be removed by RRT or pheresis (13). Finally, water-soluble drugs are more likely to be removed by dialysis. Antimicrobials such as ceftazidime, ceftriaxone, vancomycin, or aminoglycosides should be administered after pheresis procedures if feasible (14). The important therapy-specific factors include RRT modality, blood and effluent flow rates, and hemofilter characteristics. Continuous RRT may result in more consistent and prolonged drug removal compared with intermittent hemodialysis (IHD), whereas IHD may be favored in intoxications to remove drugs more rapidly. In peritoneal dialysis, the peritoneal membrane's permeability and the drug's physicochemical properties influence removal with conditions such as peritonitis, leading to alterations in drug transport. Therapy-dependent factors such as blood flow rate, effluent flow rates, and administration of replacement fluids before or after filter will affect drug clearance (Table). Lastly, high-flux, high-efficiency dialyzers will have the greatest capacity for removal and can remove drugs with larger molecular weight (e.g., vancomycin, daptomycin). The estimated CrCl for the type of dialysis is summarized in the Table.

Loading doses should be adjusted based on changes in Vd (1). For example, in volume overload, the loading dose of hydrophilic drugs may need to be increased to achieve therapeutic concentrations (13). In the case of digoxin, which has a large Vd, the Vd is altered in CKD, requiring different loading doses. Maintenance doses are adjusted depending on drug pharmacokinetic and dynamic factors (13). For drugs in which a therapeutic effect should be maintained throughout the interval, the dose is reduced, and the interval is maintained (e.g., cephalosporins and time above minimum inhibitory concentration). Sampling blood concentrations should account for removal by the dialysis procedure and re-equilibrium between plasma and tissue compartments (e.g., aminoglycosides, vancomycin). Consider sampling after re-equilibrium is established.

Table. Estimated drug clearance by renal replacement therapy

Dialysis	Effluent rate	Drug clearance
$CVVH_{pre}$	UF + RF	CrCl ~ effluent rate × SC × (Q_b/Q_b + Q_r)
$CVVH_{post}$ CVVHD CVVHDF	UF + RF UF + dialysate + RF UF + dialysate + RF	CrCl ~ effluent rate × SC
IHD		CrCl < 10 mL/min
PD		CrCl < 10 mL/min

Adapted from Jang and Awdishu (13). CVVHD, continuous venovenous hemodialysis; CVVHDF, continuous venovenous hemodiafiltration; $CVVH_{post}$, continuous venovenous hemofiltration with postfilter replacement fluid; $CVVH_{pre}$, continuous venovenous hemofiltration with prefilter replacement fluid; PD, peritoneal dialysis; Q_b, blood flow rate; Q_r, replacement fluid rate; RF, replacement fluid; SC, sieving coefficient; UF, ultrafiltration.

Nephrologists play a vital role in collaborating with other health care professionals and educating patients about their estimated GFR and the optimal selection of drugs and doses to maximize efficacy and to reduce adverse effects. ■

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Environmental Justice and Kidney Health: Toxic Exposures in Vulnerable Populations

By Abhijit V. Kshirsagar and Cassandra R. O'Lenick

There is a growing understanding that the health of the physical environment relates directly to the health of its communities and individuals. Exposure to human-made and naturally occurring toxins in the air, water, and soil can lead to tissue accumulation and injury, organ dysfunction, and ultimately contribute to morbidity and mortality. Common environmental pollutants include fine particulate matter (PM) with an aerodynamic diameter of ≤2.5 μm ($PM_{2.5}$), heavy metals (arsenic, cadmium, lead, and mercury), pesticides and herbicides, and perfluorinated alkylated substances (commonly known as forever chemicals). Additionally, transient environmental events such as heat waves, wildfires, and natural disasters—globally increasing in frequency and intensity—are known to have direct effects on human health, as well as contributing to higher exposures to pollutant mixtures (e.g., polluted floodwaters and wildfire smoke) and damage to infrastructure.

Individuals with underlying kidney diseases are especially susceptible to the effects of environmental toxins, presumably from their high underlying comorbidity burden. Of the environmental toxins, $PM_{2.5}$ has been the most widely studied and has been shown to associate with 1) reduced glomerular filtration rate, 2) progressive kidney diseases among the general population and among selected individuals with glomerular disease, and 3) increased hospitalizations and mortality among patients receiving maintenance dialysis. Heavy metals lead to specific types of tubular and interstitial kidney injury, whereas the pesticides, herbicides, and forever chemicals have been postulated to lead to kidney diseases based on the known property of the chemicals, but mechanistic and epidemiological evidence is limited.

The effects of heat, including transient elevations, on kidney injury have been studied primarily in the context of community-acquired acute kidney injury and chronic kidney disease (CKD) of unknown etiology (CKDu) or CKD of nontraditional origin (CKDnt). CKDu or CKDnt often occurs among individuals engaged in intense manual labor in hot environments. A multiagency-sponsored consortium study is underway to investigate the independent and joint effects of heat, toxic pollutant exposures, and medication use on CKDu or CKDnt among outdoor workers (1). Furthermore, recent studies have demonstrated that extreme heat events are associated with increased hospitalizations and mortality for patients receiving in-center hemodialysis (2) and that natural disasters in the Americas have had an immediate impact on the ability of populations on dialysis to receive maintenance dialysis due to closure of dialysis centers, lack of electricity and clean water, and disruptions to the transportation infrastructure (3).

Concurrently, there is growing evidence that the health impacts from the environment are inequitably distributed among populations nationally and internationally according to wealth, race, and ethnicity. In the United States, racially discriminatory practices and policies, such as placement of transportation infrastructure, industrial siting, and redlining, have resulted in racial and ethnic minorities and socially marginalized communities experiencing greater exposure to urban heat and closer residential proximity to diverse sources of air and water pollution. A body of research has demonstrated that socially marginalized communities with Black and Hispanic populations, who are disproportionately impacted by CKD, are exposed to higher concentrations of $PM_{2.5}$, heavy metals (4), and forever chemicals (5) and experience greater urban heat island intensity (6). These environmental exposures do not occur in isolation, resulting in higher rates of exposure to multiple pollutants and adverse health impacts that are further compounded by poverty and a lack of access to resources. Indeed, distance to major roads, a proxy indicator for exposure to traffic-related air pollution as well as community economic status, is associated with low kidney function (7). A recent study in China of short-term air pollution exposure and kidney function among adults reported that the effects of a multipollutant mixture exceeded that of single pollutants (8). Although improvements to air quality have occurred in many industrialized countries, over the last decade, the United States has experienced widening disparities in $PM_{2.5}$ concentrations and greater health impacts among racial and ethnic minority groups (9). Climate change and its associated hazards are likely to deepen existing disparities, resulting from past and present structural racism or colonialism among communities, countries, continents, and hemispheres.

Environmental justice (EJ) emerged from the Civil Rights Movement of the 1960s to confront environmental racism (10). One of its first examples arose in North Carolina. In 1982, the low-income and majority African American community of Shocco Township protested the state's decision to dispose of dirt contaminated with polychlorinated biphenyl in their community. Over time, EJ has evolved to seek the promotion of an equitable distribution of environmental benefits and burdens among all populations, or a fairness concerning the processes and procedures (i.e., policies and enforcement) that lead to the distribution of environmental benefits and burdens.

As we study the impact of environmental toxins among vulnerable populations, it is crucial to examine it through the lens of EJ. Exposure to environmental toxins may be modifiable through individual and collective efforts locally, nationally, and internationally—ultimately leading to a reduction in the burden of kidney diseases. Yet, without using the research to promote equitable policies and enforcement, we are at risk for merely describing and indirectly perpetuating existing disparities. ■

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A Silent Threat: Perinatal Exposure to Nephrotoxins Linked With Risk of Hypertension and Kidney Diseases

By Simran Aggarwal, Jhanahan Sriranjan, and Rahul Chanchlani

Kidney development represents one of the earliest yet sustained developmental processes occurring in utero and in early childhood. Although nephrogenesis continues for up to 35 weeks' gestation, the final processes of maturation, including renal vascular development and glomerular filtration, can continue until nearly 2 years of age (1). Disruption to these critical periods of kidney development has been linked to reduced kidney mass and nephron number in adulthood and the subsequent development of chronic illnesses including hypertension and chronic kidney disease (CKD) (1). CKD and hypertension are responsible for an estimated 5 to 11 million deaths annually, although the downstream metabolic consequences of these diseases, including the development of cardiovascular disease, further highlight the global impact they have on morbidity and mortality (2–4).

In recent years, the association between perinatal environmental exposures and an increased risk for developing adult diseases has garnered growing attention. Numerous studies have highlighted the mechanisms through which exposure to pollutants, such as heavy metals, endocrine disruptors, and air pollutants, during the perinatal period may predispose fetuses and young children toward later developing CKD and/or hypertension (Table) (5). These exposures are increasingly recognized as harmful yet potentially modifiable risk factors for the development of these diseases and may be important targets for future research and legislation.

In utero, the developing fetus is reliant on the transplacental exchange of nutrients and waste products to maintain appropriate homeostasis. Although this is a highly efficient process, maternal exposures to specific environmental chemicals may subsequently expose developing fetuses to potent nephrotoxins. This can lead to a cascade of structural and functional alterations leading to glomerular hypertrophy, increased apoptosis leading to fibrosis and tubular injury, oxidative stress, and disruption of signalling pathways including the renin-angiotensin system and aryl hydrocarbon receptor pathway (5).

Air pollutants, including fine particulate matter, ozone, and polycyclic aromatic hydrocarbons, are ubiquitous, particularly in urban areas, and have been frequently linked to poor kidney outcomes including CKD and hypertension (6). Maternal exposures during the second and third trimesters to such pollutants have been associated with hypertension in infancy and early childhood, with sustained increases persisting into late childhood (7–9).

Heavy metals are another class of environmental toxins linked to nephrotoxicity and hypertension in children. For example, lead exposure, even at low levels, during pregnancy has been associated with increased systolic blood pressure in early childhood, particularly among infants born prematurely (<37 weeks' gestational age), in whom nephrogenesis is already disrupted (10). Cadmium is another metal that has nephrotoxic properties and has been associated with worsening markers of kidney injury with cumulative exposure (11).

Finally, endocrine disruptors, such as bisphenol A and phthalates, are another significant category of environmental toxins that have been postulated to affect risk of developing kidney diseases, although few studies have examined the effects of maternal exposures on childhood risk of CKD or hypertension, and this remains an area of research needing further exploration (6).

Implications of these findings extend beyond individual health outcomes and represent significant challenges for health care systems globally. In the United States, the total direct medical cost of CKD is projected to triple to $818 billion per year, with similar trends expected globally (12, 13). Addressing this issue requires a multifaceted approach guided by research initiatives and legislation. Research in this field is still relatively new, and only a limited number of environmental chemical classes have been investigated (6). Further research in this area needs to be supported that focuses on the independent effects of perinatal exposures to environmental chemicals on childhood outcomes, including particular attention to time- and dose-dependent effects of specific stressors (5). In addition, stricter regulations on the use of harmful chemicals and pollutants and increased public awareness and education, including careful product-labeling practices, need to be prioritized in high-risk environments, such as urban city centers and commercial and industrial areas.

The link between perinatal exposure to environmental toxins and the risk of hypertension and kidney diseases highlights a pressing public health issue. By advocating for stricter regulations, promoting awareness, and investing in research, we can mitigate the silent threat posed by these insidious toxins. ■

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Table. Common toxins, effects, and sources of perinatal exposures on kidney function and development

Toxins (references)	Effects	Major sources
Air pollutants		
Particulate matter (5–9)	Reduced kidney function, hypertension, and increased blood pressure	Burning of fossil fuels, industrial processes, solvent use, agriculture, and waste treatment
Polycyclic aromatic hydrocarbon (5, 6)	Reduced kidney function, proteinuria, and hypertension	Cigarette smoke; incomplete combustion of coal, oil, and gas; and charbroiled meat
Heavy metals		
Lead (5, 6, 10)	Increased systolic blood pressure at 4–6 years of age, especially in preterm infants	Soil and dust (paint, gasoline, and industrial sources), drinking water, and cigarette smoke
Cadmium (5, 6, 11)	Markers of kidney dysfunction, including creatinine, cystatin C, and blood nitrogen urea	Fossil fuel combustion, phosphate fertilizers, batteries, and contaminated food
Mercury (5, 6)	Proximal tubular damage and necrosis of tubular epithelial cells from chronic exposure	Coal-fired power plants, smelters, and municipal waste incineration
2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (5, 6)	Fibrosis, which may lead to hydronephrosis and over-reliance on healthy tubular epithelial cells, ultimately leading to reduced kidney function, proteinuria, and hypertension	Consumption of animal products with high fat content, manufacturing of pesticides, bleaching of wood pulp, and waste incineration
Melamine (5, 14)	Nephrolithiasis and chronic kidney inflammation, secondary to tubular dilatation and interstitial edema from high doses	Plastics, dishware, kitchenware, commercial filters, laminates, adhesives, molding compounds, coatings, and flame retardants
Minocycline	Reduced glomerular filtration rate and increased blood pressure	Antibiotic, primarily used for management of acne vulgaris
Perfluorobutane sulfonate (5, 15)	Dysregulation of renin-angiotensin-aldosterone system expression	Water, oil, soil, and grease repellents for use on paper and packaging; carpets and fabrics; and fire-fighting foams
Endocrine disruptors		
Glucocorticoids (5)	Reduced nephron number and functional kidney mass, renal injury, glomerulosclerosis, reduced glomerular filtration rate, and proteinuria from exposure during late gestation	Released in response to environmental stress and given to women at risk of preterm delivery
Bisphenol A (5, 6)	Glomerular abnormalities, impaired nephrogenesis, and hypertension in adult offspring	Plastic containers, lenses, medical tubing, and devices
Phthalates (5, 6)	Reduced kidney function, albuminuria, and hypertension	Vinyl plastics, shampoos, cosmetics, food packaging, medical tubing, and devices
Perfluoroalkyl and polyfluoroalkyl substances (6)	Reduced kidney function and hypertension	Electrochemical fluorination, telomerization, surfactants, food packaging, nonstick cooking surfaces, surface protection agents, and fire-retarding foams
Other		
Nicotine (5)	Reduced kidney weight and congenital urogenital malformations	Various smoking products such as cigarettes, vapes, and e-cigarettes

Paraquat Poisoning 101 for the Nephrologist

By Nikhil Saxena and Divya Bajpai

Paraquat (1,1′-dimethyl-4,4′-bipyridinium dichloride) is a highly potent nonselective contact herbicide that is inexpensive and widely used in Southeast Asia, the Americas, and the Pacific (1). Although short-term dermal contact is relatively safe, ingestion has a very high fatality case rate (up to 60%–80%) (2), with a lethal dose as low as 30 mg/kg (10–20 mL of 20% solution) (1, 2). Intoxication—either accidental or deliberate—primarily happens via ingestion or inhalation, and it is a significant health concern, especially in agricultural communities.

Following ingestion, the stomach absorbs 20% of the poison, which is rapidly distributed to tissues with high blood flow and energy requirements (lungs, kidneys, liver, and muscles). Peak tissue concentrations are reached in 6 hours. Intracellularly, paraquat is oxidized in the presence of nicotinamide adenine dinucleotide phosphate hydrogen (NADPH) cytochrome P450 reductase and nitric oxide synthase, generating superoxide, peroxynitrite, and hydroxyl radicals (3). These free radicals lead to increased expression of nuclear factor-κB and activation of nucleotide-binding oligomerization domain, leucine-rich repeat, and pyrin (NLRP) inflammasome, ultimately leading to the generation of cytokines, including interleukin-1β, interleukin-18, and tumor necrosis factor α. Paraquat also induces the intracellular activity of death-associated protein kinase, which is required to assemble the NLRP protein 3 (NLRP3) inflammasome. Ultimately, NADPH depletion and free radical generation cause mitochondrial and cell membrane damage, nuclear condensation, and DNA fragmentation, culminating in apoptosis.

Paraquat is excreted, primarily unchanged by the kidneys, within 24 hours in cases of minor poisoning. However, the half-life can exceed 100 hours in patients with acute kidney injury (AKI) (4); this increases systemic exposure and worsens its toxicity. The toxin is secreted in the proximal tubular epithelial cells in the kidneys, causing tubular injury and AKI. Although there is a rapid decline in the glomerular filtration rate following paraquat ingestion, the rise in creatinine is disproportionately high (attributed to oxidative stress). Acidosis seen in the context of paraquat poisoning also increases creatinine production. It has also been hypothesized that paraquat acts as a noncompetitive inhibitor of paraquat uptake at the level of the renal tubule. Hence, cystatin C is believed to be a better marker of kidney function in patients with AKI following paraquat ingestion (5). Unlike AKI, which occurs early and reduces over a few weeks (6), lung injury is usually a delayed complication that presents as progressive pulmonary fibrosis over weeks and leads to mortality due to respiratory failure. Acute hepatitis and pancreatitis are also reported.

Initial symptoms include severe corrosive oral burns, nausea, vomiting, and abdominal pain. A generalized burning skin sensation is a sign of systemic toxicity associated with mortality. Patients with hypoxia requiring oxygen therapy almost uniformly have fatal outcomes. Ages older than 50 years, the presence of underlying kidney diseases, and development of AKI are associated with mortality. The Severity Index of Paraquat Poisoning score is a significant predictor for the development of AKI and subsequent survival (likely with a score <10%) (7). It is calculated by multiplying the time from paraquat ingestion to intensive treatment and serum paraquat levels at admission. A urine or serum dithionite test and serum paraquat concentration remain the gold standards for diagnosis. Initially, alkalemia may be present due to excessive vomiting, which later becomes lactic acidosis and respiratory acidosis. Interestingly, some ecological studies have linked chronic exposure of paraquat to the development of chronic kidney disease; however, this needs further evaluation (8).

The treatment of paraquat poisoning is primarily supportive, and none of the treatment modalities shows benefit in later stages, even when used aggressively in combination. Decontamination with activated charcoal or Fuller's earth is recommended within 2–4 hours of ingestion. The latter is preferred, as clay inactivates paraquat. Gastric lavage is contraindicated (5). Resuscitation with

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large volumes of crystalloids may be required in patients with delayed presentation to avoid hypovolemia. Oxygen therapy must not be administered until hypoxia is confirmed, as it exacerbates free radical injury. Extracorporeal therapy (hemoperfusion or hemodialysis) for toxin removal is useful only within the first 4 hours of paraquat ingestion.

The efficacy of hemoperfusion in paraquat poisoning is also controversial, as it does not reduce uptake in the lungs, and the toxin may rebound from tissues after the procedure. Once AKI sets in, the hemodialysis indications are as per standard indications. Hemoperfusion reduces paraquat absorbed by the lungs by a negligible amount (9). Alveolar inflammation following paraquat ingestion has been treated by intravenous high-dose dexamethasone and cyclophosphamide in smaller studies with equivocal results (10).

Other experimental therapies include antioxidants (N-acetylcysteine, high-dose vitamin C), salicylic acid, deferoxamine, and vitamin E. Edaravone is being evaluated in paraquat poisoning, which, owing to its antioxidant and anti-inflammatory properties, can delay the development of AKI and pulmonary fibrosis (11).

Owing to its lethal nature, the use of paraquat has been banned in the European Union, Sri Lanka, Kuwait, South Korea, Indonesia, and the Philippines. However, it continues to be widely used throughout Mexico, the United States, Latin America, and Southeast Asia due to its low cost and effective results as an herbicide and pesticide (12). It is time to give a clarion call to authorities to either ban this toxin or restrict its availability to only licensed pesticide applicators in nonresidential areas to reduce fatal human exposures. ■

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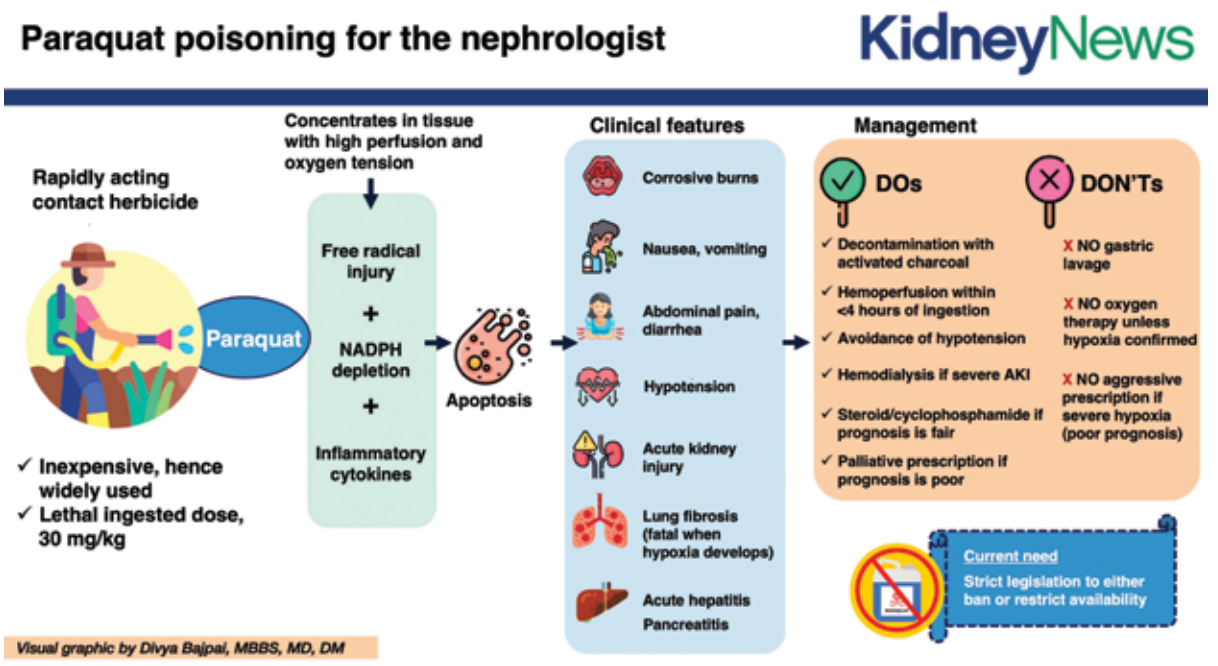

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Approach to a Poisoned Patient: Fundamentals Nephrologists Need to Know

By Mythri Shankar

The World Health Organization estimates that 3 million cases of intoxication occur globally each year due to various toxic agents, according to a recent article in the *Journal of Family Medicine and Primary Care* (1). Treatment of an individual who is poisoned starts with providing supportive care, evaluating organ dysfunction, and identifying potential or confirmed toxins. It is important to consider the likelihood of multiple substances being ingested, especially in cases of deliberate exposure or suicide attempts.

Most poisonings occur through ingestion, with enteric decontamination aimed at preventing toxin absorption from the gastrointestinal tract. This typically includes activated charcoal, which adsorbs various toxins if administered within 1 hour of consuming the toxin (2). Other methods like gastric lavage, cathartics, and ipecac-induced emesis are generally not recommended due to a lack of evidence for a clinical benefit and potential risks, such as aspiration and pneumonitis. Whole bowel irrigation may be beneficial in specific instances involving sustained-release or enteric-coated drugs or ingesting substances such as lithium, iron, or potassium tablets. However, it is generally not advised as a routine procedure and is contraindicated in patients with bowel complications (3).

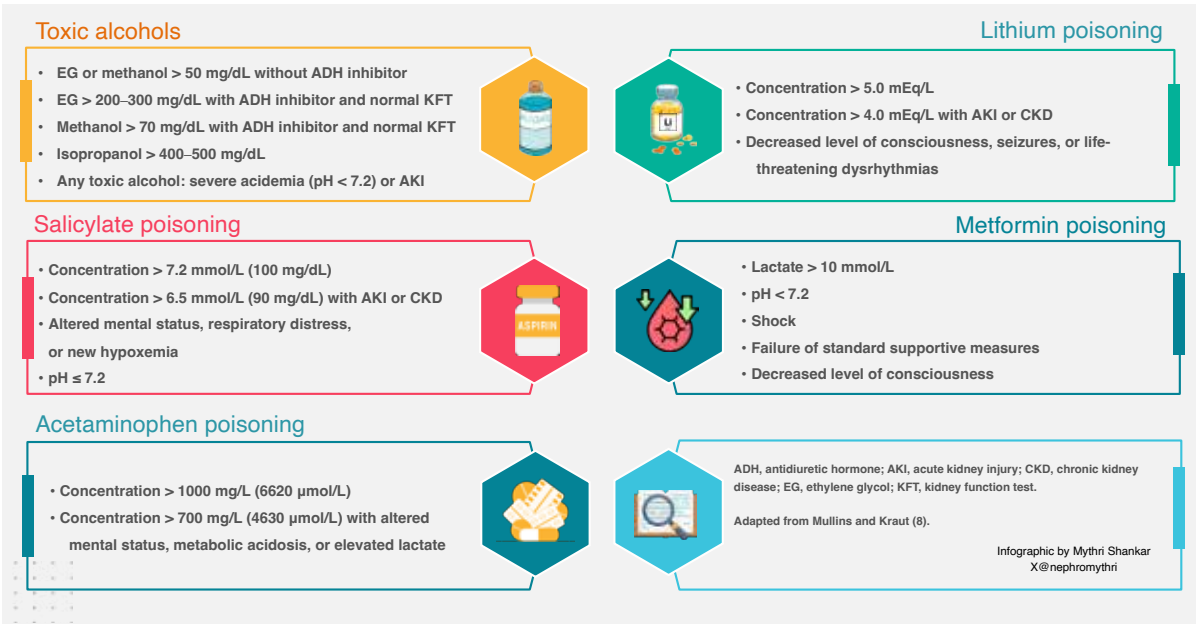
Antidotes mitigate toxicity using mechanisms like competitive receptor antagonism, accelerating the metabolism of the toxin to less harmful substances, inhibiting the production of toxic metabolites, promoting immune clearance, and exerting various other molecular effects (4) (Table).

Intravenous lipid emulsion (Intralipid 20%) (5) is suggested off-label for strong poisoning from local anesthetics such as bupivacaine, which can cause cardiac arrest, and intractable cases with amitriptyline and bupropion. However, caution is advised because of possible adverse effects, including fat embolism, lung injury, and complications while performing extracorporeal membrane oxygenation.

Enhancing elimination techniques involve increasing the clearance of drugs or toxins by modulating urinary pH (6), ion trapping, diuresis, or forced diuresis (7) and using enteric decontamination and extracorporeal therapies. Drug excretion is enhanced by ion trapping by adjusting urine pH to ensure that drugs remain ionized within the urinary lumen, thus preventing reabsorption. For instance, increasing the urine pH above 7.5 can significantly enhance the elimination of salicylates, which are weak acids, by keeping them in an ionized state (6). Conversely, acidification of urine can increase the clearance of basic drugs like amphetamines by maintaining a low urine pH. These maneuvers, however, require careful monitoring of electrolytes and pH levels due to potential complications such as alkalosis and hypokalemia. Alkalinization is also used in managing moderate salicylate poisoning and as part of the strategy to prevent toxicity from high-dose methotrexate. However, acidification is generally discouraged due to risks like exacerbating myoglobinuric renal injury.

Intermittent hemodialysis, using high-efficiency and high-flux biocompatible synthetic membranes, is the most common extracorporeal modality used for poisoning treatment, with hemofiltration being used occasionally and hemoperfusion very rarely. Clinical indications for dialysis

Figure. Indications for hemodialysis in poisoning



include patients with deteriorating conditions despite supportive care, acute kidney injury, electrolyte disturbance, or acid-base imbalances (Figure) (8). Hemodialysis factors influencing drug removal include molecular weight (preferably <500 Da), water solubility, the degree of protein binding, distribution volume, and the equilibration rate from tissue to plasma. Modern dialyzers enhance this process by allowing both diffusive and convective solute removal, effectively clearing substances like lithium, methanol, ethylene glycol, and salicylates (9).

Hemofiltration targets larger molecules up to 50,000 Da, which is especially useful for drugs with large distribution volumes or slow plasma equilibration. It is often used in continuous modes like continuous venovenous hemofiltration for patients who are hemodynamically unstable. Hemoperfusion, although less frequently used due to its limitations and cost, involves drug adsorption from blood using activated charcoal or resin columns. It effectively removes a range of molecules from 100 to 40,000 Da. Despite its specific use for certain poisonings like paraquat, hemodialysis with high-flux membranes has largely supplanted hemoperfusion due to its broader applicability, lower cost, and higher solute clearance capabilities.

Peritoneal dialysis is usually used in younger children when other extracorporeal therapies are unavailable. Patients who are already on peritoneal dialysis can perform rapid exchanges for removing dialyzable drugs.

Chelation therapy uses chelators to bind and excrete toxic metals from the body. It is commonly applied to treat metal intoxications such as arsenic, lead, and mercury, which are known neurotoxins. Chelation therapy must be approached with caution due to the potential depletion of essential minerals such as copper, selenium, zinc, and magnesium, necessitating close monitoring for deficiencies.

Combining chelation with extracorporeal detoxification methods, such as dialysis or hemofiltration, enhances the removal of metal-chelator complexes. For example, deferoxamine treats iron overload when used with high-flux polysulfone membranes compared with charcoal hemoperfusion. The pairing of dimercaptosuccinic acid or dimercaptopropane sulfonate with dialysis has shown promise in managing heavy metal toxicity, particularly in kidney dysfunction.

A novel method involving displacer-augmented hemodialysis has been developed to enhance the clearance of highly protein-bound toxins. This technique uses competitive binding inhibitors like ibuprofen to displace toxins from albumin, thereby increasing their unbound fraction and removal efficiency during dialysis. This approach could revolutionize the treatment of poisoning from highly protein-bound drugs. Specifically, studies are done by using ibuprofen for carbamazepine and aspirin for phenytoin intoxication. ■

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Table. Antidotes for drug overdoses and poisoning

Antidote	Poisoning or overdose
Antivenom	Snake (rattlesnake/*Crotalidae*, coral/*Micrurus fulvius*), spider (black widow/*Latrodectus mactans*), scorpion, and other causes of envenomation
Atropine and pralidoxime	Organophosphate
Diazepam	Chloroquine
Digoxin immune Fab (Digibind)	Digoxin or oleander
Flumazenil	Benzodiazepine
Fomepizole	Methanol and ethylene glycol
Glucagon	Beta-blocker
Glucarpidase	Methotrexate or nephrotoxicity
Hydroxocobalamin, amyl nitrite, sodium nitrite, and sodium thiosulfate	Cyanide
Idarucizumab (Praxbind)	Dabigatran (Pradaxa)
Methylene blue	Methemoglobinemia, carbon monoxide, and cyanide
N-Acetylcysteine	Paracetamol
Naloxone	Opiate and opioid
Octreotide	Hypoglycemia (oral)
Phentolamine	Vasopressor extravasation
Physostigmine	Atropine or datura
Phytonadione/vitamin K	Warfarin
Prothrombin complex	Anticoagulant
Pyridoxine	Isoniazid
Sodium bicarbonate	Tricyclic antidepressant and ion trapping in salicylate

Adapted from Ornillo and Harbord (10).

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Envenomation for the Nephrologist

By Sachin Naik and Divya Bajpai

Envenomation is a significant yet underreported cause of community-acquired acute kidney injury (AKI) in warm tropical and subtropical areas of South Asia, Central and South America, the Middle East, Sub-Saharan Africa, Australia, and the Pacific Islands (1). Kidneys are specifically vulnerable to toxins from snakes, scorpions, spiders, bees, wasps, and certain marine animals. These "neglected tropical diseases" disproportionately affect populations with limited income in rural areas and children (2).

Snake envenomation

According to a recent World Health Organization estimate, approximately 5.4 million people worldwide are bitten by snakes, resulting in 1.8 to 2.7 million envenomations and 140,000 deaths each year (1). Snake envenomation is a medical emergency with severe kidney complications. Most venomous snakes belong to either the Elapidae or Viperidae family. Kidney involvement is more common with hemotoxic (Viperidae) and myotoxic (Viperidae, sea snakes) snakes, with AKI incidence ranging from 8% to 60% and mortality rates up to 45% (3). However, some Elapidae (neurotoxic) species can also cause local tissue injury, leading to rhabdomyolysis and AKI.

AKI following snake envenomation is multifactorial due to the direct and indirect effects of snake venom. The different mechanisms by which venom induces kidney damage include direct nephrotoxicity, a systemic inflammatory response causing oxidative stress, hemodynamic collapse leading to kidney ischemia, hemolysis leading to hemoglobinuria, rhabdomyolysis leading to myoglobinuria, and venom-induced consumption coagulopathy causing thrombi in renal microvasculature (4) (as shown in the visual graphic). Kidney histopathology may show acute tubular necrosis, cortical necrosis, pigment nephropathy, thrombotic microangiopathy, and acute interstitial nephritis. Rarely is proliferative glomerulonephritis with crescents reported with Russell's viper and Echis carinatus bites (5).

Early diagnosis and timely management are the keys to improved outcomes (Table). Clinical findings evolve with time, and AKI onset may vary from hours to days after envenomation, depending on the type and the amount of venom injected. Patients may present with bleeding, local tissue necrosis, hypotension, tachycardia, muscle cramps, oliguria, red- or brown-colored urine, elevated serum creatinine, and electrolyte imbalances. Management involves supportive care and prompt administration of species-specific antivenom to neutralize the circulating toxin. Outcomes range from death, persistent kidney failure requiring dialysis, and partial or complete kidney recovery. Progression to chronic kidney disease (CKD) is reported in up to 30%–40% of survivors (6). This can further strain the overwhelmed kidney care infrastructure in resource-limited countries, which are commonly affected by envenomation.

Other venoms and kidney injury

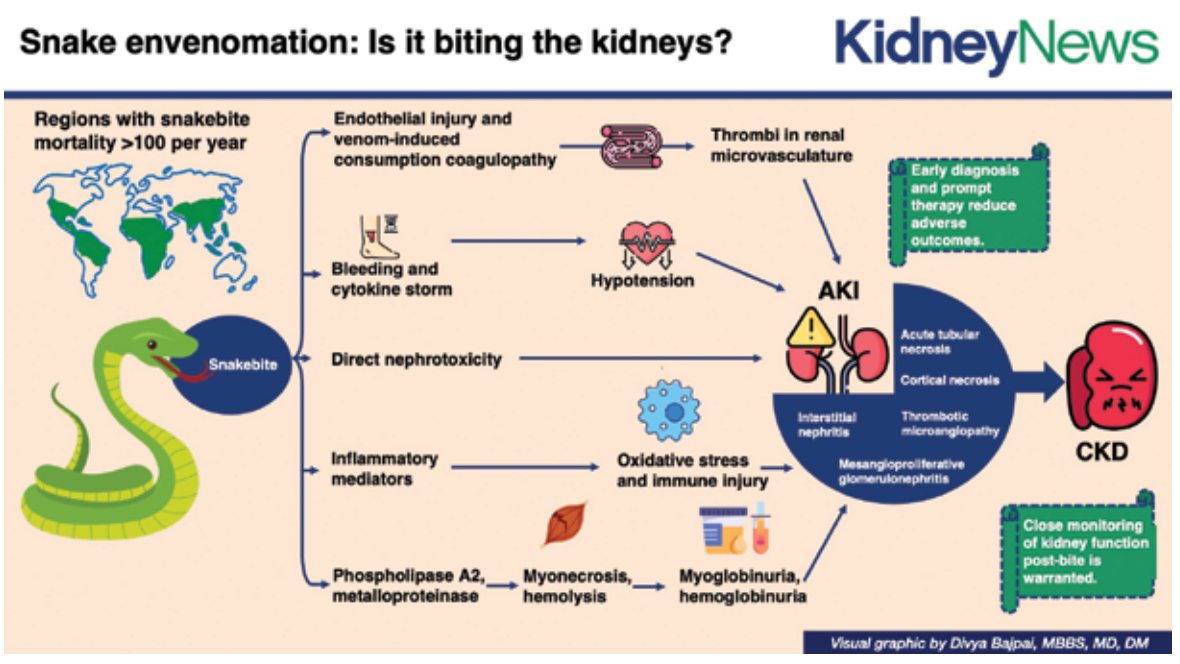
Scorpion venom contains a variety of neurotoxins that disrupt ion channels, causing a massive release of neurotransmitters. This results in an "autonomic storm" characterized by severe circulatory disturbances with either hypertension or hypotension and arrhythmias. Kidney injury occurs due to direct nephrotoxicity or due to kidney ischemia (7). Management includes using antivenom, prazosin, and atropine if bradycardia is present. In some cases of wasp and bee stings, severe anaphylactic reactions and kidney injury can be seen due to hemolysis, rhabdomyolysis, hypotension, direct toxicity, and rarely acute interstitial nephritis (8, 9). Due to the lack of specific antivenoms, the management mainly includes supportive care.

Marine envenomation leading to AKI is generally caused by bites or stings from sea snakes, jellyfish, and sea anemones (10, 11). AKI results from severe muscle damage leading to acute tubular necrosis. Early identification and administration of venom-specific antidotes are warranted.

These sinister neglected tropical diseases caused by toxic envenomation mandate a call to action from the local and international medical fraternity. Vital strategies include sensitizing at-risk populations and improving access to early care, ensuring widespread availability to species-specific antivenom, minimizing the "bite-to-needle" time, standardized treatment protocols for supportive care, timely management of AKI and electrolyte disturbances, and long-term monitoring of kidney function in patients with partial kidney recovery. ■

Table. Dos and don'ts in the management of snake envenomation

DO	DON'T
Immobilize the injured part of the body in a functional position with a splint.	Do not allow the victim to walk because exertion and, with bite wounds on the lower extremity, local muscle contraction may increase snake venom absorption.
Transport the patient to the nearest medical facility as quickly as possible.	Do not implement local incision, oral or mechanical suction, or cryotherapy.
	Do not apply tourniquets.
Apply pressure immobilization in the case of purely neurotoxic snakebites with no local tissue damage.	Do not remove pressure immobilization until monitoring and complete assessment are done, and, if needed, antivenom is injected.
Management DOs	
Airway, breathing, and circulation stabilization	
Respiratory failure may require immediate airway support with oxygen and bag-mask ventilation followed by prompt, rapid sequence intubation.	
A 20-minute whole blood-clotting test at admission, repeated at 6 hours	
Rapid infusion of balanced crystalloid solution or blood to correct hypotension	
Pain management with acetaminophen (paracetamol), morphine, or codeine phosphate, avoiding nonsteroidal anti-inflammatory drugs	
Closely monitor volume status, as there is risk of pulmonary edema.	
Watch for electrolyte and acid–base disturbances.	
In cases of severe AKI, in which conservative measures fail, dialysis may be necessary. Both intermittent hemodialysis and continuous renal replacement therapy have shown benefit.	
Initiation of antibiotics covering both aerobic and anaerobic microbes may be indicated depending on the severity of the wound.	
Antisnake venom (ASV) administration: ➤ Monovalent or polyvalent ASV can be used. ➤ ASV should only be administered if there is a sign of envenomation such as coagulopathy, hemorrhages, neurotoxicity, nephrotoxicity, myotoxicity, cardiotoxicity, and rapid extension of local swelling. ➤ Give intravenous administration, and monitor closely for any allergic reactions during administration. ➤ Dosing is determined by the snake species, individual patient characteristics, and average amount of venom expected from the snakebite. ➤ Monitor the response to the ASV in the form of stoppage of active bleeding and improvement in whole blood-clotting time, hypotension, and improvement in neuroparalysis. ➤ Repeat the ASV if no clinical improvement is noted. ➤ In neurotoxic snakebites, use a neostigmine combination with atropine to prevent cholinergic crisis.	
Monitor kidney functions to look for recovery and need of kidney biopsy where indicated.	
Long-term follow-up of kidney functions, especially in cases of incomplete recovery, to prevent further progression of CKD is suggested.	



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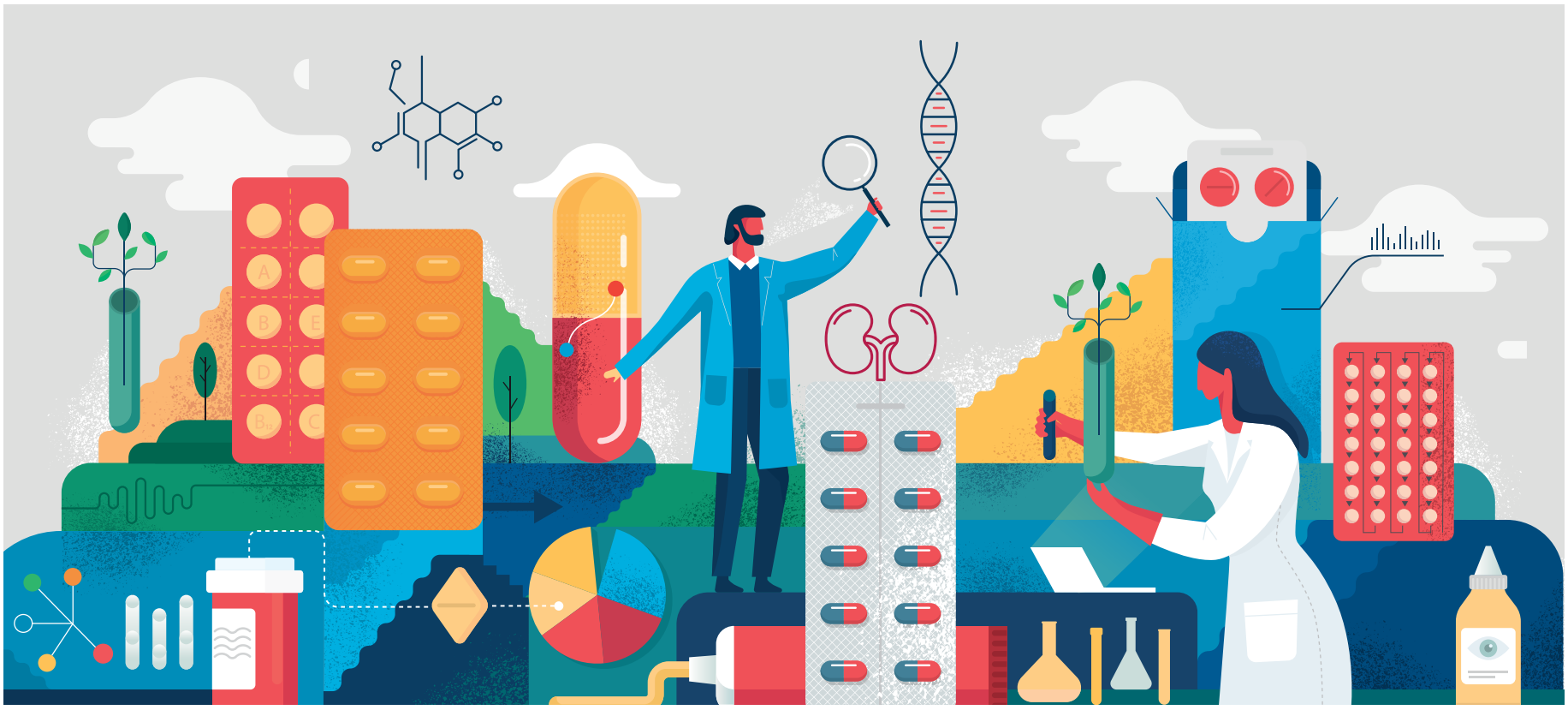

Herbal and Dietary Supplements: Hidden Dangers to Kidney Health

By Rolando Claure-Del Granado and Jonathan Chávez-Íñiguez

In an era in which wellness trends dominate social media and supermarket shelves, herbal and dietary supplements have exploded in popularity, promising a cornucopia of health benefits. However, beneath this facade of wellness lurks a potential threat, which poses hidden dangers to kidney health (Table).

Widespread use

Unlike prescription medications, herbal and dietary supplements are often categorized as food products, leading to lax regulations. This means that the ingredients may not be fully disclosed, their quality can vary significantly, and potential side effects often go unreported. The kidneys are particularly vulnerable to toxic injury because of their high blood flow rate, large endothelial surface area, high metabolic activity, active uptake by tubular cells, medullary interstitial concentration, and low urine pH (1).

One of the primary contributors to kidney damage is the widespread use of herbal supplements. Herbal medicine can be a source of kidney injury through several mechanisms: the presence of known herbs with unknown or underestimated toxicity, toxic effects resulting from incorrect preparation or the use of substitutes, contamination or adulteration, indirect toxicity due to interactions between drugs and herbs or between different herbs, and the presence of active biological compounds. For instance, aristolochic acid, found in certain traditional Chinese herbs, has been linked to chronic kidney disease (CKD) and urinary tract cancers (2). Similarly, Cape aloe (Aloe capensis)—used extensively in Africa as a laxative, as an anti-inflammatory and antioxidant, and for treating skin conditions like eczema—has been implicated in cases of acute kidney injury due to acute interstitial nephritis and acute tubular necrosis as a result of dehydration (3).

Nearly half of Americans use dietary supplements (4), which may be mislabeled, interact with medications, or contain kidney-harming substances. People with CKD are particularly vulnerable, yet many supplements remain unstudied in this group, raising safety concerns (5). In the National Health and Nutrition Examination Survey cohort, 27.8% of patients with CKD reported supplement use, with flaxseed oil being common (4). A minority (2.6%), notably those with diabetes or hypertension, used high-risk supplements.

Adverse events from supplements are under-reported. In 63 US emergency departments, 23,005 annual visits and 2154 hospitalizations were supplement related, mostly among young adults using herbal or nutritional products. Weight loss and energy supplements caused 71% of adverse effects, including cardiac palpitations (6). Weak regulations worsen risks to kidney health. Manufacturers can easily sell products with undisclosed ingredients or false claims, endangering consumers.

Prevention strategies

Addressing the hidden dangers posed by herbal and dietary supplements requires a multifaceted approach. First, there is an urgent need for enhanced regulation and oversight of the supplement industry to ensure product safety and transparency. Regulatory bodies must enforce rigorous testing protocols and stringent labeling requirements to inform consumers accurately about potential risks to kidney health. Consumers should exercise caution and adopt a critical mindset (7).

Additionally, health care professionals play a crucial role in educating the public about the potential dangers of supplement use, particularly in vulnerable populations such as the elderly and individuals with pre-existing kidney conditions. Encouraging open dialogue between patients and health care professionals can facilitate informed decision-making regarding supplement use, minimizing the risk of adverse renal outcomes. Furthermore, promoting evidence-based practices and emphasizing the importance of a balanced diet and lifestyle interventions can help mitigate the reliance on supplements as quick-fix solutions.

The widespread availability and consumption of herbal and dietary supplements pose significant yet often overlooked risks to kidney health. By addressing regulatory gaps, enhancing consumer awareness, and promoting evidence-based approaches to wellness, we can safeguard against the hidden dangers lurking within the supplement aisle, ensuring that individuals can pursue health and vitality without compromising the well-being of their kidneys. ■

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Table. Kidney syndromes associated with the use of herbal and dietary supplements

Kidney pathology	Herbal and dietary supplements	Common local uses	Country or region
Acute tubular necrosis	Securidaca longepedunculata, Euphorbia matabelensis, Crotalaria laburnifolia, Heliotropium, Symphytum, Senecio plants, Callilepis laureola, Atractylis gummifera, Cape aloes	Headache, fever, rheumatism, snake bites, inflammation, antimicrobial agent, skin diseases, respiratory issues, pain reliever, wound healing, parasitic and other infections, purgative, bone fractures and sprains, menstrual disorders, diuretic, analgesic, laxative	Africa
	Crotalaria spp., Cassia auriculata, Holarrhena antidysenterica	Cough and asthma, inflammation, diabetes, laxative, infections, anthelmintic, amoebiasis, dysentery and diarrhea, bronchitis	Sri Lanka
	Niu Huang Chieh Tu Pien, herbs contaminated with arsenic	Antioxidant	China
	Takaout roumia	Hair dye (additive in henna for darker coloring)	Morocco
	Paraphenylenediamine, Cantharidin	Dysentery, cancer, enlarged spleen, headache, jaundice, skin conditions	Sudan
Acute interstitial nephritis	Cat's claw (Uncaria tomentosa)	Inflammation, antioxidant, immune system booster, gastrointestinal disorders, antiviral	South America (Peru and Bolivia)
	Cape aloes	Laxative	Africa, South America
	Taxus celebica, herbs adulterated with NSAIDs (Tung Shueh pills)	Cancer, arthritis, muscle pain, joint issues	China
Chronic interstitial nephritis	Herbs or Kampo containing aristolochic acids (Aristolochia spp., Akebia spp., Mu Tong, Boui-ougi-tou, Mokutsu)	Inflammation, body detoxifier, infections and snake bites, diuretic, menstrual disorders, blood circulation, lactation, fever, arthritis, pain	China
	Jia Wey Guo Sao pills (herbal mixtures without Aristolochia spp.)	Blood circulation, inflammation, pain, gastrointestinal disorders, overall health	China
Proximal tubulopathy (Fanconi syndrome)	Glycyrrhiza spp. (herbal cough blends, herbal tea, gancao, Boui-ougi-tou)	Digestive and respiratory health, inflammation, immune support, hormonal regulation, stress	China, East Asia
	Herbs containing Aristolochic acids (Akebia spp., Boui-ougi-tou, Mokutsu)	Diuretic, inflammation, menstrual health, lactation, Qi (energy), digestive health, immune support, prolapse	China, East Asia
Analgesic nephropathy (papillary necrosis)	Willow bark (Salix spp.)	Analgesic, inflammation, antipyretic, joint pain and tendonitis, blood thinning	China, East Asia, Europe, North America
	Herbs adulterated with NSAIDs (indomethacin, diclofenac, mefenamic acid, phenylbutazone): pills containing Chuifong Tuokuwan and Tung Shueh	Pain and inflammation	China, East Asia, Southeast Asia, North America, Europe, Australia, New Zealand
Hypertension	Glycyrrhiza spp. (herbal cough mixtures, herbal teas, gancao, Boui-ougi-tou)	Digestive and respiratory health, inflammation, immune support, hormonal regulation, stress	China, East Asia, Middle East, Europe, North America
	Ephedra-containing herbal preparations (Ma Huang, dietary supplements containing ephedra alkaloids)	Weight loss, energy boost, respiratory decongestant	China, East Asia, United States, India, Middle East
Kidney stones	Ephedra-containing herbal preparations (Ma Huang, nutritional supplements containing ephedra alkaloids), cranberry juice and vitamin C (oxalates)	Weight loss, energy boost, respiratory decongestant, UTI, antioxidant, immune support, collagen synthesis, iron absorption	Worldwide
Acute rejection of kidney transplant	Immunosuppressant interactions with alternative medicines: St. John's wort	Depression, anxiety, seasonal affective disorder, wound healing	Worldwide (particularly in North America, Europe, Australia, and parts of Asia; most popular in Germany)
	Immunostimulatory compounds: alfalfa (Medicago sativa)	Diuresis and detoxification, nutrition, cholesterol	Worldwide
	Ashwagandha	Anxiety, cognitive function, inflammation, antioxidant, immunomodulatory properties, physical performance	India
Urinary retention	Datura spp. (sobi-lobi)	Pain, asthma, sedative, antispasmodic	Niger
	Rhododendron molle, Rehmannia glutinosa, Carthamus tinctorius, Atropa belladonna, Hyoscyamus niger, Datura spp.	Inflammation, analgesic, antimicrobial, anemia, chronic fatigue, liver and kidney diseases, menstrual and cardiovascular disorders, antispasmodic, anticholinergic, sedative, pain, asthma	China, Japan, Korea, Tibet, India, Middle East, Europe, North America, Africa, Latin America
Urinary tract carcinoma	Herbs containing Aristolochia spp. (Belgian slimming regimen)	Weight loss	China, East Asia
Chronic kidney disease	Ginseng and red ginseng, methyl sulfonyl methane, lutein-containing supplements, propolis, amino acids and proteins, milk thistle	Fatigue, energy levels, cognitive performance, immunomodulatory properties, antioxidant, inflammation, blood sugar levels, erectile dysfunction, osteoarthritis and joint pain, allergies, muscle recovery and growth, eye health, wound healing, immune support, oral health, metabolism, neurotransmitter synthesis, liver health, detoxification	South Korea, China, Japan, North America, Europe, Australia, New Zealand, Brazil, Russia
Glomerulonephritis	Astragalus (Astragalus membranaceus)	Kidney function, inflammation, immune system, overall vitality	China, East Asia
	Cordyceps (Cordyceps sinensis)	Inflammation, immunomodulatory properties	China, Tibet
	Rehmannia (Rehmannia glutinosa)	Kidney disorders	China, East Asia
	Bupleurum (Bupleurum chinense)	Fever, inflammation, chronic kidney disease	China, East Asia
	Licorice (Glycyrrhiza spp.)	Inflammation, immune boosting	China, East Asia, Europe
	Horsetail (Equisetum arvense)	Diuretic	Europe, North America
	Dandelion (Taraxacum officinale)	Diuretic, inflammation	Europe, North America
	Stinging nettle (Urtica dioica)	Diuretic, inflammation	Europe, North America
	Cat's claw (Uncaria tomentosa)	Inflammation, immunomodulatory properties	South America (Amazon rainforest)
	Goldenrod (Solidago virgaurea)	Diuretic, inflammation	Europe, North America

NSAIDs, nonsteroidal anti-inflammatory drugs; UTI, urinary tract infection.

House Unveils L-HHS Appropriations Bill Featuring ASN Policy Victories Alongside Cuts and Reforms for HHS and Underlying Agencies

By Ryan Murray

On June 27th, the House Appropriations Subcommittee on Labor, Health and Human Services, Education, and Related Agencies (L-HHS) advanced legislation to drastically cut the budget of the Department of Health and Human Services (HHS) in fiscal year (FY) 2025 by 7% and to significantly reorganize the National Institutes of Health (NIH). Advancing out of the subcommittee in a voice vote along party lines, the bill, although unlikely to pass in its current form, will serve as the starting point in negotiating with the Senate Committee on Appropriations, which is more aligned with the President's Budget.

As released, the L-HHS Appropriations Act calls for the NIH FY25 funding to remain flat at FY24 levels of $48 billion. This is $700 million short of President Biden's proposed 2% increase for FY25. Despite the cuts to HHS and its underlying agencies, several key ASN policy priorities were included in the bill. Although the House bill included a $1.7 billion, or 22%, cut for the Centers for Disease Control and Prevention, it did, however, provide a $1 million increase to the organization's chronic kidney disease surveillance program (1).

The Kidney Innovation Accelerator (KidneyX), which was not included in the President's Budget, was included in the House bill at a flat funding rate of $5 million despite a clear appetite for budget cuts in the House. This small but key policy victory for the kidney community is a testament to KidneyX's congressional champions on both sides of the aisle and the program's popularity (1). The bill's report language also specifically recognized the impact of KidneyX and encouraged the Advanced Research Projects Agency for Health (ARPA-H) to build on KidneyX's progress in advancing the development of an artificial kidney.

The bill also focused on several transplant policy areas and provided the Health Resources & Services Administration's Organ Procurement & Transplantation Network Modernization Initiative an increase of $2 million and a $1 million increase for the Living Organ Donor Reimbursement Program (currently run by the National Living Donor Assistance Center).

The subcommittee also noted that funding for kidney research has lagged behind that of NIH overall, despite the significant toll on Americans living with kidney diseases and kidney diseases' impact on Medicare spending. The subcommittee members concluded: "Thus, the Committee strongly urges NIDDK [National Institute of Diabetes and Digestive and Kidney Diseases] to increase its support for kidney research funding in fiscal year 2025" (1). Furthermore, the bill's report language specifically called for "NIDDK to prioritize research into endogenous filtration markers, activities that spur the adoption of new equations for estimating glomerular filtration rate that do not include race as a modifier, and interventions to eliminate racial and ethnic disparities" (1).

However, the bill features several concerns beyond the significant fiscal cuts to HHS. Building on a growing interest on Capitol Hill for NIH reform, the bill includes a plan released earlier on June 14th by the House Energy and Commerce Committee to enact significant reforms at the public health agency.

The framework unveiled by the House Energy and Commerce Committee recommends increased oversight, reforms to indirect costs and grants, reorganizing the NIH structure, instituting term limits for institutes' and centers' leadership, and assimilating the 2-year-old ARPA-H into a new NIH institute (2). Although the proposal would keep funding levels the same for NIH, largely by redistributing $1 billion in funding originally provided to ARPA-H in FY24, it would reduce the number of research centers from 27 to 15. The proposal recommends that the National Heart, Lung, and Blood Institute; the National Institute

of Arthritis and Musculoskeletal and Skin Diseases; and NIDDK be combined into a new National Institute on Body Systems Research. The new National Institute on Body Systems Research would receive $7.1 billion in FY25 funding, an increase of $123 million from the combined FY24 levels for the three institutes (1).

The proposal's inclusion in the FY25 bill to reorganize NIH has met opposition on Capitol Hill from those who believe that a decision of such magnitude requires more discussion. When asked why there was not a

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House Unveils L-HHS Appropriations Bill

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hearing on the NIH reorganization to provide the details necessary for such a decision, Rep. Steny Hoyer (D-MD) said, "We did not have a single hearing on NIH. The secretary was here, but we didn't plumb for…intellectual knowledge on what we're doing" (3).

As of press time, ASN has joined more than 220 organizations from the broader medical and scientific research community in a letter urging the House Appropriations Committee to remove the language to restructure NIH and called for congressional hearings and a deliberate bipartisan and bicameral process before advancing legislation to restructure NIH (4).

ASN also intends to respond to the original framework released by the House Energy and Commerce Committee. The ASN Policy and Advocacy Committee is currently reviewing the framework and will begin drafting recommendations for ASN Council to approve before submission. ASN members and their institutions are encouraged to share their thoughts on the proposed framework directly with the House committee by emailing NIHReform@mail.house.gov by August 16th.

To keep track of ASN's policy efforts throughout the congressional appropriations process, follow coverage in *Kidney News* and the ASN podcast feed, and visit ASN's policy webpage (http://www.asn-online.org/policy). For real-time updates from ASN Policy, follow @ASNAdvocacy on X. ■

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Gaining a Deeper Understanding of Rare Kidney Diseases: Insights from RaDaR

By Muhammad A. Mujtaba and Divya Monga

The definition of rare kidney disease (RKD) differs globally. In Europe, a disease is defined as rare when the prevalence is <1 in 2000 individuals, whereas in the United States, the designation of rare disorder applies when <200,000 Americans are affected (1).

Recent findings published in *The Lancet*, "Effects of Rare Kidney Diseases on Kidney Failure: A Longitudinal Analysis of the UK National Registry of Rare Kidney Diseases (RaDaR) Cohort" (2), offer insights into the unique challenges and outcomes faced by individuals with an RKD. This retrospective study used extensive data from RaDaR, including individuals from across 108 UK kidney care facilities, tracked over a median of 9.6 years. The stark contrast in outcomes between these patients and the general population with chronic kidney disease (CKD) calls for a re-evaluation of our current medical and research strategies.

Data were collected for 27,285 patients in 28 rare disease groups. The primary outcomes included mortality and kidney failure. Analyses indicate that people with RKDs face a disproportionate risk of kidney failure, with a significantly higher 5-year cumulative incidence (28%) compared with the broader population affected by all causes of CKD (1%). Notably, despite the greater risk of kidney failure, these patients show better survival rates when compared with the population with all-cause CKD, reflected in a standardized mortality ratio of 0.42.

This paradox highlights a crucial aspect of RKDs: their complex, aggressive progression to kidney failure, which necessitates more intensive and prolonged use of kidney replacement therapy (KRT). The variation in outcomes, such as age at kidney failure and survival postdialysis initiation, across different RKDs underscores the heterogeneity of these diseases and the need for personalized treatment approaches (Table). Their results also align with prior data, showing that a majority of pediatric patients undergoing KRT are diagnosed with an RKD (3).

This study, therefore, provides useful insights into the prospective research domains in the field of RKDs.

1. It highlights the need for dedicated research into the pathophysiology, detection, and progression of RKDs to develop more effective management regimens. This is crucial, not just for improving patient outcomes but also for reducing the long-term demand for KRT resources. As an example, in 2023, the National Center for Advancing Translational Sciences (NCATS) funded RKD researchers, providing data to compile the Kidney Tissue Atlas (4), which is the most comprehensive human kidney cell and tissue catalog, to date. The data were gathered over more than 1 decade through the Nephrotic Syndrome Study Network (NEPTUNE), which is part of the NCATS-led Rare Diseases Clinical Research Network.
2. The establishment of centers that focus on RKDs could provide the concentrated expertise necessary for managing these complex conditions. The centers could also serve as hubs for ongoing research and clinical trials, accelerating the development of innovative therapies.
3. Increasing awareness about RKDs among health care practitioners and the public is essential. Enhanced practitioner education through dedicated seminars, webinars, and inclusion in nephrology fellowship core curriculum should be introduced. Nephrology professional societies, like ASN, the International Society of Nephrology, and the National Kidney Foundation, should also serve as training resources.
4. Enhanced support for patients is vital. This includes medical and psychological support and help in accessing the benefits of new research findings and therapies as they become available. Kidney support networks with focus on RKDs should be encouraged, similar to the NCATS-led Genetic and Rare Diseases Information Center. Genetic counselors and experts in RKDs can provide guidance to individuals and their families.

Table. Pertinent outcomes in patients with RKDs

Types of RKDs	Median age at kidney failure, years[a]	Median duration in therapeutic trial window, years[b]
Autosomal-dominant polycystic kidney disease	59	11
Cystinosis	15	8.2
Immunoglobulin A nephropathy	55	4
Atypical hemolytic uremic syndrome	41	1.8
Antineutrophil cytoplasmic antibody-associated vasculitis	89	10.5

[a]Kidney failure is defined as the need for chronic KRT or an estimated glomerular filtration rate (eGFR) of <15 mL/min/1.73 m² for 4 weeks or more.

[b]Duration in the therapeutic trial window is defined as the time between the last eGFR (≥75 mL/min/1.73 m²) and the first eGFR (<30 mL/min/1.73 m²) with no subsequent higher eGFR values.

In 2017, the Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference brought together a panel of multidisciplinary clinical practitioners and patient advocates to address central issues for patients with RKDs (1). It was concluded that advancements in diagnosing and treating RKDs rely on the cooperative efforts of clinicians, patients, industry stakeholders, regulatory bodies, and government agencies.

In conclusion, the RaDaR cohort study sheds light on the significant impact of RKDs on individuals and health care systems and emphasizes the urgent need for targeted research and specialized care. By addressing these needs, we can hope to improve the quality of life and outcomes for this vulnerable group of patients, ultimately reducing the burden on health care resources dedicated to KRT. ■

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Dr. Mujtaba reports serving on the Advisory Board of Mallinckrodt. Dr. Monga reports no conflicts of interest.

What are the effects of rare kidney diseases on kidney failure? A longitudinal analysis of the UK National Registry of Rare Kidney Diseases (RaDaR) cohort

KidneyNews

Methods and Cohort

- RaDaR: UK National Registry of Rare Kidney Diseases
- Longitudinal retrospective study (N = 27,285)
- 108 UK renal care facilities
- 28 Rare disease groups
- Follow-up period: 9.6 years
- Study period: January 2010–July 2022

Findings

Primary Outcomes

Deaths	➢ SMR with kidney failure	3.99
	➢ SMR without kidney failure	1.32
Need for KRT or eGFR ≤15 mL/min/1.73 m²	➢ aHUS and anti-GBM cohort	

Secondary Outcomes

Median age at kidney failure	68 years
Median age at death	>75 years (cystinosis: 56.4 years)
Time from diagnosis to eGFR threshold	MGRS, C3GN, cystinosis, SRNS-FSGS
CI of kidney failure at 5 years	28%

Conclusions: Patients with rare kidney diseases have a higher 5-year rate of kidney failure with fairly good survival on maintenance hemodialysis. Early specialist referral, diagnosis, and starting rare disease-specific therapies to slow the progression of kidney failure are most appropriate in this cohort.

aHUS, atypical hemolytic uremic syndrome; C3GN, C3 glomerulonephritis; CI, cumulative incidence; eGFR, estimated glomerular filtration rate; GBM, glomerular basement membrane; MGRS, monoclonal gammopathy of renal significance; SMR, standardized mortality ratio; SRNS-FSGS, steroid-resistant nephrotic syndrome-focal segmental glomerulosclerosis.

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Visual abstract by Priyadarshini John, MD, DM

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Low Rate of Recommended CKD Screening in Type 2 Diabetes

Fewer than one-fourth of patients with type 2 diabetes (T2D) undergo recommended screening for chronic kidney disease (CKD), reports a study in *JAMA Network Open*.

The retrospective analysis included 316,234 adults without known CKD who made an outpatient visit related to T2D from 2015 through 2020. Patients were seen at 20 health care systems participating in The National Patient-Centered Clinical Research Network (PCORnet). The median age was 59 years; approximately one-third of patients were Black (21.7%) and Hispanic (10.3%).

The study focused on concordance with CKD screening guidelines, defined as the measurement of creatinine and the urine albumin-creatinine ratio. Among patients who tested positive for CKD, prescriptions of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers and sodium-glucose cotransporter-2 (SGLT2) inhibitors were assessed.

Only 24.9% of patients with T2D underwent measurement of both creatinine and the urine albumin-creatinine ratio. One of the two screening tests, usually a creatinine measurement, was performed in 56.5% of patients. Neither test was performed in 18.6% of patients.

Screening nonconcordance was more likely for Hispanic patients (relative risk, 1.16). Women and older patients were more likely to undergo screening, as were patients with heart failure, peripheral arterial disease, or hypertension.

Among 4215 patients with CKD and albuminuria, 78.0% were prescribed an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker, whereas 4.6% received an SGLT2 inhibitor. Twenty-one percent of patients with CKD received neither treatment. Treatment was less likely for patients with peripheral arterial disease and lower kidney function and was more likely for those prescribed a diuretic or statin or diagnosed with hypertension.

Annual CKD screening is recommended for people with T2D. Low screening rates contribute to underdiagnosis and undertreatment of CKD in this high-risk population.

Adding to previous evidence, this analysis of data contributed to PCORnet showed inadequate adherence to guideline-recommended CKD screening in adults with T2D. The study also found that more than 20% of patients with CKD received no recommended treatments, including "a paucity of SGLT2 inhibitor prescriptions." Identification of demographic and clinical factors associated with CKD screening and treatment has implications for strategies to improve concordance with recommended screening [Edmonston D, et al. Concordance with screening and treatment guidelines for chronic kidney disease in type 2 diabetes. *JAMA Netw Open* 2024; 7:e2418808. doi: 10.1001/jamanetworkopen.2024.18808].

Sex Differences in CKD-Related Cardiovascular Disease Risks

Among patients with chronic kidney disease (CKD), the risk of atheromatous cardiovascular disease (ACVD) is lower in women compared with men, whereas non-ACVD (N-ACVD) risk does not vary by sex, reports a study in the *American Journal of Kidney Diseases*.

The researchers analyzed a nationally representative cohort of 1044 women and 1976 with moderate to severe CKD, drawn from the CKD-Renal Epidemiology and Information Network study. The median age was 67 years for women and 69 years for men; the mean estimated glomerular filtration rate (eGFR) was 32 and 33 mL/min/1.73 m^2, respectively.

Incidence rates of ACVD events (ischemic coronary, cerebral, or peripheral artery disease) and N-ACVD events (heart failure, hemorrhagic stroke, or arrhythmias) were compared between the sexes. The median follow-up was 5.0 years.

The composite rate of fatal and nonfatal ACVD events was lower in women compared with men with CKD: 2.1 versus 3.6 per 100 patient-years. However, rates of N-ACVD events were similar between groups: 5.7 versus 6.4 per 100 patient-years.

The reduction in ACVD risk among women compared with men weakened as CKD progressed. The hazard ratio increased from 0.42 at an eGFR of 45 mL/min/1.73 m^2, to 0.72 at an eGFR of 45 mL/min/1.73 m^2, to no significant difference at 15 mL/min/1.73 m^2.

In contrast, sex was unrelated to N-ACVD risk at any level of kidney function. This was so even after further adjustment for history of cardiovascular events.

For both types of events, there were no significant interactions between sex and age, diabetes, obesity, low-density lipoprotein cholesterol, or the urine albumin-creatinine ratio.

It is unclear whether or how the known sex-related differences in cardiovascular risk—both ACVD and N-ACVD—are affected by the presence of CKD. This large cohort study confirms a lower incidence of ACVD among women with CKD compared with men. The difference, partly explained by women's better cardiovascular risk profile, "attenuates fully with kidney disease progression."

"The equal risk of N-ACVD between sexes across CKD stages and its steeper association with eGFR suggest an important contribution of CKD to the development of this CVD type," the researchers write. They conclude that women and men with CKD "should be considered at equally high risk for cardiovascular events, requiring close monitoring and follow-up" [Faucon A-L, et al.; CKD-REIN study collaborators. Sex and the risk of atheromatous and non-atheromatous cardiovascular disease in CKD. *Am J Kidney Dis*, published online June 24, 2024. doi: 10.1053/j.ajkd.2024.04.013].

Amino Acid Infusion During Cardiac Surgery Reduces AKI Risk

Intravenous amino acid infusion reduces the risk of acute kidney injury (AKI) associated with cardiac surgery, reports a clinical trial in *The New England Journal of Medicine*.

The randomized, double-blind Intravenous Amino Acid Therapy for Kidney Protection in Cardiac Surgery (PROTECTION) trial included 3511 adults undergoing cardiac surgery with cardiopulmonary bypass, recruited from 22 centers in three countries. Patients assigned to the intervention group received balanced amino acid infusions, up to 2 g/kg of ideal body weight per day, for 3 days. Placebo controls received infusions of Ringer's solution.

Rates of AKI, based on Kidney Disease: Improving Global Outcomes criteria, were compared between groups. Secondary outcomes included AKI severity, need for

kidney replacement therapy, and 30-day all-cause mortality.

Amino acid infusions were associated with a significant reduction in the incidence of AKI: 26.9% versus 31.5%; relative risk, 0.85. A stronger protective effect was observed for stage 3 AKI: 1.6% versus 3.0%; relative risk, 0.56. Rates of kidney replacement therapy were 1.4% in both the amino acid group and the control group. Mortality and other secondary outcomes were similar between groups.

Reduced kidney perfusion is a contributing factor to AKI associated with cardiac surgery. By increasing perfusion and recruiting functional reserve, amino acid infusion might reduce the occurrence of AKI in this high-risk group.

The PROTECTION trial found that short-term amino acid infusion reduced AKI risk in patients undergoing cardiac surgery compared with crystalloid infusion. The effect appears greatest in the prevention of severe AKI. The researchers conclude that their findings are "clinically and epidemiologically important," given the high numbers of patients undergoing cardiac surgery and the risk of adverse outcomes associated with AKI [Landoni G, et al. A randomized trial of intravenous amino acids for kidney protection. *N Engl J Med*, published online June 12, 2024. doi: 10.1056/NEJMoa2403769].

High Burden and Costs of Polypharmacy in Patients Undergoing Dialysis

The numbers of prescriptions and daily pill burdens are similar for patients receiving hemodialysis (HD) compared with those receiving peritoneal dialysis (PD), whereas medication costs are much higher for patients undergoing HD, reports a study in *Nephrology Dialysis Transplantation*.

Using the population-based Alberta Kidney Disease Network, the researchers analyzed the prevalence and costs of polypharmacy among adults receiving maintenance dialysis. Among 2248 patients included in the analysis, 1781 were undergoing HD, and 467 were undergoing PD. Use of up to 29 medication categories was assessed for each patient; use of potentially inappropriate medications (PIMs) was evaluated for those aged 65 years or older. The numbers of drug categories, daily pill burden, and annual medication costs were compared with those of an age- and sex-matched general population. Costs were expressed in 2021 Canadian dollars.

Overall, the patients on dialysis had prescriptions from a median of six drug categories, with a median daily pill burden of eight pills per day. Some patients had even higher pill counts: 15 or more for 16.5% of patients and 21.7 or more for 5% of patients. Median daily pill burden was approximately eight in both the HD and PD groups compared with 2.3 in the matched population.

Median annual medication cost was $3381 per patient, amounting to approximately $11.6 million per year for all patients undergoing dialysis. The median cost was $4087 for patients undergoing HD versus $2982 for patients undergoing PD compared with $340 in the general population sample. "Miscellaneous" drugs accounted for 83% of costs for the top 10 medication categories, mainly reflecting costs for erythropoietin-stimulating agents. For 10% of patients on dialysis, annual costs exceeded $10,000.

Among patients aged 65 or older, the median number of PIMs prescribed was two in the HD group versus one in the PD group. Twelve percent of patients were prescribed at least one medication that was contraindicated in kidney failure.

There is incomplete evidence on polypharmacy and use of PIMs among patients on dialysis. This study documented high daily pill burdens and medication costs for patients who underwent both HD and PD. Drug costs were higher for patients who underwent HD, largely reflecting use of erythropoiesis-stimulating agents.

Use of contraindicated medications and PIMs is relatively common as well. The researchers highlight the need for regular medication review along with new interventions to reduce polypharmacy for patients on dialysis [Ghimire A, et al. Prescribing patterns and medications costs in patients on maintenance hemodialysis and peritoneal dialysis. *Nephrol Dial Transpl*, July 4, 2024. doi: 10.1093/ndt/gfae154].

Get With the FLOW!

By Ben Catanese and Matthew A. Sparks

The FLOW trial represents the first prospective glucagon-like peptide-1 (GLP-1) receptor agonist randomized clinical trial with kidney events as the primary outcome. It is akin to the CREDENCE (Evaluation of the Effects of Canagliflozin on Renal and Cardiovascular Outcomes in Participants With Diabetic Nephropathy) trial for sodium-glucose cotransporter-2 inhibitors (SGLT2is) in ushering a new agent to slow the progression of kidney diseases in diabetes. Results were presented at the 2024 European Renal Association Congress in Stockholm, Sweden, and published in *The New England Journal of Medicine* (1).

The Effect of Semaglutide Versus Placebo on the Progression of Renal Impairment in Subjects With Type 2 Diabetes and Chronic Kidney Disease (FLOW) trial enrolled 3533 participants across 387 sites in 28 countries from June 2019 through May 2021. Participants with type 2 diabetes were randomized to once-weekly semaglutide versus placebo. To qualify for the trial, the required estimated glomerular filtration rate (eGFR) was between 50 and 75 mL/min/1.73 m^2 with a urinary albumin-to-creatinine ratio (UACR) of >300 mg/g Cr and <5000 mg/g Cr or between 25 and <50 mL/min/1.73 m^2 with a UACR of >100 mg/g Cr and <5000 mg/g Cr. Further eligibility requirements included being treated with a stable maximum dose (or highest dose without side effects) of a renin-angiotensin system inhibitor (angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers). Although not an inclusion or exclusion criteria, use of SGLT2i was implemented to stratify patients as they were randomized in the trial. Approximately 15% of patients in the trial were being treated with a SGLT2i. Lastly, there was no weight inclusion criteria, and mean body mass index in the study was 32.0 kg/m^2.

The trial was stopped early for efficacy following a prespecified interim analysis triggered in October 2023 when two-thirds of the total planned number of primary outcome events had occurred. The median participant follow-up period was 3.4 years. The primary outcome was a composite of the onset of kidney failure (dialysis, transplantation, or an eGFR of <15 mL/min/1.73 m^2 sustained for ≥28 days), at least a 50% reduction in the eGFR from baseline (for ≥28 days), or death from kidney-related or cardiovascular causes. The risk of the primary outcome was 24% lower in the semaglutide group as compared with the placebo group (hazard ratio [HR], 0.76; 95% confidence interval [CI], 0.66–0.88). The significant reduction in events was maintained when cardiovascular death was separated from the kidney-specific components (HR, 0.79; 95% CI, 0.66–0.94). The secondary outcomes were tested hierarchically, and all significantly favored semaglutide.

Among the secondary outcomes was the mean annual slope of eGFR, which was significantly less steep with semaglutide as compared with placebo (–2.19 versus –3.36 mL/min/1.73 m^2). To confirm this result, a cystatin C-based eGFR was used to show a similar significant difference in the loss of kidney function favoring semaglutide. This was an important analysis, as muscle mass can decrease with weight loss associated with GLP-1 receptor agonist use, thus theoretically leading to a misleading drop in creatinine-based eGFR. Notably, weight loss was not as robust in other GLP-1 receptor agonist trials but still significantly different between the study arms. By week 104, the semaglutide group had 5.6 kg weight loss as compared with 1.5 kg in the placebo group.

Notably, the FLOW trial examined only patients with type 2 diabetes and presumed diabetic kidney disease. However, a prespecified analysis of long-term kidney outcomes in the SELECT (Semaglutide Effects on Cardiovascular Outcomes in People With Overweight or Obesity) trial was also presented at the 2024 European Renal Association Congress and published in *Nature Medicine* (2). The SELECT trial randomized 8803 patients with obesity (body mass index, ≥27 kg/m^2), established cardiovascular disease, and no diabetes to semaglutide versus 8801 patients to placebo with the primary outcome of major adverse cardiovascular events. The kidney composite endpoint used in this prespecified analysis included death from kidney diseases, initiation of chronic kidney replacement therapy, onset of persistent eGFR <15 mL/min/1.73 m^2, persistent ≥50% reduction in eGFR, or onset of persistent macroalbuminuria (UACR, ≥300 mg/g). The occurrence of the prespecified kidney composite endpoint was lower with semaglutide (1.8%) as compared with placebo (2.2%; HR, 0.78; 95% CI, 0.63–0.96) but notably, was also low overall in general. Furthermore, kidney function was mostly preserved, as only one-fifth of patients had an eGFR <60 mL/min/1.73 m^2 to start, and the average decline at 104 weeks was –0.86 mL/min/1.73 m^2 in the semaglutide arm and –1.61 mL/min/1.73 m^2 in the placebo arm. The reduction in the endpoint was driven by a persistent ≥50% reduction in eGFR and onset of persistent macroalbuminuria.

The FLOW trial has ushered in another medication that nephrologists can add to their list of options to treat diabetic kidney disease. The endpoints selected in this trial are meaningful to patients, and the reduction in cardiovascular-related death is also particularly important considering this is the most common cause of death among patients with chronic kidney disease (3). As we continue to add more medications that improve outcomes for patients with diabetic kidney disease, we will need to decide how we go about giving patients these medications, and we will need further trials to determine if there are benefits to being treated with as many kidney-protective medications as there are to offer—SGLT2is, renin angiotensin system inhibitors, mineralocorticoid receptor antagonists, and now GLP-1 receptor agonists. Currently, initiation of each of these medications will need to be individualized for patients, as each medication has its strengths and adverse effects to be considered.

Although the FLOW trial and the secondary analysis of the SELECT trial have demonstrated important kidney benefits of semaglutide, the kidney-protective effects of other GLP-1 receptor agonists are less well known, as there have not been prospective trials with kidney outcomes, and it is unclear whether the benefits of these medications are a class effect or are medication specific. There do not appear to be any other ongoing large kidney outcome trials researching GLP-1 receptor agonists or newer dual or triple agonists, but it will be exciting to see in the future the results of smaller ongoing trials and hopefully additional large prospective clinical trials with kidney outcomes. ■

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The authors report no conflicts of interest.

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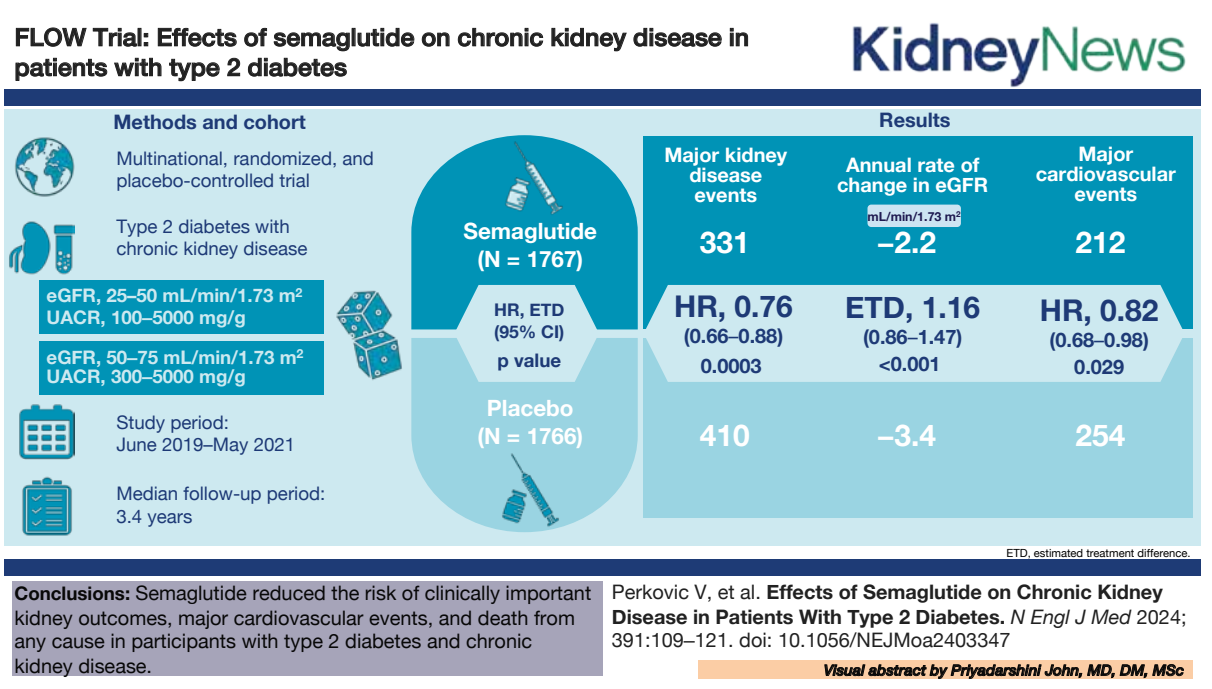

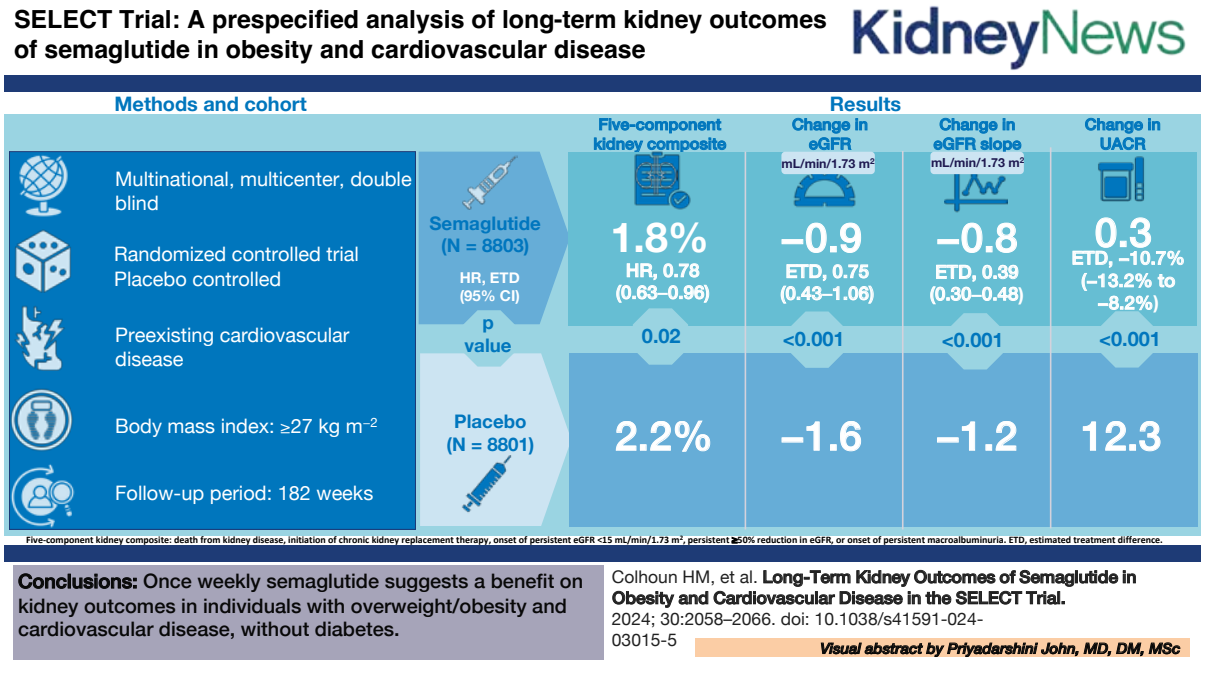

PARASOL Effort Progresses to Address Clinical Trial Endpoints in FSGS

By Howard Trachtman and Melissa West

Focal segmental glomerulosclerosis (FSGS) is a rare, primary glomerular disorder with a disproportionate impact on health outcomes, especially in socially disadvantaged populations. It is a significant cause of kidney failure in children and adults. Most importantly, there are no approved treatments for FSGS. Prompted by the urgent need to develop safe and effective therapies for people with FSGS, the Proteinuria and GFR [glomerular filtration rate] as Clinical Trial Endpoints in FSGS (PARASOL) initiative was conceived with the aim of defining a traditional or reasonably likely surrogate endpoint for use in FSGS clinical trials. A surrogate endpoint will enable accelerated approval of novel therapies and expedite access to effective treatments for this rare but devastating glomerular disorder. PARASOL represents a partnership among NephCure, the National Kidney Foundation, the International Society of Glomerular Disease, and the Kidney Health Initiative and brings together all of the relevant parties—patients, clinical nephrologists, industry sponsors, basic scientists, biostatisticians, and regulatory authorities.

After a successful meeting in December 2023 to launch the PARASOL initiative (1), the group reconvened this year on June 8th and 9th in Reykjavik, Iceland, for an interim assessment of the effort. The meeting was held at the former home of Iceland's first prime minister in a historic Nordic building that was just the right size to allow the participants to breathe easily and mingle comfortably. The weather was cold and breezy but rain-free throughout. There were 63 in-person attendees and 40 online participants, including 31 adult nephrologists, 8 pediatric nephrologists, 35 industry representatives, 9 biostatisticians, 15 patient and kidney health nonprofit organization advocates, as well as representatives from US and European regulatory agencies.

Under the leadership of Josh Tarnoff (NephCure); Laura H. Mariani, MD, MS, FASN (University of Michigan); Matthias Kretzler, MD (University of Michigan); and Tobias B. Huber, MD, FASN (International Society of Glomerular Disease), the meeting opened with a brief review of the unmet clinical need, PARASOL operations, and the features of the individual patient-level data that are required for inclusion and ultimate success of the initiative. An impressive 26 global patient cohorts and registries have confirmed that they have the required patient-level data and are able and willing to contribute to the effort (Table). Four cohorts are fully incorporated into the database and were used for the initial analysis: the Nephrotic Syndrome Study Network (NEPTUNE), Cure Glomerulonephropathy (CureGN), the Kidney Research Network (KRN), and the University of North Carolina at Chapel Hill Glomerular Disease Collaborative Network (GDCN). The additional cohorts were charged with completing the administrative requirements and approvals by August 15th for inclusion in the final analysis. "We are overwhelmed by the community response to PARASOL, including the enthusiasm of the nephrologists and teams that have agreed to share their data," Kretzler commented. "It was commonplace for each willing participant registry or patient cohort to identify another potential source of well-characterized patients with FSGS that could be approached to join PARASOL."

Significant time was spent reviewing characteristics of deidentified patients who have already been entered into the shared data repository. Since the focus of the PARASOL initiative is regulatory considerations of the aggregated data and their use in the development of an endpoint for use in clinical trials, it is important that the heterogeneity of FSGS is considered, and relevant subgroup analyses are addressed in the effort.

Three principle topics that are essential in understanding patients with FSGS and the application to clinical trial endpoints are: 1) the nature of the data regarding the estimated GFR (eGFR) trajectory, 2) the association of proteinuria and eGFR outcomes, and 3) the association of proteinuria and risk of progression to kidney failure. There was an understanding that additional follow-up work will be needed to define the clinical application of the findings by nephrologists in practice.

Following the overview and review of the patient-level data and data sources, Margaret Helmuth, MS, and Abigail Smith, PhD, members of the biostatistical team, presented a rich initial analysis supported by clear graphics. There were breakout groups to drill down deeper into key aspects of the data, deficiencies, and gaps and potential future research questions and analyses. "With an incredible group of experts in attendance, we spent time discussing how to optimize the endpoint(s) to meet the needs of patients, clinicians, and sponsors for feasible trial designs; analyze complex data from pediatric patients; incorporate information from medications; and identify additional specific patient subgroups to test the robustness of the model," said Mariani. "The feedback received is instrumental for the next phase of data analysis and presentation to the community in October 2024."

The atmosphere in Reykjavik was open and collegial, which promoted engaging conversation and interaction at all levels. The participants appreciated and respected the urgency of the task at hand. Defining a surrogate endpoint for immunoglobulin A nephropathy clinical trials has had an immediate impact for patients and families, with two drug approvals and ongoing interest from the pharmaceutical and biotech industry. The group in attendance in Iceland expressed the hope that achieving a successful outcome in PARASOL would similarly energize clinical research in FSGS and speed up the development of new treatments for people with FSGS. In addition, the successful implementation of a shared data resource to develop clinical trial endpoints in FSGS spurred enthusiasm for similar efforts in other rare kidney diseases such as membranous nephropathy and complement 3 glomerulopathy.

From its inception, the PARASOL initiative set an ambitious timeline of 11 months. The gathering of all participants at this interim meeting confirmed that the project is on schedule and moving full steam ahead and in the right direction. The next milestone is a public scientific workshop cosponsored by the US Food and Drug Administration to be held October 7–8, 2024, in Washington, DC. The goal of the workshop is to present the key findings of the PARASOL team and deliver a viable surrogate endpoint for traditional and/or accelerated approval use in FSGS clinical trials. Additional presentations will be offered for the larger community at ASN Kidney Week later that month in San Diego, CA.

To learn more about PARASOL, please visit https://www.is-gd.org/parasol, or contact Dr. Mariani at lmariani@med.umich.edu or Laurel Damashek, MA, at ldamashek@is-gd.org.

Howard Trachtman, MD, FASN, is a pediatric nephrologist with the University of Michigan, Ann Arbor. Melissa West is ASN's Senior Director for Strategic Relations and Patient Engagement. Dr. Trachtman and Ms. West serve on the PARASOL Organizing Committee.

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Guiding principles of PARASOL data analysis

- Nature of the data regarding the eGFR trajectory
- Association of proteinuria and eGFR outcomes
- Association of proteinuria and risk of progression to kidney failure

Table. PARASOL contributors

ACTION (Ph2 Study of the Efficacy and Safety of DMX-200 in Patients With FSGS Who Are Receiving an ARB) Trial
C-PROBE (Clinical Phenotyping and Resource Biobank)
CKiD (Chronic Kidney Disease in Children Study)
CureGN
DAPA-CKD (Dapagliflozin in Patients With Chronic Kidney Disease) Trial[a]
DUET (Dual Endothelin Receptor and Angiotensin Receptor Blocker, in Patients With Focal Segmental Glomerulosclerosis [FSGS]: A Randomized, Double-Blind, Active-Control, Dose-Escalation Study) Trial
EMPA-Kidney (Study of Heart and Kidney Protection With Empagliflozin) Trial
ERKNet (The European Rare Kidney Disease Reference Network)[a]
FSGS Clinical Trial
GDCN
Glosen Cohort (Spain) (Glomerular Diseases Working Group of the Spanish Society of Nephrology)
Hamburg Glomerulonephritis Registry
I-TANGIBLE (Indian Translational Glomerulonephritis Biology Network)
Indiana University Registry/Regenstrief Institute
Istituto Giannina Gaslini
Kaiser Permanente Southern California[a]
Karolinska Institute[a]
KRN
NEPTUNE
Ottawa Registry
PodoNET Registry
RaDaR (UK National Registry of Rare Kidney Diseases)
Toronto Glomerulonephritis Registry
University of Bari Aldo Moro cohort (Italy)
University of Ioannina cohort (Greece)
Uruguay National Glomerulonephritis Registry

ARB, angiotensin receptor blocker.
[a]Potential contributor.

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Meeting the Needs of Living Kidney Donors: How Can We Do Better?

By Sunita K. Singh

Living donor kidney transplantation is the preferred treatment for people living with kidney failure. However, rates of living kidney donation have not increased significantly over the past decade (1). Furthermore, although the absolute risks are low, living kidney donors (LKDs) lose approximately 30%–35% of their kidney function and have a slightly higher risk of developing kidney failure (2, 3). Thus, research efforts have focused on understanding the care needs of LKDs and the barriers to living donation.

In the February 2024 issue of *Kidney International*, Loban et al. (4) report the results of their qualitative study of 49 LKDs. Using semi-structured interviews, the aim of the study was to understand the care needs of LKDs from the patient perspective as they traverse the continuum of care, from living donor candidate to the post-donation phase.

There were several important findings from this study. First, LKDs expressed satisfaction with the communication and coordination of care *within* the donation program. However, it was felt that the coordination *between* health care teams (i.e., between primary care practitioners and donation programs) was suboptimal and disjointed. This is an important finding since most LKDs in Canada receive long-term follow-up care after donation by their family physician or nurse practitioner. Second, the authors identified substantial variability in the delivery of follow-up care provided to LKDs, both in the short and long term after donation. As a result, a subset of donors expressed feelings of abandonment after donation, in keeping with prior work (5). Third, this study identified a lack of psychosocial support for LKDs, notably in the postdonation phase. Although the majority of LKDs have excellent psychosocial outcomes after donation, a subset of LKDs do experience psychosocial distress, particularly in the event of graft failure in the recipient (6). A prior study has identified that in addition to long-term health outcomes, such as kidney function and kidney failure, psychosocial effects of donation were also highly important outcomes to LKDs (7). The Loban et al. (4) study highlights an important psychosocial care gap among LKDs.

This study yields important insights into the lived experiences of LKDs. Of note, the majority (87%) of LKDs included in the study were White, and further work is needed to better understand the perspectives of racial and ethnic minorities, for whom disparities in access to living donor kidney transplant persist (8). Nevertheless, this study is an important step in better understanding the care needs of LKDs, which is critical in advocating for the necessary infrastructure and dedicated funding to deliver comprehensive and high-quality care to LKDs. Although we have gained a better understanding of the long-term outcomes of LKDs, this study underscores the importance of a comprehensive and collaborative framework to enhance the care and well-being of LKDs. ■

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The author reports no conflicts of interest.

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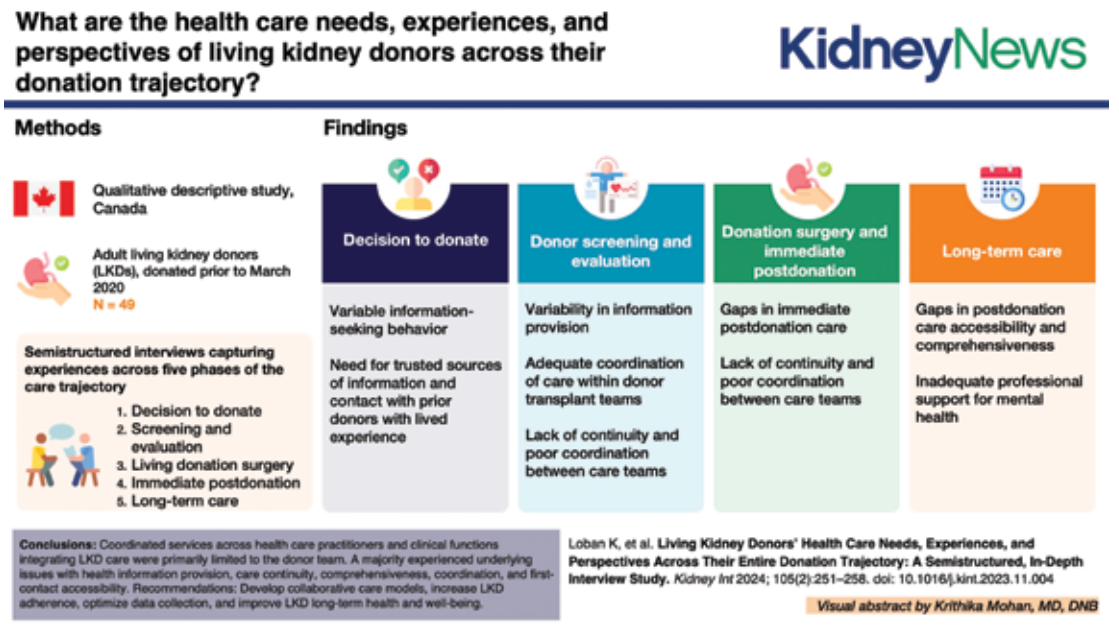

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