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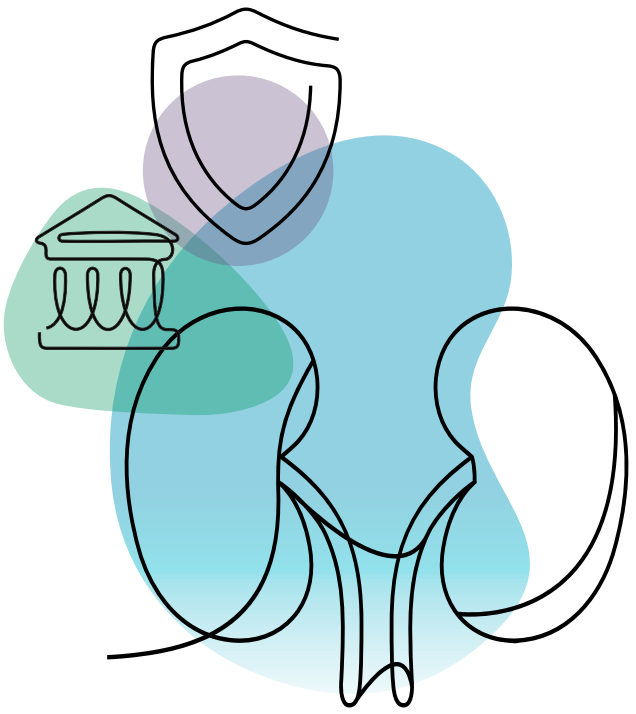
Legislation Aims to Protect Access to Private Insurance for Patients with Kidney Failure

By Bridget M. Kuehn



Transitioning to dialysis poses many challenges for patients with kidney failure. They are often medically unstable, they must adopt an entirely new lifestyle around their treatment schedule, and they often rely on family and friends to help with their care and transportation to treatment. "Dialysis is a part-time job no one signs up for," explained Suzanne Watnick, MD, FASN, professor of medicine at the University of Washington, Seattle, and ASN Kidney Health Policy Scholar.

Bipartisan legislation introduced in December 2023 aims to ensure that these vulnerable patients do not also face the prospect of abruptly transitioning from private insurance to Medicare and risk losing family coverage (1). The 2023 Restore Protections for Dialysis Patients Act aims to protect access to private insurer coverage for up to 30 months after qualifying for Medicare coverage for patients with kidney failure. US Representatives Mike Kelly (R-PA), Yvette Clarke (D-NY), Neal Dunn, MD (R-FL), Danny Davis (D-IL), John Joyce (R-PA), and Raul Ruiz (D-CA) drafted the legislation in response to a 2022 US Supreme Court ruling that many policy experts feared could force patients with kidney failure onto Medicare sooner by limiting coverage for dialysis (2).

"The Restore Protections for Dialysis Patients Act will protect people receiving dialysis' access to private insurance and mitigate the most drastic consequences of a 2022 Supreme Court decision," said ASN Past President Michelle A. Josephson, MD, FASN, in a statement during her tenure (3). "These potential impacts include loss of coverage of critical services and medications provided through employer plans and loss of coverage for family members upon kidney failure diagnosis."

Supreme Court shake-up

Since 1973, most patients with kidney failure have been guaranteed Medicare coverage for dialysis care or transplant regardless of age through an amendment to the Social Security Act that created the Medicare End-Stage Renal Disease (ESRD) benefit (4). Congress updated the

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Observational Study Finds Association of Dialysate Sodium with Mortality

By Karen Blum

How much dialysate sodium to give patients during hemodialysis treatments has been an area of interest for decades.

The amount of dialysate sodium prescribed has fluctuated over the years, from early days of dialysis, when 130 mmol/L or lower was common, to a peak of approximately 140 mmol/L in the mid-2000s, said Brendan Smyth, PhD, of the National Health and Medical Research Council Clinical Trials Centre at The University of Sydney in Australia. In the past 10 to 15 years, there has been a shift back down to 136 to 138 mmol/L, he said, although "without any large-scale data to prove that this was the right thing to do." Dialysate sodium concentrations have fallen in each of the 12 countries included in the Dialysis Outcomes and Practice Patterns Study reports (1), a prospective cohort study of over 50,000 patients.

"The rationale for the change is straightforward: Sodium is bad," Smyth said. "These [patients] are sodium overloaded, they've lost the ability to excrete sodium, [and] they're water overloaded as well; the last thing we want is to give them more sodium in their dialysate. Indeed, small studies consistently show that lower dialysate sodium concentrations result in positive changes in fluid status with less weight gained in between [patient] dialysis sessions and better blood pressure."

Now, new research published in *JASN* (2) has found, perhaps paradoxically, that lower dialysate sodium

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Inside

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.

A non-binder approach is now here

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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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Legislation Aims to Protect Access to Private Insurance

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Medicare Secondary Payer Act (MSPA) in 1980 to protect access to private insurance coverage for patients with kidney failure for up to 30 months after qualifying for Medicare coverage for ESRD (5). The law was enacted in 1981.

During the 30-month period, patients can choose to keep private or commercial insurance as their primary insurance, and Medicare provides secondary insurance. The legislation specifies that insurers cannot differentiate between patients with and without kidney failure by offering them different coverage, and they cannot consider patients' access to Medicare coverage. After those 30 months, the two payers swap, and Medicare becomes the primary insurer, and commercial insurance becomes the secondary payer, noted Daniel Weiner, MD, MS, FASN, associate professor at Tufts University School of Medicine in Boston, MA, and a councilor-at-large on the ASN Council.

But in 2022, the Supreme Court ruled 7 to 2 in favor of the Marietta Memorial Hospital Employee Health Benefit Plan. The dialysis company, DaVita Inc., had sued Marietta, arguing that its plan violated the 1981 MSPA by limiting coverage for outpatient dialysis. The plan offered only lower, out-of-network rates for dialysis care. The Supreme Court ruled that the plan did not differentiate because all individuals, regardless of whether they had kidney failure or not, were offered only out-of-network rates for outpatient dialysis.

The dissenting opinion, written by Justice Elena Kagan with Justice Sonia Sotomayor, noted that the need for "outpatient dialysis is almost a perfect proxy for end stage renal disease. Virtually everyone with end stage renal disease—and hardly anyone else—undergoes outpatient dialysis," they wrote (2). "As the majority recognizes, the MSPA's renal disease provisions were designed to prevent plans from foisting the cost of dialysis onto Medicare…. Yet the Court now tells plans they can do just that, so long as they target dialysis, rather than the patients who rely on it, for disfavored coverage," Kagan and Sotomayor noted.

Financial fallout?

The decision may prove costly for patients, dialysis facilities, and Medicare, as limitations on private coverage would force many patients to shift to Medicare early.

"The Supreme Court decision, which allows these plans to limit dialysis coverage, could result in [patients with kidney failure] losing critical benefits and being shifted prematurely to Medicare," said LaVarne Burton, MA, president and chief executive officer of the American Kidney Fund, Rockville, MD, a nonprofit group that advocates for patients with kidney diseases. "Medicare coverage alone for dialysis patients is insufficient for most patients."

Burton explained that Medicare only covers 80% of outpatient procedures like dialysis. She said that patients pay 20% of the costs with no annual out-of-pocket maximum, which results in an average of $10,000 per year in out-of-pocket expenses. She also noted that 17 states do not require insurers to offer private health insurance through Medigap plans (Medicare Supplement Insurance) to beneficiaries of Medicare ESRD who are younger than 65 years to help defray these costs.

"Our strong concern is that the impact will be felt deeply, particularly among patients of color who are disproportionately affected by kidney failure," Burton said. "Our worry is that access to life-saving care will be jeopardized and that patients with kidney failure will be targeted by employer-group health plans and lose access to high-quality kidney care."

Watnick noted that other health systems offering employee health coverage are looking at providing more limited dialysis coverage as a cost-saving measure. Weiner said patients may not feel the full impact of the ruling until this year or next as commercial health insurance companies factor in the court decision to their plans. He noted that insurers have a strong financial incentive to limit dialysis coverage. "It is just a matter of time before this takes hold," he said.

The savings for private insurers could lead to additional costs for Medicare, costing Medicare about $100,000 per year (6). Dialysis companies are also likely to feel the pinch. Medicare does not cover the total cost of dialysis. For example, Weiner noted that Medicare currently pays dialysis facilities in Massachusetts $185 per hemodialysis treatment, but dialyzing a patient costs approximately $100 more than that. Medicaid reimbursements are even lower. As a result, he explained that dialysis facilities often rely on higher reimbursements from private insurers to help offset these losses. Dialysis facilities in which few patients have private insurance or Medicare with Medigap secondary insurance will lose money.

"If there is no opportunity to cross-subsidize with private insurance, you are going to get increasing numbers of facility closures or [reduction in services]," Weiner said. For example, he noted that facilities may eliminate night shifts, which may make it more difficult for individuals on dialysis to continue working.

Dialysis companies may also pull out of the most vulnerable communities with lower rates of private insurance, Watnick said. Smaller dialysis facilities and those serving rural communities, large numbers of Medicaid patients, or other populations with limited access to care will likely be hardest hit. "If a dialysis facility is going to remain there for the community, [it has] to at least break even or make a small profit," she said.

Despite concerns about cost-shifting from private insurers to Medicare, a 2022 version of the Restore Act backed by dialysis companies was scored poorly by the Congressional Budget Office (CBO), which determined that the bill would cost the government instead of saving it money. Many policy experts disagreed with the assessment or found it puzzling, Watnick said. Weiner agreed and expressed that the CBO assessment likely doomed the 2022 iteration of the bill. The CBO will evaluate the 2023 version of the bill, and its score may change.

The 2023 version simplifies the language. The bill specifies that it restores MSPA protections for patients with ESRD by ensuring that insurers do not discriminate against them or adversely classify dialysis compared with other services. It also prohibits health insurance plans from shifting primary responsibility for ESRD care costs to Medicare. It clarifies that singling out dialysis care for disfavored treatment compared with other health services is considered an inappropriate differentiation.

"It seems reasonable to me because this is a population that already has a lot of vulnerabilities, already has a lot of financial stress," Weiner said. "If an individual wants to keep the commercial insurance they have, they should be allowed to do so without making it so onerous and burdensome [that] they are essentially forced to move to public insurance."

Protecting patients, families

Keeping their commercial plans as long as possible may benefit patients with kidney failure. Watnick explained that patients face the highest risk of death during the first 6 months of starting dialysis, and many die within the first 2½ years of starting dialysis. "The transition to kidney replacement therapy is so upending; anything you can do to smooth the transition is beneficial," she said.

Weiner noted that many patients may have to take medical leave or struggle to keep their jobs as they adjust to the demands of dialysis. Patients forced to transition from their private insurance before they are ready say it feels like "having the rug pulled out from under them," Watnick said. "It's not just you that loses your health insurance, but also your family," she said. Patients may also experience gaps in dental, vision, or hearing services for themselves and their families if they lose their private insurance.

Losing their private health insurance during this vulnerable time could create more upheaval. Patients may lose access to physicians or dialysis facilities with which they have a relationship. "The patient-physician relationship is a sacred one, especially for people with end stage kidney disease," Watnick said. She explained that patients with kidney failure see their physicians weekly or monthly, and they often become a crucial part of their support system.

Once patients become established on dialysis, it can be easier to transition to Medicare, Watnick added. She explained that they will likely have a relationship with a social worker at their facility who can walk them through their options. Having more time can also help them plan to transition their families to alternate insurance plans.

Keeping their employee-sponsored insurance may also ease the path to qualifying for a kidney transplant and help patients get on the transplant list more quickly, Watnick said. The evaluation process includes visits with multiple specialists, and employer-based insurance often has low copays. Additionally, patients must demonstrate they have dental insurance, and, without employer-sponsored dental insurance, they may not meet transplant qualification requirements. Medicaid coverage for dental care is rare, she noted, and this can be a barrier to transplant for those with Medicaid instead of private insurance. "Once you [undergo a transplant], you are able to go back to work," she said. "You may be able to access the same plan or a different [commercial insurance plan] if you get a new job. It's a new lease on life."

Burton said the Restore Act would reinstate protections for access to private insurance that patients with ESRD had for 40 years before the 2022 Supreme Court decision. "The Restore Act is a much-needed solution that would help protect patient access to their individual or employer-sponsored health care coverage and [physicians] for as long as possible and enable patients with kidney failure to better plan for the transition from private insurance to Medicare," she said. ■

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Observational Study Finds Association of Dialysate Sodium with Mortality

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concentrations (≤138 mmol/L) were associated with higher mortality compared with higher dialysate sodium concentrations (>138 mmol/L), even after adjusting for multiple confounders.

The work, the largest observational study to our knowledge—in a multinational cohort of 68,196 patients receiving care from 875 Fresenius Medical Care NephroCare clinics in 25 countries—found that lower dialysate sodium was associated with a 57% increase in all-cause mortality (hazard ratio [HR], 1.57; 95% confidence interval [CI], 1.25–1.98).

The results were "very surprising," said lead study author Jule Pinter, MD, of the University Hospital Würzburg in Germany. "I never thought there's a mortality association with the lower dialysis sodium. I would have thought that we'd see there is a cardioprotective effect or a null effect even."

Pinter, Smyth, and colleagues (2) analyzed real-time electronic health records from a NephroCare clinical database between 2010 and 2019. The database contains patient characteristics, daily hemodialysis treatment data based on the values set for machines during each session, laboratory parameters, and medications. The authors included all patients starting maintenance hemodialysis treatment who had at least one bioimpedance spectroscopy measurement recorded within the first 90 days of their first treatment. Patients were followed until death, transplantation, change of modality, transfer to a non-Fresenius dialysis site, withdrawal from dialysis, or December 4, 2019.

Over 2.1 million patient-months of exposure, from more than 21.4 million hemodialysis sessions, were available for analysis. During the study period, 31.7% of patients (n = 21,644) died, 9.1% (n = 6217) received a kidney allograft, and 28.5% (n = 19,419) reached the end of the study date. The remaining 30.7% (n = 20,916) were withdrawn from the study before the end of follow-up.

Most patients (63.2%) received a dialysate sodium of 138 mmol/L; 15.8%, 139 mmol/L; or 20.7%, 140 mmol/L. The remainder received other prescriptions ranging from 132 to 137 mmol/L. The cohorts of patients receiving lower versus higher dialysate sodium prescriptions shared similar characteristics. Two-thirds were men, the mean age was 63, and the average relative fluid overload was not clinically significant. Most clinics (78.6%) used a default dialysate sodium policy under which all patients at the clinic received the same dialysate sodium prescription, unless altered by their physician.

The mortality risk associated with higher dialysate sodium was present regardless of patient serum sodium (HR, 2.56 [95% CI, 2.00–3.28] for those with hyponatremia; HR, 1.91 [95% CI, 1.49–2.46] for those with isonatremia; and HR, 1.68 [95% CI, 1.30–2.17] for those with hypernatremia).

"These observational findings stress the need for randomized evidence to reliably define optimal standard dialysate sodium prescribing practices," the authors wrote. "It was clear to us that we saw a strong effect on mortality and it's worthwhile to keep on going to get better and randomized evidence to address" a critical question of how much dialysate sodium is appropriate, Pinter said. Smyth and colleagues also wrote an editorial (3) on the study.

Pinter and Smyth said that the findings highlight the importance of the ongoing Randomised Evaluation of Sodium Dialysate Levels on Vascular Events (RESOLVE) trial, a multinational effort, in which they are involved. RESOLVE, which aims to recruit 400 dialysis centers in multiple countries, is randomizing centers to use a default of either 137 mmol/L or 140 mmol/L dialysate sodium concentrations. Outcomes, including mortality and cardiovascular events, will be assessed on individual patients receiving care at those sites. So far, since 2016, investigators have enrolled over 200 centers in Australia, Germany, the United Kingdom, Malaysia, India, and Canada. Results are expected in 2026. Although there is not a substantial difference between the two concentrations being studied, "it's large enough that we expect that we should see a difference if one truly exists," Smyth said.

How to remove water (and by default, salt) has been an ongoing critical question, Pinter noted, but not a lot of studies have been conducted to provide this needed evidence. In 2014, a consensus opinion (4) from the chief medical officers of 14 large dialysis companies in the United States recommended dialysate sodium be lowered as part of a "volume first" approach to lowering cardiovascular morbidity and death, Pinter said. "But [the authors] also acknowledged at the time that there were only 310 patients [who] had ever been included in randomized dialysate sodium trials worldwide."

While the nephrology community awaits results of the RESOLVE trial, Pinter advises that nephrologists working with patients undergoing dialysis be conservative and careful but not to rely on observational data to change their prescription practices. "Do not change care until randomized evidence becomes available," Pinter suggested.

Smyth agreed. "I would not suggest that a dialysis unit change [its] practice based on [this] paper," he advised. "The data [are] observational, which means that dialysate sodium could be acting as a marker of some other difference in the way these patients are cared for," he explained. While investigators tried to account for differences among sites, there is only so much that can be done statistically. "[The *JASN* article] should be seen as a call for a randomized study, and fortunately, we've got one on the way."

For more information about the RESOLVE trial, see https://clinicaltrials.gov/study/NCT02823821. To join the RESOLVE study team, contact Brendan Smyth at brendan.smyth@sydney.edu.au.

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ASN President's Update

Awareness Precedes Action

By Deidra C. Crews

"I had no idea something was wrong with my kidneys."

The first research project I pursued was motivated by the many patients I saw during internal medicine residency training who arrived at our emergency department only to be told for the first time that they were experiencing kidney failure. One of these patients made an indelible impact on me. He was a young man in his 30s who had for weeks been feeling tired with little desire to eat or drink. Otherwise, he appeared well despite having a serum creatinine of 37 mg/dL (normal range, 0.6–1.3 mg/dL) and ultrasound findings consistent with long-standing kidney disease. He shared, with tears in his eyes, that he had never been told that he had kidney disease and therefore, had no opportunity to take action(s) that might have prevented his developing kidney failure.

My patient's experience from 20 years ago continues to be the reality for far too many people. Ideally, people first learn the status of their kidney health in a primary care setting. US policies, such as the Affordable Care Act (ACA) in 2013, made it easier for many Americans to access health coverage through several interventions. These included expanded Medicaid coverage in participating states to adults younger than 65 years old with incomes less than 138% of the federal poverty line, which led to greater access to health insurance and narrowing of racial and ethnic disparities in insurance coverage in those states (1). However, the ACA has not resulted in greater awareness of kidney diseases among affected individuals (2). To cross the chasm of health care access to greater kidney health awareness and action, we must address gaps in screening, detection, and—importantly—communication of results.

The US Preventive Services Task Force is currently reviewing the topic of screening for chronic kidney disease (CKD) among US adults, with a focus on CKD stages 1–3. According to the task force, CKD stages 1–3 are "more likely to be asymptomatic and managed in primary care" (3). Its findings and potential screening recommendations will be particularly critical to prepare for the projected increase in US adults meeting diagnostic criteria for CKD as a result of implementation of the 2021 CKD Epidemiology Collaboration (CKD-EPI) equations without inclusion of coefficients for race (4).

When asked for their views on communicating with patients about their kidney health and managing CKD, a group of primary care clinicians noted several barriers, including their patients' limited awareness of their own kidney diseases and clinician challenges in staying current with CKD guidelines particularly when faced with limited time and resources (5). A study of patients with CKD that captured audio recordings of patient visits with their primary care clinicians found that awareness of kidney diseases as assessed by a "yes" response to the question, "Do you have a kidney problem or chronic kidney disease?" was no different among patients whose doctors did or did not discuss CKD during their visit (6).

A study has documented that the way we assess CKD awareness among our patients has implications for our ability to fully capture what they know about their condition (7). However, it also seems that how we communicate about kidney health and kidney diseases is of central importance. For example, focusing primarily on discussing laboratory findings (e.g., "Your creatinine was a little elevated.") may not help people to understand and retain information about their kidney health as much as explaining how the kidneys function in health and disease and how that might impact the way they feel.

March is National Kidney Month in the United States, the #NephMadness competition takes place (https://ajkd-blog.org/category/nephmadness/), and the annual celebration of World Kidney Day is Thursday, March 14, 2024. All three are terrific opportunities to raise awareness, wear kidney-themed garments, and communicate the renewed optimism in our community about the future of kidney health.

This year's theme for World Kidney Day is "Kidney Health for All: Advancing equitable access to care and optimal medication practice" (8). The timing of this theme is perfect because we must advocate for access to optimal medication practice while highlighting mounting concerns that newer, highly effective treatments for kidney diseases are not reaching populations who have historically faced barriers to receiving health care (9).

The theme aligns well with ASN's newly launched effort to begin producing Kidney Health Guidance. Such guidance will encourage high-quality, person-directed equitable care across the spectrum of kidney health and diseases from screening and early detection to diagnosis, treatment, and palliative care. ASN will focus on guidance topics that are important for the interdisciplinary kidney care team and their patients, and will prioritize topics wherein there is unmet clinical need or clinical ambiguity. To help address the vast amount of information that clinicians often have to sift through to guide the care of their patients, ASN Kidney Health Guidance will be brief, targeted, and aimed at more timely translation of evidence to support clinical decision-making (10). Later this year, ASN will produce its first Kidney Health Guidance on obesity and kidney diseases.

When I think about the greater awareness needed to advance kidney health and make the treatment options available to people living with kidney diseases, it is clear that each of us can contribute. For example, nephrologists and other clinicians can educate our patients in a timely way about their kidney health, using their preferred language and without the use of medical jargon. We can connect our patients and their families to high-quality educational resources that they might return to often, on their own time, when they feel most ready to receive the information.

Researchers can work to uncover new measures to facilitate early detection of kidney diseases, particularly among populations at a disproportionate risk for progression to kidney failure. Researchers can also examine and test new educational strategies that make use of innovative technologies, such as augmented intelligence, for people with kidney diseases. Such insights could facilitate increased awareness and generate more interest among policymakers in funding additional research. The research recruitment and enrollment process can also serve to educate individuals and their caregivers about kidney diseases.

And finally, it is time for us to consider a sustained campaign to raise awareness about kidney health. Such a movement could lead to improved detection and documentation of the burden of kidney diseases and increased government resources for kidney care and research and could reignite interest in nephrology careers. At a global level, a crusade of this kind could improve access to kidney care in many countries in which such access is extremely limited (11).

Building off of the National Kidney Foundation's "You're in the 33%" campaign (https://www.kidney.org/phi/155274/awareness), which emphasized that one-third of the population is at risk for kidney diseases, ASN's "We're United 4 Kidney Health" campaign (https://4kidneyhealth.org/about/) focused on four goals: 1) Intervene earlier to prevent, diagnose, coordinate care, and educate; 2) Transform transplant and increase access to donor kidneys; 3) Accelerate innovation and expand patient choice; 4) Achieve equity and eliminate disparities.

Although these complementary campaigns have raised awareness of kidney diseases in the United States and produced results, most notably last year's passage of the Securing the US Organ Procurement and Transplantation Network Act, we must think bigger, bolder, and—frankly—better. I believe this is the time for global action.

Partnerships among the global kidney community are strengthening, spurred by our recent need to respond together to the COVID-19 pandemic, natural and human-made disasters, and climate change. We are ready to come together to raise awareness about the more than 850 million people worldwide living with kidney diseases.

So, let us use this month to redouble our commitment to raising awareness about the importance of kidney health and the actions we are each taking to advance it. And let us use *every* month to champion the millions of people with kidney diseases, including the people who will "crash" into dialysis today, tomorrow, and next week, unaware their kidneys are failing. ■

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ASN's Policy Priorities in 2024

By Ryan Murray

ASN looks to build off the momentum of the policy success the kidney community experienced in 2023 and to advance several key goals this year across the following policy priority areas: intervening earlier, transforming transplant, accelerating innovation, achieving equity, and bolstering the kidney health workforce.

Intervening Earlier

Ensure that the US Preventive Services Task Force (USPSTF) establishes a screening recommendation for kidney diseases.

With 90% of people living with kidney diseases remaining unaware that they are affected due to the asymptomatic nature of the early stages of kidney diseases, ASN recognizes the importance of and advocating for intervening earlier through routine screening. In 2023, ASN and the entire kidney community clearly articulated concerns that any USPSTF decision that takes a step back from early disease detection and intervention would negatively impact patients with kidney diseases. This year, ASN will continue to coordinate with the kidney community in developing new approaches to inform USPSTF's research and recommendation development process and promote kidney health by delaying the progression to kidney failure in addition to finding cures and examining the management of kidney failure.

Transforming Transplant

Secure fiscal year (FY)25 funding for the Health Resources and Services Administration's (HRSA's) Organ Procurement and Transplantation Network (OPTN) Modernization Initiative.

Only 37 pieces of legislation became law in 2023, which included the Securing the US OPTN Act through the advocacy of ASN and the entire kidney community. The law calls on the HRSA to bring transformational changes to the US transplant network, including improvements in the OPTN governance that will increase accountability as well as reforms to ensure patients are served by best-in-class operators in each of the many functions of the OPTN—such as information technology management, policymaking, and research and evaluation. Recognizing that the nation's transplant system has been under-resourced for decades, the legislation also lifted the statutory cap on the amount of funding Congress could legally allocate to the HRSA to support transplant activities.

The HRSA and the Biden administration, which support and requested these statutory reforms, are implementing the aims of the Securing the US OPTN Act under the auspices of the "OPTN Modernization Initiative," centered around increasing transparency, accountability, and overall system performance on behalf of patients. However, for the HRSA to fulfill the aims of the Securing the US OPTN Act and reform the nation's organ donation and transplantation system, it must receive the appropriate funding from Congress. Securing funding for HRSA's OPTN Modernization Initiative in FY25 is ASN's top appropriations advocacy goal this year.

ASN will continue to work closely with the HRSA and the OPTN Modernization Initiative this year, focusing on maximizing patient access to transplantation and ensuring that access is equitable.

Establish a unified Office of Kidney Health and Transplantation (OKHT) within the US Department of Health and Human Services (HHS).

Today, at least 10 separate agencies or offices within the HHS have a role in helping the nation achieve kidney health. ASN believes that an opportunity exists for stronger coordination on kidney and transplant research across the federal government and in particular across the National Institutes of Health. ASN is proposing and evaluating the feasibility of the HHS establishing an OKHT. A potential OKHT, situated in the HHS Immediate Office of the Secretary, could ensure that all components that have a role in kidney health would work in coordination while bringing additional emphasis to and creating efficiencies across the care continuum.

Influence development of a new Center for Medicare and Medicaid Innovation (CMMI) model for transplant.

For several years, ASN has advocated for the creation of a CMMI model that focused on transplantation. After intense kidney community dialogue in 2022 and 2023 with CMMI and other kidney health stakeholders, the community has excitedly received confirmation that such a model was imminent. At the time of publication, the model was currently being reviewed by the Office of Management and Budget before it will be released to the public. If and when a new model is released for public comment this year, ASN will provide feedback to the CMMI to influence its development before it is fully enacted.

Accelerating Innovation

Socialize approaches to payment pathways for new and innovative technology.

ASN has emphasized the importance of innovation within the kidney space and its ability to advance kidney care for patients by including funding for the Kidney Innovation Accelerator (KidneyX) and the National Institute of Diabetes and Digestive and Kidney Diseases in its annual congressional appropriations advocacy. However, the payment system within which kidney care operates is extremely constrictive and stifles innovation.

As innovators reimagine what a kidney looks like and explore ways to bioengineer a kidney or successfully conduct xenotransplantation, among other groundbreaking opportunities, the payment system must be prepared for when these new therapies are safely approved and ready to be brought to market. Patients will ultimately suffer if they are unable to access the latest advances, so ASN will socialize novel approaches to payment pathways for new and innovative technologies.

Influence the future of End-Stage Renal Disease Treatment Choices (ETC) and Kidney Care Choices (KCC) models.

The ETC and KCC models were designed to incentivize delaying dialysis and to encourage home dialysis and kidney transplants for Medicare beneficiaries. As the Centers for Medicare & Medicaid Services (CMS) reviews and refines each model, ASN will continue to seek to impact the future of both models through annual comment periods. Specifically, ASN will advocate that the 10% "stretch goal" achievement threshold escalators for the later model years be removed, that participants within the ETC are credited for a kidney transplant for the life of the transplant, and that all models factor in and prepare for the impact of Medicare Advantage so that they are not entirely based on participants with fee-for-service plans.

Achieving Equity

Develop and promote specific policies to address the impact of climate change on kidney health, and advance climate health.

People living with kidney diseases are uniquely vulnerable to the effects of climate change, which itself threatens to increase the incidence and prevalence of kidney diseases, disrupt access to care, and widen inequity in kidney health. ASN will advocate for the collection and distribution of data that identify the direct impact of climate change on kidney health (i.e., increased heat exposure, dehydration, degrading air quality, and secondary effects that arise from disruptions in care caused by the increasing pace of severe weather events) and will evaluate the contributions kidney care has on climate change, drawing attention to the large environmental footprint of existing therapies to manage kidney failure.

Ensure appropriate access to sodium-glucose cotransporter-2 inhibitor (SGLT2i)/agonists.

For decades the kidney community has seen a dearth of new drugs and therapies compared with other diseases. Now that new therapeutic options are on the horizon and several, such as SGLT2i/agonists, have already entered the marketplace and begun to improve patients' lives, it is essential that every patient be able to access these new therapies. ASN will advocate for equitable access to SGLT2i/agonists and any other future therapeutic.

Advance racial equity in health care.

On January 20, 2021, President Biden signed Executive Order 13985–Advancing Racial Equity and Support for Underserved Communities Through the Federal Government–which charged the federal government with advancing equity for all, including communities that have long been underserved, and addressing systemic racism in the nation's policies and programs. ASN will continue to work across all of the HHS to further the goals of this order to assure equitable access to kidney care for all Americans from early detection, encourage efforts to slow kidney diseases' progression, and secure choice of modalities for those who reach kidney failure to access to kidney transplantation. ASN will also continue working with the CMS to promote the collection of data on social determinants of health (SDOH), the development of policies to address the impact of SDOHs, and other strategies to reduce health care disparities for all.

Bolstering the Kidney Health Workforce

Sustain and expand funding for physician training.

A robust, highly qualified, and diverse workforce is necessary to meet the nation's kidney care needs. To attract the best and brightest talent to the nephrology specialty, ASN will explore opportunities to expand funding for physician training through programs like Medicare Graduate Medical Education and HRSA Health Workforce (Title VII).

Ensure stability in the physician workforce by addressing physician payment.

The 26% decline over the past 2 decades in physician payment via the Medicare Physician Fee Schedule must be reversed. A 3.4% payment cut is expected to take place in 2024, resulting in approximately 1% payment reduction for nephrology. ASN seeks to reverse these cuts through the Medicare Physician Fee Schedule with congressional action. ASN will also advocate to expand access to federal student loan forgiveness for kidney health professionals.

As a new member of the American Medical Association, ASN will also coordinate its efforts with the broader health professional community.

Shape the future of the Merit-Based Incentive Payment System (MIPS).

ASN will provide feedback to the CMS on improving MIPS and its quality payment program, during the annual open comment period. During the beginning of the COVID-19 pandemic, the CMS automatically applied a hardship exemption for MIPS. In 2022, the hardship exemption was no longer automatic, and physicians had to apply. With a 2-year lag in payment, 2024 MIPS payments will be based on 2022 costs of care data. That data have not been as readily available as they were before the COVD-19 pandemic, and ASN is monitoring the impact of the data without a hardship exemption and advocating for appropriate payment policy adjustments.

To keep track of ASN's efforts to intervene earlier, transform transplant, accelerate innovation, achieve equity, and bolster the kidney health workforce in 2024, follow coverage in *Kidney News* and the ASN podcast feed, and visit the ASN policy webpage (https://www.asn-online.org/policy/). For real-time updates, follow ASN policy on X @ASNAdvocacy.

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

New Resource Empowers Patients with Diabetic Kidney Disease and Their Families

By Karen Blum

A new, free learning module from ASN's Diabetic Kidney Disease Collaborative (DKD-C) aims to empower people with DKD to learn more about their condition and become active participants in their care. Health care professionals are encouraged to share this resource, called "Your Kidneys and Your Health: Living with Diabetes," with their patients to help them understand DKD and improve communication with their health care team.

The module has several sections, starting with a primer chapter called **Kidney Disease 101**, which explains how the kidneys work and what they do, how diabetes impacts the kidneys, and the stages of kidney diseases. Additional chapters are:

- **Engaging with Your Care Team**, which covers questions patients can ask their clinicians, the importance of effective communication, and treatment options. It also features forms to download to track medical test results and medications.
- **Healthy Lifestyles in Diabetic Kidney Disease**, which explains nutrition and diet management; the importance of protein, exercise, and medical nutrition therapy; and advice for parents of children who have diabetes.
- **Progress Towards Health Equity**, which covers how unique life experiences and social determinants of health can impact the care patients need and receive and how they can talk to their physicians.
- **Diabetes, Blood Pressure, the Heart, and the Kidneys**, which presents educational information about chronic kidney disease, diabetes and kidney damage, high blood pressure and diabetes, and the connection between heart disease and kidney diseases.
- **Patient/Pharmacy Assistance Information**, which provides material about how pharmacists can help patients access financial assistance to afford their medications.

Upon completing the module, participants can print an attendance certificate and complete an evaluation.

This is the second module from the DKD-C, which in 2022, published an online course for clinicians on management of chronic kidney disease in people with diabetes, covering topics such as diet and exercise, racial and socioeconomic disparities, and treatments for diabetes and kidney diseases. After success with the first module, members of the collaborative wanted the information to be available to patients as well, so they adapted it into easily digestible information for laypeople and their families and caregivers, said Amy Mottl, MD, MPH, FASN, who is featured in the Kidney Disease 101 chapter and is an associate professor of medicine in the Division of Nephrology and Hypertension at the University of North Carolina School of Medicine in Chapel Hill.

"It was a joint venture between our patient advocates as well as other diabetes and chronic kidney disease experts from a whole multitude of specialties," Mottl said. "It was really fun to get this information disseminated to patients so that they can benefit from the same information that is available to clinicians."

During the planning, the group, led by patient advocate Patrick O. Gee Sr., PhD, JLC, founder of iAdvocate, Inc., in North Chesterfield, VA, decided to present much of the information through short videos thought to be relatable to patients and accessible to view on their mobile devices, said Susanne Nicholas, MD, PhD, MPH, FASN, tenured professor of medicine and a clinical hypertension specialist in the Division of Nephrology at the David Geffen School of Medicine at the University of California, Los Angeles. Many sessions feature Gee or other patient advocates interviewing experts.

"It made the information more easily accessible to patients because it's designed such that a physician specialist or pharmacist is in open discussion with a patient on a specific topic," Nicholas said. "It allows the patient advocates to provide their perspective and describe their experiences related to an interaction with their physician or how the physician perceived them at the initial visit and the information they did or did not receive…. When they view these videos, I think patients will be able to identify with them and say, 'Yes, that happened to me.'"

The module also offers recommendations for patients in the different topic areas, she continued: "There are specific questions provided for patients of what they can ask their physicians to make sure that the experience that they're receiving and how they interact with their physician [are] really valuable for them."

Individuals do not have to complete the course in order, Nicholas said. For example, if they had an upcoming doctor's appointment, they could go straight to the section on engaging with the care team and review questions to ask clinicians or a glossary of kidney-related medical terms.

We give them the verbiage of how to describe their kidney function, albuminuria, and things like that, so that when they go to their doctors they are really equipped and they have added knowledge," Nicholas explained. "My hope would be that patients use this not only in terms of educating themselves about the different aspects of their care related to diabetic kidney disease, but they use it as a guide for how to speak with their physician or what questions to ask, what medications they should be on, and what type of lifestyle approaches they could use."

Mottl, who has spent decades trying to better the knowledge base for patients with diabetes and chronic kidney disease, said participating in the project was personal for her. "With the increase in number of available treatments, I wanted to provide that knowledge base to patients in order to improve outcomes," she said. "People have better diabetes control and somewhat better hypertension control. But we don't do a very good job, especially in the United States, in getting people on guideline-driven treatments. I wanted to expand the opportunity to provide these treatments to patients, and what better way to do that than to go to patients themselves?"

The collaborative plans to promote the module with an upcoming publication, Mottl said, and will update the sections as needed using participant feedback.

The DKD-C was launched by ASN in July 2019 in response to the development of new therapies for people with DKD. The collaborative works to increase coordination among primary care physicians, nephrologists, and other specialists to deliver appropriate therapies to people living with DKD. It also aims to provide educational information to help nephrologists and other health professionals provide high-quality care to people with DKD and to address legislative, regulatory, and policy issues that affect the ability of nephrologists and other health professionals to provide high-quality care to people with DKD. DKD remains one of the most common and serious complications of type 2 diabetes.

To view the module or refer the resource to patients, see https://epc.asn-online.org/learning_course/your-kidneys-and-your-health/.

Fellows First

Favorable Outcomes following Kidney Transplant in Patients with AA Amyloidosis

By Rose Mary Attieh

Occurring in patients with chronic inflammatory conditions, AA amyloidosis is a form of systemic amyloidosis characterized by the extracellular deposition of serum amyloid A (SAA) protein fibrils. Renal manifestations are observed in as many as 90% of cases, with up to 10% of patients presenting with kidney failure at the time of diagnosis (1). Due to the prevalent frailty and multi-organ involvement in individuals with kidney failure secondary to AA amyloidosis, these patients have frequently faced exclusion from kidney transplant. This exclusion is also driven by concerns about the heightened risk of disease recurrence in the allograft, observed in up to 25% of cases (2).

Novel biotherapies such as interleukin (IL)-1, IL-6, and tumor necrosis factor-α inhibitors have demonstrated efficacy in halting SAA synthesis and, consequently, amyloid deposition. Therefore, Schwarz and colleagues (3) hypothesized that the increase in use of these biotherapies, coupled with advancements in post-transplant care, may improve outcomes of kidney transplant recipients (KTRs) with AA amyloidosis. The investigators conducted a retrospective cohort study analyzing outcomes in 86 patients who underwent kidney transplant between 2008 and 2018 across 26 centers in France. Patients were eligible for inclusion if they were 18 years or older at the time of transplant and only if the diagnosis of renal AA amyloidosis was established through either kidney biopsy or the presence of AA amyloid deposition in another tissue. The mean KTR age was 49.4 years. Familial Mediterranean fever was the cause of amyloidosis in 43% of cases.

Although the study was unable to assess the association of biotherapy use with post-transplant outcomes due to the low percentage (18.6%) of KTRs receiving these drugs, it did yield interesting observations. Patient survival rates were not inferior to the general kidney transplant population in France (4), reaching 94.0% at 1 year and 85.5% at 5 years post-transplant. Allograft survival also aligned with national data, with a 10.5% cumulative incidence of graft loss at 1 year and 13.0% at 5 years post-transplant. Recurrence of AA amyloidosis was documented in only 5.8% of cases. Notably, there was a high rate of infection requiring hospitalization, involving 55.8% of cases, despite the use of per-protocol antimicrobial prophylaxis in each center. Infection therefore emerged as the leading cause of post-transplant death. In addition, there was an increased incidence of acute allograft rejection of 27.9%. Interestingly, the use of biotherapy post-transplant showed no correlation with either acute rejection or infection. Furthermore, multivariable analysis revealed that the C-reactive protein level at the time of transplant was associated with both patient survival (hazard ratio [HR], 1.01; 95% confidence interval [CI], 1.00–1.02; p = 0.01) and allograft survival (HR, 1.68; 95% CI, 1.10–2.57; p = 0.02), highlighting the importance of adequate control of the underlying inflammatory process to attain good outcomes post-transplant.

In sharp contrast to earlier reports, this study is the first, to our knowledge, to demonstrate favorable outcomes in KTRs with AA amyloidosis, arguing that these patients should not be denied transplant. Although these results are certainly encouraging, some limitations of the study must be considered. For instance, the study lacked a matched control group. Consequently, the observed similarities in outcomes with the general kidney transplant population in France may have been partly attributed to the younger age and lower comorbidity burden in the study's cohort with AA amyloidosis (3). Furthermore, it is challenging to ascertain whether the low recurrence rate was associated with the biotherapies or under-reporting, given that only 51.2% of the cohort underwent at least one kidney biopsy with Congo red staining analysis.

Although more research is required to examine the impact of biotherapies on post-transplant outcomes, future studies should also strive to find effective treatments that can mitigate infection-related morbidity and mortality in KTRs with AA amyloidosis. ■

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The author reports no conflicts of interest.

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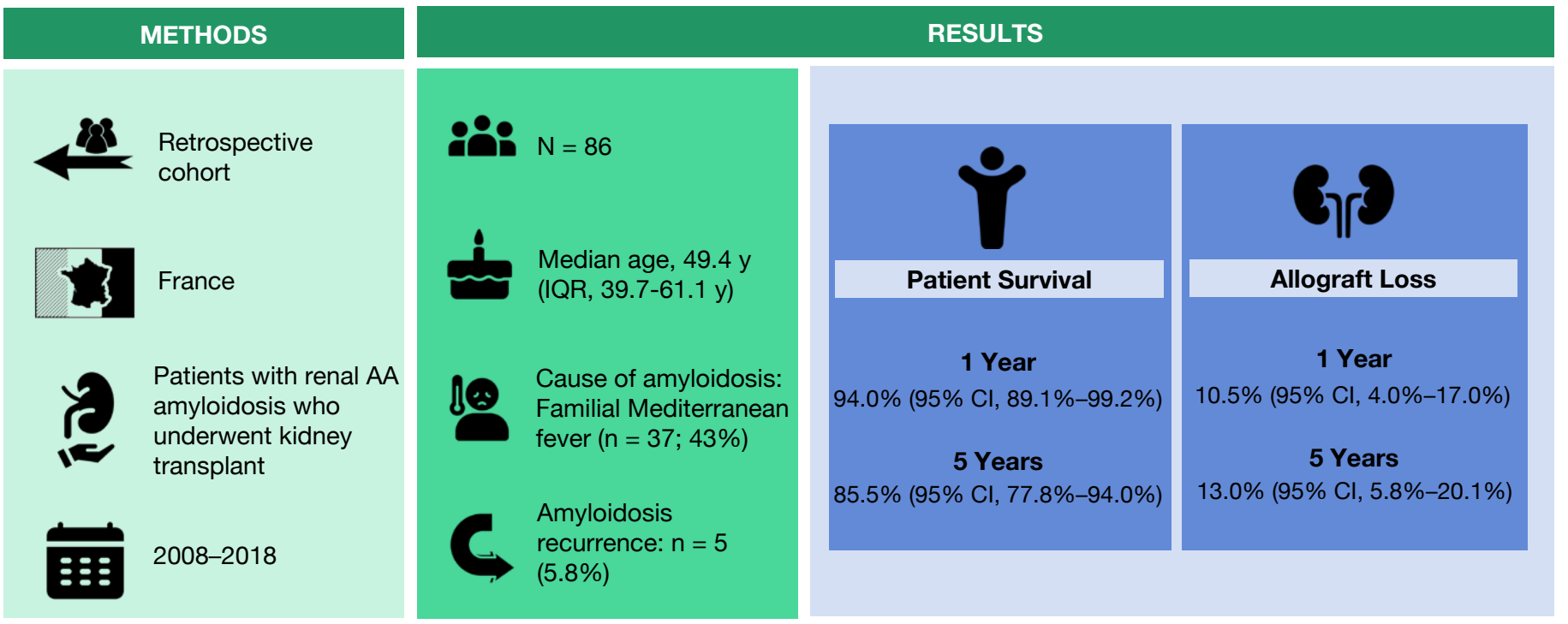
Favorable outcomes following kidney transplant in patients with AA amyloidosis

KidneyNews



Conclusion: Patients who received a kidney transplant for AA amyloidosis experienced favorable rates of survival and lower recurrence rates than previously reported. IQR, interquartile range.

Schwarz C, et al. **Kidney transplantation in patients with AA amyloidosis: Outcomes in a French multicenter cohort.** *Am J Kidney Dis* (published online September 22, 2023). doi: 10.1053/j.ajkd.2023.07.020

Visual Graphic by Jia H Ng, MD, MSCE

Can Albuminuria Predict Cancer Risk?

By Joana Gameiro and Marco Bonilla

Cancer is a significant public health problem and is one of the leading causes of morbidity and mortality in adults worldwide and the second cause of mortality in the United States. This year, the American Cancer Society estimated that there will be 2,001,140 new cancer cases and 611,720 cancer deaths in the United States (1). Delay in diagnosing and treating patients leads to an increase in advanced stage cancer and increased mortality. Thus, a crucial need arises to identify new cancer detection and prevention markers.

Albuminuria is a known marker of kidney damage, defined as a persistent albumin excretion of >300 mg/day. A 24-hour urine collection is the gold standard for determining albuminuria (2). This is a marker of kidney injury but also of endothelial dysfunction and has been consistently associated with higher risk of chronic kidney disease progression (3), cardiovascular events (4), and cerebrovascular disease (5). However, the connection between albuminuria and cancer remains unclear.

Prior studies have demonstrated a potential association between albuminuria and cancer. An observational study by Ahn et al. (6) examined the association between proteinuria and cancer incidence among 9,714,387 participants, followed over a median duration of 4 years. Their findings revealed a statistically significant increase in the overall cancer risk among participants with proteinuria (adjusted hazard ratio [HR], 1.154; 95% confidence interval [CI], 1.134–1.173). Similarly, another observational study by Tu et al. (7) investigated cancer incidence and mortality. The investigators followed 405,878 participants for an average of 8.7 years. They found that cancer incidence and mortality increased significantly with increasing severity of proteinuria. Risk increased with the severity of proteinuria: 12% (HR, 1.12; 95% CI, 1.04–1.21; p = 0.004) with trace proteinuria and 21% (HR, 1.21; 1.09–1.35; p < 0.001) with proteinuria defined as ≥+.

Recently published data from the Prevention of Renal and Vascular End-Stage Disease (PREVEND) study (8) and the Stockholm Creatinine Measurements (SCREAM) project (9) support the association of albuminuria and increased cancer risk and cancer mortality, independent of estimated glomerular filtration rate (eGFR) (Figure 1).

The PREVEND study (8) prospectively analyzed data from 8490 participants with a mean age of 49.8 ± 12.7 years, median baseline urinary albumin excretion (UAE) of 9.4 (interquartile range, 6.3–17.8) mg/24 hours, and mean baseline eGFR of 94.6 ± 17.3 mL/min/1.73 m^2. After a median follow-up of 17.7 years, the 10-year absolute risk for cancer was 8.1% (95% CI, 7.5%–8.6%). After multivariable adjustment, for every doubling of UAE, there was a 7% higher risk of overall cancer incidence, a 15% higher risk of urinary tract cancer and this association remained after adjustment for eGFR respectively. Concerning a cancer site, there was an increased risk of lung cancer (HR, 1.13; 95% CI, 1.04–1.22), and hematological cancer (HR, 1.12; 95% CI, 1.00–1.25). Additionally, the risk of cancer mortality was 9% higher per doubling of UAE after multivariable adjustment, including eGFR (HR, 1.09; 95% CI, 1.03–1.14).

The SCREAM project (9) analyzed data from two retrospective cohorts: one with 250,768 participants with at least one urine albumin-creatinine ratio (ACR) test and another with 433,850 participants with at least one dipstick albuminuria test. Patients in the ACR cohort had a mean age of 60.1 ± 15.8 years and a mean eGFR of 89.1 ± 21.8 mL/min/1.73 m^2. During a median follow-up of 4.3 years, 21,901 (8.7%) of these patients developed cancer, with a 10-year crude incidence of overall cancer of 16.2% (95% CI, 16.0%–16.5%). After multivariable adjustment including eGFR, participants had a 23% higher risk of cancer incidence with an ACR of 30–299 mg/g (HR, 1.23; 95% CI, 1.19–1.28) and a 40% higher risk with an ACR ≥300 mg/g (HR 1.40; 95% CI, 1.31–1.50) when compared with participants with an ACR <30 mg/g. This association was observed for urinary tract, gastrointestinal tract, lung, and hematological cancer (p < 0.05), and results were similar in the dipstick test cohort.

The definitive nature of this association, whether it signifies causation or mere coincidence, remains to be determined. Possible mechanisms include the role of chronic inflammation, endothelial dysfunction, and the activation of the renin-angiotensin system. These factors may collectively contribute to both albuminuria and tumor growth (9). Nonetheless, future studies are crucial to elucidate these mechanisms.

In summary, a distinct correlation between albuminuria and cancer risk, irrespective of the eGFR, has been established by Luo et al. (8, 9). Integrating routine albuminuria assessment in clinical practice is paramount, helping to identify patients with high risk of cancer. Further studies should also address whether reduction in albuminuria after initiation of intervention would be associated with improved prognoses. ■

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The authors report no conflicts of interest.

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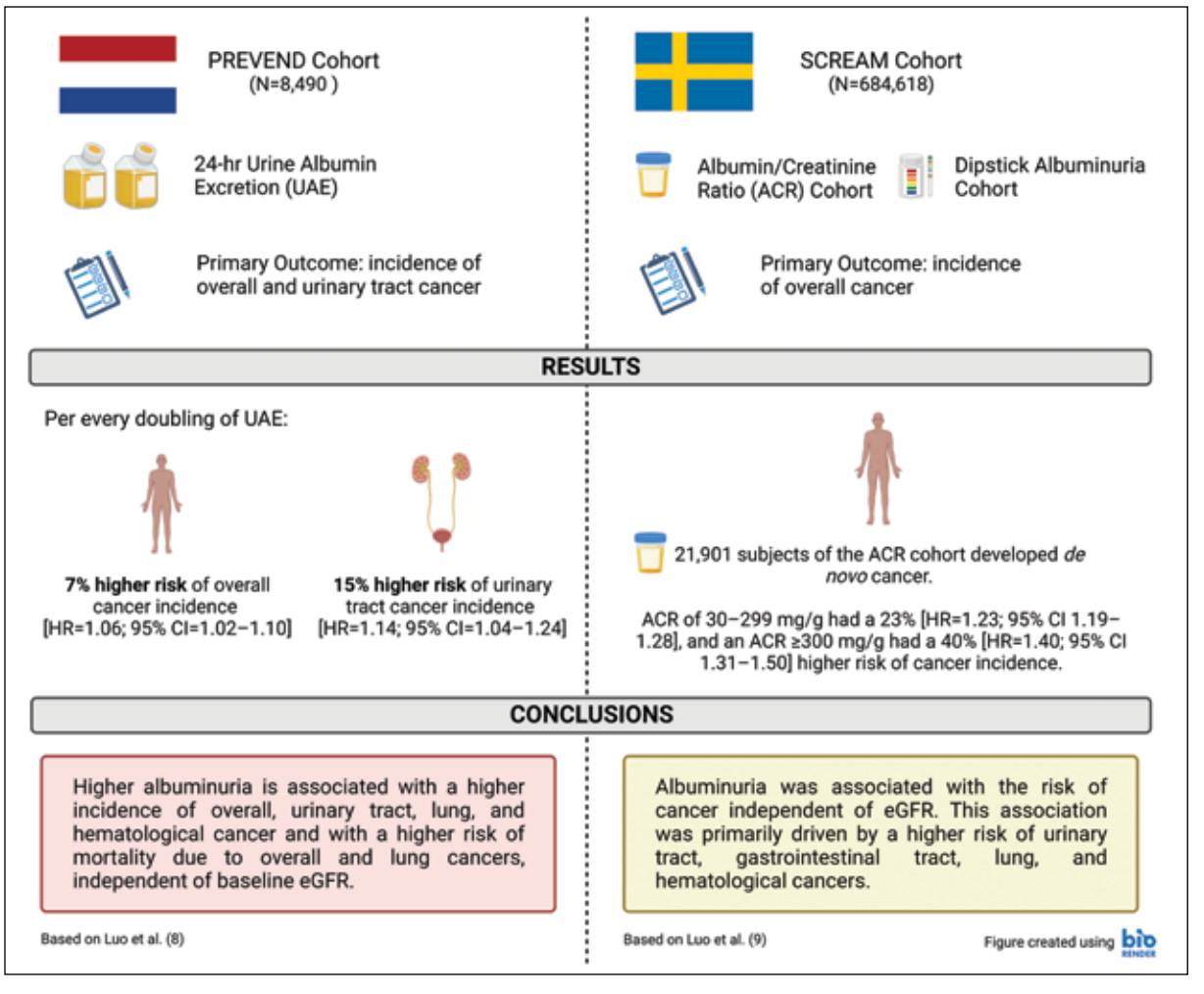
Figure 1. Can albuminuria predict cancer risk?



Visit TAVNEOSPRO.com to explore the data

INDICATION AND IMPORTANT SAFETY INFORMATION

INDICATION

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

CONTRAINDICATIONS

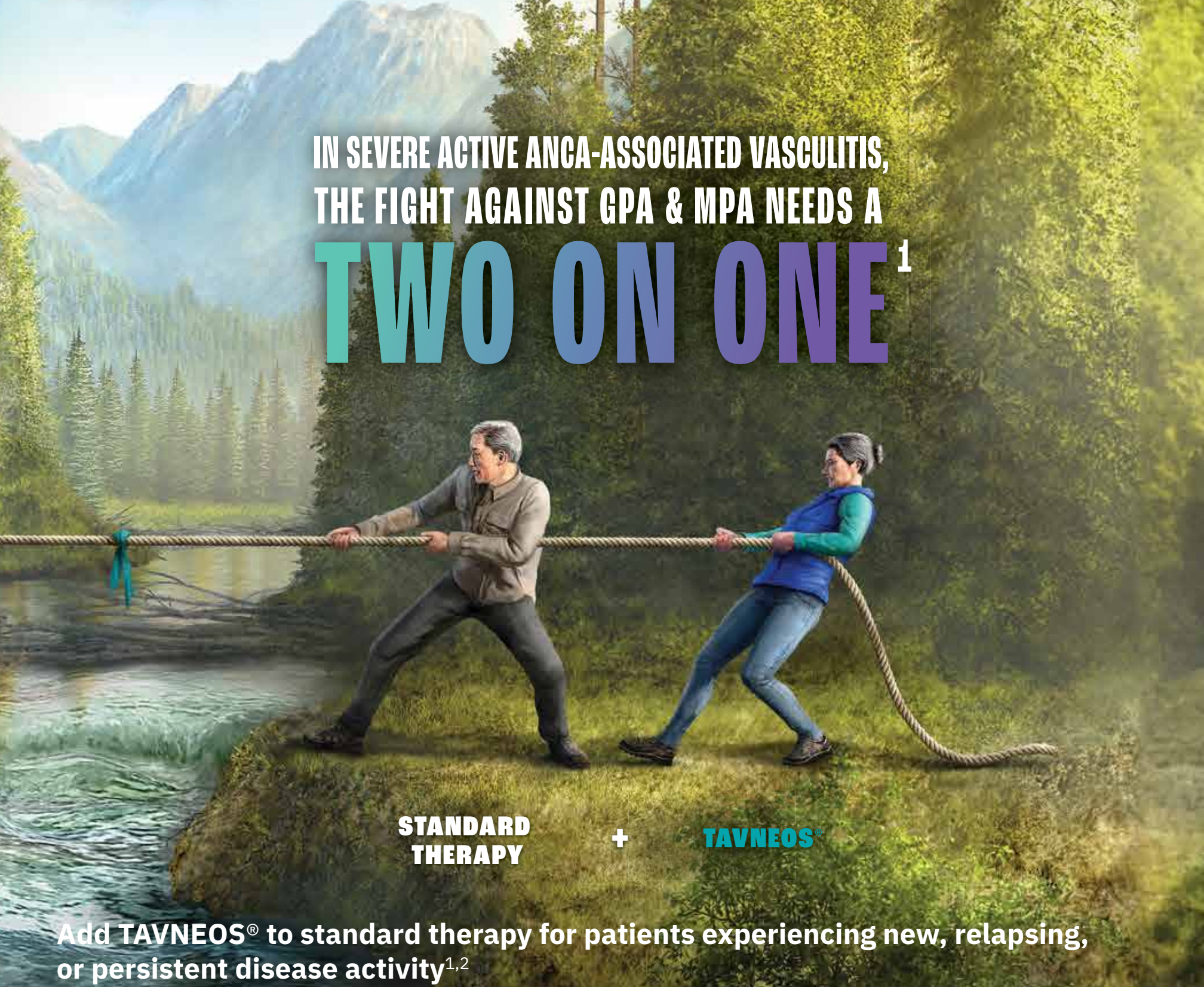
Serious hypersensitivity to avacopan or to any of the excipients.

WARNINGS AND PRECAUTIONS

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

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

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



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

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

ADVERSE REACTIONS

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

DRUG INTERACTIONS

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

TAVNEOS is available as a 10 mg capsule.

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

References: 1. TAVNEOS [package insert]. Cincinnati, OH: Amgen Inc. **2.** Chung SA, Langford CA, Maz M, et al. *Arthritis Rheumatol*. 2021;73(8):1366-1383.

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

12/23 USA-569-80504

AMGEN®

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

INDICATIONS AND USAGE

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

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

Hepatotoxicity

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

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

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

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

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

Hypersensitivity Reactions

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

Hepatitis B Virus (HBV) Reactivation

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

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

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

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

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

Serious Infections

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

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

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

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

ADVERSE REACTIONS

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

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

Clinical Trials Experience

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

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

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

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

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

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

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

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

Hepatotoxicity and Elevated Liver Function Tests

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

Angioedema

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

Elevated Creatine Phosphokinase

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

DRUG INTERACTIONS

CYP3A4 Inducers

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

CYP3A4 Inhibitors

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

CYP3A4 Substrates

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

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

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

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

Data

Animal Data

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

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

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

Lactation

Risk Summary

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

Animal Data

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

Pediatric Use

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

Geriatric Use

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

Patients With Renal Impairment

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

Patients With Hepatic Impairment

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

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

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USA-569-80226

Improving AKI Care: Will Handheld POCUS Devices Have a Role?

By Abhilash Koratala and Amir Kazory

The prevalence of fluid overload among hospitalized patients with acute kidney injury (AKI) and its negative impact on prognoses has been increasingly recognized (1). Additionally, the potential contribution of fluid overload to kidney dysfunction (congestive nephropathy) highlights the need for reliable bedside methods for objective and reliable assessment of volume status (2). Point-of-care ultrasonography (POCUS) is a clinician-performed imaging procedure using ultrasound that addresses focused clinical questions at the bedside. Although appropriately trained nephrologists can perform scans ranging from simple kidney and bladder ultrasonography to comprehensive hemodynamic assessments, the resurgence of interest in POCUS is sparked by studies exploring the role of lung ultrasonography in patients receiving hemodialysis (3–5).

Affordable handheld ultrasound devices (HUDs) with improved portability have helped with the widespread use of POCUS. Most clinical ultrasonography systems, whether conventional or HUDs, use piezoelectric crystals within the transducers. These crystals vibrate, generating ultrasound waves when a potential difference is applied across the electrodes. Upon receiving an echo, they produce an electric signal that is displayed as an image. Transducers vary in their internal crystal makeup and arrangement, influencing how they display images and the frequencies at which they operate. Conversely, certain HUDs use a more recently developed microchip technology that generates ultrasound waves through a change in capacitance. These units, constructed on silicon using micromachining techniques, retain conventional ultrasound wave properties and image characteristics but enable the amalgamation of various transducer properties into a single unit, facilitating miniaturization of the equipment.

A recent study by Soares et al. (6) investigated the efficacy of a HUD using microchip technology for lung and inferior vena cava (IVC) ultrasonography in patients with AKI who were undergoing renal replacement therapy. In this observational study that included 50 patients who were critically ill, the investigators performed lung and IVC ultrasonography at the beginning of dialysis and 60 minutes into the session using the Butterfly IQ™ microchip HUD as well as conventional piezoelectric crystal-based machines (Philips InnoSight or GE HealthCare Logiq™ P6). Dialysis prescription was not altered based on the ultrasonography findings. A strong correlation was found between the microchip and traditional piezoelectric-based ultrasound modalities in documenting the improvement in lung B-lines and IVC dynamics at two time points during hemodialysis.

B-lines on the lung ultrasonography indicate extravascular lung water, usually secondary to elevated left heart filling pressures. At the same time, IVC ultrasonography is a standard echocardiographic parameter for estimating right atrial pressure in patients with spontaneously breathing. The study's commendable use of an 8-zone lung ultrasonography method, as opposed to the more cumbersome 28-zone approach, enhances its practicality. Although acknowledging that the the study's microchip HUD is not the sole HUD available on the market, and most HUDs use piezoelectric technology, the study's findings underscore the potential role of ultraportable ultrasonography in nephrology practice. This aligns with the dynamic workflow of nephrologists who often traverse a variety of care settings.

It is, however, crucial to avoid overly optimistic conclusions extrapolating these findings to all POCUS applications. Lung ultrasonography relies on artifact interpretation, independent of high-resolution imaging capabilities; advanced settings suppressing artifacts are often disabled on larger machines to create a dedicated lung preset. Likewise, capturing images of the IVC does not usually warrant high-resolution devices, particularly considering that the average weight of patients in this study was 70 kg. Nonetheless, a comprehensive bedside hemodynamic evaluation requires more than lung and IVC ultrasonography, specifically a focused cardiac ultrasonography and selected Doppler applications (7, 8). Furthermore, IVC POCUS is not reliable in estimating right atrial pressure in patients who are mechanically ventilated. Therefore, the image quality of the device is a crucial factor for nephrologists seeking to enhance their proficiency in advanced POCUS applications. In this context, it is notable that the Butterfly IQ™ device ranked lowest among four commonly used HUDs in the United States regarding image quality (9). Although the study contributes to the evolving landscape of POCUS applications in nephrology, a nuanced approach is essential, given the diversity of available devices and the ever-advancing nature of this technology. Table 1 presents a summary of the strengths and drawbacks of various methods for evaluating volume status in individuals with kidney diseases. ■

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Table 1. Commonly used methods for evaluation of volume status

Method	Advantages	Limitations
Physical examination	• Standard bedside evaluation: physicians do not require additional training. • Positive findings are significant.	• Has poor sensitivity; misses a significant proportion of patients with volume overload.
Weight	• Short-term changes in weight reflect fluid gain or loss. • Can be done by the patient at their home.	• Errors can occur due to inadequate calibration of the equipment or comparing readings from different scales. • Changes in weight do not reflect congestion due to fluid redistribution.
Intake-output chart	• Offers a snapshot of the patient's fluid balance.	• Errors in documentation are common, particularly outside of the intensive care unit. • Does not reflect congestion due to fluid redistribution.
Bioimpedance	• Provides information on total body, extracellular, and intracellular water enabling the calculation of absolute and relative fluid overload.	• Cannot discriminate between compartmentalized edema (ascites, pericardial, and peritoneal fluid) and increased total body water. • Does not assess intravascular volume.
Continuous hematocrit monitoring	• Provides real-time data on relative changes in intravascular blood volume, allowing titration of the rate and volume of ultrafiltration.	• Application is limited to patients undergoing renal replacement therapy. • Is a nurse- or technician-driven modality; staff training is necessary. • Does not assess tissue congestion or extravascular lung water.
Pulmonary artery catheterization	• Provides insight into hemodynamic variables such as right atrial pressure, pulmonary artery pressure, pulmonary capillary wedge pressure, pulmonary vascular resistance, and cardiac output.	• Is invasive. • Monitoring hemodynamic changes in response to therapy is not possible outside specialized intensive care units. • Cannot provide information on the presence or absence of extravascular lung water. (Elevated pressure does not always imply volume.) • Does not provide information on the severity of venous congestion. • Errors can occur due to improper transducer calibration, leveling, zeroing, and over/underinflation of the balloon.
IVC ultrasonography	• Provides an estimate of right atrial pressure. • Is relatively easy to perform; most HUDs are adequate.	• Is unreliable to estimate right atrial pressure in patients who are mechanically ventilated. • A plethoric IVC is not specific to volume overload (can be seen in conditions such as cardiac tamponade, pulmonary embolism, or pulmonary hypertension). • A small, collapsible IVC does not differentiate among hypovolemia, euvolemia, and a high-output cardiac state. • IVC can be small and collapsed despite elevated right atrial pressure in cases of intra-abdominal hypertension. • IVC collapsibility depends on the strength of breath, which is highly variable among patients.
Internal jugular vein ultrasonography	• Aids in the estimation of right atrial pressure. • Is particularly useful in cases in which the IVC is inaccessible or unreliable (e.g., cirrhosis). • HUDs generally provide adequate images.	• Errors occur due to incorrect bed angle, excessive transducer pressure, and off-axis views. • The belief that the right atrial depth is 5 cm from the sternal angle has been demonstrated to be incorrect. • Precise estimation requires simultaneously focused cardiac ultrasonography. • Has variations in scanning protocols throughout the literature.
Lung ultrasonography	• Detects and quantifies extravascular lung water. • Is more sensitive than a chest radiograph for cardiogenic pulmonary edema. • HUDs provide adequate images.	• B-lines are not specific for pulmonary edema (can be seen in lung fibrosis, infections, contusion, etc.). • Some cases necessitate simultaneous measurement of left ventricular filling pressures using cardiac Doppler ultrasonography to differentiate cardiogenic and non-cardiogenic pulmonary edema.
Venous Doppler (hepatic, portal, intrarenal, and femoral)	• Detects and quantifies systemic venous congestion. • Allows monitoring the response to decongestive therapy by repeating the measurements.	• Is an advanced skill that requires competence in Doppler ultrasonography. • Lack of simultaneous electrocardiogram may limit interpretation, particularly the hepatic vein waveform. • Does not differentiate pressure and volume overload. • Needs high-end HUDs or cart-based machines.
Focused cardiac ultrasonography	• Provides information on cardiac pump function, chamber enlargement, pericardial effusion, and gross valvular lesions. • Advanced users can estimate stroke volume, pulmonary artery pressure, and left ventricular filling pressures.	• Is an advanced skill; nephrologists performing Doppler assessments usually need certification in critical care echocardiography. • Needs high-end HUDs or cart-based machines. • The reliability is contingent on having adequate acoustic windows, influenced by the patient's body habitus.

Mentorship for Pediatric Kidney Transplant in Low- and Middle-Income Countries

By Sukanya Govindan and Stephen D. Marks

Kidney transplant is the gold standard treatment for kidney failure. However, access to this life-saving procedure remains a challenge, particularly in low- and middle-income countries (LMICs). Although there is increased transplant for adults in LMICs, there is still variability in access to pediatric kidney transplants due to poor resources, in addition to lack of skilled personnel and training (1–3). To address this issue, many initiatives have been set up over the past decade, including the ISN-TTS Sister Transplant Centers program (a partnership between the International Society of Nephrology [ISN] and The Transplantation Society [TTS]) (4), the International Pediatric Nephrology Association Sister Renal Centers Program (5), and an outreach program of the International Pediatric Transplant Association (6). A recently published article in *Pediatric Nephrology* by Roberts et al. sheds light on the transformative impact of Transplant Links, one such initiative that seeks to address disparities and foster sustainable solutions for pediatric kidney transplant in LMICs (7).

Established in 2006, the Transplant Links Community (TLC) is a UK-registered charity wherein National Health Service specialists volunteer their time and mentorship to centers in LMICs, helping them create a viable kidney transplant program (8). Since its inception, the TLC has helped many centers in Africa, Asia, and the Caribbean to launch adult kidney transplant programs. It has also assisted in the establishment of pediatric programs in three Caribbean centers [the names of which were intentionally not disclosed by the authors]. The TLC mentors institutions through a unique, multi-tiered approach based on individual centers' requirements and existing skills. It might assist institutions with developing de novo transplant programs, expanding pre-existing services, providing supplementary training to multidisciplinary teams, or facilitating site visits to other transplant centers in the UK.

Potential centers are identified after reviewing their existing nephrology, surgical, and nursing personnel and their available medical and laboratory facilities. The TLC also helps local teams commit to ethical frameworks (e.g., Declaration of Istanbul and Ethical and Policy Considerations in Organ Donation after Circulatory Determination of Death) and gathers political and funding support for the program. Once established, the team of doctors at the TLC undertakes in-person visits complemented by internet-based teaching and mentoring sessions.

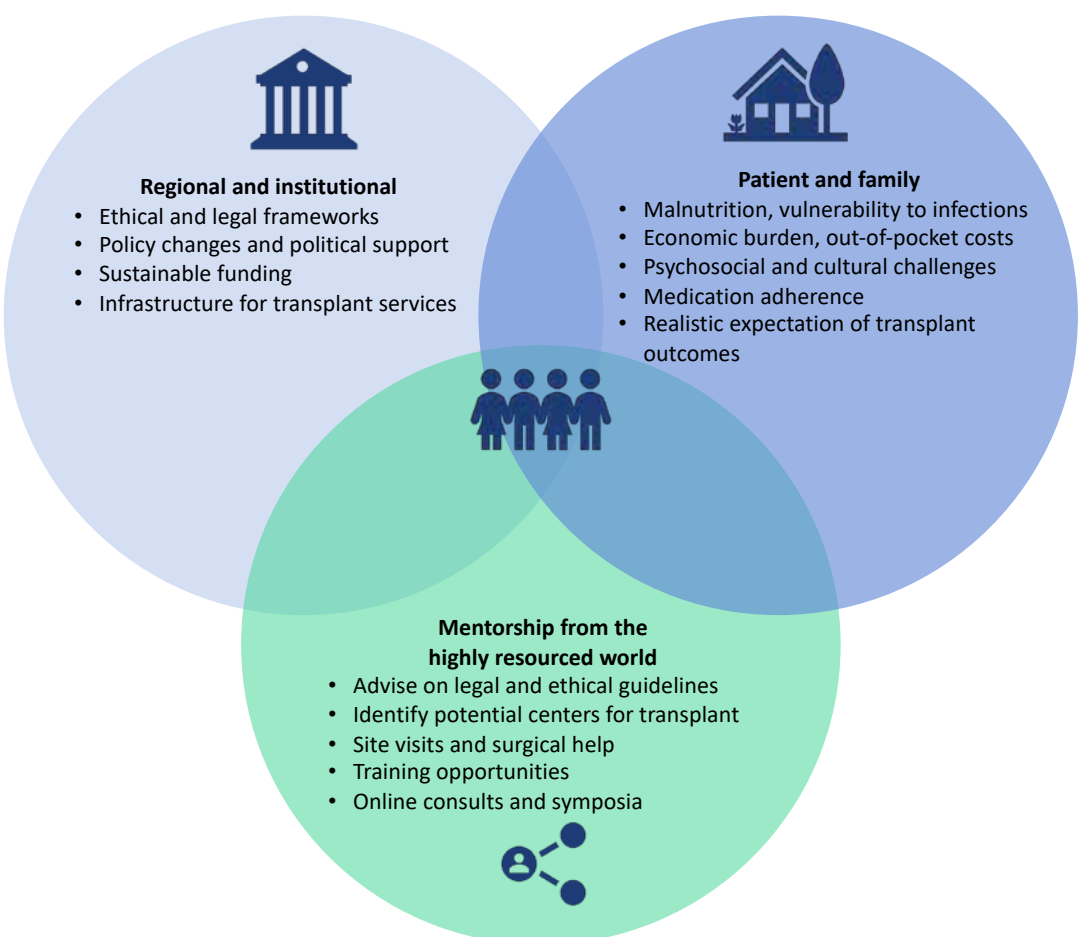
A prior published study of TLC's 10-year outcomes shows excellent patient and allograft survival, and a significant number of supported centers have progressed toward self-sufficiency in adult kidney transplant (9). Unfortunately, the documented results for transplant in children have been dismal. Roberts and colleagues emphasize the difficulties the TLC faces when establishing pediatric kidney transplant programs (7). The primary obstacles encountered are:

- insufficient expertise in pediatric specialty care and allied health fields
- inconsistent access to immunosuppressive medications and therapeutic drug-level monitoring
- the financial burden associated with post-transplant complications and care
- non-adherence to medications

The relatively small number of potential pediatric transplant recipients also results in inadequate and inconsistent political support than what is required to sufficiently develop these programs (7). These challenges are unfortunately common and, to our knowledge, are shared by all LMICs in establishing sustainable pediatric kidney transplant programs.

Pediatric chronic kidney disease is associated with extensive morbidity and mortality, especially in LMICs. Although the TLC's model has been effective in setting up adult kidney transplant services in LMICs, significant hurdles exist in the pediatric domain. More efforts are urgently required to address the training gaps and to overcome additional barriers in developing pediatric transplant programs. Concerted effort is required from key stakeholders (Figure 1), including local transplant professionals, policymakers, and politicians, to overcome the existing challenges. ■

Figure 1. Key stakeholders involved in pediatric kidney transplant in LMICs



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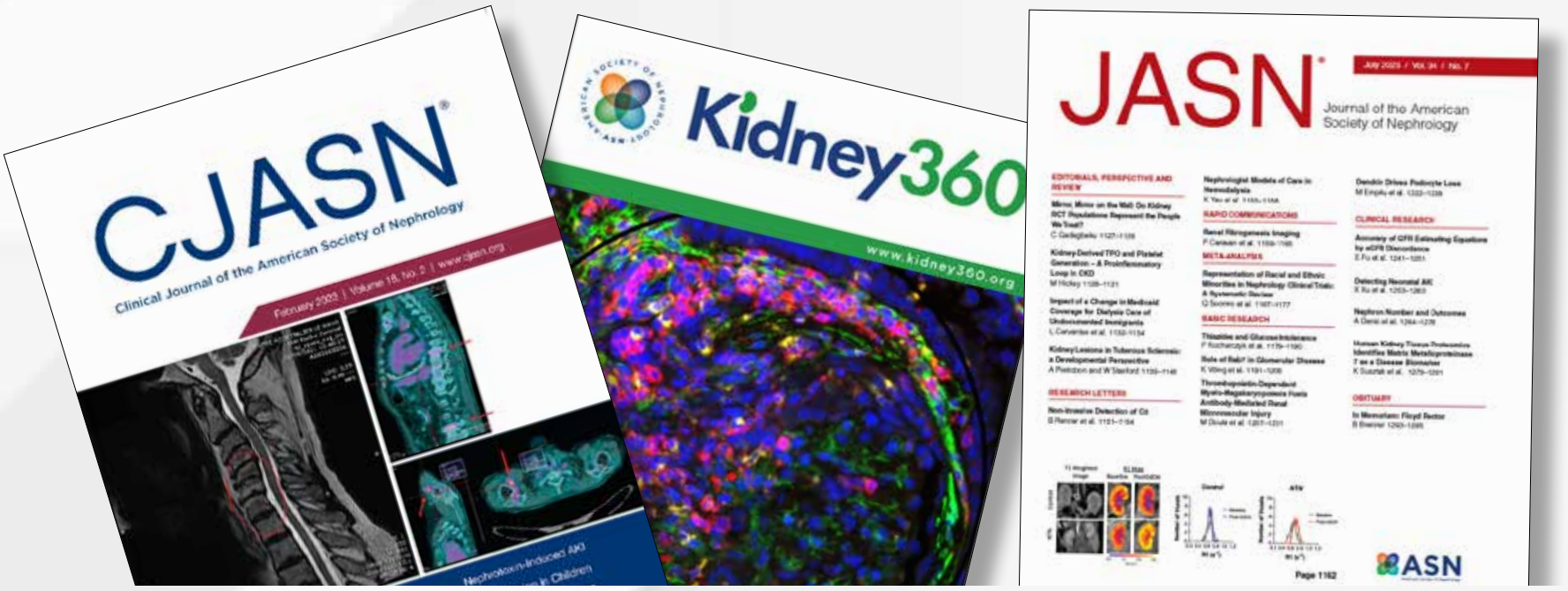

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Serving the Underserved

The following article is the third of a five-issue series focused on caring for patients in underserved populations. Inspired by several sessions at Kidney Week 2023, this series features unique patient and physician perspectives, explains legal protections and limitations, and seeks to identify opportunities to improve kidney care for these communities.

Incarceration Linked to Kidney Risk and Care Access Challenges

By Bridget M. Kuehn

For 10 years, Laura Maursetter, DO, FASN, associate professor of medicine at the University of Wisconsin–Madison and section chief of nephrology at the William S. Middleton Memorial Veterans' Hospital in Madison, has provided telehealth care to individuals with kidney diseases in 31 of the 36 correctional facilities in Wisconsin. A medical assistant works with Maursetter and coordinates six, 30-minute visits each week with patients in the facilities. The facilities run laboratory tests and fax her the results.

"It ends up being pretty seamless, and as you get to know the facilities a little bit better, it becomes a lot easier to communicate," she said.

Maursetter's work has given her a window into the high rates of kidney diseases among people who are incarcerated and the challenges they face both in prison and as they transition to life after prison. She noted that patients who are incarcerated face unhealthy dietary options and may or may not have control over their medications or when they are administered. There are also only two facilities in the state that have dialysis services.

"Patients who need dialysis have to go to [those facilities] even if it doesn't align with the level of security they require," said Maursetter, who shared her experience at the "Serving the Underserved: Improving Kidney Health in Underserved Populations" at Kidney Week 2023 in Philadelphia, PA.

These challenges are not unique to Wisconsin. A recent review of the literature in *Current Hypertension Reports* identified a lack of chronic disease care and access to specialists, limited control over lifestyle, and difficulties transitioning to care in the community after release as widespread challenges affecting individuals with kidney diseases who are incarcerated (1). Maursetter noted that a staggering 1.9 million people are incarcerated across the United States, and an estimated 5% or 96,000 of them may have kidney conditions (2).

"This is a uniquely vulnerable population," said the recent review's senior author (1), Katherine Rizzolo, MD, a nephrologist and assistant professor of medicine at Boston University Chobanian & Avedisian School of Medicine, MA, in an interview with *Kidney News*. She explained that many individuals lack health care access before involvement with the criminal justice system, and there are limited data available about their experiences during incarceration and after to help guide efforts to improve their care. "We don't know what we are dealing with," she said.

Magnified disparities

The United States has the highest incarceration rate in the world (3). Maursetter noted that this is the result of changes in sentencing policies that have accelerated incarcerations despite no increase in crime rates. There are also extreme disparities among those who are incarcerated in the United States, with many individuals who already face kidney disease-linked health disparities being disproportionately affected.

Men comprise the bulk of people who are incarcerated in the United States. Most are between the ages of 25 and 54 years, but the population 55 years and older who are incarcerated increased 300% between 1990 and 2009, Maursetter said. "We have an aging population in our prison system," she said.

There are also marked racial, ethnic, and economic disparities among these populations. A White man has a 1 in 17 risk of incarceration compared with a 1 in 3 chance for a Black man in the United States, she noted. Poverty and educational levels also play a role. For example, a White man between the ages of 20 and 34 years without a high school degree has a 1 in 8 chance of incarceration compared with a 1 in 57 chance for peers with a high school degree. Maursetter said a boy whose family is in the bottom 10% of US incomes is 20 times more likely to be in prison by the age of 30 years than is a boy whose family is in the top 10% of incomes. She clarified that it is not that these groups are more likely to commit crimes but rather that these groups are more scrutinized.

Many of the same factors that are associated with increased incarceration risk—being a member of a minoritized racial or ethnic group, poverty, and lower educational level—are also linked with elevated kidney risks, she noted.

Jail or prison conditions may exacerbate those risks. Life in correctional facilities is stressful, with limited opportunities for exercise. Dietary options often feature high-fat and high-sodium foods. Individuals who are incarcerated may work for 14 to 60 cents per hour, earning money that they may use for co-pays or purchasing supplementary food, including few healthy options, Maursetter said. For example, a patient of Maursetter's was repeatedly hospitalized for fluid overload. When she reviewed the list of supplemental foods that he was purchasing, she discovered that ramen noodles (which can contain 1600 mg of salt per package) were a staple in the facility.

People who are incarcerated were granted the right to health care in 1976. But Maursetter noted that there is little incentive for private or public prisons or jails to screen for, diagnose, and treat individuals in custody. "Standards can be quite different among groups providing care," she said. Routine appointments are often limited or may require a co-pay of as much as $100 per year. A physician or advanced practice practitioner may staff the facility, but patients or their guards may control medications. "You are not necessarily sure whether people are getting the medicines they are using," Maursetter said. A 2023 study found that people who are incarcerated are 3 times less likely to be treated with diabetes medications and 2.4 times less likely to receive anti-hypertensives (4).

Lead author of the review (1), Nathan Rockey, MD, a resident at the University of Colorado, Aurora, and Denver Health, said in an interview that prison and jail health care systems often focus on providing acute emergency care or transitioning patients who require hospital care. In that setting, he noted, it may be difficult to establish initiatives to recognize and treat chronic diseases.

Rizzolo, who treats patients with kidney diseases through a federally qualified health center that has a partnership with a prison and local jails, said there are limitations to the care she can provide. Often, routine testing and screenings are not available. "Sometimes, as a [practitioner], I feel helpless," she said. "We'll do the best, but we can't screen or treat patients like we normally would."

Hemodialysis is often the default option for patients with kidney failure, the review found (1), although some programs have successfully tried home peritoneal dialysis. Few people with kidney diseases who are incarcerated are considered for transplant despite evidence that it can be both efficacious and cost-effective among this population (5). Rizzolo noted that concern about whether the individual will have access to insurance or adequate finances after release is often a barrier. She, however, argued that nephrologists should consider transplants because the law requires a community standard of care for people who are incarcerated, and transplant is the gold standard.

Tenuous transitions

Circumstances can become tenuous for individuals after release. Although health care is an individual's right while in prison, they may face barriers to access after release. Some states provide coverage through Medicaid, but navigating the enrollment process can be a challenge, Rockey said.

Individuals who have been newly released often have poorly controlled diseases and face elevated rates of mortality during the post-release period, Maursetter noted. They may receive 30 days of medications upon release but have limited time to access insurance, find a physician, and make appointments to get refills, Maursetter continued. Discrimination in accessing care or employment, high rates of homelessness, and other psychosocial challenges after leaving prison may create additional challenges, Rockey said. "Upon release from prison, there is so much going on socially, and seeking a [practitioner] for chronic diseases can take a back burner by necessity," Rockey explained. "You are trying to find a job, restart a life, and reintegrate."

However, there are ways to create more seamless access to care. Some institutions have created transition clinics that work with individuals nearing release (6), Rockey said. These clinics rely on multidisciplinary teams, including physicians, social workers, case managers, and others, who work with patients to help them transition into community care more smoothly and address social determinants of health, such as employment, housing, and transportation. "There are a lot of opportunities to intervene to make it more logistically seamless and to improve disparities," Rockey said.

According to Rizzolo, there is a huge need for more research on this vulnerable population, including qualitative research that captures individuals with lived experience with chronic diseases while incarcerated and after release and the barriers to care that they experienced. Advocacy is also needed to promote system-wide change in the care received by people during incarceration and as they leave the system and to reduce US incarceration rates, she said.

Maursetter recommended routine screening for kidney diseases among individuals who are incarcerated and the implementation of standardized care. She also encouraged nephrologists to provide care for this population and to collaborate with social workers and others to address the unique needs of the population. "How can we help facilitate care a little better, open up our offices, and take care of patients in a way that is a little bit more holistic?" Maursetter asked. ■

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Trends in US Incidence of ESKD: Differences by Race and Age

The rate of increase in US incidence of end stage kidney disease (ESKD) has slowed since the 1980s, although risk continues to be higher among Black patients compared with White patients across age groups, reports an article in *JASN*.

The researchers analyzed age- and race-specific trends in ESKD incidence using US Renal Data System data from 1980 to 2019. Annual percent changes in ESKD were analyzed for Black and White individuals aged 13 to 17 years, 18 to 64 years, and 65 years and older. The study included analyses to identify the time at which a significant change in the annual percent change slope occurred in each group.

In all groups, ESKD incidence increased after 1980. At that time, age-standardized rates were 237.7 per million among Black adults (aged 18 to 64) versus 66.7 per million among White adults. Among Black adults, the rate peaked at 771.8 per million in 1998 and then decreased to 608.5 per million in 2019. In contrast, White adults showed a continued increase in ESKD incidence (up to 236.8 per million in 2019).

Different patterns were seen for Black and White older adults and for adolescents. However, in all groups and at all times, ESKD incidence was higher among Black patients compared with White patients. In the aged 18 to 64 years' group, the disparity narrowed over time, reflecting a decrease in age-standardized incidence among Black adults and continued increases among White adults.

White adults showed no decrease in ESKD incidence at any time during the 4-decade study period. The rate of increase was faster among White males compared with White females.

The data suggest "an arc of rising and declining incidence" of ESKD among Black and White individuals in the United States from adolescence into older adulthood. Although the study clearly shows a continued higher ESKD burden among Black patients, "some mitigation of disparities can be discerned especially among Black adolescents," the researchers write. They discuss some possible reasons for the observed trends as well as "population-specific opportunities" to alter the incidence trends and address ongoing racial disparities [Fwu C-W, et al. Age- and race-specific changes in end-stage kidney disease incidence over four decades. *J Am Soc Nephrol*, published online January 30, 2024. doi: 10.1681/ASN.0000000000000310].

Empagliflozin Slows Change in eGFR Slope in CKD

Treatment with the sodium-glucose cotransporter-2 (SGLT2) inhibitor empagliflozin slows progression of chronic kidney disease (CKD) across a range of patient characteristics, according to randomized clinical trial data reported in *The Lancet Diabetes & Endocrinology*.

The researchers present a prespecified secondary analysis from the multicenter, international Study of Heart and Kidney Protection with Empagliflozin (EMPA-KIDNEY). In that trial, 6609 patients with CKD were assigned to treatment with empagliflozin (10 mg/day) or placebo. Enrolled patients had an estimated glomerular filtration rate (eGFR) between 20 and 45 mL/min/1.73 m^2 or an eGFR between 45 and 90 mL/min/1.73 m^2 with a urinary albumin-to-creatinine ratio (UACR) of at least 200 mg/g. The main EMPA-KIDNEY results showed significant reduction in progressive kidney diseases or cardiovascular death among patients assigned to empagliflozin.

The new analysis focused on the tertiary outcome of an annualized rate of change in the eGFR slope, which has been proposed as a potential surrogate for CKD progression. Outcome analysis included the acute eGFR slope (from baseline to 2 months) and the chronic slope (from 2 months onward).

Median follow-up was 2 years. Patients were "broadly representative" of patients with CKD with risk of disease progression and a range of eGFR and UACR values.

Among the total patients, 46% were diabetic.

Empagliflozin treatment was associated with an acute dip in eGFR (2.12 mL/min/1.73 m^2) for a relative reduction of 6%. After 2 months, the chronic slope was reduced by about half (from −2.75 to −1.37 mL/min/1.73 m^2 per year).

Effects on the chronic slope varied according to diabetes status as well as baseline eGFR and UACR. Patients with lower initial UACR had a lower absolute difference in chronic slope. However, because this group had a slower rate of CKD progression, they had a larger relative difference in chronic slope: 86% among patients with a baseline UACR less than 30 mg/g compared with 29% among those with an initial UACR of 2000 mg/g or greater.

The findings suggest substantial slowing of long-term progression of CKD with empagliflozin treatment.

"If widely implemented, use of SGLT2 inhibitors could have a substantial effect on the public health impacts of chronic kidney disease," the investigators conclude. They cite a companion paper (see reference 12 in the article) reporting broadly similar effects of empagliflozin in patients with different types of primary kidney diseases [EMPA-KIDNEY Collaborative Group. Effects of empagliflozin on progression of chronic kidney disease: A prespecified secondary analysis from the EMPA-KIDNEY trial. *Lancet Diabetes Endocrinol* 2024; 12:39–50. doi: 10.1016/S2213-8587(23)00321-2]. ■

Reduced Kidney Mass Associated with Higher Preterm Delivery Risk

For pregnant women, even small reductions in kidney mass are associated with shorter gestation times and increased risk of preterm delivery, according to a recent article in *Kidney International*.

Using an observational database from two Italian centers, the researchers identified 529 patients with a diagnosis of

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Reduced Kidney Mass

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tubulointerstitial kidney disease and live-born singleton infants. Of these women, 421 had stage 1 chronic kidney disease (CKD) without hypertension but with proteinuria of less than 0.5 g/day. A control group consisted of 842 women from a low-risk pregnancy cohort, propensity score-matched for age, parity, body mass index, ethnicity, and center. Pregnancy outcomes were compared between groups, with a focus on the effects of reduced maternal kidney mass.

Time to delivery was shorter in the group with tubulointerstitial kidney disease (range from quartile 1 to 3, 37.0 to 39.0 weeks) compared with the control group (range from quartile 1 to 3, 38.0 to 40.0 weeks). Delivery occurred before 37 weeks' gestation in 10.8% of women with a history of acute pyelonephritis, 9.7% of those with other tubulointerstitial diseases, and 31.1% of those with a single kidney compared with 7.4% in the control group.

The same group with tubulointerstitial kidney disease had progressive reductions in neonatal birthweight compared with the control group. Pre-eclampsia occurred in 3.6% of women with CKD versus 1.7% of the low-risk control group.

The study provides new evidence regarding the association of tubulointerstitial disease with maternal-fetal outcomes. "[E]ven a small reduction in functional kidney mass, such as a pyelonephritic scar, is associated with a shorter duration of pregnancy and an increased risk of preterm delivery," the researchers write. They add that their findings "[highlight] the importance of being particularly attentive to all patients with even early CKD in pregnancy" [Piccoli GB, et al. Any reduction in maternal kidney mass makes a difference during pregnancy in gestational and fetal outcome. *Kidney Int*, published online January 29, 2024. doi: 10.1016/j.kint.2023.12.018].

Since 1990s, Slower Declines in GFR with Standard Care for CKD

Outcomes data on standard-of-care (SOC) control groups from chronic kidney disease (CKD) treatment trials over the past 3 decades suggest slower declines in kidney function, reports a systematic review in the *American Journal of Kidney Diseases*.

The researchers analyzed "secular trends" in glomerular filtration rates (GFRs) among patients with nondialysis CKD randomized to SOC treatment in clinical trials published from 1990 to 2023. A meta-analysis included data on 32,202 patients assigned to SOC groups in 92 trials.

The analysis suggested dramatic improvement in the rate of GFR decline among patients assigned to SOC. Annual decline in GFR was 5.44 mL/min/1.73 m^2 for studies published from 1991 to 2000 versus 3.20 mL/min/1.73 m^2 from 2011 to 2023, a reduction of approximately 41%. This was despite increasing age (from 51 to 58 years, respectively) and comorbidity in the study cohorts.

Slowing of estimated GFR (eGFR) decline was associated with rising use of renin-angiotensin-aldosterone system inhibitors: 16% from 1991 to 2000 versus 85% from 2011 to 2023. Other significant factors included improved blood pressure control and decreased proteinuria. In a multivariable meta-regression model, age and baseline proteinuria level were the only factors independently associated with eGFR decline.

The researchers note some key limitations of their observational study, including variation in methods of assessing GFR.

Recent studies have provided evidence that "multifaceted nephrology care" can substantially slow the rate of progression of CKD—representing a major paradigm shift in treatment. "Nevertheless," the researchers write, "solid evidence demonstrating that CKD management has improved over the years is still lacking."

The meta-analysis shows substantial improvement in rates of GFR decline among patients assigned to SOC treatment for nondialysis CKD from the 1990s to the current decade. The authors discuss relevant changes in patient characteristics and evidence-based treatment for CKD, along with implications for future randomized clinical trials [Garofalo C, et al. Secular trend in GFR decline in non-dialysis CKD based on observational data from standard of care arms of trials. *Am J Kidney Dis*, published online November 11, 2023. doi: 10.1053/j.ajkd.2023.09.014].

Cardiac, Renal, and Metabolic Overlap: A Public Health Crisis?

By Waseem Farooq and Agnes S. Kim

Cardiovascular disease (CVD), chronic kidney disease (CKD), and type 2 diabetes mellitus (T2DM), which form the cardiac, renal, and metabolic (CRM) triad, are the leading causes of death, disability, and rising health care costs in the United States (1, 2). CRM conditions share overlapping risk factors and common pathophysiological mechanisms, including impaired glucose metabolism, dyslipidemia, hypertension, and obesity (3). T2DM, obesity, and metabolic syndrome contribute to endothelial dysfunction, inflammation, and oxidative stress, setting the stage for atherogenesis (4). CKD contributes to salt and volume retention, overactivation of the sympathetic and renin-angiotensin-aldosterone system, and generalized endothelial dysfunction, leading to hypertension and heart failure (5). Conversely, uncontrolled hypertension and heart failure (i.e., CVD) can deteriorate renal function. Although it has been known that CRM conditions are deeply interconnected, the prevalence and overlap of CRM multimorbidity among US adults had not been known until a recent study published in *JAMA Cardiology* (6).

Using the National Health and Nutrition Examination Survey (NHANES) database, Ostrominski et al. (6) found a high and increasing prevalence of CRM multi-morbidity in the last 2 decades. Between 1999 and 2020, the proportion of US adults with at least one CRM condition increased from 21.2% to 26.3%; with two conditions, from 5.3% to 8.0%; and with all three conditions, from 0.7% to 1.5%. Older (aged >65 years) and male participants had a higher CRM comorbidity burden, as did self-reported non-Hispanic Black participants and those with low socioeconomic status, those who were unemployed, and participants without a high school degree. Among those aged 65 years or older, one-third had one CRM condition, 17.1% had two conditions, and 5.0% had all three conditions. In particular, CKD had been historically underreported and underdiagnosed, and the current study highlights the growing recognition of the predominance of CKD. The prevalence of key CRM risk factors (hypertension, obesity, and prediabetes) is also increasing.

The CRM public health crisis is exacerbated by the undertreatment of CRM and its risk factors. Common medications, such as statins, angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARBs), and relatively newer agents like sodium-glucose cotransporter-2 (SGLT2) inhibitors and glucagon-like peptide-1 receptor agonists (GLP-1 RAs), for which abundant data have now been presented on their cardiovascular and nephroprotective effects, were shown to be severely underutilized (6). Despite strong guideline recommendations, almost one-third of participants with three CRM conditions were not treated with a statin. Only 46.8% of patients with CVD plus CKD and 60.7% of those with CKD plus T2DM reported use of an ACE inhibitor or ARB. Utilization of GLP-1 RAs and SGLT2 inhibitors was rare even among patients with CVD plus CKD and CKD plus T2DM, only 4.8% and 3.0%, respectively (6). Furthermore, previous research has shown that low socioeconomic status and racial inequalities are associated with undertreatment (7). Given recent data on the role of novel therapies and the significant reduction in the risk of major adverse cardiovascular events in patients with T2DM and CVD, more patients with CRM overlap should be treated with these medications (8).

Figure 1 proposes key steps for the comprehensive and collaborative management of patients with, or at risk for, CRM conditions. First, we assess the patient's risk profile and use guideline-directed therapy for CV prevention, including lifestyle changes as well as using anti-hypertensive, anti-hyperlipidemic, anti-platelet, and anti-hyperglycemic medications as needed. Next, we perform a comprehensive evaluation using history, physical, and laboratory data, along with a detailed evaluation of social determinants of health. There is increasing evidence that generalized screening for CKD with at least annual assessment of urinary albumin (e.g., spot urinary albumin-to-creatinine ratio) and estimated glomerular filtration rate is worthwhile, especially in patients with T2DM and hypertension (9). For CRM management, a team-based, multi-disciplinary approach should be taken with an emphasis on the use of SGLT2 inhibitors and GLP-1 RAs, which have promising results from CV outcome trials (8). The interdisciplinary care would involve primary care physicians working together with cardiovascular, nephrology, and endocrine colleagues to deliver optimal results. Patients with T2DM and concurrent atherosclerotic CVD (ASCVD), heart failure, or kidney disease or who are at high risk for ASCVD should be strongly considered for either SGLT2 inhibitors or GLP-1 RAs for cardiovascular and renal benefits (3). Treatment of obesity, which lies at the crux of the CRM overlap, is critically important (3). Finally, population-based interventions that promote health equity, such as improved access to care and affordability of the newer therapies, will be important. These strategies should ideally be incorporated into national guidelines. ■

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The authors report no conflicts of interest.

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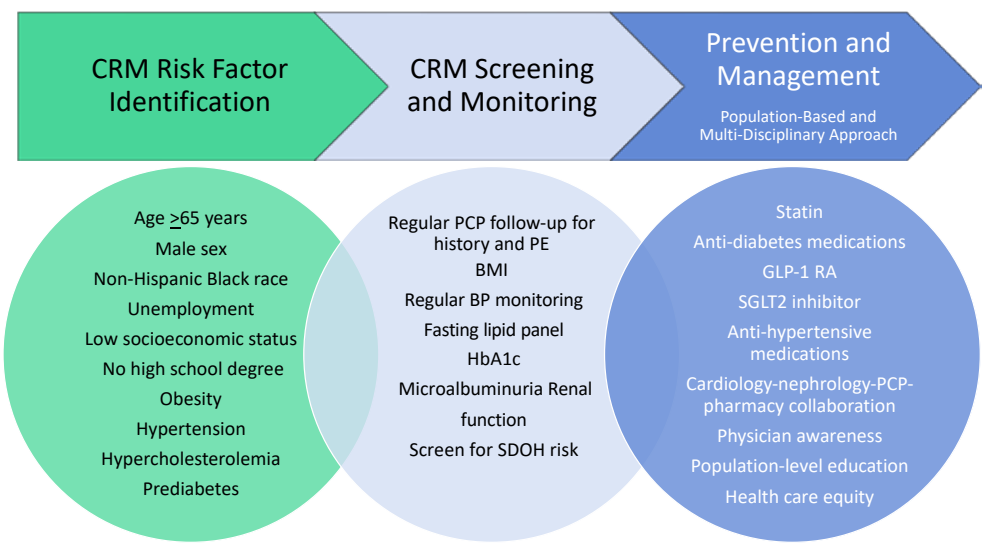
Figure 1. Key steps for management of patients with or at risk for CRM



BMI, body mass index; BP, blood pressure; HbA1c, hemoglobin A1c; PCP, primary care physician; PE, physical examination; SDOH, social determinants of health.

NephMadness Tournament Is Back in 2024

NephMadness is back again this year for participants to celebrate and discuss the many exciting advances in nephrology. Now in its 12th year, NephMadness is an engaging way for your practice, division, department, residency, or fellowship program to showcase your knowledge and celebrate the future of kidney health during National Kidney Month.

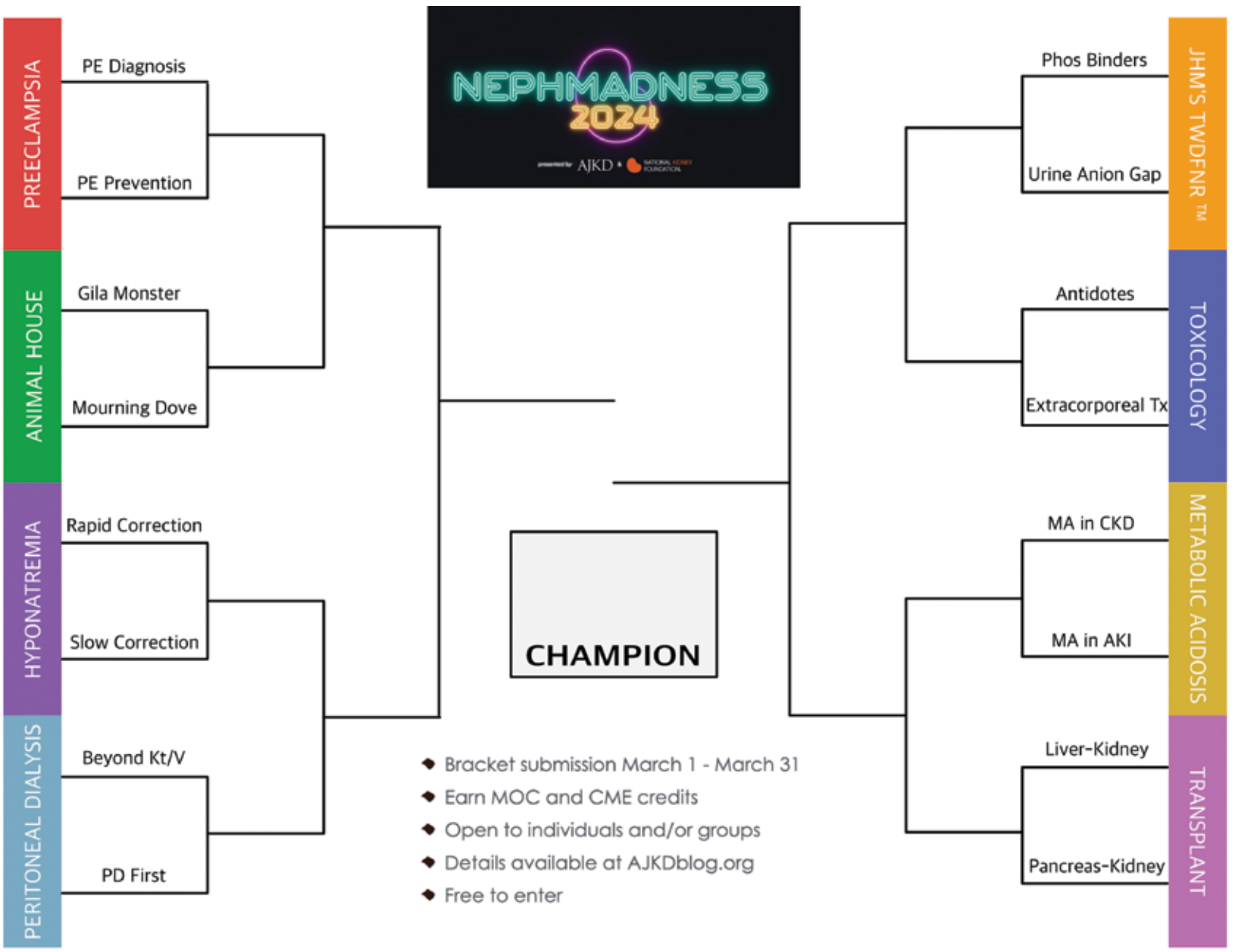
NephMadness is a single-elimination tournament consisting of 16 nephrology concepts divided into 8 distinct regions. The purpose of the tournament is to learn, discuss, and debate each topic, with a little friendly competition! We encourage you and your group to throw a NephMadness party, and we made it easy with a PowerPoint presentation describing each of the concepts. You can engage with the online nephrology community on social media using the hashtag #NephMadness. NephMadness will also feature eight podcasts covering each of the regions in what is called a PodCrawl, featuring podcasts by The Nephron Segment, Freely Filtered, GN in Ten, EMCRIT, The Intern At Work, Curious Clinicians, Critical Care Time, and PD Exchange.

Fill out your brackets either individually or as a team, and discover if your picks match those of the diverse nine-member Blue Ribbon Panel of fellows, nephrologists, and kidney patients. Winners of each matchup will be determined by the panel. The four rounds of voting will culminate in the crowning of the 2024 NephMadness champion.

A Zoom virtual background and instructions for completing your bracket as a group with Zoom polls can be found at AJKDblog.org. NephMadness is free to enter, and you can get Continuing Medical Education (CME) and Maintenance of Certification (MOC) credit! NephMadness bracket submissions are open from March 1 through March 31, 2024.

This year's regions are Preeclampsia (PE), Animal House 4, Hyponatremia, Peritoneal Dialysis (PD), *Journal of Hospital Medicine*'s "Things We Do For No Reason" (*JHM*'S TWDFNR™), Toxicology, Metabolic Acidosis (MA), and Transplant (Figure 1).

Figure 1. 2024 NephMadness Tournament Bracket



Patient Solicitation in Nephrology Practices: Ethical Boundaries and Patient Autonomy

By Prakash Gudsoorkar, Amy Beckrich, Yaakov Liss, and Robert Blaser

The Renal Physicians Association (RPA) recently released a position paper on the ethical challenges surrounding patient solicitation in the field of nephrology (1). As medical professionals, nephrologists navigate a complex intersection of ethical, financial, and systemic factors in health care delivery. In light of the evolving health care landscape, it is imperative to spotlight the ethical principles that should guide our profession, particularly as it relates to patient solicitation. Nephrologists must understand both federal ethical standards and specific legal requirements in their practice areas, as ignorance of state-specific laws regarding patient solicitation is not excusable and can result in severe repercussions, including professional sanctions and loss of licensure.

Doctor-patient covenant and the complexity of modern nephrology practices

The central tenet of our medical practice is the duty to prioritize the needs and interests of the patient, a commitment that stands apart from commercial interests and is rooted in the ethical principles of trust, beneficence, and non-maleficence. It is ultimately this commitment to the patient, above all else, and the sacredness of the patient-doctor relationship that should drive all decision-making by nephrologists on behalf of their patients. The evolving landscape of health care, with its practice consolidations, hospital system mergers, and proliferation of accountable care organizations (ACOs) and value-based care delivery models, presents complex ethical challenges, particularly as they relate to patient solicitation and care transitions. Historically, avoiding patient solicitation within the field of nephrology meant not interacting with another practice's patients with the intention of luring the patient away to one's own medical practice, especially in the setting of a dialysis center or hospital.

With recent changes in the health care landscape, more nuanced scenarios have arisen that require thoughtfulness to ensure that patient solicitation is not taking place and that decisions are made with the best interests of the patient in mind. For example, some important questions follow.

- When a patient transfers into a dialysis center without an assigned nephrologist, should this patient automatically be assigned to the medical director, or should there be a fair and impartial process in which the patient is presented with a list of all available nephrologists at that dialysis center?
- Similarly, if a hospitalized patient requires a nephrology consult, should the patient automatically be assigned to the nephrologist employed by the hospital, or should there be a fair and impartial process in which the patient is presented with a list of all available nephrologists at that hospital?
- When a patient is admitted to a hospital in which the patient's regular nephrologist does not have privileges, what steps should be taken upon discharge to encourage the patient to return to follow up with their established nephrologist?
- If a patient's medical practice participates in an ACO, should all referrals automatically occur amongst doctors who participate in that ACO, or should the patient be given options of other doctors who do not participate in the ACO?
- Should patients be informed of financial relationships that referring nephrologists have with specific dialysis centers or vascular access centers? If the answer is yes, what is the proper way to disclose this information so that the patient is informed, but the disclosure does not also inadvertently present the appearance of impropriety when there is none?
- If a nephrology practice dissolves or if a nephrologist leaves a practice, what is the optimal way for those patients to continue receiving their nephrology care?

These example scenarios risk compromising the ethical integrity central to our profession and may erode the trust that patients place in their health care practitioners. The questions demand careful consideration, as they vary in their ethical implications across different states and health care settings, highlighting the need for a nuanced understanding of these dilemmas and a steadfast commitment to ethical principles in patient care.

Principles-based approach

It is important to note that although the RPA position paper broadly discusses the aforementioned scenarios (1), detailed guidance on how to resolve these situations is not provided because the details of each situation are different, and there is no way to broadly mandate best practices for every individual case. Rather, the RPA's position paper emphasizes a principles-based approach to ethical dilemmas in nephrology, stressing the importance of patient autonomy and the right to informed decision-making. This approach should involve nephrologists, primary care physicians, and dialysis units working together to ensure that patients have access to transparent information and the freedom to choose the nephrologist who best meets their needs (Table 1).

Central to this strategy is the equitable treatment by health care practitioners of patients, not as commodities but as individuals entitled to justice, autonomy, beneficence, and non-maleficence in their care. The RPA paper is a timely reminder of our duty to uphold these values, ensuring that patient-centered care remains at the heart of our practice. ■

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The authors report no conflicts of interest.

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Table 1. Roles of various stakeholders to help with seamless patient transitions

Role/scenario	Task	Description/physician duties
Primary care physician and current primary nephrologist	Change notification	Inform patient of nephrologist's departure and need for new referral.
	Specialist referral	Find and refer to a suitable, new nephrologist.
	Care transition	Manage transfer of medical records to new nephrologist.
	Support and communication	Stay in touch with the patient during transition.
	Monitor care continuity	Check patient's ongoing care under new nephrologist.
Dialysis unit	Change explanation	Brief patient on the reason and process of a physician change.
	Transition guidance	Give stepwise instructions for switching to a new nephrologist.
	New physician coordination	Aid in care transfer, and send relevant medical details.
	Address concerns	Answer questions, and provide support regarding the change.
	Care continuity	Ensure that the dialysis schedule and care plan remain unaffected.
	Ethical compliance	Disclose joint ventures or interests under ethical standards.
General procedures	Patient notification	Update patient about the transition and new nephrologist details.
	Assignment	Designate a coordinator for the transition.
	Electronic health records' updates	Modify electronic health records to new primary nephrologist, and transfer records.
	Financial considerations	Update insurance, and inform patient of potential costs.
	Ethical disclosure	Declare any joint ventures or interests, and maintain transparency.
	Follow-up	Set initial meetings with new nephrologist, and ensure patient satisfaction.
Hospitalized patient with an established nephrologist	Physician duties	Update the patient's regular nephrologist on the plan of care; ensure that post-discharge follow-up returns the patient to their established doctor.
New patient undergoing dialysis without an established nephrologist	Physician duties	Present the patient with available choices of units and nephrologists, disclose any ownership interests, and ensure a transparent decision-making process.

Navigating the Outcomes of Hospital-Acquired Hypernatremia

By Urmila Anandh and Sabarinath Shanmugam

Hypernatremia, like hyponatremia, is a disorder of water balance, most frequently arising from a combination of excess loss of water or hypotonic fluid with an insufficient compensatory intake. In medical literature, hypernatremia is frequently eclipsed by its more prevalent counterpart, hyponatremia, receiving comparatively less attention in scholarly discussions. Hypernatremia may exist at admission (community-acquired hypernatremia) or develop 24 hours after admission (hospital-acquired hypernatremia). The prevalence of hypernatremia among hospitalized patients has been reported to be between 1% and 6% (1–3). A report by Tsipotis et al. (4) found that the hypernatremia spectrum in unselected hospitalized patients is independently associated with increased in-hospital mortality and is often associated with inappropriate correction (5, 6).

A study recently published in *CJASN* (7) explored the outcomes and discharge dispositions of various levels of hospital-acquired hypernatremia in patients with or without chronic kidney disease. This was a retrospective study, using data from the Cerner Health Facts database (2000–2018), which analyzed 1.7 million patients with normal serum sodium (Na) levels of 135 to 145 mEq/L up to 24 hours after admission. Of this cohort, only 6% of patients developed hypernatremia after hospitalization. The patients with hypernatremia were older and had a lower estimated glomerular filtration rate (eGFR) at presentation. In addition to analyzing the in-hospital mortality, discharge dispositions (to hospice, to a nursing facility, or home) and length of hospital stay were primary outcomes. The risk of all outcomes was significantly greater for a serum Na >145 mEq/L when compared with the reference interval (serum Na, 135–145 mEq/L). The in-hospital mortality and discharge to nursing facilities were 12% and 25%, respectively, in the hypernatremia group, whereas they were only 0.6% and 9%, respectively, in the normonatremic group. Patients with hypernatremia had higher odds for in-hospital mortality (odds ratio [OR], 14.04), discharge to hospice (OR, 4.35), and discharge to nursing facilities (OR, 3.88; p = 0.001 for all). Furthermore, the adjusted models showed that the ORs of in-hospital mortality became significantly higher as serum Na increased >145 mEq/L and as eGFR decreased <90 mL/min/1.73 m^2 when compared with the reference groups.

A previous study on "community-acquired hypernatremia" from the same database found similar results (8). The risk of in-hospital mortality and discharge to a hospice or nursing facility was highest among those with a serum Na >155 mEq/L. The community-acquired hypernatremia study addressed the knowledge gap by examining the association between various degrees of hospital-acquired hypernatremia and specific outcomes in a sizable and diverse population, focusing on kidney function status. Although associations between hypernatremia and adverse outcomes were identified, the study appropriately underscored the need for caution in inferring direct causation.

Although it offers valuable insights, a nuanced examination reveals limitations that necessitate careful consideration in interpreting its findings. The Sequential Organ Failure Assessment score is a crucial tool for assessing the severity of illness in predicting outcomes, particularly among patients who are critically ill. The lack of use of this assessment in this study is a notable limitation. Furthermore, without a granular examination of specific diagnoses, the study may have overlooked the heterogeneity within the hypernatremic population. The complex interplay of various factors influencing outcomes makes it challenging to eliminate the possibility of confounding variables affecting the reported results. The high mortality in these patients may just mean that they were terminally ill, and the high Na was a bystander "marker."

Thus, optimizing outcomes in hypernatremia necessitates a multifaceted approach involving the identification of the vulnerable population at heightened risk, early diagnostic interventions, discernment of underlying etiologies, and judicious correction of hypernatremia at a rate aligned with established guidelines. ■

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The authors report no conflicts of interest.

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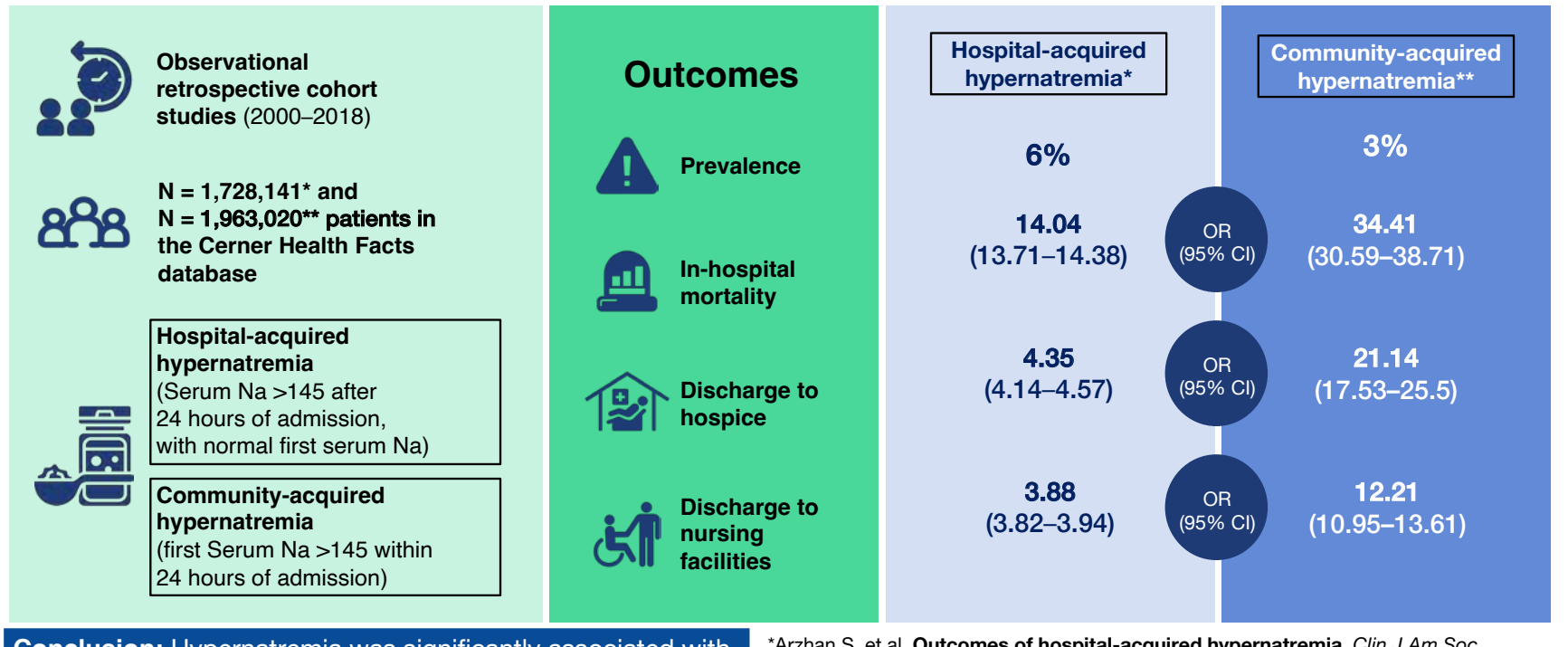
What are the outcomes of hospitalized patients with hypernatremia?

KidneyNews



Conclusion: Hypernatremia was significantly associated with in-hospital mortality and discharge to a hospice or nursing facility.

*Arzhan S, et al. **Outcomes of hospital-acquired hypernatremia.** *Clin J Am Soc Nephrol* 2023; 18:1396–1407. doi: 10.2215/CJN.000000000000025
Arzhan S, et al. **Hypernatremia in hospitalized patients: A large population-based study. *Kidney360* 2022; 3:1144–1157. doi: 10.34067/KID.0000702022

Visual Graphic by Sabarinath Shanmugam, MD, FASN

Why Sodium Levels Might Matter for Patients with Advanced Kidney Cancer Treated with Nivolumab

By Biruh T. Workeneh and Helbert Rondon-Berrios

A recent study by Catalano et al. (1) has cast a light on an underappreciated factor that may hold a potential target for improved outcomes in patients with metastatic renal cell carcinoma (mRCC) treated with nivolumab: serum sodium (SNa) levels. The study was a retrospective cohort study, including patients treated with nivolumab as second-line or subsequent therapy from October 2015 to November 2019 across multiple Italian oncology centers. The main focus was on the association of pre- and post-immune checkpoint inhibitor (ICI) sodium levels with overall survival, progression-free survival, objective response rate, and disease control rate. The study's findings indicate that a higher SNa (≥140 mEq/L) before and/or after treatment with nivolumab was associated with better clinical outcomes, including overall survival, progression-free survival, and disease control rate. While previous research has hinted at the prognostic value of SNa among patients with mRCC (2), the association of SNa and outcomes in patients with mRCC receiving ICI has not been studied.

There are, of course, limitations to any retrospective analysis. A notable aspect of this study is the examination of SNa before and after ICI (approximately 4 weeks). Immunotherapy toxicity may develop within this period, but it is important to note that complications such as hyponatremia can occur even several months after the initial exposure to immunotherapy. Furthermore, an unreported number of patients received combination therapy of nivolumab plus ipilimumab as a first-line option for patients with intermediate-risk and poor-risk disease.

There are several mechanisms by which hyponatremia could develop in this population. Hyponatremia could be the direct result of mRCC, usually by causing the syndrome of inappropriate antidiuresis, or it could appear as a complication of immunotherapy, including the syndrome of inappropriate antidiuresis, hypovolemia from diarrhea in the setting of colitis, and less commonly, adrenalitis and hypophysitis (3, 4). Hyponatremia can also be the result of comorbidities such as advanced heart failure or cirrhosis, which were not considered in the analysis. Furthermore, most patients in this cohort had undergone prior nephrectomy, adding a layer of complexity. This is because a reduced glomerular filtration rate can be associated with increased use of medications, including diuretics and the presence of additional comorbidities that may influence both SNa and survival. The surprising aspect of this report is the observation that SNa levels, even when within the conventional, normal range of 135–139 mEq/L, are correlated with decreased survival probabilities in mRCC. Since SNa determinations are frequently obtained, perhaps a method that examined SNa over time using a mixed-effects model would have been more indicative of the impact of SNa on survival.

The study indicates that the International mRCC Database Consortium (IMDC) score significantly influences the hazard rate, possibly driven by the Karnofsky performance status score, which is an element of the IMDC score. Further analysis of variables driving the score could offer valuable insights into the interplay among these factors, SNa, and survival rates. To elucidate further, it is worth considering that elements contributing to a reduced score might also affect SNa values, such as limited solute intake. Conversely, a low SNa might in turn contribute to a diminished risk score. To deepen our understanding, follow-up investigations could explore additional factors such as hemodynamic status, medications (especially diuretics), the presence of liver disease or heart failure, and urinary indices, including urine osmolality.

Ultimately, the work by Catalano et al. (1) should be commended because the study highlights the potential importance of SNa as a predictor of outcomes among patients with mRCC. At the very least, we can hypothesize that those at low risk for developing hyponatremia before nivolumab treatment have a stronger likelihood of improved outcomes. Additionally, patients who maintain a normal SNa after exposure to nivolumab tend to fare better. This raises the possibility of integrating SNa into patient risk assessments and may be an impetus to involve consultants, such as nephrologists, earlier who can focus on managing hyponatremia.

While several questions remain about the mechanisms underlying this association, whether this phenomenon is present with other ICI therapies, and whether it can be generalized to other cancers, these findings open the possibility for further studies unlocking modifiable avenues for enhancing the care and outcomes for patients with cancer. ■

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The authors report no conflicts of interest.

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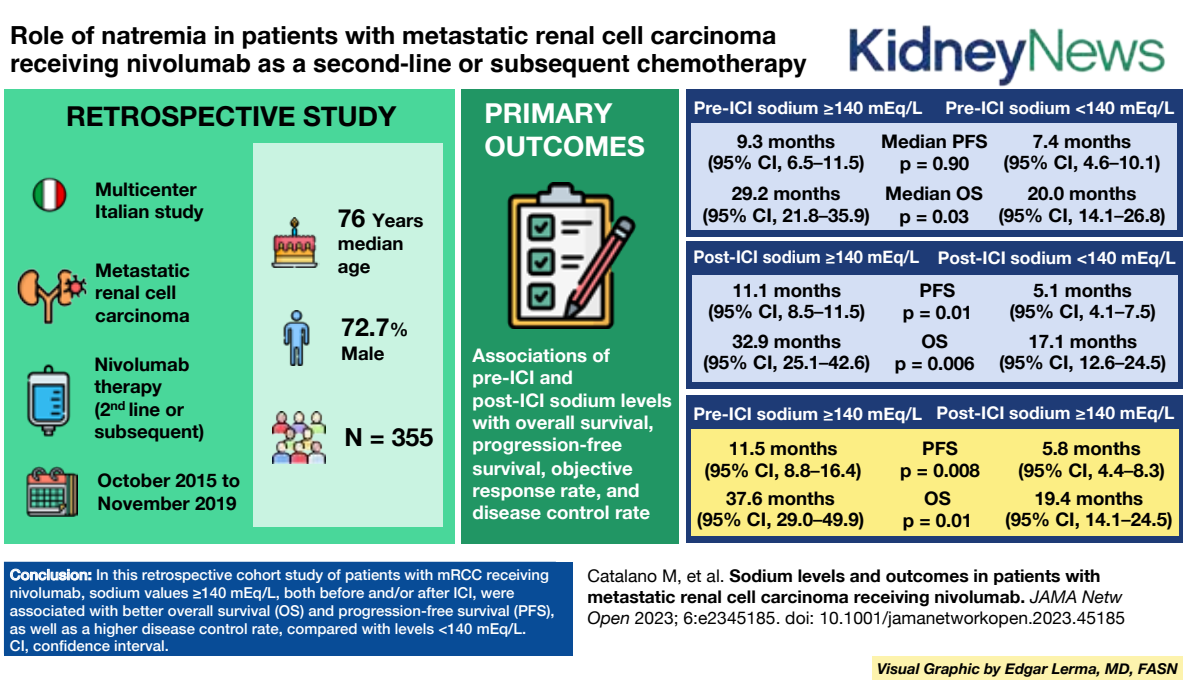

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Perspectives of Polypharmacy and Its Effects on Quality of Life by Patients on Dialysis

By Jennifer Bergeron

Polypharmacy, or the use of five or more medications, is rampant among the population undergoing dialysis. Patients on dialysis in the United States take a median of 19 pills per day from 11 different prescriptions (1). Polypharmacy is associated with non-adherence from 13% to 99% of patients on dialysis (2), as well as with medication errors and adverse drug events (3), financial strain (4), and lower health-related quality of life (1). However, until a recent article in *Kidney Medicine* by Colombijn et al. (5), no studies, to our knowledge, had evaluated the patient's perspective on how polypharmacy impacts their well-being. Unfortunately, their results were bleak: patients on dialysis find their medications to be a burdensome but necessary evil.

Colombijn and colleagues (5) interviewed 28 individuals on in-center hemodialysis or peritoneal dialysis in the Netherlands about their experiences with polypharmacy. They quickly learned that the participants had varied definitions of "medicine," especially regarding vitamins, binders, laxatives, creams, and herbal preparations. They found that most participants "were well aware of which medications they were taking," reported good adherence, and developed unique routines to remember to take them.

Participants perceived their medications as burdensome but had resigned themselves to taking them. They associated their medications with "garbage," shame, and dependency. Participants felt they took "a lot" of medication and wished they could take fewer. Many participants did not notice the efficacy of their medications (or dialysis for that matter) and had more favorable perceptions of the medications that provided symptom relief. Even worse, the participants noted that several of their medications triggered unpleasant physical reactions (from difficulty swallowing to myriad side effects). Dishearteningly, the authors note that these experiences with polypharmacy echo those of recipients of kidney transplant (6) and patients not on dialysis (7), but the patients on dialysis "take the burden of polypharmacy relatively lightly because the burden of medication pales in comparison to dialysis."

Participants did emphasize that not taking their medication would lead to their health worsening, which was not in line with their goals. The realization that their medications are important for their health helped mitigate the negative impact of polypharmacy on their quality of life. The investigators explored this thread further to identify ways that health care clinicians could help with patients' medication regimen. Practical tips for doing so are outlined in Table 1.

As qualitative studies are beginning to garner more weight in medicine, it is important to note the aspirational methods that Colombijn and colleagues (5) used. The interviewers had no personal relationship with the participants, dialysis, or polypharmacy, and all but one of the interviewers had a background in cultural anthropology (i.e., they were experts at a scientific interview). The participants chose the interview location, allowing for privacy, convenience, and rapport. The data were analyzed starting with the interviews rather than a preconceived framework to identify themes.

Although every qualitative study is limited by generalizability, there can be no doubt that polypharmacy negatively affects patients' quality of life. Further studies will develop strategies to improve a patient's experience of medication and allow for effective prescribing and deprescribing to limit polypharmacy. ■

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Table 1. Practical recommendations for managing polypharmacy in patients receiving dialysis

Discussing medications with patients	• Regularly discuss medications at monthly intervals. • Evaluate medications' clinical and side effects. • Link laboratory value improvements to the responsible medication to demonstrate efficacy. • Be aware that patients have varying definitions of "medication."
Managing medication regimens	• Support patients in developing acceptable medication routines. • Allow more time for laboratory values or symptoms to self-resolve rather than adjusting medications. • Adjust dialysis to resolve signs and symptoms if appropriate instead of prescribing more medication.
Reducing the negative impact of medication on quality of life	• Prescribe medications that are easier to swallow. • Limit the number of times each day that a patient must take medication. • Combine dialysis and medication routines if appropriate. • Capitalize on medications that make patients' lives more comfortable.

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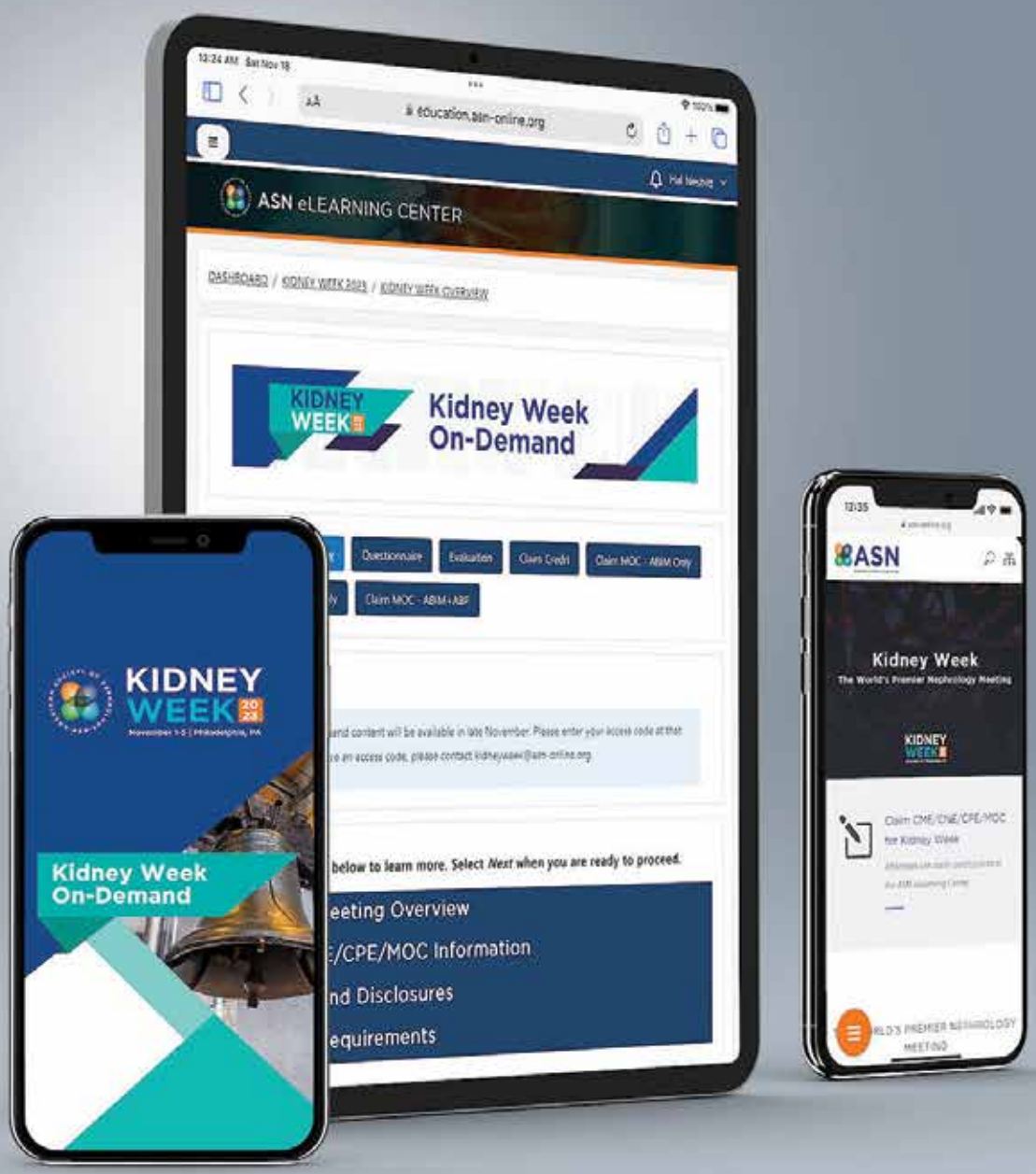

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