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Caregiver Support Critical to the Nephrology Workforce

By Bridget M. Kuehn

For Megan Prochaska, MD, MPH, a nephrologist and assistant professor of medicine at The University of Chicago Pritzker School of Medicine, Chicago, IL, working at an institution that supports her role as a caregiver of two young children has allowed her to thrive as a clinician-researcher. In addition to having a flexible culture that supports and values caregivers, she has been able to take a 12-week parental leave after the birth of each of her children.

"I can prioritize those things where and when I need to and not feel like I'm going to be punished or have negative consequences in my professional life," she said. That flexibility has helped give her the comfort and confidence that she needs to simultaneously pursue her professional goals, she expressed.

That kind of support is essential, according to a pair of recent reports from the National Academies of Sciences, Engineering, and Medicine (NASEM). One report highlights the difficulties that physicians and scientists face in juggling the demands of their careers and caregiving for children, elders, spouses, or other relatives or being pulled between multiple types of caregiving (1). Women, particularly women of color, shoulder a disproportionate burden of these responsibilities and may be sidelined from careers in research and medicine without support, the report notes. As many as 4 in 10 clinician-investigators leave their field within the first 10 years of being appointed to faculty, partly because caregiving is unsupported in their workplace (2). The second report lays out how institutions can better support caregivers (3).

"The early career stage is a very critical stage in terms of attrition from the biomedical research workforce," said Rasheed Gbadegesin, MD, MBBS, FASN, a pediatric nephrologist, Wilburt C. Davison Distinguished Professor of Pediatrics, and Associate Dean for Physician-Scientist Development at Duke University School Medicine in Durham, NC. "This is a stage of life where so many things are happening: People are having families, and parents are getting older. In addition to clinical and research responsibilities, those caregiving responsibilities just show up."

Across the country, programs and organizations are experimenting with different approaches to helping nephrologists and kidney disease researchers navigate their careers and caregiving responsibilities. These concepts include a push to make professional meetings more family-friendly, institutional support for family leave and flexibility, and efforts to provide supplemental funding for researchers facing

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Early Medical Student Involvement Is Key to Bolstering Interest in Nephrology

By Tejwinder Sandhu, Olivia Schreiber, and Vinay Srinivasan

Nephrology fellowship programs continue to face challenges in filling positions, with only 66% of positions filled for the appointment year 2024 National Resident Matching Program Medical Specialties Matching Program, including medicine and pediatric specialties (1). Although several strategies have been proposed to improve recruitment along the nephrology trainee continuum, there is growing concern that demand may soon surpass the supply of the existing nephrology workforce (2–6). Fostering interest in nephrology at the resident level may be too late; therefore, we urge medical education leaders to invest more resources in early nephrology experiences for medical students to combat these alarming trends. Here, we highlight how engaging with medical students as early as the second year of medical school can both spark and maintain interest in the subspecialty.

In his second year of medical school, one of the authors (T.S.) encountered a nephrology mentor who developed a project for him—to create patient-centered materials on glomerular diseases and emerging therapeutics for the Glomerular Disease Study and Trial Consortium (GlomCon). Creating these educational materials ignited a deeper curiosity in nephrology for T.S.; his involvement with patient education, especially concerning emerging therapeutics, highlighted nephrology as a field teeming with diagnostic and therapeutic innovations, challenging

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Inside

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INDICATION

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

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

XPHOZAH is contraindicated in:

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

WARNINGS AND PRECAUTIONS

Diarrhea

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

MOST COMMON ADVERSE REACTIONS

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

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

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

ardelyx®

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

1 INDICATIONS AND USAGE

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

4 CONTRAINDICATIONS

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

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

5 WARNINGS AND PRECAUTIONS

5.1 Diarrhea

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

6 ADVERSE REACTIONS

6.1 Clinical Trial Experience

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

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

Most Common Adverse Reaction

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

7 DRUG INTERACTIONS

7.1 OATP2B1 Substrates

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

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

7.2 Sodium Polystyrene Sulfonate

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

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

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

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

Animal Data

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

8.2 Lactation

Risk Summary

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

8.4 Pediatric Use

Risk Summary

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

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

Juvenile Animal Toxicity Data

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

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

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

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

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

8.5 Geriatric Use

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

10 OVERDOSAGE

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

17 PATIENT COUNSELING INFORMATION

Advise Patients:

Diarrhea

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

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

Administration and Handling Instructions

Instruct Patients:

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

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Caregiver Support Critical to the Nephrology Workforce

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a caregiving crunch. "We have a workforce crisis for clinical nephrologists and a more severe workforce crisis for biomedical researchers," Gbadegesin said. "We cannot afford to let [kidney disease investigators] drop off."

Caregiving stigma

Caregiving is a common experience. Forty percent of US households include children, and nearly one in five US adults provides care for another adult (3). Despite the ubiquity of caregiving, those shouldering these responsibilities in biomedical fields face a strong stigma and often lack necessary support, the second NASEM report notes.

Robert L. Phillips, Jr., MD, MSPH, founding executive director of The Center for Professionalism & Value in Health Care, Washington, DC, and a member of the committee that drafted the NASEM reports, explained that clinicians may feel that it is unprofessional to take time away for caregiving. He explained that they often feel that their mission to care for patients is very important and feel pressure to carry their weight and not let their teams down. "That ideal worker model in STEMM [science, technology, engineering, mathematics, and medicine] is so pervasive that it is difficult for us to even think about being caregivers and giving ourselves a break to do that," Phillips said.

Michelle Rheault, MD, director of the Division of Pediatric Nephrology and director of the Center for Women in Medicine and Science at the University of Minnesota in Minneapolis, noted that one of the biggest challenges for clinicians may be having the flexibility to attend to caregiving needs as they arise. For example, clinic schedules may be set weeks in advance, but school-related events or other caregiving needs may come up on much shorter notice. Elder care can pose similar challenges.

Phillips noted that failing to account for these challenges fuels attrition and may also contribute to pervasive burnout in these fields. "Those that we don't lose, we lose their hearts," Phillips said. "They feel so torn and unsupported in those new roles. It affects their well-being."

The second of the two NASEM reports lays out recommendations for best practices for academic institutions. One of them is to ensure that their institutions are following applicable state and federal laws, such as the Family and Medical Leave Act, Title IX, and the Pregnant Workers Fairness Act. "A lot of academic health centers are not always following the federal or state laws already in existence," Phillips noted.

Institutions should also go beyond compliance to provide students, trainees, faculty, and staff with options that offer flexibility or ease their work burden. Prochaska said that she appreciates her section chief's flexibility and willingness to schedule meetings around the team's children's school or childcare drop-off and pick-up times.

Having parental leave and equal access to support both parents are also important, Rheault said. Her institution recently extended 6 weeks of parental leave for all parents. Previously, men were eligible for 2 weeks, whereas women were eligible for 6 weeks. To alleviate stress on caregivers taking leave, she has also advocated for her institution to create coverage plans that avoid requiring "make-up" time before or after leave. She noted that covering extra shifts before or after leave can unnecessarily add to caregivers' stress.

Institutions should also consider direct support for caregiving, such as on-site care and subsidies for off-site care, the second NASEM report recommends. Rheault remembers having to rush to wrap up her end-of-the-day clinical duties in order to pick up her children on time because of her childcare center's limited hours. On-site childcare aligned with the clinician's schedule can help, particularly for early career staff who cannot afford a nanny or other live-in care and who may struggle to find childcare for evening or weekend shifts. Prochaska said that she relies on her parents, who live nearby, for help in a pinch, but she noted that The University of Chicago also offers on-site childcare and emergency drop-in care, which colleagues who do not have family or other support nearby find very helpful.

Ultimately, Phillips said that institutions need to create the internal infrastructure to support the needs of individuals who may temporarily need to step away from some of their work to address caregiving needs. He said that building that infrastructure supports caregivers and allows the enterprise to run smoothly. It helps reduce burnout and turnover, attract new talent, and improve clinician well-being. "This is an investment in attracting and retaining an excellent workforce," he expressed.

"Helping hands"

The second NASEM report also recommends piloting innovative approaches to tackling these problems. One example cited in the report is the Fund to Retain Clinical Scientists, a pilot program launched by the Doris Duke Foundation in 2015 to help reduce attrition among early career investigators with caregiving challenges (4). Gbadegesin, who codirected the program at Duke University, noted that these challenges are often transient, lasting 6 to 12 months, but can derail researchers just getting started. "People are faced with the choice of either you continue with your career and neglect your life, or you forget about your career, and you continue with your life," he said. "That is absolutely wrong."

In its first round, the Fund to Retain Clinical Scientists selected 10 institutions to receive grants that would allow them to provide $30,000–$50,000 to investigators with caregiving challenges. Women made up approximately 75% of the scholars who received support, noted Sindy Escobar Alvarez, PhD, program director for medical research at the Doris Duke Foundation. In 2021, the Doris Duke Foundation expanded the program to 22 institutions, with additional funding from the American Heart Association, the Burroughs Wellcome Fund, the Rita Allen Foundation, and the Walder Foundation to help offset the increased caregiving burden that many investigators faced during the pandemic.

Gbadegesin, who also directed Duke University's COVID-19 Fund to Retain Clinical Scientists, the pandemic-targeted program funded by the Doris Duke Foundation and its partners, and his colleagues received an overwhelming response to their calls for applications for assistance. They were able to fund 30% of them. All of the applicants received mentoring and coaching. Those who received grants could spend the money on helping hands, such as hiring a research technician, a grant writer, a research coordinator, or a statistician to help free up the investigator's time. Escobar Alvarez noted that other institutions also allowed investigators to use the funds to "buy back" clinical time to free up time for research. An evaluation of the Fund to Retain Clinical Scientists program found several benefits for participating institutions (5). "It normalizes the discussion [about caregiving] institutionally," Escobar Alvarez said. "It also endorses that you are important; your contributions are important."

As the seed funding from the Doris Duke Foundation ends, many participating organizations are looking for ways to continue their programs. Duke University has agreed to continue supporting a smaller scale version, Gbadegesin said. He and his colleagues also want to create an endowment to help fund the program. "Our ultimate goal is to make it sustainable," he explained. "Any academic institution in the United States that is serious about building the biomedical research workforce, attracting and retaining people, should invest in this program."

Gbadegesin also urged funders like the National Institutes of Health to consider offering small supplemental grants to its grantees facing caregiving challenges. He noted that spending $25,000–$50,000 to help an investigator facing a temporary caregiving challenge is a small investment compared with the $800,000 or $1 million that the National Institutes of Health may have already committed to funding these investigators over 5 years. "This is a career and a lifesaving program," he said. He noted that three-quarters of the participants at Duke University were on the verge of leaving their careers when they entered the program. But everyone has continued their research, including three kidney disease investigators, and many have gone on to receive additional grants for their research.

Normalizing caregiving

It has become the norm at pediatric nephrology conferences for investigators to have children in tow and for conferences to have on-site childcare. "They are super family-friendly," Rheault said. "People don't feel bad about bringing their kids."

Child-friendly conferences can help early career investigators to participate in vital continuing education, networking, and sharing their work, notes a document by the Women in Nephrology organization (6). It also recommends that nephrology meetings become more family-friendly, including by allowing children into conference sessions, having on-site childcare, and providing lactation facilities. Some associations, including ASN, have adopted more child-friendly policies. For example, Kidney Week allows meeting attendees to register children to attend Kidney Week with them and has links to information on childcare in the area (7).

Rheault highlighted the benefits of such policies in helping to recruit individuals to the profession and urged conferences do even more to support caregivers. "If medical students and residents see women and men who are [at meetings] with their children, it shows the family-friendly nature of the specialty," she said.

Last September, Women in Nephrology hosted a leadership conference and offered caregiver grants of $200–$300 to help defray caregiving-related meeting costs, Rheault said. For example, the grants covered the costs of additional childcare at home or helped to cover the costs of bringing someone along to help. Rheault noted that her mother tagged along to meetings when her children were infants to help with their care.

Women in Nephrology also offers a mentor match program. Rheault shared that many women who apply for the program are looking for mentoring on work-life balance. They want to talk with others with a career in nephrology and who have children about how they balance it, she said.

Rheault suggested that there is also a place for leaders to normalize caregiving in their institutions, for example, not scheduling early or late meetings that may interfere with school or childcare pick-up or drop-off times. She also keeps pictures of her children in her office and is open with colleagues about when she cannot stay late—for example, because she must attend her child's soccer game. "We need more people to role model that caregiving is normal," she said. ■

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Early Medical Student Involvement Is Key to Bolstering Interest in Nephrology

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the misconception that nephrology is a specialty with limited future prospects.

The second author's (O.S.) interest in nephrology emerged from her personal experience with a loved one who received peritoneal dialysis for kidney failure. By the second year of medical school, O.S. discovered nephrology mentors who identified projects that suited both her interest in nephrology and science writing. She submitted a case report and literature review on fibrillary glomerulonephritis and now contributes editorials for the GlomCon newsletter, a weekly publication reaching over 6000 nephrology fellows and attendings worldwide. The author participated in a month-long nephrology Visiting Student Learning Opportunities program during her fourth year of medical school and continues to tutor students in the preclinical nephrology course.

Both authors attended ASN Kidney Week 2023, yet another opportunity to expel the unfair position that nephrology lacks in diagnostic or therapeutic advancement. The authors' stories send a compelling message that is lacking in the current literature: Early engagement in medical education is essential to sow the seeds so that the next generation of nephrologists may grow.

These experiences need not be unique. Medical educators must act now to maintain and augment the nephrology workforce. Young trainees may express early interest in nephrology for a variety of reasons; attending nephrologists can play a key role in maintaining students' interest, both through mentorship and identification of personalized, appropriate-level projects. Faculty, with strong teaching skills and a willingness to use new teaching methods, should lead the nephrology–physiology course, as this course tends to "make or break" a student's ability to envision a career in nephrology (7). They may also choose to advise a medical student nephrology interest group, effectively creating a "nephrology pipeline." Medical students who rotate on a nephrology elective should be offered additional experiences in outpatient hemodialysis, peritoneal dialysis, glomerular disease, transplant, and other subspecialty clinics if available. The Table further outlines current opportunities for medical students interested in nephrology.

Expanding the resident nephrology experience is important and should be continued; however, work must begin early and continue throughout a medical student's training to make a significant impact. Mentorship is the key agent in synthesizing specialists; the first two authors continue to engage in nephrology research, education, and patient outreach with encouragement from enthusiastic mentors. Practicing nephrologists know that nephrology does not just begin and end with hyperkalemia in patients with kidney failure; it is an exciting field that offers a wide breadth of pathology and opportunity to make a difference in patients' lives. However, nephrologists alone will not be the ones to save their profession. Education leaders and faculty must recognize that to effectively combat the declining match rates, work must be done to engage medical students now so that they can envision a future career in nephrology. ■

Tejwinder Sandhu is a medical student at the College of Osteopathic Medicine, Touro University California, Vallejo. Olivia Schreiber, MA, is a medical student at Cooper Medical School, Rowan University, Camden, NJ. Vinay Srinivasan, MD, MBA, is an assistant professor of medicine at Cooper Medical School, Rowan University, and a nephrologist at Cooper University Hospital.

The authors report no conflicts of interest.

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Table. Overview of medical student opportunities in nephrology

Program	Eligible audience	Description of program	Learn more
Nephrology Interest Group	M1, M2, M3, M4	The interest group offers mentorship, project identification, and physician panels for medical students interested in nephrology.	Home institution
ASN Kidney Students and Residents (STARS)	M1, M2, M3, M4	STARS is a program designed to stimulate interest in nephrology careers through tailored events and networking opportunities; participants also receive travel support and complimentary registration to attend ASN Kidney Week.	https://www.asn-online.org/grants/travel/details.aspx?app=MSR
ASN Kidney Tutored Research and Education for Kidney Scholars (TREKS)	M1, M2, M3, M4	TREKS offers a week-long research course and mentorship to medical students interested in nephrology.	https://www.asn-online.org/treks/
ASN Kidney Mentoring and Awareness Program for Students (MAPS)	Premedical, M1, M2, M3, M4	MAPS offers mentoring and kidney disease awareness programs for premedical and medical students who are interested in nephrology.	http://www.asn-online.org/education/training/students/maps/
ASN Kidney Week	M1, M2, M3, M4	Kidney Week offers free registration for medical students to attend the event with numerous learning opportunities and lectures.	https://www.asn-online.org/education/kidneyweek/
Nephrology electives	M3, M4	Inpatient and outpatient experiences are available in various areas such as transplant, home dialysis, peritoneal dialysis, hemodialysis. consult, and glomerular disease.	Home or away institution
Research opportunities	M1, M2, M3, M4	Opportunities are available in clinical, basic science, and quality improvement research in nephrology.	Not applicable
Student-led patient outreach	M1, M2, M3, M4	Community-based initiatives are available for hypertension, diabetes, and kidney disease screenings led by students.	Home institution

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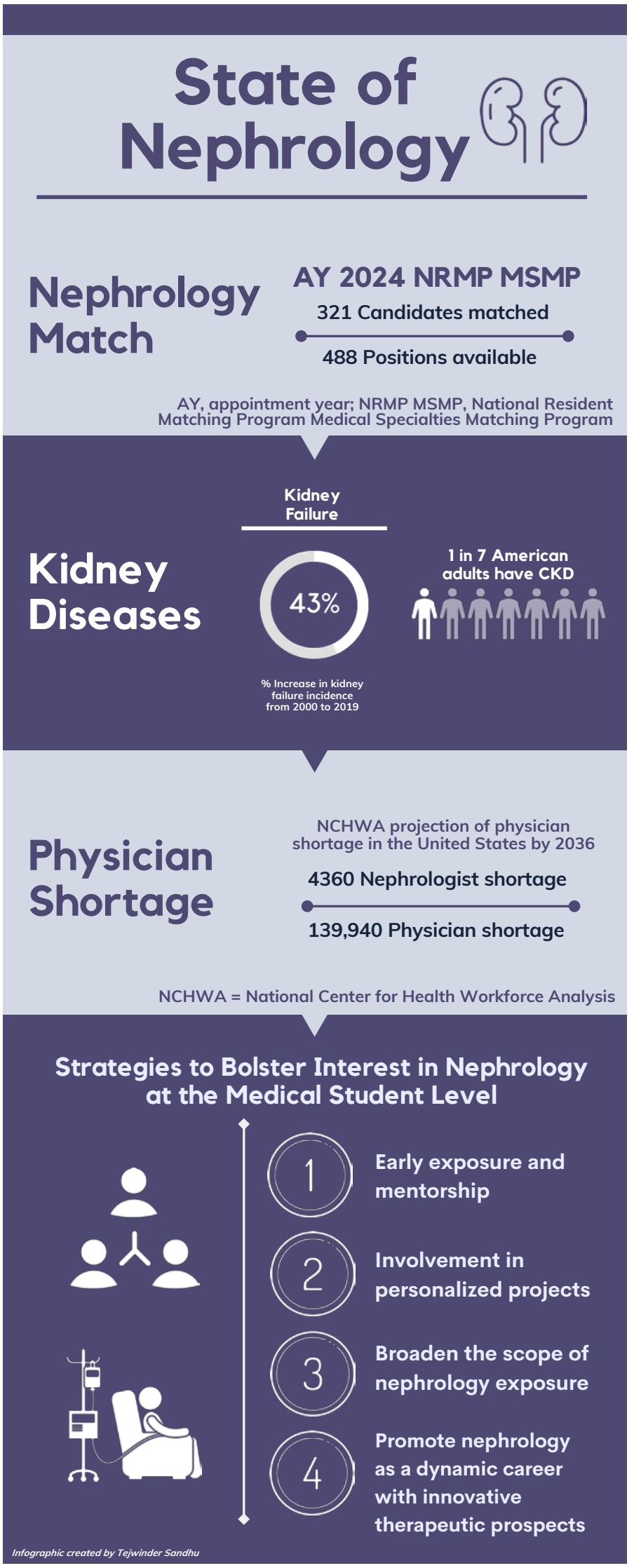

Correction

The Findings article "Taurolidine and Heparin Lock Product Lowers CRBSI Risk" published in January 2024 *Kidney News* contained an inaccurate report of event rates among groups studied by the "LOCK-IT-100" (Study Assessing Safety & Effectiveness of a Catheter Lock Solution in Dialysis Patients to Prevent Bloodstream Infection) trial.

The original article stated, "Event rates were 0.3 for heparin only versus 0.46 for taurolidine and heparin per 1000 catheter days. The hazard ratio for CRBSI was 0.28 in the taurolidine and heparin group."

The sentences should read:
"Event rates were 0.46 for heparin only versus 0.13 for taurolidine and heparin per 1000 catheter days. The hazard ratio for CRBSI was 0.29 in the taurolidine and heparin group."

CKCC Model Updates Seek to Mitigate RTA Effects

By Lauren Ahearn

Following several calls for action by ASN, the Renal Physicians Association (RPA), and other community organizations, the Center for Medicare and Medicaid Innovation (CMMI) announced policy changes and updates on April 16, 2024, pertinent to the Comprehensive Kidney Care Contracting (CKCC) model, including changes to address the effect of the Retrospective Trend Adjustment (RTA) on the model and associated program modifications.

In the CKCC model, CMMI provides nephrologists with a "benchmark" (or baseline funding number) that is the government's projection for what the total health care spending is expected to be during that year for an individual patient with kidney disease. Nephrologists invest in services and staff to enhance patient care and outcomes, comparing their expenditures against this benchmark to determine their performance in the model. Participants can benefit from savings if spending is lower than what is set in the benchmark.

Last year, CMMI announced an RTA for benchmark years 2022 and 2023 due to inaccurate projections on its part, resulting in reduced reimbursement or paybacks for participants in the model long after care is provided. Alarmed by the idea of a retroactive change to the benchmark after investment in care, nephrologists, dialysis facilities, and value-based care organizations raised concerns that the unforeseen financial risk could cause some participants to drop out of the model.

In response to these concerns, ASN and RPA sent a letter to the Department of Health and Human Services and CMMI urging the Centers for Medicare & Medicaid Services (CMS) to narrow the risk corridors within the model or consider other proposals to ensure continued participation in the CKCC by nephrologists and other participants (1). In addition, ASN and RPA urged Congress to request that CMMI address the RTA's potential impact on model participation (2). ASN was concerned that the RTA decision would unfairly hurt participants and could potentially reduce enrollment in innovative care models, inhibiting access to care focused on delaying the progression of kidney diseases and expanding patient choice.

CMS announced that it plans to make two policy changes for performance year (PY)2024 for Kidney Contracting Entities (KCEs) (3):

1. There will be no changes to the financial methodology for payment years 2022 and 2023. However, after reviewing updated data, CMMI intends to update the CKCC model risk corridors by making them narrower for both the chronic kidney disease and end stage renal disease benchmark. These updates include:
   - KCEs are now responsible for absorbing the first 3% of any RTA adjustment.
   - KCE's responsibility decreases incrementally for adjustments between 3% and 6%, with CMS shouldering 50% of the adjustment.
   - The exposure for KCE's shared losses in a PY are capped at 4.5%.
2. KCEs will also be permitted to switch from the Global to the Professional option for the 2024 period, an option that was not available prior to this change. This change allows KCEs to project a shared loss in PY2024 based on the new RTA adjustments to mitigate its losses and share any potential savings or losses with CMMI.

ASN will continue to monitor the impact of these policy changes on CKCC model participants and advocate for the adoption of policies to promote access to kidney care that emphasizes earlier intervention, access to transplant care, and care coordination. ■

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

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ASN Advocates for Increased Funding for US Transplant System

By Killian Gause

On April 18, 2024, volunteer leaders of ASN met with their congressional delegations to discuss the need to provide $67 million in fiscal year 2025 for the Health Resources and Services Administration Organ Transplantation Program to implement the Securing the US Organ Procurement and Transplantation Network (OPTN) Act, included as part of Health Resources and Services Administration's OPTN Modernization Initiative.

Currently, more than 100,000 people are waiting for an organ transplant, including more than 90,000 people waiting for a kidney. Although approximately 27,000 kidney transplants were performed in the United States in 2023, this accomplishment is far short of the need of the tens of thousands of people who were waiting for a life-saving kidney transplant that same year.

In 2023, Congress passed the Securing the US OPTN Act, which aims to improve the performance, transparency, and efficiency of our transplant system by modernizing the information technology infrastructure, establishing independent governance, enabling competition, and revitalizing core functions of the OPTN. This legislation includes some of the most significant improvements to the OPTN in its 40-year history.

As Congress begins to draft funding legislation for fiscal year 2025, ASN members urged their members of Congress to continue their commitment to implementing the Securing the US OPTN Act and provide funding to support these vital patient-centered improvements. ASN will continue to advocate for funding of the transplant network as Congress continues its funding process so that people seeking a kidney transplant can benefit from increased transparency, accountability, and best-in-class services. ■

Killian Gause is a policy and government affairs associate at ASN.

FTC Bans Noncompete Clauses, Court Challenges Loom

By Lauren Ahearn

On April 23, 2024, the Federal Trade Commission (FTC) voted 3 to 2 in favor of a near-total ban on noncompete clauses (1), which limit the ability of workers to change employers within an industry. FTC projects that this rule could reduce health care costs by up to $194 billion in the next decade. In both the proposed and final rule, it cited evidence that noncompete agreements encourage consolidation and drive-up health care prices (2). The American Medical Association estimates that between 37% and 45% of physicians are affected by "noncompetes" (3).

ASN expressed support for this ban when it was first proposed by FTC in April 2023 (4). At the forefront of ASN's response was a desire, above all else, to preserve the patient-doctor relationship. ASN argued that noncompetes have the potential to disrupt these relationships when noncompetes force health care professionals to relocate, thus forcing some patients (especially those in rural communities) to travel long distances to access care.

In addition to voicing support for the ban, ASN expressed concern over the unsolved question of how it will apply to not-for-profit health care employers. In the proposed rule, it was suggested that not-for-profit organizations would be exempt from the ban. ASN asked FTC to clarify this issue and expand the proposed rule by including not-for-profit health care employers, as doing such would level the playing field for all health care employers, including nephrologists. In the final rule, FTC recognized that although it does not have jurisdiction over not-for-profit entities, it reserved the right to evaluate an entity's nonprofit status and noted that "entities that claim tax-exempt status may in fact fall under the Commission's jurisdiction" (5).

The ban is set to take effect 120 days after its publication in the *Federal Register*; however, it is already being challenged in court. Business groups led by the U.S. Chamber of Commerce announced in May that they are suing FTC and will seek a block to the ban (6). In a complaint filed in a Texas federal court, the nation's largest business lobby argued that FTC lacks the authority to issue rules that define unfair methods of competition. This question over FTC's jurisdiction is political and will likely become a growing topic of debate as we near the upcoming November election. This case will likely reach the Supreme Court, in which the conservative majority has shown deep skepticism toward what it views as agency overreach. ■

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Management of Diabetic Kidney Disease: The Era of the Four Pillars

By Vikas S. Sridhar and David Z. I. Cherney

Until 2019, management of chronic kidney disease (CKD) in the setting of diabetes was limited to the renin-angiotensin system (RAS) blockade, in conjunction with blood pressure and glycemic control (1). With the CREDENCE (Evaluation of the Effects of Canagliflozin on Renal and Cardiovascular Outcomes in Participants With Diabetic Nephropathy) trial (2), canagliflozin became the first new agent to be approved for the management of type 2 diabetes (T2D) and CKD, swiftly followed by dapagliflozin and empagliflozin. Sodium-glucose cotransporter-2 (SGLT2) inhibitors are currently a cornerstone in the management of T2D and CKD in addition to atherosclerotic cardiovascular disease and heart failure (3). More recently, with FIDELITY (Finerenone in Chronic Kidney Disease and Type 2 Diabetes: Combined FIDELIO-DKD [Finerenone in Reducing Kidney Failure and Disease Progression in Diabetic Kidney Disease] and FIGARO-DKD [Efficacy and Safety of Finerenone in Subjects With Type 2 Diabetes Mellitus and the Clinical Diagnosis of Diabetic Kidney Disease] Trial Programme Analysis), nonsteroidal mineralocorticoid receptor antagonists (nsMRAs) have also been approved for the management of T2D and albuminuric CKD as an add-on to the RAS blockade and SGLT2 inhibitors (4). Finally, with highly anticipated results of the FLOW (A Research Study to See How Semaglutide Works Compared to Placebo in People With Type 2 Diabetes and Chronic Kidney Disease) trial (5), in which semaglutide lowered the risk of kidney events by 24%, glucagon-like peptide-1 receptor agonists (GLP-1RAs) are expected to be the fourth pillar of CKD management in the setting of T2D. GLP-1RAs are already recommended to be used in the setting of T2D and atherosclerotic cardiovascular disease (6).

SGLT2 inhibitors, nsMRAs, and GLP-1RAs are being increasingly used in combination in the management of T2D and albuminuric CKD (7). However, the combined use of these agents has yet to be studied in large outcome trials. To estimate the combined cardiorenal-protective effects of these agents, Neuen et al. (8) performed an age-based analysis using pooled participant-level data from the CANVAS (Canagliflozin Cardiovascular Assessment) program, CREDENCE, FIGARO-DKD, and FIDELIO-DKD, as well as a trial-level meta-analysis of eight GLP-1RA outcome trials. Conventional care with the RAS blockade served as the control therapy in this analysis. The primary outcome was major adverse cardiovascular events (MACEs), with secondary heart failure hospitalization and CKD progression outcomes, and an assumption of independent and additive effects of all therapeutic classes. Compared with conventional care, combination therapy was estimated to have a hazard ratio (HR) of 0.65 (95% confidence interval [CI], 0.55–0.76) with respect to MACEs and a HR of 0.42 (95% CI, 0.31–0.56) with respect to kidney disease progression. When estimating absolute risk reductions with combination therapy, 23 patients would need to be treated for 3 years to prevent one MACE and one CKD progression outcome, and 33 patients would need to be treated to prevent one death. These gains were noted across all age groups studied, with the greatest absolute benefit noted in younger patients.

The combined use of SGLT2 inhibitors, nsMRAs, and GLP-1RAs will soon be recommended by cardiology, nephrology, and endocrinology guidelines in the management of T2D and CKD. Faced with increasing therapeutic options and the associated "pill burden," side-effect profiles, and economic costs, patients and practitioners alike require adequate information to guide clinical decision-making. Although trials studying these agents in combination are underway, the analysis by Neuen and colleagues (8) offers an early estimate of anticipated benefits in cardiorenal outcomes in this new era of diabetic kidney disease management. ■

Vikas S. Sridhar, MD, and David Z. I. Cherney, MD, PhD, are with the Toronto General Hospital Research Institute, University Health Network; Division of Nephrology, Department of Medicine, University Health Network; and the Department of Medicine, University of Toronto, Toronto, Ontario, Canada.

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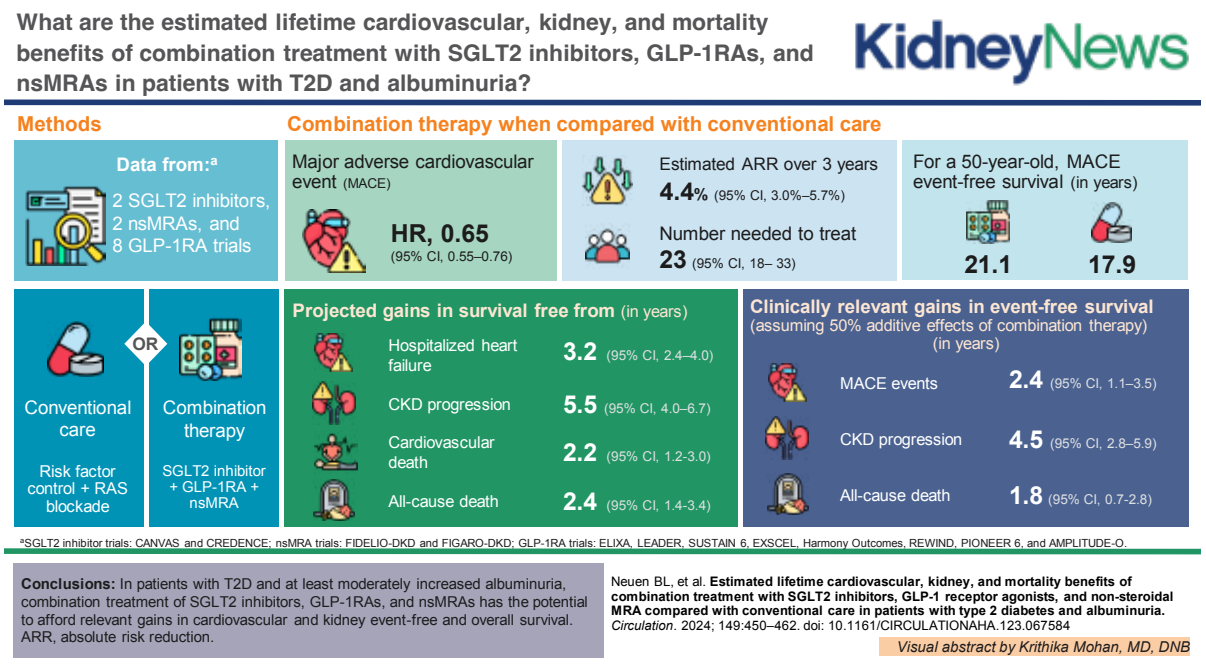


Visit TAVNEOSPRO.com to explore the data

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

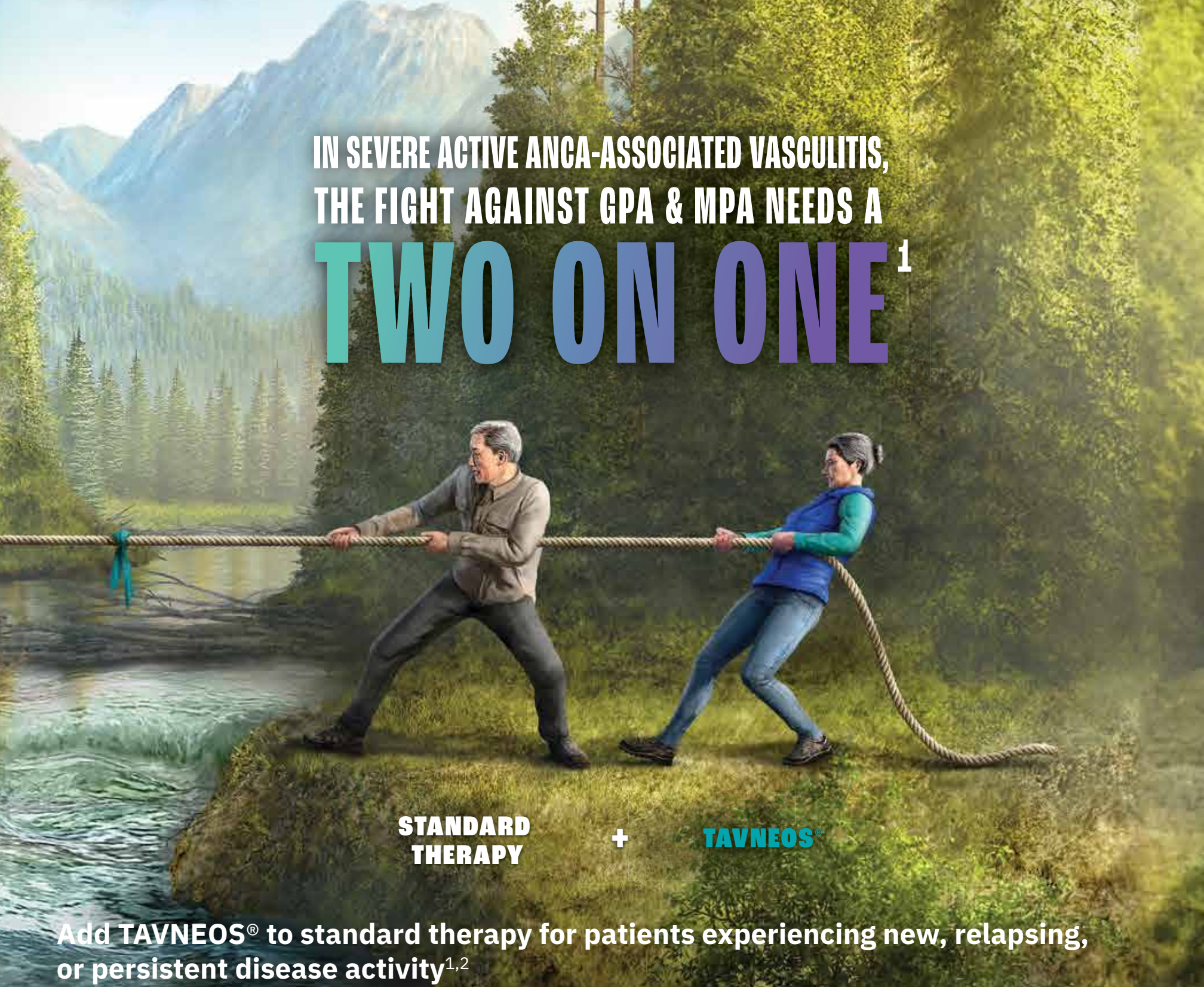
Serious hypersensitivity to avacopan or to any of the excipients.

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.

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

12/23 USA-569-80504

AMGEN®

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

INDICATIONS AND USAGE

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

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

Hepatotoxicity

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

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

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

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

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

Hypersensitivity Reactions

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

Hepatitis B Virus (HBV) Reactivation

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

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

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

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

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

Serious Infections

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

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

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

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

ADVERSE REACTIONS

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

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

Clinical Trials Experience

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

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

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

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

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

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

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

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

Hepatotoxicity and Elevated Liver Function Tests

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

Angioedema

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

Elevated Creatine Phosphokinase

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

DRUG INTERACTIONS

CYP3A4 Inducers

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

CYP3A4 Inhibitors

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

CYP3A4 Substrates

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

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

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

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

Data

Animal Data

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

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

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

Lactation

Risk Summary

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

Animal Data

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

Pediatric Use

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

Geriatric Use

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

Patients With Renal Impairment

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

Patients With Hepatic Impairment

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

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

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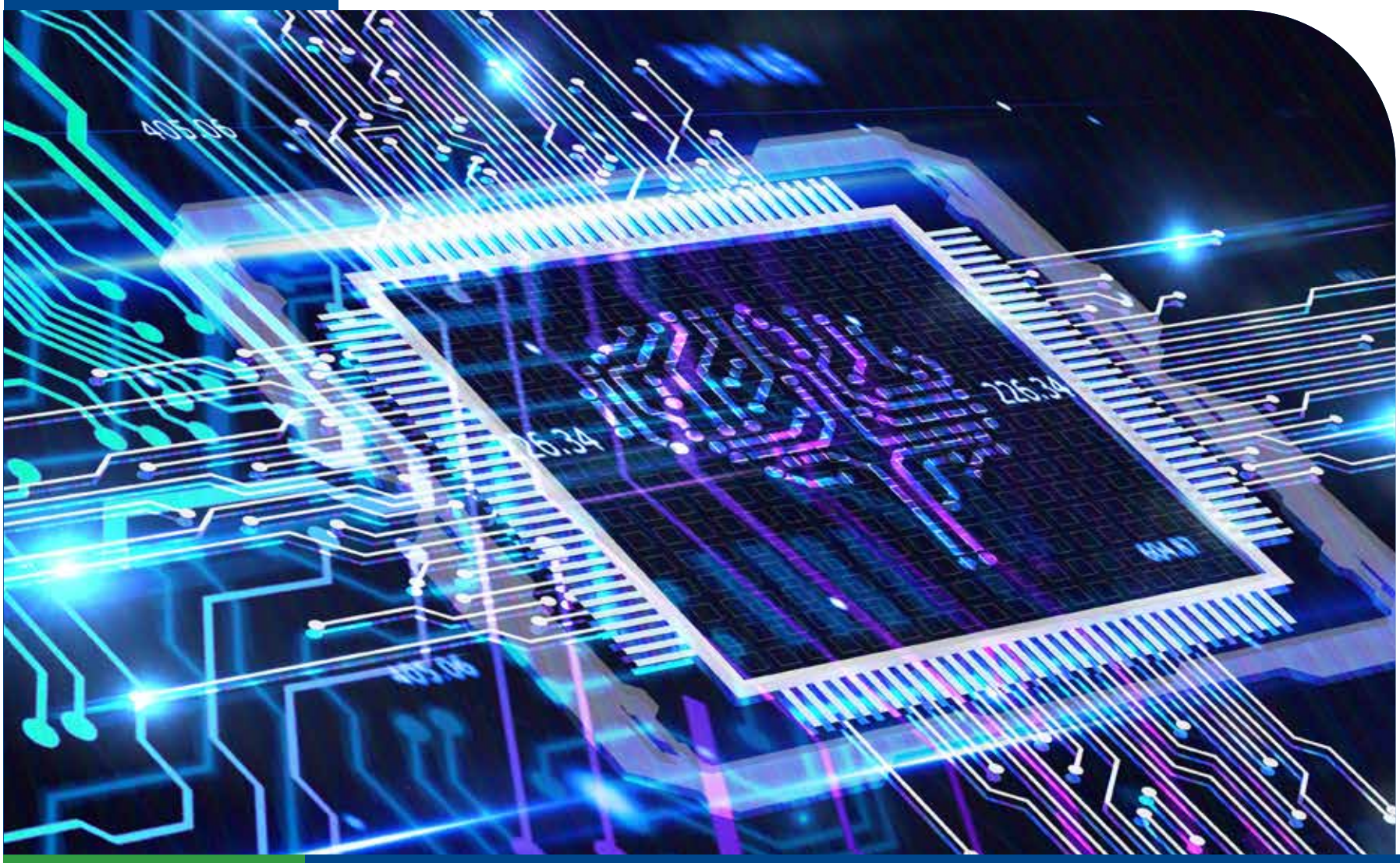

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SPECIAL INTRODUCTION BY THE ASN PRESIDENT

EATING FOR KIDNEY HEALTH

By Deidra C. Crews

Across the continuum of kidney health, the question of *what to eat* is pervasive among patients, caregivers, and clinicians alike. My patients and their families have often pointed out to me how challenging—and confusing—it is to keep track of the vast, and sometimes disparate, recommendations they are given regarding what they should and should not eat.

In this special section of *Kidney News*, the authors address several timely questions about nutrition and kidney health. Farthest upstream is a discussion of dietary practices, such as sugary drink consumption and its associated risk of developing kidney diseases (1). Relevant to the self-management and care of people living with nondialysis-dependent chronic kidney disease, this issue details approaches to assessing nutritional status for people with kidney diseases and the impact of various dietary patterns on systemic inflammation. These topics include the time-honored dilemma of how much and what type of protein should be consumed. Additionally, the section explores potential approaches to the dietary management of kidney diseases through use of artificial intelligence-based support. Authors in this issue also discuss a new era in the care of people treated with hemodialysis, wherein plant-based diets can be more frequently considered, if not encouraged, particularly given the broad availability of potassium binders. These emerging approaches underscore the need for multidisciplinary teams, inclusive of dietitians trained in current trends for the specialized care of patients with kidney diseases, to ensure their successful implementation.

In bringing attention to nutrition and kidney health, we should remember that many people at disproportionate risk of developing kidney diseases and its health consequences also experience food insecurity. The United Nations defines food insecurity as a lack of "regular access to enough safe and nutritious food for normal growth and development and an active and healthy life" (2). Food insecurity, sometimes referred to as "food poverty," may have different implications for health, including kidney health, in different settings. For example, in low- and middle-income countries, food insecurity may result in starvation. Whereas in high-income countries, food insecurity is more often associated with greater risk of overweight and obesity, likely because when people experiencing food insecurity in these countries access foods, they tend to be energy-rich (i.e., high caloric content) but nutrient-poor foods (3).

An individual's ability (or inability) to access the types of foods nephrologists and other clinicians might recommend to people with or at risk for kidney diseases is critical to consider, as is environmental climate change that threatens both food security and nutrition (4). Climate change is already having significant impacts on the kidney health of many people with social and geographic vulnerabilities across the globe (5).

This special section of *Kidney News* invites us to learn the latest about the role of nutrition in our field—and it *also* invites us to redouble our efforts to ensure everyone has the opportunity to eat for their kidney health.

Deidra C. Crews, MD, ScM, FASN, is professor of medicine at Johns Hopkins University School of Medicine, Baltimore, MD, deputy director of the Johns Hopkins Center for Health Equity, and ASN president.

The author reports no conflicts of interest.

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Kidney News thanks Clara García Carro, MD, PhD, and María José Soler Romeo, MD, PhD, FERA, for expertly selecting and coediting these articles.

Dr. García Carro is a nephrologist at San Carlos Clinical Hospital, Madrid, Spain. Dr. Soler is a nephrologist at Hospital del Vall d'Hebron, Barcelona, Spain; deputy chair of the International Society of Nephrology's Western Europe Regional Board; and vice president of Sociedad Española de Nefrología.

The section coeditors report no conflicts of interest.

Mesoamerican Nephropathy: An Emerging Entity Associated With Consumption of Sugary Drinks

By Jorge Rico Fontalvo and Vicente Sánchez Polo

Chronic kidney disease (CKD) is a highly prevalent condition with a high incidence (1, 2). Diabetes mellitus (DM), hypertension (HT), cardiovascular disease, metabolic syndrome, and obesity, are among the best known causes of CKD globally, with DM being the leading factor (1, 2).

However, in agricultural communities in Mesoamerica—a region and cultural area that begins in the southern part of North America and extends to the Pacific coast of Central America—as well as other regions of the world, heatstroke has been associated with CKD, along with other potential variables such as exposure to environmental toxins, infections, and genetic factors. Often, individuals are exposed to heatstroke and strenuous exercise during agricultural work, leading to dehydration that gradually causes kidney damage at the tubulointerstitial level (3). This entity is referred to as CKD of unknown origin (CKDu) or Mesoamerican nephropathy. Factors associated with kidney damage in CKDu include sustained dehydration, strenuous exercise, and rehydration with sweet and carbonated beverages. Additionally, social determinants such as poverty, low birth weight, and malnutrition contribute to the development of a slow, progressive, and irreversible form of CKD (3, 4) (Figure 1).

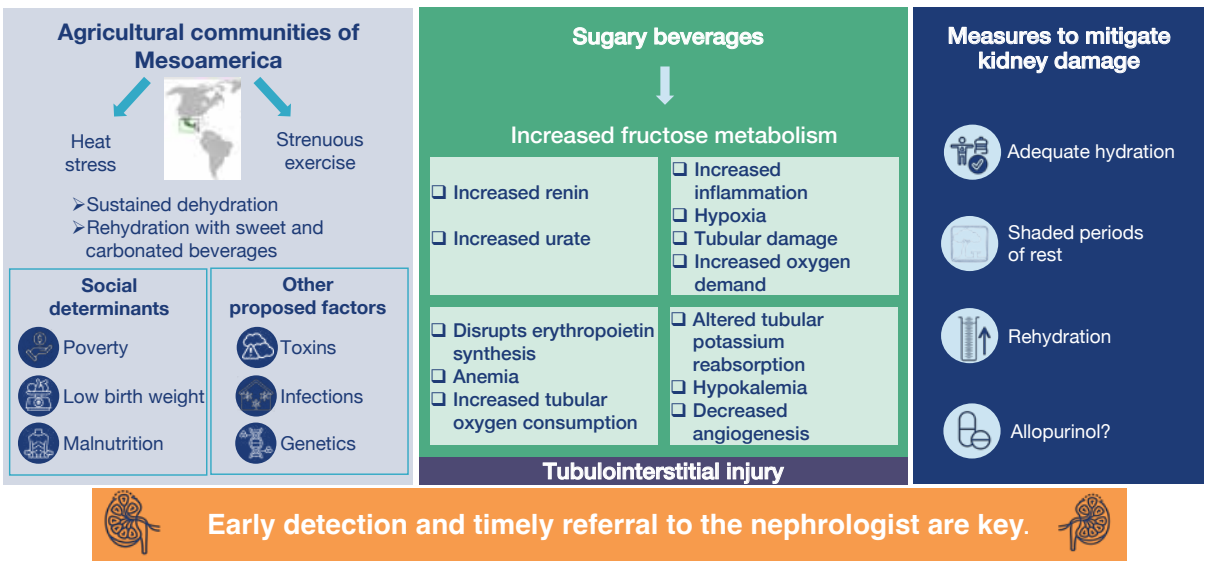
There is sufficient evidence that high consumption of sugary beverages is associated with DM, HT, obesity, and the consequent incidence and progression of CKD (5–7). Several indirect and direct mechanisms could explain this association. Sugary beverages contain added sugars and associated energy, which, when consumed regularly, lead to a high positive-energy balance, resulting in weight gain and obesity development. Obesity is a risk factor for DM, cardiovascular disease, and CKD. Additionally, these beverages, with high fructose as well as other sugars, can increase serum renin and urate concentrations, leading to interstitial fibrosis and renal vascular disease, all directly contributing to the development of kidney diseases (5).

On the other hand, in the physiology of CKDu, rehydration with sugary beverages after strenuous exercise and heatstroke exposure stimulates fructose activity, which generates inflammation, hypoxia, and tubular damage, increasing oxygen demand. In addition, this disrupts erythropoietin synthesis, causing anemia, which also increases tubular oxygen consumption. Tubular potassium reabsorption is also altered, leading to hypokalemia, which limits angiogenesis, further affecting oxygen consumption. All of this causes tubulointerstitial damage, which, with continued exposure to heat and probably other insults such as environmental toxins, produces chronic tubulointerstitial damage. This repeated damage leads to a slow, progressive, and asymptomatic form of CKD in the young population of the agricultural zones of Mesoamerica. Furthermore, fructose activation is also implicated in kidney damage in this population. Additionally, there is a local accumulation of uric acid, which induces hypoxia, inflammation, and general tubular damage (8–10) (Figure 2).

Among the actions proposed to prevent and delay the progression of kidney damage are: 1) removing the individual from the risk area, 2) ensuring adequate hydration with electrolyte-based solutions, 3) increasing the periods of rest in the shade, and 4) rehydrating during work. Due to the potential involvement of uric acid in the pathophysiology of the disease, the use of allopurinol has also been proposed to mitigate kidney damage (11, 12).

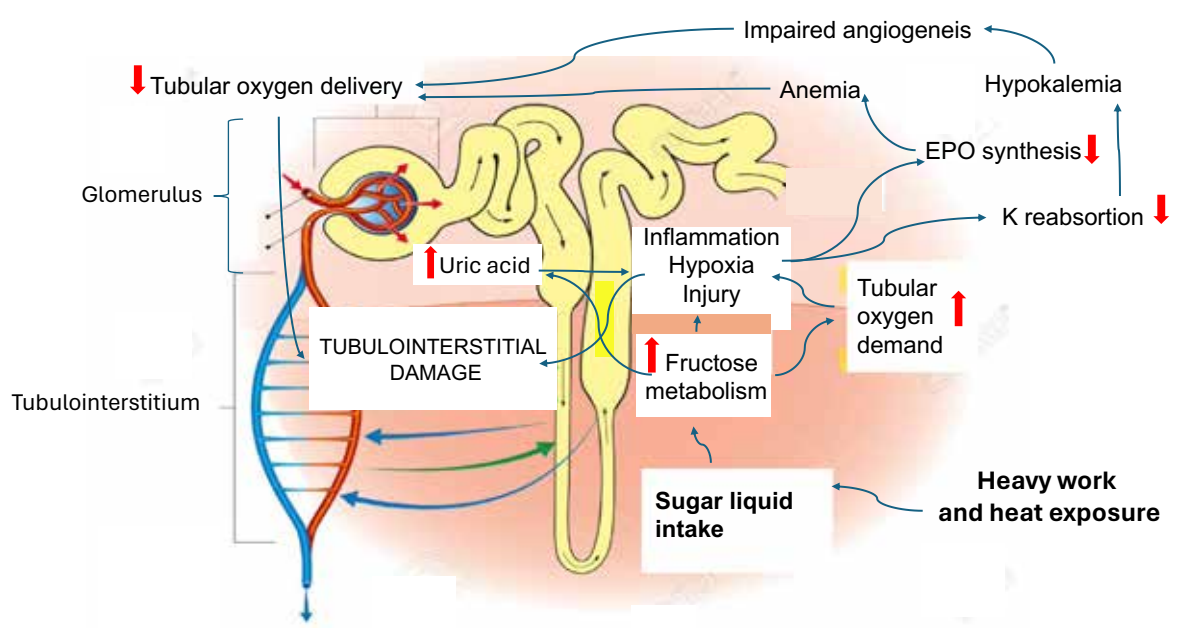
The hydration pattern of individuals, especially those with risk factors for developing CKD, should be based on healthy fluids with a good electrolyte content and low sugar. ■

Figure 1. Mesoamerican nephropathy: What we know about the etiology and effects of consuming sugary drinks



Infographic by Priyadarshini John, MD, DM

Figure 2. Pathophysiology of CKDu: Sugar liquid intake and kidney risk



EPO, erythropoietin; K, potassium.

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The authors report no conflicts of interest.

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Nutritional Screening and Assessment in Chronic Kidney Disease

By Guillermina Barril and Mar Ruperto

Nutritional risk and malnutrition related to chronic kidney disease (CKD) are common disorders that usually appear from CKD stages 3–5 and are more frequent among patients undergoing renal replacement therapy, mainly among those receiving hemodialysis therapy.

The prevalence of malnutrition has been reported in up to 54% of patients living with CKD, leading to a significant increase in morbidity and mortality (1–3). Nutritional screening is a preassessment method of nutritional status to identify patients at risk of malnutrition and, in turn, to indicate nutritional assessment for those with increased nutritional risk and/or probable malnutrition. Since the 1980s, several nutritional screening tools have been implemented in CKD (Figure 1).

The subjective global assessment (SGA), originally developed by Detsky and colleagues in the 1980s (4), was adapted and validated in 1996 as a seven-point scale (7-point SGA) (5, 6). Recommended by clinical practice guidelines for regular nutritional assessment in patients with CKD and undergoing dialysis (7), this 7-point SGA is based on clinical history data (body weight, dietary intake, gastrointestinal symptoms, and functional capacity, as well as comorbidities related to nutritional needs) and includes a physical examination of body mass (subcutaneous fat and muscle) and the detection of edema. Studies (8, 9) have shown that low 7-point SGA scores are associated with a high risk of mortality in patients living with CKD and undergoing dialysis. In 1999, the dialysis malnutrition score (DMS) was developed (10), which used the original 7-point SGA scale and included a score from 1 to 5 for each item. Subsequently, the Malnutrition-Inflammation Score (MIS) questionnaire, a semiquantitative tool that is based on the subjective 7-point SGA and also includes objective parameters (body mass index, serum albumin, and total iron binding capacity) (11), has been extensively correlated in previous studies (11, 12) with hospital admission and mortality. MIS is a validated nutritional screening tool for patients with CKD and undergoing dialysis (11, 12) and has been recommended for routine use for the nutritional assessment of patients with kidney failure (7). The Dialysis Outcomes and Practice Patterns Study (9) used the quantitative modified SGA (m-SGA), developed in 2002, based on caregiver ratings of weight loss, appetite loss, gastrointestinal symptoms, and disease burden. Patients with a severe m-SGA score had significantly higher mortality risk compared with those with moderate or normal m-SGA scores.

An expert panel in 2008 (13) suggested using specific markers from four different categories—biochemistry, body mass, muscle mass, and dietary intake—for the clinical diagnosis of the so-called protein-energy wasting (PEW) syndrome. Three of these four categories should be included, with at least one being a biochemical marker. PEW is a complex syndrome that, combined with the inflammation, uremic toxicity, and endocrine-metabolic disorders of CKD, has been shown to significantly increase the mortality rate at a 5-year follow-up (13) (Figure 2).

Most recently in 2019, unified diagnostic criteria for disease-related malnutrition were proposed within the framework of the Global Leadership Initiative on Malnutrition (GLIM) (14). The GLIM approach includes one phenotypic criterion (low body mass index, unintentional body weight loss, or low muscle mass) and at least one etiologic criterion (reduced food intake, disease burden, or inflammation state) for diagnosing disease-related malnutrition. At present, the applicability of GLIM criteria in CKD and dialysis is still being developed. Further studies with large samples are warranted to validate GLIM criteria for the diagnosis of PEW.

In summary, the first step in detecting nutritional risk can be performed using well-established and validated nutritional screening tools, whereas nutritional assessment requires the combination of several parameters to diagnose PEW in populations with CKD and undergoing dialysis. A single marker by itself is not able to identify or diagnose nutritional disorders. ■

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The authors report no conflicts of interest.

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Figure 1. Timeline of nutritional screening tools and diagnostic criteria used in populations with CKD and undergoing dialysis

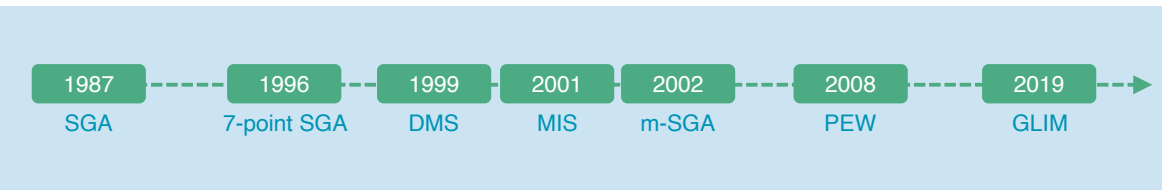
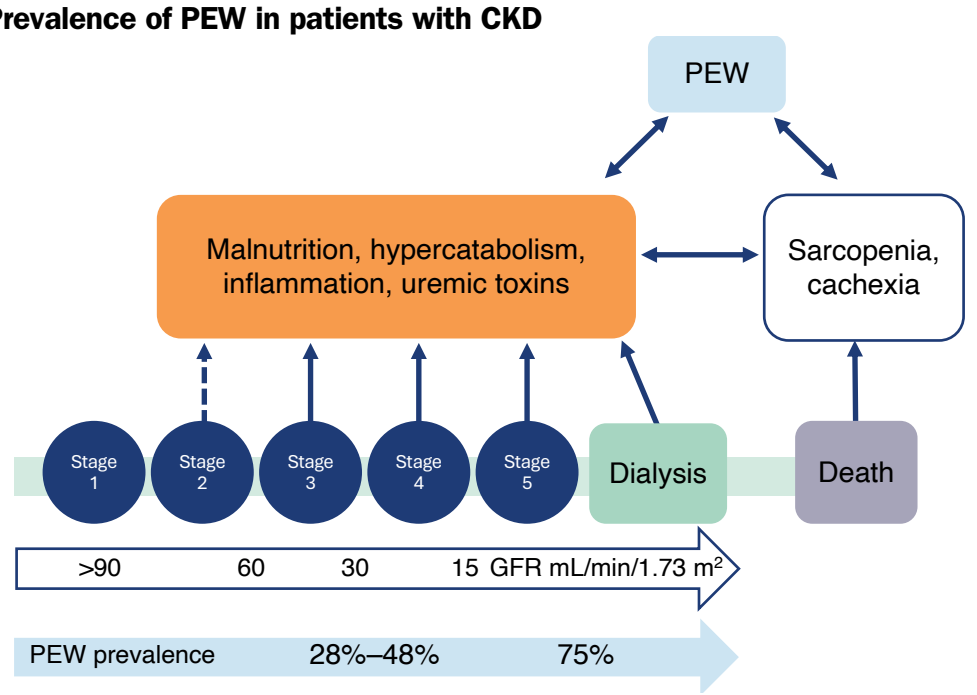


Figure 2. Prevalence of PEW in patients with CKD



Conceptual scheme modified from Hanna et al. (15). GFR, glomerular filtration rate.

Nutritional Screening and Assessment in Chronic Kidney Disease

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A Potential Paradigm Shift: Potassium Binders in K+-Restricted Diets in Patients With CKD

By Deborah J. Clegg and Biff F. Palmer

Individuals with chronic kidney disease (CKD) and those receiving kidney replacement therapies are often prescribed diets that are extremely challenging to adhere to. In addition to being low in phosphorus, these diets typically are restrictive in potassium (K^+)-containing foods. The rationale for K^+ restriction among this patient population was derived years ago and was based on K^+ balance studies in which individuals with CKD receiving dialysis were given K^+ supplements. When given as K^+ salts, development of hyperkalemia was common and provided the rationale for K^+-restricted diets. More recent data suggest that consumption of diets rich in fruits and vegetables (food items rich in K^+) in individuals with CKD and on dialysis do not significantly increase plasma K^+ concentration (1, 2). Reflexively encouraging patients with CKD not to consume fresh fruits and vegetables and/or a Mediterranean diet has the potential for harm since these diets have proven health benefits. As a result, there is a growing trend focusing on liberalization of K^+ in the diet among people with advanced CKD and/or on dialysis. One strategy to allow patients to ingest diets higher in dietary K^+ is with simultaneous use of new K^+-binding drugs. A shift toward a more lenient, plant-based diet may be plausible and may enhance compliance while fostering better overall health (3).

Patiromer and sodium zirconium cyclosilicate are new oral drugs that function as K^+-binding agents in the gastrointestinal tract and have demonstrated efficacy in treating hyperkalemia. Both drugs have demonstrated sustained efficacy and tolerability when used on a chronic basis. Patiromer is a nonabsorbed polymer that binds K^+ in exchange for calcium and acts primarily in the colon. Sodium zirconium cyclosilicate has a nonabsorbed microporous structure allowing for binding of K^+ in the gastrointestinal tract in exchange for sodium. Both drugs reduce plasma K^+ in patients with CKD, enabling the chronic use of renin-angiotensin-aldosterone system inhibitors, and in patients with heart failure, CKD, and established cardiovascular disease. Diet was not controlled in studies of these drugs, but patients were instructed to avoid high K^+ intake. What is not known is whether novel binding agents could enable patients who are vulnerable to hyperkalemia to increase their consumption of K^+-enriched fruits and vegetables without inducing hyperkalemia. Such trials would be of great utility. If such trials demonstrated that these drugs were effective in liberalizing the diet, patients with high risk of CKD would be granted the health benefits of K^+-enriched diets and likely would enjoy a better quality of life (4, 5).

The current management of individuals with hyperkalemia is to reflexively impose dietary restrictions on fresh fruits and vegetables, depriving them of the cardiovascular benefits of these foods. This strategy has the potential to contribute to ongoing development of atherosclerosis in patients with CKD. Dietary surveys conducted by the National Health and Nutrition Examination Survey indicate that the average consumer takes in approximately 2000 mg of K^+ per day, and therefore, K^+ has been listed as a nutrient of concern because of inadequate intake (6). This is important because patients with advanced CKD and undergoing dialysis are prescribed low K^+ diets, which provide 2000 mg per day—exactly what consumers are typically (inadequately) eating. We contend that there is insufficient evidence to justify the extent to which K^+ restriction is commonly enforced in many patients with CKD. In cases of hyperkalemia, it is important to note that there are nondietary factors such as metabolic acidosis, poorly controlled diabetes mellitus leading to hypertonic states, increased catabolism, tissue breakdown, constipation, and medications, all of which contribute to hyperkalemia and should be considered first prior to dietary restriction. In addition, there are several characteristics of diets enriched in fruits and vegetables that serve to limit development of hyperkalemia (Table). Nevertheless, dietary counseling remains essential, especially for individuals consuming large quantities of foods rich in K^+ additives or high in sodium content. ■

Table. Characteristics of a diet enriched in fruits and vegetables that minimize hyperkalemia

Carbohydrate load causing stimulation of insulin release and shift of K^+ into cells
Increased alkali content • Shift of K^+ into cells • Increased K^+ secretion brought about by the pH effect on the renal outer medullary channel in the collecting duct
High fiber content • Increased stool bulk and less K^+ absorption • Decreased constipation • Increased kidney K^+ secretion via gastric-kidney crosstalk
Lack of exogenous administration of K^+ for flavoring as commonly present in processed foods

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Plant-Based Diet in Hemodialysis: Risk or Benefit?

By David E. St-Jules and Juan J. Carrero

Oh, I like avocados, but I am not supposed to eat them! Sound familiar?

In case you have not done so already, you can probably recycle your handouts containing long lists of foods and beverages for patients to avoid. Indeed, many of the underlying assumptions that guided the traditional low-potassium, low-phosphorus, high-protein dialysis diet plans have been comprehensively criticized over the last several years (1, 2), establishing the requisite clinical equipoise to justify exploring new dietary approaches and strategies in this population.

The traditional dialysis diet generally restricted otherwise healthy plant-based food options (including whole grains; high-potassium fruits and vegetables; and nuts, seeds, and legumes), along with low-fat dairy products, to manage hyperkalemia and hyperphosphatemia risk. At the same time, it promoted excess intake of eggs, meat, fish, and poultry to prevent protein-energy wasting (3). This diet is difficult to adhere to and not appreciated by most patients.

The term *plant-based* has been increasingly adopted in the literature to describe alternative diet plans that instead promote whole grains, encourage a balance of plant-based and animal-based protein foods, and/or eliminate restrictions on high-potassium fruits and vegetables (4). There is nothing unique about this plant-based diet; it simply emphasizes consuming a variety of healthy foods and is largely consistent with other healthy eating patterns such as the Mediterranean and DASH (Dietary Approaches to Stop Hypertension) diets that have been found to have many potential health benefits (4).

There are many potential benefits of transitioning from the traditional nutrient-based dialysis diets to plant-based diets. Eliminating what were probably unnecessary dietary restrictions may enable patients to adopt a more varied, enjoyable diet while reducing the stress and burden of trying to follow a diet that allows peaches and tangerines, for example, but not nectarines and bananas (3, 5). Along with these modifications, the time and effort that had been dedicated to counseling patients to adopt this complicated, restrictive, and generally unhealthy eating pattern can be redirected to other potentially more positive aspects of health promotion such as increasing fruit and vegetable intake, enjoying more homemade meals, and reading food labels (6, 7).

With so many abandoning the rapidly sinking traditional diet "ship," it seems destined to sail off and fade into the annals of medical misadventures. It shall not be missed. And although it may no longer guide care, the legacy of the nutrient-based dialysis diet can continue to instruct. The fact that such a diet was adopted for so long without being tested should serve as a reminder about the potential complexity of diet therapy and value that dietary intervention trials provide in promoting evidence-based dietetic practice.

That dearth persists today; so care. It is likely possible that plant-based diets may provide benefits and satisfaction to patients. However, it is also possible that some degree of moderation and restriction is still needed in some patients prone to certain complications (e.g., hyperkalemia) or during periods in which these complications can magnify. Indeed, the best diet for the average patient may not be the best diet for your patient, and as with all diets, potential pitfalls with plant-based diets have been identified (8).

Ultimately, there are still many avenues to study before the potential of diet therapy to prevent and manage nutrition-related complications in people with kidney diseases can be fully realized. But, as alternative dietary strategies are explored, dietetic professionals will be better equipped to provide tailored medical nutrition therapy that addresses nutrition-related complications while promoting a healthy diet. Although there is still much to do, given the many proposed diet and health benefits that could be derived from a more liberal, healthier, plant-based diet, there is good reason for optimism. ■

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Protein Intake in CKD: The Everlasting Dilemma

By Giorgina Barbara Piccoli, Abril Gutierrez, and Claudia D'Alessandro

To recommend or not to recommend? This is the question that many clinicians ask themselves when considering low protein diets for people living with chronic kidney disease (CKD). Historically, reducing protein intake was the only tool to reduce the production of uremic toxins, which could alleviate symptoms of kidney failure. A low protein diet may indeed help in controlling several metabolic derangements due to uremia; decreasing phosphate intake; reducing acidosis; helping to manage bone disease; and decreasing inflammation, protein carbamylation, endothelial dysfunction, and cardiovascular damage. Conversely, a high protein diet increases the glomerular filtration rate, and, over time, in a diseased kidney, glomerular hyperfiltration may induce further damage on the remnant nephrons (1).

The literature lists several low protein diet options, conventionally divided into "moderately restricted" (i.e., with a protein intake of 0.6 g/kg per day). These include traditional diets, based on the quantity and on the distribution of food; vegan-vegetarian or plant-based, plant-dominant diets; and very low protein (0.3–0.4 g/kg per day) diets, using protein-free foods and mixtures of essential amino acids and ketoacids (2). However, because most Western diets have a higher protein content compared with the recommended daily allowances of 0.8 g/kg per day for the general population, as recommended by the World Health Organization and other organizations, normalization of dietary protein intake should usually be a first step, and sometimes the best option, to reduce protein intake against a high background (3).

Furthermore, the quantity of proteins is not everything. The focus is progressively shifting from *quantity* to *quality* of proteins. A diet supplying higher vegetable content and minimally processed foods offers several health benefits, including, in the overall population, a decrease in the incidence of renal dysfunction and, in patients with CKD, possibly a lower progression of kidney function impairment (4, 5).

The Modification of Diet in Renal Disease study (6) was a turning point in the implementation of low protein diets. This large randomized clinical trial showed no benefit from dietary protein restriction in the primary analysis but suggested an advantage in the per-protocol analysis, thus highlighting the importance of compliance or adherence to low protein intake (6). Later, further randomized controlled trials have shown beneficial effects of restricted protein intake, so that the Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines on kidney nutrition strongly recommended, in patients with CKD who are nondiabetic, protein restriction (0.3–0.6 g/kg per day) for CKD stages 3–5 with a high grade of evidence (7) (Figure). Conversely, the recent Kidney Disease: Improving Global Outcomes (KDIGO) guidelines about CKD management suggest normalization of protein intake (0.8 g/kg per day) but leave the door open for further restriction in selected cases (8).

Randomized trials are probably not the best way to convince clinical nephrologists of the benefits of different diets because the selected populations enrolled usually differ from those encountered in their daily practice. Adherence may be difficult, and there is still fear of promoting malnutrition or protein energy wasting by restricting protein intake.

We are the offspring of the so-called "nutrition transition," leading to low consumption of natural, homemade meals and low intake of fruits, vegetables, legumes, beans, nuts, and whole grains. In this context, helping patients achieve a healthy diet, rich in plant-based sources and limited in ultraprocessed food, is probably the first step to undertake. Thus, the new challenge on protein intake in patients with CKD should probably start from selecting better-quality protein sources and high-fiber meals and teaching healthy cooking to achieve a better quality of diet (9, 10).

Attention to "quality first" should not divert attention from quantity. A low protein diet may slow CKD progression and delay or reduce dialysis needs by stabilizing the metabolic balance with lower drug burden. This should be kept in mind, particularly in the more advanced CKD stages. In any case, it is important to stress that protein selection and restriction are only a part, even if probably the most CKD specific, of the nutritional management in patients with CKD (11).

Precision medicine and nutrition precision focus on personalized approaches for a patient-centered management. These are not just words. Dietary recommendations should be based on individual habits, preferences, needs, and disease characteristics. Furthermore, as we seek sustainable nephrology and nutritional practices, we may also remind ourselves that "what is good for the patient is probably also good for the planet" (12). ■

Figure. The protein intake balance in people living with CKD

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Food as Medicine for Inflammation in CKD

By Marcia Ribeiro and Denise Mafra

Chronic kidney disease (CKD), a noncommunicable metabolic and silent disease, is considered a serious public health problem affecting more than 37 million adults in the United States (1). Several factors are associated with kidney failure progression and complications in patients with CKD, such as oxidative stress, mitochondrial dysfunction, premature aging, gut dysbiosis, and endothelial dysfunction. The chronic inflammation that represents a pathological change and directly implies worsening CKD prognoses and cardiovascular outcomes should be highlighted (2). Diabetes mellitus, hypertension, obesity, physical inactivity, age, diet, anemia, metabolic acidosis, altered immune system, gut dysbiosis, and uremia per se can all contribute to inflammation. At the cellular level, oxidative stress, senescence cells, and mitochondrial dysfunction are directly involved in the inflammation observed in persons with CKD (3).

Corroborating this scenario, mitochondrial dysfunction with consequent overproduction of reactive oxygen species promotes increased inflammation through the activation of the nuclear transcription factor kappa B (NF-κB), which is related to the production of inflammatory cytokines, such as several interleukins (ILs) and tumor necrosis factor-alpha. In addition, inflammasome activation, mainly the nucleotide-binding oligomerization domain, leucine-rich repeat, and pyrin domain containing 3 (NLRP3), enormously exacerbates inflammation in patients with CKD since it releases IL-1β and IL-18 (4, 5). In contrast, the master of the antioxidant system, nuclear factor 2 related to erythroid 2 (NRF2), a transcription factor involved in synthesizing many antioxidant enzymes, seems to have reduced mRNA expression in patients with CKD. Thus, the expression of this transcription factor is inversely associated with inflammation (5).

All of these systems can be repressed or inducible, and nutrients play a crucial role in activating the NRF2 and repressing the NF-κB and NLRP3 signaling pathways, exerting therapeutic effects against inflammation. Current evidence indicates that many bioactive compounds found naturally in foods, such as isothiocyanates in cruciferous vegetables; catechins in dark chocolate; and polyphenols in fruits, propolis, and fermented food, can act as modulators of transcription factors involved in inflammation and oxidative stress, providing anti-inflammatory and antioxidant effects in individuals with CKD. Therefore, the concept of "food as medicine" becomes especially relevant for CKD (5).

Studies indicate that several bioactive compounds—such as curcumin, allicin, quercetin, sulforaphane, and catechins—can promote increased mRNA expression of NRF2 and antioxidant enzymes—such as heme oxygenase-1 (HO-1) and NADPH quinone dehydrogenase-1 (NQO-1)—in addition to attenuating the expression of the inflammasome and NF-κB. Also, they can inhibit essential proteins in the inflammatory cascade such as mitogen-activated protein kinase, inhibitory kappa B kinase alpha, and nuclear factor of kappa light polypeptide gene enhancer in B cells inhibitor alpha (6–8).

Given the above information, improving the quality of the diet of patients with CKD, including healthy foods rich in bioactive compounds such as fruits, vegetables, seeds, nuts, tea, cocoa, coffee, whole grains, and spices like turmeric and cinnamon, can be a potential strategy to prevent and treat inflammation in these individuals (Figure). ■

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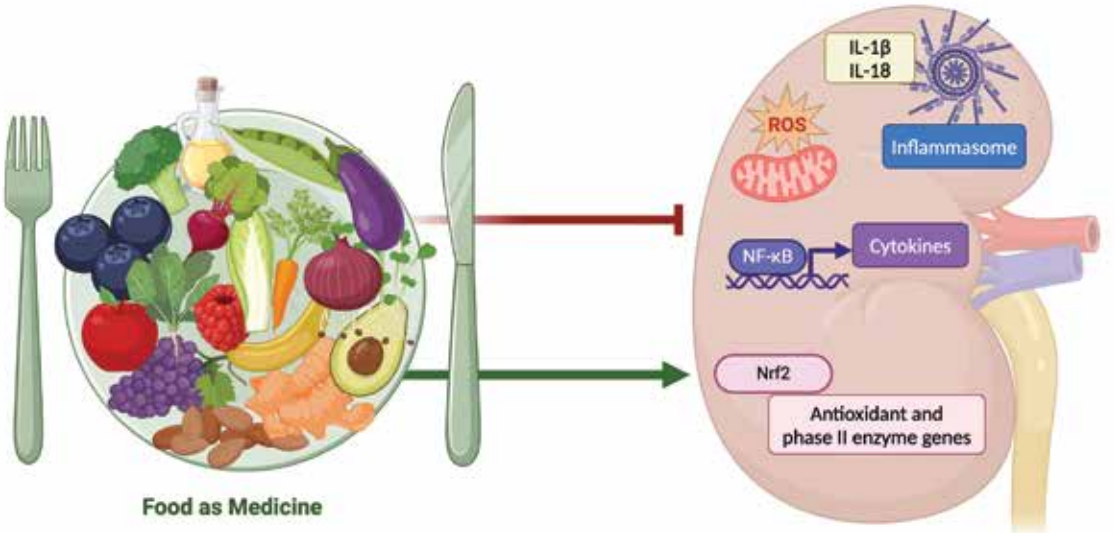
Figure. Mechanisms by which foods and nutrients exert anti-inflammatory and antioxidant effects in patients with CKD



Bioactive compounds, naturally present in foods, have anti-inflammatory properties and can inactivate the inflammasome by reducing the expression of IL-1β and IL-18 and the overproduction of reactive oxygen species (ROS) and attenuate the NF-κB pathway with a consequent reduction in the expression of inflammatory cytokines such as ILs and tumor necrosis factor-alpha, in addition to stimulating the NRF2 pathway, increasing the synthesis of phase II antioxidant enzymes. Created by BioRender.com.

Recipe for Success? The Power of AI to Enhance Kidney Diet Support

By Jing Miao, Charat Thongprayoon, and Wisit Cheungpasitporn

Chronic kidney disease (CKD) is a progressive condition impacting over 10% of the global population, predominantly afflicting older individuals and those with diabetes mellitus or hypertension (1). The importance of kidney diet education in CKD cannot be overstated (2). Proper dietary management can significantly slow the progression of CKD, reduce the risk of complications such as hyperkalemia and hyperphosphatemia, and improve the quality of life for patients. A kidney diet typically involves the careful control of nutrient intake, including potassium, phosphorus, and protein, to alleviate the kidneys' workload and prevent further damage. Navigating the complexities of a kidney diet for individuals with CKD requires careful planning and monitoring.

The rapid development of artificial intelligence (AI) technologies, particularly advanced generative models such as OpenAI's ChatGPT, has sparked extensive research and exploration across various domains, including health care (3). Within nephrology, we have thoroughly explored the utility of ChatGPT alongside other language models such as Google's Gemini (formerly known as Bard) and Microsoft's Copilot (formerly known as Bing Chat) (4). One of these investigations focused on the capability of various AI models to accurately identify the potassium and phosphorus levels in foods (5). A selection of 240 food items, derived from the *Mayo Clinic Renal Diet Handbook* (5), tailored for patients with CKD, was evaluated through each model. GPT-4, the latest iteration of ChatGPT, exhibited exceptional proficiency in identifying potassium levels, successfully classifying 81% of the food items (Figure, A). It demonstrated a remarkable accuracy rate of 99% in identifying high potassium foods, surpassing the performance of Gemini (79%) and Copilot (81%) (Figure, B). In the analysis of phosphorus content, Gemini emerged as the most accurate, achieving a perfect 100% accuracy rate, significantly outperforming Copilot (89%) and GPT-4 (77%) (Figure, A). The study also extended to evaluating the chatbots' effectiveness in categorizing foods based on oxalate content (6). Out of 549 food items, Gemini led with an 84% accuracy rate in classifying food items based on the oxalate levels, followed by Copilot at 60% and GPT-4 at 52% (Figure, A). AI models demonstrated greater accuracy in identifying foods with low oxalate than those with moderate or high levels (Figure, B).

Notably, a study showed that ChatGPT passed the Chinese Registered Dietitian exam, with 96% of ChatGPT's answers preferred by professional dietitians (7). It was also suggested that ChatGPT could offer personalized nutritional guidance for individuals with obesity, cardiovascular diseases, and type 2 diabetes, although its capability to formulate balanced meal plans should be further improved (8, 9). Additionally, research on ChatGPT's diet advice for those with food allergies found it could occasionally suggest unsafe diets that include allergens. ChatGPT might also make mistakes in food quantities and energy values and suggest repetitive diets lacking in variety (10).

Our findings, in conjunction with those from other studies, underscore the potential of AI as an impactful tool in enhancing dietary planning for patients with CKD, although its efficacy demands further improvement. This indicates a pivotal moment in health care utilizing technology to tackle complex health challenges. However, concerns over AI's ability to filter out erroneous information underline the importance of complementing, not replacing, professional judgment. It necessitates expert oversight to ensure the accuracy of AI-recommended diets. As medicine and AI evolve, their integration must reflect core medical values: care, empathy, and trust. Future studies should focus on the ethical integration of AI into health records, emphasizing safety and ethics. Health care professionals, including nephrologists, should endeavor to continuously adapt to the evolving landscape of AI. With AI's progress and increased accuracy, we are optimistic about its role in CKD dietary support. With ongoing research and addressing current limitations, we believe that AI will significantly aid in CKD diet planning. ■

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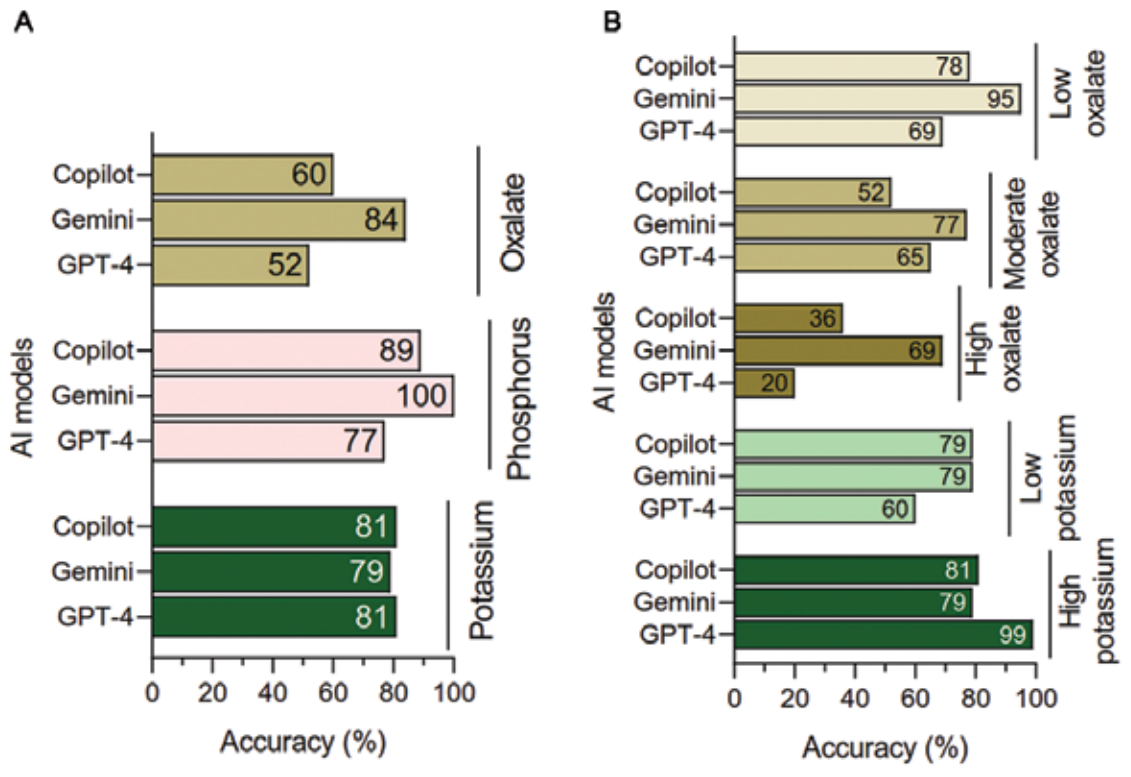
Figure. Performance of AI models in supporting kidney diet management



(A) The accuracy of AI models in categorizing food items based on potassium, phosphorus, and oxalate levels, respectively. (B) The accuracy of AI models in identifying food items with high potassium; low potassium; as well as high (>8 mg per serving), moderate (5–8 mg per serving), and low (<5 mg per serving) oxalate levels.

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Establishing the Incidence of CKD in Irish Adults

By Donal Sexton

Investigators at The Irish Longitudinal Study on Ageing (TILDA), School of Medicine, Trinity College Dublin, Ireland, have conducted a study to discover the incidence and prevalence of chronic kidney disease (CKD) in community-dwelling individuals aged 50 years or over in Ireland (1).

TILDA was established at Trinity College Dublin to assemble comprehensive health, social, and economic data from Irish adults aged 50 years or over at a national level. TILDA recruited a stratified clustered sample, representative of the community-living Irish population. A random sampling of geographical clusters was used to select households (RANSAM sampling framework), so that each residence in Ireland had an equal probability of selection. Data collection involved an in-home interview, a self-completion questionnaire (using the Computer-Assisted Personal Interview instrument), and a comprehensive health assessment undertaken in a health center or at the respondent's home. The baseline (i.e., wave 1, 2009–2011) sample included 8175 adults, of whom subsequently, 5751 participants completed the health assessment at wave 1. All components of the above design were repeated at wave 3 (2014–2015). All of the participants provided informed signed consent. These data were linked with Irish census data from the Central Statistics Office from 2016. The Research Ethics Committee of Trinity College Dublin approved the study protocol.

Using the race-adjusted combination serum creatinine and serum cystatin C CKD Epidemiology Collaboration (CKD-EPI) estimated glomerular filtration rate (eGFR) equation, CKD was present in 11.7% of the Irish general population at wave 1 and rose to 15.6% of participants at wave 3. This 15.6% equates to approximately 225,937 people or 1 in 7 of the general population in the same age range. Using the race-neutral combination of the serum creatinine and serum cystatin C CKD-EPI eGFR equation resulted in slightly lower estimates of CKD at wave 3, at 13.29% (192,234 in the same-age population). Surprisingly, 98% of people in the community with CKD were unaware of it.

During the 13,851 person-years of follow-up, 218 individuals developed CKD stage 3 or higher using the race-adjusted cystatin-creatinine CKD-EPI combination equation eGFR threshold. Accordingly, 208 new CKD cases were estimated using the race-neutral GFR equation. The overall CKD incidence rate was 16 per 1000 person-years (95% confidence interval [CI], 13–18) using the race-adjusted eGFR equation. The incidence increased gradually with increasing age category from 5 per 1000 person-years in participants aged 50 to 59 years up to 87 per 1000 person-years in participants aged 80 years or older. Additionally, the incidence rates for CKD were 16 (95% CI, 13–19) per 1000 person-years in male and 15 (95% CI, 13–18) per 1000 person-years in female participants and were more than two times higher in those with prevalent comorbidities (i.e., self-reported diabetes or hypertension) (Figure).

Prevalent CKD became more common over time in Ireland, consistent with the country's rapidly aging demographic profile. Thus, highlighting the importance of action in primary and secondary care to raise awareness and improve the outcomes for people living with CKD in Ireland is essential.

This was the largest CKD study performed in Ireland to date and provides unique data pertaining to trends in prevalence of CKD over time as well as the incidence of CKD with aging. The presence of CKD identifies individuals who are at increased risk of adverse health outcomes, including cardiovascular disease, premature death, and potentially progression to requiring dialysis or a kidney transplant. As such, preventing and managing CKD constitute a key public health priority. In Ireland, the incorporation of CKD into the primary care chronic disease management program may allow for improved treatment of CKD, particularly in light of the availability of contemporary treatments with proven benefits in reducing the progression of CKD, as well as adverse cardiovascular outcomes, including sodium-glucose cotransporter-2 inhibitors, glucagon-like peptide-1 analogues, and finerenone, in addition to blood pressure management and renin-angiotensin system antagonism. ■

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The author reports no conflicts of interest.

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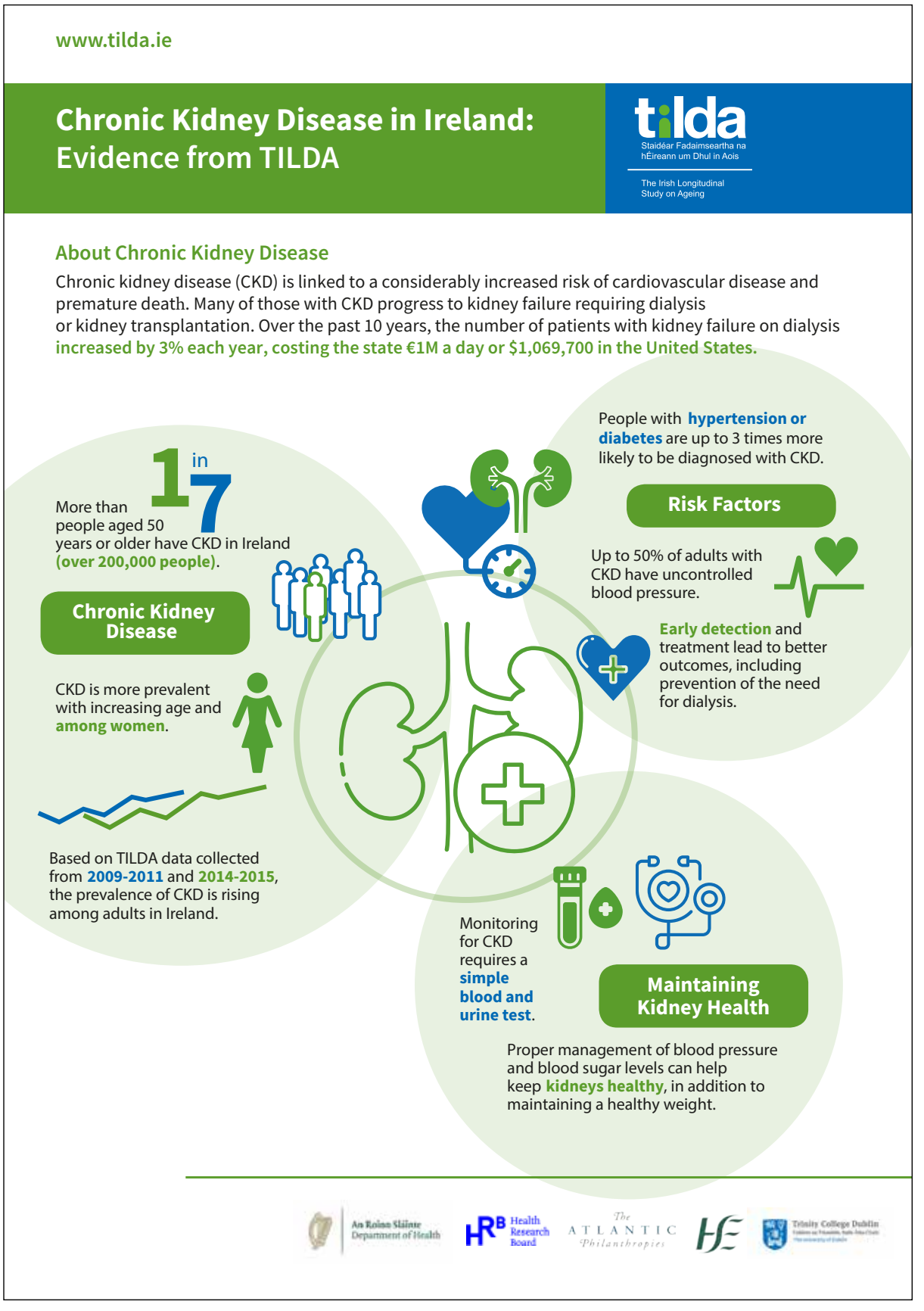
Figure. Chronic kidney disease in Ireland: Evidence from TILDA



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There is a growing movement, particularly in the United States, focusing on enhancing wellness initiatives for trainees at various levels across all specialties. Notable adjustments include reduced call hours, more weekends off, and dedicated study leave. Although these changes have received praise, there is some concern among educators regarding potential unintended consequences, such as less effective training and lack of preparedness for an attending position after graduation. To gain insights into the impact of these initiatives on trainees' well-being and education, *Kidney News* Editorial Fellows asked both a current fellow and a program director to provide their opinions on the matter.

Improving Nephrology Education: Beyond Duty-Hour Restrictions

By Alexis Gomez

Over the past few decades, there has been a growing focus on trainee well-being. Starting with duty-hour restrictions in 2002, efforts are now expanding to focus on reducing call burden, increasing weekends off, protecting didactic time, and factoring in other wellness initiatives (1). Seemingly every program within and outside of nephrology has put trainee wellness under a microscope. Of course, with these initiatives comes the chorus of outcries that training necessarily suffers.

Understanding why there is mixed evidence surrounding the impact of duty-hour reductions on trainee experience and education is essential to knowing how best to proceed. For example, a systematic review published in 2015 of studies on duty hours concluded that there was no difference with respect to the impact on patient care. Yet, it should be noted that many studies in the review showing no impact or a negative impact examined surgical residents, for whom extended shifts may have been necessary for interns and residents to see a surgery through to completion (2). In general, outcomes are more neutral to positive in studies focused on internal medicine or pediatric residents. Various studies found improvements in patient length of stay when trainees' hours were reduced, with others demonstrating an improved breadth of notes, an increasing volume of patients, and a greater likelihood of conference attendance (2–4). Additionally, over half of nephrology fellows report frequency of weekend and overnight calls as "extremely important" when evaluating job offers, indicating that reducing the number of these shifts does have an impact on wellness and quality of life (5).

Still, results are not always consistent, and the reasons for this are varied. For example, shifting to night float is not always accompanied by a concerted effort to include night-float trainees in didactics during their shifts, resulting in decreased educational opportunities. Other studies report results on statistically significant yet functionally meaningless reductions in duty hours, including one study published in *JAMA Internal Medicine* in 2013 in which the authors concluded harm in duty-hour restriction with a reduction of fewer than 3 hours per week (6). In contrast, another study with more significant reductions found much more positive results when looking at errors and preventable adverse events (7). Perhaps most importantly, with the large volume and increasing complexity of patients seen in many training hospitals in recent years, simply attempting to enforce a reduction in hours without adjustments to address workload compression results in trainees feeling forced to either falsify hours (with one report finding nearly half of residents falsifying hours) (8) or to provide substandard care due to these time restrictions (9, 10).

In my experience as an internal medicine and pediatrics trainee across nine different hospitals over the past 7 years, I feel this last issue of workload compression is most pertinent. I have found that many decry training these days as inadequate for independent practice, and the most cited reason is hour restriction. To many pushing this narrative, so too is my generation often described as a "lazy" one, seemingly endlessly wanting more personal time without considering whether we are adequately prepared. We are deemed in a perpetual state of adolescence, unable to accurately self-assess preparedness, rather than as stakeholders in our own adult education.

Yet, with the number of patients steady or increasing and the complexity of encounters on the rise, a generation of educators should ask themselves why they see a generation of physicians they deem unprepared for practice (9, 10). Although a minimum number of encounters are undoubtedly necessary, without addressing work compression, trainees increasingly find themselves unable to debrief patient encounters with attendings and to learn from missteps to care for each patient better as we advance. As we strive to take better care of patients, with inadequate time to do so, education is the only thing left to steal time away from in the day. I find that few, if any, trainees are willing to provide subpar care to protect this time.

When faced with this reality, program responses are varied. For example, some programs carefully assess the number of encounters and time needed to train in chronic rather than acute dialysis and limit this to the necessary minimum. Others choose to use trainees as the sacrificial lambs for the inevitable 6 a.m. pages managing patients with chronic stable dialysis in lieu of learning opportunities on general or subspecialty consults, leaving us inadequately prepared to manage these patients going forward.

Fellows must be treated as important educational stakeholders and adult learners. Programs must consider not only the concern that we may be falling short but also our input on why this may be occurring. To address these issues, it is time for educators and program leadership to go back to the drawing board and overhaul fellow education, focusing first on adequately preparing us for the future rather than using us for adequate hospital staffing. ■

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The author reports no conflicts of interest.

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Well-Being in Nephrology Education

By Ursula C. Brewster

The *Kidney News* editors want 300 to 500 words on well-being in nephrology education—not an easy task for a program director. I believe that program directors profoundly believe in maintaining a sense of well-being for our patients, our fellows, and our communities. That is, after all, why we are physicians. But the practicalities of our jobs, the needs of our patients, and the regulatory and financial pressures can make things murky.

Clinical nephrology, physiology, and research techniques are expanding at a breakneck pace, as are the Accreditation Council for Graduate Medical Education requirements for teaching important topics like population health, data science, team-based health, and quality/safety. As educators, we promise our applicants, the American Board of Internal Medicine, our patients, and society-at-large that we will have fellows ready to practice nephrology independently and safely within 2 years. There is simply more to do in the same amount of time, and we all feel the pressure of that great responsibility. Program directors should support the well-being of our fellows, and given the diversity of career trajectories possible, we need to listen carefully to what an individual fellow thinks that they need to be prepared to embark on that career journey. But at a systems level, a focus on fellow well-being is sometimes paired with a perceived lesser emphasis on attending well-being and can result in tension in the training environment, which should never be the case.

This is where our current systems of payment, reimbursement, and education let us down. Fellows need reasonable work hours, time for self-care, and supportive environments for learning, as do practicing nephrologists, our nurses, and social workers. Although the Accreditation Council for Graduate Medical Education can leverage change through accreditation requirements focusing on trainee wellness, the Centers for Medicare & Medicaid Services and private payers focus on cost abatement and reductions in reimbursement, making it challenging for fellows to find balance when they graduate. To head home in the evening, coach our children, and get some sleep at night, practicing physicians know that we must learn the medicine cold, so we do not spend hours second-guessing all of our decisions. However, we also need to learn to efficiently manage a long list of patients on a clinic day when we were on call the night before. As program directors and faculty, we feel a great responsibility to get our fellows ready for the very real reality of practicing medicine in 2024, in order to ensure lifelong wellness.

A fellow's job is to understand the enormous privilege and responsibility that lies ahead of them, and they need to do all that they can to be ready for it. And as program directors and attendings, our job is to provide them with a supportive learning environment and guidance to help them grow and stretch, often beyond what they have done before. As physicians, we hold a covenant with the community of patients who we are here to serve—to protect their health and well-being. Ours is a profession, a calling, and so much more than "a job." This profession brings wonderful opportunities our way, provides us with financial and social stability, and fills our worlds with a sense of wonder at what is possible, day in and day out. And although challenging, it is our profession that is often the very thing that restores us when least expected. Wellness is, after all, what we are about as doctors. ■

Ursula C. Brewster, MD, is a professor of medicine and program director of the Nephrology Fellowship Program at the Yale School of Medicine, New Haven, CT.

The author reports no conflicts of interest.

KRYSTEXXA **can change the course** of uncontrolled gout[1]

KRYSTEXXA with methotrexate:

>80% RELATIVE IMPROVEMENT
in patient response;
71% (71/100) vs 39% (20/52) complete response compared to KRYSTEXXA alone[1]*

87% RELATIVE REDUCTION
in infusion reactions;
4% (4/96) vs 31% (15/49) compared to KRYSTEXXA alone[1]

Best results were seen at 6-12 months.[1]

The optimal treatment duration has not been established. Individual results vary.[1]

QD, every day; QW, every week; Q2W, every 2 weeks; sUA, serum uric acid.

A 52-week, randomized, double-blind trial conducted in adult patients with chronic gout refractory to conventional therapy to evaluate administration of KRYSTEXXA 8 mg Q2W co-administered with 15 mg oral methotrexate QW and 1 mg oral folic acid QD vs KRYSTEXXA alone.[1]

*Complete sUA response: The primary efficacy endpoint was the proportion of responders, defined by patients achieving and maintaining sUA <6 mg/dL for at least 80% of the time during Month 6.[1]

INDICATION

KRYSTEXXA® (pegloticase) is indicated for the treatment of chronic gout in adult patients who have failed to normalize serum uric acid and whose signs and symptoms are inadequately controlled with xanthine oxidase inhibitors at the maximum medically appropriate dose or for whom these drugs are contraindicated.

Limitations of Use: KRYSTEXXA is not recommended for the treatment of asymptomatic hyperuricemia.

IMPORTANT SAFETY INFORMATION

WARNING: ANAPHYLAXIS AND INFUSION REACTIONS, G6PD DEFICIENCY ASSOCIATED HEMOLYSIS AND METHEMOGLOBINEMIA

- **Anaphylaxis and infusion reactions have been reported to occur during and after administration of KRYSTEXXA.**
- **Anaphylaxis may occur with any infusion, including a first infusion, and generally manifests within 2 hours of the infusion. Delayed hypersensitivity reactions have also been reported.**
- **KRYSTEXXA should be administered in healthcare settings and by healthcare providers prepared to manage anaphylaxis and infusion reactions.**
- **Premedicate with antihistamines and corticosteroids and closely monitor for anaphylaxis for an appropriate period after administration of KRYSTEXXA.**
- **Monitor serum uric acid levels prior to each infusion and discontinue treatment if levels increase to above 6 mg/dL, particularly when 2 consecutive levels above 6 mg/dL are observed.**
- **Screen patients at risk for glucose-6-phosphate dehydrogenase (G6PD) deficiency prior to starting KRYSTEXXA. Hemolysis and methemoglobinemia have been reported with KRYSTEXXA in patients with G6PD deficiency. KRYSTEXXA is contraindicated in patients with G6PD deficiency.**

CONTRAINDICATIONS:

- In patients with G6PD deficiency.
- In patients with history of serious hypersensitivity reactions, including anaphylaxis, to KRYSTEXXA or any of its components.

KRYSTEXXA has not been studied to reverse damage to the heart, kidneys, or any organ.

Dissolve years of systemic urate deposition **with KRYSTEXXA**[2,3]

ChangeTheCourse.com

WARNINGS AND PRECAUTIONS

Gout Flares: An increase in gout flares is frequently observed upon initiation of anti-hyperuricemic therapy, including KRYSTEXXA. Gout flare prophylaxis with a non-steroidal anti-inflammatory drug (NSAID) or colchicine is recommended starting at least 1 week before initiation of KRYSTEXXA therapy and lasting at least 6 months, unless medically contraindicated or not tolerated.

Congestive Heart Failure: KRYSTEXXA has not been formally studied in patients with congestive heart failure, but some patients in the pre-marketing placebo-controlled clinical trials experienced exacerbation. Exercise caution in patients who have congestive heart failure and monitor patients closely following infusion.

ADVERSE REACTIONS

The most commonly reported adverse reactions (≥5%) are:

KRYSTEXXA co-administration with methotrexate trial:
KRYSTEXXA with methotrexate: gout flares, arthralgia, COVID-19, nausea, and fatigue; KRYSTEXXA alone: gout flares, arthralgia, COVID-19, nausea, fatigue, infusion reaction, pain in extremity, hypertension, and vomiting.

KRYSTEXXA pre-marketing placebo-controlled trials:
gout flares, infusion reactions, nausea, contusion or ecchymosis, nasopharyngitis, constipation, chest pain, anaphylaxis, and vomiting.

Please see Brief Summary of Prescribing Information for KRYSTEXXA on following page.

References: 1. KRYSTEXXA (pegloticase) [prescribing information] Horizon. **2.** Sundy JS, et al. *JAMA.* 2011;306:711-720. **3.** Schlesinger N, et al. *Arthritis Rheumatol.* 2017;69(suppl 10):1-4426.

KRYSTEXXA® pegloticase

AMGEN Rare Disease

KRYSTEXXA® (pegloticase) injection, for intravenous use

Brief Summary - Please see the KRYSTEXXA package insert for Full Prescribing Information.

WARNING: ANAPHYLAXIS and INFUSION REACTIONS, G6PD DEFICIENCY ASSOCIATED HEMOLYSIS and METHEMOGLOBINEMIA

See full prescribing information for complete boxed warning.

- **Anaphylaxis and infusion reactions have been reported to occur during and after administration of KRYSTEXXA.**
- **Anaphylaxis may occur with any infusion, including a first infusion, and generally manifests within 2 hours of the infusion. However, delayed hypersensitivity reactions have also been reported.**
- **KRYSTEXXA should be administered in healthcare settings and by healthcare providers prepared to manage anaphylaxis and infusion reactions.**
- **Pre-medicate with antihistamines and corticosteroids and closely monitor for anaphylaxis for an appropriate period of time after administration of KRYSTEXXA.**
- **Monitor serum uric acid levels prior to each infusion and discontinue treatment if levels increase to above 6 mg/dL, particularly when 2 consecutive levels above 6 mg/dL are observed.**
- **Screen patients at risk for G6PD deficiency prior to starting KRYSTEXXA. Hemolysis and methemoglobinemia have been reported with KRYSTEXXA in patients with G6PD deficiency. KRYSTEXXA is contraindicated in patients with G6PD deficiency.**

INDICATIONS AND USAGE

KRYSTEXXA® (pegloticase) is indicated for the treatment of chronic gout in adult patients refractory to conventional therapy.

Gout refractory to conventional therapy occurs in patients who have failed to normalize serum uric acid and whose signs and symptoms are inadequately controlled with xanthine oxidase inhibitors at the maximum medically appropriate dose or for whom these drugs are contraindicated.

Limitations of Use:
KRYSTEXXA is not recommended for the treatment of asymptomatic hyperuricemia.

CONTRAINDICATIONS

KRYSTEXXA is contraindicated in:

- Patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency *[see Warnings and Precautions]*
- Patients with history of serious hypersensitivity reactions, including anaphylaxis, to KRYSTEXXA or any of its components

WARNINGS AND PRECAUTIONS

Anaphylaxis

In a 52-week controlled trial, which evaluated KRYSTEXXA co-administered with methotrexate compared to KRYSTEXXA alone, patients were pre-treated with standardized infusion reaction prophylaxis and were discontinued from treatment with KRYSTEXXA if serum uric acid levels increased to above 6 mg/dL at 2 consecutive visits after the initiation of KRYSTEXXA therapy to reduce the risk of anaphylaxis. One patient randomized to the group treated with KRYSTEXXA co-administered with methotrexate (1%) experienced anaphylaxis during the first infusion and no patients experienced anaphylaxis in the group treated with KRYSTEXXA alone *[see Adverse Reactions]*.

During pre-marketing clinical trials with KRYSTEXXA alone, KRYSTEXXA was not discontinued following 2 consecutive serum uric acid levels above 6 mg/dL. Anaphylaxis was reported with a frequency of 6.5% (8/123) of patients treated with KRYSTEXXA every 2 weeks and 4.8% (6/126) for the every 4-week dosing regimen. There were no cases of anaphylaxis in patients receiving placebo. Anaphylaxis generally occurred within 2 hours after treatment.

Diagnostic criteria of anaphylaxis were skin or mucosal tissue involvement, and, either airway compromise, and/or reduced blood pressure with or without associated symptoms, and a temporal relationship to KRYSTEXXA or placebo injection with no other identifiable cause. Manifestations included wheezing, peri-oral or lingual edema, or hemodynamic instability, with or without rash or urticaria, nausea or vomiting. Cases occurred in patients being pre-treated with one or more doses of an oral antihistamine, an intravenous corticosteroid and/or acetaminophen. This pre-treatment may have blunted or obscured symptoms or signs of anaphylaxis and therefore the reported frequency may be an underestimate.

KRYSTEXXA should be administered in a healthcare setting by healthcare providers prepared to manage anaphylaxis. Patients should be pre-treated with antihistamines and corticosteroids. Anaphylaxis may occur with any infusion, including a first infusion, and generally manifests within 2 hours of the infusion. However, delayed type hypersensitivity reactions have also been reported. Patients should be closely monitored for an appropriate period of time for anaphylaxis after administration of KRYSTEXXA. Patients should be informed of the symptoms and signs of anaphylaxis and instructed to seek immediate medical care should anaphylaxis occur after discharge from the healthcare setting.

The risk of anaphylaxis is higher in patients whose uric acid level increases to above 6 mg/dL, particularly when 2 consecutive levels above 6 mg/dL are observed. Monitor serum uric acid levels prior to infusions and discontinue treatment if levels increase to above 6 mg/dL. Because of the possibility that concomitant use of oral urate-lowering therapy and KRYSTEXXA may potentially blunt the rise of serum uric acid levels, it is recommended that before starting KRYSTEXXA patients discontinue oral urate-lowering medications and not institute therapy with oral urate-lowering agents while taking KRYSTEXXA.

Infusion Reactions

In a 52-week, controlled trial which evaluated KRYSTEXXA co-administered with methotrexate compared to KRYSTEXXA alone *[see Adverse Reactions]*, patients were pre-treated with standardized infusion reaction prophylaxis and were discontinued from treatment with KRYSTEXXA if serum uric acid levels increased to above 6 mg/dL at 2 consecutive visits after the initiation of KRYSTEXXA therapy to reduce the risk of infusion reactions. Infusion reactions were reported in 4% of patients in the KRYSTEXXA co-administered with methotrexate group compared to 31% of patients treated with KRYSTEXXA alone experienced infusion reactions *[see Adverse Reactions]*. In both treatment groups, the majority of infusion reactions occurred at the first or second KRYSTEXXA infusion and during the time of infusion. Manifestations of these infusion reactions were similar to that observed in the pre-marketing trials.

During pre-marketing 24-week controlled clinical trials with KRYSTEXXA alone, KRYSTEXXA was not discontinued following 2 consecutive serum uric acid levels above 6 mg/dL. Infusion reactions were reported in 26% of patients treated with KRYSTEXXA 8 mg every 2 weeks, and 41% of patients treated with KRYSTEXXA 8 mg every 4 weeks, compared to 5% of patients treated with placebo. These infusion reactions occurred in patients being pre-treated with an oral antihistamine, intravenous corticosteroid and/or acetaminophen. This pre-treatment may have blunted or obscured symptoms or signs of infusion reactions and therefore the reported frequency may be an underestimate.

Manifestations of these reactions included urticaria (frequency of 10.6%), dyspnea (frequency of 7.1%), chest discomfort (frequency of 9.5%), chest pain (frequency of 9.5%), erythema (frequency of 9.5%), and pruritus (frequency of 9.5%). These manifestations overlap with the symptoms of anaphylaxis, but in a given patient did not occur together to satisfy the clinical criteria for diagnosing anaphylaxis. Infusion reactions are thought to result from release of various mediators, such as cytokines. Infusion reactions occurred at any time during a course of treatment with approximately 3% occurring with the first infusion, and approximately 91% occurred during the time of infusion.

KRYSTEXXA should be administered in a healthcare setting by healthcare providers prepared to manage infusion reactions. Patients should be pre-treated with antihistamines and corticosteroids. KRYSTEXXA should be infused slowly over no less than 120 minutes. In the event of an infusion reaction, the infusion should be slowed, or stopped and restarted at a slower rate.

The risk of infusion reaction is higher in patients whose uric acid level increases to above 6 mg/dL, particularly when 2 consecutive levels above 6 mg/dL are observed. Monitor serum uric acid levels prior to infusions and discontinue treatment if levels increase to above 6 mg/dL. Because of the possibility that concomitant use of oral urate-lowering therapy and KRYSTEXXA may potentially blunt the rise of serum uric acid levels, it is recommended that before starting KRYSTEXXA patients discontinue oral urate-lowering medications and not institute therapy with oral urate-lowering agents while taking KRYSTEXXA.

G6PD Deficiency Associated Hemolysis and Methemoglobinemia

Life threatening hemolytic reactions and methemoglobinemia have been reported with KRYSTEXXA in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency. Because of the risk of hemolysis and methemoglobinemia, do not administer KRYSTEXXA to patients with G6PD deficiency *[see Contraindications]*. Screen patients at risk for G6PD deficiency prior to starting KRYSTEXXA. For example, patients of African, Mediterranean (including Southern European and Middle Eastern), and Southern Asian ancestry are at increased risk for G6PD deficiency.

Gout Flares

In a 52-week, randomized, double-blind trial which evaluated KRYSTEXXA co-administered with methotrexate compared to KRYSTEXXA alone, patients were administered gout flare prophylaxis similar to that in the pre-marketing, placebo-controlled trials. In this trial, the percentages of patients with any flare for the first 3 months were 66% and 69% for the group treated with KRYSTEXXA co-administered with methotrexate and the group treated with KRYSTEXXA alone, respectively. In the group treated with KRYSTEXXA co-administered with methotrexate, the percentages of patients with any flare for the subsequent 3 month increments of treatment were 27% during Month 6, 8% during Month 9 and 9% during Month 12. In the group treated with KRYSTEXXA alone, the percentages of patients with any flare were 14% during Month 6, 9% during Month 9 and 21% during Month 12.

During pre-marketing, 24-week controlled clinical trials with KRYSTEXXA alone, the frequencies of gout flares were high in all treatment groups, but more so with KRYSTEXXA treatment during the first 3 months of treatment, and decreased in the subsequent 3 months of treatment. The percentages of patients with any flare for the first 3 months were 74%, 81%, and 51%, for KRYSTEXXA 8 mg every 2 weeks, KRYSTEXXA 8 mg every 4 weeks, and placebo, respectively. The percentages of patients with any flare for the subsequent 3 months were 41%, 57%, and 67%, for KRYSTEXXA 8 mg every 2 weeks, KRYSTEXXA 8 mg every 4 weeks, and placebo, respectively. Patients received gout flare prophylaxis with colchicine and/or nonsteroidal anti-inflammatory drugs (NSAIDs) starting at least one week before receiving KRYSTEXXA.

Gout flares may occur after initiation of KRYSTEXXA. An increase in gout flares is frequently observed upon initiation of anti-hyperuricemic therapy, due to changing serum uric acid levels resulting in mobilization of urate from tissue deposits. Gout flare prophylaxis with a non-steroidal anti-inflammatory drug (NSAID) or colchicine is recommended starting at least 1 week before initiation of KRYSTEXXA therapy and lasting at least 6 months, unless medically contraindicated or not tolerated. KRYSTEXXA does not need to be discontinued because of a gout flare. The gout flare should be managed concurrently as appropriate for the individual patient *[see Dosage and Administration]*.

Congestive Heart Failure

KRYSTEXXA has not been formally studied in patients with congestive heart failure, but some patients in the pre-marketing, 24-week controlled clinical trials experienced exacerbation of congestive heart failure. Two cases of congestive heart failure exacerbation occurred during the trials in patients receiving treatment with KRYSTEXXA 8 mg every 2 weeks. No cases were reported in placebo-treated patients. Four subjects had exacerbations of pre-existing congestive heart failure while receiving KRYSTEXXA 8 mg every 2 weeks during the open-label extension study.

Exercise caution when using KRYSTEXXA in patients who have congestive heart failure and monitor patients closely following infusion.

Re-treatment with KRYSTEXXA

No controlled trial data are available on the safety and efficacy of re-treatment with KRYSTEXXA after stopping treatment for longer than 4 weeks. Due to the immunogenicity of KRYSTEXXA, patients receiving re-treatment may be at increased risk of anaphylaxis and infusion reactions. Therefore, patients receiving re-treatment after a drug-free interval should be monitored carefully *[see Adverse Reactions]*.

ADVERSE REACTIONS

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

- Anaphylaxis *[see Warnings and Precautions]*
- Infusion Reactions *[see Warnings and Precautions]*
- G6PD Deficiency Associated Hemolysis and Methemoglobinemia *[see Warnings and Precautions]*
- Gout Flares *[see Warnings and Precautions]*
- Congestive Heart Failure *[see Warnings and Precautions]*

Clinical Trials Experience

Because clinical studies are conducted under widely varying and controlled conditions, adverse reaction rates observed in clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug, and may not predict the rates observed in a broader patient population in clinical practice.

Co-administration with Methotrexate

A 52-week, randomized, double-blind trial was conducted in adult patients with chronic gout refractory to conventional therapy to evaluate administration of KRYSTEXXA 8 mg every 2 weeks co-administered with weekly administration of oral methotrexate 15 mg, compared to KRYSTEXXA alone. In this trial, patients who were able to tolerate two weeks on methotrexate 15 mg were then randomized to receive four additional weeks on either methotrexate 15 mg or matching placebo prior to initiating KRYSTEXXA therapy. A total of 152 subjects were randomized, and of these, 145 subjects completed the 4-week methotrexate run-in period and received KRYSTEXXA (96 subjects received KRYSTEXXA co-administered with methotrexate and 49 received KRYSTEXXA plus placebo) during the treatment period. All patients received pre-treatment with an oral antihistamine, intravenous corticosteroid and acetaminophen. These patients were between the ages of 24 and 83 years (average 55 years); 135 patients were male and 17 and were female; 105 patients were White/Caucasian, 22 were Black/African American,

14 were Asian, 5 were Native Hawaiian/Other Pacific Islander and 5 identified as Other; 28 were Hispanic or Latino. Common co-morbid conditions among the enrolled patients included hypertension (63%), osteoarthritis (25%), hyperlipidemia (24%), gastroesophageal reflux disease (22%), obesity (20%), type 2 diabetes (18%) and depression (16%). Patients with an eGFR <40 mL/min/1.73 m² were excluded from this trial.

The most commonly reported adverse reaction during the methotrexate pre-treatment periods was gout flare. The most commonly reported adverse reactions that occurred in ≥ 5% in either treatment group during the KRYSTEXXA co-administered with methotrexate or KRYSTEXXA alone period are provided in Table 1.

Table 1. Adverse Reactions Occurring in 5% or More of Patients in Either the KRYSTEXXA Co-administered with Methotrexate or KRYSTEXXA Alone Treatment Period

Adverse Reaction	KRYSTEXXA with Methotrexate (N=96) n (%)	KRYSTEXXA Alone (N=49) n (%)
Gout flare	64 (67%)	35 (71%)
Arthralgia	13 (14%)	5 (10%)
COVID-19	9 (9%)	3 (6%)
Nausea	5 (5%)	6 (12%)
Fatigue	5 (5%)	2 (4%)
Infusion reaction	4 (4%)[a]	15 (31%)
Pain in extremity	1 (1%)	3 (6%)
Hypertension	1 (1%)	3 (6%)
Vomiting	0	4 (8%)

[a] Included one case of anaphylaxis

KRYSTEXXA ALONE

The data described below reflect exposure to KRYSTEXXA in patients with chronic gout refractory to conventional therapy in two replicate randomized, placebo-controlled, double-blind 24-week clinical trials: 85 patients were treated with KRYSTEXXA 8 mg every 2 weeks; 84 patients were treated with KRYSTEXXA 8 mg every 4 weeks; and 43 patients were treated with placebo. These patients were between the ages of 23 and 89 years (average 55 years); 173 patients were male and 39 were female; and 143 patients were White/Caucasian, 27 were Black/African American, 24 were Hispanic/Latino and 18 were all other ethnicities. Common co-morbid conditions among the enrolled patients included hypertension (72%), dyslipidemia (49%), chronic kidney disease (28%), diabetes (24%), coronary artery disease (18%), arrhythmia (16%), and cardiac failure/left ventricular dysfunction (12%).

During the pre-marketing placebo-controlled clinical trials, the most commonly reported adverse reactions that occurred in greater than or equal to 5% of patients treated with KRYSTEXXA 8 mg every 2 weeks are provided in Table 2.

Table 2. Adverse Reactions Occurring in 5% or More of Patients Treated with KRYSTEXXA Compared to Placebo

Adverse Reaction	KRYSTEXXA 8 mg every 2 weeks (N=85) n[a] (%)	Placebo (N=43) n (%)
Gout flare	65 (77%)	35 (81%)
Infusion reaction	22 (26%)	2 (5%)
Nausea	10 (12%)	1 (2%)
Contusion[b] or Ecchymosis[b]	9 (11%)	2 (5%)
Nasopharyngitis	6 (7%)	1 (2%)
Constipation	5 (6%)	2 (5%)
Chest Pain	5 (6%)	1 (2%)
Anaphylaxis	4 (5%)	0 (0%)
Vomiting	4 (5%)	1 (2%)

[a] If the same subject in a given group had more than one occurrence in the same preferred term event category, the subject was counted only once.

[b] Most did not occur on the day of infusion and could be related to other factors (e.g., concomitant medications relevant to contusion or ecchymosis, insulin dependent diabetes mellitus).

Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity. The observed incidence of antibody positivity in an assay is highly dependent on several factors including assay sensitivity and specificity and assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, the comparison of the incidence of antibodies to pegloticase with the incidence of antibodies to other products may be misleading.

In a 52-week, randomized, double-blind trial which evaluated KRYSTEXXA co-administered with methotrexate compared to KRYSTEXXA alone, approximately 26% of patients had pre-existing antibodies to pegloticase. Patients with an increase in titer from baseline or who were negative at baseline and developed an anti-pegloticase response at one or more post dose time points was 30% and 51%, for the KRYSTEXXA co-administered with methotrexate and KRYSTEXXA alone treatment groups, respectively. Patients with higher antibody titers were more likely to have faster clearance and lower efficacy.

During pre-marketing 24-week controlled clinical trials with KRYSTEXXA alone, anti-pegloticase antibodies developed in 92% of patients treated with KRYSTEXXA every 2 weeks, and 28% for placebo. Anti-PEG antibodies were also detected in 42% of patients treated with KRYSTEXXA. High anti-pegloticase antibody titer was associated with a failure to maintain pegloticase-induced normalization of uric acid. The impact of anti-PEG antibodies on patients' responses to other PEG-containing therapeutics is unknown.

There was a higher incidence of infusion reactions in patients with high anti-pegloticase antibody titer: 53% (16 of 30) in the KRYSTEXXA every 2 weeks group compared to 6% in patients who had undetectable or low antibody titers.

Postmarketing Experience

The following adverse reactions have been identified during postapproval use of KRYSTEXXA. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship.

General disorders and administration site conditions: asthenia, malaise, peripheral swelling

DRUG INTERACTIONS

Methotrexate

KRYSTEXXA 8 mg every 2 weeks has been studied in patients with chronic gout refractory to conventional therapy taking concomitant oral methotrexate 15 mg weekly. Co-administration of methotrexate with KRYSTEXXA may increase pegloticase concentration compared to KRYSTEXXA alone.

PEGylated products

Because anti-pegloticase antibodies appear to bind to the PEG portion of the drug, there may be potential for binding with other PEGylated products. The impact of anti-PEG antibodies on patients' responses to other PEG-containing therapeutics is unknown.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

There are no adequate and well-controlled studies of KRYSTEXXA in pregnant women. Based on animal reproduction studies, no structural abnormalities were observed when pegloticase was administered by subcutaneous injection to pregnant rats and rabbits during the period of organogenesis at doses up to 50 and 75 times, respectively, the maximum recommended human dose (MRHD). Decreases in mean fetal and pup body weights were observed at approximately 50 and 75 times the MRHD, respectively *[see Data]*.

All pregnancies have a background risk of birth defect, loss or other adverse outcomes. In the US general population, the estimated background risk of major birth defects and miscarriage in clinical recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data

Animal Data

In 2 separate embryo-fetal developmental studies, pregnant rats and rabbits received pegloticase during the period of organogenesis at doses up to approximately 50 and 75 times the maximum recommended human dose (MRHD), respectively (on a mg/m² basis at maternal doses up to 40 and 30 mg/kg twice weekly, in rats and rabbits, respectively). No evidence of structural abnormalities was observed in rats or rabbits. However, decreases in mean fetal and pup body weights were observed at approximately 50 and 75 times the MRHD in rats and rabbits, respectively (on a mg/m² basis at maternal doses up to 40 and 30 mg/kg every other day, in rats and rabbits, respectively). No effects on mean fetal body weights were observed at approximately 10 and 25 times the MRHD in rats and rabbits, respectively (on a mg/m² basis at maternal doses up to 10 mg/kg twice weekly in both species).

Lactation

Risk Summary

It is not known whether this drug is excreted in human milk. Therefore, KRYSTEXXA should not be used when breastfeeding unless the clear benefit to the mother can overcome the unknown risk to the newborn/infant.

Pediatric Use

The safety and effectiveness of KRYSTEXXA in pediatric patients less than 18 years of age have not been established.

Geriatric Use

Of the total number of patients treated with KRYSTEXXA 8 mg every 2 weeks in the controlled studies, 34% (29 of 85) were 65 years of age and older and 12% (10 of 85) were 75 years of age and older. No overall differences in safety or effectiveness were observed between older and younger patients, but greater sensitivity of some older individuals cannot be ruled out. No dose adjustment is needed for patients 65 years of age and older.

Renal Impairment

No dose adjustment is required for patients with renal impairment. In a 52-week, randomized, double-blind trial which evaluated KRYSTEXXA co-administered with methotrexate compared to KRYSTEXXA alone, 85% of patients had chronic kidney disease based on estimated glomerular filtration rate (eGFR) of ≥ 40 to < 90 mL/min/1.73 m² at baseline. In the pre-marketing 24-week controlled clinical trials with KRYSTEXXA alone, a total of 32% (27 of 85) of patients treated with KRYSTEXXA 8 mg every 2 weeks had a creatinine clearance of ≤62.5 mL/min. No overall differences in efficacy were observed.

OVERDOSAGE

No reports of overdosage with KRYSTEXXA have been reported. The maximum dose that has been administered as a single intravenous dose is 12 mg as uricase protein. Patients suspected of receiving an overdose should be monitored, and general supportive measures should be initiated as no specific antidote has been identified.

PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Anaphylaxis and Infusion Reactions

- Anaphylaxis and infusion reactions can occur at any infusion while on therapy. Counsel patients on the importance of adhering to any prescribed medications to help prevent or lessen the severity of these reactions.
- Educate patients on the signs and symptoms of anaphylaxis, including wheezing, peri-oral or lingual edema, hemodynamic instability, and rash or urticaria, nausea or vomiting.
- Educate patients on the most common signs and symptoms of an infusion reaction, including urticaria (skin rash), erythema (redness of the skin), dyspnea (difficulty breathing), flushing, chest discomfort, chest pain, and rash.
- Advise patients to seek medical care immediately if they experience any symptoms of an allergic reaction during or at any time after the infusion of KRYSTEXXA *[see Warnings and Precautions, Adverse Reactions]*
- Advise patients to discontinue any oral urate-lowering agents before starting on KRYSTEXXA and not to take any oral urate-lowering agents while on KRYSTEXXA.

Glucose-6-phosphate dehydrogenase (G6PD) Deficiency

Inform patients not to take KRYSTEXXA if they have a condition known as G6PD deficiency. Explain to patients that G6PD deficiency is more frequently found in individuals of African, Mediterranean, or Southern Asian ancestry and that they may be tested to determine if they have G6PD deficiency, unless already known *[see Warnings and Precautions, Contraindications]*.

Gout Flares

Explain to patients that gout flares may initially increase when starting treatment with KRYSTEXXA, and that medications to help reduce flares may need to be taken regularly for the first few months after KRYSTEXXA is started *[see Warnings and Precautions, Adverse Reactions]*. Advise patients that they should not stop KRYSTEXXA therapy if they have a flare.

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Minority Patients Less Likely to Receive High-Longevity Kidneys

Under the current US allocation system, non-White transplant candidates are substantially less likely to receive high-longevity, high-quality deceased donor kidneys, reports an article in the *American Journal of Kidney Diseases*.

The researchers analyzed data on 199,444 adults listed for deceased donor kidney transplantation from 2015 through 2020, drawn from the Scientific Registry of Transplant Recipients. Race and ethnicity were classified as Asian in 7% of patients, Black in 29%, and Hispanic/Latino in 19%. Outcomes of interest were priorities for longevity matching, based on an estimated posttransplant survival (EPTS) of 20% or less, and transplantation with a high-longevity deceased donor kidney, defined by a kidney donor profile index of 20% or less.

The mean age was 52 years for Black and 50 years for Hispanic/Latino candidates compared with 55 years for White patients. White patients were less likely to have diabetes, spent less time on dialysis, and were more likely to have previous transplants.

After adjustment for age, non-White candidates were less likely to have an EPTS score of 20% or less: odds ratio, 0.86 for Asian patients; 0.52 for Black patients; and 0.49 for Hispanic/Latino patients. The same racial and ethnic groups were less likely to receive a high-longevity kidney, based on a kidney donor profile index of 20% or less: subhazard ratio, 0.70 for Asian patients; 0.89 for Black patients; and 0.73 for Hispanic/Latino patients.

Posttransplant mortality was significantly lower for Asian and Hispanic recipients: hazard ratio, 0.45 and 0.63, respectively, compared with White recipients. Posttransplant mortality was higher for Black compared with White patients, although the difference was not statistically significant.

The current allocation system prioritizes the use of high-longevity kidneys for patients with high EPTS scores, which reflect patient age, presence of diabetes, history of transplantation, and time on dialysis. This could potentially disadvantage non-White candidates, who tend to be younger but more likely to have diabetes and longer durations of dialysis. The new study finds that non-White patients are less likely to be prioritized for and to receive high-longevity deceased donor kidneys, after adjustment for age. This is despite the finding that minority recipients of high-longevity kidneys have similar or even better posttransplant outcomes than their White counterparts.

"[O]ur results demonstrate that the current EPTS score is a barrier to equity in kidney transplantation," the researchers write. They discuss potential strategies for achieving "relatively equal" access to high-quality kidneys across racial and ethnic groups [Asfour N, et al. Association of race and ethnicity with high longevity deceased donor kidney transplantation under the US kidney allocation system. *Am J Kidney Dis*, published online April 16, 2024. doi: 10.1053/j.ajkd.2024.02.017].

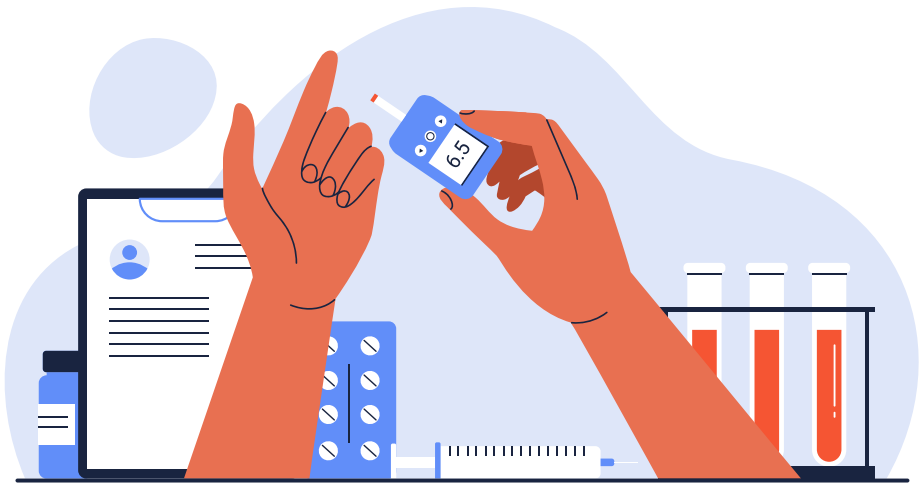
Newer Treatments for Type 2 Diabetes—Revised Guideline

An updated clinical guideline from the American College of Physicians recommends adding a sodium-glucose cotransporter-2 (SGLT2) inhibitor or glucagon-like peptide 1 (GLP-1) agonist to standard treatment for type 2 diabetes in adults. The update is published in the *Annals of Internal Medicine*.

In a 2017 guideline, the American College of Physicians Clinical Guidelines Committee recommended metformin, added to lifestyle modifications, when needed to improve glycemic control in adults with type 2 diabetes. The 2024 guideline incorporates evidence on the effectiveness and harms of newer pharmacologic agents, including GLP-1 agonists, SGLT2 inhibitors, and dipeptidyl peptidase-4 (DPP-4) inhibitors. The systematic review and recommendations focus on the benefits and harms of the newer treatments, with consideration of patients' values and preferences and medication costs.

The guideline includes a strong recommendation for SGLT2 inhibitors or GLP-1 agonists to metformin and lifestyle changes for adults with type 2 diabetes and inadequate glycemic control. That recommendation is based on high-certainty evidence that SGLT2 inhibitors can lower the risk of all-cause mortality, major adverse cardiovascular events, progression of chronic kidney disease, and heart failure hospitalization. Use of GLP-1 agonists reduces all-cause mortality and major adverse cardiovascular events as well as the risk of stroke.

The new document also includes a strong recommendation against adding a DPP-4 inhibitor to standard treatment for type 2 diabetes. That recommendation reflects a lack of evidence that DPP-4 inhibitors reduce morbidity or all-cause mortality.



Weight loss of at least 10% of body weight was a prioritized outcome, but the review did not identify adequate information for analysis. The committee notes that the guideline does not address effects on glycemic control—a common goal of type 2 diabetes treatment.

Cost-effectiveness analysis showed no substantial differences between SGLT2 inhibitors and GLP-1 agonists. The committee notes the high costs of these newer medication classes, for which generic formulations are not currently available. Although lower-cost options are available, evidence shows that they are inferior in reducing all-cause mortality and morbidity.

The updated guideline states that clinicians should prioritize the addition of SGLT2 inhibitors in patients with type 2 diabetes and congestive heart failure and GLP-1 agonists in those who are at increased risk for stroke or for whom weight loss is an important treatment goal. The recommendations and clinical considerations are summarized in an interactive visual clinical guideline [Qasseem A, et al.; Clinical Guidelines Committee of the American College of Physicians. Newer pharmacologic treatments in adults with type 2 diabetes: A clinical guideline from the American College of Physicians. *Ann Intern Med* 2024; 177:658–666. doi: 10.7326/M23-2788]. ■

Early ART Does Not Raise Kidney Risks in People With HIV Infection

In adults with HIV infection, immediate initiation of antiretroviral therapy (ART) does not adversely affect long-term kidney disease outcomes compared with delayed ART, according to a study published in *Kidney International*.

The Strategic Timing of Antiretroviral Treatment (START) trial enrolled 4684 patients with HIV infection, no previous ART, and a CD4 cell count less than 500 cells/mm^3. Patients were randomly assigned to immediate versus deferred ART.

Previous START results showed a small but significantly greater decline in the estimated glomerular filtration rate (eGFR) in the deferred ART group at a median follow-up of 2.1 years. The new analysis included extended follow-up to assess kidney health outcomes: chronic kidney disease (CKD) events, kidney failure, renal death, and changes in the eGFR and the urine albumin/creatinine ratio (UACR).

Over a median follow-up of 9.3 years, kidney failure or renal death occurred in 3 years in the immediate ART group and 5 years in the deferred group. On more comprehensive follow-up for a median of 5 years, the annual rate of decline in the eGFR was 1.19 mL/min/1.73 m^2 per year, with little or no difference by the timing of ART initiation.

The eGFR trend remained the same after adjustment for UACR, *APOL1* risk genotype, and other CKD-related baseline factors. Rates of confirmed UACR of 30 mg/g or greater were also similar between groups.

People with HIV infection are at elevated risk of CKD, related both to HIV itself and to ART exposure. Earlier initiation of ART reduces serious AIDS and non-AIDS events. However, longer exposure might lead to increased treatment toxicity, including kidney injury.

Extended follow-up from the START trial shows similarly low rates of serious CKD events with immediate versus deferred ART for people with HIV infection and high baseline CD4 cell counts. Both groups show a slightly faster decline in the eGFR for age but no significant difference in annual change in the eGFR over 5 years.

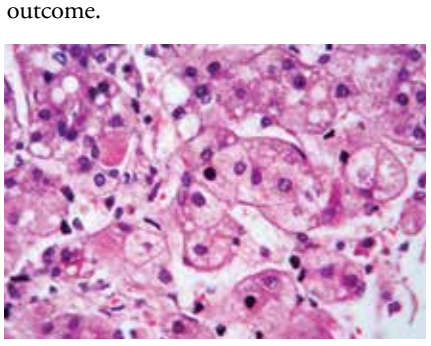
The researchers conclude: "Particularly with a shift towards ART regimens with less potential for kidney injury where resources allow, nephrologists and HIV and primary care providers should focus on modifying traditional CKD risk factors to address the increased risk of CKD and CKD progression in people with HIV" [Pelchen-Matthews A, et al.; INSIGHT START Study Group. Long-term impact of immediate versus deferred antiretroviral therapy on kidney health in people with HIV. *Kidney Int*, published online April 30, 2024. doi: 10.1016/j.kint.2024.04.010].

Longer Survival With Adjuvant Pembrolizumab for RCC

Adjuvant therapy with the anti-programmed death 1 antibody pembrolizumab improves survival in patients with clear-cell renal-cell carcinoma (RCC) at elevated risk of recurrence, according to a clinical trial report in *The New England Journal of Medicine*.

The analysis was the third prespecified interim analysis of the randomized phase 3 Safety and Efficacy Study of Pembrolizumab (MK-3475) as Monotherapy in the Adjuvant Treatment of Renal Cell Carcinoma Post Nephrectomy (MK-3475-564/KEYNOTE-564) trial. The study enrolled 994 patients with clear-cell RCC at increased risk of recurrence after nephrectomy with or without metastasectomy. Patients were assigned to receive pembrolizumab (200 mg) or placebo every 3 weeks for up to 17 cycles.

Previous analyses reported improvement in estimated disease-free survival at 24 months with pembrolizumab: 77.3% versus 68.1% with placebo; hazard ratio, 0.68. The current analysis focused on overall survival, with safety as a secondary outcome.



At 48 months, estimated overall survival was 91.2% with pembrolizumab, compared with 86.0% with placebo; hazard ratio, 0.62. Pembrolizumab improved survival across patient subgroups, including those defined by demographic characteristics, performance status, metastatic stage, and disease-risk category.

The difference in estimated survival became apparent at 15 months and continued to widen after 24 months. Patients assigned to pembrolizumab had a lower rate of subsequent therapy, likely reflecting the disease-free survival benefit and lower relapse rate.

Serious adverse events were more frequent with pembrolizumab: 20.7% versus 11.5%. Rates of grade 3 or 4 adverse events were 18.6% versus 1.2%, respectively.

The new data show "significant and clinically meaningful improvement in overall survival" with pembrolizumab in patients with clear-cell RCC at high risk of recurrence. The researchers conclude: "These results further support the use of adjuvant pembrolizumab as a standard intervention after surgery in this disease context" [Choueiri TK, et al.; KEYNOTE-564 Investigators. Overall survival with adjuvant pembrolizumab in renal-cell carcinoma. *N Engl J Med* 2024; 390:1359–1371. doi: 10.1056/NEJMoa2312695].

Posttransplant Infections Following Pretransplant Immunosuppression for Glomerulonephritis

By Grant Kirby, Robin K. Avery, and Divyanshu Malhotra

Temporal trends in the diagnosis of glomerulonephritis (GN) suggest an overall increase in incident cases over the past decades, with immunosuppression being the mainstay therapeutic approach for many of these conditions (1, 2). Despite advances in treatment, the estimated proportion of kidney failure in the United States attributable to GN remains high, with an increased need for kidney transplantation (3, 4). Various posttransplant endpoints have been studied in this and other patient populations: rates of recurrent GN, graft failure, survival, or quantifying infection risk based on degrees of immunosuppression (5, 6). Infrequently considered is the effect of the pretransplant period in individuals with GN on posttransplant outcomes. The recent article, "Infections Following Kidney Transplantation After Exposure to Immunosuppression for Treatment of Glomerulonephritis" (7), puts forward an important question in bridging this connection: Do individuals receiving pretransplant immunosuppression (PTI) in the management of GN have different rates of posttransplant infectious complications?

Massicotte-Azarniouch et al. (7) conducted a single-center retrospective cohort study, using clinical data over a 15-year period on kidney transplant recipients who were nondiabetic, to compare the rate of developing their first BK virus (BKV), cytomegalovirus (CMV), or bacterial infection in the posttransplant period between individuals receiving PTI for the treatment of GN and those who did not. PTI included a cumulative dose history of cyclophosphamide and rituximab and duration of exposure to high-dose steroids (defined as ≥20 mg of prednisone for ≥4 weeks), mycophenolate, azathioprine, and calcineurin inhibitors. Additional details included in the analysis were donor-recipient status for CMV and Epstein-Barr virus, use and type of T cell depletion for induction, and maintenance therapy prescribed at time of transplantation. The authors' primary finding demonstrated no significant difference in the hazard ratio of developing either viral (BKV or CMV) or bacterial infection posttransplantation between the two groups. Interestingly, there were decreased rates of viral infection in the PTI group after adjusting for demographics, dialysis vintage, type of transplant, and induction/maintenance therapies.

While convincing, we feel these results would be further reinforced with additional details regarding the cumulative dose of T cell depletion therapy (thymoglobulin) and its response, BKV and CMV monitoring protocols, inclusion of viral infections other than BKV and CMV, fungal infections, and longitudinal information on maintenance immunosuppression and prophylaxis. The significant differences in age, gender, and dialysis vintage also raise concern for possible residual confounding, which might contribute to the observed difference in viral infection and trend toward a higher rejection rate in the PTI group (although not significant). Finally, there is increasing recognition of the cumulative morbidity of recurrent infections (6), which is not fully reflected in analyses based on the first occurrence of an infection.

Despite these concerns, this study benefits from its large population size, years of longitudinal follow-up, detailed pretransplant and posttransplant clinical history, inclusion of cumulative drug exposure pretransplant, and thoughtful statistical analysis. These findings, along with conceptual frameworks like the "net state of immunosuppression" (8), contribute to our ability to discern which individuals may be at higher risk for posttransplant infections, which remain a significant source of both morbidity and mortality (6, 9). This research will help to add nuance to clinical practice in the field. ■

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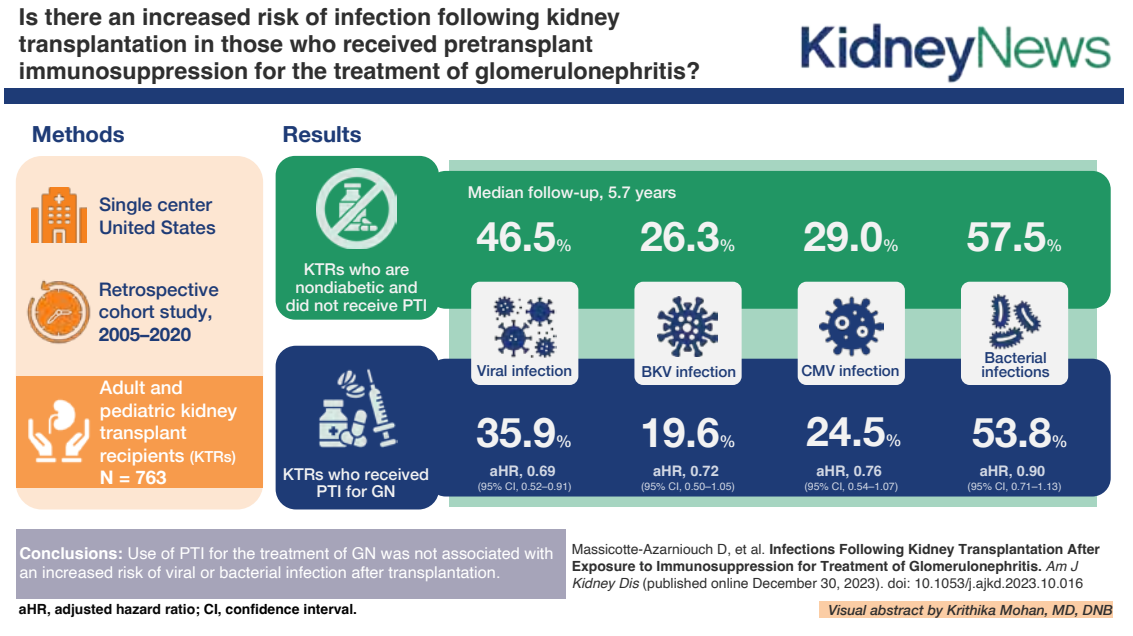

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SGLT2i: The New Wonder Drugs for Kidney Stone Prevention?

By Amy A. Yau and David S. Goldfarb

Sodium-glucose cotransporter-2 inhibitors (SGLT2i) are cardio- and renal-protective in patients with heart failure and proteinuric kidney disease. However, Paik and colleagues' newest work (1) suggests that SGLT2i may also help prevent kidney stones (or nephrolithiasis). In their retrospective analysis of over 700,000 adults with type 2 diabetes, new users of SGLT2i had a lower incidence of kidney stones compared with new users of glucagon-like peptide-1 receptor antagonists (GLP-1RA) or dipeptidyl peptidase 4 inhibitors (DPP4i). Kidney stone events were 14.9 events per 1000 person-years in the patients treated with SGLT2i compared with 21.3 events per 1000 person-years in patients treated with GLP-1RA or DPP4i at an average of 192 days. Paik and colleagues' findings (1) are similar to other studies, which also found reduced odds and reduced incidence of kidney stones in patients treated with SGLT2i (2–4). However, these studies are all retrospective, in which glucose-lowering therapy was initiated for the usual indications and not for stone prevention.

Paik and colleagues' findings (1), although exciting, present more questions than answers. It is unclear whether SGLT2i are protective against all kidney stone types, if the effects are transferrable to stone formers who are non-diabetic, and what the underlying mechanisms might be. Interestingly, there was initial concern that SGLT2i could increase urinary stone formation. In healthy adults and rats treated with SGLT2i, urinary calcium increased (5). However, urine calcium excretion was not increased in healthy volunteers treated with empagliflozin (6). Urinary citrate increased by up to 18% in both healthy volunteers and patients with type 2 diabetes treated with SGLT2i, which may or may not have mitigated against any increase in urinary calcium (6, 7). Healthy volunteers treated with empagliflozin did have a reduced relative supersaturation rate (calculated by the EQUIL2 algorithm) of calcium phosphate, specifically brushite and hydroxyapatite, with no change in that of calcium oxalate. The role of urine citrate and reduced brushite saturation may be important, as brushite crystals are considered to be the nidus of most calcium kidney stones (8). Increases in urinary citrate are the most widely suggested mechanism for stone prevention in patients treated with SGLT2i, but the mechanism by which this effect occurs remains uncertain.

SGLT2i may be more important in the prevention of uric acid kidney stones given that uric acid stones are more common in stone formers who are diabetic (9). Increases in urine bicarbonate and urine pH occurred in mice treated with empagliflozin due to reduced sodium-hydrogen exchanger 3 activity and increased glutamine-mediated ammoniagenesis (10). Although SGLT2i are also uricosuric, uric acid stone formation is more dependent on low urine pH than on high urine uric acid levels (11). Yet, in healthy adults treated with empagliflozin, there was a trend toward lower urine pH with a higher relative supersaturation rate for uric acid (6). This effect was surprising and unexplained given that treatment was also associated with an increase in citrate excretion, a circumstance usually accompanied by increased urine pH.

Other possible mechanisms for stone prevention in individuals treated with SGLT2i include other unmeasured effects in the urine such as reduced inflammatory markers and kidney stone matrix proteins like osteopontin and albumin (1, 2). What is not accounted for are changes in patients' metabolic profile and weight, which can affect urine pH (7, 9). A final suggested mechanism is increased urinary flow, reducing kidney stone risk, but these effects are transient (2, 3). At this time, the findings from Paik et al. (1) are more thought-provoking than anything else, and we eagerly anticipate further studies to better identify target patient populations, large studies examining changes in urinary profiles, and comparisons of SGLT2i with standard preventative therapies. ■

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Dr. Yau reports no conflicts of interest. Dr. Goldfarb is the owner of Moonstone Nutrition, Inc., and serves as a consultant for Alnylam, Arbor Biotechnologies, Arthrosi, Lilac Pharmaceuticals, Novo Nordisk, and Travere.

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SGLT2i and nephrolithiasis risk in patients with type 2 diabetes

KidneyNews

Methods and Cohort

- Population-based, new-user cohort comparator study from the United States
- Adults with type 2 diabetes mellitus
- ❖ 1:1 Propensity matching
- ❖ Those initiated on SGLT2i
- ❖ Comparator drugs GLP-1RA, DPP4i
- Database from 3 sources: ➢Clinformatics ➢IBM MarketScan ➢Medicare
- Enrollment period: April 2013–December 2020
- Median follow-up period: 192 days

Primary Outcome: Nephrolithiasis in inpatient/outpatient

	No. of events (IR per 1000 PY)		RD per 1000 PY (95% CI)	HR (95% CI)
SGLT2i vs GLP-1RA N = 716,406	SGLT2i	GLP-1RA	-6.4 (-7.1 to 5.7)	0.69 (0.67 to 0.72)
	14.9	21.3		
SGLT2i vs DPP4i N = 662,056	SGLT2i	DPP4i	-5.3 (-6.0 to 4.6)	0.74 (0.71 to 0.77)
	14.6	19.9		

Conclusions: In adults with type 2 diabetes mellitus, SGLT2i may lower the risk of nephrolithiasis compared with GLP-1RA or DPP4i, which could help decision-making of glucose-lowering agents for patients who may be at risk for nephrolithiasis.

Paik JM, et al. **Sodium-glucose cotransporter 2 inhibitors and nephrolithiasis risk in patients with type 2 diabetes.** *JAMA Intern Med* 2024; 184:265–274. doi:10.1001/jamainternmed.2023.7660

CI, confidence interval; HR, hazard ratio; IR, incidence rate; PY, person-years; RD, rate difference.

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