

KidneyNews

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Removing Barriers to Home Dialysis Takes a Team Approach

By Bridget M. Kuehn



Patient advocate Dawn Edwards has spent most of the last 30 years on home dialysis, including 10 years on peritoneal dialysis. She has also mentored hundreds of people with kidney disease. So, she is well aware of the burdens and barriers that can stand in the way of a patient starting and staying on home dialysis. The key, she says, is having a good team.

“It’s really important for clinical teams and interdisciplinary teams to...work together to provide patients the support and resources they need to be successful at home,” Edwards said.

Edwards was one of a panel of experts who participated in the Kidney Week 2021 Starting at Home and Staying at Home session. The panelists highlighted barriers to home dialysis and disparities in which types of patients are offered this option. They also highlighted a range of solutions to boost home dialysis initiation and continuation. Among them were improved home dialysis education for clinicians and patients, more clinical and peer support, and flexible home dialysis initiation and continuation options that can better fit patients’ clinical circumstances and lifestyles.

“If we all work together, we can make so many more

patients happier and healthier and allow them to experience the great benefits I have had being at home and being an empowered, educated patient,” Edwards said.

Getting started

A growing number of patients are on home dialysis, but they still represent a small fraction of patients with end stage kidney disease (ESKD). Currently, 12.5% of US patients requiring kidney replacement therapy are on home dialysis, according to 2020 data from the US Renal Data System (USRDS) (1). About 11% are on peritoneal dialysis, and 1.8% are on home hemodialysis, noted Lisa Koester-Wiedemann, ANP, CNN-NP, a renal nurse practitioner at Washington University School of Medicine in St. Louis, MO.

There are also disparities in which patients are offered the option of home dialysis, said Jenny Shen, an investigator at the Lundquist Institute at Harbor-University of California, Los Angeles Medical Center. Physicians may be reluctant to put patients who are older, have diabetes, or are obese on home dialysis, she said. But Shen argued that these

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Positive Patient Experience, Good Outcomes Are Top Patient Priorities

By Karen Blum

Having a positive experience as a patient, achieving good outcomes, and being seen as humans are among the priorities that are most important to patients and should be the centerpiece of diabetes and chronic kidney disease care, according to a presentation at Kidney Week 2021.

Providers know what their priorities are when caring for patients, but it’s imperative that they line up with what patients want and feel, said Matt Cavender, MD, MPH, an interventional cardiologist and assistant professor of medicine at the University of North Carolina School of Medi-

cine in Chapel Hill.

A 2021 survey by the Beryl Institute revealed some of the qualities healthcare consumers seek (1). The first takeaway, Cavender said, is that the experience of patient care is extremely important.

“They consider it to be a priority for all providers to deliver care that results in an experience [that] is overall positive,” he said.

Second, the impact on personal health and well-being and, most importantly, a desire for good outcomes are the leading reasons consumers believe that a good patient experience

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Kidney Watch 2022

With implementation of **race-free eGFR** underway, it's time to reenvision the **Kidney Donor Risk Index**.



The shifting **practice landscape** and **policies** to watch



Nephrologists taking ownership of **hypertension**, new therapeutics for **diabetic kidney disease** and **CKD progression**, and a potential biomarker for **minimal change disease**



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In adult patients with CKD associated with T2D

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KERENDIA offers a different path forward

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INDICATION:

- KERENDIA is indicated to reduce the risk of sustained eGFR decline, end-stage kidney disease, cardiovascular death, non-fatal myocardial infarction, and hospitalization for heart failure in adult patients with chronic kidney disease (CKD) associated with type 2 diabetes (T2D)

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS:

- Concomitant use with strong CYP3A4 inhibitors
- Patients with adrenal insufficiency

WARNINGS AND PRECAUTIONS:

- **Hyperkalemia:** KERENDIA can cause hyperkalemia. The risk for developing hyperkalemia increases with decreasing kidney function and is greater in patients with higher baseline potassium levels or other risk factors for hyperkalemia. Measure serum potassium and eGFR in all patients before initiation of treatment with KERENDIA and dose accordingly. Do not initiate KERENDIA if serum potassium is >5.0 mEq/L

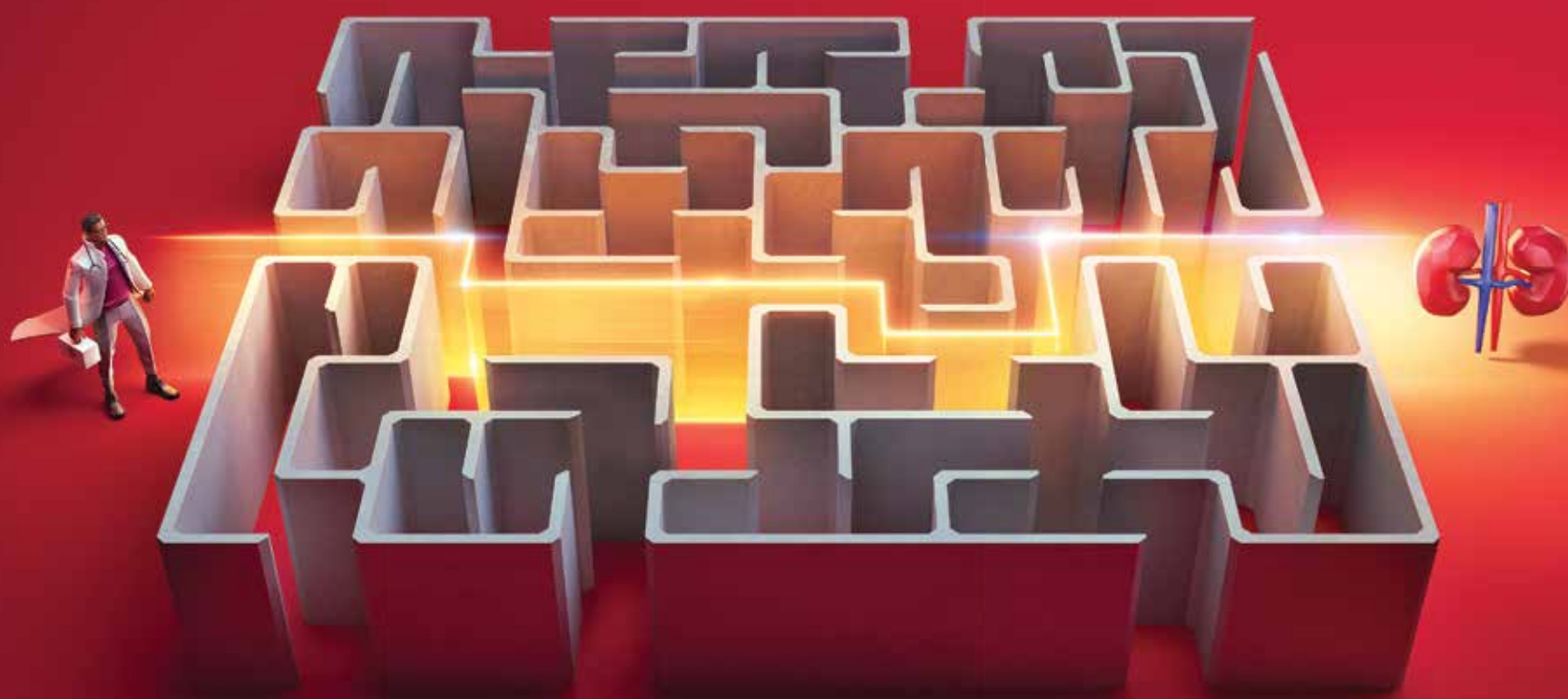
Measure serum potassium periodically during treatment with KERENDIA and adjust dose accordingly. More frequent monitoring may be necessary for patients at risk for hyperkalemia, including those on concomitant medications that impair potassium excretion or increase serum potassium

MOST COMMON ADVERSE REACTIONS:

- Adverse reactions reported in $\geq 1\%$ of patients on KERENDIA and more frequently than placebo: hyperkalemia (18.3% vs. 9%), hypotension (4.8% vs. 3.4%), and hyponatremia (1.4% vs. 0.7%)

DRUG INTERACTIONS:

- **Strong CYP3A4 Inhibitors:** Concomitant use of KERENDIA with strong CYP3A4 inhibitors is contraindicated. Avoid concomitant intake of grapefruit or grapefruit juice
- **Moderate and Weak CYP3A4 Inhibitors:** Monitor serum potassium during drug initiation or dosage adjustment of either KERENDIA or the moderate or weak CYP3A4 inhibitor and adjust KERENDIA dosage as appropriate
- **Strong and Moderate CYP3A4 Inducers:** Avoid concomitant use of KERENDIA with strong or moderate CYP3A4 inducers



Learn more about KERENDIA
and the FIDELIO-DKD trial



USE IN SPECIFIC POPULATIONS

- **Lactation:** Avoid breastfeeding during treatment with KERENDIA and for 1 day after treatment
- **Hepatic Impairment:** Avoid use of KERENDIA in patients with severe hepatic impairment (Child Pugh C) and consider additional serum potassium monitoring with moderate hepatic impairment (Child Pugh B)

Please read the Brief Summary of the KERENDIA Prescribing Information on the following page.

CKD=chronic kidney disease; CV=cardiovascular; MR=mineralocorticoid receptor; MRA=mineralocorticoid receptor antagonist; T2D=type 2 diabetes.

References: 1. KERENDIA (finerenone) [prescribing information]. Whippany, NJ: Bayer HealthCare Pharmaceuticals, Inc; July 2021. 2. Bakris GL, et al; FIDELIO-DKD Investigators. *N Engl J Med*. 2020;383(23):2219-2229.

 **Kerendia[®]**
(finerenone) tablets
10 mg • 20 mg



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KERENDIA (finerenone) tablets, for oral use
Initial U.S. Approval: 2021

BRIEF SUMMARY OF PRESCRIBING INFORMATION
CONSULT PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Kerendia® is indicated to reduce the risk of sustained eGFR decline, end-stage kidney disease, cardiovascular death, non-fatal myocardial infarction, and hospitalization for heart failure in adult patients with chronic kidney disease (CKD) associated with type 2 diabetes (T2D).

4 CONTRAINDICATIONS

Kerendia is contraindicated in patients:

- Who are receiving concomitant treatment with strong CYP3A4 inhibitors [see Drug Interactions (7.1)].
- With adrenal insufficiency.

5 WARNINGS AND PRECAUTIONS

5.1 Hyperkalemia

Kerendia can cause hyperkalemia [(see Adverse Reactions (6.1)).

The risk for developing hyperkalemia increases with decreasing kidney function and is greater in patients with higher baseline potassium levels or other risk factors for hyperkalemia. Measure serum potassium and eGFR in all patients before initiation of treatment with Kerendia and dose accordingly [see Dosage and Administration (2.1)]. Do not initiate Kerendia if serum potassium is > 5.0 mEq/L.

Measure serum potassium periodically during treatment with Kerendia and adjust dose accordingly [see Dosage and Administration (2.3)]. More frequent monitoring may be necessary for patients at risk for hyperkalemia, including those on concomitant medications that impair potassium excretion or increase serum potassium [see Drug Interactions (7.1), 7.2)].

6 ADVERSE REACTIONS

The following serious adverse reactions are discussed elsewhere in the labeling:

- Hyperkalemia [see Warnings and Precautions (5.1)]

6.1 Clinical Trials Experience

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

The safety of Kerendia was evaluated in the randomized, double-blind, placebo-controlled, multicenter pivotal phase 3 study FIDELIO-DKD. In this study, 2827 patients received Kerendia (10 or 20 mg once daily) and 2831 received placebo. For patients in the Kerendia group, the mean duration of treatment was 2.2 years.

Overall, serious adverse reactions occurred in 32% of patients receiving Kerendia and in 34% of patients receiving placebo. Permanent discontinuation due to adverse reactions occurred in 7% of patients receiving Kerendia and in 6% of patients receiving placebo. Hyperkalemia led to permanent discontinuation of treatment in 2.3% of patients receiving Kerendia versus 0.9% of patients receiving placebo.

The most frequently reported (≥ 10%) adverse reaction was hyperkalemia [see Warnings and Precautions (5.1)]. Hospitalization due to hyperkalemia for the Kerendia group was 1.4% versus 0.3% in the placebo group.

Table 3 shows adverse reactions in FIDELIO-DKD that occurred more commonly on Kerendia than on placebo, and in at least 1% of patients treated with Kerendia.

Table 3: Adverse reactions reported in ≥ 1% of patients on Kerendia and more frequently than placebo in the phase 3 study FIDELIO-DKD

Adverse reactions	Kerendia N = 2827 n (%)	Placebo N = 2831 n (%)
Hyperkalemia	516 (18.3)	255 (9.0)
Hypotension	135 (4.8)	96 (3.4)
Hyponatremia	40 (1.4)	19 (0.7)

Laboratory Test

Initiation of Kerendia may cause an initial small decrease in estimated GFR that occurs within the first 4 weeks of starting therapy, and then stabilizes. In a study that included patients with chronic kidney disease associated with type 2 diabetes, this decrease was reversible after treatment discontinuation.

7 DRUG INTERACTIONS

7.1 CYP3A4 Inhibitors and Inducers

Strong CYP3A4 Inhibitors

Kerendia is a CYP3A4 substrate. Concomitant use with a strong CYP3A4 inhibitor increases finerenone exposure [see Clinical Pharmacology (12.3)], which may increase the risk of Kerendia adverse reactions. Concomitant use of Kerendia with strong CYP3A4 inhibitors is contraindicated [see Contraindications (4)]. Avoid concomitant intake of grapefruit or grapefruit juice.

Moderate and Weak CYP3A4 Inhibitors

Kerendia is a CYP3A4 substrate. Concomitant use with a moderate or weak CYP3A4 inhibitor increases finerenone exposure [see Clinical Pharmacology (12.3)], which may increase the risk of Kerendia adverse reactions. Monitor serum potassium during drug initiation or dosage adjustment of either Kerendia or the moderate or weak CYP3A4 inhibitor, and adjust Kerendia dosage as appropriate [see Dosing and Administration (2.3) and Drug Interaction (7.2)].

Strong and Moderate CYP3A4 Inducers

Kerendia is a CYP3A4 substrate. Concomitant use of Kerendia with a strong or moderate CYP3A4 inducer decreases finerenone exposure [see Clinical Pharmacology (12.3)], which may reduce the efficacy of Kerendia. Avoid concomitant use of Kerendia with strong or moderate CYP3A4 inducers.

7.2 Drugs That Affect Serum Potassium

More frequent serum potassium monitoring is warranted in patients receiving concomitant therapy with drugs or supplements that increase serum potassium [see Dosage and Administration (2.3) and Warnings and Precautions (5.1)].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no available data on Kerendia use in pregnancy to evaluate for a drug-associated risk of major birth defects, miscarriage or adverse maternal or fetal outcomes. Animal studies have shown developmental toxicity at exposures about 4 times those expected in humans. (see Data). The clinical significance of these findings is unclear.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss or other adverse outcomes. In the U.S. 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.

Data

Animal Data

In the embryo-fetal toxicity study in rats, finerenone resulted in reduced placental weights and signs of fetal toxicity, including reduced fetal weights and retarded ossification at the maternal toxic dose of 10 mg/kg/day corresponding to an AUC_{unbound} of 19 times that in humans. At 30 mg/kg/day, the incidence of visceral and skeletal variations was increased (slight edema, shortened umbilical cord, slightly enlarged fontanelle) and one fetus showed complex malformations including a rare malformation (double aortic arch) at an AUC_{unbound} of about 25 times that in humans. The doses free of any findings (low dose in rats, high dose in rabbits) provide safety margins of 10 to 13 times for the AUC_{unbound} expected in humans.

When rats were exposed during pregnancy and lactation in the pre- and postnatal developmental toxicity study, increased pup mortality and other adverse effects (lower pup weight, delayed pinna unfolding) were observed at about 4 times the AUC_{unbound} expected in humans. In addition, the offspring showed slightly increased locomotor activity, but no other neurobehavioral changes starting at about 4 times the AUC_{unbound} expected in humans. The dose free of findings provides a safety margin of about 2 times for the AUC_{unbound} expected in humans.

8.2 Lactation

Risk Summary

There are no data on the presence of finerenone or its metabolite in human milk, the effects on the breastfed infant or the effects of the drug on milk production. In a pre- and postnatal developmental toxicity study in rats, increased pup mortality and lower pup weight were observed at about 4 times the AUC_{unbound} expected in humans. These findings suggest that finerenone is present in rat milk [see Use in Specific Populations (8.1) and Data]. When a drug is present in animal milk, it is likely that the drug will be present in human milk. Because of the potential risk to breastfed infants from exposure to KERENDIA, avoid breastfeeding during treatment and for 1 day after treatment.

8.4 Pediatric Use

The safety and efficacy of Kerendia have not been established in patients below 18 years of age.

8.5 Geriatric Use

Of the 2827 patients who received Kerendia in the FIDELIO-DKD study, 58% of patients were 65 years and older, and 15% were 75 years and older. No overall differences in safety or efficacy were observed between these patients and younger patients. No dose adjustment is required.

8.6 Hepatic Impairment

Avoid use of Kerendia in patients with severe hepatic impairment (Child Pugh C).

No dosage adjustment is recommended in patients with mild or moderate hepatic impairment (Child Pugh A or B).

Consider additional serum potassium monitoring in patients with moderate hepatic impairment (Child Pugh B) [see Dosing and Administration (2.3) and Clinical Pharmacology (12.3)].

10 OVERDOSAGE

In the event of suspected overdose, immediately interrupt Kerendia treatment. The most likely manifestation of overdose is hyperkalemia. If hyperkalemia develops, standard treatment should be initiated.

Finerenone is unlikely to be efficiently removed by hemodialysis given its fraction bound to plasma proteins of about 90%.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Finerenone was non-genotoxic in an in vitro bacterial reverse mutation (Ames) assay, the in vitro chromosomal aberration assay in cultured Chinese hamster V79 cells, or the in vivo micronucleus assay in mice.

In 2-year carcinogenicity studies, finerenone did not show a statistically significant increase in tumor response in Wistar rats or in CD1 mice. In male mice, Leydig cell adenoma was numerically increased at a dose representing 26 times the AUC_{unbound} in humans and is not considered clinically relevant. Finerenone did not impair fertility in male rats but impaired fertility in female rats at 20 times AUC to the maximum human exposure.

17 PATIENT COUNSELING INFORMATION

Advise patients of the need for periodic monitoring of serum potassium levels. Advise patients receiving Kerendia to consult with their physician before using potassium supplements or salt substitutes containing potassium [see Warnings and Precautions (5.1)].

Advise patients to avoid strong or moderate CYP3A4 inducers and to find alternative medicinal products with no or weak potential to induce CYP3A4 [see Drug Interactions (7.1)].

Avoid concomitant intake of grapefruit or grapefruit juice as it is expected to increase the plasma concentration of finerenone [see Drug Interactions (7.1)].

Advise women that breastfeeding is not recommended at the time of treatment with KERENDIA and for 1 day after treatment [see Use in Specific Populations (8.2)].

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ASN Executive Vice President's Update: A New Strategic Plan for What We Can Accomplish Together

By Tod Ibrahim

Last year, ASN President Susan E. Quaggin, MD, FASN, and I alternated sending monthly email updates to ASN members. Drafting these updates helped us put individual activities—such as the society's commitment to justice, equity, diversity, and inclusion—into a broader context. This year, we're excited to publish these updates as editorials in *ASN Kidney News*.

2022 marks Dr. Quaggin's 33rd year as a member of ASN. "Over this period, it has been amazing to witness the growth and impact of our programs, which are driving innovation and positive changes in education, research, and patient care," she told me recently. "I am so proud to be a member of a society and a community that puts patients first—always. I know that together, we can—and we will—make great strides to reach our shared vision of a world without kidney diseases."

During the past decade, ASN has evolved from a membership society to the ASN Alliance for Kidney Health. In addition to ASN, the alliance includes:

- KidneyCure, a foundation that spends more than \$3 million annually to support trainees and early-career professionals
- The Kidney Health Initiative (KHI), a partnership among ASN, the US Food and Drug Administration, and more than 100 member organizations to "catalyze innovation and the development of safe and effective patient-centered therapies for people living with kidney diseases"
- The Kidney Innovation Accelerator (KidneyX), a partnership between ASN and the US Department of Health and Human Services that has funded more than 60 innovators to date
- Nephrologists Transforming Dialysis Safety (NTDS), a partnership between ASN and the US Centers for Disease Control and Prevention that is the centerpiece of a broader effort to ensure excellence in patient care for the millions of people with kidney diseases

Last month, I summarized the alliance's accomplishments since January 2020 from "A to Z." As part of this overview, I noted that the alliance has a new strategic plan that will guide us through December 2025.

To create the alliance's vision of "a world without kidney diseases," we must work together to achieve our mission to "elevate care by educating and informing, driving breakthroughs and innovation, and advocating for policies that create transformative changes in kidney medicine throughout the world." Realizing this vision and mission requires us to accomplish five important goals.

Goal 1: Advance the work of kidney medicine.

For far too long, we've focused on kidney failure instead of kidney health. By creating a stronger focus on kidney health, we'll be better positioned to intervene earlier to prevent, diagnose, coordinate care, and educate. This approach will allow us to develop broad partnerships to address the health of the global population, promote health equity, and advocate for high-quality therapies, including home dialysis and transplant.

In addition to NTDS, the alliance's efforts to advance kidney medicine include AKI!Now: Promoting Excellence in the Prevention and Treatment of Acute Kidney Injury (AKI), the ASN Augmented Intelligence and Digital Health Task Force, the COVID-19 Response Team, the Diabetic Kidney Disease Collaborative, the Emergency Partnership Initiative, the ASN Home Dialysis Task Force, Improving Adult Immunization Rates (a project with the Council of Medical Specialty Societies [CMSS] that includes ASN and six other societies), and Project Firstline (a partnership between ASN and the American Medical Association).

Goal 2: Accelerate innovation and expand patient choice.

This goal has twin aspirations: advancing kidney health and speeding up kidney research. When fully aligned, KidneyCure, KHI, and KidneyX can support individuals and entities, including commercial enterprises, to produce amazing results and advance the field. At the same time, we must also focus on building research readiness, inclusiveness, and translation in kidney medicine, which require championing clinical trials. The best way to advance the field is to develop innovative partnerships, creatively pursue scientific opportunities, and increase public and private funding for research.

For example, National Kidney Foundation (NKF) Chief Executive Officer Kevin Longino and I recently published an op-ed on the *Health Affairs* blog. On behalf of ASN, NKF, and the rest of the community, Mr. Longino and I asserted, "To guarantee that the more than 37 million Americans with kidney disease receive the care they deserve, Congress and the Biden Administration must increase funding for kidney research" for the National Institutes of Health, KidneyX, and the Centers for Disease Control and Prevention's Chronic Kidney Disease Initiative as well as "include kidney research in any future funding related to the COVID-19 pandemic."

Goal 3: Lead culture change that creates a diverse, equitable, and inclusive pathway for advancing kidney health.

The only way to achieve equity and eliminate disparities is by identifying, confronting, and overcoming systemic racism in health care, science, and kidney medicine. That is a commitment we must make together, and we cannot waver. While focused on these issues, we must also engage future members of the kidney care team and scientists by increasing interest in kidney medicine and broadening the alliance's outreach and appeal. If successful, we'll provide a professional home that promotes and accelerates growth, opportunities, and advancement throughout all stages of your career.

When the next group of nephrology fellows starts in July 2022, ASN will provide six of them—who identify as underrepresented in medicine—with \$50,000 each over three years as part of the society's new Loan Mitigation Pilot Program. ASN has committed \$2.7 million to this pilot, which I hope becomes enduring, like the society's partnership with the Robert Wood Johnson Foundation to support the Harold Amos Medical Faculty Development Program or the travel support that ASN provides for its members to attend the National Institute of Diabetes and Digestive and Kidney Diseases Network of Minority Health Research Investigators Annual Workshop.

ASN also participates in "Equity Matters: A Diversity, Equity, Inclusion, and Antiracism Initiative for Physicians and Medical Leadership," a collaboration between the Accreditation Council for Graduate Medical Education and CMSS. This program will result in a "capstone project," likely focusing on students, residents and fellows, which would expand the society's other initiatives for trainees, such as Kidney TREKS (Tutored Research and Education for Kidney Scholars), Kidney STARS (Students and Residents), and the Karen L. Campbell, PhD, Travel Support Program for Fellows.

Table 1. Principles that drive decisions

- What is best for people with kidney diseases and their families?
- What is best for strengthening the relationship between patients and their health professionals?
- What is best for the specialty of kidney medicine?
- What is best for the kidney community?
- What is best for the ASN Alliance for Kidney Health?
 - Vision, mission, and goals
 - Resources
 - Revenue, expense, and margin

Goal 4: Create dynamic educational tools and environments, assertively communicate information about kidney medicine, identify opportunities to utilize health care data to screen for and protect kidney health, and engage everyone interested in kidney diseases.

For nearly 60 years, ASN has produced, aggregated, and promoted content, including continuing education, certification and recertification, and peer-reviewed literature. While producing content that reaches current and new audiences, organizing this content thematically, and connecting distribution channels (especially social media), the alliance must focus on credibility and excellence. Doing so requires creating a rich environment that elevates knowledge, understanding, partnerships, and other interactions.

As a result of the pandemic, education and publishing transformed forever. More correctly, expected changes to education and publishing accelerated dramatically during the past two years, and they're showing no signs of slowing down. As the producer of the most kidney-related content, the alliance must embrace these transformations while thinking differently about ASN Kidney Week, other educational activities, and the society's three peer-reviewed journals and *Kidney News*.

Goal 5: Advocate for policies that empower patients and their care partners, the kidney care team and scientists, health systems, payers, and other stakeholders with a role in kidney health.

ASN advances policies through federal legislative and regulatory advocacy that promotes kidney health, transforms transplant and increases access to donor kidneys, and champions health equity and eliminates disparities. These efforts only succeed, however, if the society builds relationships that include key stakeholders inside and outside of the kidney community. Increasingly, ASN is working to help develop, articulate, and advance a global kidney health policy agenda.

I'm often asked how ASN makes decisions about which policies to support, oppose, or remain neutral about. Table 1 summarizes the principles the society's leadership, staff, and I use to help guide such decision-making. It's hard to go wrong when you put people with kidney diseases and their families first. As Dr. Quaggin asserted, ASN, the broader alliance, and the kidney community put "patients first—always."

During her ASN President's Address at Kidney Week 2021, Dr. Quaggin remarked, "We must remember who we are, what we have achieved, and what we can accomplish together." I hope you will join Dr. Quaggin and me in helping to accomplish the new strategic plan for ASN and the broader ASN Alliance for Kidney Health. ■



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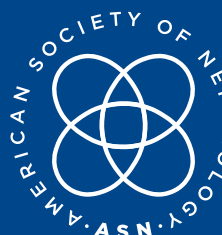
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Removing Barriers to Home Dialysis

Continued from cover

are not insurmountable barriers. In fact, studies show that more experienced home dialysis providers are less likely to discriminate based on medical factors (2).

“[The patient’s] practitioner just has to know how to tailor the medical care to the patient,” she said.

Perceived socioeconomic barriers also exist, Shen said. For example, patients with lower education levels or employment status are less likely to be on home dialysis. Having a smaller home has also been linked to lower use of home dialysis, likely because space constraints can make storing necessary equipment and supplies difficult. Patients who receive a late diagnosis or who crash into dialysis are also less likely to be offered home dialysis.

All of these perceived barriers to home dialysis disproportionately affect Black and Hispanic patients who have lower rates of home dialysis than their White counterparts, Shen noted. Only 9% of Black patients with ESKD and 10% of Hispanic patients are on home dialysis compared to 12% of White patients, according to 2018 USRDS data (3). In fact, a study by Shen and colleagues showed that Black patients are 30% less likely to start dialysis at home than White patients, and Hispanic patients are 20% less likely to do so (4). These disparities persisted even after adjusting for demographics, co-morbid medical conditions, or socioeconomic factors.

“If we address some of the known medical and socioeconomic barriers, we make some headway to increasing equitable access,” Shen said.

Edwards said she often finds that urban communities with higher concentrations of people of color often have little or no access to home dialysis programs in their community and may have to travel outside of their community to seek such care. This can make it difficult for patients who worry they will not be able to make their visits.

“We have to look at making home dialysis more accessible,” Edwards said. She said this includes having nurses and other team members who support patients in these communities. In lower socioeconomic communities, patients may live in older or public housing and may also need help with installing electrical outlets for their dialysis equipment, she said.

But these barriers can be overcome, said Shen. Already home dialysis rates have increased since the implementation of the Centers for Medicare & Medicaid Services’ ESRD payment bundles in 2011, which have increased reimbursement for home dialysis, and groups that have been historically underrepresented among home dialysis patients are seeing the largest increase, Shen noted.

“The disparities we’ve talked about in home dialysis initiation have started to narrow,” she said.

Overcoming obstacles

Better education for both home dialysis patients and providers is essential to further boost rates of home dialysis and to help keep patients on home dialysis, said several panelists. More training in home dialysis for nephrology fellows is key,

Shen said.

“If they are better trained, they will be more confident in treating home dialysis patients and be better equipped to overcome barriers to home dialysis,” Shen said.

Standardized education in home dialysis modalities is also key to boosting uptake and reducing disparities, Edwards said. She said this would provide all patients with the information they need to engage in shared decision-making with their clinician.

“We can talk about which option best suits their lifestyle[s] [and] which option suits them for the best clinical outcomes,” she said.

Shen recommended considering different approaches to home dialysis that may help meet patients’ needs. Assisted home dialysis, where patients receive in-home help, may allow people who are older, have disabilities, or just need more help get started, Shen said. People with small homes may benefit from twice-monthly supply deliveries to alleviate the space crunch, she said. The community house (5) home hemodialysis model developed in New Zealand might be another model to help those who do not want to participate in home dialysis to dialyze close to home in a home-like setting with support from other patients.

Urgent-start peritoneal dialysis (6) or transitional dialysis units (7) may help patients who crash access home dialysis, Shen said. Susie Lew, MD, professor of medicine at George Washington University in Washington, DC, also discussed the potential benefits of starting patients on incremental peritoneal dialysis, a reduced initial prescription that ramps up gradually as residual kidney function declines.

It is also important for home dialysis teams to set clear expectations for patients, Koester-Wiedemann said. She said this should include a home visit to troubleshoot and discussions about patient responsibilities including medications, clinic visits, blood draws, and how patients can stay connected to their teams.

“Setting clear expectations prior to dialysis training aided patients’ acceptance and understanding of responsibilities, which reduced their anxiety,” Koester-Wiedemann said. She also recommended using a Partner Agreement on Tasks for Home Dialysis (PATH-D) tool (8) to help establish what will be expected of the patient’s caregiver or partner.

“We find that the patient will have high expectations on the partner to do so many things, and [partners] have other responsibilities of their home such as paying the bills [and] doing the grocery shopping,” Koester-Wiedemann said. “This is where we find partner burnout.”

When Koester-Wiedemann and her colleagues looked at causes for patient dropout in their program, they found that 1 in 10 patients cited the burden of therapy. They also found that among the “non-compliant,” a patient’s burden of therapy or partner burden was a factor.

“Kidney disease doesn’t stop, but people do wear out, and self-care is a never-ending job,” Edwards said.

Brian Rifkin, MD, a nephrologist at the Hattiesburg Clinic in Mississippi, described the medical complications, including infections or catheter complications, that can cause patients to leave home peritoneal dialysis. He also highlighted some strategies to preserve peritoneal membrane function using medications and other approaches.

Support from the multidisciplinary team and from peers can help mitigate a patient’s care burden and troubleshoot

problems that can arise. For example, Koester-Wiedemann noted that her program offers 24-hour nurse and equipment support. Programs should offer respite care where patients can get help with their home dialysis unit or one nearby, Koester-Wiedemann said. Edwards said having a good respite program can give both patients and their partners a break and allow them to regroup.

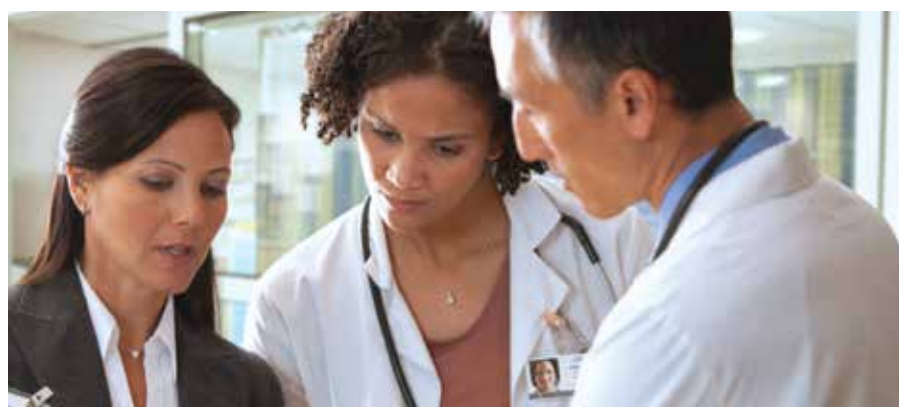
“We don’t want that machine to run their lives,” Koester-Wiedemann said. “We want them to run their lives and incorporate the machine into their lives.”

Nephrologists can help by developing a dialysis prescription that is personalized to both the patient’s medical condition and to his or her daily life, Koester-Wiedemann said. Edwards said it is essential for the care team to work with the patient to help him or her meet goals whether it is traveling or going back to school or work. Nephrologists should consider options like nocturnal dialysis, continuous ambulatory peritoneal dialysis (CAPD), or continuous cycling peritoneal dialysis (CCPD) that might better fit a patient’s needs, Koester-Wiedemann said. Lew provided detailed clinical information about urgent-start peritoneal dialysis, incremental dialysis, CAPD, and CCPD.

“We need the entire care team to lift up and support... patient[s], let them know that they’re doing a good job, provide them with the rest they need when respite is needed, [and] help them to achieve those personal goals,” Edwards said. ■

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Positive Patient Experience

Continued from cover

rience is important.

Third, consumers want to be seen as humans. “They want to be listened to and communicated with in a way that they can understand,” Cavender said. “They want to be able to have a conversation with their provider, to be able to express the things

that are important to them as a patient, and they want the provider to listen. Additionally, they want the provider to be able to incorporate what the patient is telling them as important when [providers] come up with a treatment decision.”

Consumers see the patient experience as encompassing myriad important topics, such as safety, quality, outcome, service, engagement, cost, and actions of the entire care team. This starts from the person who checks the patient into the clinic and ends with the person who checks the patient

out—and includes every staff person encountered in between, Cavender said. The experience of patients who need care from multiple areas of a health system highlights the need for collaboration and coordination of care across the continuum, he said, particularly as patients go from inpatient to outpatient or from nephrologists to other physicians in cardiology or primary care: “Patients want to be able to see there’s coordination there.”

Diving into what constitutes quality in these scenarios, providers can turn to the Six

Providers know what their priorities are when caring for patients, but it’s imperative that they line up with what patients want and feel.

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Primary Presenter

Rolando Claire-Del Granado, MD, FASN
Director, AKI/CRRT Program, Hospital Obrero, Cochabamba, Bolivia
Professor of Medicine, Universidad Mayor de San Simon, School of Medicine, Bolivia
Member at Large, International Society of Nephrology Executive Committee

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Domains of Health Care Quality from the Agency for Healthcare Research and Quality (AHRQ) (2). These include healthcare provisions that are safe and avoid harm to patients and that are effective, based on sound scientific knowledge, and offered to patients who will benefit and not offered to those who will not benefit.

The quality domains also include care that is patient centered, respectful to the patient’s values, needs, and concerns. Care also must be provided in a timely and efficient manner, avoiding unnecessary delays or waste. Finally, care must be provided equitably to all patients regardless of gender, ethnicity, geographic location, socioeconomic status, or other personal characteristics.

The Patient-Centered Outcomes Research Institute (PCORI) also has tackled questions of importance to healthcare consumers, Cavender said. These questions include the following:

- Given my personal characteristics, conditions, and preferences, what should I expect will happen to me?
- What can I do to improve the outcomes that are most important to me?
- What are my options, and what are the potential benefits and harms of those options?
- How can clinicians and the care delivery systems they work in help me make the best decisions about my health and healthcare?

To summarize these points, Cavender said, patients want to know answers to the following questions: What are the outcomes? What sort of lifestyle changes can I make with this condition? What treatments are available? And how is care going to be delivered? ■

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Reenvisioning the Kidney Donor Risk Index without Race

By Samira Farouk

Black individuals, who are at a two- to fourfold higher risk of developing end stage kidney disease in the United States, are simultaneously less likely to be referred for transplantation, to be waitlisted, or to receive a kidney transplant (KT) (1–3).

The murders of countless Black individuals sparked uprisings in 2020 throughout the United States. This included efforts spearheaded by medical students around the country to remove race as a factor in estimated glomerular filtration rate (eGFR) calculation at their institutions (4). Racialized algorithms, which include race in eGFR equations, result in higher values for individuals identified as Black, potentially delaying KT eligibility (5). As described by the following points, race: 1) lacks biological meaning, 2) is dynamic and contextually sensitive in how and by whom it is defined, and 3) often reinforces erroneous beliefs regarding the inferiority and “otherness” of minoritized groups (6, 7). Race-based medicine perpetuates race as a biological variable, rather than a social construct, contributing to inequities and healthcare disparities (6).

In fall 2021, the final report from a National Kidney Foundation and American Society of Nephrology Task Force to reassess inclusion of race in eGFR recommended “immediate implementation of the Chronic Kidney Disease Epidemiology Collaboration creatinine equation refit without the race variable” (8).

Unfortunately, the eGFR calculation is not the only arena within nephrology that must implement “race correction.” The kidney donor risk index (KDRI), implemented in 2014, uses 10 donor characteristics (Table 1), including self-reported race, to predict the relative risk of allograft failure. The kidney donor profile index (KDPI), derived from the KDRI, maps the KDRI relative risk to a cumulative percentage scale (i.e., a KDPI of 85% indicates a KDRI greater than 85% of recovered kidneys). Higher KDPI values are associated with lower longevity and donor quality and thus can impact organ acceptance practices by transplant clinicians. Furthermore, deceased donor kidneys with low KDPIs are allocated to those individuals with longer estimated posttransplant survival (EPTS), which is calculated using the recipient’s age, dialysis vintage, diabetes status, and history of prior organ transplants (9).

The KDRI was the result of a 2009 study in which a multivariable Cox regression model was estimated using allograft outcomes from 69,440 deceased donor KT recipients in the United States from 1995 to 2005 (Table 1) (10). Although not explained in the manuscript, race was likely included as a variable due to the prior observation that kidneys from Black donors were associated with a higher risk of allograft loss (11). Like eGFR equations that include race, inclusion in the KDRI calculation similarly implicates race as a biological variable. Rather than race, it is likely that these differences may be better explained by biological

factors and unequal social determinants of health. The KDRI hazard ratio for Black race was estimated to be 1.20—**higher than that for a donor with a history of hypertension or diabetes, donation after cardiac death, or cerebrovascular accident as the cause of death**—increasing the risk of estimated allograft failure by 20%. The liver donor risk index (LDRI) similarly includes race, with a 1.2 hazard ratio for Black versus White donors (12). As we seek an unbiased and more accurate and precise model toward eGFR, we must do the same to assess kidney donor quality to improve equity in kidney transplantation. One potential solution is the inclusion of the apolipoprotein L1 (*APOLI*) genotype, as allografts with high kidney risk variants (KRVs) have been associated with early allograft failure (13). A 2017 retrospective cohort study of 1149 KT recipients concluded that replacing

As we seek an unbiased and more accurate and precise model toward eGFR, we must do the same to assess kidney donor quality to improve equity in kidney transplantation.

race with the *APOLI* genotype (0/1 KRV vs. 2 KRVs) improved risk estimation for kidneys from Black donors and improved the KDRI for 85%–90% of kidneys offered (14). In current clinical practice, waiting for deceased donor *APOLI* genotyping results for KDRI calculation may significantly prolong cold ischemia time. The APOL1 Long-term Kidney Transplantation Outcomes Network (APOLLO) study may shed further light on the impact of KRVs on allograft outcomes (15). Furthermore, a recent analysis of Scientific Registry of Transplant Recipients data from 2000 to 2017 found that removal of race from the KDRI calculation did not alter the overall predictability of allograft failure or patient survival (16).

Until these newer models and coefficients can be estimated without race, transplant centers may consider re-calculation of KDRI without the race coefficient when making decisions regarding acceptance of organs or immunosuppression regimens. Furthermore, advances in the treatment of hepatitis C virus (HCV) that have allowed for the transplantation of kidneys from HCV-infected donors into HCV-negative recipients beg for a new donor quality assessment tool (17). It is imperative that the

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Reenvisioning the Kidney Donor Risk Index without Race

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Organ Procurement and Transplant Network (OPTN) and United Network for Organ Sharing (UNOS) interrogate the current calculation of the KDRI and its potential impact on organ allocation and inequity in transplantation (Table 2) (18). ■

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Table 1. Variables included in the KDRI model, with estimated coefficients

Donor characteristic	Hazard ratio
Age	
All ages	1.013
<18 years	0.98
>50 years	1.011
Height (per 10 cm increased)	0.96
Weight (per 5 kg increased below 80 kg)	0.98
Race (Black)	1.20
History of HTN	1.13
History of diabetes	1.14
CVA as cause of death	1.09
Serum creatinine	
All	1.25
>1.5 mg/dL	0.81
Positive HCV status	1.27
Donation after cardiac death	1.14

KDRI, kidney donor risk index; HTN, hypertension; CVA, cerebrovascular accident; HCV, hepatitis C virus. Adapted from Rao et al. (10).

Table 2. Comparison of KDPI among four hypothetical donors

Donor characteristic	Donor 1	Donor 2	Donor 3	Donor 4
Age (years)	50	50	50	50
Height (inches)	63	63	63	63
Weight (kg)	70	70	70	70
Race	Black	Non-Black	Black	Non-Black
History of HTN	No	No	No	No
History of diabetes	No	No	No	No
CVA as cause of death	No	No	No	No
Serum creatinine	1.0	1.0	1.0	1.0
Positive HCV status	Yes	Yes	No	No
Donation after cardiac death	No	No	No	No
KDPI (%)	85	70	65	46

KDPI, kidney donor profile index; HTN, hypertension; CVA, cerebrovascular accident; HCV, hepatitis C virus. Adapted from OPTN (18).



Shifting Practice Landscape For-Profit Companies Move into CKD Care

By Katie Westin Kwon and Eugene Lin

The past few years have seen a number of for-profit companies seeking to partner with nephrologists to manage their patients with later stage chronic kidney disease (CKD). Kidney disease is an expensive medical condition to treat: Medicare's total cost of care for patients with kidney disease in 2018 was \$81.8 billion (1). Both Medicare and private payers have advanced care models that reduce that cost. New value-based care (VBC) initiatives focus on the patient population that is at risk for developing end stage kidney disease (ESKD). These programs will financially reward providers who successfully slow kidney disease progression and increase home dialysis and transplantation rates. Companies that succeed will profit by capturing some of the resulting savings to payers.

Previously, the reimbursement structure for nephrology has primarily focused on dialysis. This, in turn, has created a landscape where an outsized portion of the nephrologist's income derives from dialysis at the expense of other aspects of kidney care. This has been cited as a contributing factor to the nephrology workforce crisis; residents perceive nephrology to be overly focused on the complicated care of patients with ESKD (2). Additionally, misaligned financial incentives prioritize keeping in-center hemodialysis chairs filled rather than guiding patients toward alternative therapies, like home dialysis or kidney transplant (3).

The new VBC models have introduced incentives to focus on patients with advanced CKD not yet on dialysis (4). For-profit companies have noticed. Start-up companies, larger for-profit healthcare providers, and venture capital firms have formed a marketplace of new products aimed at helping nephrologists improve their management of CKD at a population level (Table 1).

Population-based care requires a different set of tools compared to traditional fee for service. Enhanced data analytics allows providers to risk stratify patients so they can target care-coordination efforts to patients most at risk for poor outcomes. A practice may evaluate its entire cohort of patients to make sure they are all appropriately prescribed medications to slow progression of their CKD or may hire a care manager to see every patient post-hospitalization for care coordination. However, the indiscriminate application of intensive disease management can be expensive, especially among patients without albuminuria (5). Traditionally, such care-management tools are beyond the reach of a small- or mid-sized nephrology practice. The for-profit companies seek to meet this need. Some companies are even aggregating the patient panels of multiple practices to help smaller practices spread risk and meet the required numbers to participate in the various VBC models.

The benefit to the practicing nephrologist is a clinical rebalancing, such that the CKD clinic is no longer a "loss leader" but instead, a significant source of income. For the for-profit companies investing in nephrology, VBC represents a big growth opportunity. The challenge, as our patients' advocates, is to ensure that VBC incentives remain aligned with patients' best interests. We have been given substantial flexibility to achieve the desired outcome

of fewer people needing in-center dialysis care. Our role as nephrologists will be to direct the dollars being invested in an efficient and focused manner to create CKD care that best supports our patients. ■

Katie Westin Kwon, MD, is a partner at Lake Michigan Nephrology, which has joined Global Nephrology Solutions (GNS) and will participate in value-based care with GNS in 2023. Eugene Lin, MD, MS, is an Assistant Professor of Medicine at the Keck School of Medicine of the University of Southern California, Los Angeles.

Dr. Kwon reports no conflicts of interest. Dr. Lin receives consulting income from Acumen, LLC, a federal contractor.

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Table 1. Notable for-profit companies innovating in nephrology

Companies	Investors	Notable characteristics
Cricket	Valtruis	Virtual multidisciplinary team to support enrolled CKD patients at no cost to practice; payer contract negotiations
InterWell	Fresenius	VBC contracts; aggregates smaller practices to participate
Global Nephrology Solutions	Audax	Participating physicians own equity in GNS; services include practice management and VBC
Somatus	Longitude Capital; Anthem Healthcare	Partners with payers and nephrology practices; also with health systems to provide inpatient/outpatient dialysis
Strive	Capital Group (Division of Alphabet)	Partners with health systems, nephrologists, and primary care
CVS Kidney Care	Partnership with Satellite Healthcare	Developing a home hemodialysis machine
Evergreen Nephrology	Rubicon Founders	Partners with nephrologists for the management of full-risk Medicare patients; focuses on dialysis preparation, home dialysis, and transplantation

CKD, chronic kidney disease; VBC, value-based care; GNS, Global Nephrology Solutions.

Diabetic Kidney Disease The Future Is Now

By Edgar V. Lerma and Michelle G.A. Lim

Visual Abstracts by Michelle G.A. Lim

Diabetic kidney disease (DKD) has been in the forefront of industry publications during these challenging yet exciting times. With the advent of recognition of sodium glucose co-transporter 2 (SGLT2) inhibitors and their particular outcome benefits in patients with type 2 diabetes who are particularly prone to developing complications related to cardiovascular (CV) disease, there has been revitalization of our understanding of the mineralocorticoid receptor and the central role it plays in inflammation and fibrosis involving the kidneys.

A nonsteroidal mineralocorticoid antagonist—finerenone—was highlighted in several major randomized controlled trials (1, 2) that enrolled adult patients with chronic kidney disease (CKD) and type 2 diabetes with moderately to severely increased albuminuria (FIDELIO-DKD (1): urine albumin-creatinine ratio [UACR] 30–300 mg/g with estimated glomerular filtration rate [eGFR] 25–60 mL/min/1.73 m² and diabetic retinopathy or UACR ≥300 mg/g with eGFR 25–75 mL/min/1.73 m²; FIGARO-DKD (2): UACR 30 to <300 mg/g with eGFR 25–90 mL/min/1.73 m² or UACR 30–5000 mg/g with eGFR ≥60 mL/min/1.73 m²). During a dose-optimization period of 4–16 weeks, all patients received standard-of-care background therapy, including a maximum-tolerated labeled dose of an angiotensin-converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB).

In a prespecified, individual-level pooled analysis of FIDELIO-DKD (Figure 1) (1) and FIGARO-DKD (Figure 2) (2), the FIDELITY analysis (3) was presented during the European Society of Cardiology Congress, which was conducted virtually in August 2021. It included 13,171 patients (with CKD and type 2 diabetes) from 48 countries randomized 1:1 to receive finerenone (10 mg or 20 mg daily) versus placebo and a median duration of 3 years' follow-up. It was demonstrated that on top of an optimized renin-angiotensin system (RAS) blockade, finerenone significantly reduced the risk of the composite CV outcome (time to CV death, non-fatal myocardial infarction [MI], non-fatal stroke, or hospitalization for heart failure) by 14%, whereas it significantly reduced the risk of the composite kidney outcome (time to kidney failure, sustained ≥57% decrease in eGFR from baseline, or kidney death) by 23%. About 40% of the 13,026 patients in FIDELITY had an eGFR of >60 mL/min/1.73 m² and qualified for treatment because of moderately or severely elevated albuminuria.

Although hyperkalemia-related adverse events occurred more frequently with finerenone (14.0%) versus placebo (6.9%), no hyperkalemia-related adverse events were fatal, with 1.7% (incidence rate 0.66 per 100 patient-years) versus 0.6% (incidence rate 0.22 per 100 patient-years) leading to permanent treatment discontinuation or hospitalization (0.9% vs. 0.2%, respectively).

In another recent publication (4), while taking different trial designs into consideration, an analysis of FIDELIO-DKD and CREDENCE (UACR >300–500 mg/g with eGFR 30 to <90 mL/min/1.73 m² at screening) showed a cardiorenal composite endpoint of 43.9 per 1000 patient-years with finerenone (vs. 59.5 per 1000 patient-years with

placebo), with a 26% relative risk reduction (hazard ratio [HR] 0.74; 95% confidence interval [CI] 0.63–0.87). In CREDENCE, there was a cardiorenal composite endpoint of 43.2 per 1000 patient-years with canagliflozin (vs. 61.2 per 1000 patient-years with placebo), with a 30% relative risk reduction (HR 0.70; 95% CI 0.59–0.82).

So where does this agent fit in to our current landscape of management of DKD? It has been suggested that a four-pillar approach to DKD management in 2021 (akin to cardiology's goal medical-directed therapy) is needed (Figure 3).

Where does the current evidence bring us? We are of the opinion that the time is now to acknowledge the published

data and use the drug. Should finerenone be used in combination with SGLT2 inhibitors? Should finerenone be used with novel oral potassium binders, etc.? It is prudent to pay close attention to the evidence that we have now as well as forthcoming information. Based on these results, we formulate regimens that serve our patients best. ■

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Figure 1. FIDELIO-DKD
Does finerenone improve outcomes in CKD with type 2 diabetes?

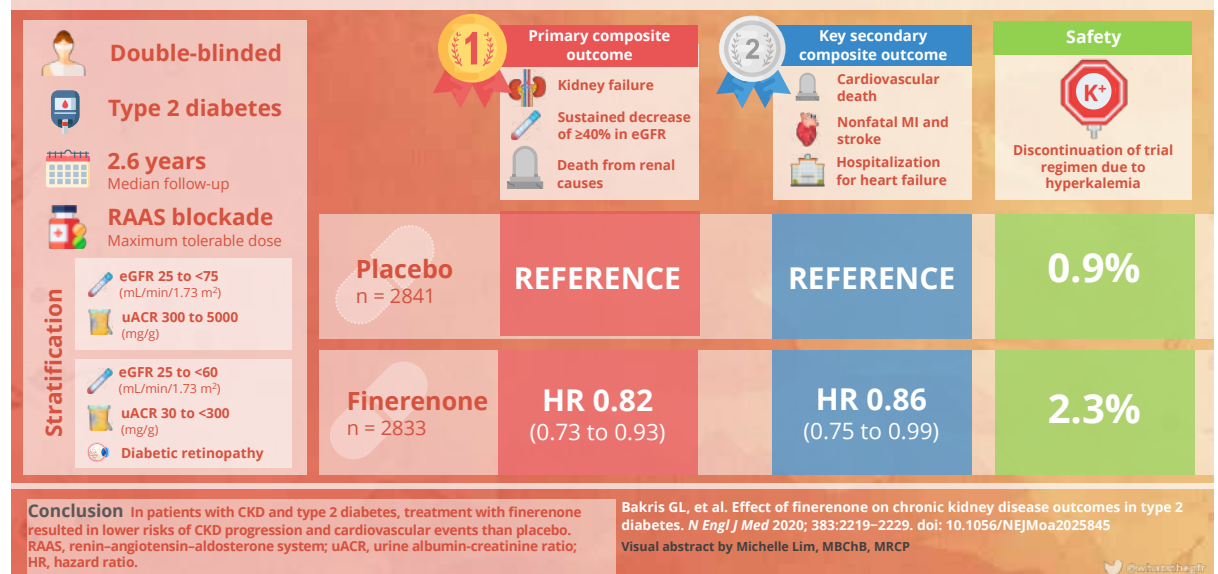


Figure 2. FIGARO-DKD
Does finerenone improve cardiovascular outcomes in type 2 diabetes and CKD?

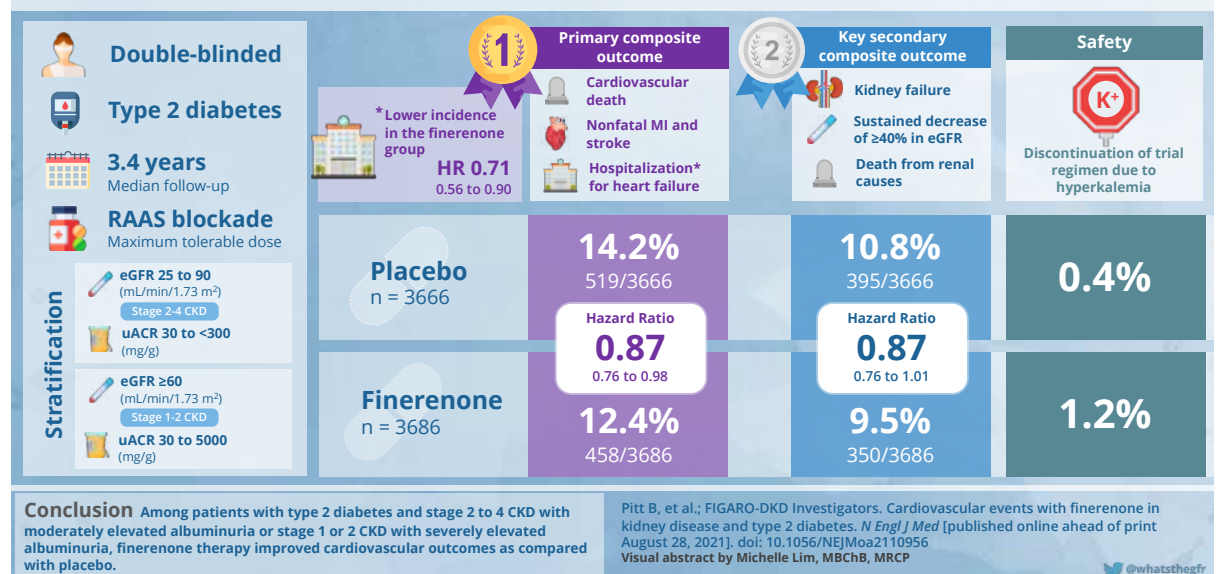


Figure 3. Four Pillars of Diabetic Kidney Disease Management in 2021



SGLT2i, SGLT2 inhibitor; FDA, US Food and Drug Administration.
Courtesy Steven Coca, DO, Associate Professor of Medicine at Icahn School of Medicine at Mount Sinai, New York, NY.

Dr. Lerma serves as a member of Bayer's RENOVATE Steering Committee. In that role, he is involved in an initiative that aims to better understand and communicate the CKD and type 2 diabetes disease state, as well as provide and develop educational materials that can be used by clinicians. He is also a member of the Bayer Speakers' Bureau. Dr. Lim reports no conflicts of interest.

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New Studies in the Pipeline with Endothelin Inhibitors

By Marina Lopez-Martinez and María José Soler

Endothelin-1 (ET-1) plays a role in chronic kidney disease (CKD) progression (1). In the kidney, ET-1 binding of the endothelin A (ETA) receptor drives afferent arteriole vasoconstriction, cell proliferation, podocyte and glycocalyx damage, matrix accumulation, and proinflammatory effects, whereas binding of the endothelin B (ETB) receptor produces vasodilation, antifibrotic effects, and decreased sodium reabsorption and natriuresis (1, 2). Although renin-angiotensin-aldosterone system (RAAS) inhibition has proven a reduction of albuminuria and a proportional effect on kidney protection (3, 4), residual albuminuria still implies a significant risk of CKD progression (5). Therefore, other therapies, such as endothelin receptor antagonists (ERAs), are currently being evaluated as promising treatments for different proteinuric nephropathies (1, 2).

The first phase 3 clinical trial of ERAs was the ASCEND study (A Study of Cardiovascular Events in Diabetes) (6), published in 2009. It compared, in 1392 patients with diabetic kidney disease, avosentan (ETA:ETB receptor blockade ≈ 50–300:1) with placebo in addition to continued angiotensin-converting enzyme inhibition (ACEi) and/or

angiotensin receptor blockade (ARB) (Table 1). In patients who were treated with avosentan 25 mg/day, 50 mg/day, and placebo, the median reduction of the albumin-to-creatinine ratio (ACR) was 44.3%, 49.3%, and 9.7%, respectively (p < 0.0001). However, the trial was ended prematurely because of an excess of cardiovascular events with avosentan associated with fluid retention, which may be in part explained by the antinatriuretic effect secondary to the ETB receptor blockade (6). Since then, all future clinical trials have been designed to reduce cardiovascular events, by excluding patients with brain natriuretic peptide (BNP) ≥ 200 pg/mL or with a history of heart failure.

Sitaxsentan (ETA:ETB receptor blockade ≈ 6000:1), at a dose of 100 mg daily, was studied in nondiabetic CKD patients (7). This ERA (Effects of Sitaxsentan on Proteinuria, 24-Hour Blood Pressure, and Arterial Stiffness in CKD Subjects [FCRD01]) was withdrawn due to two cases of fatal hepatic failure in 2010. The SONAR study (Study of Diabetic Nephropathy with Atrasentan) (8) included, after an enrichment period (excluding patients who did not have albuminuria reduction and/or edema), 2648 patients with diabetes who received either 0.75 mg of atrasentan (ETA:ETB

receptor ≈ 1200:1) or placebo, on top of RAAS inhibition, during a median follow-up of 2.2 years. The primary outcome was the efficacy of atrasentan in delaying progression of CKD (composite endpoint): patients treated with atrasentan had a significantly lower risk of doubling serum creatinine or end stage kidney disease (hazard ratio [HR] 0.65, 95% confidence interval [CI] 0.49–0.88, p = 0.0047) compared with placebo. Adjudicated hospital admission for heart failure occurred in 3.5% of patients in the atrasentan group compared with 2.6% in the placebo group (HR 1.33, 95% CI 0.85–2.07, p = 0.65). This study was performed in a selected diabetic kidney disease group of patients without heart failure and normal BNP.

As additive effects on proteinuria were observed with ERA and ACEi/ARB, sparsentan, a molecule with a dual-acting angiotensin type 1 receptor blocker and highly selective ETA receptor antagonist (negligible ETB receptor blockade) has been recently evaluated in other proteinuric kidney diseases. DUET (Dual Endothelin Receptor and Angiotensin Receptor Blocker, in Patients with Focal Segmental

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Table 1. Randomized clinical trials with endothelin receptor antagonists in patients with kidney disease

Study	Study type	Drug and effect	Disease	Number of subjects	Primary outcome (PO)
ASCEND	Phase 3	Avosentan (ETA:ETB receptor blockade ≈ 50–300:1)	DKD	n = 1392	PO: No significant differences in primary composite end point of doubling creatinine, end stage kidney disease, or death; SO: The median UACR significantly declined similarly by 40% to 50% in both avosentan groups (p < 0.0001).
FCRD01	Phase 2	Sitaxsentan (ETA:ETB receptor blockade ≈ 6000:1)	Proteinuric CKD (non-DKD)	n = 27	Reduction of 24-h proteinuria and UPCR by 30% by study end (p < 0.01)
SONAR	Phase 3	Atrasentan (ETA:ETB receptor blockade ≈ 1200:1)	DKD	n = 2648	Lower risk of doubling of serum creatinine or end stage kidney disease (HR 0.65, 95% CI 0.49–0.88, p = 0.0047)
DUET	Phase 2	Sparsentan (ETA receptor inhibitor + ARB)	Primary FSGS	n = 96	Reduction in UPCR of 45%–47% (95% CI 52.7%–35.7%) and systolic BP of 7.2 mm Hg
DUPLEX	Phase 3	Sparsentan (ETA receptor inhibitor + ARB)	Primary FSGS	n ≈ 300	Ongoing: Slope of eGFR weeks 6–108, proportion of patients achieving UPCR ≤1.5 g/g, and a >40% reduction from baseline at week 36
PROTECT	Phase 3	Sparsentan (ETA receptor inhibitor + ARB)	IgA nephropathy	Estimated n = 380	Ongoing: Change from baseline in the UPCR based on a 24-h urine sample at week 36
ZENITH-CKD	Phase 2	Zibotentan (ETA inhibitor)	Proteinuric CKD	Estimated n = 660	Ongoing: Change in UACR and BP from baseline to week 12
ZEBRA	Phase 2	Zibotentan (ETA inhibitor)	Systemic sclerosis + CKD/ scleroderma renal crisis	n = 13	PO: Unpublished; SO: 12% improvement of eGFR at 52 weeks (p = 0.0082)

PO, primary outcome; ETA, endothelin A; ETB, endothelin B; DKD, diabetic kidney disease; SO, secondary outcome; UACR, urine albumin-to-creatinine ratio; CKD, chronic kidney disease; UPCR, urine protein creatinine ratio; HR, hazard ratio; CI, confidence interval; ARB, angiotensin receptor blockade; FSGS, focal segmental glomerulosclerosis; BP, blood pressure; eGFR, estimated glomerular filtration rate; IgA, immunoglobulin A.

New Studies in the Pipeline with Endothelin Inhibitors

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Glomerulosclerosis [FSGS]: A Randomized, Double-blind, Active-Control, Dose-Escalation Study) (9), a phase 2 trial, studied the effect of 200 mg, 400 mg, and 800 mg daily in primary FSGS. All doses of sparsentan compared with 300 mg of irbesartan achieved greater reductions in the protein-to-creatinine ratio (45% vs. 19% with 200 mg; 47% vs. 19% with 400 mg and 800 mg). Blood pressure was also reduced in the sparsentan group, and estimated glomerular filtration rate (eGFR) was stable in both treatments. The incidence of adverse events was similar between groups. Moreover, a post hoc analysis (DUET-Open-Label Extension [OLE]) concluded that 40% of patients treated with sparsentan achieved complete remission of proteinuria (≤ 0.3 g/g) on at least one occasion (10).

DUPLEX (Study of Sparsentan in Patients with Primary FSGS) (11) is the phase 3 study that will evaluate the long-term antiproteinuric efficacy, nephroprotective potential, and safety profile of sparsentan compared with irbesartan in patients with primary FSGS. Also, in immunoglobulin A (IgA) nephropathy, which is the most prevalent primary glomerulonephritis worldwide, the potential benefit of 200–400 mg of sparsentan on kidney function will be evaluated by analyzing changes in proteinuria and eGFR as compared to 150–300 mg of irbesartan in the PROTECT study (A Study of the Effect and Safety of Sparsentan in the Treatment of Patients with IgA Nephropathy; ClinicalTrials.gov: NCT03762850).

Sodium glucose co-transporter 2 inhibitors (SGLT2i) cause, through tubuloglomerular feedback, afferent arteriole vasoconstriction and have also proven kidney protection from CKD progression (12). Therefore, a potent antagonist of ETA with no effect on the ETB receptor (zibotentan) is being evaluated in ZENITH-CKD (Zibotentan and Dapagliflozin for the Treatment of CKD), a phase 2b study in patients with CKD and proteinuria (ClinicalTrials.gov: NCT04724837), as monotherapy and in addition to the SGLT2i, dapagliflozin. Zibotentan has already been studied

in ZEBRA (Zibotentan Better Renal Scleroderma Outcome Study; ClinicalTrials.gov: NCT02047708), with positive results in the scleroderma renal crisis.

In conclusion, ERAs are a strategic therapy with promising effects on proteinuria and CKD progression. However, their incorporation into clinical practice has been delayed as a consequence of their adverse effects in terms of fluid retention. New molecules seem to achieve results with statistical power and safe results that will finally allow us to include them soon in day-to-day practice. In the near future, the treatment of patients with CKD is expected to mimic the sequential treatment offered currently for patients with heart failure. ■

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How We Learn Principles and Perspectives in Nephrology

By Tiffany Truong, Matthew R. Sinclair, and Sam Kant

Medical education, like medicine itself, has evolved over time—from the days of professional guilds and apprenticeships to the establishment of structured postgraduate residency training to duty-hours' restrictions, changes in licensing exams, and the growth of innovative educational resources (1). As the design of medical training changes, so too does the type of physician it produces. After all, medical education is not simply the acquisition of knowledge or even of skills and experiences but a process of shaping and the metamorphosis of the learner.

In a field like medicine, interwoven as it is with the science and humanity of life, the training is not only transformative but also inherently lifelong. Learning—and teaching—becomes a skill in itself. *How we learn* in addition to *what we learn* is pivotal to the type of physician we become. How then do we learn best? If we are to shape our own transforma-

tion in the years of our formal training in nephrology, what constitutes a “good” education? And what currently is the landscape of this training in nephrology?

To answer these questions, we gathered a few perspectives from a group of nephrology fellows and attendings with backgrounds in medical education and surveyed the literature on frameworks of adult learning as it may apply to medical training.

In the 1960s, Malcolm Knowles described an early theory of adult education that he called “andragogy” (in contrast to “pedagogy” for education during childhood, although this is acknowledged to be a continuum) (2). The basic principles of andragogy are assumptions about how adults learn. Among these assumptions are that adults must want to learn, that they need to know the reason for learning something and its relevance, that they are more centered on problem solving and their experiences, and that they need to be self-motivated or responsible for the planning of their instruction (2).

What we heard from both nephrology fellows and attendings was strikingly consistent with these assertions. Foremost, a sense of purpose and relevance is important. Many reported that learning is most effective when the applicability is clear, citing a preference for teaching that focuses on clinical relevance, for example, with bedside teaching and case-based approaches. Clinical experiences and the application of physiologic principles in a clinical context are the core of medical training, and learning this explicitly provides direct applicability. In particular, Free Open Access Medical Education (FOAMed) has been cited as a valuable resource to meet the challenges to early engagement in nephrology, including

the perception that it is very technical, making it difficult to appreciate clinical applications early on (3).

Yet, clinical context is not enough. We cannot encounter every clinical scenario either directly or through cases. In another model of education—Kolb's cycle of experiential learning—learning is a cycle of feeling (having experiences), watching (observing and reflecting), thinking (abstraction and generalization), and then doing (applying concepts in new situations) (2). Learners have different strengths in this cycle, for example, “activists” who feel and do, “theorists” who watch and think, or “pragmatists” who think and do (2). In medicine, “feeling” would equate to having a clinical experience, and “doing” would mean applying that experience to a new situation. The concrete steps of having an experience and being able to apply that experience are separated by the more abstract steps of reflection and abstraction, which also allow for generalization. For many fellows, effective learning is not only about gaining clinical experiences but also involves how best to reflect and process information outside of the clinical environment.

In this regard, educational resources in nephrology abound with options to engage learners of every kind, with many recommendations for textbooks, auditory or visual material such as podcasts and pathology videos, question sets, as well as virtual courses and simulations of clinical cases. Leticia Rolon, MD, a nephrology attending and educator at the University of California in San Francisco, states, “Different platforms have different strengths. For acid-base and electrolyte physiology, you can go back to basics and read Burton Rose. But you don't have to read it alone now—you

can listen to a podcast called *Channel Your Enthusiasm* to add some comedic relief or clinical pearls. The National Kidney Foundation's (NKF's) *Primer on Kidney Diseases* is good for learning glomerulonephritis. And for fellows studying for the boards, I enjoyed the ASN Board Review Course."

Both nephrology fellows and attendings have championed FOAMed as "an interactive learning experience," which can be "more digestible" and simply "fun." Regardless of the media, the key is, as Dr. Rolon states: "A good medical education in general focuses on foundational concepts that are applicable broadly. Be an expert in what you do, and know the basics of everything else. This is the idea behind novel teaching programs [that] focus on diagnostic schemas and pattern recognition. The focus is not on memorizing details disconnected from each other, but on building upon levels of understanding and tiered learning."

Beyond the resources granted to us by the teachings of well-known but faraway nephrologists, professional societies, and social media, resources that are closer to home and institution specific can also be invaluable. Helen Johnson-Wall, MD, a second-year nephrology fellow at the Medical College of Georgia, advocates for interactive approaches, including chalk talks by faculty and flipped classroom approaches where small group discussions are held after individual reading at home. Other nephrology fellows tout dedicated time with a nephropathologist and institution-specific resources. Raad Chowdhury, MD, the chief nephrology fellow at the University of Pittsburgh, remarks, "One of the resources I am very proud of at our institution is the University of Pittsburgh's Renal Handbook, titled *How to Avoid Spilling the Beans*. It is essentially a survival guide created by esteemed faculty to help fellows stay afloat.... It is practical, clear, and concise."

Another interesting aspect of self-motivation and the desire to guide our own instruction is the value fellows place on engaging in teaching themselves. The common adage in medical training states we must "See one, do one, teach one." Most nephrology fellows reported enjoying teaching, and some reported it was useful to their own learning. However, this enthusiasm was not uncommonly tempered by limitations in time due to competing interests, including their own need for dedicated time to learn. Indeed, time is frequently our most precious resource. Dr. Rolon asserts that although the responsibility of the educator is to highlight important teaching points and their relevance, and the responsibility of the learner is to bring forth intellectual curiosity, the learning environment itself must provide clinical experiences while allowing trainees the time and space apart from their responsibilities to build on their curiosity and avoid burnout.

What makes an excellent nephrology fellowship? Dr. Rolon and Matthew Sparks, MD, the program director of the nephrology fellowship program at Duke University, both find that the key to a successful program is its ability to adapt to the complex and evolving nature of nephrology as well as the diverse interests, strengths, and aspirations of its trainees. Dr. Sparks states, "The program should excel in allowing fellows to achieve excellence in patient care, have a longitudinal comprehensive curriculum, provide growth and development opportunities, and most importantly, give the same level of attention to each fellow regardless of career path."

As we embark on a new year and reflect on the past, many nephrology fellows are sum-

miting the halfway point of the academic year. Faculty have started to anticipate newly matched incoming classes. We recognize the breadth and depth of lessons left to teach and learn and remain ever thankful for these seasons of change that bring opportunities for new growth and fresh beginnings. ■

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2021 AASLD Guidance update confirms...



THE KIDNEYS CAN'T WAIT SOONER IS BETTER FOR HRS-AKI / HRS-1^{1,2}

The American Association for the Study of Liver Diseases (AASLD) has updated their Guidance with a key recommendation: elimination of an absolute serum creatinine (SCr) threshold for diagnosis of hepatorenal syndrome acute kidney injury (HRS-AKI / HRS-1). This Guidance, which aligns with a 2015 recommendation from the International Club of Ascites (ICA), may lead to earlier diagnosis and improved treatment outcomes.^{1,2}

- Earlier treatment by approximately 4 days³
- Initiation of treatment when SCr levels were, on average, approximately 1 mg/dL lower³
- Treatment before a further ≥1.5-fold increase in SCr (in 47% of patients)³

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Four Policies Every Nephrologist Should Be Aware of in 2022

By Lin Wang and Eugene Lin



The flurry of kidney-related policies continues unabated, and 2022 brings to the fore another set of policy challenges and opportunities (Figure 1).

A new eGFR equation

In 2020, the National Kidney Foundation (NKF) and the American Society of Nephrology (ASN) established a joint task force aimed at addressing the use of race in the estimated glomerular filtration rate (eGFR). In a highly anticipated recommendation, the task force published alternatives to using race, a social construct, in eGFR. The task force also tackled challenges for the nephrology community moving forward (1). Two key recommendations have emerged. First, the task force recommends that all laboratories immediately implement a new Chronic Kidney Disease-Epidemiology Collaboration (CKD-EPI) equation refit without the race variable (2). Second, because cystatin C-based equations are less biased, national efforts should be made to facilitate increased availability and access to cystatin C. Notwithstanding uniform agreement that cystatin C is more accurate, cystatin C still requires laboratory standardization, a faster turnaround time, and a lower price tag. Now that consensus opinion has been achieved, the nephrology community and policymakers must address the challenge of implementing these recommendations.

COVID-19 vaccinations and new therapeutics

Vaccinations for the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) were a welcome addition to combating the global pandemic. However, the standard two-dose regimens do not appear sufficient to prevent infection, especially in immunocompromised transplant recipients where even four doses may not convey a humoral response (3–5). At the end of 2021, the US Food and Drug Administration (FDA) authorized the use of a single booster shot from either Moderna or Pfizer-BioNTech for all adults 18 and older, especially those who are immunocompromised, including those who received kidney transplant. In 2022, we anticipate further studies on whether additional booster doses will be warranted. Additionally, new therapeutics are now on the horizon (6, 7) and may signal the start of overcoming the pandemic in 2022.

The ESRD Treatment Choices and Kidney Care Choices models

Medicare's End-Stage Renal Disease (ESRD) Treatment Choices (ETC) model formally started in January 2021, whereas the Kidney Care Choices (KCC) model was delayed until January 2022 due to the coronavirus pandemic. Thus far, anecdotal feedback from the ETC is limited. This year, Medicare has proposed new equity adjustments to help address difficulties that safety-net providers might have in meeting benchmarks (8). Once both models have been fully implemented, we anticipate feedback from participants in the kidney community.

The Improving Access to Home Dialysis Act of 2021

With tailwinds from the ETC and KCC, home dialysis advocacy remains strong. On September 29, 2021, the Improving Access to Home Dialysis Act of 2021 (H.R.5426) was introduced to the House of Representatives as bipartisan legislation to help improve access and education for home dialysis modalities. The proposed bill would provide coverage for staff-assisted home dialysis and ensure comprehensive patient education on all dialysis modality options (9). Undoubtedly, this bill would have large implications on the ESRD Prospective Payment System (PPS) by expanding home dialysis to patients who otherwise could not perform home dialysis on their own.

We are optimistic that these policies will help improve kidney health and shape the future of nephrology. ■

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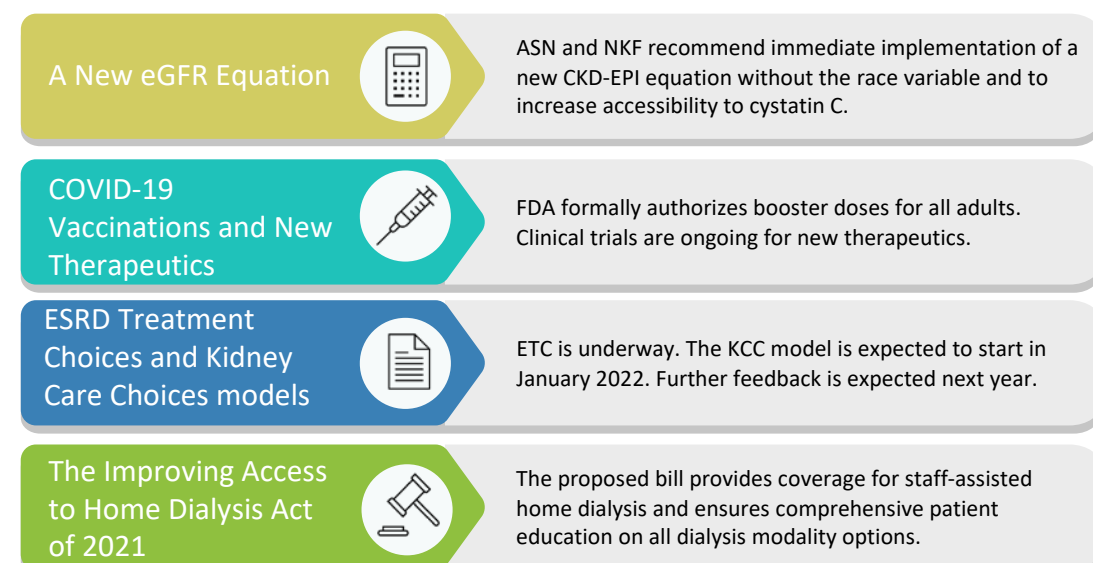
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Figure 1.

Policies to Watch in 2022



Hypertension 2022: Nephrologists in Charge

By Kenar Jhaveri

The knowledge and understanding of hypertension (HTN) have always been cornerstones of nephrology, and over the last 3 decades, nephrologists have emerged at the forefront of HTN management. As we look back over the last few years, several major trials and findings have emerged, leading to some changes in our ways of thinking and practice. I'll highlight the top 10 major findings and studies that are making an impact in HTN management. In 2022, we need to continue to take ownership of HTN as nephrologists.

10. Managing hyperkalemia when using anti-HTN agents. Chronic kidney disease (CKD) and HTN are common in heart failure (HF). Use of renin-angiotensin-aldosterone system inhibitors (RAASi) is frequently underused in HF and even in CKD due to hyperkalemia risk. The advent of patiromer and sodium zirconium cyclosilicate has made practice changes in nephrology. A much-awaited trial will be the LIFT (Lokelma for RAAS Maximisation in CKD & Heart Failure) trial (1), which will randomize 130 patients with CKD and HF (HFrEF [HF with reduced ejection fraction]; i.e., ejection fraction <40%) to novel potassium-lowering binders or placebo and allow for maximizing RAASi use. The primary outcome will be the proportion of participants who achieve maximum RAASi dose while maintaining normokalemia using sodium zirconium cyclosilicate. I believe this study and similar studies can change the way we practice nephrology and manage HTN, CKD, and HF with agents we once avoided due to hyperkalemia.

In 2022, we need to continue to take ownership of [hypertension] as nephrologists.

many long-term benefits. The SYMPPLICITY HTN-3 (Renal Denervation in Patients with Uncontrolled Hypertension) trial, which enrolled more than 500 participants with resistant HTN, demonstrated no difference in blood pressure (BP) reduction with renal denervation compared with sham-control procedures. SYMPPLICITY HTN-3 was criticized by denervation enthusiasts for several study-design limitations, including a variable number of ablations and the enrollment of a heterogeneous patient population (2). More recently, three randomized, multi-center, single-blinded, sham-controlled trials have reported results using improved approaches: SPYRAL HTN OFF-MED, SPYRAL HTN ON-MED, and RADIANCE-HTN SOLO (A Study of the ReCor Medical Paradise System in Clinical Hypertension) (3–5). All three trials reported consistent reductions in ambulatory and office BP in the short (2–3 months) and medium (6 months) term post-procedure with radiofrequency (SPYRAL trials) or highly focused ultrasound-based (RADIANCE-HTN SOLO) denervation. Hence, the story continues. Will we consider such procedures for our patients with resistant HTN? We need to wait to learn more about the long-term risks and benefits of these approaches. Time will tell.

8. Do we intensify HTN management in the elderly? Do we control BP similarly in the elderly (>60 years of age) as we do in the general population? Or is there an increased risk of falls, acute kidney injury (AKI), etc.? Improving BP control in this population may require a better understanding of the specific challenges for BP control at an older age. A recent study published in 2021 answered this question (6). A Chinese cohort of 8000 patients was randomly assigned to intensive arm (110 to <130 mm Hg) versus standard treatment arm (130 to <150 mm Hg). At the 1-year follow-up, the intensive arm had a mean systolic BP (SBP) of 127 mm Hg, and the standard arm had 135 mm Hg, with fewer cardiovascular (CV) events in the intensive arm. The results for safety and kidney outcomes did not differ significantly between the two groups, except for the incidence of hypotension, which was higher in the intensive-treatment group. Although this study was performed in a Chinese population, this may be something we need to consider in the general US and European populations.

7. CLICK on the thiazides for CKD-related HTN. Traditionally, loop diuretics have been preferred in later-stage CKD-related HTN. Use of thiazides has been considered but never well studied. In this recent CLICK (Chlorthalidone in Chronic Kidney Disease) trial (7), patients with CKD stage 4 and HTN were randomly assigned to receive chlorthalidone from a 12.5-mg dose to a maximum of 50 mg per day or placebo. To my surprise, the thiazide arm had better BP control at 12 weeks with a change of ~11 mm

Continued on page 18 >

Table 1. Key takeaways from the KDIGO 2021 HTN guidelines

Standardized BP measurement. The importance of appropriate preparations and the measurement technique, not the type of device, is emphasized with standardized BP measurement. The relationship between routine office BP and standardized office BP is highly variable; therefore, it is not possible to apply a correction factor to translate a given routine BP value to a standardized BP value.

Home BP monitoring (HBPM). When a clinic visit is not practical, HBPM may be particularly important for the management of BP. However, at present, HBPM should only be used to complement standardized office measurement.

CKD patients not on dialysis. Adults with high BP and CKD should be treated to a target SBP <120 mm Hg. Targeting SBP <120 mm Hg reduces the risks of CV events and all-cause mortality in CKD; however, the effects on progression of kidney disease are uncertain.

BP in CKD subgroups. The SBP target of <120 mm Hg also applies to the subgroups of older adults and those with increased albuminuria. The balance of benefits and harms is less certain in people with CKD G5 and in those with severely increased albuminuria.

BP in diabetic CKD. The benefits of intensive BP lowering are less certain among patients with concomitant CKD and diabetes, compared to patients with CKD without diabetes.

Anti-HTN agents in CKD. RAASi (angiotensin-converting enzyme inhibitor [ACEi] or angiotensin-receptor blocker [ARB]) should be used in patients with CKD and increased albuminuria, with or without diabetes. The evidence for use of RAASi in patients with moderately increased albuminuria is lower in quality than in severely increased albuminuria.

Lifestyle changes. Low sodium intake (<2 g/day) and moderate-intensity physical activity (≥150 minutes/week) are suggested in accordance with recommendations for the general population.

Kidney transplant patients. For adult kidney transplant recipients, a target of <130/<80 mm Hg is still a reasonable goal. A lower SBP goal (<120 mm Hg) for kidney transplant recipients would require additional data on the risks and benefits in this population. Dihydropyridine calcium channel blocker (CCB) or ARB should be used as the first-line anti-hypertensive agent in adult kidney transplant recipients, given their efficacy and the importance of preventing graft loss.

BP in children. BP target in children with high BP and CKD should be lowered to less than or equal to the 50th percentile for age, sex, and height, according to 24-hour mean arterial pressure (MAP) by ambulatory BP monitoring (ABPM). When ABPM is not available, a standardized auscultatory office measurement should be used to target SBP less than the 90th percentile. The best agents for treatment are ACEi/ARBs.

Accurate reading of BP in the office/home. Steps include the following: quiet room (no talking by patient or observer); no smoking, caffeine, or exercise for <30 minutes before measurement; and empty bladder. Relax for >5 minutes. Do not talk during rest period and between measurements. Pick appropriate cuff size for the patient. The arms should be bare and resting. The BP should be at level of mid-arm at midpoint of the sternum. Feet should be on the floor. Finally, a validated oscillometric or manual auscultatory device that is calibrated periodically should be used.

Hypertension 2022

Continued from page 17

Hg in SBP compared to placebo. The percent change in the urinary albumin/creatinine ratio was improved as well. There was more hypokalemia, hyperuricemia, dizziness, and hypercreatinemia with the thiazide arm. The change in SBP is really dramatic. This is a practice-changing study and may lead to more use of chlorthalidone in 2022. As we prescribe more of this, monitoring for electrolyte changes is essential.

6. More and more guidelines and ever-changing target for BP control. 2021 saw the final report of the SBP intervention trial (Systolic Blood Pressure Intervention Trial [SPRINT]), which assessed additional primary outcome events adjudicated after data lock for the primary analysis and included a post-trial observational period for 1 year (8). The report had concluded that among patients who were at increased CV risk, targeting a SBP of less than 120 mm Hg resulted in lower rates of major adverse CV events and lower all-cause mortality than targeting a SBP of less than 140 mm Hg—both during receipt of the randomly assigned therapy and after the trial. The Kidney Disease: Improving Global Outcomes (KDIGO) revised 2021 guidelines propose a SBP target of less than 120 mm Hg using standardized office reading for most people with CKD not receiving dialysis, the exception being children and kidney transplant recipients (Table 1). These guidelines simplify things a bit for us as we move into 2022.

5. Potassium is important in HTN management. 2021 taught us, via two trials, that potassium is an important player in HTN management. A salt-substitute study (9), performed in China, randomly assigned participants with HTN to a salt substitute that had 75% sodium chloride and 25% potassium chloride or a control group of 100% sodium chloride. Among people who had a history of stroke or were 60 years of age or older and had HTN, the rates of stroke, major CV events, and death from any cause were lower with the salt substitute than with regular salt. Another study published online in 2021 showed that higher sodium and lower potassium intakes, as measured in multiple 24-hour urine samples, were associated in a dose-response manner with a higher CV risk (10). The role of potassium in HTN management continues to gain momentum. This may be something to watch out for in 2022 as we understand this story better.

4. Quartet may be the magic pill. The multi-center Australian clinical trial of a potential future “quadpill” dose of four medications, termed Quadruple Ultra-Low-Dose Treatment for Hypertension (QUARTET) (11), demonstrated that a single pill containing an ultra-low quadruple combination is much more effective than the traditional approach of starting with monotherapy (single drug). The pill contained irbesartan at 37.5 mg, amlodipine at 1.25 mg,

indapamide at 0.625 mg, and bisoprolol at 2.5 mg. The primary outcome was the significantly reduced BP in the group starting on the quadpill at 12 weeks. These differences were sustained, with BP control still better with the quadpill approach compared to the standard approach at 12 months and no differences in side effects. This was the first study to show that the benefits are maintained long term without any reduction over time. Although I am not a fan of multiple pills in one, this may help change the polypharmacy we see in medicine. Will something similar be in the making for diabetic nephropathy in 2022?

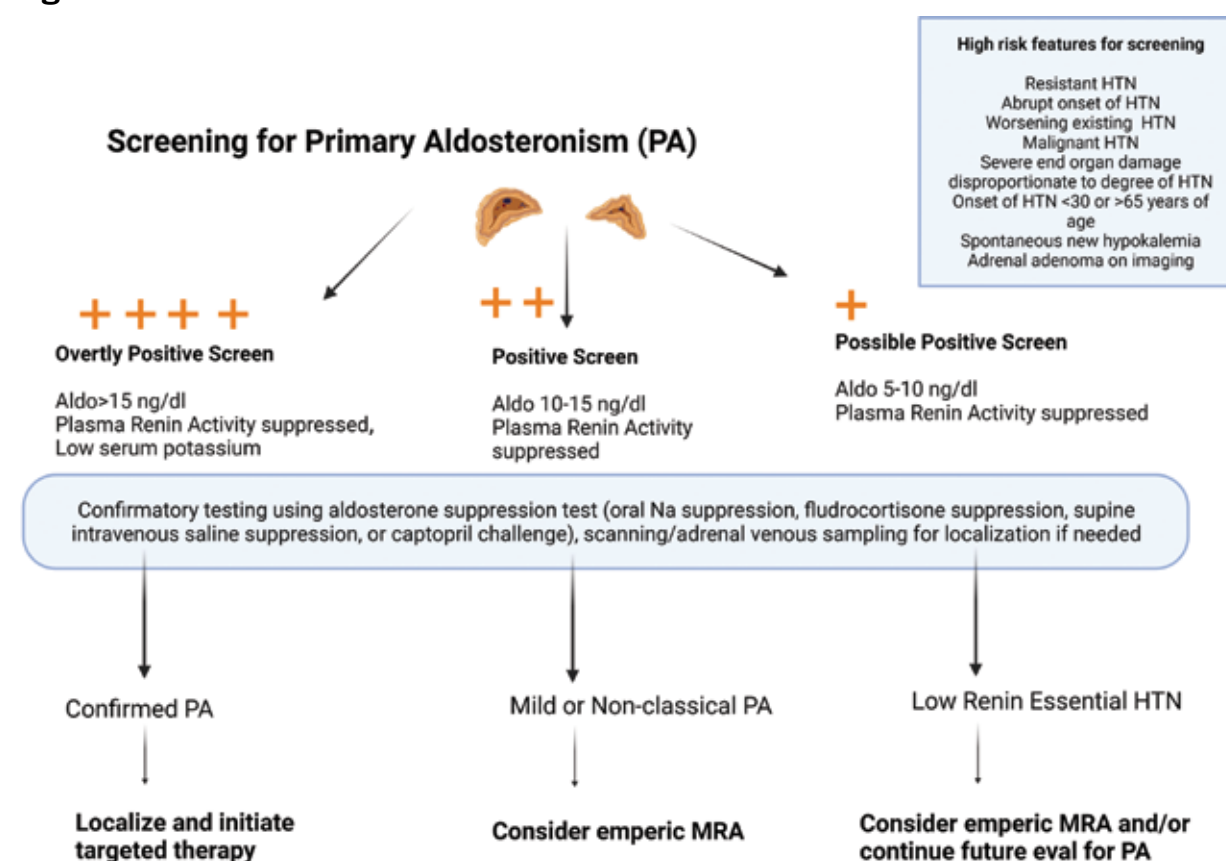
3. Inequalities exist in HTN management. COVID-19 has exacerbated the preexisting inequities in HTN management and control in the United States (12). Virtual healthcare is now widespread because of COVID-19, and this may widen the divide in healthcare access across race/ethnicity, wealth, geography, and education levels. BP control rates are declining, especially among communities of color and those without access to healthcare or health insurance (13). Bress et al. (13) performed a qualitative study that underscored environmental and socioeconomic factors that are deeply embedded in US healthcare and research that impact inequities in HTN. As suggested by the authors, there is an urgent need to improve the implementation of community-based interventions and BP self-monitoring, which can help build patient trust and increase healthcare engagement in all communities.

2. Rise of the MRAs. Resistant HTN is not uncommon in the world of nephrology. The PATHWAY 2 trial showed us that the mineralocorticoid receptor antagonist (MRA) spironolactone is a clear winner in the treatment of resistant HTN (14). The superiority of spironolactone supports a primary role of sodium retention in this condition. More recently (15), another MRA (finerenone), when used in patients with CKD and type 2 diabetes, resulted in lower risks of CKD progression and CV events than placebo. Interestingly, the impact of finerenone in BP control was minimal, hinting at direct kidney anti-fibrotic effects. Although we worry about potassium increases and hypercreatinemia, the use of MRAs in HTN management has been limited (16).

1. Rise of the “aldo”—missed aldosteronism. We need to recognize and treat more primary aldosteronism. A 2021 multi-center study found that only 1.6% of patients with treatment-resistant HTN were appropriately tested for primary aldosteronism (16). A nephrology or endocrinology visit was associated with a higher likelihood of diagnosis, and testing and diagnosis increased the likelihood of therapy with MRA and better BP control over time. Another recent study found a similarly low rate of screening for primary aldosteronism as well (17). A prior study found that adjusted prevalence estimates for biochemical-overt primary aldosteronism were close to 11% in resistant HTN (18)—a very high number—indicating that we are missing the opportunity to treat many patients with the most appropriate medication.

The aldosterone/renin ratio has a poor sensitivity and negative-predictive value. Low plasma renin activity should prompt a diagnosis of primary aldosteronism (and most cases will not have an adenoma but will still respond well to MRAs). Our threshold criteria for defining aldosterone levels may also not be accurate. Figure 1 suggests that the diagnosis of primary aldosteronism need not rely on binary thresholds; rather, it may exist across a continuum of severity, whereby mild and non-classical cases may be detected as well. It is time that we redefine primary aldosteronism, as it may have a role in what we keep calling “essential HTN.” The rise of aldo has begun. In 2022, let’s all start blocking its untoward effect. ■

Figure 1.



Proposed modifications to the diagnostic approach to detect overt and milder forms of primary aldosteronism. Biochemical screening for primary aldosteronism is generally pursued when classical indications are observed, as recommended by the Endocrine Society. A positive screen for primary aldosteronism should suggest renin-independent aldosterone secretion, whereby aldosterone levels are relatively high in the context of a suppressed renin. In the absence of overt evidence for renin-independent aldosteronism on screening, confirmatory testing can be used to affirm the diagnosis. Failure or relative failure to suppress aldosterone on dynamic testing may confirm the diagnosis, whereas marked suppression of aldosterone may instead suggest a diagnosis of low-renin hypertension. Modified from Vaidya et al. (19). Created using BioRender.com.

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Incretin Our Chances: Are GLP-1 Receptor Agonists the Next Big Thing in Diabetic Kidney Disease?

By Susan Murray and Matthew A. Sparks

Drugs that are derived from nature are prevalent in nephrology. For example, the first angiotensin-converting enzyme inhibitor (captopril) was isolated from the venom of the Brazilian pit viper, *Bothrops jararaca* (1). Interestingly, the first sodium glucose co-transporter (SGLT) inhibitor (phlorizin) was isolated from the bark of the apple tree (2). What else does nature have in store?

An unlikely place to look is the saliva of *Heloderma suspectum*, better known as the Gila monster. This is a venomous lizard native to the United States and Mexico. It turns out that the Gila monster only eats 5 to 10 times per year. Thus, these meals are huge, and as a result, considerable biological adaptation has occurred to deal with this food bolus. One of the mechanisms the Gila monster uses to metabolize this massive caloric hit is to upregulate the incretin system (3).

Incretins, such as human glucagon-like peptide 1 (GLP-1), are a group of gut hormones that stimulate the release of insulin from pancreatic β cells and inhibit glucagon in response to hyperglycemia and nutrient intake. The Gila monster has evolved to release an incretin hormone called exendin-4 in response to these food boluses. Incretin-4 has 53% amino acid sequence homology to human GLP-1 (4). Importantly, exendin-4 is resistant to enzymatic inactivation by dipeptidyl peptidase 4 (DPP-4); thus, it has a prolonged duration of action. Exenatide, a synthetic form of exendin-4 administered subcutaneously, was the first GLP-1 agonist and was approved by the US Food and Drug Administration (FDA) in 2005. Since that time, six GLP-1 agonists have been approved by the FDA (subcutaneous: exenatide, dulaglutide, albiglutide, liraglutide, and lixisenatide; oral: semaglutide). In addition, four DPP-4 inhibitors are FDA approved (oral: sitagliptin, saxagliptin, linagliptin, and alogliptin) (5).

GLP-1 receptor agonists are effective therapies for diabetes mellitus (lowering A1c by 0.8%–1.7%) and reduce adverse cardiovascular outcomes that have been available for 15 years. They have an additional benefit in that they result in weight loss. However, they might not be on the tip of the tongue of many nephrologists (like SGLT2 inhibitors are). However, GLP-1 agonists might just be the next blockbuster in the treatment of diabetic kidney disease (DKD). Let's take a look at where we are.

GLP-1 trials are encouraging

Some early signs from recent trials suggest that GLP-1 receptor agonists may have a role in slowing progression of chronic kidney disease (CKD) in DKD. The cardiovascular outcome trials for the GLP-1 receptor agonists showed a reduced risk of major adverse cardiovascular events among those taking liraglutide, semaglutide, and dulaglutide (6–8). Some early signals in these trials suggest they may be of benefit in slowing decline of the estimated glomerular filtration rate (eGFR)

and reductions in albuminuria. However, these studies all have a cardiovascular primary outcome.

Secondary outcomes in a recent trial (AWARD-7) of 577 patients suggest that in patients with macroalbuminuria, the risk of reaching a composite endpoint of kidney failure or >40% decline in eGFR was >50% lower in those receiving dulaglutide than in those receiving insulin glargine (9). A prespecified secondary analysis of the LEADER trial in which 9340 patients with type 2 diabetes mellitus and high cardiovascular risk were randomized to the GLP-1 receptor agonist liraglutide and placebo showed reductions in kidney outcomes primarily driven by fewer episodes of new-onset macroalbuminuria in those taking liraglutide (10). Similar results were seen in the 3297-patient SUSTAIN-6 randomized clinical trial in which secondary outcomes in patients with type 2 diabetes mellitus demonstrated reduced new or worsening kidney outcomes with semaglutide (6).

We are awaiting the results of clinical trials in which kidney outcomes are the primary focus. The FLOW trial will be the first and most impactful (11). It will be assessing kidney disease outcomes in 3500 patients with type 2 diabetes, comparing the GLP-1 receptor agonist semaglutide (subcutaneous route) with placebo, and has finished recruitment and is expected to be complete in 2024 (Table 1). Other semaglutide trials to watch include the SOUL study (12), examining cardiovascular outcomes in type 2 diabetes mellitus, and the SELECT (13) trial, observing cardiovascular outcomes in patients with obesity and no diabetes (Table 1).

Because GLP-1 receptor agonists can be used in individuals with an eGFR >15 mL/min/1.73 m², they are recommended in those who cannot receive SGLT2 inhibitors or metformin, such as those with an eGFR between 15 and 25 mL/min/1.73 m². As noted above, each of the GLP-1 receptor agonists is given subcutaneously, except that semaglutide has an oral formulation. Since these drugs are more potent and decrease blood sugar, adjustment of other antiglycemic agents could be indicated.

Studies in DPP-4 inhibitors are not as convincing as GLP-1 receptor agonists. Although DPP-4 inhibitors are effective at reducing hemoglobin A1c, they have failed to exhibit a cardiovascular benefit (14–16). Moreover, saxagliptin and alogliptin show a signal for increased hospitalizations for heart failure. The mechanism for this is not completely understood but is thought to be related to the degradation of other proteins by DPP-4, which include SDF-1 (stromal cell-derived factor 1), NPY (neuropeptide Y), and substance P. Thus, these could activate the sympathetic nervous system and stimulate β -adrenergic receptors (17). Kidney outcomes in DPP-4 inhibitors, like GLP-1 receptor agonists, are derived from secondary outcomes of cardiovascular trials. DPP-4 inhibitors have been shown to reduce albuminuria, but the effects on kidney function have not been seen (18).

Will we see the fifth pillar of DKD therapy with GLP-1 receptor agonists? We await the FLOW trial results eagerly. It is clear that the outpatient nephrologist should stay well versed in the latest research in diabetes. It is exciting to see these developments materialize. ■

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Table 1. Promising trials focusing on kidney outcomes

Name	Drug	Year of estimated completion	Number of participants	Primary outcome	Inclusion
FLOW	Semaglutide	2024	3508	Kidney	DM2; A1c < 10; eGFR 50–75 with ACR 300–5000 mg/g eGFR 25–50 with ACR 100–5000 mg/g Max ACEi/ARB
SOUL	Semaglutide	2024	9642	Cardiovascular	DM2; A1c 6.5–10
SELECT	Semaglutide	2023	17,500	Cardiovascular	BMI > 27; established CV disease (MI, stroke, PAD, amputation) Exclusion: DM1/2; A1c > 6.5

DM1/2, diabetes mellitus type 1/2; ACR, albumin-to-creatinine ratio; ACEi/ARB, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; BMI, body mass index; CV, cardiovascular; MI, myocardial infarction; PAD, peripheral arterial disease.

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A Novel Non-invasive Biomarker for Minimal Change Disease: Will Anti-nephrin Antibodies Be the Next Anti-PLA2R?

By Mayuri Trivedi and Kirk N. Campbell

Novel biomarkers have been changing our understanding of glomerular disease physiology by improving our diagnostic and prognostic capabilities while opening the door to more precise therapeutic options. Most notably, the discovery of the anti-phospholipase receptor-2 antibody (anti-PLA2R Ab) in 2009 has facilitated diagnostic algorithms where some patients with high PLA2R titers may not need a kidney biopsy. Titer levels are followed clinically to monitor response to treatment and risk of relapse, whereas novel therapeutics are being developed to specifically inhibit presumed pathogenic properties of PLA2R Abs (1).

Nephrin, an important component of the slit diaphragm, has been one of the most widely studied proteins in experimental glomerular disease. The identification in 1998 of mutations in NPHS1, the gene encoding nephrin, in patients with congenital nephrotic syndrome (CNS) of Finnish type opened the door to the subsequent identification of dozens of other gene mutations impacting the glomerular filtration barrier, greatly improving our understanding of its molecular architecture (2). Interestingly, analogous to what happens in Alport syndrome, where de novo anti-glomerular basement membrane (anti-GBM) disease can develop posttransplant, children with CNS due to complete nephrin deficiency have also been reported to develop recurrent nephrosis after transplantation, where anti-nephrin antibodies develop upon exposure to this novel antigen not encountered during fetal maturation. Anti-nephrin antibodies have also been shown to cause massive albuminuria in animal models and redistribution away from the slit diaphragm in cultured podocytes. Taken together, these findings suggest a pathogenic role for anti-nephrin antibodies.

The recent study by Watts, Keller, et al. (3), published in *JASN*, hypothesized a role for circulating anti-nephrin antibodies in the pathogenesis of minimal change disease (MCD) (Figure 1). With the use of a custom-developed indirect enzyme-linked immunosorbent assay (ELISA) and established thresholds, the authors found 18 of 62 (29%) patients of biopsy-proven MCD and active disease showing the presence of this autoantibody in the serum. The threshold for anti-nephrin antibody positivity was set as the maximum titer (187 U/mL) detected in a healthy control population (n = 30). With the use of this standard, only 1 of 54 (2%) of PLA2R+ patients was also positive for anti-nephrin antibodies. Interestingly, anti-nephrin antibodies were reduced or completely absent in seropositive MCD patients during a complete or partial remission. Histologically, the authors identified punctate immunoglobulin G (IgG) colocalizing with nephrin, which they speculate represents in situ nephrin autoantibody binding in patients with circulating anti-nephrin antibodies. Finally, they identified a patient—with steroid-dependent childhood MCD progressing to end stage kidney disease, with no underlying genetic basis—who developed massive posttransplant recurrence of proteinuria in the setting of high pre-transplant anti-nephrin antibodies.

Overall, the possibility of anti-nephrin antibodies proving to be a novel glomerular biomarker for a subset of MCD seems attractive. However, the study had some limitations, including the fact that patients initiated therapy prior to the earliest serum sample being collected and the small sample size. Another point to mention is that the patient with anti-nephrin antibodies and posttransplant proteinuria, discussed previously, had focal segmental glomerulosclerosis (FSGS) on a pre-transplant biopsy, so this is not a straightforward MCD story. The assay will also need to be further validated and threshold value limits defined.

Nonetheless, this observation may pave the way for use of anti-nephrin antibodies, not only for diagnosis but also as a marker of response to therapy or for predicting an impending relapse or recurrence posttransplantation. It is also possible that anti-nephrin antibodies could play a role in the pathogenesis of non-genetic FSGS, particularly given shared features with MCD, but this remains to be seen.

Whereas we celebrate an important step in better understanding the pathogenesis of MCD, we still have a long way to go in establishing a definitive association, causality, and potential use in clinical nephrology. ■

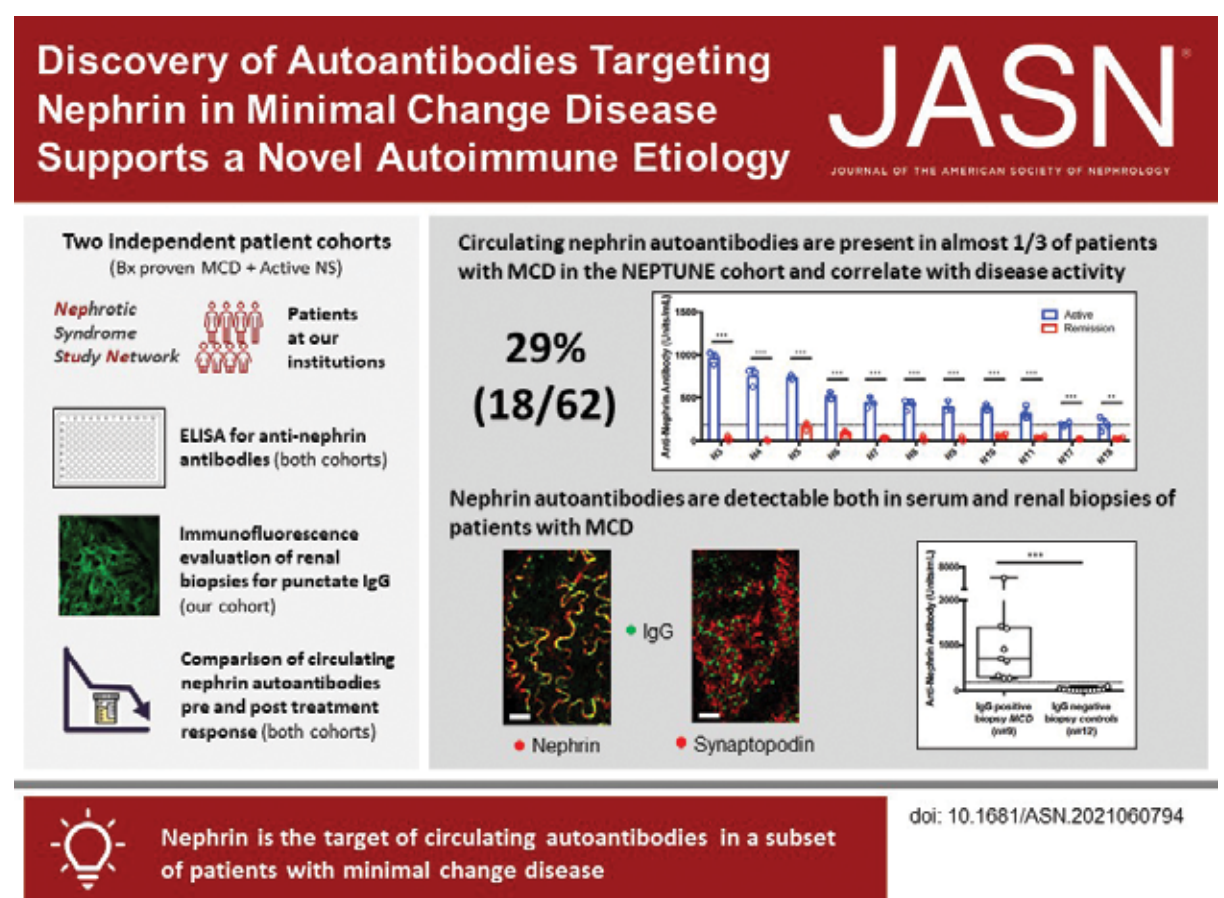
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The authors report no conflicts of interest.

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Figure 1.



The Potential Impact of the New eGFR Equation in the United States and around the World

By Jia Hwei Ng

Self-identified race is a complex interplay of social identity, genetic ancestry, and socioeconomic status (1). In the setting of chronic kidney disease (CKD), classifying patients using race purely as a surrogate for genetic ancestry is problematic because social constructs and socioeconomic status play a large role in the development of CKD (2, 3). The use of race adjustment in the estimated glomerular filtration rate (eGFR) equation to determine kidney function has been questioned for several years because the race-based equation underestimates the prevalence and severity of CKD for patients self-identified as African American (4). Many have argued that the race-based eGFR increases the healthcare disparities between African Americans and non-African Americans (3). Given that African Americans have a higher risk of developing CKD and experience faster progression of kidney disease, early identification of kidney disease will allow earlier access to resources for kidney medical care (4). In September 2021, the National Kidney Foundation and American Society of Nephrology (NKF/ASN) Task Force on Reassessing the Inclusion of Race in Diagnosing Kidney Disease recommended the elimination of the race-based eGFR in all laboratories in the United States (5).

The recommendation made by the task force will lead to both clinical and social implications in the United States (Figure 1). A study by Diao et al. (6), recently published in the *Journal of the American Medical Association*, showed that the removal of the race modifier in creatinine-based eGFR calculations will increase the prevalence of CKD among patients who identify as African American, resulting in a higher proportion meeting eligibility for nephrology referral, kidney transplantation,

coverage for kidney disease education, and coverage for medical nutrition therapy. On the other hand, the lower eGFR would exclude more African American patients from being eligible as a living kidney donor (6) or from receiving anti-cancer therapy (7). Therefore, the kidney medical community will need to monitor the impact of the non-race-based eGFR to ensure continued patient safety and health equity.

Would the new recommendation affect the reporting of kidney function in laboratories outside of the United States?

Other than the United States, only a few countries report a race-based eGFR. In France, the eGFR equation with and without the African American adjustment has been reported in laboratories. However, the use of the African American race adjustment for the eGFR equation in France has been debatable because the European Black populations are not comparable to the African American population in terms of factors such as body composition, diet, or muscle metabolism (8). Similarly, studies looking at the use of race eGFR in populations in the African nations and with African Europeans and African French have been noted to be imprecise (9). With the November 2021 publication in *The New England Journal of Medicine* (10) regarding the new creatinine- and cystatin C-based eGFR equation without race, laboratories in France have been gradually removing the race-adjusted eGFR.

In the United Kingdom, only a single eGFR is being reported. A UK-based study published in August 2021 in *The Lancet Oncology* (7) found that the race-based adjustment for people self-reported as Black has led to an overestimation of eGFR and potentially reduced access to care. In Japan, however, the laboratories report a single eGFR but one that has been validated for the Japanese population (11). Government hospitals in countries of middle and upper-middle income economies (e.g., India and Malaysia) report only serum creatinine levels without the eGFRs. According to the Global Kidney Health Atlas project, the availability of serum creatinine and eGFR in low-income countries is only 30% and 0%, respectively (12).

Thus, the recommendation by the NKF-ASN task force will not substantially impact the reporting of eGFR in laboratories around the globe. However, this pivotal move has shed light on a bigger conversation, i.e., recognizing problems that arise from health inequities and taking first steps toward reducing health disparities. Additional work focusing on the delivery of kidney care will be needed to truly achieve healthcare equity. ■

Acknowledgment

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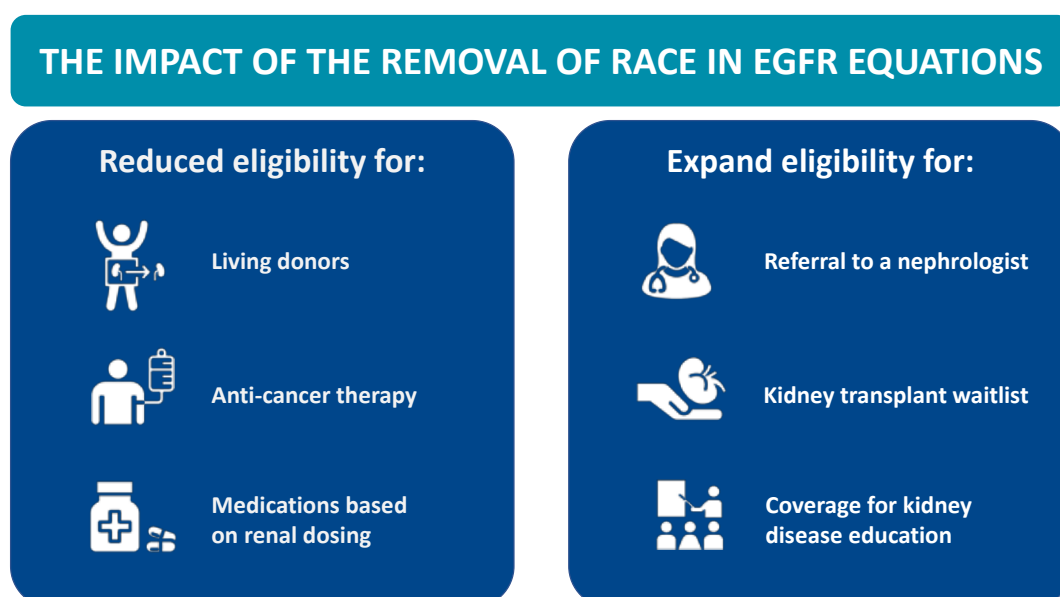
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The author reports no conflicts of interest.

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Figure 1.





COVID-19, AKI, and Acute Kidney Care

By Anitha Vijayan

The COVID-19 pandemic and kidney involvement constitute an evolving story with various twists and turns, and we expect new challenges as we enter the third year of the pandemic. In spring and summer of 2020, COVID-19-associated acute kidney injury (AKI) was one of the biggest challenges in hospitals, as physicians and staff dealt with a surge of COVID-19 patients on the wards and in the intensive care units (ICUs). The incidence of COVID-19-associated AKI in ICUs ranged from 61% to 76% in the United States, with approximately 30% of ICU patients needing kidney replacement therapy (KRT) (1). Patients with COVID-19 and AKI have a very high morbidity and mortality (2) and COVID-19-associated AKI is associated with a significant delay in recovery of renal function when compared to AKI from other causes (3). The etiology of AKI is multifactorial, with hypotension, systemic inflammation, and mechanical ventilation-associated hemodynamic alterations all playing a role. Other factors implied in AKI include rhabdomyolysis, thrombotic microangiopathy, and direct SARS-CoV-2 transduction of tubular epithelial cells. AKI in COVID-19 has been shown to be independent of severity of illness, suggesting that direct viral involvement or other unmeasured inflammatory mediators may play a role in inciting kidney injury (4).

During subsequent surges in COVID-19 infections in United States, the incidence of AKI was significantly lower, and studies are underway to understand the declining rates of AKI with COVID-19 (5, 6). Possible explanations for lower incidence of AKI in subsequent surges include early use of dexamethasone and remdesivir, increased use of non-invasive ventilation (e.g., bi-level positive airway pressure [BiPAP]), and patients with fewer comorbidities.

The term “acute kidney care” refers to the provision of nephrology care as well as KRT to hospitalized patients, whether with AKI, chronic kidney disease (CKD), or end stage kidney disease (ESKD). Hospitals rapidly adapted their KRT programs to allow for provision of KRT to large numbers of patients, implementing prolonged, intermittent KRT utilizing continuous KRT (CKRT) machines (allowing two to three patients to be treated with a single machine) and adopting peritoneal dialysis (previously not utilized for adult patients with AKI) in the ICU. Utilization of existing and implementation of new anti-coagulation protocols for CKRT became essential, as hypercoagulability is extremely common with COVID-19. Even with a lower incidence of AKI, hospitals and nephrologists have to remain vigilant and prepared to provide KRT as hospitals face additional surges during the COVID-19 pandemic. For example, even in late 2021, as hospitals in Texas became inundated with large numbers of patients, those who needed KRT could not be transferred from smaller hospitals to larger centers that provide KRT due to a systemwide shortage of staffed beds.

The omicron variant of SARS-CoV-2 spread rapidly across the African continent and in Europe and is now in North America. Data regarding the severity of illness, risk of hospitalization, and efficacy of vaccines against omicron remain murky. The ASN COVID-19 Task Force and Acute Kidney Care Committee continue to keep abreast of the latest developments and disseminate information and education to the kidney community on a regular basis. We strongly recommend that nephrology directors of inpatient services support disaster and planning committees and lead the way to advocate for adequate staffing and resources for inpatient kidney care (Figure 1) (7). Nephrology leadership must anticipate the need for KRT as we head into 2022 and ensure that adequate personnel, equipment, and supplies are available to provide care for every patient who will benefit from nephrology services and KRT. ■

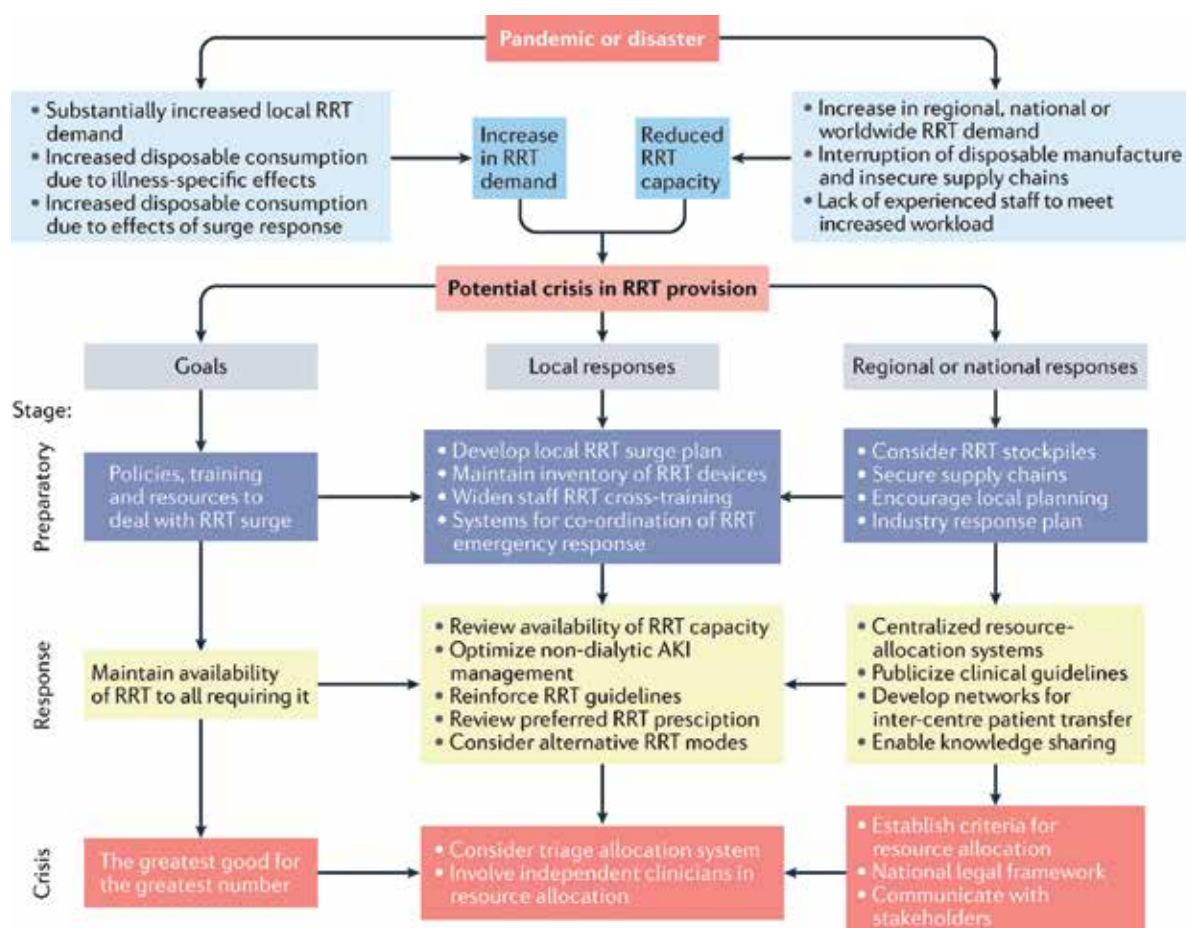
Anitha Vijayan, MD, is a member of the ASN COVID-19 Task Force and chair of the Acute Kidney Care Committee.

The author reports no conflicts of interest.

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Figure 1. Preparing for a surge in kidney replacement demand during a pandemic or disaster



Adapted from Acute Disease Quality Initiative 25, www.ADQI.org, CC BY 2.0 (<https://creativecommons.org/licenses/by/2.0/>), as published in Nadim MK et al. *Nat Rev Nephrol* 2020; 16: 747–764. *Nat Rev Nephrol* ISSN 1759-507X (online) ISSN 1759-5061 (print).

KRYSTEXXA (PEGLOTICASE) IS A RECOMBINANT INTO ALLANTOIN¹



Artist's renditions.

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INDICATION AND IMPORTANT SAFETY INFORMATION

INDICATIONS AND USAGE

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.

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

IMPORTANT SAFETY INFORMATION

WARNING: ANAPHYLAXIS AND INFUSION REACTIONS

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-type hypersensitivity reactions have also been reported. KRYSTEXXA should be administered in healthcare settings and by healthcare providers prepared to manage anaphylaxis and infusion reactions. Patients should be premedicated with antihistamines and corticosteroids. Patients should be closely monitored for an appropriate period of time for anaphylaxis after administration of KRYSTEXXA. Monitor serum uric acid levels prior to infusions and consider discontinuing treatment if levels increase to above 6 mg/dL, particularly when 2 consecutive levels above 6 mg/dL are observed.

The risk of anaphylaxis and infusion reactions is higher in patients who have lost therapeutic response.

Concomitant use of KRYSTEXXA and oral urate-lowering agents may blunt the rise of sUA levels. Patients should discontinue oral urate-lowering agents and not institute therapy with oral urate-lowering agents while taking KRYSTEXXA.

In the event of anaphylaxis or infusion reaction, the infusion should be slowed, or stopped and restarted at a slower rate.

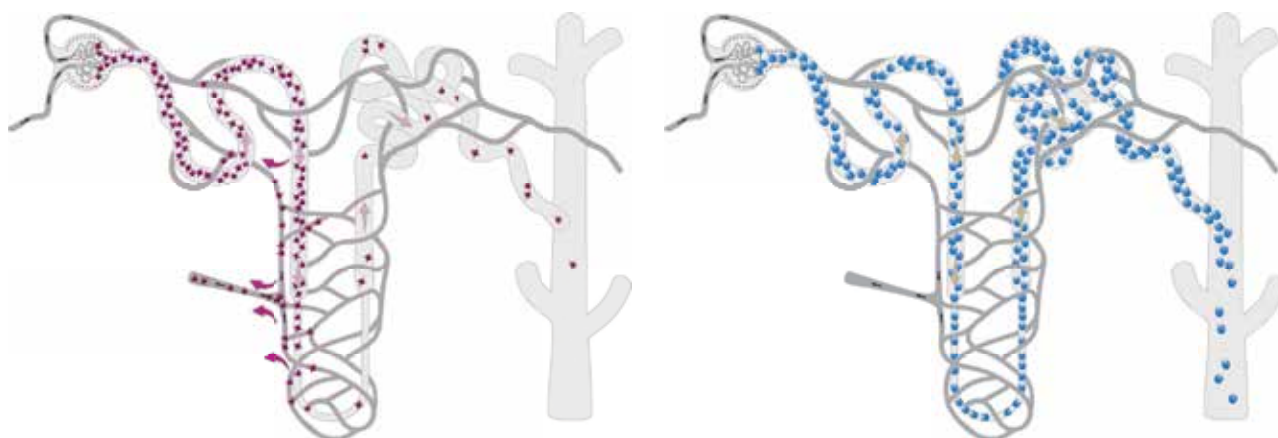
References: **1.** KRYSTEXXA (pegloticase) [prescribing information] Horizon. **2.** McDonagh EM, et al. *Pharmacogenet Genomics*. 2014;24:464-476. **3.** Terkeltaub R, et al. *Arthritis Res Ther*. 2006;8(suppl 1):S4.



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Inform patients of the symptoms and signs of anaphylaxis, and instruct them to seek immediate medical care should anaphylaxis occur after discharge from the healthcare setting.

CONTRAINDICATIONS: G6PD DEFICIENCY ASSOCIATED HEMOLYSIS AND METHEMOGLOBINEMIA

Screen patients for G6PD deficiency prior to starting KRYSTEXXA. Hemolysis and methemoglobinemia have been reported with KRYSTEXXA in patients with G6PD deficiency. Do not administer KRYSTEXXA to these patients.

GOUT FLARES

An increase in gout flares is frequently observed upon initiation of anti-hyperuricemic therapy, including treatment with KRYSTEXXA. If a gout flare occurs during treatment, KRYSTEXXA need not be discontinued. 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 studied in patients with congestive heart failure, but some patients in the clinical trials experienced exacerbation. Exercise caution when using KRYSTEXXA in patients who have congestive heart failure and monitor patients closely following infusion.

ADVERSE REACTIONS

The most commonly reported adverse reactions in clinical trials with KRYSTEXXA are gout flares, infusion reactions, nausea, contusion or ecchymosis, nasopharyngitis, constipation, chest pain, anaphylaxis and vomiting.

Please see Brief Summary of Prescribing Information, including Boxed Warning, for KRYSTEXXA on the following page.

KRYSTEXXA
pegloticase



(pegloticase injection), for intravenous infusion

Brief Summary - Please see the KRYSTEXXA package insert for Full Prescribing 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. However, delayed-type hypersensitivity reactions have also been reported.**
- **KRYSTEXXA should be administered in healthcare settings and by healthcare providers prepared to manage anaphylaxis and infusion reactions.**
- **Patients should be pre-medicated with antihistamines and corticosteroids.**
- **Patients should be closely monitored for an appropriate period of time for anaphylaxis after administration of KRYSTEXXA.**
- **Monitor serum uric acid levels prior to infusions and consider discontinuing 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. Do not administer KRYSTEXXA to patients with G6PD deficiency.**

INDICATIONS AND USAGE

KRYSTEXXA® (pegloticase) is a PEGylated uric acid specific enzyme 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.

Important Limitations of Use:

KRYSTEXXA is not recommended for the treatment of asymptomatic hyperuricemia.

CONTRAINDICATIONS

Glucose-6-phosphate dehydrogenase (G6PD) deficiency

WARNINGS AND PRECAUTIONS

Anaphylaxis

During pre-marketing clinical trials, 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. 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 consider discontinuing 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

During pre-marketing controlled clinical trials, 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 consider discontinuing 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

During the controlled treatment period with KRYSTEXXA or placebo, 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.

Congestive Heart Failure

KRYSTEXXA has not been formally studied in patients with congestive heart failure, but some patients in the clinical trials experienced exacerbation. 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.

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

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 6-month 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.

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.

The most common adverse reactions that occurred in $\geq 5\%$ of patients treated with KRYSTEXXA 8 mg every 2 weeks are provided in Table 1.

Table 1. Adverse Reactions Occurring in 5% or More of Patients Treated with KRYSTEXXA Compared to Placebo

Adverse Reaction (Preferred Term)	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

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.

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.

Postmarketing Experience

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

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.

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. 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).

General Information

Provide and instruct patients to read the accompanying Medication Guide before starting treatment and before each subsequent treatment.

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.
- 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.
- 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.

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. Advise patients that they should not stop KRYSTEXXA therapy if they have a flare.

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New Data Highlight Acute Kidney Injury Associated with Immune Checkpoint Inhibitors

By Mitchell H. Rosner

The past decade has seen a revolution in the treatment of patients with cancer with novel therapies that harness the power of the immune system to kill tumor cells (1). This has been achieved by removing checkpoints on the immune system that typically are exploited by tumor cells that allow for proliferation and growth. Two classes of immune checkpoint inhibitors are available: drugs that act against checkpoint proteins programmed death 1 (PD-1) or cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) or both (2). An expected side effect of these drugs is the occurrence of immune-related adverse events (irAEs) that manifest as autoimmunity affecting a wide range of organ systems, including the development of acute kidney injury (AKI), usually due to immune-related interstitial nephritis (3).

A large observational study by Gupta and colleagues (4) adds to our understanding of the risks and presentation of immune-related AKI associated with these novel agents. This is a study of over 400 patients at 30 clinical sites, features that should make their findings more generalizable.

What are the key takeaway messages? In those patients who had a kidney biopsy, tubulointerstitial nephritis was the most common lesion (82.7%) seen, but other lesions, such as glomerulonephritis, were also encountered. AKI was more common in patients with higher baseline serum creatinine values, although 71% of AKI cases occurred in patients with an estimated glo-

merular filtration rate (eGFR) > 60 mL/min/m². Nearly one-half of patients with AKI experienced non-renal irAEs, and the presence of prior or coexisting irAEs was associated with a twofold higher risk of AKI. Interestingly, the use of proton pump inhibitors (PPIs), drugs independently associated with the development of interstitial nephritis, was also associated with the development of AKI from immune checkpoint inhibitors. Importantly for clinicians, the timing of AKI was variable, occurring at a median of 16 weeks after therapy, but was seen as early as 8 weeks and as late as 1 year after therapy. Outcomes of AKI associated with immune checkpoint inhibitors demonstrated that approximately two-thirds of patients had renal recovery, and this was associated with early initiation of corticosteroids. Last, and somewhat surprising, was that rechallenge of patients who had AKI with immune checkpoint inhibitors was only associated with recurrent AKI in less than 20% of cases.

The findings from this study will greatly influence our thinking about immune checkpoint inhibitor AKI. For instance, PPIs should be used with caution in these patients, and the presence of extra-renal irAEs and AKI should raise suspicion that the mechanism of AKI is related to immune checkpoint inhibitor therapy. However, the study did not identify any clinical features that were so reliable that they clearly pointed to a diagnosis of an immune-related kidney injury over other etiologies, and thus there remains an important role for kidney biopsy to obtain a definitive diagnosis and guide appropri-

ate therapy. In addition, more data are needed regarding dosing and duration of corticosteroid therapy as well as outcomes from this therapy, including risks on progression of the underlying cancer. Still, the authors should be congratulated for bringing together an international group to shed additional light on this evolving area. ■

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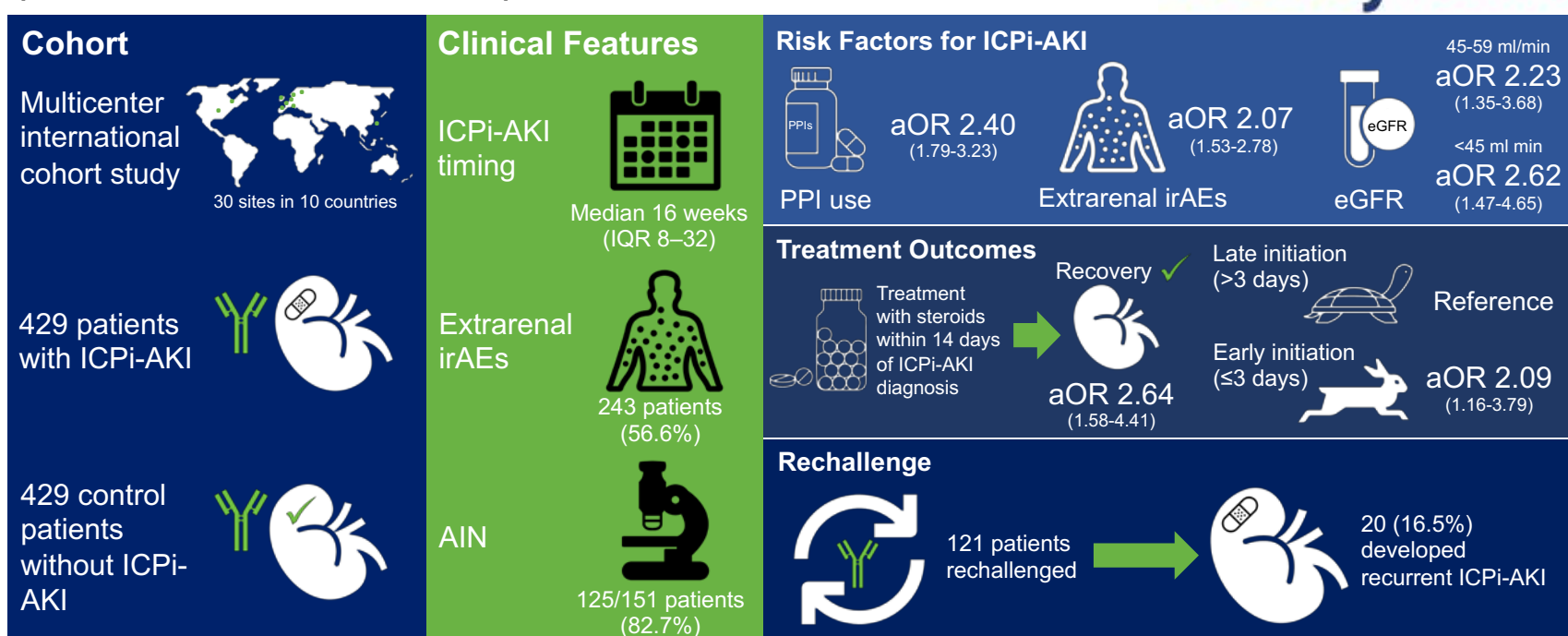
The author reports no conflicts of interest.

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What are the risk factors, clinical features, and outcomes in patients with immune checkpoint inhibitor-associated AKI?

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Conclusions: Patients who developed ICPI-AKI were more likely to have impaired renal function at baseline, use a PPI, and have extrarenal irAEs. Two-thirds of patients had renal recovery following ICPI-AKI. Treatment with corticosteroids was associated with improved renal recovery.

Gupta S, et al. Acute kidney injury in patients treated with immune checkpoint inhibitors. *Journal for Immunotherapy of Cancer*. doi:10.1136/jitc-2021-003467. Visual Abstract @PabloGarciaMD

Mind the Gap: Augmenting Kidney Care Services as Older Nephrologists Look to Retire

By Karen Blum

Preparing nephrology fellows for current workflows and incorporating advanced practice providers (APPs) and international medical school graduates into nephrology practices are ways to augment nephrology services to meet patient needs during a challenging time, a panel of experts said during Kidney Week 2021. This could also help bridge the current time period where some older nephrologists are looking to retire, and there is a shortage of newer trainees in the field, they said.

“The goal of nephrology training is to ensure fellows are well equipped to take on the care of a diverse patient population, while adapting to the ever-changing medical, societal, business, and regulatory changes,” said Matthew A. Sparks, MD, FASN, associate professor and director of the nephrology fellowship program at Duke University School of Medicine in Durham, NC, during the session, “Developing a Workforce So That We Can Retire One Day.”

Trainees need a solid foundation in patient care, Sparks said, but their experiences should be interwoven with educational opportunities to ensure they are not only able to diagnose but are also able to treat patients using the best evidence-based approach. Professional growth and development are also important, and all activities should occur in a supportive and positive environment. Flexibility should be given so fellows can switch tracks if they choose or if their life occurrences change, he noted.

On the patient-care side, inpatient services continue to get busier, and nephrologists’ roles are expanding throughout the healthcare system, but work-life balance should be a priority for trainees and attendings, Sparks said. Additionally, there is continued subspecialization in the field and a need to ensure scholarly activity and research. Furthermore, trainers need to teach business and regulatory issues that are becoming more complex.

Going forward, Sparks said, the Advancing American Kidney Health initiative, launched in 2019 during the administration of former President Trump, is changing the landscape of care such that nephrology training will need to include a foundation of peritoneal and home dialysis, kidney transplantation, and outpatient nephrology (both prevention and patient education).

To achieve this, several skills will be needed, Sparks said. Fellows will need to be able to handle a large volume of patients and be efficient. Ethical dilemmas and issues will arise and should be embedded into training programs. Nephrologists also need to learn to lead multidisciplinary teams and to have work-life balance to achieve a sustainable workforce.

With medical information being rapidly disseminated, it is important to teach fellows lifelong learning skills, said Sparks. They need to understand how to clinically reason, critically appraise literature, prepare for and pass board exams, and learn communication skills. Free open access medical education (FOAMed) is transforming how education and learning are happening, he said, with increased interest in podcasts, simulators, conferences, virtual fellowship programs, and more. Continued training must also address topics in the business of nephrology, such as billing and coding, and value-based care and payment models.

Sparks offered the following advice for training program leaders:

- Listen to your trainees—that is how you know what their needs are.
- Provide opportunities for growth, and invest in them.
- Be proactive in building mentorship and sponsorship teams.
- Push trainees to develop new skills.
- Anticipate future obstacles and help traverse them.

Incorporating APPs also can help expand a nephrology practice’s reach, said Leah Smith, MS, APRN, CNN-NP, FNP, NP, director of APPs at Metrolina Nephrology Associates in Charlotte, NC. With the number of kidney patients continuing to rise in the chronic kidney disease (CKD) and end stage kidney disease (ESKD) populations, APPs “can be a great solution to help get you to the point of being able to successfully retire from your practices,” Smith said.

APPs can provide general patient care as well as lead CKD clinics, manage hypertension clinics or edema or fluid overload issues, support hemodialysis clinics, run education programs for patients, and see new or follow-up hospital patients, among other tasks. “The possibilities are endless,” Smith said.

If you choose to go this route, she said, first, make sure you have the budget to hire. Also determine what the roles of APPs will be, and where you will use them, such as in outpatient dialysis, acute care settings, home care, etc. If you need board approval to go this route, prepare to make your case. It helps to have a physician champion who understands the roles of APPs and can state the benefits of adding them, she said.

Setting up an onboarding process for new APPs is key for the best integration of these healthcare extenders and for longevity in the practice, Smith said. Nephrology is not taught specifically in schools for nurse practitioners or physician assistants, she said, so your practice will need to offer some hands-on education and training. Choose how much time you will spend on classroom time, or give them materials or resources to study at home versus clinical observations or rotations, she noted. Then have them spend time with the physicians or other APPs you identify as trainers. Make sure some time is spent observing their performance to check their skills and ensure they understand your protocols. Work them up slowly, from one patient or a few patients to a full workload. Teach them how to use your electronic health records.

Also, have new APPs meet with Human Resources to set up benefits and tax forms. Introduce them to your staff and collaborative partners. If you have credentialing team members, have them work with the new APPs to get them credentialed. Assess the competency of APPs periodically, and offer opportunities for continuing education through support for meeting attendance.

Adopting APPs can often add revenue but can also bring additional quality or help practices meet certain measures such as dialysis history and physicals, she said.

Another way to extend a practice’s breadth is through

hiring and supporting international medical graduates (IMGs), said Samira Farouk, MD, MSCR, FASN, an assistant professor of medicine and medical education and associate director of the Nephrology Fellowship Program at the Icahn School of Medicine at Mount Sinai in New York, NY.

Nearly 250,000 physicians in the United States workforce—almost 25% of all US physicians—are IMGs, Farouk said, citing 2018 statistics from the American Immigration Council (1). Percentages are higher in nephrology, as 50% of practicing nephrologists (2) and 65% of nephrology residents and fellows (3) were IMGs in 2019, according to the American Association of Medical Colleges.

The two main pathways for clinical training for IMGs in this country are through the J-1 and H-1B visas, Farouk said. To stay on after training to practice, one option is the Conrad 30 waiver program, which allows J-1 foreign medical graduates to apply to waive the requirement to return to their home country for 2 years. However, the program is administered by the states and will approve applications for a maximum of 30 physicians per year. Other avenues include the Appalachian Regional Commission, which can provide waivers for individuals living in the Appalachian area, and the Delta Regional Authority, which can provide waivers for those living in Delta communities. The Department of Veterans Affairs also can sponsor individuals and provide waivers, although there are fewer spots. An alternative for individuals focused on research and clinical care is the US Department of Health and Human Services Exchange Visitor Program, which accepts waiver applications for those doing research in a high-priority area of interest.

Leaders of academic programs or practices interested in pursuing these pathways for trainees should start their discussions by late spring to early summer, Farouk advised, or even as early as the prior September, to allow time for waiver applications to process. The caveat is that practices or institutions must be in areas with an underserved population or in an area with a physician shortage.

“Preparation and timing [are] key,” she said. “Individuals really have to be careful and work with their program leadership to meet these deadlines so that they do not miss them.” It is also important to have a backup plan in case the waiver is not approved, or there is a challenge with the application. Legal help is often required.

“We as a community really have to advocate for this group of individuals,” Farouk said. “They are incredibly important to our workforce, not only as a whole but particularly within nephrology.” ■

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