ASN American Society of Nephrology

# KidneyNews

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# Dropping eGFR Race Factor Would Increase CKD Diagnoses in Black Patients

By Eric Seaborg

Dropping the use of the race coefficient in estimating the glomerular filtration rate (GFR) from serum creatinine would significantly increase the number of Black patients diagnosed with chronic kidney disease and result in about one-third of CKD patients being reclassified to a more severe stage, according to a pair of recent studies.

"Both papers try to estimate the impact of removing the race multiplier in terms of how many patients would be impacted by a reclassification in CKD stage," said Mallika Mendu, MD, MBA, assistant professor at Harvard Medical School and co-author of a study published in the October *Journal of General Internal Medicine* (*JGIM*). Although the two studies looked at different population datasets, the findings "very much aligned."

The studies are designed to provide data to inform the debate as the use of a race coefficient for Black patients in GFR estimation has come under increasing scrutiny. Many institutions have dropped the use of the coefficients.

In August 2020, ASN and the National Kidney Foundation formed a joint task force (ASN-NKF) to focus on the use of race in the GFR estimation. The task force plans to issue an interim report in January and a final report in the spring.

"The task force has been receiving expert testimony and assessing the scientific literature, including newly published articles like these. It is now deliberating to meet its charge to ensure that GFR estimation equations provide an unbiased assessment of kidney function," said Tod Ibrahim, ASN Executive Vice President. "ASN and NKF are committed to reversing the racial health inequities in the United States through efforts that address both health disparities and social determinants of health."

Both studies examined the impact of the race modifier in computing eGFR from serum creatinine using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI). The CKD-EPI equation modifier increases eGFR for Blacks by nearly 16%.

The *JGIM* study, co-authored by Ahmed et al. (1), looked at a CKD registry at two large academic medical centers. A research letter online on Dec. 2, 2020, in the *Journal of the American Medical Association* (*JAMA*), by Diao et al. (2), used data from the National Health and Nutrition Examination Survey (NHANES), a cross-sectional sample of the U.S. population, during 2001–2018.

The *JGIM* study found: "Of 2225 African American patients, 743 (33.4%) would hypothetically be reclassified to a more severe CKD stage if the race multiplier were removed from the CKD-EPI equation. Similarly, 167 of 687 (24.3%) would be reclassified from stage 3B to stage 4."

*Continued on page 7*

# Immunosuppression in Older Adult Transplants

Older adult kidney transplant recipients may benefit from lower-intensity, steroid-sparing immunosuppression regimens that better take into account recipient and donor characteristics, according to a nationwide database study in *Transplantation*.

The percentage of kidney transplants in older adults has increased dramatically in recent years, yet immunosuppressive management in this age group is challenging and little evidence exists to guide clinical decision-making.

With the use of data from the US Renal Data System, the researchers identified 67,632 patients with Medicare claims for immunosuppression after kidney transplantation in 2015–2016. Induction and maintenance immunosuppressive drugs were classified into seven regimens and analyzed for associations with acute rejection, graft failure, and mortality. The findings for older adults (age 65 or older) and younger adults were assessed by multivariable regression analysis.

Older adult kidney transplant recipients were less likely to receive anti-thymocyte globulin (TMG) or alemtuzumab (ALEM) induction with triple maintenance immunosuppression (the reference regimen): 36.9% compared to 47.0% in younger adults. Older adults were also less likely to receive TMG/ALEM plus steroid avoidance, 19.2% vs. 20.1%; mammalian target of rapamycin inhibitor (mTORi)-based regimens, 6.7% vs. 7.7%. In contrast, patients aged 65 or older were more likely to receive interleukin-2-receptor antibody (IL2rAb) plus triple maintenance, 21.1% vs. 14.7%; IL2rAb plus steroid avoidance, 4.1% vs. 1.8%; and cyclo-

*Continued on page 7*

## Inside

WHEN TREATING HYPERKALEMIA

# GO WITH LOKELMA

## CHOOSE THE PATH TO RAPID* AND SUSTAINED† $K^+$ CONTROL[1,2]

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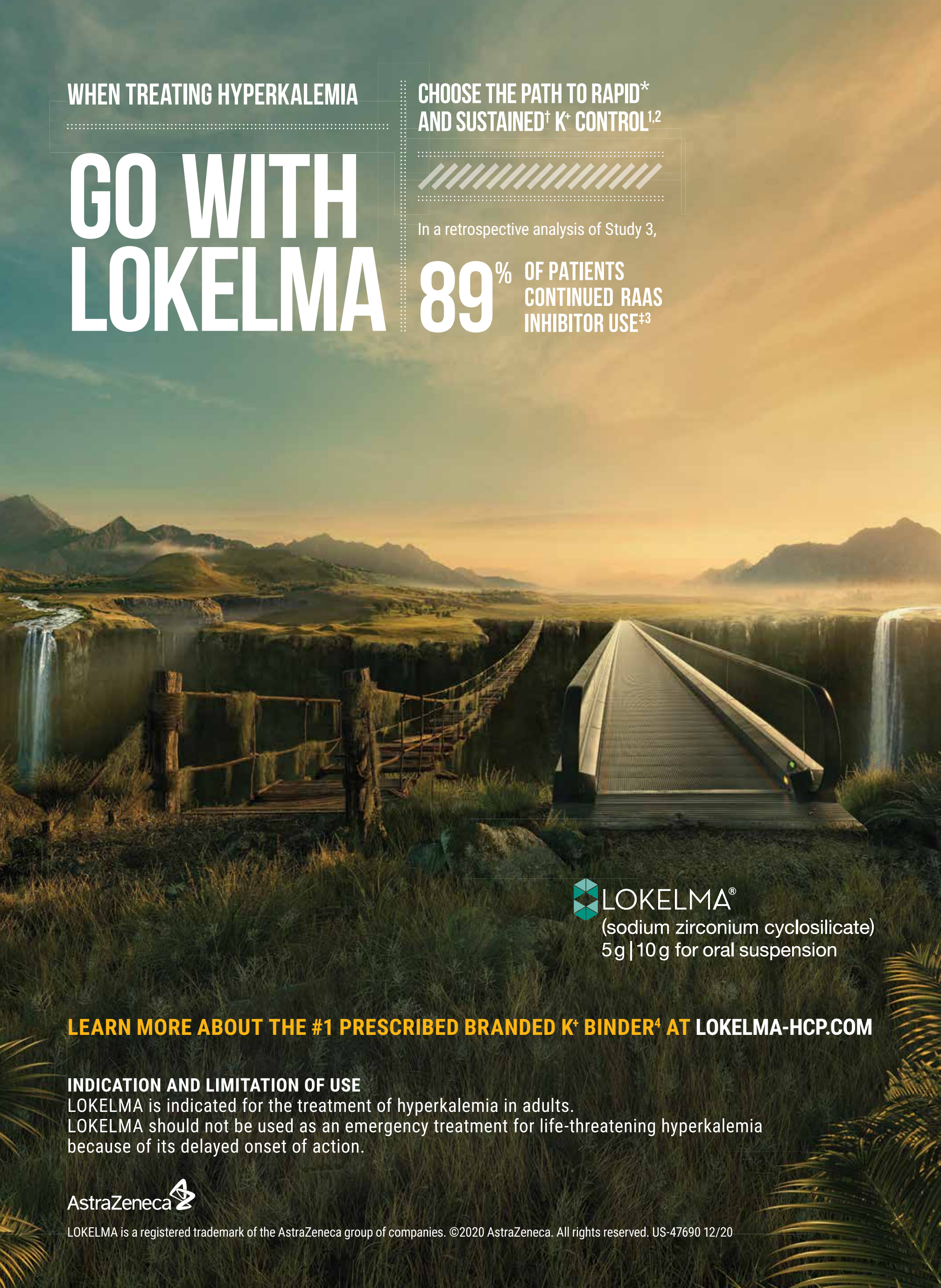

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LOKELMA is indicated for the treatment of hyperkalemia in adults.
LOKELMA should not be used as an emergency treatment for life-threatening hyperkalemia because of its delayed onset of action.

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*In Study 1, LOKELMA 10 g tid demonstrated a greater reduction in serum $K^+$ levels vs placebo at 48 hours ($P$<0.001) and started to work as early as 1 hour in patients with hyperkalemia not on dialysis.[1,2]

†In Study 2, patients with hyperkalemia who achieved normokalemia with LOKELMA in the 48-hour initial phase entered into the 28-day maintenance phase, where those who continued LOKELMA maintained lower mean serum $K^+$ levels vs those who switched to placebo, with a greater proportion of patients having mean serum $K^+$ in the normal range with LOKELMA vs placebo. Patients in Study 2 who continued into the open-label, 11-month extension phase sustained normokalemia with continued LOKELMA dosing.[1]

‡In a retrospective analysis of data from Study 3, 483 patients were receiving RAAS inhibitor at baseline. Of those patients, 74% maintained dose, 13% increased dose, 14% decreased dose, and 11% discontinued RAAS inhibitor use during the 12-month open-label trial. Patients were counted more than once if they required more than 1 RAAS inhibitor adjustment, so the total percentage across all 4 categories may exceed 100%.[3]

**References: 1.** LOKELMA® (sodium zirconium cyclosilicate) [prescribing information]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; 2020. **2.** Packham DK, Rasmussen HS, Lavin PT, et al. Sodium zirconium cyclosilicate in hyperkalemia [article and supplementary material]. *N Engl J Med*. 2015;372(3):222-231. **3.** Spinowitz BS, Fishbane S, Pergola PE, et al; ZS-005 Study Investigators. Sodium zirconium cyclosilicate among individuals with hyperkalemia: a 12-month phase 3 study. *Clin J Am Soc Nephrol*. 2019;14(6):798-809. **4.** Data on file, US-41202, AZPLP.

## IMPORTANT SAFETY INFORMATION FOR LOKELMA® (sodium zirconium cyclosilicate)

### WARNINGS AND PRECAUTIONS:

- **Gastrointestinal Adverse Events in Patients with Motility Disorders:** Avoid LOKELMA in patients with severe constipation, bowel obstruction or impaction, including abnormal post-operative bowel motility disorders. LOKELMA has not been studied in patients with these conditions and it may be ineffective and may worsen gastrointestinal conditions.
- **Edema:** Each 5-g dose of LOKELMA contains approximately 400 mg of sodium, but the extent of absorption by the patient is unknown. In clinical trials of LOKELMA in patients who were not on dialysis, edema was observed and was generally mild to moderate in severity and was more commonly seen in patients treated with 15 g once daily. Monitor for signs of edema, particularly in patients who should restrict their sodium intake or are prone to fluid overload (eg, heart failure or renal disease). Advise patients to adjust dietary sodium, if appropriate. Increase the dose of diuretics as needed.

  In a clinical trial of LOKELMA in patients on chronic hemodialysis in which most patients were treated with doses of 5 g to 10 g once daily on non-dialysis days, there was no difference in the mean change from baseline in interdialytic weight gain (a measure of fluid retention) between the LOKELMA and placebo groups.
- **Hypokalemia in Patients on Hemodialysis:** Patients on hemodialysis may be prone to acute illness that can increase the risk of hypokalemia on LOKELMA (eg, illnesses associated with decreased oral intake, diarrhea). Consider adjusting LOKELMA dose based on potassium levels in these settings.

### ADVERSE REACTIONS:

The most common adverse reaction in non-dialysis patients with LOKELMA was mild to moderate edema. In placebo-controlled trials up to 28 days, edema was reported in 4.4%, 5.9%, 16.1% of non-dialysis patients treated with 5 g, 10 g, and 15 g of LOKELMA once daily, respectively vs 2.4% of non-dialysis patients receiving placebo.

### DRUG INTERACTIONS:

LOKELMA can transiently increase gastric pH. In general, oral medications with pH-dependent solubility should be administered at least 2 hours before or 2 hours after LOKELMA. Spacing is not needed if it has been determined the concomitant medication does not exhibit pH-dependent solubility.

### DOSING:

- **Non-hemodialysis Patients:** For initial treatment of hyperkalemia, the recommended starting dose is 10 g administered three times a day up to 48 hours. For maintenance treatment, the recommended starting dose is 10 g once daily. Monitor serum potassium and adjust dose of LOKELMA at 1-week intervals or longer in increments of 5 g based on serum potassium and desired target range. The recommended maintenance dose range is from 5 g every other day to 15 g daily. Discontinue or decrease the dose of LOKELMA if serum potassium is below the desired target range.
- **Hemodialysis Patients:** For patients on chronic hemodialysis, administer LOKELMA only on non-dialysis days. The recommended starting dose is 5 g once daily on non-dialysis days. Consider a starting dose of 10 g once daily on non-dialysis days in patients with serum potassium greater than 6.5 mEq/L. Monitor serum potassium and adjust the dose of LOKELMA based on the pre-dialysis serum potassium value after the long interdialytic interval and desired target range. During initiation and after dose adjustment, assess serum potassium after one week. Discontinue or decrease the dose of LOKELMA if serum potassium falls below the desired target range based on pre-dialysis value after the long interdialytic interval or the patient develops clinically significant hypokalemia. The recommended maintenance dose range is from 5 g to 15 g once daily, on non-dialysis days.

**Please read Brief Summary of Prescribing Information on adjacent page.**

## LOKELMA® (sodium zirconium cyclosilicate) for oral suspension

Brief Summary of Prescribing Information.
For complete prescribing information consult official package insert.

### INDICATIONS AND USAGE

LOKELMA is indicated for the treatment of hyperkalemia in adults.

Limitation of Use

LOKELMA should not be used as an emergency treatment for life-threatening hyperkalemia because of its delayed onset of action *[see Clinical Pharmacology (12.2) and Clinical Studies (14) in the full Prescribing Information]*.

### DOSAGE AND ADMINISTRATION

#### Recommended Dosage

For initial treatment of hyperkalemia, the recommended dose of LOKELMA is 10 g administered three times a day for up to 48 hours. Administer LOKELMA orally as a suspension in water *[see Dosage and Administration (2.3) in the full Prescribing Information]*.

For continued treatment, the recommended dose is 10 g once daily. Monitor serum potassium and adjust the dose of LOKELMA based on the serum potassium level and desired target range. During maintenance treatment, up-titrate based on the serum potassium level at intervals of 1-week or longer and in increments of 5 g. Decrease the dose of LOKELMA or discontinue if the serum potassium is below the desired target range. The recommended maintenance dose range is from 5 g every other day to 15 g daily.

#### Dosage Adjustment for Patients on Chronic Hemodialysis

For patients on chronic hemodialysis, administer LOKELMA only on non-dialysis days.

The recommended starting dose is 5 g once daily on non-dialysis days. Consider a starting dose of 10 g once daily on non-dialysis days in patients with serum potassium greater than 6.5 mEq/L. Monitor serum potassium and adjust the dose of LOKELMA based on the pre-dialysis serum potassium value after the long inter-dialytic interval and desired target range.

During initiation and after a dose adjustment, assess serum potassium after one week. The recommended maintenance dose range is from 5 g to 15 g once daily, on non-dialysis days.

Discontinue or decrease the dose of LOKELMA if:

- serum potassium falls below the desired target range based on the pre-dialysis value after the long interdialytic interval, or;
- the patient develops clinically significant hypokalemia

#### Reconstitution and Administration

In general, other oral medications should be administered at least 2 hours before or 2 hours after LOKELMA *[see Drug Interactions (7) in the full Prescribing Information]*.

Instruct patients to empty the entire contents of the packet(s) into a drinking glass containing approximately 3 tablespoons of water or more if desired. Stir well and drink immediately. If powder remains in the drinking glass, add water, stir and drink immediately. Repeat until no powder remains to ensure the entire dose is taken.

### CONTRAINDICATIONS

None.

### WARNINGS AND PRECAUTIONS

#### Gastrointestinal Adverse Events in Patients with Motility Disorders

Avoid use of LOKELMA in patients with severe constipation, bowel obstruction or impaction, including abnormal post-operative bowel motility disorders, because LOKELMA has not been studied in patients with these conditions and may be ineffective and may worsen gastrointestinal conditions.

#### Edema

Each 5 g dose of LOKELMA contains approximately 400 mg of sodium, but the extent of absorption by the patient is unknown. In clinical trials of LOKELMA in patients who were not on dialysis, edema was observed and was generally mild to moderate in severity and was more commonly seen in patients treated with 15 g once daily. Monitor for signs of edema, particularly in patients who should restrict their sodium intake or are prone to fluid overload (e.g., heart failure or renal disease). Advise patients to adjust dietary sodium, if appropriate. Increase the dose of diuretics as needed *[see Adverse Reactions (6) in the full Prescribing Information]*.

In a clinical trial of LOKELMA in patients on chronic hemodialysis in which most patients were treated with doses of 5 to 10 g once daily on non-dialysis days, there was no difference in the mean change from baseline in interdialytic weight gain (a measure of fluid retention) between the LOKELMA and placebo groups.

#### Hypokalemia in Patients on Hemodialysis

Patients on hemodialysis may be prone to acute illness that can increase the risk of hypokalemia on LOKELMA (e.g., illnesses associated with decreased oral intake, diarrhea). Consider adjusting Lokelma dose based on potassium levels in these settings.

### ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail elsewhere in the label:

- Edema *[see Warnings and Precautions (5.2) in the full Prescribing Information]*.

#### Clinical Studies Experience

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

The total exposure to LOKELMA in the safety and efficacy clinical trials of patients not on dialysis with hyperkalemia was 1,760 patients with 652 patients exposed to LOKELMA for at least 6 months and 507 patients exposed for at least one year.

The population (n=1,009) in the placebo-controlled trials included patients aged 22 to 96 years, females (n=454), Caucasians (n=859) and Blacks (n=130). Patients had hyperkalemia in association with comorbid diseases such as chronic kidney disease, heart failure, and diabetes mellitus.

In placebo-controlled trials in which patients who were not on dialysis were treated with once daily doses of LOKELMA for up to 28 days, edema was reported in 4.4% of patients receiving 5 g, 5.9% of patients receiving 10 g and 16.1% of patients receiving 15 g LOKELMA compared to 2.4% of patients receiving placebo. In longer-term uncontrolled trials in which most patients were maintained on doses <15 g once daily, adverse reactions of edema (edema, generalized edema and peripheral edema) were reported in 8% to 11% of patients.

Laboratory Abnormalities

In clinical trials in patients who were not on dialysis, 4.1% of LOKELMA-treated patients developed hypokalemia with a serum potassium value less than 3.5 mEq/L, which resolved with dosage reduction or discontinuation of LOKELMA. In a clinical trial of LOKELMA in patients on chronic hemodialysis, 5% of patients developed pre-dialysis hypokalemia (serum potassium <3.5 mEq/L) in both the LOKELMA and placebo groups; 3% and 1% of patients developed a serum potassium < 3.0 mEq/L in the LOKELMA and placebo groups, respectively.

### DRUG INTERACTIONS

LOKELMA can transiently increase gastric pH. As a result, LOKELMA can change the absorption of co-administered drugs that exhibit pH-dependent solubility, potentially leading to altered efficacy or safety of these drugs when taken close to the time LOKELMA is administered. In general, other oral medications should be administered at least 2 hours before or 2 hours after LOKELMA *[see Dosage and Administration (2.3) and Clinical Pharmacology (12.3) in the full Prescribing Information]*. LOKELMA is not expected to impact systemic exposure of drugs that do not exhibit pH-dependent solubility and so spacing is not needed if it has been determined that the concomitant medication does not exhibit pH-dependent solubility.

### USE IN SPECIFIC POPULATIONS

#### Pregnancy

Risk Summary

LOKELMA is not absorbed systemically following oral administration and maternal use is not expected to result in fetal exposure to the drug.

#### Lactation

Risk Summary

LOKELMA is not absorbed systemically following oral administration, and breastfeeding is not expected to result in exposure of the child to LOKELMA.

#### Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

#### Geriatric Use

Of the total number of subjects in clinical studies of LOKELMA, 58% were age 65 and over, while 25% were 75 and over. No overall differences in safety or effectiveness were observed between these patients and younger patients.

### PATIENT COUNSELING INFORMATION

Dosing

Instruct the patient how to reconstitute LOKELMA for administration. Inform the patient that it is necessary to drink the full dose *[see Dosage and Administration (2.3) in the full Prescribing Information]*.

Instruct dialysis patients who experience acute illness (e.g., decreased oral intake of food or fluids, diarrhea) to contact the health care provider. The dose of Lokelma may need to be adjusted. *[see Warnings and Precautions (5.3) in the full Prescribing Information]*.

Drug Interactions

Advise patients who are taking other oral medications to separate dosing of LOKELMA by at least 2 hours (before or after) *[see Drug Interactions (7) in the full Prescribing Information]*.

Diet

Advise patients to adjust dietary sodium, if appropriate *[see Warnings and Precautions (5.2) in the full Prescribing Information]*.

U.S. Patent No: 6332985, 8808750, 8877255, 8802152, 9592253



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# Jhaveri Poised to Bring Innovative Ideas to *ASN Kidney News*

By Karen Blum

As a child, Kenar Jhaveri, MD, FASN, often found creative ways to demonstrate his school learning, from performing skits to creating crossword puzzles. That continued in his nephrology career teaching medical trainees. Now, Jhaveri is excited to bring his passion for innovation and education to *ASN Kidney News*, where he becomes the new editor-in-chief in January 2021.

ASN's monthly newsmagazine "does a great job of reaching the whole nephrology community, covering a good mix of fun and serious topics," said Jhaveri, professor of medicine at the Donald and Barbara Zucker School of Medicine at Hofstra/Northwell and associate chief of the Division of Kidney Disease and Hypertension at Northwell Health, NY. He wants to build upon that to make the magazine the most innovative in the field.

"I want to enhance the magazine by bringing more of an international presence," he said. "I want to include more policy information because a lot of things are changing in nephrology. I also want to make the publication more visual, incorporating more figures and visual abstracts to summarize articles using graphics. With our diverse and dynamic editorial board, I think this is not an impossible task to achieve."

Longer articles written in straight text appeal to readers and nonvisual learners, but they potentially can lose audience members who learn best through visual information, Jhaveri noted.

The magazine can be positioned to showcase interesting work in nephrology to attract more medical students and residents to the field, he added. There has been a decline in applicants for nephrology training positions for a number of reasons, he said, including the potential difficulty in mastering the science, a shortage of good mentors in some hospitals, and declining reimbursement for some patient care services.

"The good news is, the tides are turning," Jhaveri said. "A lot of places have restructured how they teach and rotate residents and students in nephrology, and this was the first year we saw a positive trend toward residents applying for nephrology fellowships. "The COVID-19 pandemic has a silver lining for nephrology," he noted. "Nephrologists were on the front lines supervising dialysis being given to COVID-19 patients, and residents and students saw us being the consultants who were needed in the time of a crisis."

Jhaveri's editorial history dates back to 2011, when he was selected as the inaugural editor of AJKD blog, the launching platform for NephMadness in 2013, which became the first online game in medicine. Jhaveri also is the creator and longtime editor of the popular *Kidney News* column "Detective Nephron," which features a Sherlock Holmes-type master clinician helping a budding nephrologist form diagnoses for interesting cases. Jhaveri devised the idea himself, and pitched it to the magazine.

"My whole interest has been in innovation and education in nephrology. I always thought, 'Why are we stuck with this one way of teaching?'" he said. "Ten years ago I started using crossword puzzles, anagrams, comic strips, blogs, and other social media methods to expand the way of teaching nephrology. It keeps me excited about it, too."

The clinical cases discussed in Detective Nephron were sometimes thought up by Jhaveri, sometimes based on his patients, and sometimes written to include trends in nephrology. Jhaveri also gathered information about interesting cases from other nephrologist colleagues.

Jhaveri received his medical degree from State University of New York–Upstate Medical University in Syracuse in 2004. He completed a residency in internal medicine at Yale New Haven Hospital in Connecticut and a fellowship in nephrology at New York Presbyterian Hospital, in New York City. He joined the faculty at Northwell Health in 2009.

In addition to being an active member of numerous professional medical societies, he serves on the editorial boards of *CJASN*, *AJKD*, *Kidney International*, *Nephrology Dialysis Transplantation*, *Clinical Kidney Journal*, and *Journal of Onconephrology*. Jhaveri also developed a nephrology blog, nephronpower.com, to inform and connect with academics.

His current research projects include studying kidney toxicities of targeted anti-cancer agents and immunotherapy, kidney disease after hematopoietic stem cell transplantation, glomerular diseases in cancer patients, the use of immunotherapy in kidney transplant patients, and COVID-19–related kidney disease. Two recent studies on AKI patients hospitalized with COVID-19 were published in *Kidney International* (1) and *AJKD* (2).

"I want to thank ASN for giving me this opportunity," he said. "With a diverse and dynamic editorial board and a talented and experienced editor, we want to show our readers the vibrant research happening in nephrology. We want to share the upcoming news and important topics relevant to our readers in a timely and creative manner."

**References**

1. Hirsch JS, et al. Acute kidney injury in patients hospitalized with COVID-19. *Kidney Int* 2020; 98:209–218. doi: 10.1016/j.kint.2020.05.006
2. Ng JH, et al. Outcomes among patients hospitalized with COVID-19 and acute kidney injury [published online September 19, 2020]. *Am J Kidney Dis* doi: 10.1053/j.ajkd.2020.09.002

# Prioritizing COVID-19 Vaccination in Dialysis

By Thomas H. Watson, Daniel E. Weiner, Jerry Yee, and Jeffrey Silberzweig for the Outpatient Dialysis Subcommittee of the American Society of Nephrology COVID-19 Response Team

Additional Committee Members: Danilo Concepcion; Mandy Hale; Glenda Harbert; Alan Kliger, MD; Brigitte Schiller, MD; Felicia Speed; and ASN staff including Darlene Rodgers, Bonnie Freshly, Matthew Howard, Kerry Leigh, Javier Rivera, and Susan Stark

COI Statement: T.H.W. serves on the Fresenius Kidney Care Medical Advisory Board. D.E.W. is the Medical Director for Clinical Research for Dialysis Clinic, Inc. J.S. provides consulting services for Alkahest, Inc., and Kaneka Medical America.

Nearly 800,000 patients in the United States have end-stage kidney disease, with more than 550,000 receiving maintenance dialysis (1). Compared to the general population, dialysis patients incur a greater burden of illness, with more comorbid conditions, including diabetes mellitus, hypertension, intrinsic pulmonary disease, cardiovascular and cerebrovascular disease, obesity, and frailty. Individuals dependent on maintenance dialysis are extremely vulnerable to the effects of infection with Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), the virus that causes Coronavirus Disease 2019 (COVID-19), with COVID-associated mortality likely exceeding 20% (2).

In October 2020, the National Academy of Medicine released its plan for vaccination against COVID-19 (3), prioritizing vaccination of healthcare workers, followed by older individuals and those with chronic medical conditions. On December 1, 2020, the Advisory Committee on Immunization Practices of the Centers for Disease Control and Prevention voted to recommend that both healthcare workers and residents of long-term care facilities be first in line for any coronavirus vaccines (4), with the lone dissenting voter expressing concerns that vaccines had not been tested in a long-term care population. The members of the American Society of Nephrology (ASN) COVID-19 Outpatient Dialysis Subcommittee support these recommendations, stressing that: 1) dialysis facility staff must be included with other healthcare workers as priority vaccine recipients, and 2) patients on dialysis should be the next priority after long-term care facility residents, reflecting their limited ability to physically distance, heightened vulnerability to infection, and poor outcomes if infected (2, 5). This is consistent with the position statement of the UK kidney community released on December 4, 2020, indicating highest priority for vaccination for those patients treated by dialysis (6).

With the recognition that physical distancing is not feasible for patients on dialysis, this prioritization not only benefits these individual patients but also myriad personnel who encounter them frequently, including transportation providers and family members who transport patients to and from dialysis facilities and the greater network of healthcare providers who care for these patients in ambulatory and inpatient settings.

While dialysis facilities have performed well in the pandemic, with few described cases of transmission within the facility, hemodialysis facilities remain high-risk settings. We contend that strategic prioritization of patients on dialysis for COVID-19 vaccination will increase safety in dialysis facilities, reducing the risk of infection among patients who are obligatorily congregated during relatively prolonged hemodialysis sessions alongside dialysis workers. While better able to physically distance, home dialysis patients share several risk factors for infection with in-center patients, including frequent healthcare encounters. With clear-eyed recognition of the hazards of the mandatory congregate hemodialysis setting, the dialysis community has modeled excellent practices regarding 2 of the "3 Ws" of "wearing masks," "washing hands," and "watching your distance." The latter remains a challenge while caring for patients congregated within a dialysis facility. From the outset of the pandemic, dialysis facilities rapidly adopted universal intake screenings for fever, symptoms, and exposure(s) to COVID-19. For patients who were identified as having symptoms potentially consistent with COVID-19 and for dialysis patients with COVID-19, dialysis facilities implemented rigorous protocols, including proactive cohorting to provide dialysis separately to patients who were either positive for COVID-19 or under investigation for COVID-19. This often involved creating separate "COVID shifts" or dedicating facilities entirely to the care of hemodialysis patients with COVID-19 (7). These tactics have been largely successful at preventing spread within dialysis facilities.

The best way to maximize dialysis patient safety is to limit exposures to risk. For other infectious diseases, this has been accomplished through proactive campaigns within dialysis facilities to increase patient and staff vaccination rates, including for influenza and hepatitis B viruses, as well as mandatory reporting of dialysis facility staff influenza vaccination in the quality incentive program (8). These lessons, including a focus on both patient and staff vaccination, can be extended to COVID-19, where, to maximize safety, both dialysis staff and dialysis patients must be high priority for vaccination. Patient vaccination will have downstream benefits beyond those to the individual, reflecting that dialysis patients often travel in groups to dialysis units, frequently reside in long-term care facilities, and may have large familial-social networks engaged in their care. Staff vaccination has similar benefits, recognizing that many dialysis staff work at multiple dialysis facilities and hospitals, increasing the number of potential exposures should they have COVID-19.

Prior to the pandemic, maintenance dialysis patients had an annual mortality rate of 18% to 20%, primarily attributable to cardiovascular disease and infectious causes. Per the United States Renal Data System, all-cause mortality has increased dramatically since March 2020, the onset of the COVID-19 pandemic in the United States. For patients receiving maintenance dialysis, mortality was 37% greater during April 2020 compared to the same calendar-weeks of 2017 to 2019; similarly, mortality was also 16% higher in weeks 18 to 27 of 2020 (roughly late April to June). This upsurge of mortality was ascribed to documented SARS-CoV-2 infections, undocumented viral infections, and decreased access to necessary non-dialysis-related medical care (1).

The success of a proposed conjoint strategy of immunizing patients receiving dialysis and associated healthcare workers depends on the immune response of patients on dialysis to vaccines. This is an area of some uncertainty; although data suggest that many dialysis patients do respond to vaccines, patients receiving maintenance dialysis are variably and somewhat unpredictably immunosuppressed. Anergy during tuberculous antigen testing and suboptimal antibody titer generation following a hepatitis B vaccination series or vaccination against influenza viruses are well-documented displays of suboptimally functioning immune systems. T cell and antigen-presenting cell dysfunction are also central to the vulnerability of patients on dialysis. Further, many patients with chronic kidney disease, including those treated with dialysis, are prescribed immunosuppressive medications.

Patients receiving maintenance dialysis have not been enrolled widely in COVID-19 vaccination trials. Initial vaccines will incorporate two technologies. The mRNA vaccines, including those produced by Pfizer and Moderna, instruct patients' own bodies to manufacture a spike protein that is found on the surface of SARS-CoV-2 that the body then recognizes as foreign and generates an immune response. The goal is for this immune response to be durable. Critically, there is no live or attenuated virus incorporated in this technology, and symptoms associated with vaccination reflect upregulation of the immune response (9). In contrast, other vaccines, such as that from AstraZeneca/Oxford, are more traditional, using a modified adenovirus vector to deliver a COVID-19 spike protein to patients in order to trigger an immune response and antibody development. While there is no reason to expect that vaccine safety for either of these vaccine technologies will differ between dialysis patients and the general population, efficacy remains unknown, and studies are urgently required in dialysis and immunocompromised populations.

Vaccination logistics are critical for dialysis-dependent patients and dialysis staff, and the earliest available mRNA vaccines require ultra-cold storage and repeat vaccination after 3 to 4 weeks. The choice of vaccine for patients receiving dialysis may be critical, with advantages associated with vaccines that only require conventional storage possibly outweighing possible increased efficacy. Critically though, dialysis facilities are uniquely positioned to administer vaccines to this highly vulnerable population at a three- to four-week interval, given the numerous and repeated contacts (thrice weekly for in-center patients and monthly for home patients).

Dialysis facilities are proficient at tracking vaccine administration and infection. Most facilities operate with robust electronic health records, and all are familiar with data reporting to various federal and state monitoring databases. Critically, for patients treated with hemodialysis, where bloodstream access is easy, quality improvement protocols could be implemented to assess vaccine response via serologic testing, with widespread dissemination of results to inform national vaccination strategies. Ultimately, through public data sharing, confidence regarding the safety and efficacy of COVID-19 vaccines would be engendered (10).

As expected, patients receiving dialysis are already presenting their individual preferences and beliefs to their care providers. In this way, they are exactly the same as the general population, only with disproportionately high burdens of fear and anxiety by comparison. Many are eager to be first in line for vaccination, whereas others will wait for safety data to emerge. A minority will likely re-

fuse vaccination, irrespective of such results, with public health needs invariably colliding with the need to maintain patient autonomy. In this situation, it is critical that dialysis facility staff, including the nephrologists, nurses, social workers, and other clinicians who have established relationships with these patients, work with patients to overcome fears and trepidation regarding vaccination. A challenging discussion lies ahead regarding the possibility of mandating vaccination for patients and staff at dialysis facilities.

In sum, patients on dialysis, particularly those receiving maintenance in-center hemodialysis, represent a relatively large population of vulnerable individuals who are obligated to congregate multiple times per week and are at high risk of death should they develop COVID-19. These patients and the healthcare workers who care for them are a priority for immunization. Critically, the immune responses to immunization against SARS-CoV-2 are unknown due to lack of trial data, and, in the absence of rigorous current data, monitoring plans need to be put into place with minimal barriers to evaluate vaccine safety and efficacy. Finally, dialysis providers and the public health community will need to work together to address potential logistic barriers to vaccine administration in dialysis facilities in order to maximize the uptake of vaccines in this vulnerable population. ■

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## Dropping eGFR Race Factor

*Continued from page 1*

Some 64 of 2069 patients (3.1%) would have their eGFR moved below the 20 mL/min/1.73 $m^2$ criterion for being added to the transplant list.

The *JAMA* research letter found that in its sample of 9522 Black adults, the removal of race would result in a median decrease in eGFR of 14.1 mL/min/1.73 $m^2$. "Removing race may increase the prevalence of CKD among Black adults from 14.9% to 18.4%. Concurrently, 29.1% of Black adults with existing CKD may be reclassified to more severe stages of disease, with significant clinical and pharmacological implications," the authors write. And although the reclassification would make more patients eligible to receive a transplant, it would also disqualify more people from being eligible to donate a kidney.

In an editorial accompanying the research letter, Norris et al. (3) state that extrapolating this 14.9% to 18.4% increase in prevalence "could possibly indicate an estimated 1 million Black adults having a new diagnosis of CKD."

Mendu, who is a member of the ASN-NKF task force, said she was surprised at the size of the effects: "The argument we have heard from many is that this isn't a big deal and it is not really going to affect many people whether we use [the race multiplier] or don't use it. What both papers show is that it is affecting a lot of the patients it is being applied to, so it can't be ignored."

According to the *JAMA* research letter, "Removal of race adjustment may increase CKD diagnoses among Black adults and enhance access to specialist care, medical nutrition therapy, kidney disease education, and kidney transplantation, while potentially excluding kidney donors and prompting drug contraindications or dose reductions for individuals reclassified to advanced stages of CKD."

The accompanying editorial notes that reclassifying patients to CKD stage 4 would make "patients no longer eligible for certain treatments (e.g., metformin and sodium glucose transporter-2 inhibitors)" and would thus involve a trade-off between "the potential benefits of significantly slowing CKD progression among potentially a million or more individuals vs. the loss of treatment among a much smaller group of individuals in the late stages of disease (who might inevitably progress toward kidney failure)."

The *JAMA* research letter notes: "This potential for benefits and harms must be interpreted in light of persistent disparities in care, documented biases of eGFR without race, and the historical misuse of race as a biological variable to further racism."

Neil R. Powe, MD, MPH, MBA, a co-author of the *JAMA* letter, said a careful examination of the data in the articles indicates that healthcare "disparities are driven by other factors than the equation and that the equation has become a scapegoat. We need to concentrate on the real drivers of disparities to make change."

Powe is professor of medicine at the University of California, San Francisco, and co-chair of the ASN-NKF task force on race and GFR estimation.

"Clinicians must recognize that regardless of race, eGFR is an imprecise measure at the patient level," the *JGIM* authors note. "The risk of underestimation versus overestimation must be recognized and mitigated by the use of biomarkers such as cystatin C that can estimate GFR without the use of race." They add, "many African-Americans face the challenge of more rapid acceleration to ESRD compared with other racial groups, so on average, they would likely benefit from earlier counseling and preparation for renal replacement therapy as well as earlier nephrology and transplant referral."

The ASN-NKF task force is hosting online forums to solicit input: Jan. 15, 6–8 p.m. ET, focused on input from clinicians, scientists, and other health professionals; and Jan. 22, 6–8 p.m. ET, focused on patients, family members, and other public stakeholders. ■

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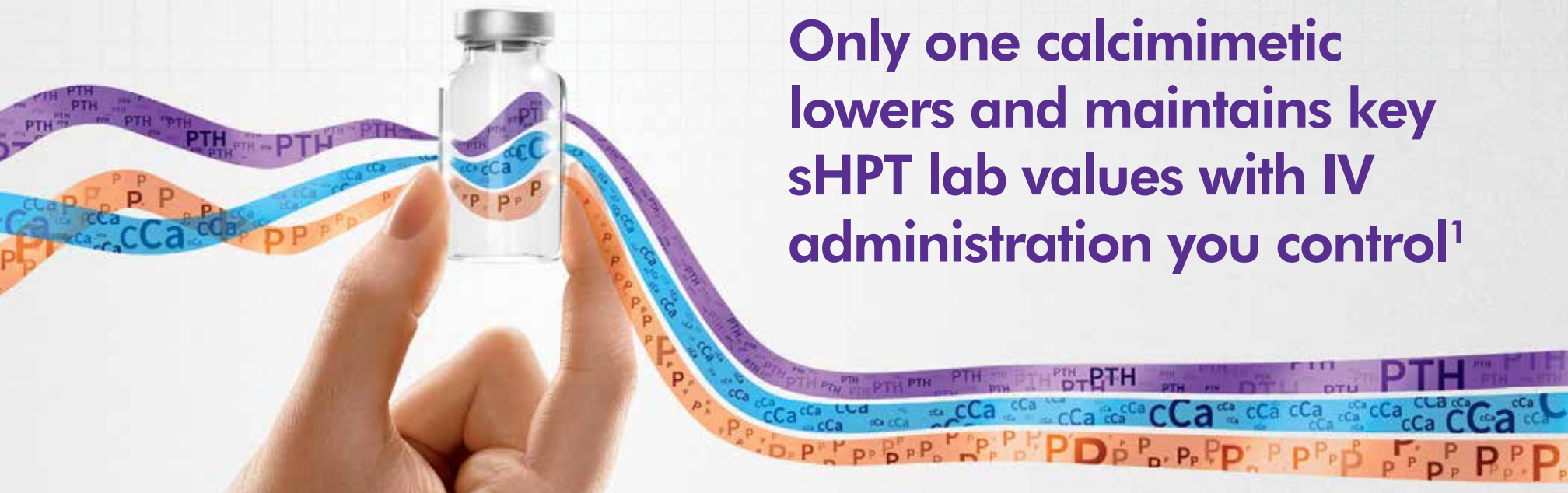
## Immunosuppression

*Continued from page 1*

sporine-based immunosuppression, 8.3% vs. 6.6%.

Compared to TMG/ALEM plus triple maintenance, steroid-sparing immunosuppressive regimens were associated with a lower risk of acute rejection in older adults: adjusted odds ratio 0.52 with TMG/ALEM plus steroid avoidance and 0.55 with IL2rAb plus steroid avoidance. Compared to the reference regimen, risk of death-censored graft failure was higher for older adults receiving tacrolimus plus antimetabolite avoidance, adjusted hazard ratio (HR) 1.78; mTORi-based immunosuppression, HR 2.14; and cyclosporine-based regimens, HR 1.78. In both age groups, mTORi- and cyclosporine-based regimens were associated with higher mortality: HR 1.24 and 1.37 in older recipients and 1.35 and 1.24 in younger recipients, respectively.

The new study provides insights into trends in immunosuppressive regimens for older adult kidney recipients, including associations with clinical outcomes. "These data support the move to further personalize the immunosuppressive regimen according to recipient and donor characteristics and limit exposure to more intense immunosuppressive regimens," the researchers write [Lentine KL, et al. Immunosuppression regimen use and outcomes in older and younger adult kidney transplant recipients: A National Registry analysis. *Transplantation*, published online ahead of print November 18, 2020. doi: 10.1097/TP.0000000000003547; https://journals.lww.com/transplantjournal/Abstract/9000/Immunosuppression_Regimen_Use_and_Outcomes_in.95464.aspx ]. ■



# Only one calcimimetic lowers and maintains key sHPT lab values with IV administration you control[1]

**Not an actual Parsabiv™ vial.**
**The displayed vial is for illustrative purposes only.**

Measure corrected serum calcium prior to initiation of Parsabiv™. Do not initiate in patients if the corrected serum calcium is less than the lower limit of normal. Monitor corrected serum calcium within 1 week after initiation or dose adjustment and every 4 weeks during treatment with Parsabiv™. Measure PTH 4 weeks after initiation or dose adjustment of Parsabiv™. Once the maintenance dose has been established, measure PTH per clinical practice.

## Indication

Parsabiv™ (etelcalcetide) is indicated for the treatment of secondary hyperparathyroidism (HPT) in adult patients with chronic kidney disease (CKD) on hemodialysis.

### Limitations of Use:

Parsabiv™ has not been studied in adult patients with parathyroid carcinoma, primary hyperparathyroidism, or with CKD who are not on hemodialysis and is not recommended for use in these populations.

## Important Safety Information

**Contraindication:** Parsabiv™ is contraindicated in patients with known hypersensitivity to etelcalcetide or any of its excipients. Hypersensitivity reactions, including pruritic rash, urticaria, and face edema, have occurred.

**Hypocalcemia:** Parsabiv™ lowers serum calcium and can lead to hypocalcemia, sometimes severe. Significant lowering of serum calcium can cause QT interval prolongation and ventricular arrhythmia. Patients with conditions that predispose to QT interval prolongation and ventricular arrhythmia may be at increased risk for QT interval prolongation and ventricular arrhythmias if they develop hypocalcemia due to Parsabiv™. Closely monitor corrected serum calcium and QT interval in patients at risk on Parsabiv™.

Significant reductions in corrected serum calcium may lower the threshold for seizures. Patients with a history of seizure disorder may be at increased risk for seizures if they develop hypocalcemia due to Parsabiv™. Monitor corrected serum calcium in patients with seizure disorders on Parsabiv™.

Concurrent administration of Parsabiv™ with another oral calcimimetic could result in severe, life-threatening hypocalcemia. Patients switching from cinacalcet to Parsabiv™ should discontinue cinacalcet for at least 7 days prior to initiating Parsabiv™. Closely monitor corrected serum calcium in patients receiving Parsabiv™ and concomitant therapies known to lower serum calcium.

**Worsening Heart Failure:** In Parsabiv™ clinical studies, cases of hypotension, congestive heart failure, and decreased myocardial performance have been reported. Closely monitor patients treated with Parsabiv™ for worsening signs and symptoms of heart failure.

**Upper Gastrointestinal Bleeding:** In clinical studies, 2 patients treated with Parsabiv™ in 1253 patient years of exposure had upper gastrointestinal (GI) bleeding at the time of death. The exact cause of GI bleeding in these patients is unknown and there were too few cases to determine whether these cases were related to Parsabiv™.

Patients with risk factors for upper GI bleeding, such as known gastritis, esophagitis, ulcers or severe vomiting, may be at increased risk for GI bleeding with Parsabiv™. Monitor patients for worsening of common Parsabiv™ GI adverse reactions and for signs and symptoms of GI bleeding and ulcerations during Parsabiv™ therapy.

**Adynamic Bone:** Adynamic bone may develop if PTH levels are chronically suppressed.

**Adverse Reactions:** In clinical trials of patients with secondary HPT comparing Parsabiv™ to placebo, the most common adverse reactions were blood calcium decreased (64% vs. 10%), muscle spasms (12% vs. 7%), diarrhea (11% vs. 9%), nausea (11% vs. 6%), vomiting (9% vs. 5%), headache (8% vs. 6%), hypocalcemia (7% vs. 0.2%), and paresthesia (6% vs. 1%).

***Please see Brief Summary of full Prescribing Information on adjacent page.***

IV = intravenous; sHPT = secondary hyperparathyroidism; PTH = parathyroid hormone; P = phosphate; cCa = corrected calcium.

**Reference: 1.** Parsabiv™ (etelcalcetide) prescribing information, Amgen.

Parsabiv™
(etelcalcetide) Injection for intravenous use
2.5mg/0.5mL | 5mg/1mL | 10mg/2mL



Visit **ParsabivHCP.com** for more information.

BRIEF SUMMARY OF PRESCRIBING INFORMATION

**Parsabiv™**
(etelcalcetide) Injection for intravenous use
2.5mg/0.5mL | 5mg/1mL | 10mg/2mL

**Please see package insert for full Prescribing Information.**

## INDICATIONS AND USAGE

PARSABIV is indicated for the treatment of secondary hyperparathyroidism (HPT) in adult patients with chronic kidney disease (CKD) on hemodialysis.

Limitations of Use:

PARSABIV has not been studied in adult patients with parathyroid carcinoma, primary hyperparathyroidism, or with chronic kidney disease who are not on hemodialysis and is not recommended for use in these populations.

## CONTRAINDICATIONS

### Hypersensitivity

PARSABIV is contraindicated in patients with known hypersensitivity to etelcalcetide or any of its excipients. Hypersensitivity reactions, including pruritic rash, urticaria, and face edema, have occurred with PARSABIV *[see Adverse Reactions (6.1) in PARSABIV full prescribing information]*.

## WARNINGS AND PRECAUTIONS

### Hypocalcemia

PARSABIV lowers serum calcium *[see Adverse Reactions (6.1) in PARSABIV full prescribing information]* and can lead to hypocalcemia, sometimes severe. Significant lowering of serum calcium can cause paresthesias, myalgias, muscle spasms, seizures, QT interval prolongation, and ventricular arrhythmia.

*QT Interval Prolongation and Ventricular Arrhythmia*

In the combined placebo-controlled studies, more patients treated with PARSABIV experienced a maximum increase from baseline of greater than 60 msec in the QTcF interval (0% placebo versus 1.2% PARSABIV). In these studies, the incidence of a maximum post-baseline predialysis QTcF > 500 msec in the placebo and PARSABIV groups was 1.9% and 4.8%, respectively *[see Adverse Reactions (6.1) in PARSABIV full prescribing information]*. Patients with congenital long QT syndrome, history of QT interval prolongation, family history of long QT syndrome or sudden cardiac death, and other conditions that predispose to QT interval prolongation and ventricular arrhythmia may be at increased risk for QT interval prolongation and ventricular arrhythmias if they develop hypocalcemia due to PARSABIV. Closely monitor corrected serum calcium and QT interval in patients at risk receiving PARSABIV.

*Seizures*

Significant reductions in corrected serum calcium may lower the threshold for seizures. Patients with a history of seizure disorder may be at increased risk for seizures if they develop hypocalcemia due to PARSABIV. Monitor corrected serum calcium in patients with seizure disorders receiving PARSABIV.

Concurrent administration of PARSABIV with another oral calcium-sensing receptor agonist could result in severe, life-threatening hypocalcemia. Patients switching from cinacalcet to PARSABIV should discontinue cinacalcet for at least 7 days prior to initiating PARSABIV *[see Dosage and Administration (2.4) in PARSABIV full prescribing information]*. Closely monitor corrected serum calcium in patients receiving PARSABIV and concomitant therapies known to lower serum calcium.

Measure corrected serum calcium prior to initiation of PARSABIV. Do not initiate in patients if the corrected serum calcium is less than the lower limit of normal. Monitor corrected serum calcium within 1 week after initiation or dose adjustment and every 4 weeks during treatment with PARSABIV *[see Dosage and Administration (2.2) in PARSABIV full prescribing information]*. Educate patients on the symptoms of hypocalcemia, and advise them to contact a healthcare provider if they occur.

If corrected serum calcium falls below the lower limit of normal or symptoms of hypocalcemia develop, start or increase calcium supplementation (including calcium, calcium-containing phosphate binders, and/or vitamin D sterols or increases in dialysate calcium concentration). PARSABIV dose reduction or discontinuation of PARSABIV may be necessary *[see Dosage and Administration (2.2) in PARSABIV full prescribing information]*.

### Worsening Heart Failure

In clinical studies with PARSABIV, cases of hypotension, congestive heart failure, and decreased myocardial performance have been reported. In clinical studies, heart failure requiring hospitalization occurred in 2% of PARSABIV-treated patients and 1% of placebo-treated patients. Reductions in corrected serum calcium may be associated with congestive heart failure, however, a causal relationship to PARSABIV could not be completely excluded. Closely monitor patients treated with PARSABIV for worsening signs and symptoms of heart failure.

### Upper Gastrointestinal Bleeding

In clinical studies, two patients treated with PARSABIV in 1253 patient-years of exposure had upper gastrointestinal (GI) bleeding noted at the time of death while no patient in the control groups in 384 patient-years of exposure had upper GI bleeding noted at the time of death. The exact cause of GI bleeding in these patients is unknown, and there were too few cases to determine whether these cases were related to PARSABIV.

Patients with risk factors for upper GI bleeding (such as known gastritis, esophagitis, ulcers, or severe vomiting) may be at increased risk for GI bleeding while receiving PARSABIV treatment. Monitor patients for worsening of common GI adverse reactions of nausea and vomiting associated with PARSABIV *[see Adverse Reactions (6.1) in PARSABIV full prescribing information]* and for signs and symptoms of GI bleeding and ulcerations during PARSABIV therapy. Promptly evaluate and treat any suspected GI bleeding.

### Adynamic Bone

Adynamic bone may develop if PTH levels are chronically suppressed. If PTH levels decrease below the recommended target range, the dose of vitamin D sterols and/or PARSABIV should be reduced or therapy discontinued. After discontinuation, resume therapy at a lower dose to maintain PTH levels in the target range *[see Dosage and Administration (2.1) in PARSABIV full prescribing information]*.

## ADVERSE REACTIONS

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

- Hypocalcemia *[see Warnings and Precautions (5.1) in PARSABIV full prescribing information]*
- Worsening Heart Failure *[see Warnings and Precautions (5.2) in PARSABIV full prescribing information]*
- Upper Gastrointestinal Bleeding *[see Warnings and Precautions (5.3) in PARSABIV full prescribing information]*
- Adynamic Bone *[see Warnings and Precautions (5.4) in PARSABIV full prescribing information]*

### 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 with rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

The data in Table 2 are derived from two placebo-controlled clinical studies in patients with chronic kidney disease and secondary hyperparathyroidism on hemodialysis. The data reflect exposure of 503 patients to PARSABIV with a mean duration of exposure to PARSABIV of 23.6 weeks. The mean age of patients was approximately 58 years, and 60% of the patients were male. Of the total patients, 67% were Caucasian, 28% were Black or African American, 2.6% were Asian, 1.2% were Native Hawaiian or Other Pacific Islander, and 1.6% were categorized as Other.

Table 2 shows common adverse reactions associated with the use of PARSABIV in the pool of placebo-controlled studies. These adverse reactions occurred more commonly on PARSABIV than on placebo and were reported in at least 5% of patients treated with PARSABIV.

**Table 2: Adverse Reactions Reported in ≥ 5% of PARSABIV-Treated Patients**

| Adverse Reaction* | Placebo (N = 513) | PARSABIV (N = 503) |
|---|---|---|
| Blood calcium decreased[a] | 10% | 64% |
| Muscle spasms | 7% | 12% |
| Diarrhea | 9% | 11% |
| Nausea | 6% | 11% |
| Vomiting | 5% | 9% |
| Headache | 6% | 8% |
| Hypocalcemia[b] | 0.2% | 7% |
| Paresthesia[c] | 1% | 6% |

*Included adverse reactions reported with at least 1% greater incidence in the PARSABIV group compared to the placebo group

[a] Asymptomatic reductions in calcium below 7.5 mg/dL or clinically significant asymptomatic reductions in corrected serum calcium between 7.5 and < 8.3 mg/dL (that required medical management)

[b] Symptomatic reductions in corrected serum calcium < 8.3 mg/dL

[c] Paresthesia includes preferred terms of paresthesia and hypoesthesia

Other adverse reactions associated with the use of PARSABIV but reported in < 5% of patients in the PARSABIV group in the two placebo-controlled clinical studies were:

- Hyperkalemia: 3% and 4% for placebo and PARSABIV, respectively.
- Hospitalization for Heart Failure: 1% and 2% for placebo and PARSABIV, respectively.
- Myalgia: 0.2% and 2% for placebo and PARSABIV, respectively.
- Hypophosphatemia: 0.2% and 1% for placebo and PARSABIV, respectively.

Description of Selected Adverse Reactions

*Hypocalcemia*

In the combined placebo-controlled studies, a higher proportion of patients on PARSABIV developed at least one corrected serum calcium value below 7.0 mg/dL (7.6% PARSABIV, 3.1% placebo), below 7.5 mg/dL (27% PARSABIV, 5.5% placebo), and below 8.3 mg/dL (79% PARSABIV, 19% placebo). In the combined placebo-controlled studies, 1% of patients in the PARSABIV group and 0% of patients in the placebo group discontinued treatment due to an adverse reaction attributed to a low corrected serum calcium.

*Hypophosphatemia*

In the combined placebo-controlled studies, 18% of patients treated with PARSABIV and 8.2% of patients treated with placebo had at least one measured phosphorus level below the lower normal limit (i.e., 2.2 mg/dL).

*QTc Interval Prolongation Secondary to Hypocalcemia*

In the combined placebo-controlled studies, more patients treated with PARSABIV experienced a maximum increase from baseline of greater than 60 msec in the QTcF interval (0% placebo versus 1.2% PARSABIV). The patient incidence of maximum post-baseline predialysis QTcF > 500 msec in the placebo and PARSABIV groups was 1.9% and 4.8%, respectively.

*Hypersensitivity*

In the combined placebo-controlled studies, the subject incidence of adverse reactions potentially related to hypersensitivity was 4.4% in the PARSABIV group and 3.7% in the placebo group. Hypersensitivity reactions in the PARSABIV group were pruritic rash, urticaria, and face edema.

**Immunogenicity**

As with all peptide therapeutics, there is potential for immunogenicity. The detection of anti-drug binding antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody positivity in an assay may be influenced by several factors, including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to etelcalcetide with the incidence of antibodies to other products may be misleading.

In clinical studies, 7.1% (71 out of 995) of patients with secondary hyperparathyroidism treated with PARSABIV for up to 6 months tested positive for binding anti-etelcalcetide antibodies. Fifty-seven out of 71 had pre-existing anti-etelcalcetide antibodies.

No evidence of altered pharmacokinetic profile, clinical response, or safety profile was associated with pre-existing or developing anti-etelcalcetide antibodies. If formation of anti-etelcalcetide binding antibodies with a clinically significant effect is suspected, contact Amgen at 1-800-77-AMGEN (1-800-772-6436) to discuss antibody testing.

## USE IN SPECIFIC POPULATIONS

**Pregnancy**

Risk Summary

There are no available data on the use of PARSABIV in pregnant women. In animal reproduction studies, effects were seen at doses associated with maternal toxicity that included hypocalcemia. In a pre- and post-natal study in rats administered etelcalcetide during organogenesis through delivery and weaning, there was a slight increase in perinatal pup mortality, delay in parturition, and transient effects on pup growth at exposures 1.8 times the human exposure for the clinical dose of 15 mg three times per week. There was no effect on sexual maturation, neurobehavioral, or reproductive function in the rat offspring. In embryo-fetal studies, when rats and rabbits were administered etelcalcetide during organogenesis, reduced fetal growth was observed at exposures 2.7 and 7 times exposures for the clinical dose, respectively.

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

Data

*Animal Data*

There were no effects on embryo-fetal development in Sprague-Dawley rats when etelcalcetide was dosed at 0.75, 1.5, and 3 mg/kg/day by the intravenous route during organogenesis (pre-mating to gestation day 17) at exposures up to 1.8 times human exposures at the clinical dose of 15 mg three times per week based on AUC. No effects on embryo-fetal development were observed in New Zealand White rabbits at doses of etelcalcetide of 0.375, 0.75, and 1.5 mg/kg by the intravenous route (gestation day 7 to 19), representing up to 4.3 times human exposures based on AUC. In separate studies at higher doses of 4.5 mg/kg in rats (gestation days 6 to 17) and 2.25 mg/kg in rabbits (gestation days 7 to 20), representing 2.7 and 7 fold clinical exposures, respectively, there was reduced fetal growth associated with maternal toxicities of hypocalcemia, tremoring, and reductions in body weight and food consumption.

In a pre- and post-natal development study in Sprague-Dawley rats administered etelcalcetide at 0.75, 1.5, and 3 mg/kg/day by the intravenous route (gestation day 7 to lactation day 20), there was a slight increase in perinatal pup mortality, delay in parturition, and transient reductions in post-natal growth at 3 mg/kg/day (representing 1.8-fold human exposures at the clinical dose of 15 mg three times per week based on AUC), associated with maternal toxicities of hypocalcemia, tremoring, and reductions in body weight and food consumption. There were no effects on sexual maturation, neurobehavioral, or reproductive function at up to 3 mg/kg/day, representing exposures up to 1.8-fold human exposure based on AUC.

**Lactation**

Risk Summary

There are no data regarding the presence of PARSABIV in human milk or effects on the breastfed infant or on milk production. Studies in rats showed [$^{14}$C]-etelcalcetide was present in the milk at concentrations similar to plasma. Because of the potential for PARSABIV to cause adverse effects in breastfed infants including hypocalcemia, advise women that use of PARSABIV is not recommended while breastfeeding.

Data

Presence in milk was assessed following a single intravenous dose of [$^{14}$C]-etelcalcetide in lactating rats at maternal exposures similar to the exposure at the human clinical dose of 15 mg three times per week. [$^{14}$C]-etelcalcetide-derived radioactivity was present in milk at levels similar to plasma.

**Pediatric Use**

The safety and efficacy of PARSABIV have not been established in pediatric patients.

**Geriatric Use**

Of the 503 patients in placebo-controlled studies who received PARSABIV, 177 patients (35.2%) were ≥ 65 years old and 72 patients (14%) were ≥ 75 years old.

No clinically significant differences in safety or efficacy were observed between patients ≥ 65 years and younger patients (≥ 18 and < 65 years old). No differences in plasma concentrations of etelcalcetide were observed between patients ≥ 65 years and younger patients (≥ 18 and < 65 years old).

## OVERDOSAGE

There is no clinical experience with PARSABIV overdosage. Overdosage of PARSABIV may lead to hypocalcemia with or without clinical symptoms and may require treatment. Although PARSABIV is cleared by dialysis, hemodialysis has not been studied as a treatment for PARSABIV overdosage. In the event of overdosage, corrected serum calcium should be checked and patients should be monitored for symptoms of hypocalcemia, and appropriate measures should be taken *[see Warnings and Precautions (5.1) in PARSABIV full prescribing information]*.

AMGEN®

PARSABIV™ (etelcalcetide)

**Manufactured for:**
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Patent: http://pat.amgen.com/Parsabiv/

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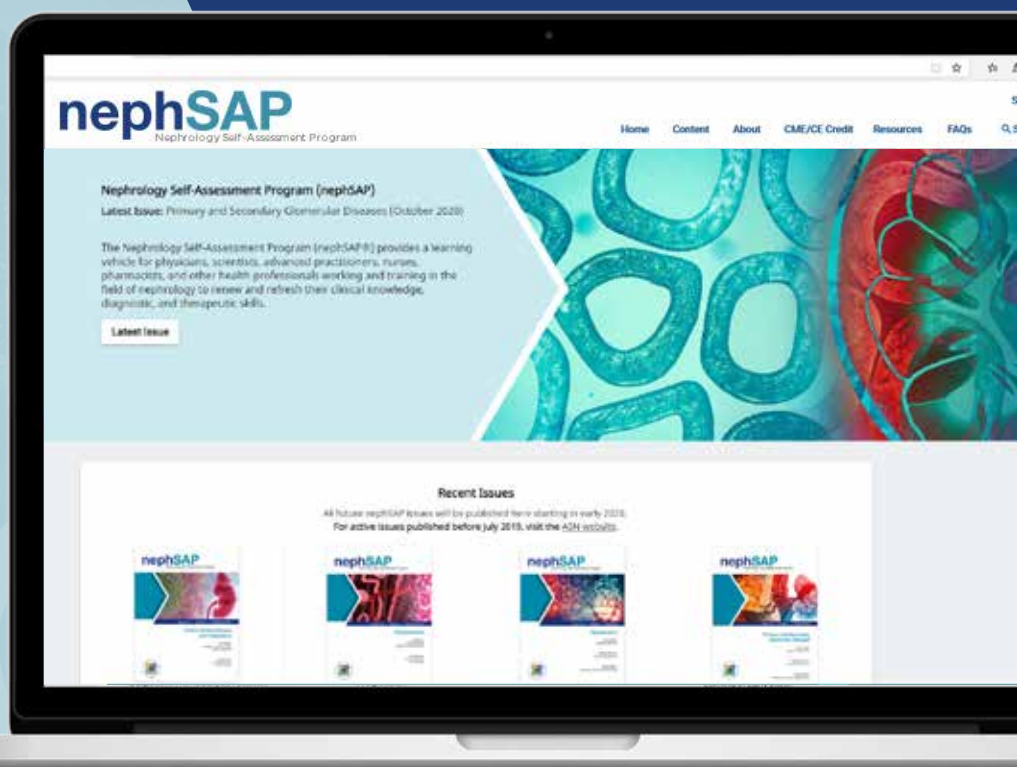


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**Planned Issues, Volume 20 (2021)**

1. End-Stage Kidney Disease and Dialysis
2. Electrolytes and Acid-Base Disorders
3. Acute Kidney Injury and Critical Care Nephrology
4. Chronic Kidney Disease and Progression
5. Transplantation

ASN
American Society of Nephrology

Fellows First

# Back to the Future 2020–2021

## The Nephrology Fellows Edition

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

*Visual Abstract by Tiffany Truong*

For many years to come, just thinking of the year 2020 will put most of us into sympathetic overdrive. Coronavirus infectious disease 2019 (COVID-19) has dominated every part of our practice and continues to do so as we enter 2021. But if we track the arc of time, each tumultuous period has also spurred strides of innovation. Despite the odds, we have witnessed and continue to look forward to new landmark trials in nephrology that will have a lasting impact on our clinical practice. As our foray into the inaugural Fellows First column, we recap highlights of 2020 and anticipate what compelling topics will characterize 2021, from the rear view mirror and lens of a discerning nephrology fellow.

## 2020

### COVID-19

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infections have led to high rates of acute kidney injury (AKI; up to 60% of patients in ICU) (1). Moreover, patients with chronic kidney disease (CKD) or end-stage kidney disease (ESKD) and kidney transplant recipients are more vulnerable to COVID-19 and its associated complications. The surge of new patients requiring kidney replacement therapy (KRT) has led to inpatient shortages of staffing, hemodialysis (HD) machines, and dialysis fluid, whereas outpatient HD centers have had to grapple with strategies for infection control among vulnerable patients with routine exposure to healthcare settings. These challenges have been driving factors to increase the use of acute peritoneal dialysis (PD) and hybrid therapies, such as prolonged intermittent KRT (PIKRT), and to develop innovative protocols, such as the generation of on-site continuous renal replacement therapy (CRRT) fluid (2). Nephrologists have also led investigative conversations, as we look to answer if angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) increase or decrease the risk or clinical course of COVID-19 and to solve the conundrum of if the virus does actually "infect" the kidney.

### SGLT2 inhibitors

Any article recapping 2020 without mentioning sodium glucose cotransporter-2 inhibitors (SGLT2i) would be incomplete. Nephrology has waited about two decades for an upgrade in the armamentarium to slow the progression of CKD. Canagliflozin started the revolution when it was featured in Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE), which focused primarily on kidney outcomes in patients with type 2 diabetes, as opposed to prior studies centered on cardiovascular outcomes. The relative risk of the kidney-specific composite was lower by 34% with canagliflozin (3). SGLT-2i did not stop there and in 2020, made their march toward non-diabetic kidney disease (non-DKD) with Dapagliflozin in CKD (DAPA-CKD). Even including patients without diabetes, dapagliflozin demonstrated a more than 40% reduction in a sustained decline in the estimated glomerular filtration rate (eGFR) of at least 50%, ESKD, or death from kidney causes (4). There is more to come in 2021, as we will discuss in the next section. For now, we can go beyond offering ACE inhibitors and ARBs to our patients.

### Finerenone

Just when we thought we had enough to rejoice about regarding therapeutics in CKD, finerenone entered the fray. A NephJC commentary put it aptly: "Can finerenone fiddle the forgotten A of the [renin-angiotensin-aldosterone system] RAAS string?" Finerenone, a non-steroidal mineralocorticoid antagonist that is more potent and selective in nature than spironolactone and eplerenone, has previously demonstrated greater protection from kidney and cardiac events, along with improved structural cardiac remodeling in animal studies (5). Mechanistically, it decreases macrophage expression of the pro-fibrotic genes—tumor growth factor-β1 and plasminogen activator inhibitor-1—and increases the expression of anti-fibrotic genes (6). This translated into the success of the Finerenone in Reducing Kidney Failure and Disease Progression in DKD (FIDELIO-DKD) trial, which demonstrated an 18% reduction in primary composite outcome (decrease of at least 40% in the eGFR from baseline or death from kidney causes). One of the primary concerns of hyperkalemia associated with use will remain and hopefully can be further addressed in 2021.

### PEXIVAS

Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) continued to see advances in 2020. Induction and maintenance regimens have attained a nuanced approach as a result of multiple trials, but optimal use of steroids and plasmapheresis [plasma exchange (PLEX)] still required further nuance in practice (7). PEXIVAS (PLEX and Glucocorticoids for Treatment of AAV) partially solved this quandary by showing non-inferiority with a lower-dose steroid regimen. However, PLEX did not demonstrate benefit with respect to the development of ESKD, but a few caveats need to be discussed:

1. Kidney biopsy was not an entry criterion for the study. Therefore, we cannot truly assess acuity vs. chronicity of disease to ascertain who would benefit from PLEX.
2. A subgroup of patients with non-severe and severe pulmonary hemorrhage did benefit from PLEX, albeit the benefit was not statistically significant. This was likely because relatively few patients with severe pulmonary hemorrhage were enrolled, a population for which many physicians traditionally opt to use PLEX.

Although an argument could be made not to use PLEX in most patients with mild to moderate AAV disease, it may still be prudent to use it with severe disease and/or those with pulmonary hemorrhage. The jury is still out on the latter population and will need more research.

### Transplantation

Given that our attention was crowded by so much in 2020, a few good pivotal developments did fly under the radar, especially in the realm of transplantation. Generation of immune tolerance continues to be the Holy Grail in transplantation. Since the discovery of tolerance in 1945 in the freemartin cattle (8), various strategies for tolerance induction have been attempted with no clinically translatable success and frequently associated with graft-versus-host disease (GVHD). In 2020, a phase 1 trial (n = 10) was successful in demonstrating not only safety but also efficacy with the injection of modified immune cells (leukapheresis-derived donor monocytes treated with mitomycin C). These cells developed features of immature dendritic cells and resulted in profound suppression of the T cell response, with ensuing development of durable immune tolerance (9). It remains to be seen how phase 2 trials (n = 200) of this strategy will progress, but one thing is for sure: the search for the Holy Grail could be getting closer.

## 2021

Although 2020 was a memorable year, many exciting topics remain on the horizon in 2021. Whereas some subjects will build on the advancements of 2020, some will be new in their own right. Following are five dominant topics that fellows are looking forward to as we move into the new year.

### Race and eGFR

We learned in medical school that there were various creatinine-based formulas used to estimate GFR and that some of them [namely, the Modification of Diet in Renal Disease (MDRD) (10) and CKD-Epidemiology Collaboration (CKD-EPI) (11) equations] included a race coefficient. With the use of this coefficient, Black and White patients with otherwise similar characteristics would receive different eGFR results, with Black patients having up to a 20% higher eGFR.

But if race is a cultural, not scientific, construct, based largely on phenotypic features rather than genetic differences, how can we in the nephrology community base some of our most important equations on it? Furthermore, where does this equation stand in an increasingly multiracial world, where our patients are diverse and often cannot be placed into a binary "Black or White" category? Is it possible that these equations have been underestimating the severity of kidney disease in our Black patients, thus delaying valuable care and possibly even preventing patients from getting listed on the kidney transplant list? It was only over the past few years that medical students and other trainees from around the country started to ask these questions, forcing us all to think critically about this important issue. This has led to a number of institutions removing the coefficient, in addition to the National Kidney Foundation (NKF) and American Society of Nephrology (ASN) forming a joint task force (12) to address the issue of race in eGFR equations. The task force aims to issue initial recommendations by January 2021, and we look forward to continued discussions both from the task force and within our own institutions from around the country on this critically important topic.

### SGLT2i

2020 was an incredibly exciting year for SGLT2i, with the publication of DAPA-CKD in October opening the door for use of this medication class to improve outcomes in patients with CKD and importantly without diabetes (4). We now eagerly await the results of the EMPA-KIDNEY (The Study of Heart and Kidney Protection with Empagliflozin) trial, which will be the largest trial to date to look at the use of SGLT2i in an entirely non-diabetic population of patients with CKD and albuminuria at risk of progression. Importantly, this trial is enrolling patients with eGFR as low as 20 mL/min/1.73 $m^2$, which is the lowest eGFR to be included in an SGLT2i trial to date (13). Although the trial is not scheduled to be completed until October 2022, we look forward to seeing what promising results may be presented in 2021. Furthermore, we are excited to incorporate SGLT2i into our clinical practices, providing the most impactful, new therapeutic option to our patients with CKD since RAAS inhibitors.

### Finerenone

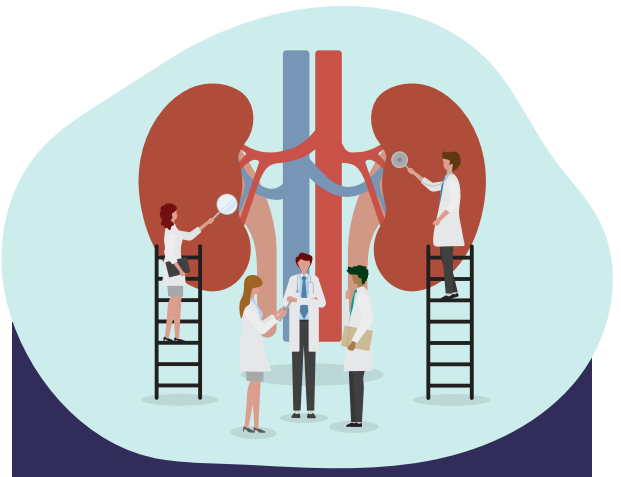
Because we're on the topic of novel therapeutics, it seems only appropriate to discuss finerenone, the selective, nonsteroidal mineralocorticoid antagonist that resulted in lower risk of DKD progression (albeit with a nearly twofold increase in risk of hyperkalemia) when compared to placebo in adult patients with type 2 diabetes, CKD, and proteinuria in the recently published FIDELIO-DKD trial (14). In February 2021, we expect the completion of the long-awaited Finerenone in Reducing Cardiovascular Mortality and Morbidity in DKD (FIGARO-DKD) trial, also comparing finerenone to placebo in patients with DKD. Having enrolled >7000 participants to date, this multi-center, international trial will be larger than FIDELIO-DKD. Although the trial will look primarily at cardiovascular endpoints, important kidney secondary outcomes will be examined as well (15). We look forward to comparing and contrasting the results of this important trial to FIDELIO-DKD and making evidence-based decisions as to whether we may have yet another valuable medication in our arsenal to delay the progression of DKD.

### Home dialysis modalities

As nephrologists, we all recognize the importance of our patients maintaining their quality of life once they have to begin dialysis. Unfortunately, >85% of patients in the United States still initiate dialysis in-center (16), meaning they often have to go on disability, potentially lose their job, and are forced to commute at least thrice weekly for their life-saving therapy. Contrast this to peritoneal dialysis (PD) and home HD, in which patients are trained to safely perform dialysis in the comfort of their own home, allowing for a more normal lifestyle. It is no surprise then that in a 2010 survey on the topic, >90% of nephrologists stated they would choose either home HD or PD as their initial KRT modality while awaiting a transplant (17). Perhaps the only shocking thing is that it took until 2019 and the issuance of an executive order to get the ball rolling in prioritizing home dialysis modalities for our patients and making sure that payment models would reflect the importance of this order (18). Now with the Centers for Medicare & Medicaid Services (CMS) set to begin reimbursing more for Medicare beneficiaries using home modalities in January 2021 (19), we hope to see many more conversations between nephrologists and patients needing to start dialysis, emphasizing the benefits of home modalities and reflecting the reality of what most nephrologists would want for themselves.

### COVID-19

How could we finish an "anticipated topics" list without talking about COVID-19? The pandemic has had profound effects in both our personal and professional lives. Conflicting information has come out about the potential interaction between inhibitors of the renin-angiotensin system and whether they may be harmful or helpful in patients with COVID-19 (20). We have seen high rates of AKI among patients with COVID-19 and higher rates of comorbidity and death among those patients (21). Of those patients with AKI and COVID-19 who survived their illness but were discharged from the hospital requiring KRT, it is still unknown how many of these patients will end up developing ESKD. In patients with ESKD who are hospitalized with COVID-19, adjusted rates of in-hospital death and prolonged length of stay are significantly higher than in patients without ESKD (22). Furthermore, adjustments have had to be made to outpatient dialysis facilities, often opening up separate shifts dedicated to patients with COVID-19.



**Despite the odds, we have witnessed and continue to look forward to new landmark trials in nephrology that will have a lasting impact on our clinical practice.**

In addition to the impact of COVID-19 on our patients and clinical practice, nephrology fellows have quickly adapted to changes in academic medicine. Telemedicine has been incorporated in outpatient dialysis rounds, inpatient rounds, clinics, as well as teleconferences held within institutions and internationally. How we interact with our patients as well as our colleagues, mentors, and nephrology community has changed and so too will our clinical practice and academic discourse. Meanwhile, many of us remain on the front lines and face continued fears of infectious exposure or the threat that a community's medical resources may be overwhelmed during a surge of cases. Needless to say, we are all ready for some glimmer of hope with the recent news of encouraging results in multiple phase III SARS-CoV-2 vaccine trials. In the meantime, we look forward to the ASN COVID-19 Fellows Only Roundtable to be held virtually on January 13, which will give fellows the chance to share our fears, uncertainties, and stressors, as well as anything else we want to discuss surrounding COVID-19, in a safe environment.

*Continued on page 14* >

## Back to the Future 2020–2021

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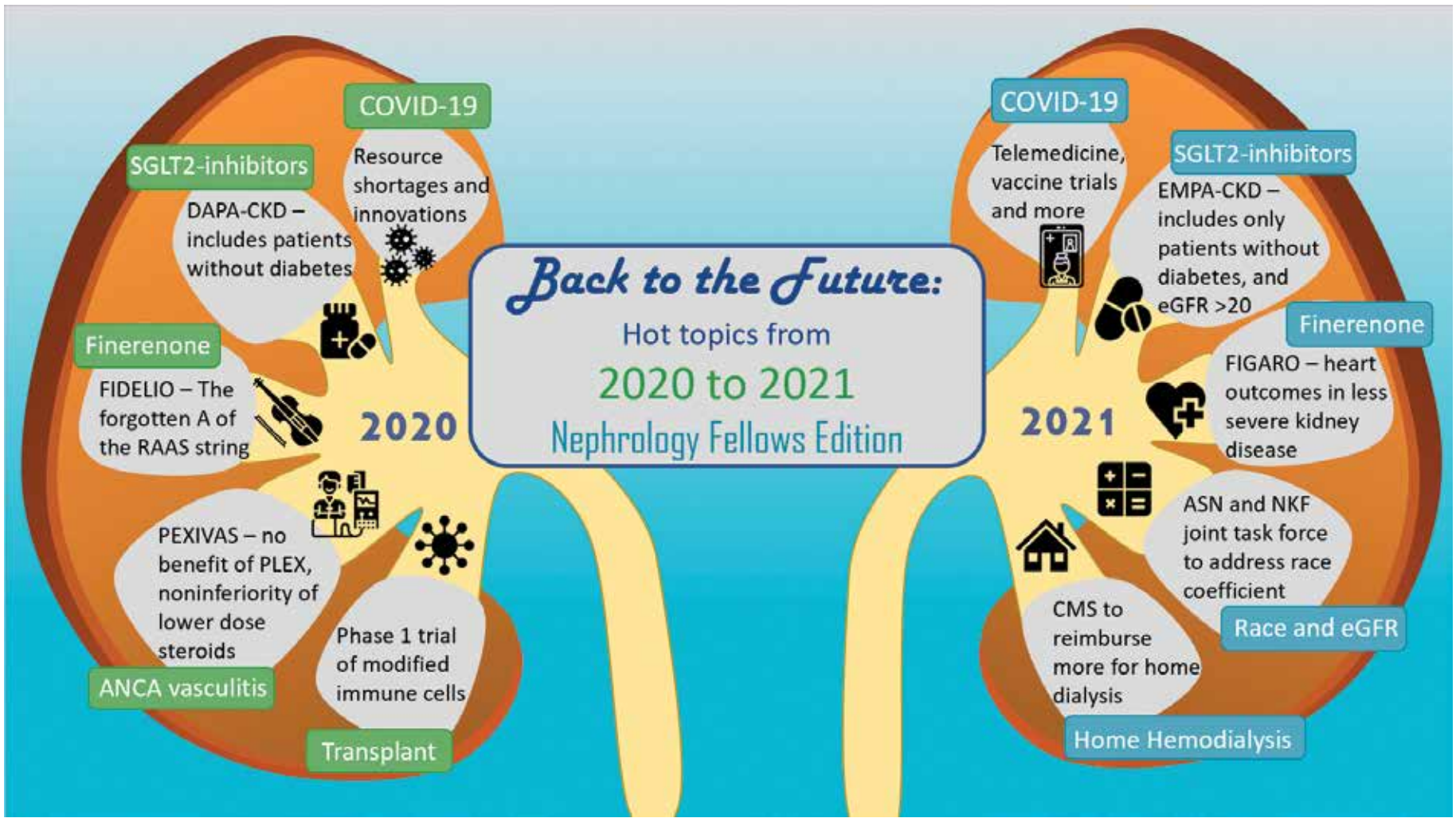


So many important things happened in 2020 in the world of nephrology, and we are excited to see what 2021 will bring us. One thing is for sure: as fellows, we will be intricately involved in many of the things that will shape the future of nephrology. As we begin a new year at *Kidney News*, we can't wait to put "fellows first" as we listen to feedback, glean valuable insight, and highlight stories from nephrology trainees around the world. ■

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# Nephrology in Europe in 2021:
## Modifying the Programs for Home-Based Dialysis and Telemedicine in Nephrology

By Maria Jose Soler Romeo

The year 2020 brought a pandemic that prompted the kidney community to modify daily clinical practice to avoid severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection in our patients with advanced chronic kidney disease (CKD). Advanced CKD and solid organ transplantation have been identified as risk factors for mortality in patients with coronavirus infectious disease 2019 (COVID-19) (1). Moreover, patients with end-stage kidney disease (ESKD) were also identified to be at high risk of mortality compared to the general population (2).

Amid the pandemic, how do we communicate with our high-risk patients? How do we take care of patients with ESKD and patients with kidney transplants in a safe manner? New technologies have come out and developments have occurred in the field of telemedicine. For these reasons, European nephrologists modified their clinical practice in two ways: 1) increased the use of home-based dialysis modalities, and 2) implemented telemedicine in outpatient nephrology care. Similar processes were employed in other parts of the world (3, 4).

In my opinion, 2021 is a year of positive changes, and I foresee many modifications in the treatment and follow-up of patients with kidney diseases. In the past, most patients in Europe who needed kidney replacement therapy were treated in a dialysis facility either outside of or inside the hospital. Home-based dialysis modalities were mainly reserved for patients in rural areas with remote access to referral hospitals. In 2021, it is expected that home-based dialysis—namely, home hemodialysis and peritoneal dialysis—will sharply increase.

In addition, in 2021, the types of telemedicine currently implemented in non-nephrology specialties, such as critical care, neurology, and cardiology, will be expanded to nephrology. Patients with CKD will have the possibility to be in a tele-nephrology program for follow-up visits, including blood pressure, weight, and edema, among others. Mobile device-based applications will continue to be developed in nephrology, and our patients will only need a smartphone with an application as easy as "WhatsApp" to contact their nephrology team.

It is expected that the aforementioned changes, such as implementation of tele-nephrology programs, nephrology follow-up applications, and an increase in the use of home-based dialysis modalities in nephrology, will be implemented and will see expanded use in 2021 (Table 1). These developments may help patients avoid unneeded visits to medical centers. ■

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**Table 1. Nephrology care in the pre- and post-COVID-19 pandemic era**

| Pre-COVID-19 | Post-COVID-19 |
|---|---|
| • Majority of ESKD patients in hospital or center-based dialysis<br>• Few home-based dialysis modalities<br>• Multiple outpatient clinic visits | • Increase in home-based dialysis modalities<br>• Development of tele-nephrology<br>• Follow-up via apps' development and implementation<br>• Decrease in outpatient clinic visits |

# Trends in Reimbursement in Nephrology

By Katie Kwon

Compensation for physicians in nephrology has long lagged behind that for other more procedure-based medical specialties. The past few years have shown signs of hope in addressing the compensation gap. The Advancing American Kidney Health initiative introduced more value-based payment models, both voluntary and mandatory. Up to half of the 10,000 nephrologists in the country will be participating in these programs, which seek to rein in costs while improving patient outcomes. A third have been enrolled in the mandatory model, whereas the optional Kidney Care Choices/Comprehensive Kidney Care Contracting (KCC/CKCC) models have attracted applicants representing roughly another 20% of the workforce (1). The primary focus is on delaying progression to end-stage kidney disease (ESKD) and increasing the rates of home dialysis and transplantation. Practices that are successful in achieving these laudable goals will be financially rewarded, and those that fall below performance benchmarks will be penalized.

The continued focus is on payment for specific outcomes, rather than reimbursing episodes of care. Population health management tools are critically important in this endeavor. Electronic health records (EHRs) are currently optimized for billing rather than for patient care, and integration among different systems remains fragmented and incomplete. It remains to be seen whether the offered financial incentives will be enough to tempt practices to invest the significant sums required to upgrade their EHR capabilities. EHR costs will continue to be a barrier to improved delivery of care for the foreseeable future. Dialysis corporations are included in the risks and benefits of several of the payment models, and as they provide the EHRs for their units we may see better alignment of interests toward EHR improvement.

The payment models are restricted to patients with traditional Medicare. Starting in 2021, patients with ESKD will be eligible to enroll in Medicare Advantage plans. One unintended consequence of these intersecting policies is that practices in the mandatory model can reduce their exposure by steering patients toward Medicare Advantage programs. Although patients may benefit with lower out-of-pocket expenses, they may be restricted in their choice of nephrologists, given the plans' restricted physician networks.

The nephrology community should rejoice with the new relative value unit (RVU) update, which increased the value of most of the commonly billed codes for inpatient and outpatient dialysis. It remains to be seen how much the RVU increases will translate into improved nephrology reimbursements, however. The conversion factor for RVUs (the multiplier that translates RVUs into dollar amounts) may be decreased to maintain budget neutrality (2). The net effect may be a rebalancing of the value of cognitive work compared with procedures but limited growth in compensation.

As the new administration takes charge in 2021, we hope they also continue the new focus on improving payment models for nephrologists and improved care models for our patients. ■

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# Four Nephrology-Related Policies to Watch in 2021

By Annika Khine and Eugene Lin

On the heels of an historic election with record voter turnout comes no shortage of kidney policies. While coronavirus infectious disease 2019 (COVID-19) remains the priority, developments in kidney policies will continue unabated, including two payment models, new Medicare Advantage rules, and reductions in barriers to kidney transplantation.

## COVID-19

During the pandemic, the kidney community led the nation in innovating infection control measures, especially in dialysis facilities. Tragically, patients on dialysis still experienced a disproportionate share of hospitalizations and mortality. One silver lining is that peritoneal dialysis was associated with fewer hospitalizations (1), which may provide tailwinds for efforts to increase home dialysis use. Promising vaccine trials are a big step, although production and distribution remain a daunting task.

## The ESRD Treatment Choices (ETC) and Kidney Care Choices (KCC) models

Medicare's ESRD Treatment Choices (ETC) and Kidney Care Choices (KCC) models formally start in 2021 (2). These models incentivize home dialysis use, kidney transplantation, and pre-dialysis care coordination (Figure 1). Special attention goes to the ETC, which has randomly assigned 30% of nephrologists and dialysis facilities in the United States to mandatory participation (https://innovation.cms.gov/media/document/etc-hrr-report lists the mandatory geographic areas) (3). Anecdotal feedback from providers and patients is anticipated by year's end.

## Medicare Advantage

Prior to January 2021, patients on dialysis could only hold Medicare Advantage if they enrolled *prior to developing* end-stage kidney disease (ESKD). Starting in January 2021, the 21st Century Cures Act will allow patients on dialysis to *newly enroll* in Medicare Advantage plans (4). Experts expect a 50% increase in Medicare Advantage enrollment by 2022 and 100% by 2026 (5, 6). Small studies suggest that Medicare Advantage might effectively promote chronic disease management and improved kidney disease outcomes (7). However, the consolidated dialysis industry may result in large increases in Medicare Advantage prices and limited benefits for patients.

## Kidney transplant

The Living Donor Protection Act, which would protect living organ donors from insurance discrimination and extend Family and Medical Leave Act job protection during the post-donation period, will again make the rounds on the Hill and may see a vote. Separately, we might see an uptick in the availability of deceased donor kidneys owing to the finalization of stricter outcome measures for organ procurement organizations (i.e., assessing successful donation and transplantation rates), even though formal enforcement begins in 2022 (8).

We remain optimistic that 2021's myriad kidney policies will help the kidney community better coordinate high-quality care for patients with kidney diseases. ■

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**Figure 1. Comparison between payment models**


Sources : Centers for Medicare & Medicaid Services. ESRD Treatment Choices (ETC) Model. https://innovation.cms.gov/innovation-models/esrd-treatment-choices-model. Accessed November 24, 2020.
Centers for Medicare & Medicaid Services. Kidney Care Choices Model. https://innovation.cms.gov/innovation-models/kidney-care-choices-kcc-model. Accessed November 24, 2020.
Infographic generated using Piktochart.

# 2021: YEAR OF THE GLOMERULUS

By Kenar D. Jhaveri

**Kenar D. Jhaveri, MD**

The past decade has seen continual progress in the diagnosis and treatment of primary glomerular diseases. The discovery of disease-causing autoantibodies in membranous nephropathy (MN) and mutations in podocyte genes in focal segmental glomerulosclerosis (FSGS), together with the availability of modern immunosuppressive drugs, has provided new avenues for individualized therapy, and several important studies have been published in the past several years.

Whereas antibodies to the phospholipase A2 receptor (PLA2R) were discovered over 10 years ago and have entered mainstream practice, several novel antigens surfaced in the nephrology literature in 2020 (Figure 1). With the advent of novel autoantibodies like neural epidermal growth factor-like 1 (NELL-1) and exostosin 1 and 2 (EXT1 and EXT2), the science of MN is advancing (1, 2). In 2021, perhaps we will be better able to define the exact MN subtype and decide on appropriate workup (cancer screening/autoimmune workup) and individualized therapy.

While we are figuring out the type of autoantibodies, the treatment of MN is still in flux. The MENTOR trial (3) paved the road for rituximab to take the lead as a first-line therapy. However, the STARMEN trial, published in 2020 (4), is putting cyclophosphamide back in the spotlight. This trial compared the criterion standard used for decades (cyclophosphamide and alternating corticosteroids for 6 months) with tacrolimus as a bridge to rituximab. Complete remission at 24 months occurred in 26 patients (60%) in the corticosteroid-cyclophosphamide group and in 11 patients (26%) in the tacrolimus-rituximab group. Anti-PLA2R titers showed a significant decrease in both groups, but the proportion of anti-PLA2R-positive patients who achieved immunologic response (depletion of anti-PLA2R antibodies) was significantly higher at 3 and 6 months in the cyclophosphamide-corticosteroid group (77% and 92%, respectively) in comparison with the tacrolimus-rituximab group (45% and 70%, respectively). Relapses occurred in one patient in the cyclophosphamide-corticosteroid group and three patients in the tacrolimus-rituximab group. Serious adverse events were similar in both groups.

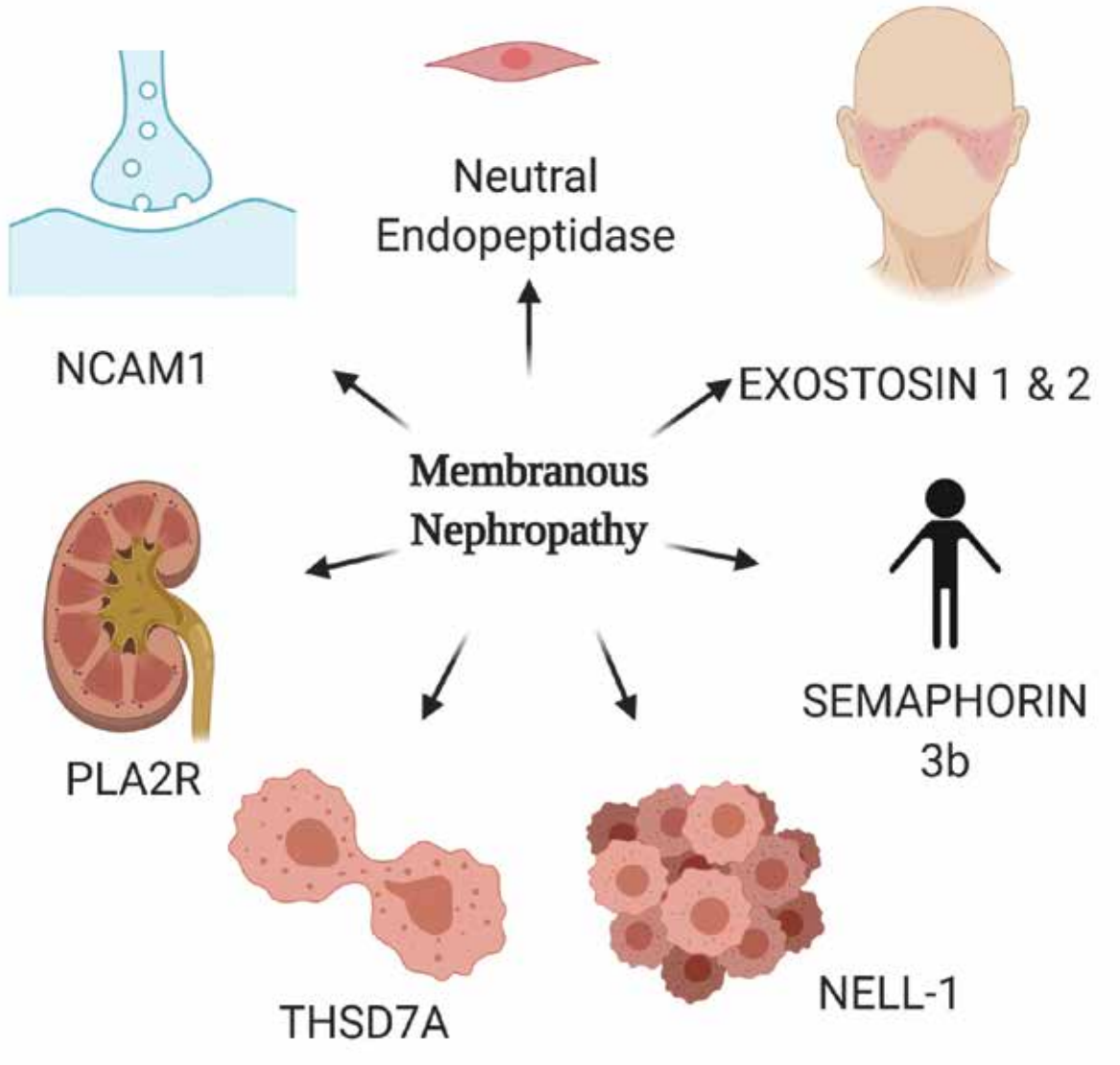
A critique of the STARMEN trial was the use of only one dose of rituximab with no monitoring of B cells. Another trial that is yet to be published is the RI-CYCLO trial (presented as a late-breaking poster at Kidney Week 2020), which also compared rituximab with cyclophosphamide and corticosteroids (5). The trial showed no difference in benefit or harm in the two arms, the cyclophosphamide-corticosteroid regimen induced remission earlier, and adverse events were equal in both arms. Will there ever be a superiority trial? That is less likely according to the authors because recruitment in such trials is usually slow. Will the older agent return as the top choice for nephrologists treating MN? Let's await the publication of RI-CYCLO to see where the regimens will fall in the treatment choices for MN: rituximab, cyclophosphamide-glucocorticoids, or calcineurin inhibitors.

Novel therapies for lupus nephritis are emerging rapidly. The BLISS trial showed that patients with lupus nephritis who received belimumab (B cell activating factor inhibitor) plus standard therapy were significantly more likely to have a kidney response at 2 years than were those given placebo plus standard care (6). The kidney response was the primary endpoint: the ratio of urinary protein to creatinine of ≤0.7, an estimated glomerular filtration rate (GFR) that was no worse than 20% below the value before the kidney flare (preflare value) or ≥60 mL/ min per 1.73 $m^2$ of body surface area, and no use of rescue therapy. At week 104, 43% of patients assigned to the belimumab group had a primary efficacy kidney response compared with 32% of those in the placebo group. The majority of patients had class III or IV nephritis, most were Asian; only 14% were Black, and almost 90% were women. By week 24, more patients in the belimumab group had a primary efficacy kidney response, and by 1 year, 47% met this endpoint compared with 35% of the placebo group (odds ratio [OR], 1.6; 95% confidence interval [CI], 1.1 to 2.4; p = 0.02). This study is one of the first studies to bring in a new medication to treat lupus nephritis since the ALMS trial that made mycophenolate mofetil (MMF) common place (7).

For patients with lupus nephritis, kidney response improves when voclosporin, a novel calcineurin inhibitor, is added to MMF and low-dose corticosteroids, according to results from the yet-to-be-published phase 3 AURORA trial (presented at ASN Kidney Week 2020) (8). This international, double-blind, randomized, placebo-controlled trial compared the effectiveness and safety of twice-daily oral voclosporin 23.7 mg with placebo. All 357 study participants also received MMF 2 g daily and rapidly tapered low-

Continued on page 18

**Figure 1. Various novel antigens associated with membranous nephropathy**



## Year of the Glomerulus

*Continued from page 17*

dose oral corticosteroids. At 1 year, the kidney response rate was higher in the voclosporin group than in the placebo group (40.8% vs. 22.5%; OR, 2.65; $p < 0.001$). The median time to the achievement of a urine protein-to-creatinine ratio below 0.5 mg/mg was significantly and clinically better with voclosporin than with placebo (169 vs. 372 days; log rank $p < 0.001$). The year 2021 is going to see a paradigm change in the treatment of lupus nephritis.

Finally, in IgA nephropathy, we may have stumbled on a potential treatment with the use of dapagliflozin (DAPA) in patients with chronic kidney disease (CKD). Whereas the STOP-IgA (9) and TESTING (10) trials had patients using steroids for IgA nephropathy, 6% of patients in the DAPA-CKD study had IgA nephropathy and did well with treatment with sodium glucose cotransporter-2 (SGLT2) inhibitor (11). There were more patients in the DAPA-CKD study with IgA nephropathy (270) than in the STOP-IgA trial (162) and the TESTING trial (262). This may spark more use of SGLT2 inhibitors to decrease the progression of IgA nephropathy.

As I scratch the surface of novel markers and treatments and studies on the horizon for MN, IgA nephropathy, and lupus nephritis, several other glomerular diseases will see changes in management as 2021 arrives. Are we going to use less plasmapheresis in antineutrophil cytoplasmic antibody vasculitis (12), and when will oral complement inhibitors in trials (13) be the standard of care for vasculitis and C3 glomerulonephritis? That is yet to be seen. ■

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# Diabetic Kidney Disease and Beyond

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

*Visual Abstracts by Michelle G.A. Lim*

Sodium glucose cotransporter-2 (SGLT2) inhibitors currently approved by the US Food and Drug Administration include empagliflozin (Jardiance), canagliflozin (Invokana), dapagliflozin (Farxiga), and ertugliflozin (Steglatro). Combination formulations are also available: empagliflozin/metformin (Synjardy), canagliflozin/metformin (Invokamet), dapagliflozin/metformin (Xigduo XR), and ertugliflozin/metformin (Segluromet).

For this year's Kidney Watch, we look once again at the diabetic kidney disease (DKD) space as these agents enter the world of nephrology (1).

On September 30, 2020, the Kidney Disease: Improving Global Outcomes (KDIGO) Clinical Practice Guideline for Diabetes Management in Chronic Kidney Disease (2) was published. There continues to be increased discussion surrounding the use of SGLT2 inhibitors, glucagon-like peptide-1 (GLP-1) agonists, and dipeptidyl peptidase-4 (DPP-4) inhibitors. These novel agents are particularly notable for being strongly supported by several studies that looked at primary outcomes, e.g., major adverse cardiovascular events (MACE) or CKD progression and kidney outcomes [effects on albuminuria or albuminuria-containing composite outcomes and effects on estimated glomerular filtration rate (eGFR) loss]. Interestingly, there have been several more publications that did not make it to the KDIGO guideline document but nevertheless, are worthy of mention because they will influence how we will use these agents in our respective clinical practices.

### EMPEROR-Reduced (3)

This was a multicenter, double-blind randomized controlled trial (RCT) that enrolled 3730 patients with heart failure and a left ventricular ejection fraction (LVEF) 40% or less who were receiving recommended therapy for heart failure. The primary outcome was a composite of cardiovascular (CV) death or hospitalization for worsening heart failure. This study demonstrated that in patients with or without diabetes, those who received empagliflozin had significantly lower rates of CV death or hospitalization for heart failure (as compared to those who received placebo), hazard ratio (HR) 0.75, 95% confidence interval (CI) 0.65–0.86, $p < 0.001$.

### VERTIS CV (4)

This study is a multicenter, double-blind (non-inferiority) RCT that enrolled 8246 patients who were randomized to receive 5 mg or 15 mg of ertugliflozin or placebo once daily. Note that as compared to other studies cited in this article, this one, in particular, only had CV endpoints [MACE: a composite of death from CV causes, non-fatal myocardial infarction (MI), or non-fatal stroke]. This study showed that among patients with type 2 diabetes and atherosclerotic CV disease (ASCVD), ertugliflozin was non-inferior with regard to MACE.

### DAPA-CKD (5)

This is another RCT that enrolled 4304 patients with CKD [eGFR 25–75 and urine albumin-to-creatinine ratio (UACR) 200–5000 mg/g]. With the primary outcome being a composite of a sustained decline in eGFR (at least 50%), end-stage kidney disease (ESKD), or death from causes related to the kidneys or CV disease, *this trial was stopped early because of efficacy*. The primary outcome event occurred in 9.2% (197/2152) of the dapagliflozin group vs. placebo 14.5% (312/2152), HR 0.61, 95% CI 0.51–0.72, $p < 0.001$.

### SCORED (6)

This is a multicenter, double-blind RCT that enrolled 10,584 patients with type 2 diabetes (A1C ≥ 7%), CKD (eGFR 25–60), and risks for CV disease. Interestingly, the primary endpoint was changed to the composite of the total number of deaths from CV causes and hospitalizations' urgent visits for heart failure. This study showed that those patients with diabetes and CKD (with or without albuminuria) who received sotagliflozin (first dual SGLT1/SGLT2 inhibitor approved for diabetes) had a lower rate of deaths from CV causes (2.2/100 patient-years vs. 2.4/100 patient-years, HR 0.74, 95% CI 0.73–1.12, $p < 0.35$). However, there was a signal for adverse events, namely diarrhea, genital mycotic infections, volume depletion, and diabetic ketoacidosis (DKA).

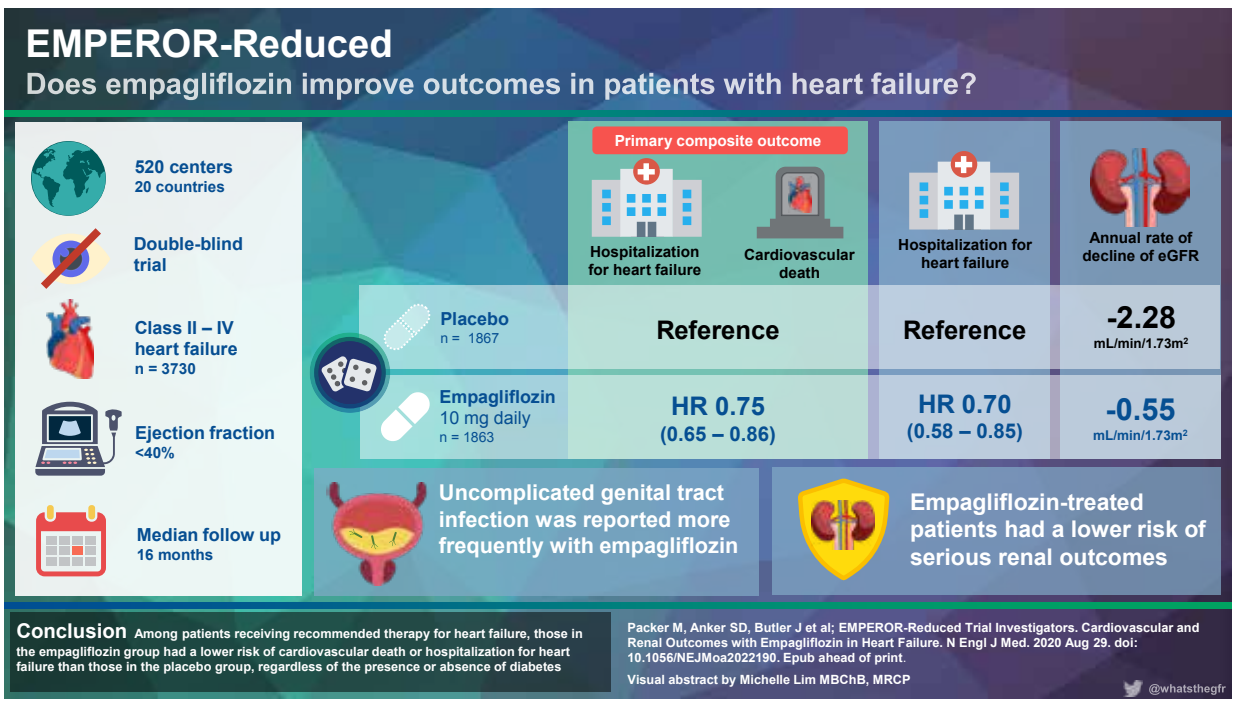
This trial ended early due to funding issues.

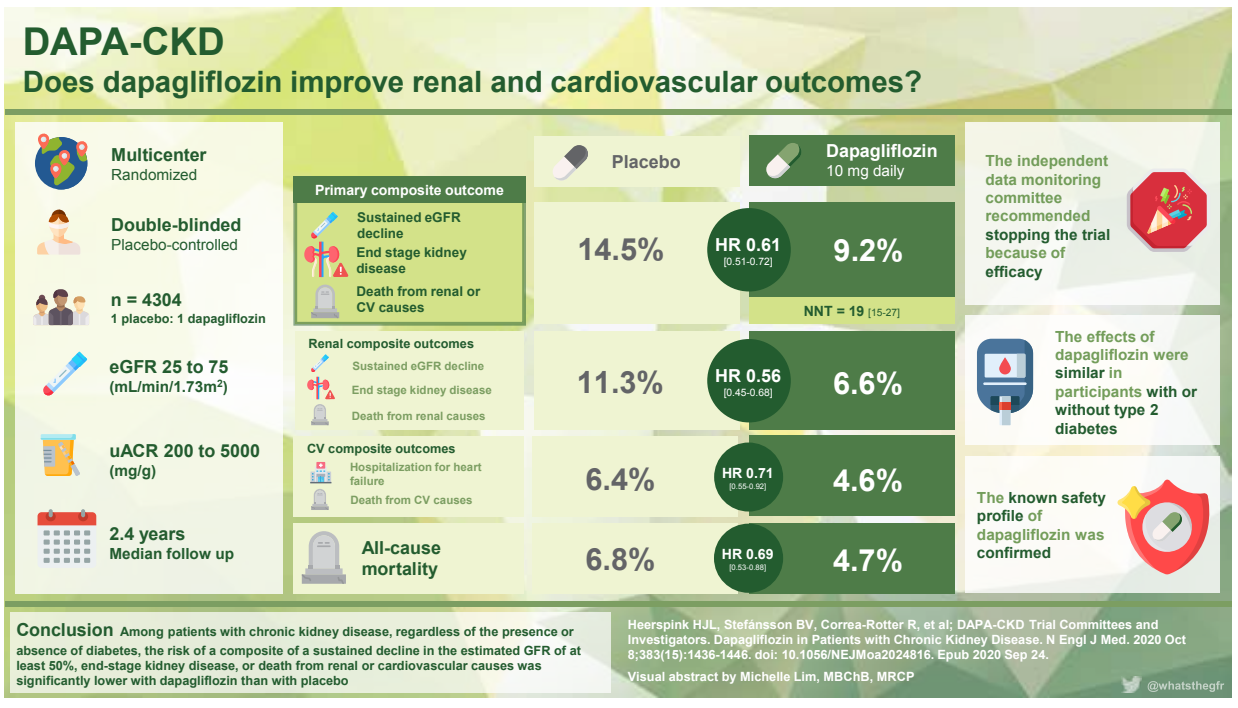
### FIDELIO-DKD (7)

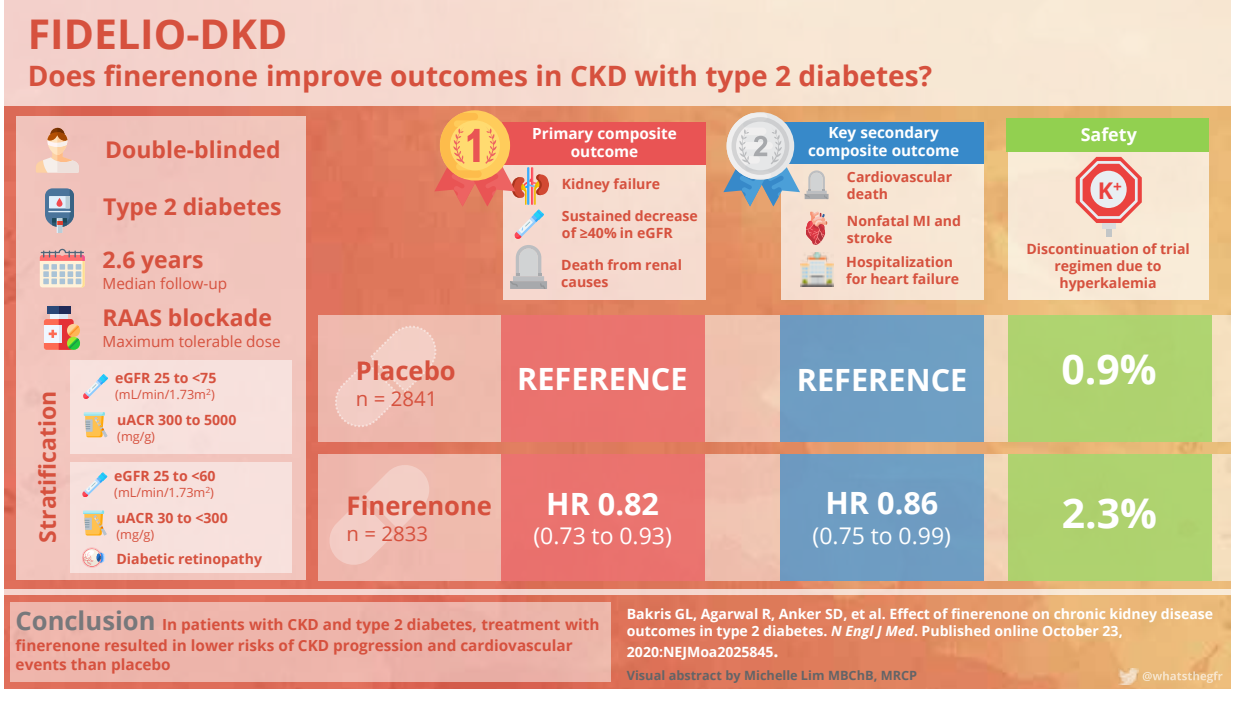
This is a double-blind, multicenter, international RCT that enrolled 5734 patients who were randomized in a 1:1 ratio to receive finerenone (a non-steroidal mineralocorticoid antagonist) or placebo. Eligibility criteria included the following: CKD (eGFR 25 to <60 and UACR

30 to <300 mg/g) and type 2 diabetes with diabetic retinopathy or CKD (eGFR 25 to <75 and UACR 300–5000 mg/g). The primary composite outcome was kidney failure, a sustained decrease in eGFR (at least 40% from baseline), or death from causes related to the kidneys. It occurred in 17.8% (504/2833) patients who received finerenone vs. placebo 21.1% (600/2841), HR 0.82, 95% CI 0.73–0.93, p = 0.001. Although the frequency of adverse events was similar in the finerenone and placebo groups, there was a higher incidence of hyperkalemia-related discontinuation in the former (2.3% vs. 0.9%).

Certainly, there are more studies down the road that will further shape how physicians use these agents in their respective clinical practices. The question now that all of these guidelines have officially come out, and additional randomized clinical trials continue to be published, is: Are we nephrologists willing to step up to the plate and be the champions for the use of these novel agents? ■

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In Dr. Lerma's role as KDIGO Knowledge Translation Lead, he is responsible for creating implementation tools based on the KDIGO Controversies Conferences that are used to educate clinicians around the world and prepare them for the newly updated guidelines.

He is also 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.

# Fellowship Education: What to Watch (and from Where)

By Matthew A. Sparks

2020 was a challenging year in nephrology education. In-person annual meetings shifted virtual, and many of us learned firsthand the concept of "Zoom fatigue," as our institutional meetings and conferences moved virtually. The National Institutes of Health (NIH) made a big announcement that will likely have a long-lasting impact on research training. Home dialysis education was front and center. How will the nephrology education landscape continue to evolve in 2021?

## Virtual conferences are here to stay

There is no denying that virtual education is here to stay. Coronavirus infectious disease 2019 (COVID-19) resulted in an almost complete shift to the use of virtual platforms to host local, national, and international conferences (1). The nephrology community worked hard to adapt, with major conferences, like ASN Kidney Week and the National Kidney Foundation (NKF) Spring Clinical Meeting, among others, moving virtual.

Fellows, who were looking forward to a break in a new city from busy clinical work, in-person education, and networking, were instead faced with several days of screen time. How would they be able to network effectively? This was especially concerning given that fellows are just getting started in nephrology and have more limited collaborator, mentor, and sponsor networks than more established nephrologists. The nephrology conference landscape for fellows was impressive leading up to 2020 and COVID-19 with offerings for private practice (National Business Leadership University), education (KIDNEYcon), home modalities (Home Dialysis University), critical care (CRRT Academy), and cardio-nephrology (Cardio Renal Connections), among many others. Many of these conferences provided funding for travel and lodging to trainees. Thankfully, most of these important educational offerings are trying to make the most of video-conferencing platforms as well.

The online nephrology space has one of the most well-developed communities in medicine, with educational programming in a variety of modalities from websites to Twitter, to podcasts, to videos (2). In addition, year-long programs for trainees include the Nephrology Social Media Collective (NSMC) Internship, the *American Journal of Kidney Diseases* (*AJKD*) Editorial Internship, the newly established GlomCon Virtual Glomerular Disease Fellowship, and NephSIM Nephrons mentoring program. We will be watching to see how the nephrology community continues to adapt in the virtual space during 2021. Even if in-person meetings return in 2021 and beyond, it is becoming clear that at least some virtual component is here to stay.

## Changes in NIH's National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) T32 Program

NIH's National Research Service Award (NRSA) T32 Program has been a mainstay of funding for fellowship programs to secure protected academic time for fellows interested in pursuing careers as physician scientists (3). In spring 2020, the NIDDK's Division of Kidney, Urologic, & Hematologic Diseases (KUH) announced an unexpected and sudden end to the T32 program. The KUH T32 programs will now be replaced by an Institutional Network Award for Research Training (U2C/TL1) mechanism. This announcement has led to considerable concerns from the nephrology research community. So how is the U2C/TL1 mechanism different? Following are some of the differences:

- An emphasis on fostering a community of trainees
- One application that supports at least five trainees across kidney, urology, and hematology research areas
- Encouragement for multiple institutions within the same metropolitan area to submit a single, joint application

American Society of Nephrology (ASN) Senior Policy Specialist Ryan Murray reviewed this change in *Kidney News Online* (July 2020), due to concern about how the change will affect funding for nephrology fellows (4). Some concerns noted are the diminished number of overall awards available, the even smaller proportion of training slots that go to nephrology fellows, and the potential to favor larger institutions. Time will tell how this policy change will impact the overall number and long-term success of our trainees wishing to pursue research careers in nephrology.

## More emphasis on home dialysis modalities in fellowship

Under the Advancing American Kidney Health (AAKH) Initiative (5), use of home dialysis modalities by patients with kidney failure is expected to increase. Will nephrologists be able to care for this growing population of patients?

A survey of US nephrology fellows in 2017 showed that almost one-half of all respondents indicated they had little or no training in peritoneal dialysis or home hemodialysis (6). It is incumbent upon our fellowship programs to ensure that fellows are adequately prepared. A recent survey of 76 US nephrology fellows who attended Home Dialysis University courses in 2019 showed that a majority were moderately confident in administering peritoneal dialysis, but most had low confidence in home dialysis (7). These findings underscore the importance of including more training in home dialysis modalities in fellowship programs. Educational curricula should include both didactic sessions and a focus on longitudinal care of patients using these modalities during the two-year Accreditation Council for Graduate Medical Education (ACGME) fellowship. Additionally, select fellows can enroll in an additional year of training. ■

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# Acquiring Novel Agents for Kidney Disease in India: A Pipe Dream or Science Fiction?

By Mayuri Trivedi

Recently, the world of nephrology rejoiced at another "positive" trial in nephrology: Dapagliflozin in Patients with Chronic Kidney Disease (DAPA-CKD) (1). But in India and other nations in the South Asian subcontinent we also are deeply concerned by the fact that the sodium glucose cotransporter-2 inhibitors (SGLT2i) are scarcely available and, when they are, place a huge financial burden on our patients who manage to procure them. Dapagliflozin costs the US dollar equivalent of $0.89 for a 10-mg tablet in India (compared to one 75-mg tablet of aspirin [ASA] at $0.038 and one 10-mg tablet of atorvastatin 10 mg at $0.12), and the costs of drugs are not covered by the insurance companies.

On second thought, at least this drug is available, albeit not as freely as we would want. An expanding list of drugs seems to have lost "novel" status in the Western world, but physicians in the South Asian subcontinent have not had the pleasure of experiencing the magic of these drugs in their patients. Many might not be aware that drugs such as patiromer and sodium zirconium cyclosilicate, which were approved for use in the United States in 2015 and 2018, respectively, remain unavailable in India. Eculizumab, an anti-C5 monoclonal antibody, which was approved in 2007 by the US Food and Drug Administration as a game changer in patients with atypical hemolytic uremic syndrome (2), is still available only through a restricted access program in India as a research molecule. The BENEFIT trial clearly showed better patient and graft survival after kidney transplantation, with higher rates of estimated GFR for belatacept in a 7-year follow-up study published in 2016 (3). Although centers in

India were part of this multicenter trial, this drug remains unavailable in India as of today.

The lists of medications that promise to mitigate some of the kidney maladies continue to remain a clinician's dream in India despite comparable rates of kidney disease burden globally. This glaring disparity in the distribution of resources, including the newer drugs in the nephrologist's tool kit, seems to significantly contribute to the abysmal outcomes for kidney diseases in India and other nations in the South Asian subcontinent. The delivery of healthcare in India, including kidney disease healthcare, rests on the shoulders of an overburdened public sector infrastructure and a large, yet expensive, private sector. More often than not, patients end up paying for the drugs and for disposables personally, inasmuch as insurance schemes and government health policies are restricted in their outreach and their benefits. Integral to providing holistic kidney disease care is ensuring the availability of all recent and novel drugs that are proving to reduce morbidity and mortality in our patients. Perhaps nephrologists in the Western world can help change this situation. Table 1 lists potential ideas on how this can be achieved.

Until we overcome this deep abyss in the South Asian subcontinent, we will continue to regard these novel kidney drugs as part of science fiction. Many of us identify well with this quote by the American author Ray Bradbury: "I have never listened to anyone who criticized my taste in space travel, sideshows, or gorillas. When this occurs, I pack up my dinosaurs and leave the room." ■

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**Table 1. Possible solutions for easing the procurement of novel nephrology drugs in South Asia**

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| **1.** Development of generic brands of novel drugs produced locally in each country |
| **2.** Innovative insurance schemes targeted at specific diseases that collect regular small amounts per person per month to provide the required high-budget drugs |
| **3.** Government-aided schemes for specific drugs |
| **4.** Dedicated nongovernmental organizations or groups that may help in crowd-funding for specific drugs |
| **5.** Rational, transparent, and protocol-based process of approval of newer drugs in India that is patient-centric and without bureaucratic hurdles |
| **6.** Group efforts by relevant nephrology societies with adequate representation to urge government bodies to hasten procurement and availability of life-saving drugs |

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# Pediatric Nephrology Developments Anticipated for 2021

By Ray Bignall II

Children are our future, and the year ahead in pediatric nephrology holds tremendous promise to advance healthcare for children with kidney diseases. The pediatric nephrology community has been hard at work championing the innovations and advocating for the change necessary to make a brighter future a reality for children with kidney diseases, their families, and those who care for them. With so many exciting advances across the spectrum of pediatric kidney care, here are a few of the areas to follow closely in 2021.

## Neonatal nephrology—the nascent field is now full term

There is growing appreciation for the role of prenatal and neonatal kidney health in nephron endowment at birth and long-term risks for chronic kidney disease (CKD). Despite the technical limitations that make studying the mechanisms of neonatal kidney pathophysiology so challenging, advances continue, particularly in the area of neonatal acute kidney injury (AKI) (1).

Recent research has resulted in a better understanding of the prevalence of neonatal AKI, and strategies for AKI mitigation and nephrotoxicity reduction are emerging (2, 3). Now with the help of the Neonatal Kidney Collaborative, a coalition of neonatologists, nephrologists, and scientists dedicated to improving kidney outcomes in neonates, pediatric kidney professionals around the world are connecting and sharing best practices (4). Several children's hospitals [including Riley Children's in Indiana, Nationwide Children's in Ohio, and Medical University of South Carolina (MUSC) Shawn Jenkins Children's in South Carolina] have launched jointly run clinical services with both nephrology and neonatology. These partnerships serve to streamline referrals, facilitate the identification of neonatal kidney disease, and improve outcomes. The field of neonatal nephrology will continue to mature in the year to come.

## Kidney support therapies—little machines that pack a big punch

The adage "children are not little adults" is as old as the field of pediatrics itself. Yet, when it comes to the use of kidney support therapies, children have been treated as little adults. The year 2020 saw the introduction of the first pediatric-specific kidney support device ever approved by the US Food and Drug Administration (FDA) for use in children under 10 kg: the Cardio-Renal Pediatric Dialysis Emergency Machine (CARPEDIEM) (5). Along with the Newcastle Infant Dialysis and Ultrafiltration System (NIDUS) (6) and the adaptation of ultrafiltration-specific devices for modified kidney replacement therapy (7), the emergence of pediatric-specific, miniaturized devices, which feature lower blood flows and circuit volumes, is something to watch this year.

## Coronavirus infectious disease 2019 (COVID-19), kids, and kidneys—are we sure the kids are alright (8)?

Mercifully, children have been spared much of the morbidity and mortality associated with severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection. In summer 2020, early data suggested that the incidence of COVID-19 was no different for children with kidney disease on systemic immunosuppression (e.g., those with kidney transplants, glomerulonephritis) than children not on immunosuppression (9). However, data from late 2020 demonstrated an AKI prevalence of 44% in children critically ill with COVID-19, which mirrors the prevalence among critically ill adults (10) and is higher than that of critically ill children without SARS-CoV-2 (11). As the course of the pandemic changes and novel coronavirus vaccines become widely available, pediatric nephrologists will be watching closely for clues as to the long-term impact on our patients. ■

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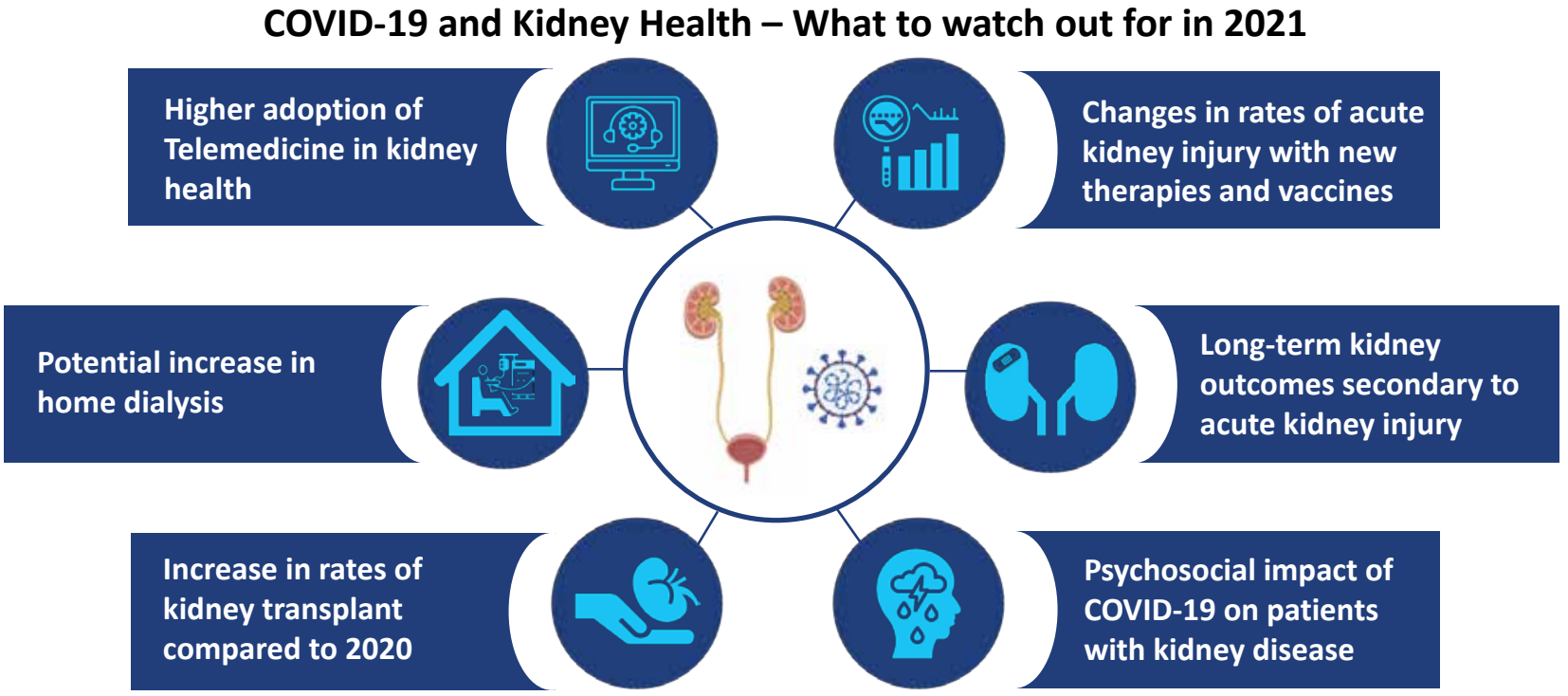
Visual abstract by Jia H. Ng

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# Acute Kidney Injury in 2021

By Anitha Vijayan

In 2020, acute kidney injury (AKI) came to the forefront during the COVID-19 pandemic as nephrologists struggled to understand the pathophysiology of COVID-19-associated AKI and to provide timely and effective nondialytic and dialytic care to the large volume of patients who overwhelmed healthcare facilities. Recently, personal communications among the members of the ASN COVID-19 Response Team have indicated that the rate of AKI requiring kidney replacement therapy (KRT) in the current wave of the pandemic is lower than that experienced in the spring. The decreasing incidence of severe AKI was also documented in a study of >5000 veterans who were hospitalized with COVID-19 between March and July 2020 (1). The decreased incidence of severe AKI probably reflects changes in patient characteristics and management of the disease. Younger patients, patients with fewer comorbid conditions, early use of dexamethasone and remdesivir, delay in invasive ventilation, and other relevant factors could all have played a role in the decreasing rates of AKI requiring KRT. As the pandemic moves to 2021, we expect the rates of COVID-19-associated AKI and the need for KRT to remain at the current level.

Biomarkers for the early diagnosis and prognostication of AKI remain a work in progress, and trials are ongoing to establish whether early diagnosis of AKI can lead to changes in management and improve outcomes. Similarly, electronic alerts and algorithms to predict AKI have shown promise (2, 3), and additional studies may help determine whether these measures can be used to prevent AKI in the setting of potential nephrotoxins. The mainstay of treatment of AKI in critically ill patients with sepsis is timely initiation of KRT (4). Amid the pandemic, hemoperfusion and cytokine absorption techniques have received authorization for emergency use from the US Food and Drug Administration. The indications to use these measures are extremely vague, inasmuch as existing data are based on case reports, expert opinions, and anecdotes. Ongoing randomized controlled trials will shed light on whether these therapies will offer meaningful improvement in clinical outcomes.

The appropriate treatment of patients with AKI after discharge is extremely important to reduce readmissions and mortality, and the National Institutes of Health has announced a Request for Application for further research in this area (5). The Caring for OutPatiEnts after Acute Kidney Injury (COPE-AKI) consortium that will be formed as a result will be responsible for developing and testing specific interventions to improve the care of patients with AKI after hospital discharge.

In summary, 2021 will be an exciting year as we await further developments in the field of biomarkers, electronic alerts, and management of AKI. ■

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# When Will the "Manels" Go Away?

By Samira S. Farouk

#NoMoreManels, a hashtag that continues to trend on social media in 2021, both within and outside nephrology, is used to draw attention to panels of all-men speakers and moderators, despite an active US physician workforce that is over one-third women (1).

As with its inception as a field more than 50 years ago, nephrology remains a man-dominated discipline, with 30% women nephrologists (2). There exist gender disparities, not only in representation of women nephrologists but also in significant imbalances in compensation and leadership positions. Women earn a mean of $31,000 per year less than their male colleagues. Only 15% and 16% of department chairs and deans, respectively, are women. A recent analysis of National Institutes of Health funding found that women receive smaller grants than men, despite adjustment for research potential (3). The impact of the coronavirus infectious disease 2019 (COVID-19) pandemic on academic productivity has been described as greater for women than for men, with a 19% decrease in COVID-19–related articles with a woman as first author compared with women as first authors in the same journals in 2019. Further, a pre-pandemic study found that up to 80% of peer reviewers are men, and only one-third of journal articles have women as primary authors (4). Between 2011 and 2019, only 12% of American Society of Nephrology (ASN) lifetime achievement awards were given to women (5). Moreover, each of these awards is named after its own "manel" of nephrologists (Belding H. Scribner, Donald W. Seldin, Homer W. Smith, John P. Peters, and Robert G. Narins).

Results from a large 2017 survey of nephrologists that asked about their race or ethnicity using US Census Bureau criteria found that 7% chose Hispanic/Latino and 5% chose Black/African American, with low percentages of women among these groups (6). An Association of American Medical Colleges analysis in 2016 found that women of color make up 11% of all full-time faculty in US medical schools. Despite Black women making up 54% of Black faculty, they made up only one-third of Black full professors (7).

Have we made any progress? Analysis of data from the ASN found that the proportion of women moderators and speakers had increased to 47% and 40%, respectively, in 2019 from approximately 20% in 2011 (5). Organizations like Women in Nephrology strive to support and provide mentorship for women developing careers within nephrology and to advocate within the nephrology community for education and research relevant to women, while also providing mentoring opportunities for all.

As a nephrology community, we must strive for gender equity and creative inclusive environments that foster and promote excellence for women and for transgender, nonbinary, and gender-nonconforming individuals who face barriers to employment and advancement. The solution to this problem lies beyond the inclusion of women as speakers and moderators. Institutional guidelines should aim to create a supportive and equitable environment for all faculty members with attention to hiring practices, effective mentorship of all faculty, and transparency of compensation policies and information

Continued on page 24

## KIDNEY WATCH

### "Manels"

*Continued from page 23*

about expectations and practices regarding tenure and promotion. Diversity and inclusion must be prioritized at all levels, from nephrology fellowship application review to the formation of committees and selection of department chairs. Representation is not enough. Mentorship and leadership programs are needed. Rampant sexual harassment, in which prevalence in academic medicine is almost double that in other science or engineering specialties (8), must be combatted with a climate of respect and inclusion. Institutions may seek guidance and consultation from organizations like Advancing Health Equity (9) that seek to "engage with healthcare and related organizations around bias and racism in healthcare with the goal of mobilizing for health equity and eradicating racialized health inequities."

We have work to do. And it is time for things to change. ■

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## Policy Update

# Payment Boost, Extreme Circumstances Exemption in MIPS Greet Nephrologists in New Year

In a rush to complete regulatory activities before both the end of the year and the transition to an incoming Biden-Harris administration, the Centers for Medicare & Medicaid Services (CMS)—as well as other federal agencies—announced several administrative steps and final rules important to both nephrologists and other clinicians.

CMS announced that it is accepting the impact of COVID-19 as a condition for receiving an Extreme and Uncontrollable Circumstances exemption in the Merit-based Incentive Payment System (MIPS). MIPS is the largest quality payment program administered by CMS.

An Extreme and Uncontrollable Circumstances exemption would allow clinicians, groups, and virtual groups to submit an application requesting reweighting of one or more MIPS performance categories due to the current COVID-19 public health emergency. In the past, these exemptions were usually associated with natural disasters, for example, when reporting re-

quirements have been interrupted by hurricanes or wildfires. In addition to extending this option to clinicians and practices significantly affected by COVID-19, the agency is extending the application deadline for 2020 to Monday, February 1, 2021, at 8 p.m. Eastern Time.

MIPS is one of two payment tracks in CMS' Quality Payment Program (QPP) along with Advanced Alternative Payment Models. MIPS is a mandatory quality pay-for-performance program, except for clinicians excluded due to certain criteria such as low volume of Medicare patients, where clinicians report their performance on four categories of measures: Quality, Promoting Interoperability, Improvement Activities, and Cost. In 2018, there were a total of 7120 nephrologists who identified in MIPS, according to the American Medical Association Physician Masterfile (December 2017). Excluding nephrologists who did not report MIPS data in 2018 for various reasons, the participating number was 6117.

## Payment boost

After a longer than average time period between closing the comment period on the proposed Medicare Physician Fee Schedule (MPFS) rule and issuing the final rule, CMS finalized the rule and now nephrologists will receive boosts in payments, especially in the rate for reimbursement for home dialysis, starting on January 1, 2021. The increases to nephrologists' reimbursements were part of a multi-year push by ASN to increase the values incorporated in the reimbursement calculations.

This long-delayed rule reflects the current federal policy priority focused on increasing rates of home dialysis. The final rule includes an overall 6% increase in payments for nephrologist-provided services with an approximate 30% increase for home dialysis reimbursement. The increases were due to the upward adjustment of relative value units (RVUs) being applied to nephrology billing codes. CMS also increased the RVU value of the Transitional Care Management (TCM) codes.

"This is a big win for continuity of hospital-to-dialysis care for our patients. After years of advocacy by ASN, Medicare is supporting nephrologists with rates that better reflect our work and the value of home dialysis, a top priority for ASN," said Anupam Agarwal, MD, FASN, ASN President.

In another priority victory for nephrologists, CMS finalized steps allowing 14 ESRD codes to be billed concurrently with TCM codes. TCM codes allow for payment for hospital follow-up care. This change promotes better follow-up post-hospitalization and provides fair reimbursement for nephrologists' time. These developments are also seen as complementing the upcoming mandatory ESRD Treatment Choices (ETC) Model beginning January 21, 2021.

While ASN was pleased to see the increases in home dialysis rates, there is still room for added valuations in order to achieve payment parity with in-center rates. The society will advocate for further increases when Medicare develops proposals for the CY 2022 Medicare Physician Fee Schedule (MPFS). There was also a code in pediatric nephrology that was not increased. ASN will work with the American Society of Pediatric Nephrology in the months ahead to address this issue before the next MPFS is proposed. ■



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## Lower HbA1c Linked to Lower AKI Risk in Chronic Kidney Disease

Better control of blood glucose levels may reduce the risk of AKI in adults with type 2 diabetes and CKD, according to an analysis of US and Swedish data in *Diabetes Care*.

The study included data on two observational cohorts of patients with type 2 diabetes and confirmed stage G3 to G5 CKD receiving routine care in one US and one Swedish health system. The US cohort, drawn from the Geisinger Health System in Pennsylvania, consisted of 22,877 patients: median age 72 years, 55% female, and estimated glomerular filtration rate (eGFR) 52 mL/min/1.73 $m^2$. The Swedish cohort included 12,157 patients from the Stockholm Creatinine Measurements (SCREAM) project: median age 77 years, 50% women, eGFR 51 mL/min/1.73 $m^2$. Baseline HbA1c and time-varying HbA1c were evaluated for incident AKI, defined as a 0.3 mg/dL or greater increase in creatinine over 48 hours or a 1.5-fold increase over 7 days.

A total of 7060 AKI events occurred over 3.1 years of follow-up in the US cohort and 2619 events over 2.3 years in the Swedish cohort. On adjusted analysis, the risk of AKI was increased by about 30% for patients with baseline HbA1c over 9%, compared to values of 6% to 6.9%: hazard ratio (HR) 1.29 in the US cohort and 1.33 in the Swedish cohort. Particularly in the US cohort, there was a J-shaped association between baseline HbA1c and AKI, with higher risk at both the lower and higher end of the range.

The findings were similar on analysis of time-varying HbA1c and on stratified analysis with death as a competing risk. Higher and lower HbA1c values were also associated with increased mortality. At baseline HbA1c of 9% or higher, HRs for mortality were 1.30 in the US and 1.46 in the Swedish cohort. At HbA1c under 6%, HRs were 1.11 in both cohorts [Xu Y, et al. Glycemic control and the risk of acute kidney injury in patients with type 2 diabetes and chronic kidney disease: Parallel population-based cohort studies in U.S. and Swedish routine care. *Diabetes Care* 2020; 43:2975–2982. doi: 10.2337/dc20-1588].

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