Nephrology Times

Practical News, Trends, and Analysis

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NKF-TOS Workshop on Managing Obesity in Patients With CKD

In the face of growing evidence that obesity is a major contributor to chronic kidney disease (CKD) and a predictor of adverse outcomes in patients with CKD, and an awareness that effective treatment of obesity, including lifestyle intervention, weight loss medication, and metabolic surgery can have beneficial effects for that patient population, the National Kidney Foundation (NKF) and The Obesity Society (TOS) cosponsored a multispecialty international workshop. The aim of the April 2021 workshop was to advance the understanding and management of obesity in adults with CKD.

Attendees included experts in kidney disease, obesity medicine, endocrinology, diabetes, bariatric/metabolic surgery, endoscopy, transplant surgery, and nutrition. Patients with obesity and CKD also took part. Outcomes of the workshop included strategies to increase patient and provider engagement in management of obesity, an outline of a collaborative action plan to engage obesity medicine experts and nephrologists in obesity management, and identification of research opportunities to address gaps in knowledge regarding the interaction between obesity and kidney disease.

Allon N. Friedman, MD, and other workshop attendees provided a report in the *American Journal of Kidney Diseases* [2022;80(6):783-793].

More than 650 million people worldwide are affected by obesity. Obesity is

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Therapy With RAS Inhibitors in Advanced CKD

The use of renin-angiotensin system (RAS) inhibitors, including angiotensin-converting-enzyme (ACE) inhibitors and angiotensin-receptor blockers (ARBs), in patients with mild-to-moderate chronic kidney disease (CKD) has been shown to reduce blood pressure, slow decline in estimated glomerular filtration rate (eGFR), reduce proteinuria, and delay progression to advanced CKD (stage 4 or 5).

Patients who progress to stage 4 or 5 CKD have impaired quality of life and an increased risk of renal replacement therapy (RRT), cardiovascular events, and death. However, according to **Sunil Bhandari, PhD,** and colleagues in the United Kingdom, there are few data available on the benefits of RAS inhibitor use in patients with advanced

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Health Care Use and Costs Increase With KDIGO CKD Stage

Recent estimates suggest that 37 million adults in the United States, one in seven, have chronic kidney disease (CKD), excluding those with end-stage renal disease. As the population in the United States ages and as the prevalence of risk factors for CKD such as hypertension and obesity increase among all age groups, CKD is expected to become even more common.

CKD is most prevalent among US adults ≥65 years of age; most of the research on the economic burden of CKD has focused on the Medicare population. Excluding patients with ESRD, costs from patients with CKD accounted for more than 22% ($81 billion) of the Medicare fee-for-service spending in 2018. Increasing CKD stage as well as common comorbidities such as heart failure and type 2 diabetes mellitus (T2DM) contribute to cost of care for this patient population.

There are fewer data available on the burden of CKD for commercial payers. Results of some studies have suggested that an increase in all-cause costs due to increasing CKD stages among patients <65 years of age is similar to the observed increases among those ≥65 years of age. However, according to **Haechung Chung, MPH,** and colleagues, there is a gap in understanding the role of comorbidities in the burden of CKD in patients with commercial health coverage.

The researchers conducted an observational, descriptive, retrospective cohort study to describe the economic and health care resource utilization (HCRU) burden

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Therapy With RAS Inhibitors

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CKD. Results of an observational study suggested that discontinuation of RAS inhibitors in that patient population may increase eGFR. Current guidelines do not offer specific recommendations on whether to stop or continue ACE inhibitors or ARBs for advanced CKD.

The researchers conducted the multicenter, randomized, open-label STOP-ACEi trial of patients with advanced and progressive CKD. The trial was designed to determine whether the discontinuation of RAS inhibitors would increase or stabilize eGFR. Results were reported in the *New England Journal of Medicine* [2022;387(22):2021-2032].

Patients with advanced and progressive CKD (eGFR <30 mL/min/1.73 m^2) were randomly assigned to either discontinue or to continue therapy with RAS inhibitors. The primary outcome of interest was eGFR at 3 years as calculated according to the Modification of Diet in Renal Disease (MDRD) study updated in 2005; eGFR values that were obtained following initiation of RRT were excluded. Secondary outcomes were the development of end-stage kidney disease (ESKD); a composite of a decrease of >50% in eGFR or the initiation of RRT, including ESKD; hospitalization; blood pressure; exercise capacity; and quality of life. Prespecified subgroups were defined according to age, eGFR, type of diabetes, mean arterial pressure, and proteinuria.

Analyses were based on the intention-to-treat (ITT) principle and were adjusted for the minimization variables and baseline values (where available). The ITT population included all patients who had undergone randomization, regardless of what treatment (if any) they had received. The between-group difference in eGFR at 3 years was estimated using a repeated-measures, mixed-effects, linear regression model that included a term for the interaction of time with treatment group. The researchers repeated analyses for the primary outcome with the use of two other four-variable equations for the eGFR calculation: the Chronic Kidney Disease Epidemiology Collaboration 2009 (CKD-EPI 2009) equation and the MDRD186 equation.

A total of 17,290 patients were screened from July 11, 2014, to June 19, 2018, at the 39 participating centers in the United Kingdom. Of the 17,290 patients, 1210 were invited to participate in the trial. Of those, 411 at 37 centers underwent randomization to a trial group; 206 were assigned to the discontinuation group and 205 were assigned to the continuation group. Follow-up continued until June 19, 2021; median follow-up was 3 years.

Median age of the total cohort was 63 years, 68% (n=281) were male, and 15% (n=60) were non-White. At baseline, median eGFR was 18 mL/min/1.73 m^2; 118 patients (29%) had eGFR <15 mL/min/1.73 m^2. Median protein-to-creatinine ratio was 1018 and median hemoglobin level was 11.6 g/dL. Thirty-seven percent (n=153) had been diagnosed with diabetes (either type 1 or type 2), 21% (n=87) with diabetic nephropathy, 17% (n=68) with hypertensive or renovascular nephropathy, 20% (n=81) with genetic diseases, and 18% (n=76) with glomerulonephritis.

At 3 years, the least-squares mean eGFR was 12 mL/min/1.73 m^2 in the discontinuation group and 13.3 mL/min/1.73 m^2 in the continuation group (difference, –0.7; 95% CI, –2.5 to 1.0; *P*=.42), with a negative value favoring the outcome in the continuation group. There was no heterogeneity in outcome according to the prespecified subgroups.

At 3 years, 128 of 206 patients (62%) in the discontinuation group had reached ESKD or RRT, as had 115 of 205 patients (56%) in the continuation group (adjusted hazard ratio [HR], 1.28; 95% CI, 0.99-1.65). The number of patients who initiated RRT (including those with ESRD) or had a decrease of >50% in eGFR was 140 of 206 (68%) in the discontinuation group and 127 of 202 (63%) in the continuation group (adjusted relative risk, 1.07; 95% CI, 0.94-1.22).

The numbers of hospitalizations for any reason were similar in the discontinuation group and the continuation group (414 and 413, respectively), as were the numbers of cardiovascular events (108 and 88, respectively). A total of 20 patients in the discontinuation group and 22 patients in the continuation group died (HR, 0.85; 95% CI, 0.46-1.57).

In the 15 months following randomization, systolic and diastolic blood-pressure values were higher in the discontinuation group compared with the continuation group. After the first 15 months, values were similar in the two groups. The number of antihypertensive medications prescribed were also similar in the two groups.

At 3 years, the least-squares mean distance covered during a 6-minute walk test was 394 meters in the discontinuation group and 412 meters in the continuation group. The two groups were similar in various measurements of quality of life. There was little difference between the two groups in the urinary protein-to-creatinine ratio at 3 years. Mean hemoglobin was also similar in the two groups.

Limitations cited by the authors included poor representation of patients with non-White ethnic backgrounds, limiting the generalizability of the findings; the open-label design that may have affected clinical care and subjective end points, including quality of life and exercise capacity; and the possibility that the findings may not generalize to patients with higher levels of proteinuria.

In conclusion, the researchers said, "In this trial, the discontinuation of RAS inhibitors in patients with advanced and progressive chronic kidney disease did not lead to a clinically relevant change in the eGFR or a between-group difference in the long-term rate of decline in eGFR." ■

TAKEAWAY POINTS

- Researchers in the United Kingdom reported results of a study in patients with advanced and progressive chronic kidney disease to assess whether the discontinuation of renin-angiotensin system (RAS) inhibitors would increase or stabilize estimated glomerular filtration rate (eGFR).
- Patients were randomized to discontinue or continue therapy with RAS inhibitors, There was no association between the discontinuation of RAS inhibitors and a significant between-group difference in the long-term rate of decrease in eGFR.
- The two groups were similar regarding adverse events, including cardiovascular events and death.

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highly prevalent among patients with CKD and is a prime inducer of CKD and other kidney diseases. Because of the complexity and heterogeneity of obesity, the workshop recommendations include a team-based approach comprising several disciplines to provide lifestyle-based, pharmacological, and/or surgical therapies that are individually tailored to the patient. Advocacy efforts of specialists treating kidney disease and obesity would also provide an opportunity to improve insurance coverage and payment policies, expanding patient access to effective care.

OBSTACLES TO OBESITY MANAGEMENT

Discussions at the workshop centered on barriers to effective care for obesity, the ways the barriers affect patients with coexisting CKD, and possible pathways to overcome the barriers. Identification of which patients with obesity have CKD is a major obstacle to effective care. There are no clear and established criteria for treating obesity in CKD and scant evidence that routine screening for kidney disease in individuals with obesity improves clinical outcomes.

Cystatin C is generally considered a more robust marker of kidney filtration than creatinine in the setting of obesity or weight loss, but it is not entirely independent of lean or fat mass. Estimating glomerular filtration rate (GFR) using equations that combine serum creatinine and cystatin C would potentially improve on equations based on creatinine alone to help guide clinical decision making, research, and public health policy in those undergoing treatment with bariatric/metabolic surgery or anti-obesity medications.

Of particular interest at the workshop was the management of obesity in patients with advanced CKD or kidney failure and following kidney transplantation. While there are some centers in the United States that provide obesity management services, including bariatric/metabolic surgery to facilitate kidney transplantation, most do not, according to the workshop report.

The attendees also discussed the scarcity of diets that induce sufficient or durable weight loss to demonstrate substantial, long-term improvement in most complications related to obesity. In those with CKD, current nutrition guidelines that may restrict dietary options and limit dietary protein intake serve to compound the problem. The source of dietary protein is another issue to be dealt with in this patient population. Protein from animal sources is more likely to promote inflammation and increase GFR and renal plasma flow, resulting in negative outcomes.

Recent safe and effective anti-obesity medications provide a new opportunity for management and treatment of obesity. At the workshop, nephrologists and other clinicians who were not obesity medicine specialists emphasized their limited knowledge and lack of experience using the new medications, and expressed concerns relating to their safety. A planned randomized controlled trial of semaglutide designed with a primary renal end point will provide information on renoprotection and weight loss benefits in patients with CKD, type 2 diabetes, and obesity (ClinicalTrials.gov identifier NCF03819153).

IMPROVING PATIENT ENGAGEMENT

The workshop attendees agreed that patients with CKD and obesity are generally ill-informed about the association of obesity with their kidney disease as well as the kidney-related benefits of effective obesity management. Patients participating in the workshop felt that information on the biological control of satiety would help them understand that obesity cannot be controlled merely by adjusting the type and amount of food consumed.

Expansion of support groups for patients undergoing medical or surgical treatment of obesity to include patients with CKD was cited as a potential aid in improving patient engagement.

ENGAGING NEPHROLOGISTS AND OBESITY MEDICINE SPECIALISTS IN MANAGING OBESITY

Bridging common ground is essential to developing successful strategies for engaging nephrologists and obesity medicine specialists in managing obesity in patients with CKD. Obesity interventions in earlier stages of CKD and obesity may result in improved long-term outcomes by helping prevent the development of more overt kidney disease and complications. There are also patients with more advanced CKD and obesity who would benefit from obesity management strategies. Strategies to manage obesity in patients with CKD may differ depending on CKD stage and severity.

Of particular interest at the workshop was the management of obesity in patients with advanced CKD or kidney failure and following kidney transplantation.

The workshop group cited four areas that could facilitate nephrologists' engagement with obesity management: (1) a strong evidence base; (2) development of collaborative approaches to CKD management in patients with CKD that include obesity medicine specialists, bariatric/metabolic surgeons, nephrologists, dietitians, and transplant surgery teams; (3) improved treatment payment structures; and (4) overcoming systemic barriers to access to anti-obesity medications and surgical interventions, particularly in underserved populations.

CONCLUSION

The 2021 NKF-TOS workshop identified questions, challenges, and knowledge gaps to lay the foundation for a productive approach to effective management of obesity in patients with CKD that is scientifically based and multidisciplinary as a means to improve kidney-related outcomes in that patient population.

"This is an important issue given the importance of obesity in amplifying the already elevated risks associated with CKD and the growing prevalence of obesity in the CKD population," the researchers said. "Future progress in this area will require collaboration between the nephrology and obesity medicine communities to educate patients and practitioners; advance our understanding of the relationship between obesity and kidney disease; appreciate the unique characteristics and needs of patients with these disorders; and develop, test, and implement clinical strategies that optimize the health of the growing population with obesity and CKD." ■

TAKEAWAY POINTS

- The National Kidney Foundation and The Obesity Society cosponsored a multidisciplinary international workshop in April 2021 to address the understanding and management of obesity in adults with chronic kidney disease (CKD).
- Attendees included experts in kidney disease, obesity medicine, endocrinology, diabetes, bariatric/metabolic surgery, endoscopy, transplant surgery, and nutrition, as well as patients with obesity and CKD.
- The workshop's conclusions will help lay a foundation for the development of an effective scientific and multidisciplinary approach to the management of obesity in patients with CKD.

Health Care Use and Costs Increase

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of CKD in three patient groups: T2DM only, CKD only, and both T2DM and CKD. Eligible patients were 45 to 64 years of age with commercial health insurance. For patients with CKD only and with CKD and T2DM, the cost burden was also described by Kidney Disease: Improving Global Outcomes (KDIGO) CKD estimated glomerular filtration rate-based stage categories. Results were reported in the *Journal of Managed Care & Specialty Pharmacy* [2023;29(1):80-89].

The study utilized administrative medical and pharmacy claims integrated into data on laboratory results in the HealthCore Integrated Research (HIRD) database from January 1, 2017, to December 31, 2019. For each of the three study groups, all-cause and disease-specific HCRU and costs in total, by medical and pharmacy benefits and across all places of service, were described for 12 months following the index date.

The HIRD includes adjudicated administrative claims for 14 commercial and Medicare Advantage insurance plans, covering more than 70 million enrollees from all US census regions. A total of 10.3 million members had at least 1 day of health plan enrollment between January 1, 2018, and December 31, 2018. Following application of inclusion and exclusion criteria, the researchers identified three mutually exclusive groups: T2DM only (n=203,576); CKD only (n=22,689); and CKD and T2DM (n=38,587). From those groups, the researchers identified commercially insured members 46 to 64 years of age as of their index date: T2DM only (n=120,364); CKD only (n=7876); and CKD and T2DM (n=13,052).

The three groups were similar in age distribution; mean age was around 56 years for each group. The T2DM only and CKD only groups were similar in sex compositions: 44.5% female in the T2DM only group and 43.2% female in the CKD only group. The proportion of female patients was slightly lower in the CKD and T2DM group (39.7%). In all three groups the majority of participants resided in the Midwest and South regions of the United States (26.5% and 42.0% in the T2DM only group, 25.2% and 40.1% in the CKD only group, and 26.3% and 41.2% in the CKD and T2DM group, respectively).

The CKD and T2DM group had the highest crude baseline comorbidity burden, followed by the CKD only group and the T2DM only group (Quan Enhanced-Charlson Comorbidity Index ≥3: 19.8%, 11.3%, and 4.2%). Across the three groups, the most prevalent comorbid conditions were hypertension, dyslipidemia, and obesity. Cardiovascular conditions were twice as prevalent in the CKD and T2DM group compared with the T2DM only and CKD only groups.

Across all places of service, the CKD and T2DM group had the highest crude post-index all-cause and CKD/T2DM-related HCRU, followed by the CKD only group and the T2DM only group. The CKD and T2DM group had the highest proportion of patients with at least one hospitalization (19.4% vs 13.3% vs 8.5%), highest proportion of patients with at least one emergency department visit (24.3% vs 19.0% vs 18.6%), highest mean number of outpatient encounters per patient (32.1 vs 27.0 vs 19.9), and highest mean number of prescription fills per patient (32.2 vs 21.9 vs 24.1).

Mean 12-month all-cause costs for the CKD and T2DM group were $35,649, compared with $25,010 for the CKD only group and $16,121 for the T2DM only group. For CKD-T2DM-related costs, the mean total 12-month costs were relatively similar in the T2DM only and CKD only groups ($6388 vs $5086. Costs in the CKD and T2DM group were about two to three times as high as those costs ($16,078).

For both all-cause and CKD/T2DM-related costs, inpatient costs represented the greatest proportion of mean total costs in the CKD only and the CKD and T2DM groups. In the T2DM only group, the greatest proportion of mean total costs were prescription costs.

When stratified according to KDIGO CKD stage, total cost trends were similar. For a given CKD stage, both all-cause and CKD/T2DM-related crude costs for the CKD and T2DM group tended to be greater than costs for the CKD only group. As CKD stage increased, costs tended to increase, with increases beginning at KDIGO stage 3b and higher. For the CKD and T2DM group, mean CKD/T2DM-related costs were lowest at stage 1 ($13,193) and only slightly increased at stage 2 ($16,982) and stage 3a ($17,452). Compared with those earlier stages, costs were substantially higher at stage 3B ($25,234), stage 4 ($27,023), and stage 5 ($59,121). At all stages in the CKD only and the CKD and T2DM groups, all-cause and CKD/T2DM-related medical costs were much higher than pharmacy costs.

Limitations to the study findings cited by the authors included using claims provided by major managed care health plans, the possibility of selection bias, the lack of a washout period, and the descriptive nature of the study.

In conclusion, the researchers said, "To our knowledge, this real-world study was among the first to describe the HCRU and cost burden of CKD with and without T2DM in a commercially insured population. Individuals with CKD and T2DM had substantial burden in terms of HCRU and costs. Additionally, costs began to increase at KDIGO CKD stage 3b and continued increasing in later stages, as quantified by the magnitude described in the study. Therefore, there is an opportunity to reduce the burden of CKD in this population by investing in interventions to prevent or delay CKD disease progression." ■

TAKEAWAY POINTS

- Researchers reported results of a study of health care use and costs across three groups: patients with type 2 diabetes mellitus (T2DM), patients with chronic kidney disease (CKD), and patients with both T2DM and CKD.
- Health care use and costs were highest among those in the group with both T2DM and CKD.
- Health care use and costs increased across Kidney Disease Improving Global Outcomes CKD stages, and increased most rapidly at stage 3b and higher.

CONFERENCE COVERAGE KIDNEY WEEK 2022

Risk of CKD Associated With COVID-19 Reduced With Vaccination

Patients with COVID-19 face an increased risk of chronic health conditions, identified as postacute sequelae of COVID-19 (PASC). The more transmissible variants increase the likelihood that the global population will eventually be exposed to the spike protein of SARS-CoV-2, either through natural infection or vaccination. There are few available data on the effect vaccination may have on renal manifestations of PASC.

Hamza Mir, MS, MSW, and colleagues at the University of New Mexico Health Science Center, Albuquerque, conducted an analysis of data to examine the effects of vaccination on chronic kidney disease (CKD) manifestations of PASC. Results were reported during a poster session at the American Society of Nephrology Kidney Week 2022 in a poster titled *Vaccination Reduces Risk of CKD Associated With COVID-19 Disease*.

The researchers searched TrinetX, a large health research network that aggregates data from multiple centers in the United States. Patients were classified as C19+ve (with a positive molecular test for SARS-CoV-2 or a clinical diagnosis of COVID-19) and Vax7+ve for those with at least one dose of any COVID-19 vaccine and no breakthrough COVID-19 infection.

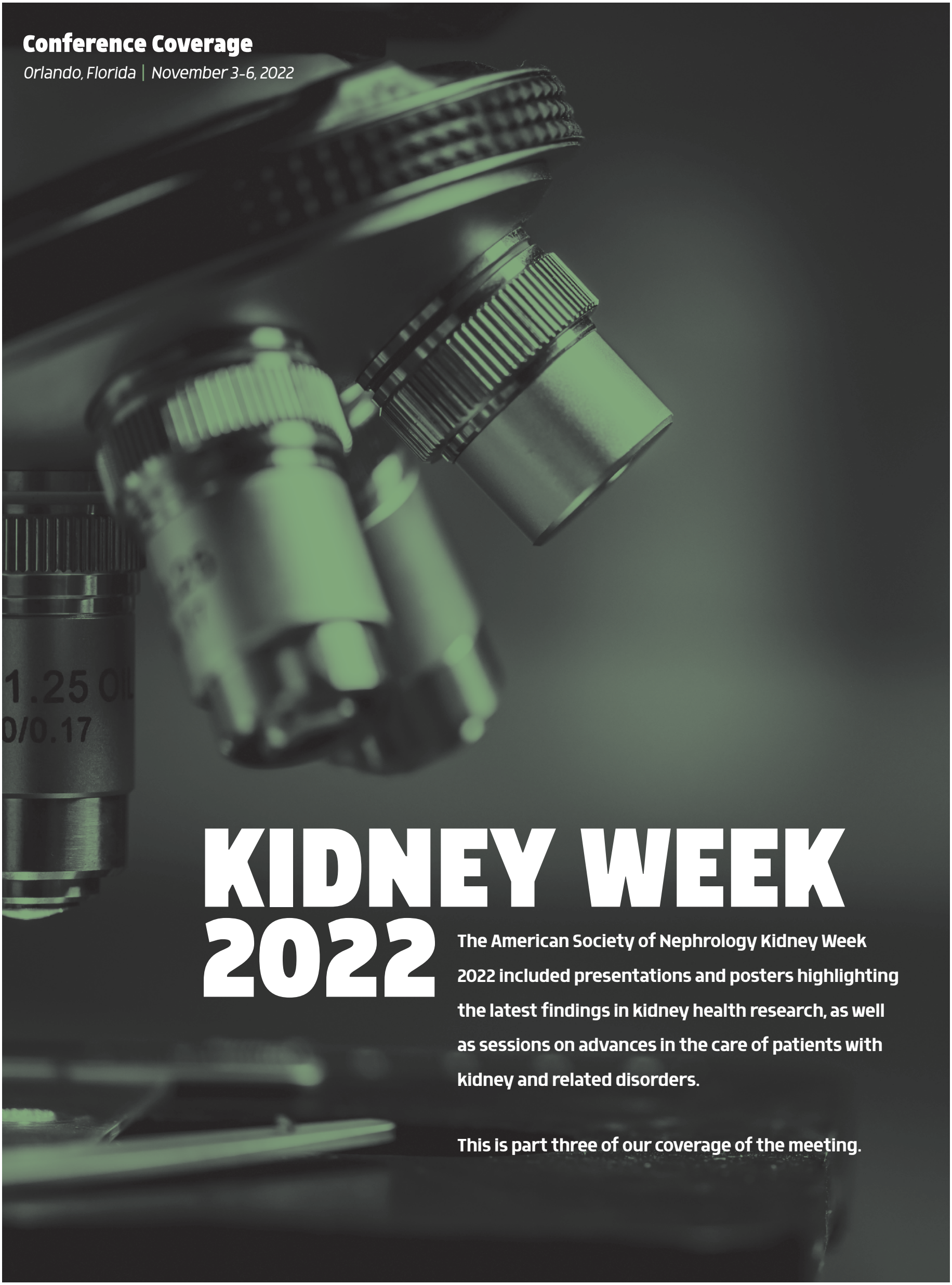
The analysis included demographics, comorbidities, and diagnoses for up to 2 years following any COIVD-19 polymerase chain reaction (PCR) test (index event). The two cohorts were balanced on age, sex, Hispanic ethnicity, Black race, hypertension, diabetes, heart failure, and atherosclerosis with a 1:1 propensity score matching using the nearest neighbor method. Patients with a kidney-specific diagnosis prior to their COVID-19 PCR test were excluded.

The search identified 2,780,576 C19+ve patients and 735,966 Vax7+ve patients. Following propensity score matching, each group included 736,034 patients.

Mean age was 51.5 years, 58.8% were female, 14.9% were Black, and 9.9% were Hispanic or Latino. There was an association between COVID-19 vaccination and a reduced risk of incident CKD, unspecified kidney failure, and nephritic syndrome. There was no reduction in risk for nephrotic syndrome or glomerulonephritis.

"Vaccination may reduce the risk of CKD associated with PASC. If confirmed in a prospective study, our findings can expand the known benefits of vaccination on the acute disease to PASC manifestations, potentially improving the uptake of the COVID-19 vaccines by the population," the authors said.

Source: Mir H, Roumelioti M-E, Argyropoulos C. Vaccination reduces risk of CKD associated with COVID-19 disease. TH-P0903. Abstract of a poster presented at the American Society of Nephrology Kidney Week 2022; November 3, 2022; Orlando, Florida.



KIDNEY WEEK 2022

The American Society of Nephrology Kidney Week 2022 included presentations and posters highlighting the latest findings in kidney health research, as well as sessions on advances in the care of patients with kidney and related disorders.

This is part three of our coverage of the meeting.

Patiromer for Hyperkalemia in Patients With and Without Diabetes

The gold standard therapy for patients with heart failure with reduced ejection fraction (HFrEF) and chronic kidney disease (CKD) is treatment with renin-angiotensin-aldosterone system inhibitors (RAASi). According to **Gerasimos Filippatos, MD,** National and Kapodistrian University of Athens, Athens, Greece, suboptimal RAASi use has been associated with hyperkalemia.

Results of the DIAMOND trial demonstrated that treatment with patiromer, a novel potassium binder, maintained lower serum potassium compared with placebo and facilitated optimal RAASi therapy, including mineralocorticoid receptor antagonists (MRAs) in patients with HFrEF. Dr. Filippatos conducted a prespecified analysis of patient subgroups with and without diabetes in the DIAMOND trial.

Results were reported during a poster session at the American Society of Nephrology Kidney Week 2022. The poster was titled *Patiromer for Hyperkalemia Management in Patients Receiving Renin-Angiotensin-Aldosterone System Inhibitors for Heart Failure (DIAMOND): Prespecified Analysis of Patients With or Without Diabetes.*

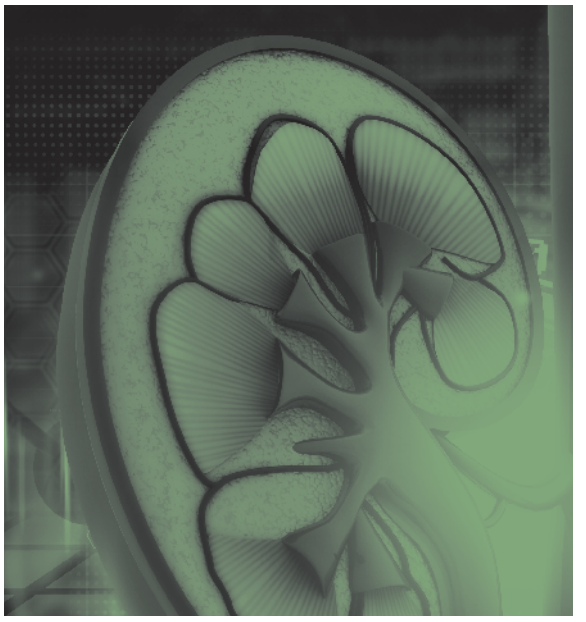
The analysis included patients with HFrEF with current hyperkalemia or a history of hyperkalemia who entered a single-blinded run-in phase of up to 12 weeks for optimization of patiromer and RAASIs. Following the run-in period, patients were randomized to receive either double-blind continued patiromer or placebo (patiromer withdrawal).

The primary end point was mean change in serum potassium from baseline to the end of the trial. Secondary end points were serum potassium >5.5 mEq/L, durable enablement of MRA at target dose, adverse events related to hyperkalemia, hyperkalemia-related hard outcome end points, and a win ratio of novel RAASi use score based on the sequence of all-cause mortality, hospitalization related to cardiovascular causes, and RAASi use.

A total of 1195 patients entered the run-in phase. Of those, 878 were randomized. A total of 356 randomized patients (41%) had diabetes. The treatment effect of patiromer compared with placebo was consistent in patients with and without diabetes.

"Patiromer can effectively control serum potassium and facilitate optimization of MRAs in patients with HFrEF irrespective of diabetes," Dr. Filippatos said.

Source: Filippatos G. Patiromer for hyperkalemia management in patients receiving renin-angiotensin-aldosterone system inhibitors for heart failure (DIAMOND): prespecified analysis of patients with and without diabetes. TH-P0604. Abstract of a poster presented during the American Society of Nephrology Kidney Week 2022; November 3, 2022; Orlando, Florida.



Patients With CKD Face Increased Risks for Adverse Outcomes in COVID-19

Patients with chronic kidney disease (CKD) and end-stage renal disease (ESRD) are at increased risk of severe disease and worse outcomes in COVID-19. **Lucas Wang, MD,** and colleagues at the Methodist Dallas Medical Center, Dallas, Texas, conducted a study to compare outcomes in unvaccinated COVID-19 patients with established CKD/ESRD with COVID-19 patients with normal kidney function at baseline.

Results of the study were reported during a poster session at the American Society of Nephrology Kidney Week 2022 in a poster titled *Outcomes in CKD Patients With COVID-19.* The outcomes of interest were rates of hospital mortality, major adverse cardiovascular events (MACE), and respiratory failure requiring mechanical ventilation.

The researchers utilized an observational database to identify 3183 unvaccinated COVID-19 polymerase chain reaction-positive patients hospitalized at Methodist Health System from March 2020 to December 2020. The primary end point was all-cause hospital mortality.

Severe disease was defined as MACE or respiratory failure requiring mechanical ventilation. MACE was defined as congestive heart failure exacerbation, myocardial infarction, stroke, pulmonary embolism, deep venous thrombosis, or shock. Observed variables were analyzed via chi-square, Fischer's exact test, and odds ratio (OR) tests.

Of the 3183 identified patients, 15% (n=476) had preexisting kidney disease (CKD or ESRD), 5.4% (n=170) were receiving maintenance dialysis, and 8.79% (n=279) had CKD stages 1-5. Compared with the group without kidney disease, there was an increased risk for all-cause hospital mortality in the group with CKD/ESRD (OR, 141; 95% CI, 1.04-1.83; $P<.04$). The risk of a MACE was also higher in the group with CKD (OR, 1.24; 95% CI, 1.03-1.48; $P<.02$), specifically higher risk of congestive heart failure exacerbation and shock (OR, 3.28; 95% CI, 2.16-4.97; $P<.001$ and OR, 1.36; 95% CI, 1.01-1.84; $P<.004$, respectively).

The two groups were similar in the risk of respiratory failure requiring mechanical ventilation (OR, 1.06; 95% CI, 0.78-1.44; $P=.70$).

"The COVID-19 pandemic had worldwide devasting outcomes for vulnerable groups such as CKD patients," the researchers said. "In our study, we demonstrated that CKD and ESRD is associated with a higher incidence of mortality and MACE in COVID-19. By understanding the clinical course of these patients, clinicians may better anticipate and attempt to improve outcomes during inpatient visits."

Source: Wang L, Canela V, Sidhu M. Outcomes in CKD patients with COVID-19. TH-P0913. Abstract of a poster presented at the American Society of Nephrology Kidney Week 2022; November 3, 2022; Orlando, Florida.

Disparities in Placement of Arteriovenous Access at Hemodialysis Initiation

Studies have shown that there are racial and ethnic disparities in the type of arteriovenous access (AVA)–arteriovenous fistula (AVF) versus arteriovenous graft (AVG)–used at incident hemodialysis. **Melandrea L. Worsley, MD,** and colleagues at Baylor College of Medicine, Houston, Texas, performed an analysis designed to assess racial and ethnic disparities in the anatomic location of hemodialysis AVA.

Results were reported during a poster session at the American Society of Nephrology Kidney Week 2022. The poster was titled *Racial and Ethnic Disparities in the Anatomic Location of Arteriovenous Access (AVA) for Hemodialysis (HD) Initiation.*

The researchers utilized clinical records of a large dialysis organization to evaluate patients ≥16 years of age with incident end-stage renal disease who initiated hemodialysis at an outpatient center. Eligible patients initiated hemodialysis via an AVF or an AVG between 2006 and 2021. Patients who initiated hemodialysis via catheter access, who had multiple access types/locations reported at incident hemodialysis, were on peritoneal dialysis, or had a kidney transplant were excluded from the analysis.

Race/ethnicity was categorized as White, Black, Hispanic, or other. Access location was identified as forearm or nonforearm. Associations of race/ethnicity with AVA forearm location were estimated using multivariable logistic regression. Race x year interaction terms were used to assess AVA location trends over time.

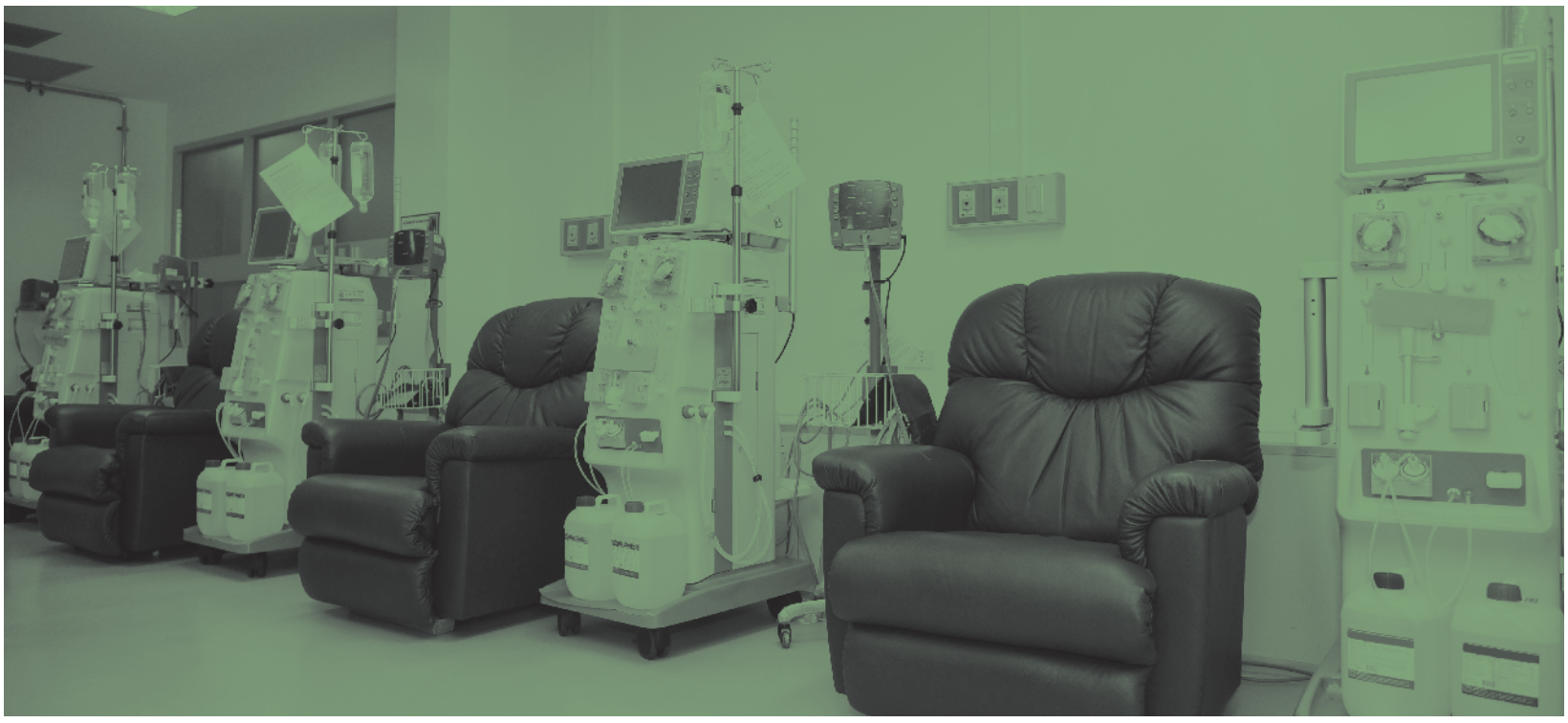
The eligible cohort included 42,373 participants. Of those, 22,596 were White, 10,729 were Black, 5054 were Hispanic, and 3994 were other races/ethnicities. Of the total cohort, 61% had diabetes and 6% had heart failure.

In all race/ethnicity groups, there was a decrease in hemodialysis initiation via a forearm AVA over time: in 2006, 48% had a forearm AVA compared with 28% in 2021. An omnibus test for interaction of race x calendar time was significant (P=.006).

In 2021, compared with White patients, Black patients were 24% (95% CI, 16%-31%) less likely to initiate hemodialysis with a forearm AVA, and Hispanic patients were 19% (95% CI, 8%-28%) less likely to initiate hemodialysis with a forearm AVA. The findings were consistent within the subgroups with AVF and AVG access. Patients of other races were 23% (95% CI, 8%-41%) more likely to initiate hemodialysis with a forearm AVA than White patients.

In summary, the researchers said, "Racial disparities exist in the anatomic location of AVA used for initiation of outpatient hemodialysis, with Black and Hispanic patients being less likely than White patients to have a forearm location. Use of forearm AVA, generally the preferred anatomic location, has decreased over time across all racial/ethnic groups. Further investigation is needed into factors influencing these disparities and temporal trends."

Source: Worsley ML, Winkelmayer WC, Erickson KF, Niu J, Gregg LP. Racial and ethnic disparities in the anatomic location of arteriovenous access (AVA) for hemodialysis (HD) initiation. FR-PO859. Abstract of a poster presented at the American Society of Nephrology Kidney Week 2022; November 4, 2022; Orlando, Florida.



Treating Gout in Kidney Transplant Recipients on Immunosuppression

Immunomodulator cotherapy has been shown to improve the efficacy of pegloticase by reducing its immunogenicity. Results of the PROTECT study, an open-label, single-arm study in kidney transplant recipients on stable immunosuppressants with uncontrolled gout suggested that pegloticase was effective in reducing serum urate levels, with a high responder rate of 89% (serum urate <6 mg/dL for ≥80% of the time during month 6, while preserving key indicators of graft function).

Abdul A. Abdellatif, MD, and colleagues conducted a study to assess the pharmacokinetics and immunogenicity of pegloticase in patients with uncontrolled gout with a history of kidney transplant on immunosuppression. Results were reported during a poster session at the American Society of Nephrology Kidney Week 2022 in a poster titled *Pharmacokinetics and Immunogenicity of Pegloticase in Patients With Kidney Transplants Revoicing Pegloticase for Uncontrolled Gout*.

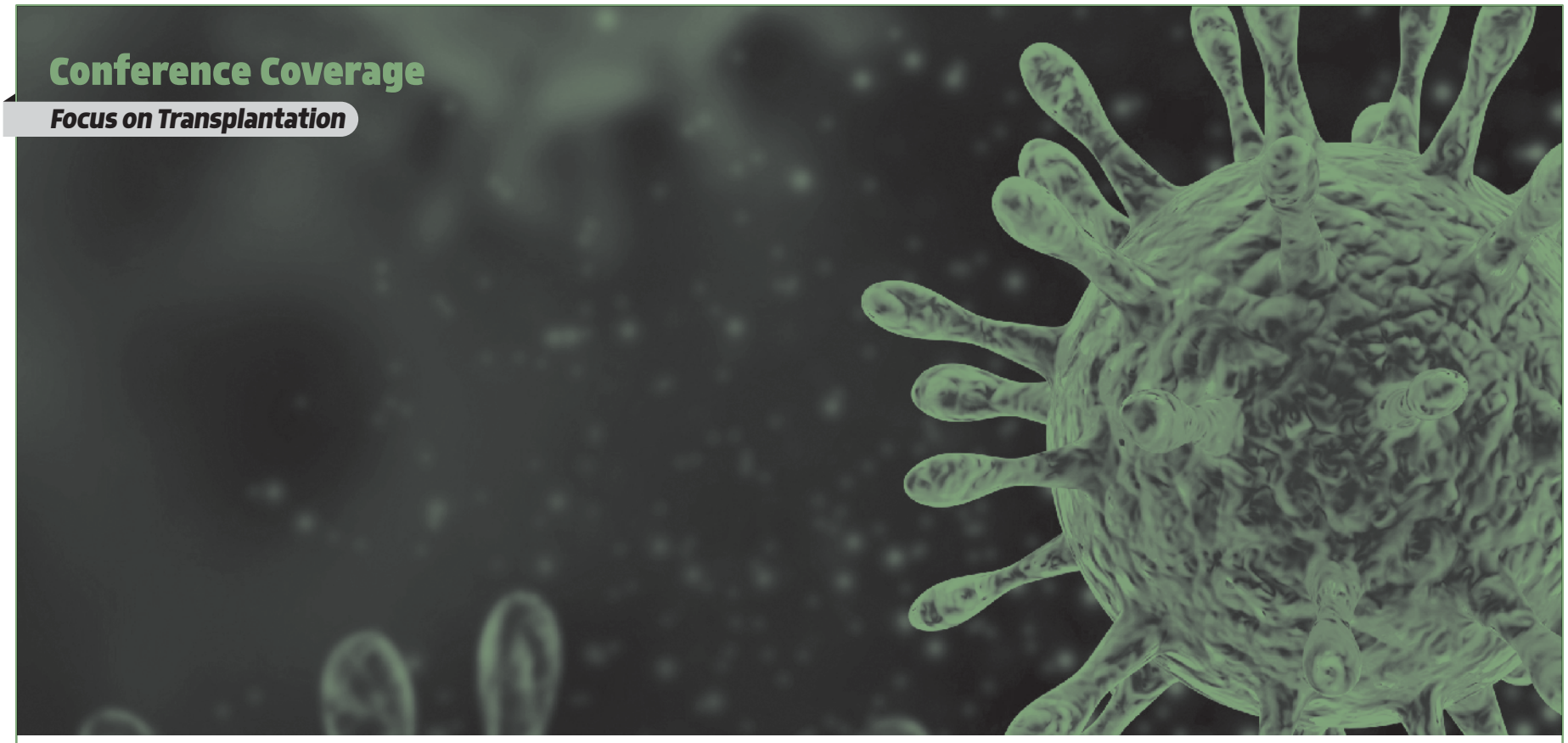
Pegloticase was administered via intravenous (IV) infusion 8 mg every 2 weeks for 24 weeks. Pharmacokinetics and immunogenicity analyses were conducted using serum samples collected pre- and postdose at multiple visits.

The analysis included 20 patients who received at least one dose of pegloticase. Among serum urate responders, measurable pegloticase concentrations were maintained through month 6. Following initiation of pegloticase treatment, median pre- and postdose pegloticase concentration ranged from 0.97 to 1.59 µg/mL and 1.57 to 3.60 µg/mL, respectively. Conversely, the two nonresponders both had predose concentrations of pegloticase below the limit of quantification (BLQ), and one had a BLQ value postinfusion, consistent with the immunogenicity results.

Pegloticase exposures were higher in patients observed with pegloticase monotherapy, consistent with previously observed improved pharmacokinetic seen with methotrexate cotherapy. There were no reactions or anaphylaxis during the trial period.

"Pegloticase 8 mg IV every 2 weeks with standard-of-care immunosuppressants in transplant patients resulted in a high serum urate responder rate and improved pegloticase exposure," the researchers said.

Source: Abdellatif AA, Xin Y, Chamberlain J, et al. Pharmacokinetics and immunogenicity of pegloticase in patients with kidney transplants receiving pegloticase for uncontrolled gout. FR-PO232. Abstract of a poster presented at the American Society of Nephrology Kidney Week 2022; November 4, 2022; Orlando, Florida.



Mortality From COVID-19 Infection in Kidney Transplant Recipients Over Time

Yorg Al Azzi, MD, and colleagues at Montefiore Medical Center, Bronx, New York, conducted an analysis to examine the variation in mortality from SARS-CoV-2 infection in kidney transplant recipients during the course of the pandemic. Results were reported during a poster session at the American Society of Nephrology Kidney Week 2022 in a poster titled *Decreased Mortality From SARS-CoV-2 in Kidney Transplant Recipients Over the Course of the Pandemic.*

During the study period of March 16, 2020, to May 4, 2022, a total of 537 patients at the center were diagnosed with SARS-CoV-2 infection by reverse transcription polymerase chain reaction test. Of the 537 patients, 59% were male, median age was 58 years, 51.2% were Hispanic, and 29% were African American. Three-quarters (75.4%) had received a deceased-donor renal transplant and 55% received anti-thymocyte induction. Most of the patients were on triple immunosuppression (96% calcineurin inhibitors, 87% antimetabolite, and 99% on prednisone).

During the first peak of the pandemic (March 16-April 30, 2020), the mortality rate was 35% (n=47/128). The mortality rate significantly decreased to 11% (n=7/61) from May 1, 2020, to the end of December 2020 with social distancing and use of facemasks. With the introduction of vaccines and monoclonal antibodies, the mortality rate further declined to 7.7% (n=10/129) between January 1, 2021, and November 5, 2021. When the Omicron variant and subvariants were predominant (November 6, 2021, to May 4, 2022) the mortality rate was 5.5% (n=12/219).

Among the patients diagnosed during the Omicron predominant wave, 85.8% (n=188/219) had received two doses of COVID-19 vaccine and 37.4% (n=82/219) had received a third dose. After introduction of the use of monoclonal antibodies, 93 patients received a combination of casirivimab/imdevimab during the period of the initial SARS-CoV-2 variants and sotrovimab then bebtelovimab during the time of dominance of Omicron and subvariants. Only one death occurred in the group that received monoclonal antibody treatment; that patient had been hospitalized for severe COVID-19.

There were 23 reinfections in the study cohort. Most of the reinfected patients had received at least two doses of COVID-19 vaccine; only five received a third dose. None of the patients who were reinfected required hospitalization or died.

In summary, the authors said, "Mortality from SARS-CoV-2 infection in kidney transplant recipients has significantly decreased over time. This could be explained by initial exposure to higher viral load due to lack of personal protection and social distancing. However, since the judicious use of monoclonal antibodies and vaccination, in addition to social distancing and use of facemasks, the mortality in kidney transplant recipients has decreased over time."

Source: Al Azzi Y, Liriano-Ward LE, Kapoor S, Ajaimy M, Akalin E, Pynadath CT. Decreased mortality from SARS-CoV-2 in kidney transplant recipients over the course of the pandemic. TH-P0945. Abstract of a poster presented during the American Society of Nephrology Kidney Week 2022; November 3, 2022; Orlando, Florida.

Vaccinated Kidney Transplant Recipients Hospitalized for COVID-19

Results of studies have suggested suboptimal immunological response to COVID-19 vaccination in kidney transplant recipients. **Ali Waris Rizvi, MD,** and colleagues at the Allegheny Health Network, Pittsburgh, Pennsylvania, conducted a descriptive study utilizing chart review to identify specific characteristics of vaccinated kidney transplant recipients who required hospitalization for COVID-19 infection.

Results were reported during a poster session at the American Society of Nephrology Kidney Week 2022. The poster was titled *Characteristics of Vaccinated Kidney Transplant Recipients Requiring Hospitalization for COVID-19 Infection.*

The chart review included kidney transplant recipients who were hospitalized for a COVID-19 infection between March 2020 and January 2022 in an integrated health network. The researchers identified demographic characteristics of kidney transplant recipients who received two or more doses of COVID-19 vaccine prior to hospitalization.

A total of 114 kidney transplant recipients were admitted to the hospital with COVID-19 infection during the study period. Of those, 39% (n=44) had received two or more doses of COVID-19 vaccine prior to hospitalization; 35 patients had received two vaccine doses and nine had received two or more vaccine doses.

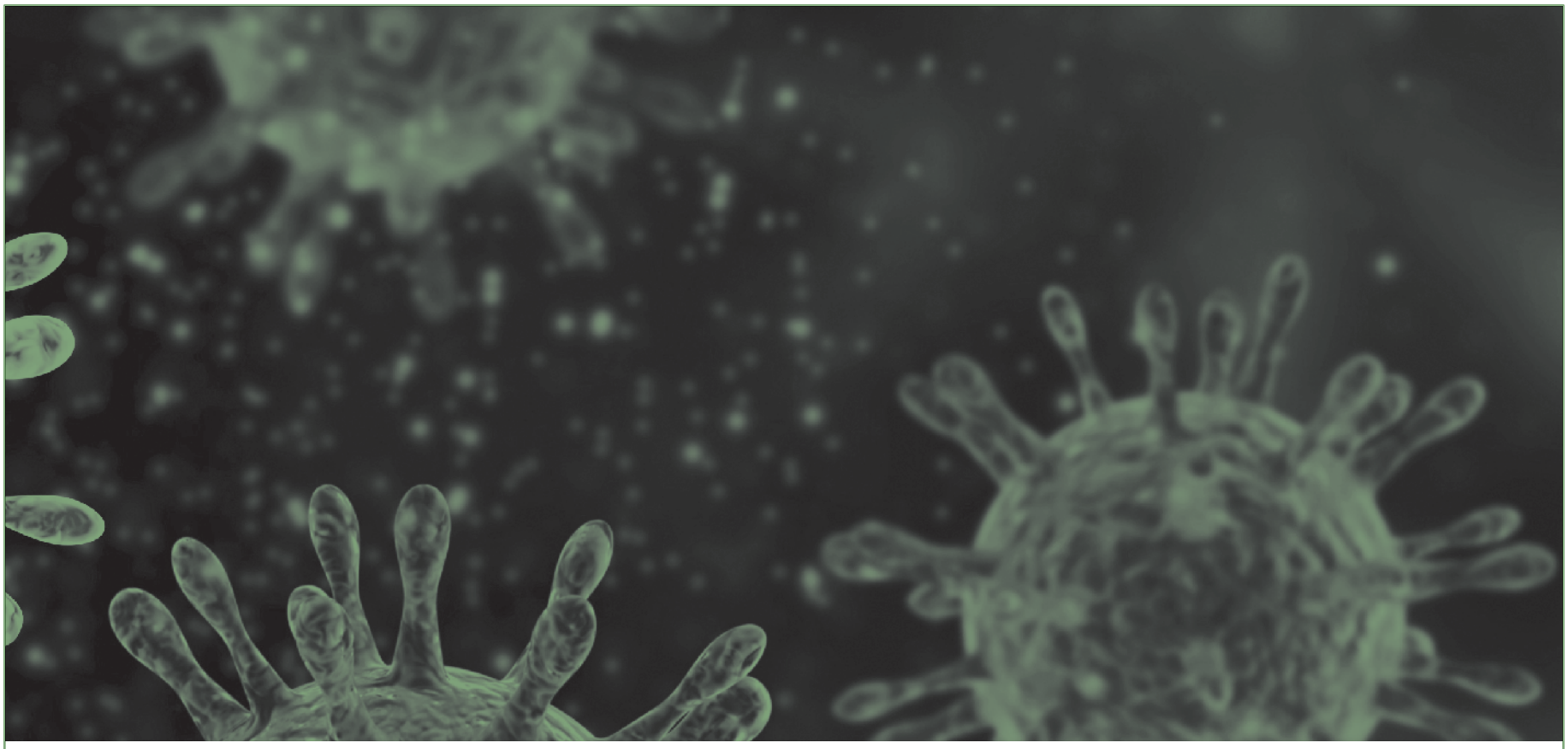
Of the 44 patients included in the analysis, mean age was 61.6 years, body mass index was 29.1 kg/m^2, 43% (n=19) were female, and 66% (n=29) were White, 27% were Black (n=12), and 7% (n=3) were other races. Common comorbidities were hypertension, diabetes, coronary artery disease, congestive heart failure, and chronic obstructive pulmonary disease.

Immunosuppression regimens were tacrolimus (93%, n=41), mycophenolate mofetil (82%, n=36), and steroids (57%, n=25). Three-quarters of the cohort (n=33) received a deceased donor transplant.

Vaccinated patients who required hospitalization were generally older and more likely to be male. Of the hospitalized patients, 18% required dialysis and 90-day mortality was 20%.

In summary, the authors said, "Despite receiving at least two doses of preventative vaccination, many kidney transplant recipients developed COVID-19 infection requiring hospitalization. Our findings are consistent with studies showing reduced antibody and cell-mediated response to vaccination in kidney transplant recipients. Every effort should be made to education and encourage this vulnerable population about measures to prevent infection, especially vaccination with subsequent booster doses."

Source: Rizvi AW, Turk M, Alhuneafat L, et al. Characteristics of vaccinated kidney transplant recipients requiring hospitalization for COVID-19 infection. TH-P0951. Abstract of a poster presented at the American Society of Nephrology Kidney Week 2022; November 3, 2022; Orlando, Florida.



COVID-19 Vaccine Response in Kidney Transplant Recipients

Risks of complications and mortality related to COVID-19 infection are higher among kidney transplant recipients than in the general population. Vaccination is the most important strategy to protect kidney transplant recipients from serious complications related to COVID-19.

Debargha Basuli, MD, and colleagues at East Carolina University, Greenville, North Carolina, conducted a study to examine the antibody response to mRNA vaccines in kidney transplant recipients. Results of the study were reported during a poster session at the American Society of Nephrology Kidney Week 2022 in a poster titled *A Single Center Study of SARS-CoV-2 Spike Antibody Response to Vaccination in Renal Transplant Recipients.*

The researchers examined antispike IgG response to mRNA vaccines (BNT162b2 and mRNA-1273) against SARS-CoV-2 in adult kidney transplant recipients at the center. The study utilized preserved blood samples from kidney transplant recipients undergoing routine monitoring. SARS-CoV-2 antibody response was detected using the LABScreen COVID Plus Assay (One Lambda). Fisher's exact test was used to compare categorical variables, and a t-test was used to compare continuous variables.

A total of 120 kidney transplant recipients at the center received two doses of the vaccine. Of those, only 61.7% (n=74) elicited a positive response with antispike antibody. Following a third dose/first booster vaccine, 81.4% (n=35/43) had a positive response.

There were no statistically significant differences between the responders and the nonresponders in age, sex, race, blood group, time since transplant, or vaccine type. Compared with two doses, a third vaccine dose produced a statistically significant increase in antibody response. A third dose induced a serological response in seven of eight individuals who did not respond after the first two doses. None of the participants developed donor-specific human leukocyte antibody in response to COVID-19 infection or the vaccine.

"In this single-center retrospective study, we demonstrated that the antibody response to SARS-CoV-2 mRNA vaccine was most prevalent after 4 months since the second dose. In addition, a third dose induced an antibody response in a larger number of kidney transplant recipients (81.3% vs 61.67%; *P*=.018), suggesting that this patient population may benefit from receiving multiple doses of mRNA vaccines," the authors said.

Source: Basuli D, Ross B, Briley K, Ali H, Rebellato L. A single center study of SARS-CoV-2 spike antibody response to vaccination in renal transplant recipients. TH-P0935. Abstract of a poster presented at the American Society of Nephrology Kidney Week 2022; November 3, 2022; Orlando, Florida.

Impact of COVID-19 Vaccination Among Kidney Transplant Recipients

Due in part to the need for immunosuppression regimens, recipients of kidney transplant are at increased risk for severe complications from COVID-19. Prior to availability of COVID-19 vaccines, the prevalence of acute kidney injury and death among kidney transplant recipients with COVID-19 at Weill Cornell Medicine, New York, New York, was 39% and 13%, respectively.

During a poster session at the American Society of Nephrology Kidney Week 2022, **Perola Lamba, MD,** and colleagues at the center reported on the impact of COVID-19 on patient and allograft outcomes in kidney transplant recipients with and without COVID-19 vaccination. The analysis also included data on outcomes in that patient population with and without response (SARS-CoV2-spike/anti-S antibody) to COVID-19 vaccines. The poster was titled *Outcomes in Kidney Transplant Recipients With COVID-19 Illness in the Era of Vaccines.*

The retrospective cohort analysis included 142 kidney transplant recipients with COVID-19 between July 1, 2021, and February 10, 2022. The researchers collected data on patient demographics, COVID-19 vaccine doses, anti-S levels, and clinical outcomes (graft dysfunction, hospitalization, admission to the intensive care unit [ICU], and death).

Of the 142 kidney transplant recipients in the cohort, 80% (n=113) were fully vaccinated (+/- booster) and 20% (n=29) were unvaccinated or partially vaccinated. Sixty of the 113 vaccinated patients were tested for anti-S levels between COVID-19 vaccination and COVID-19 diagnosis; 68% tested positive and 32% tested negative for anti-S antibodies.

Episodes of allograft dysfunction and hospitalization were less frequent among the fully vaccinated group compared with the unvaccinated cohort. Forty-seven percent of the unvaccinated cohort experienced allograft dysfunction (increase in creatinine, new or worsening proteinuria, or both) compared with 24% of the vaccinated cohort (odds ratio [OR], 3.46; 95% CI, 1.47-8.15; *P*=.004). In the unvaccinated cohort, 59% (n=17/29) were hospitalized compared with 28% (n=32/113) of the vaccinated cohort (OR, 3.59; 95% CI, 1.54-8.35; *P*=.003). There was no difference between the two groups in admission to the ICU and death.

In the vaccinated cohort, there was a trend toward less graft dysfunction among those with positive anti-S compared with those with negative anti-S (15% vs 33%). There were no differences between anti-S levels in hospitalization, admission to the ICU, and death.

In summary, the authors said, "In our cohort, kidney allograft dysfunction and hospitalization were less common [among] vaccinated versus unvaccinated kidney transplant recipients with COVID-19. Additionally, there is a trend toward lower graft dysfunction in those with positive anti-S antibodies. No significant differences were observed in death and ICU admission with vaccination or positive anti-S. Vaccination to COVID-19 and maintaining positive anti-S antibodies (with boosters or monoclonal antibodies) are important in preventing graft dysfunction and hospitalization following COVID-19."

Source: Lamba P, Stryjniak GJ, Lee JR, et al. Outcomes in kidney transplant recipients with COVID-19 illness in the era of vaccines. TH-P0956. Abstract of a poster presented at the American Society of Nephrology Kidney Week 2022; November 3, 2022; Orlando, Florida.

Roxadustat to Treat Anemia in Patients With Erythropoietin Hyporesponsiveness

The most common renal replacement therapies for patients with end-stage renal disease (ESRD) are peritoneal dialysis and hemodialysis. More than 500,000 individuals in China are receiving dialysis treatment, and more than 90% of patients on dialysis experience renal anemia. Anemia has been associated with increased risk for cardiovascular complications, diminished quality of life, and mortality.

Insufficient erythropoietin (EPO), iron deficiency, and inflammation are among the main causes of renal anemia. In the past 30 years, erythropoiesis-stimulating agents (ESAs) have been used to treat EPO deficiency. However, for patients with poor initial responses to ESAs, increasing the dose to achieve target hemoglobin levels has been associated with an increase in the risk of cardiovascualr events and death. Approximately 10% of patients treated with ESAs have EPO hyporesponsiveness, defined as a sustained substandard hemoglobin (<10.0 g/dL), despite sufficient iron levels (ferritin >100 ng/dL), and exogenous EPO administration (≥6000 IU/week). Management of patients with EPO hyporesponsiveness is challenging.

When activated, hypoxia-inducible factors (HIFs) induce the production of EPO. Roxadustat is a prolyl hydroxylase inhibitor that can simulate hypoxic stimulation to stabilize HIF expression under normoxic conditions. **Junjie Chen, MD,** and colleagues conducted a single-center, before and after treatment, self-controlled study to examine the efficacy and safety of roxadustat in patients with renal anemia and EPO hyporesponsiveness who are receiving continuous ambulatory peritoneal dialysis (CAPD). Results were reported in the *Journal of Renal Nutrition* [2022;32(5):595-604].

The study enrolled 55 patients on CAPD with renal anemia and EPO hyporesponsiveness. The primary follow-up parameters were routine blood, liver, and kidney function, electrolyte, blood lipid, high-sensitivity C-reactive protein (hsCRP), and iron tests. Interleukin-6 (IL-6) and tumor necrosis factor-a levels (TNF-α) were determined using serum samples via enzyme linked immunosorbent assay. The Modified Quantitative Subjective Global Assessment (MQSGA) score and Malnutrition-Inflammation Score (MIS) prior to and following treatment were recorded, as were adverse events during treatment. Follow-up observation time was 12 weeks. The researchers also collected data 12 to 24 weeks prior to enrollment as well as post-follow-up data at 36 weeks.

Of the 55 individuals in the study cohort, the intent-to-treat population, two withdrew consent and three others did not return to the hospital in a timely manner for re-examination and dropped out at week 2. The remaining 50 patients completed the 12-week follow-up.

Mean age of the overall cohort was 47.6 years, 47.3% (n=26) were male, mean weight was 60.4 kg, mean body mass index was 25.0 kg/m^2, mean duration of peritoneal dialysis was 2.5 years, and 100% (n=55) were receiving oral iron therapy. The baseline EPO dose was 11,166.7 IU/week.

The mean hemoglobin level at baseline was 8.0 g/dL, compared with 11.2 g/dL after 12 weeks of treatment with roxadustat. At all measured time points, the increases in hemoglobin with roxadustat treatment were statistically significant compared with the baseline value (P<.05). Hematocrit and erythrocyte counts were also correspondingly higher than baseline values. No one in the study cohort received a blood transfusion during the follow-up period.

At 12 weeks, 50% of the patients reached the target hemoglobin level (≥11.0 g/dL). A hemoglobin increase of 1.0 g/dL was considered a response, resulting in a response rate of 80% at 12 weeks. The doses of roxadustat were reduced compared with baseline; at 12 weeks the reduction was approximately14.3%, and hemoglobin was still well maintained. Up to week 36, the final dose was achieved at 4.2 mg/kg/week.

Subgroup analyses divided patients into two groups: low hsCRP (hsCRP <5 mg/L, n=24) and high hsCRP (hsCRP ≥5 mg/L, n=23) based on baseline hsCRP level. There was no statistically significant difference in hemoglobin levels between the two subgroups at all time points (0, 4, and 12 weeks) (P>.05). The hemoglobin increases at 4 weeks and 12 weeks were statistically significant for both groups (P<.05 for both time points).

Clinical biochemical indices related to inflammation were measured at baseline and following treatment with roxadustat (hsCRP, white blood cell counts, neutrophilic percentage, neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, IL-6 levels, and TNF-α levels). Following treatment with roxadustat, there were no statistical differences in levels of any of the prespecified clinical biochemical indices and the corresponding baseline levels (P<.05). Analysis of serum samples of the IL-6 and TNF-α levels were also not significantly different between 4 weeks and baseline. Results demonstrated that treatment with roxadustat did not affect the inflammation status of CAPD patients.

There were no significant changes in mean overall blood lipid indices (triglycerides, total cholesterol, and lipoproteins). In addition, there were no statistically significant changes in nutrition-related indicators such as albumin, pre-albumin, creatinine, and blood urea nitrogen from baseline values. The mean MQSGA score at 12 weeks was slightly reduced from baseline (13.0 points vs 14.4 points, respectively; P<.05). There was also a slight decrease in mean MIS from baseline (10.6 points vs 9.8 points; P<.05).

There were no serious adverse events observed during the follow-up period.

In citing limitations to the study, the researchers included the small sample size, the lack of a parallel control group with EPO, and insufficient follow-up time. The authors noted the need for clinical trials with larger sample sizes and longer follow-up times.

"Our research suggests that for patients with EPO hyporesponsiveness on CAPD, roxadustat can effectively and safely improve anemia and nutritional status without promoting inflammation. Roxadustat provides an effective and safe treatment strategy for these populations," the researchers said. ■

TAKEAWAY POINTS

- Researchers reported results of a study designed to assess the efficacy and safety of roxadustat in patients with renal anemia and erythropoietin hyporesponsiveness who are on continuous ambulatory peritoneal dialysis.
- Hemoglobin increased at all time points during the study period; the increases over baseline values were statistically significant.
- No serious adverse events were observed during the study period.

Uremic Solutes and Cardiovascular Mortality in DKD

In the population of patients with chronic kidney disease (CKD), particularly those with diabetes as the underlying cause of CKD, cardiovascular disease is a major cause of morbidity and mortality. While diabetic kidney disease (DKD) and cardiovascular disease have some risk factors in common, the pathogenesis of cardiovascular disease in the context of DKD is not completely understood, compounded by a lack of accurate biomarkers associated with cardiovascular outcomes in patients with DKD.

Compared with the general population, the association between the traditional risk factors for cardiovascular disease (age, sex, diabetes, duration, total cholesterol, high-density lipoprotein cholesterol, smoking, systolic blood pressure, hypertensive therapy) is not as strong in patients with CKD.

The uremic solutes trimethylamine-N-oxide (TMAO) and asymmetric and symmetric dimethylarginine (ADMA, SDMA) have been linked to cardiovascular disease in kidney failure with kidney replacement therapy (KFRT), but there are limited data in populations with diabetes and less severe kidney disease. **Hima Sapa, PhD,** and colleagues assayed plasma and urine for ADMA, SDMA, and TMAO in a random subcohort of participants with diabetes and baseline estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2 from the REGARDS (Reasons for Geographic and Racial Differences in Stroke) cohort study.

The results enabled the researchers to examine the associations with plasma concentrations and urine to plasma solute ratios with the primary outcome of cardiovascular mortality and the secondary outcomes of all-cause mortality and incident KFRT. Results were reported in the *American Journal of Kidney Diseases* [2022;80(4):502-511].

Plasma concentrations and ratios of urine to plasma concentrations of ADMA, SDMA, and TMAO were tested for association with the outcomes. Adjusted Cox regression

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models were fitted and hazard ratios of outcomes were calculated per standard deviation and per doubling, and as interquartile comparisons.

There were 555 participants in the subcohort of patients with diabetes and eGFR <60 mL/min/1.73 m^2. Women, those with less education, and White participants tended to have higher levels of ADMA. Male sex and Black race were associated with higher SDMA levels. There were associations between male sex and White race and higher TMAO levels.

For all three uremic solutes, plasma levels inversely and moderately correlated with eGFR; SDMA had the strongest correlation. There was also direct correlation between the plasma concentrations and UACR; however, those correlations were weaker than those with eGFR. For the ratio of urine to plasma levels of the uremic solutes, there were very strong pairwise correlations with eGFR and urine creatinine and moderately strong correlations with UACR.

Mean follow-up was 6.2 years. During the follow-up period, there were 120 cardiovascular deaths (mean rate of 3.31% per year). The cardiovascular mortality rate increased progressively with greater uremic solute plasma concentration quartile. Hazard ratios (HRs) were attenuated following adjustment for demographic and traditional cardiovascular risk factors, including eGFR and UACR. There were no differences in results when HRs were adjusted using a race-independent GFR estimating equation.

In an analysis of associations of the ratio of urine to plasma concentrations of the uremic solutes with cardiovascular mortality, there were independent associations between lower ratios of all three uremic solutes and cardiovascular mortality. The strengths of the associations ranged from 38% higher risk per two-fold lower urine-to-plasma ratio of TMAO to 69% higher risk for the corresponding SDMA associations. There were no significant associations between urinary concentrations or fractional excretion of ADMA, SDMA, and TMAO with cardiovascular death.

Over the course of the study, there were 285 all-cause deaths (7.67% per year). There were significant associations between higher concentrations of all three solutes and all-cause mortality. There were also consistent associations between lower ratios of urine to plasma concentrations with all-cause mortality.

In multivariable-adjusted models, there were strong and significant associations with ascending quartiles of plasma SDMA concentration and incident KFRT risk; the association did not reach statistical significance in the continuous model.

The researchers cited some limitations to the study, including the possibility of residual confounding by GFR, and the lack of data on dietary intake.

In conclusion, the authors said, "Higher plasma concentrations and lower ratios of urine to plasma concentrations of uremic solutes were independently associated with cardiovascular and all-cause mortality in DKD. Associations of ratios of urine to plasma concentrations with mortality suggest a connection between renal uremic solute clearance and cardiovascular disease pathogenesis.

"If validated in other cohorts, lower ratios of urine to plasma concentrations of ADMA, SDMA, and TMAO could be used to identify the subset of patients with diabetes and cardiovascular disease who are at particularly high risk for cardiovascular and all-cause mortality." ■

Decongestion Rate and Renal Outcomes in Acute Heart Failure

Patients with heart failure with reduced ejection fraction (HFrEF) commonly experience reduced kidney function, a condition associated with adverse clinical outcomes. Further, there is also an association between declines in estimated glomerular filtration rate (eGFR) over a period of months and increased risk of mortality and cardiovascular events. Previous studies have focused on the risk factors associated with short-term declines in eGFR, such as those that occur during hospitalization for acute heart failure.

One of the most common reasons for hospitalization with acute heart failure is volume overload, which has been shown to be a risk factor for poor clinical outcomes. A greater degree of congestion at the time of admission for acute heart failure is associated with a higher risk of poor cardiovascular and renal outcomes. Previous studies have demonstrated an association between decongestion (fluid removal) and decreased risk of mortality.

There are few data available on the risk factors for longitudinal declines in eGFR in patients with HFrEF. **Wendy McCallum, MD, MS,** and colleagues conducted a post hoc analysis of trial data to assess whether the rate of in-hospital decongestion is associated with longer term kidney function decline. Results were reported in the *American Journal of Kidney Diseases* [2022;80(1):65-78].

The analysis utilized data from the EVEREST (Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study with Tolvaptan) trial. Eligible patients had two or more kidney measures: one at discharge and at least one additional kidney assessment postdischarge.

The exposure of interest was the in-hospital rate of change in assessments of volume overload (B-type natriuretic peptide [BNP], N-terminal proB-type natriuretic peptide [NT-proBNP], and clinical congestion score [0-12]), and the rate of change in hemoconcentration, including measures of hematocrit, albumin, and total protein. The primary outcome of interest was incident chronic kidney disease GFR category 4 or 5 (CKD G4-G5), defined by a new eGFR of ≤30 mL/min/1.73 m^2. The secondary outcome of interest was decline in eGFR of >40%.

A total of 3500 patients who met eligibility criteria were included in the analysis. Median follow-up was 10.1 months. Patients had a median of eight measures of creatinine over the duration of the follow-up period.

Patients were stratified into quartiles based on slope of BNP and slope of hematocrit. Patients in BNP quartile 1 had the least rapid decline and even some increase (least negative or positive slope), and those in quartile 4 had the fastest decline in BNP (most negative slope). Overall, 71% of the patients had hypertension, 38% had diabetes, and median eGFR at discharge was 55 mL/min/1.73 m^2.

The majority of patients had declines in measures of volume overload and increases in measures of hemo-concentration. Those with the least rapid rates of decongestion (quartile 1) tended to have evidence of greatest volume overload, with higher baseline BNP and NT-proBNP at randomization and higher congestion score. They also tended to have lower hematocrit, albumin, and total protein. There were no differences in discharge eGFR among patients with more rapid or less rapid decline in BNP or hematocrit.

There was a linear relation between greater rate of decrease in BNP, NT-proBNP, and congestion score with lower risk of incident CKD G4-G5. There was an association between a more rapid decline in BNP and a lower hazard for incident CKD G4-G5 in both unadjusted and adjusted analyses. The adjusted hazard ratio (aHR) for incident CKD G4-G5 was 0.68 (95% CI, 0.58-0.79).

In comparison with the quartile with the slowest decline in BNP, quartiles with more rapid decline were associated with lower hazard of reaching incident CKD G4-G5. The pattern was similar for NT-proBNP. There was also an association between a more rapid decline in congestion score and lower hazard for incident CKD G4-G5 (HR, 0.82; 95% CI, 0.71-0.94) per every standard deviation (~1 point) decrease per week. The association grew stronger following adjustment for the baseline congestion score.

For the secondary outcome, the associations between the slopes of decrease in BNP, NT-proBNP, and congestion score were similar. There were associations between greater rates of decrease in BNP, NT-proBNP, and congestion score and lower hazard of decline in eGFR of >40%.

In both unadjusted and adjusted analyses, there was a linear relation between greater rate of increase in hematocrit, albumin, and total protein with lower risk of incident CKD G4-G5. In unadjusted analyses, there was a trend toward more rapid increase in hematocrit being associated with lower hazard for incident CKD G4-G5. The association grew stronger and reached statistical significance in adjusted analyses (adjustedHR, 0.73; 95% CI, 0.64-0.84) per every standard deviation (~1%) increase in hematocrit per week.

In both unadjusted and adjusted analyses, there was a linear relation between greater rate of increase in hematocrit, albumin, and total protein with lower risk of incident CKD G4-G5.

Compared with the quartile with the slowest increase in hematocrit, there were associations between quartiles with more rapid increase and lower hazard of reaching incident CKD G4-G5. The pattern was similar for albumin and total protein.

The authors cited some limitations to the analysis results, including the possibility of residual confounding, and lack of data on kidney parameters such as albuminuria or dose titration of angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers.

In summary, the researchers said, "Among patients with HFrEF, more rapid rates of decongestion during hospitalizations for acute heart failure were associated with decreased risk of future kidney function decline. That is, more rapid declines in BNP, NT-proBNP, and clinical congestion score or more rapid rates of decongestion are not placing patients with HFrEF at risk for future kidney function decline." ■

TAKEAWAY POINTS

- In patients with heart failure with reduced ejection fraction, decongestion is associated with improved survival outcomes, but may be associated with decline in estimated glomerular filtration rate.
- Researchers reported results of a study to examine whether the rate of in-hospital decongestion is associated with longer-term kidney function decline.
- Study results suggested that there was no association between more rapid decongestion in patients with acute heart failure and the risk of adverse renal outcomes.

INCIDENCE OF ORGAN DONATION AND TRANSPLANTS DURING MAJOR MOTORCYCLE RALLIES

A major public challenge in the United States is the ongoing shortage of organs available for transplant. In January 2022, there were more than 106,000 patients on a solid organ transplant waiting list. However, in 2021 there were only 33,000 transplants performed. Demand continues to exceed supply, and an estimated 16 patients die each day waiting for a transplant.

Deceased organ donation accounts for 84% of all organ transplants. Traumatic injury from motor vehicle accidents is a common source of deceased donor organs, accounting for 11% of all organ donors in 2021. Compared with passenger vehicle motorists, motorcyclists are disproportionately more likely to die in a crash, and unhelmeted motorcyclists are three times as likely to become organ donors when involved in fatal crashes.

Large-scale motorcycle rallies attract thousands of attendees and are associated with increased trauma-related morbidity and mortality. **David C. Cron, MD, MS,** and colleagues conducted a population-based, retrospective cross-sectional study to examine the association of major motorcycles rallies in the United States with the incidence of organ donation and transplants. Results of the study were reported in *JAMA Internal Medicine* [2023;183(1):22-30].

The researchers compared rates of motor vehicle trauma-related organ donation and transplant for all solid organs in the 4 weeks prior to and following seven major US motorcycle rallies to test the hypothesis that the rates of motor vehicle trauma-associated organ donation and transplant would be higher during motorcycle rallies and in their associated regions compared with surrounding weeks.

The seven rallies all had estimated annual attendance from 200,000 to 500,000. The included rallies were the Sturgis Motorcycle Rally (Sturgis, South Dakota); Daytona Bike Week (Daytona Beach, Florida); Laconia Motorcycle Week (Laconia, New Hampshire); Myrtle Beach Bike Week Spring Rally (Myrtle Beach, South Carolina); Atlantic Beach Bikefest (Myrtle Beach, South Carolina following the former rally); Republic of Texas Biker Rally (Austin, Texas); and Bikes, Blues & BBQ (Fayetteville, Arkansas). The rallies occurred from March through September.

All donors ≥16 years of age involved in a motor vehicle crash between March 2005 and September 2021 were identified. The primary outcome measures were the number of distinct organ donors per day and transplant recipients per day per Organ Procurement and Transplantation Network (OPTN) region. The main outcome of interest was the incidence of motor vehicle crash-related organ donation and the number of patients

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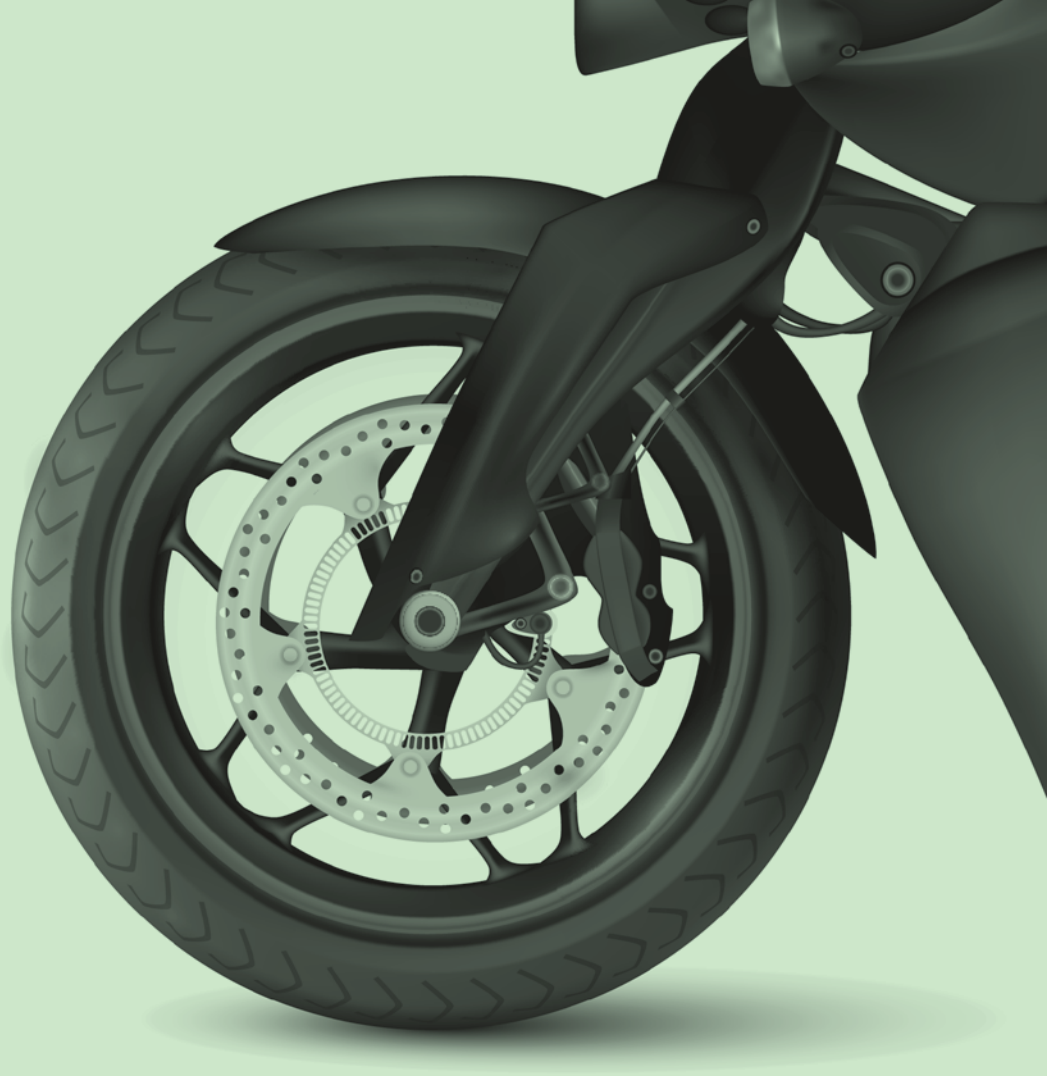
In regions with a motorcycle rally, there were 21% more organ donors per day during rally dates compared with the 4 weeks prior to and following the rally.



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receiving a solid organ transplant from those donors. The transplant recipient outcome was a count of the total number of recipients receiving one or more organs from each given donor linked temporally and geographically relative to the donor.

The analysis included 10,798 organ donors (70.9% male; mean age, 32.5 years) and 35,329 transplant recipients (64.0% male; mean age, 49.3 years). The transplanted organs were heart (n=5128), lung (n=2749), liver (n=8916), kidney (n=17,201), pancreas (n=614), kidney-pancreas (n=1951), and intestinal (n=104). A total of 30,074 region-days were analyzed; of those, 2.8% (n=854) involved a motorcycle rally.

During the rally dates, there were 406 organ donors (29.3% female; 70.7% male; mean age, 31.7 years) and 1400 transplant recipients (34.8% female; 65.2% male; mean age, 49.0 years). During the surrounding weeks, there were 2332 donors (29.4% female; 65.2% male; mean age, 32.2 years) and 7714 transplants (35.5% female, 64.5% male, mean age, 49.5 years).

Demographic and clinical characteristics were similar in donors during rally dates and nonrally dates, with the exception of donors during rally dates being more likely to be from racial minority groups compared with donors during nonrally dates in the surrounding weeks (19.0% vs 14.1%; *P*=.01). There were no statistically significant differences in transplant recipients in demographics, time spent on the waiting list, disease severity, or organ ischemia time between those who received a transplant on rally dates and those who received a transplant on nonrally dates.

In rally regions during rally dates compared with the surrounding 4 weeks in the same regions there were more organ donors per region-day (mean, 0.48 vs 0.42 per region-day; *P*=.03) and more transplanted organs (mean 1.69 vs 1.44 per day; *P*=.02). Organ yield (the number of organs procured and transplanted from a single donor) was similar during rally and nonrally dates.

Following adjustment for OPTN region, day of the week, week of the year, and year, the incidence of organ donation was higher on rally dates compared with surrounding nonrally dates. In regions with a motorcycle rally, there were 21% more organ donors per day during rally dates compared with the 4 weeks prior to and following the rally (incidence rate ratio [IRR], 1.21; 95% CI, 1.09-1.35; *P*=.001; absolute increase, 0.08 donors per region-day; 95% CI, 0.03-0.12 donors per region-day). Across the mean duration of a motorcycle rally (9 days), this reflected 0.7 (95% CI, 0.3-1.1) in additional organ donors for a typical rally.

In control (distant) regions, there was no significant difference in the number of organ donors per day during the dates of the motorcycle rally compared with the 4 weeks before and the 4 weeks after the rally (IRR, 1.06; 95% CI, 0.98-1.14; *P*=.14; absolute change, 0.22 donors per region-day; 95% CI, –0.01 to 0.04 donors per region-day). The net effect of motorcycle rallies (rally effect minus control effect) was 14% more organ donors per day during rally dates compared with nonrally dates (IRR, 1.14; 95% CI, 1.01-1.30; *P*=.04).

Following adjustment for OPTN region, day of week, week of year, and year, more patients received organ transplants on rally dates compared with nonrally dates. In regions with a motorcycle rally, there were 26% more transplant recipients per day during rally dates compared with nonrally dates (IRR, 1.26; 95% CI, 1.12-1.42; *P*<.001; absolute change, 0.34 transplant recipients per region-day; 95% CI, 0.15-0.52 transplant recipients per region-day), reflecting 3.1 (95% CI, 1.2-4.7) additional transplant recipients for a typical motorcycle rally.

In control regions, there was no significant difference in the number of transplant recipients per day during the dates of the motorcycle rally compared with nonrally dates (IRR, 1.06; 95% CI, 0.97-1.15; *P*=.18; absolute change, 0.06 transplant recipients per region-day; 95% CI, –0.03 to 0.14 transplant recipients per region day). The net effect of motorcycle rallies was 19% more transplant recipients per day during rally dates compared with nonrally dates (IRR, 1.91; 95% CI, 1.04-1.37; *P*=.01).

Study limitations cited by the authors included the observational design, the inability to assess whether the increase in organ transplants during rallies led to improved transplant outcomes associated with earlier transplants, and the possibility that the findings were due to chance alone.

"In this cross-sectional study, an increase in motor vehicle crash-related organ donors and an increase in the number of organs transplanted was observed during dates of major US motorcycle rallies in regions where these rallies were held," the researchers said. "Motorcycle rallies and other large-scale events are common, and though the priority must be public safety and minimizing excess morbidity and mortality during these events, the potential downstream association with organ donation should be recognized." ■

TAKEAWAY POINTS

- Researchers reported results of a study examining the association of major US motorcycle rallies and the incidence of organ donations and transplants.
- The study findings showed that there was an increase in motor vehicle crash-related organ donors and an increase in the numbers of organs transplanted during the dates of US major motorcycle rallies during the dates of the rallies in the regions where the rallies were held.
- During rallies, there were 21% more organ donors per day and 26 more transplant recipients per day in the regions where the rallies were held.

Virtual Reality Education Program Funded in Mississippi

In a press release, Fresenius Medical Care North America (FMCNA), a leading provider of kidney care, announced the receipt of a grant from the Office of Rural Health and Primary Care in the Mississippi Department of Health. The grant is intended to expand kidney education through virtual reality (VR).

The $130,000 grant will fund VR educational programs from Fresenius Kidney Care (FKC), the care delivery arm of FMCNA, on the advantages of home therapy for patients in rural Mississippi. The VR simulation will enable patients to participate in a virtual patient's journey through home dialysis to illustrate the way home dialysis works.

The grant will allow FKC to provide its dialysis centers in Mississippi with VR headsets and initially offer the immersive experience of following a patient navigating the path to home dialysis. IKONA Health, an immersive learning company and partner of FMCNA, will also develop additional modules for patients as well as care teams.

Dean Chan, vice president of Kidney Care Advocates at FKC, said, "An initial diagnosis of chronic kidney disease can be daunting for patients. The virtual reality education for our patients is another way we can enhance our patient education and show them how to be in control of their treatment. Expanding this innovative project into rural areas of Mississippi will allow our Kidney Care Advocates and care teams to offer patients in underserved areas a more informed experience of the decision to move to home therapy and help them be successful."

Tim Fitzpatrick, cofounder and CEO of IKONA Health, said, "We are excited to expand this innovative platform to rural communities, where patients can greatly benefit from decreased travel time and treatment duration with home therapy. We have an opportunity to scale effective, VR-based learning experiences to underserved communities to improve understanding, health literacy, and overall health outcomes."

NKF Statement on State of the Union Address

Following President Biden's State of the Union Address, **Kevin Longino,** CEO of the National Kidney Foundation (NKF) and a kidney transplant recipient, issued the following statement:

"Every day, kidney patients experience challenges such as difficulty navigating complicated health care systems, struggles affording prescription medication, and trouble accessing much needed mental health services. We applaud the President for recognizing and speaking to many of these issues during the State of the Union Address.

"But kidney patients have many other priorities that weren't referenced in [the] speech, including the need to invest in kidney research and prevention activities, enhance access to home dialysis, and ensure that no one dies waiting for a lifesaving transplant.

"The NFK stands ready to work with the President, Congress, and other state and local leaders on all of these issues to improve the lives of the 37 million Americans with kidney disease."

AKF and USPSTF CKD Screening Guidelines

The American Kidney Fund (AKF) has initiated a campaign to urge the US Preventive Services Task Force (USPSTF) to develop a chronic kidney disease (CKD) screening recommendation. In a letter to the USPSTF, the AKF outlined the reasons for their support for the screening recommendation.

The support stems from concerns regarding the increasing number of people with kidney failure and the need for dialysis or transplantation, as well as the health disparities associated with kidney disease and the need for clinical assessment tool available to primary care physicians and other providers when screening for CKD. The letter notes that the USPSTF last considered kidney screenings guidelines in 2012, prior to the availability of two classes of drugs to slow the progression of CKD (sodium-glucose cotransporter-2 inhibitors and glucagon-like peptide 1 receptor agonists).

AFK is requesting that the guidelines include a recommendation that every patient at increased risk for kidney disease, particularly those who have been diagnosed with hypertension, diabetes, or cardiovascular disease, be screened for CKD. In addition, AFK is calling for a recommendation to include all racial and ethnic minorities in CKD screening, focusing on communities more likely to develop kidney failure, as well as a recommendation that all people who utilize community health centers or federally qualified health centers should be screened at each annual visit.

Two other suggested recommendations include (1) all patients at risk for CKD have an annual estimated glomerular filtration (eGFR) test and a urine albumin-to-creatinine ratio test and (2) primary care providers should refer a patient to a nephrologist when a patient reaches CKD stage 4 (GFR <30 mL/min/1.73 m^2) or severely increased albuminuria (>300 mg/g).

OPTN Approves Process to Improve Transplant Equity

The Organ Procurement and Transplantation Network (OPTN) released a paper on a proposal to provide a pathway for waiting time modifications for Black kidney transplant candidates on the transplant waiting list who have been affected by race-inclusive estimated glomerular filtration rate (eGFR) calculations. The report was generated in cooperation with the OPTN Minority Affairs and Kidney Transplantation Committees.

In early 2022, the two committees cosponsored a public comment period on a proposal to prospectively prohibit the use of eGFR calculations that include a race-based variable in OPTN policy. The proposal received widespread support and was passed by the OPTN Board of Directors on June 27, 2022, and implemented on July 27, 2022.

At a meeting on December 5, 2022, the OPTN Board of Directors unanimously approved a process intended to improve transplant equity by backdating the waiting times of Black kidney transplant candidates who were disadvantaged by previous use of a race-inclusive calculation to estimate GFR.

The recently published paper offers programs a 365-day timeframe to review waiting lists and request eGFR waiting time modifications for registered Black candidates who have been impacted by race-inclusive eGFR calculations. The paper includes a summary of the committees' original recommendations and adjustments to those recommendations based on community input and additional discussion.

Research Provides Insights Into the Role of Glucose in Cyst Formation

The National Institutes of Health (NIH) issued a press release describing a new approach to understand the biology of polycystic kidney disease (PKD). Scientists combined two ways to model the disorder—organ-in-a-dish and organ-on-a-chip technologies—to illustrate the role of glucose in forming PKD cysts.

Benjamin Freedman, PhD, of the University of Washington School of Medicine, who led the work, said, "We're able to boil down a complex process of cyst formation in tubules into a process in a petri dish that takes just a few weeks. Animal models are helpful, but translating the results of those studies to people has been a challenge."

The researchers demonstrated that exposing the PKD organoid-on-a-chip model to a combination of water, sugar, amino acids, and other nutrients causes cysts to expand

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relatively quickly. They found that the cysts were absorbing glucose and pulling in water from the fluid passing over them, making the cysts grow larger.

"It wasn't a huge surprise that the cysts could absorb glucose, but it was surprising that they were dependent on it. It's a new way of thinking of how these cysts form," Dr. Freedman said.

The research was supported by NIH's National Center for Advancing Translational Sciences; the National Institute of Diabetes and Digestive and Kidney Diseases; and the National Heart, Lung, and Blood Institute through NIH grants.

Positive Topline Results From XRX-OXY Trial

In a recent press release, XORTX Therapeutics, Inc. announced positive topline results from the XRX-OXY-101–Bridging Pharmacokinetics Clinical Trial. XORTX Therapeutics is a late-stage clinical pharmaceutical company working to develop innovative therapies to treat progressive kidney disease. Results from the study demonstrated that XORLO™ was well tolerated across various dosing spectrums.

Allen Davidoff, MD, CEO of XORTX, said, "We are pleased to have achieved this important milestone in the development of XORLO, the company's proprietary oral formulation of oxypurinol. The comprehensive characterization of this drug and its unique proprietary formulation provide a substantial understanding of how the XORLO formulation behaves pharmacokinetically in individuals. Importantly, the compiled data set from the four parts of this study demonstrates an innovative and substantial improvement on the drug product that can now be used to guide development of population pharmacokinetic models to inform dosing in individuals with ADPKD in our upcoming late stage phase 3 registration trial."

Early Detection of CKD With Technology From Osteolab

According to a recent press release, osteolabs reported results from recent clinical feasibility studies that demonstrated the possibility for the company's proprietary Calcium Isotope Marker detection technology to detect metabolic bone disorders such as chronic kidney disease at an early stage.

Principal investigator **Burkhard H. Brandt, PhD,** said, "These initial results are very encouraging so far, especially due to the observed statistical discriminatory power between healthy and affected patients. This is due to osteolab's highly innovative Calcium Isotope Marker detection technology making it possible to detect the slightest changes in calcium metabolism at a very early disease stage."

Stefan Kloth, managing director at osteolabs, said, "We are highly intrigued by those recent findings showing the potential for our technology potential to become an universal biomarker

platform for a large number of patients with metabolic bone disorders. Further clinical validation work in the near future will be needed to confirm the applicability of our highly sensitive and accurate detection method allowing precise and early detecting for burdening disease that affect more than 1 billion patients worldwide."

PKD Foundation Names New President

The Polycystic Kidney Disease Foundation (PKD) has announced the selection of Susan Bushnell as president and chief executive officer, effective February 1, 2023. The foundation, bBased in Kansas City, Missouri, funds research into PKD and provides programs serving the PKD community.

In a press release from PKD, Ms. Bushnell said, "I look forward to bringing my experience in mission funding, galvanizing supporters, and growing revenue to the PKD Foundation. I am impressed with the executive team and board's commitment to supporting the PKD community and am excited to lead the charge for this wonderful organization."

Robert Roth, PKD Foundation board chair, said,

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"As we celebrate our 40th anniversary, we are thrilled to welcome Susan as the new president and CEO of the PKD Foundation to lead our organization in findings treatments and a cure for polycystic kidney disease by funding research, education, advocacy, support, and awareness on a national and local level. We are confident that with Susan's extensive leadership track record, she will maximize the skills of our high-performing team, moving our organization closer to our goals in support of the PKD community."

The PKD Foundation has funded more than 1300 research projects since 1982 and has leveraged $1.5 billion in research funds. Projects funded include basic, translational, and clinical research; nephrology fellowships; and scientific meetings designed to identify and deliver treatments and a cure for PKD.

CDC Vital Signs Report on Bloodstream Infections

Results of a recent Vital Signs report from the Centers for Disease Control and Prevention (CDC) found that adults with end-stage kidney disease being treated with dialysis were 100 times more likely to have a Staphylococcus aureus (staph) bloodstream infection compared with adults not on dialysis during 2017-2020.

Approximately one in every three people on dialysis is Black and one in every five is Hispanic. The CDC report found that patients in those groups had higher rates of staph bloodstream infections compared with White patients on dialysis.

CDC data confirmed that replacing central venous catheters with lower-risk alternatives such as fistulas and grafts reduced the risk of infection.

In a press release from the CDC, **Debra Houry, MD, MPH,** CDC chief medical officer, said, "Preventing bloodstream infections begins by detecting chronic kidney disease in its early stages to prevent or delay the need for dialysis. Health care providers can promote preventative practices, including methods to manage diabetes and high blood pressure, as well as providing education on treatment options among all patients and particularly those at greatest risk, to slow the progression of chronic kidney disease."

The report can be accessed at www.cdc.gov/vitalsigns.

CVS Recruiting Patients for REACT® Clinical Trial

CVS Health Clinical Trial Services and ProKidney Corp have announced a collaboration enrolling patients with type 2 diabetes and chronic kidney disease (CKD) into the proact 1 (REGENB-006) phase 3 clinical trial of REACT®. REACT (renal autologous cell therapy) is ProKidney's lead product candidate with the potential to slow and stabilize the progression of CKD and, in some cases, drive meaningful improvement in kidney function.

Clinical Trial Services will recruit patients at 39 proact (REGEN-606) clinical sites, using a machine learning model to identify patient populations that align with trial inclusion and exclusion criteria. ■

COVID-19

Risk Factors for Hyponatremia in COVID-19

Pakistan Journal of Medical Sciences. 2023;39(1):275-279

Muhammad Anees, MD, and colleagues at Farooq Hospital West Wood Branch, Lahore, Punjab, Pakistan, conducted a study designed to identify risk factors for hyponatremia in patients with COVID-19. The retrospective review included medical records of all patients admitted to the center's COVID-19 isolation intensive care unit from July 1, 2020, to September 30, 2020.

COVID-19 was diagnosed using real time polymerase chain reaction test. Patients with confirmed COVID-19 and hyponatremia, defined as serum sodium (s/NA+<135 mEq/L), were included in the review. Patients with eunatremia, defined as s/Na+ within 135-145 mEq/L, were considered controls. Patients with hypernatremia, defined as s/NA+ >145 mEq/L, at admission were excluded, as were those with incomplete medical records and women who were pregnant.

The overall cohort included 182 patients. Of those, 79.1% (n=144) were male, 40.7% (n=74) had diabetes mellitus, and 44.5% (n=81) had hypertension. Eighty-six patients (47%) had hyponatremia and 96 (52.7%) were eunatremic. Ninety patients (49%) had acute kidney injury (AKI) and nine patients (4.9%) died.

Risk factors for hyponatremia were age >60 years (odds ratio [OR], 2.52; *P*=.006), diabetes mellitus (OR, 2.79; *P*=.001), hypoxemia (OR, 3.74; *P*<.001), lymphopenia (OR, 7.62; *P*<.009), hypoalbuminemia (OR, 9.15; *P*<.001), high serum ferritin (OR, 4.46; *P*<.001), high neutrophil-to-lymphocyte ratio (OR, 3.58; *P*<.001), and AKI (OR, 3.40; *P*<.001).

"Hyponatremia was common in COVID-19 hospitalized patients," the researchers said. "Increasing age, diabetes mellitus, hypoxemia, hypoalbuminemia, high serum ferritin, and AKI were the most significant risk factors for hyponatremia. Hyponatremic patients had comparatively higher mortality than eunatremic patients."

Urinary Biomarkers as Predictors of AKI in COVID-19

Clinical Nephrology. doi:10.5414/CN110952

Acute kidney injury (AKI) is a common complication among patients hospitalized with COVID-19. There are only a few reports of use of urinary biomarkers in COVID-19 and no available data comparing the prognostic use of individual biomarkers to predict adverse outcomes.

Diana Racovitan, MD, and colleagues conducted a prospective monocentric study on the value of urinary biomarkers in predicting the composite end point of transfer to the intensive care unit (ICU), the need for renal replacement therapy, mechanical ventilation, and in-hospital mortality. The cohort included 41 patients hospitalized for COVID-19. Shortly after admission, urine samples were obtained in order to assess neutrophil gelatinase-associated lipocalin (NGAL), kidney injury molecule-1 (KIM-1), calprotectin, and vascular noninflammatory molecule-1 (vanin-1).

The researchers identified calprotectin as a predictor of a severe course of COVID-19 requiring admission to the ICU (area under the curve [AUC], 0.728; *P*=.016). Positive and negative predictive values were 78.6% and 76.9%, respectively, using a cut-off concentration of 127.8 ng/mL. NGAL tended to predict AKI in patients with COVID-19; however, the association was not statistically significant (AUC, 0.669; *P*=.052).

NGAL was the best predictor of in-hospital mortality (AUC, 0.674; *P*=.077). There were no statistically significant associations between KIM-1 and vanin-1 for any of the end points of interest.

In conclusion, the authors said, "While KIM-1 and vanin-1 did not provide prognostic clinical information in the context of COVID-19, the present study shows that urinary calprotectin is moderately predictive of the need for ICU admission, and NGAL may be modestly predictive of AKI in COVID-19. Calprotectin and NGAL show promise as potential helpful adjuncts in the identification of patients at increased risk of poor outcomes or complications in COVID-19."

ADPKD

Genetic Detection in ADPKD Diagnosis

Frontiers in Cell and Developmental Biology. doi.org/10.3389/fcell.2022.937580

The most common inherited kidney disease is autosomal dominant polycystic kidney disease(ADPKD). According to **Shunlai Shang, PhD,** and colleagues, while next generation sequencing (NGS) technology can be used to sequence tens of thousands of DNA molecules simultaneously, it has poor capture efficiency for the six *PKD1* pseudogenes and GC-rich regions. Consecutive deletions of exons can be detected using multiplex ligation-dependent probe amplification (MLPA). However, MLPA is less sensitive for single-base mutations.

Even using those methods, pathogenic genes might not be detected in some patients the researchers said. Improving the detection rate of pathogenic genes is a technical problem that hinders clinical diagnosis of ADPKD.

The researchers conducted a study to examine the efficacy of a novel method for the genomic analysis of *PKD1* mutation in patients with ADPKD. Four pedigrees of ADPKD patients with mutation sites not identified by NGS were examined using alternative methods.

MLPA was performed, followed by subjecting pedigrees where MLPA did not identify pathogenic genes to multiplex polymerase chain reaction (MPCR) and targeted region sequencing. The detected mutation sites were then verified by Sanger sequencing.

Results demonstrated that MPLA detected the following *PKD1* exonic deletion mutations in three pedigrees: PKD1-18 nt-290 nt, PKD1-up-257 nt, PKD1-up-444 nt, and PKD1-3 nt-141 nt. In one pedigree, a new mutation site was identified via targeted region sequencing: PKD1 NM_001009944:c.151T>C at the protein level, described as p. Cys51Arg.

In summary, the authors said, "We established a system of genetic detection and analytical methods, from NGS to MPLA to targeted region sequencing and finally to Sanger sequencing. We combined MPCR and targeted region sequencing for the first time in ADPKD diagnosis, which further improved diagnosis accuracy. Moreover, we identified one new missense mutation and four new deletion mutations."

CHRONIC KIDNEY DISEASE

Vitamin D Supplementation and Hepcidin Levels

BMC Nephrology. doi:10.1186/s12882-022-03014-z

There is an association between hepcidin and the pathophysiology of renal anemia. Results of recent studies among healthy individuals have suggested a suppressive effect of vitamin D on the expression of hepcidin. **Kristin Danielson Pistis** and colleagues conducted a post hoc analysis to evaluate the effect of supplementing patients with chronic kidney disease (CKD) stage G3-G4 with a high daily dose of native vitamin D on serum levels of hepcidin-25, the hepcidin-to-ferritin ratio, and on markers of erythropoiesis.

Patients with CKD stage G3-G4 who participated in a double blind, randomized, placebo-controlled study and had available hepcidin measurements were included in the analysis. Eligible patients received either 8000 international units of cholecalciferol or placebo daily for 12 weeks. The researchers evaluated the change in markers of hepcidin expression, erythropoiesis, and iron status from baseline to week 12 and compared the change between the two groups.

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A total of 85 patients completed the study. At baseline, there was an inverse correlation between calcitriol and serum levels of hepcidin-25, but not with 25-hydroxyvitamin D (25(OH) D) (rho=–0.38; *P*<.001 and rho=0.02; *P*=.89, respectively).

In the treatment group, supplementation with vitamin D significantly raised the serum concentration of serum 25(OH) D (from 54 to 156 nmol/L; *P*<.01). There was no effect on any of the markers of hepcidin, erythropoiesis, or iron status in the overall cohort.

In a subgroup of patients in the treatment group with low baseline levels of 25(OH)D (<56 nmol/L), there was an increase in hemoglobin levels and transferrin saturation (TSAT) compared with the placebo group. Patients with high baseline 25(OH)D values (≥56 nmol/L), vitamin D supplementation was associated with a decrease in hemoglobin levels and TSAT (*P*=.056) in the treatment group in addition to a decrease in hepcidin levels compared with those in the placebo group.

In conclusion, the authors said, "High-dose vitamin D supplementation had no discernible effect on markers of hepcidin or erythropoiesis in the entire study cohort. However, in patients with low baseline 25(OH)D levels, high-dose vitamin D supplementation was associated with beneficial effects on erythropoiesis and iron availability, In contrast, patients with elevated baseline 25(OH)D levels, high-dose vitamin D supplementation resulted in a decrease in hepcidin levels, most likely due to a deterioration in iron status."

DIABETES

Individualized Frequency of Urinary Albumin Screening in Type 1 Diabetes

Diabetes Care. doi.org/10.2337/dc22-1420

Screening recommendations for kidney disease include annual testing for albuminuria following a 5-year duration of type 1 diabetes. **Bruce A. Perkins, MD, MPH,** and colleagues sought to identify a simple, risk-factor–based screening schedule to optimize early detection and testing frequency.

The researchers created piecewise-exponential incidence models assuming 6-month constant hazards using urinary albumin excretion measurements from 1343 participants in the Diabetes Control and Complications Trial. Individualized screening schedules were identified using the likelihood of the onset of moderately or severely elevated albuminuria (confirmed albumin excretion rate [AER] ≥30 or ≥300 mg/24 hours, respectively). Time with undetected albuminuria and number of tests were compared with annual screening.

The 3-year cumulative incidence of elevated albuminuria following normoalbuminuria at any time during the study was 3.2%, which was strongly associated with higher glycated hemoglobin (HbA1c) and AER. There was an association between personalized screening in 2 years for individuals with current AER ≤10 mg/24 hours and HbA1c ≤8% (low risk [0.6% 3-year cumulative incidence]), in 6 months for those with AER 21-30 mg/24 hours or HbA1c ≥9% (high risk [8.9% cumulative incidence]), and in 1 year for all others (average risk [2.4% 3-year cumulative incidence]) and a 34.9% reduction in time with undetected albuminuria and a 20.4% reduction in testing frequency, compared with annual screening. When stratified by categories of HbA1c or AER alone, the reductions were of lesser magnitude.

"A personalized alternative to annual screening in type 1 diabetes can substantially reduce both the time with undetected kidney disease and the frequency of urine testing," the researchers said.

GLOMERULAR DISEASE

Skeletal Complications in Pediatric Patients

Journal of the American Society of Nephrology. 2022;33(12):223302246

There are unique risk factors for compromised bone health among children with glomerular disease. According to **Amy J. Goodwin Davies, PhD,** and colleagues, there are few data available on skeletal complications in that patient population.

The retrospective cohort study utilized data from PEDSnet, a national network of pediatric health systems with standardized health record data for more than 6.5 million patients from 2009 to 2021. Using Poisson regression analysis, the researchers compared incidence rates (per 10,000 person-years) of fracture, slipped capital femoral epiphysis (SCFE), and avascular necrosis/osteonecrosis (AVN) in 4598 children and young adults with glomerular disease with rates among 553,624 general pediatric patients.

The cohort with glomerular disease was identified using a published computable phenotype. Inclusion criteria for the general population cohort were two or more primary care visits >1 year apart, 1 to 21 years of age, one visit or more every 18 months if followed ≥3 years, and no chronic progressive conditions, defined by the Pediatric Medical Complexity Algorithm. SNOMED-CT diagnosis codes were used to identify fracture, SCFE, and AVN; fracture required an associated x-ray or splinting/casting procedure within 48 hours.

Compared with the general pediatric cohort, there was a higher risk of fracture for the glomerular disease cohort in girls only (incidence rate ratio [IRR], 1.6; 95% CI, 1.3-1.9). Risks of hip/femur and vertebral fracture were increased in the glomerular disease cohort (adjusted IRR 2.2; 95% CI, 1.3-3.7 and 5; 95% CI, 3.2-7.6, respectively). The adjusted IRR for SCFE was 33.4 (95% CI, 1.9-5.9) and 56.2 (95% CI, 40.7-77.5) for AVN.

In conclusion, the authors said, "Children and young adults with glomerular disease have significantly higher burden of skeletal complications than the general pediatric population."

HYPERTENSION

Olmesartan-Based Combination Therapy

High Blood Pressure & Cardiovascular Prevention. doi.org/10.1007/s40292-023-00563-8

Blood pressure control remains an unmet clinical need; only approximately half of patients achieve blood pressure targets, and of those, the majority require combination and double or triple therapies. **Michel Burnier, MD,** and colleagues reviewed use of olmesartran-based combinations to improve blood pressure control in patients with hypertension.

International guidelines recommend the use of drugs with complementary mechanisms of action, and, in particular, the combination of renin-angiotensin system (RAS) inhibitors, calcium, channel blockers (CCBs), and diuretics. Olmesartan (OM), an angiotensin receptor blocker, is available as monotherapy and in dual and triple single-pill combinations (SPCs) with amlodipine (AML) and/or hydrochlorothiazide (HCTZ).

Results of phase 3 and 4 studies, as well as real-world studies, have demonstrated the benefits of combining OM with either AML or HCTZ for blood pressure control and achievement of blood pressure goals in the general population and in subgroups of patients with hypertension, including the elderly, and those with diabetes, chronic kidney disease, and/or obesity.

Ambulatory blood pressure monitoring studies designed to assess 24-hour blood pressure have also shown that dual (and triple) OM-based SPCs induce a more sustained reduction in blood pressure compared with placebo and monotherapy. In addition, triple OM-based SPC has been shown to improve therapeutic adherence in patients with hypertension compared with free combinations.

"The availability of OM combined with HCTZ, AML, or both at different dosages makes it a valuable option to customize therapy based on the levels of blood pressure and the clinical characteristics of hypertensive patients," the researchers said. ■

Sarah Tolson

Show Me the Money

One of the common struggles many medical practices are encountering is a significant increase in the cost of medications, supplies, and the labor necessary to run the practice. Unfortunately, reimbursement is increasing at a much slower rate. Significant increase in costs and minimal increase in revenue seems to be amplified in the renal industry, as the majority of patients have insurance coverage through plans that are funded by a state or the federal government. This puts many practices in a position where they need to increase their incoming revenue without adding any costs.

Recently I gave a presentation to a group of leaders in the renal industry about maximizing reimbursement. A very popular topic during the Q&A portion of the presentation was discussing services that are separately reimbursable for patients with end-stage renal disease (ESRD) that fit well in a nephrology practice. Several great ideas were discussed that may be helpful to the readers of this column, so I am sharing them here.

The most straightforward reimbursement is to ensure you are billing for services furnished to a patient with ESRD that are categorized as excluded from the Monthly Capitation Payment (MCP). Many dialysis patients see their nephrologist as their primary care provider and seek care from their nephrologist for problems unrelated to ESRD. I've talked to many providers over the years who are unclear on when they can bill for office visits and other services furnished to their ESRD patients, so they opt to just not bill and accept the MCP as payment in full.

Another reimbursable service that some providers seem hesitant to bill for is the professional portion of home dialysis training. The dialysis program and the nephrologist both play a role in providing home training, and there is separate reimbursement for each provider type. Nephrologists may bill for home dialysis training on a per-session basis or for the entire course of training once it has been completed.

The next line of revenue to explore would be Transitional Care Management (TCM) services. For nephrologists who round at a hospital and see patients in their office, TCM can be a relatively simple revenue stream to add to your practice. TCM services have specific criteria to meet to qualify for reimbursement, but meeting the criteria may only require minor changes to a practice's current policies and procedures for following up with patients who have been discharged from the hospital. In addition to providing a pathway for nephrologists to obtain reimbursement for the work they are already doing, TCM services may help to reduce hospital readmissions for patients.

Other potential revenue streams for a nephrology practice to consider include add-on services such as Remote Patient Monitoring (RPM) or Chronic Care Management (CCM). When evaluating add-on services to see what will fit best with your practice, it's helpful to consider the percentage of your current patient population that would qualify for or benefit from the services you are considering, how the workload of your practice need to change to handle the new services, and whether the additional work outweighs the benefit to your patients and the additional reimbursement. There are a multitude of vendors that provide RPM assistance or even handle the lion's share of CCM, including the labor portion of connecting with patients.

In speaking with a number of nephrologists, the underlying factor to not capturing all available reimbursement seems to be a lack of awareness of what exactly is reimbursable. In the event your program is looking to increase revenue, I would recommend starting with an audit of chart notes to identify any services currently being rendered but not billed. After reviewing the audit results, practices may consider evaluating additional services like TCM, RPM, and CCM to see if they are a fit for your practice. There may also be some benefit to connecting with a consultant who has experience implementing the services your practice is considering. ■

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