Nephrology Times

Practical News, Trends, and Analysis

November/December 2021 VOLUME 13, NUMBER 8

Age-Adapted Definition of Chronic Kidney Disease

Chronic kidney disease (CKD) is associated with substantial morbidity, mortality, and healthcare costs worldwide. The diagnosis of CKD in adults is based on the presence of abnormalities of kidney structure or function, i.e., abnormal albuminuria or estimated glomerular filtration rate (eGFR) for more than 3 months, with implications for health. Targeted screening and more precise diagnoses of CKD have resulted from the development of a uniform definition of CKD, leading to appropriate patient care and healthcare resource planning.

CKD is indicated by values of eGFR less than half the threshold of 60 mL/min/1.73 m^2, a reflection of an average loss of at least 50% of kidney function in a healthy young adult. Results of previous studies have demonstrated that, beginning at this threshold, lower eGFR values are associated with a graded increase in the relative risks of adverse outcomes in adults, including kidney failure, cardiovascular events, and mortality across all age categories.

There is a lack of consensus on the appropriateness of using a single eGFR threshold to define CKD, regardless of albuminuria. Because eGFR declines with age, using a fixed threshold may result in underdiagnosis in young adults and overdiagnosis in elderly individuals. Using a fixed-threshold definition may also be associated with an overestimation of the burden of CKD in an aging population due to people who may not

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Finerenone and Cardiovascular Events in Patients with Type 2 Diabetes and CKD

The cardiovascular risk associated with type 2 diabetes is exacerbated in chronic kidney disease (CKD). As the urinary albumin-to-creatinine ratio (with albumin measured in milligrams and creatinine measured in grams) exceeds 10 and the estimated glomerular filtration rate (eGFR) decreases below 75 mL/min/1.73 m^2, the risks of cardiovascular events and new-onset heart failure increase. The risk for cardiovascular events is higher than for kidney failure in most patients with CKD, making it important to identify and treat CKD to reduce the substantial burden of cardiovascular disease and heart failure of CKD in patients with type 2 diabetes.

In preclinical models and in patients with CKD in phase 2 studies, finerenone,

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Community-Level Vulnerability and Racial Disparities in Living Donor Kidney Transplant

There is increasing awareness of systemic inequalities in the healthcare system in the United States, providing the impetus for a national movement for advancing racial equity via policy reforms to improve infrastructure as well as opportunities for education, employment, and affordable housing for racial minority populations. Those community-level factors influence economic prosperity, development of disease, and access to quality healthcare. The World Health Organization has named improving the inequities in those social determinants of health fundamental to the elimination of health disparities.

There are well-recognized racial disparities in kidney transplant. Black populations are three times more likely to develop end-stage kidney disease (ESKD) compared with White populations. However, according to **A. Cozette Killian, MD, MPH,** and colleagues, Black patients are disproportionally impacted by barriers at each step toward transplant. Racial disparities also are present in living donor kidney transplantation, the best treatment option for ESKD. Those disparities have increased over the past 2 decades.

Dr. Killian et al. conducted a retrospective, multicenter, cross-sectional study to

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Blood Pressure Standardization is the Key to Managing BP in CKD patients

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Managing blood pressure is probably the most important intervention that a nephrologist pursues in slowing kidney progression and reducing cardiovascular risk in CKD patients.

The publication earlier this year[1] of the Kidney Disease Improving Global Outcomes (KDIGO) blood pressure (BP) management guidelines for CKD patients coupled with the commentaries that followed[2-4] generated two recommendations that caught my eye. Foremost and strongest was a level 1B recommendation that blood pressure management should be standardized. The second and weaker recommendation was "adults with high BP and CKD be treated with a target SBP of <120 mmHg, when tolerated, using standardized office BP measurements" (level 2B recommendation).

The standardization of BP measurement is not something we emphasize in managing BP. Still, based on the latest guidelines it appears to be a key issue in managing BP, especially if one does it aggressively and aims for a systolic BP target of <120 mmHg.

A 2017 study on standardization of BP by **Rajiv Agarwal, MD,** from Indiana[5] is worth spending some time on. This was a single-center study based at the Indiana VA. Dr. Agarwal recruited 275 patients with chronic kidney disease who had a BP <140/90 mm Hg when they came to the clinic. The patients were overwhelmingly men (because this was a VA population) and were on three BP medications on average.

Agarwal measured BP in a similar way to the SPRINT study. BP measurement was done generally with the patient in fasting state and in the morning. He used the Omron HEM 907 oscillometric monitor (Omron Healthcare) and ensured that the cuff size was appropriate for the arm. The participant rested quietly for 5 minutes in a seated position with the arm at the level of the heart. Three consecutive recordings approximately 30 seconds apart were made and no observer was present in the room during these measurements. The BP was deemed "research-grade." The technique was similar to that reported in the SPRINT study and in the ACCORD study (although in ACCORD there was no 5-minute quiet period).

Agarwal reported that the research-grade systolic BP was 12.7 mm Hg lower with wide limits of agreement (–46.1 to 20.7 mm Hg) as compared with routine clinic measurements. Research grade systolic BP was 7.9 mm Hg lower than daytime ambulatory systolic BP and had wide agreement limits (–33.2 to 17.4 mm Hg). Even setting aside the relative inaccuracy of research-grade BP, the point is that research-grade BPs were substantially lower than routinely measured single recordings in the clinic. Agarwal concluded that if one wants to take an aggressive SPRINT-like approach in targeting a systolic BP of <120 mmHg, it is important to use the research-grade BP methodology.

Agarwal also measured left ventricular hypertrophy by echocardiography and reported that the relationship of routine clinic recordings to target organ damage measured by echocardiographic recordings was weaker compared with research-grade or ambulatory BP recordings, further supporting the idea of adopting research-grade methodology in clinic for managing BP.

The KDIGO guideline working group writes: "It is recognized that standardized BP measurements increase the burden to patients, healthcare providers, and healthcare facilities. However, this recommendation is rated as strong because the working group considers it to be essential and it outweighs any potential burden to its implementation. The recommendation should be widely adopted in clinical practice since accurate measurements will ensure that proper guidance is being applied to the management of BP, as it is to the management of other risk factors."

The other question one could ask is whether a "fudge factor" applied to adjust down clinic BP reliably estimates research-grade BP. The answer is no: the relationship between routine office BP and standardized office BP is highly variable, for individuals with and without CKD.

So my take on this is that every nephrologist who sees patients with CKD needs to look at how BP is measured in his or her practice and move in the direction of adopting research-grade processes in measuring BP. It is one more thing to do, but it is likely to be very worthwhile if one wants to aggressively manage BP in both slowing kidney progression and reducing cardiovascular risk. ■

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5. Agarwal R. Implications of blood pressure measurement technique for implementation of Systolic Blood Pressure Intervention Trial (SPRINT). *J Am Heart Assoc*. 2017;6:e004536. This key paper demonstrated that in individuals with CKD, there is a wide variability in terms of BP measured routinely versus. by standardized technique, and that these differences are unpredictable in any given individual.

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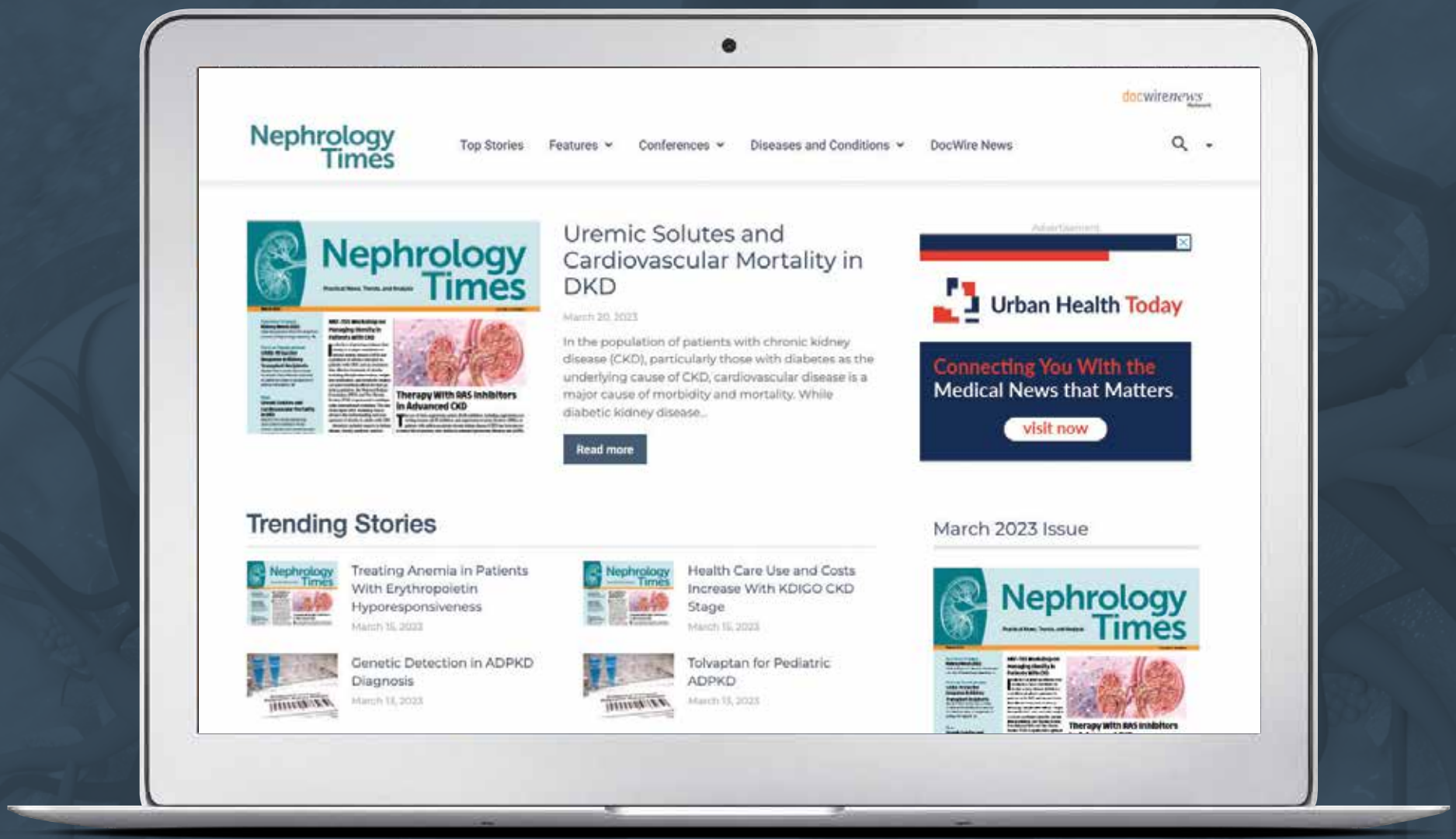

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Nephrology Times

Practical News, Trends, and Analysis

Vulnerability and Racial Disparities

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examine whether racial disparities persist in living donor kidney transplant independent of community-level vulnerability. Results were reported online in *JAMA Surgery* [doi:10.1001/jamasurg.2021.4410].

Study exposures were recipient race and the 2018 US Centers for Disease Control and Prevention (CDC) Social Vulnerability Index (SVI). Census-tract-level SVI data were linked to census tracts within each recipient zip code. Community-level vulnerability was described using the median SVI measure among the census tracts within a zip code. The primary outcomes and measures were kidney transplant donor type (deceased vs living). The association between SVI and living donor kidney transplant was evaluated using modified Poisson regression. The researchers also estimated the likelihood of living donor kidney transplant among races, independent of community-level vulnerability and recipient-level characteristics.

The study included 19,287 adult kidney only transplant recipients; of those, 32% (n=6080) received a living donor kidney transplant. All comparisons between the group of living donor transplant recipients and deceased donor transplant recipients were statistically significant. Living donor recipients were younger (median 52 years vs 55 years) and more often male (63% vs 59%). Overall, the transplant recipients were primarily White, but a larger proportion of living donor recipients were White (80% vs 56%), while smaller proportions were Black (13% vs 34%) or of other races (8% vs 11%).

A greater percentage of living donor recipients received a preemptive transplant (33% vs 8%) or had fewer median years receiving dialysis compared with deceased donor recipients (0.6 years vs 4.0 years). More living donor recipients were working for income and had greater than a high school education compared with deceased donor recipients (48% vs 25% and 66% vs 50%, respectively). White living donor recipients were living in less vulnerable communities than Black recipients (SVI, 0.4 vs 0.6).

In analyses adjusted for recipient-level characteristics, there was an association between higher SVI and 3% lower likelihood of living donor kidney transplant (adjusted relative risk [aRR], 0.97; 95% confidence interval [CI], 0.96-0.98; *P*<.001). Recipients living in communities with SVI similar to the 10457 zip code (Bronx, NY) had 26% lower likelihood of living donor kidney transplant than recipients in communities with SVI similar to the 90210 zip code (Beverly Hills, CA) (aRR, 0.74; 95% CI, 0.69-0.80; *P*<.001).

In unadjusted analyses for race, the likelihood of living donor kidney transplant was 64% lower in Black recipients than in White recipients (RR, 0.36; 95% CI, 0.34-0.39; *P*<.001) and 38% lower in recipients of other races than in White recipients (RR, 0.62; 95% CI, 0.57-0.67; *P*<.001). Following adjustment for recipient-level characteristics and community-level vulnerability, Black recipients had a 37% lower likelihood of living donor kidney transplant (aRR, 0.63; 95% CI, 0.59-0.67; *P*<.001) and recipients of other races had 24% lower likelihood of living donor kidney transplant (aRR, 0.76; 95% CI, 0.70-0.82; *P*<.001) compared with White recipients.

In a fully adjusted model, there was a significant association with the interaction between SVI and race and living donor kidney transplant. While Black recipients and recipients of other races demonstrated lower likelihood of living donor kidney transplant (aRR 0.78; 95% CI, 0.67-0.90; *P*<.001 and aRR, 0.74; 95% CI, 0.63-0.86; *P*<001, respectively) compared with White counterparts (*P* for interaction=.01), only the interaction between SVI and Black recipients was significantly associated with living donor kidney transplant (ratio of aRRs, 0.67; 95% CI, 0.51-0.87; *P*=.003). Black recipients in zip codes similar to 90210 had 24% lower likelihood of living donor kidney transplant (aRR, 0.76; 95% CI, 0.66-0.86; *P*<.001), while Black recipients in zip codes with SVI similar to the 10457 zip code had 48% lower likelihood of living donor kidney transplant (aRR, 0.52; 95% CI, 0.45-0.60; *P*<.001) compared with White counterparts.

The authors cited some limitations to the study finding: SVI may not account for other neighborhood-level determinants of health that impact access to living donor kidney transplant; the unavoidable inaccuracies in census tract-level data aggregated to the zip code level; and the retrospective study design.

In conclusion, the researchers said, "In this study of kidney transplant recipients, the CDC SVI allowed for the most comprehensive evaluation of community-level vulnerability on disparate access to living donor kidney transplant to date. While greater community-level vulnerability was associated with lower likelihood of living donor kidney transplant, accounting for this only partially explained living donor kidney transplant racial disparities. Even among recipients in the least vulnerable US communities, recipients from racial minority groups were less likely to receive living donor kidney transplant. Importantly, the negative effects of living in a more vulnerable community were worse for Black patients. Thus, while policy reform is needed to improve disparate social determinants of health, evaluation of other factors that may impact access to living donor kidney transplant among racial minority populations is warranted." ■

TAKEAWAY POINTS

- Racial disparities in living donor kidney transplant have increased over the last 20 years. Researchers conducted a study to determine whether racial disparities persist in living donor kidney transplant independent of community-level vulnerability.
- Recipients who lived in more vulnerable communities had lower likelihood of living donor kidney transplant compared with those who lived in less vulnerable communities.
- Community-level vulnerability was associated with access to living donor kidney transplant, but only partially explained racial disparities in living donor transplant. The adverse effects of living in more vulnerable communities were worse for Black recipients.

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Finerenone and Cardiovascular Events

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a selective nonsteroidal mineralocorticoid receptor antagonist, improved markers of kidney and cardiovascular damage. In the phase 3 FIDELIO-DKD (Finerenone in Reducing Kidney Failure and Disease Progression in Diabetic Kidney Disease) trial, finerenone improved kidney outcomes in patients with predominately stage 3 or 4 CKD with severely elevated albuminuria and type 2 diabetes.

The FIGARO-DKD (Finerenone in Reducing Cardiovascular Mortality and morbidity in Diabetic Kidney Disease) trial examined whether finerenone would lead to lower risks of cardiovascular events and death from cardiovascular causes in patients with either stage 2 or 4 CKD and moderately elevated albuminuria or stage 1 or 2 CKD and severely increased albuminuria. **Bertram Pitt, MD,** and colleagues reported results of FIGARO-DKD online in the *New England Journal of Medicine* [doi:10.1056/NeJMOA2110956].

FIGARO-DKD was a phase 3, multicenter, randomized, double-blind, placebo-controlled, event-driven clinical trial. Patients with CKD and type 2 diabetes were randomly assigned to receive finerenone or placebo. Eligible patients were adults ≥18 years of age treated with a renin-angiotensin system (RAS) inhibitor at the maximum dose on the manufacturer's label that did not cause unacceptable side effects. Eligibility criteria included urinary albumin-to-creatinine ratio of 30 to <300 mg/g and an eGFR of 25 to 90 mL/min/1.73 m^2 (stage 2 to 4 CKD) or a urinary albumin-to-creatinine ratio of 300 to 5000 mg/g and an eGFR of at least 60 mL/min/1.73 m^2 (stage 1 or 2 CKD).

The primary outcome of interest, assessed in a time-to-event analysis, was a composite of death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for heart failure. The first secondary outcome of interest was a composite of kidney failure, a sustained decrease from baseline of at least 40% in eGFR, or death from renal causes. Safety was measured as investigator-reported adverse events.

A total of 19,381 patients from 48 countries underwent screening from September 2015 through October 2018. Of those, 7437 patients underwent randomization. Due to critical violations of Good Clinical Practice, 85 patients were prospectively excluded, resulting in a final analysis cohort of 7352 patients; 3686 in the finerenone group and 3666 in the placebo group.

The two groups were balanced in baseline characteristics and medications, including the dose of RAS inhibitor. At baseline, 8.4% of patients were being treated with a sodium-glucose co-transporter 2 (SGLT2) inhibitor and 7.5% with a glucagon-like peptide-1 (GLP-1) receptor agonist; an additional 15.8% and 11.3% of patients, respectively, initiated treatment during the trial.

At the end of the trial, at a median follow-up of 3.4 years, vital status was ascertained for 99.8% of patients included in the primary analysis (n=7352). The trial was ongoing during the COVID-19 pandemic, resulting in trial disruption for 2096 patients (28.5%; due mostly to missed trial visits). The incidence of premature discontinuation of the trial regimen was balanced between the two groups (27.4% in the finerenone group and 27.7% in the placebo group). The mean daily dose of finerenone was 17.5 mg and the mean daily dose of placebo was 18.2 mg. Adherence to the trial regimen from randomization until receipt of the last dose was 91.5% in the finerenone group and 92.9% in the placebo group.

In the finerenone group, the incidence of the primary outcome was significantly lower than in the placebo group (12.4% [458/3686] vs 14.2% [519/3666]; hazard ratio [HR], 0.87; 95% confidence interval [CI], 0.76-0.98; *P*=.03). The benefit was driven primarily by lower incidence of hospitalization for heart failure; the incidence of hospitalization for heart failure was lower in the finerenone group than in the placebo group (3.2% [117 patients] vs 4.4% [163 patients]; HR, 0.71; 95% CI, 0.56-0.90).

There were no significant differences between the two groups in the incidence of the first secondary outcome of kidney failure, a sustained decrease from baseline of at least 40% in eGFR, or death from renal causes (9.5% [350 patients] in the finerenone group and 10.8% [395 patients] in the placebo group; HR, 0.87; 95% CI, 0.76-1.01). Following adjustment for the competing risk of death, results were consistent. Thirty-two patients in the finerenone group (0.9%) developed end-stage kidney disease compared with 49 patients (1.3%) in the placebo group (HR, 0.64; 95% CI, 0.41-0.995).

The reduction in the urinary albumin-to-creatinine ratio from baseline to month 4 was 32% greater with finerenone compared with placebo (ratio of least-squares mean change from baseline, 0.68; 95% CI, 0.65-0.70). Following adjustment for the competing risk of death, results were similar. The kidney composite outcome of kidney failure occurred in 108 patients in the finerenone group (2.9%) and 139 in the placebo group (3.8%); (HR, 0.77; 95% CI, 0.60-0.99).

There were no substantial differences between the two groups in the incidence of adverse events. The incidence of discontinuation of the trial regimen due to hyperkalemia was higher in the finerenone group than in the placebo group (1.2% vs 0.4%).

The researchers noted that generalizability of the study findings may be restricted because few Black patients underwent randomization.

In conclusion, the authors said, "Among patients with type 2 diabetes and stage 2 to 4 CKD with moderately elevated albuminuria or stage 1 or 2 CKD with severely elevated albuminuria, finerenone therapy improved cardiovascular outcomes as compared with placebo." ■

TAKEAWAY POINTS

- Researchers reported the results from the FIGARO-DKD trial in patients with type 2 diabetes and CKD.
- The primary outcome–a composite of death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for heart failure–occurred in 12.4% of patients in the finerenone group and 14.2% of those in the placebo group.
- The kidney composite outcome of kidney failure occurred in 108 patients in the finerenone group (2.9%) and 139 in the placebo group (3.8%); (HR, 0.77; 95% CI, 0.60-0.99).

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Age-Adapted Definition of CKD

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have increased risks of adverse outcomes. Researchers have proposed an age-adapted CKD definition, with eGFR thresholds of 75, 60, and 45 mL/min/1.73 m^2 for those younger than 40 years, those 40 to 64 years, and those 65 years and older, respectively.

Ping Liu, PhD, and colleagues conducted a population-based cohort study to identify adults with incident CKD according to the fixed-threshold and the age-adapted threshold definitions. The researchers sought to estimate incidence rates of CKD and the risks of kidney failure and death. They also compared the risks in people ≥65 years of age with normal to mild albuminuria who were diagnosed with CKD based only on the fixed-threshold definition (index eGFR, 45-59 mL/min/1.73 m^2) with a control group with similar characteristics who did not have CKD (sustained eGFR, 60-89 mL/min/1.73 m^2). Results were reported online in *JAMA Internal Medicine* [doi:10.1001/jamainternmed.2021.4813].

The study was conducted in Alberta, Canada, and utilized linked administrative and laboratory data from adults with incident CKD from April 1, 2009, to March 31, 2017. Controls without CKD were ≤65 years of age with a sustained eGFR of 60 to 80 mL/min/1.73 m^2 for longer than 3 months and normal/mild albuminuria. Follow-up continued until March 31, 2019.

The primary outcome of interest was the earlier of kidney failure or all-cause mortality, which were treated as competing events. Kidney failure was defined as the earlier of the initiation of kidney replacement therapy or a sustained eGFR of less than 15 mL/min/1.73 m^2 for more than 90 days.

The fixed-threshold cohort included 127,132 adults with incident CKD and the age-adapted threshold cohort included 81,209 adults with incident CKD. The incidence rate of CKD was 60% higher using the fixed-threshold definition compared with the age-adapted threshold (537 vs 343 new cases per 100,000 person-years). Among individuals ≥65 years of age, the rate differences were more pronounced: age 65-79 years, 2356 vs 714 per 100,000 person years; ≥80 years, 3767 vs 2597 per 100,000 person years. Among individuals <40 years of age, the age-adapted threshold definition yielded an 85% lower incidence rate (14 vs 91 per 100,000 person-years).

The fixed-threshold cohort was older, had a higher index eGFR, and was less likely to have moderate-to-severe albuminuria at baseline compared with the age-adapted cohort (20% vs 25%). In the fixed-threshold cohort, those in older groups were more likely to have normal/mild albuminuria (33%, 72%, and 77% for age <40, 40-64, and ≥65 years, respectively). In the age-adapted cohort, the opposite was observed (74%, 72%, and 67%, respectively).

A total of 53,906 adults were included in both cohorts. Of those, 69% (n=37,018) were captured by both definitions on the same day, 30% (n=16,157) were captured a median of 1.9 years earlier by the fixed-threshold definition, and 1% (n=731) were captured a median of 1.4 years earlier by the age-adapted definition.

Of the fixed-threshold cohort members, 72,703 did not have CKD according to the age-adapted definition (57.2%). Of those, 74.7% (n=54,342) were ≥65 years of age and had an index eGFR of 45 to 59 mL/min/1.73 m^2 with normal/mild albuminuria at baseline; 41.1% (n=30,093) had neither diabetes or cardiovascular disease.

The non-CKD elderly control group included 90,393 people ≥65 years of age with a sustained eGFR of 60 to 89 mL/min/1.73 m^2 with mild/normal albuminuria.

In the fixed-threshold cohort, the risks of kidney failure and death at 5 years were 1.7% and 21.9%, respectively. The corresponding risks in the age-adapted cohort were 3.0% and 25.4%.

Among those with an index eGFR of 15 to 44 mL/min/1.73 m^2, there was an association between lower eGFR and higher absolute risks of adverse outcomes, regardless of age. Most elderly people who entered the fixed-threshold cohort had an index eGFR of 45 to 59 mL/min/1.73 m^2. Among that group, the 5-year absolute risk of kidney failure was similar in magnitude (≤0.12%) to that seen in people without CKD (eGFR 60-89 mL/min/1.73 m^2) across age categories. Their 5-year absolute risk of death was also comparable across age categories (eGFR, 45-59 mL/min/1.73 m^2: 8.3% vs 6.1% and 37.4% vs 40.8% for age 65-69 years and ≥80 years, respectively).

Study limitations cited by the authors included the study source population being predominately White, the study population was based on current guideline recommendations for calculation of eGFR, and the possibility that the study duration was insufficient for kidney failure and mortality outcomes in younger participants.

In conclusion, the researchers said, "This population-based study suggests that current eGFR criteria for CKD that do not account for age-related eGFR decline may result in overestimation of the CKD burden in an aging population. The excess incidence of CKD with current eGFR criteria is largely explained by elderly people who have an eGFR of 45 to 59 mL/min/1.73 m^2 and normal/mild albuminuria. These people have a much higher absolute risk of death than kidney failure, and their risks of kidney failure and death are similar in magnitude to people of the same age who do not have CKD. These risk profiles suggest that an eGFR of 45 to 50 mL/min/1.73 m^2 without albuminuria in elderly individuals may deserve recognition and management strategies to target modifiable risk factors for death but may not have implications for kidney health." ■

TAKEAWAY POINTS

- Researchers conducted a population-based cohort study to compare outcomes associated with chronic kidney disease as defined by a fixed versus an age-adapted estimated glomerular filtration rate (eGFR) threshold.
- The 5-year risks of kidney failure and death were lower in the fixed-threshold cohort compared with the age-adapted cohort (1.7% vs 3.0% and 21.9% vs 25.4%, respectively).
- In elderly people, the 5-year risks of kidney failure and death were similar to those of non-CKD controls.

CONFERENCE COVERAGE SPRING CLINICAL MEETINGS

VPS Improves Clinical Decisions Related to Hyperkalemia

Amy Larkin, PharmD, and Donald Blatherwick of Medscape Education, New York, New York, tested an intervention based on virtual patient simulation (VPS) designed to improve the performance of nephrologists related to identification of patients with, and chronic management of, hyperkalemia. Results were reported during a virtual poster session at the NFK Spring Clinical Meetings 2021 in a poster titled *Success of Virtual Patient Simulation at Improving Management of Chronic Hyperkalemia.*

The intervention comprised a patient presenting at two different points in time in a VPS platform allowing learners to order laboratory tests, make diagnoses, and prescribe treatments in a manner designed to match the scope and depth of actual practice. Current evidence and recommendations were used to develop tailored clinical guidance (CG) provided after each decision; the learner was then provided the opportunity to modify decisions. Following the CG, decisions were collected and compared with each user's baseline decisions (pre-CG). *P* values were determined using a 2-tailed paired t-test. The activity was posted August 30, 2019; initial data were collected through November 7, 2019.

At the time of the poster presentation, 40 nephrologists who had completed the activity (completion was defined as providing all decisions within at least one case) were included in the results analysis:

Initial visit:

- Diagnosis of CKD stage 32: 3% pre-CG versus 45% post CG; 43% absolute improvement; $P<.01$
- Diagnosis of hyperkalemia: 50% pre-CG versus 70% post-CG; 20% absolute improvement; $P<.01$
- Initiation of a potassium binder: 30% pre-CG versus 73% post-CG; 43% improvement; $P<.01$
- Initiation of a renin-angiotensin-aldosterone (RAAS) inhibitor: 35% pre-CHG versus 73% post-CG; 38% improvement; $P<.01$
- Initiation of a sodium-glucose co-transporter-2 inhibitor or glucagon-like peptide-1 receptor agonist: 78% pre-CG versus 83% post-CG; 5% improvement; $P=.16$.

Follow-up visit:

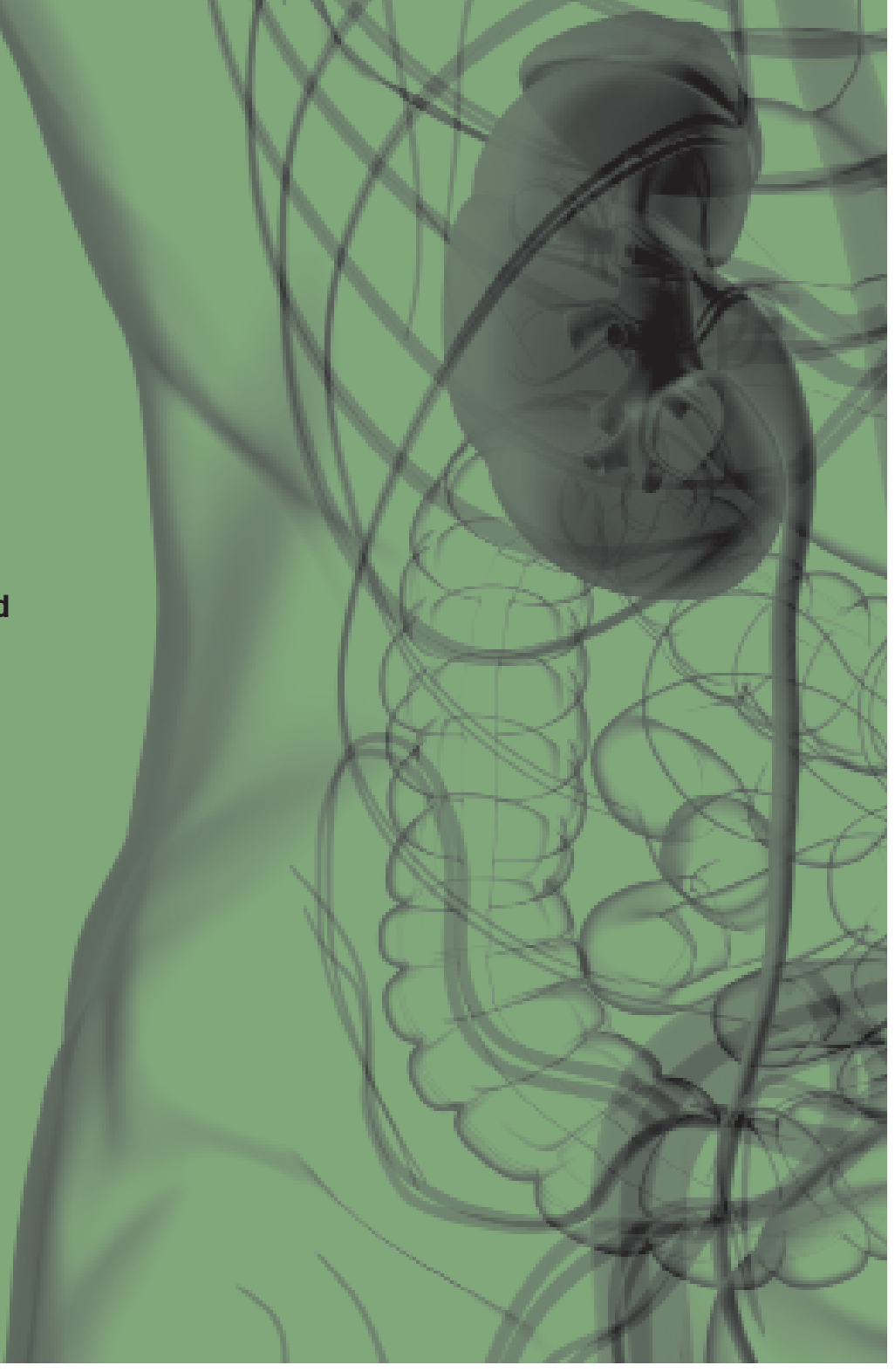
- Initiation of a potassium binder: 28% pre-CG versus 66% post-CG; 38% improvement; $P<.01$
- Initiation of a loop diuretic: 69% pre-CG versus 97% post-CG; 28% improvement; $P<.01$
- Initiation of a mineralocorticoid receptor antagonist: 0% pre-CG versus 38% post-CG; 38% improvement; $P<.01$
- Initiation of a RAAS inhibitor: 90% pre-CG versus 93% post-CG; 3% improvement; $P=.33$

In conclusion, the authors said, "VPS that immerses and engages specialists in an authentic and practical learning experience can improve evidence-based clinical decisions related to patient identification and management of hyperkalemia."

Source: Larkin, Blatherwick D. Success of virtual patient simulation at improving management of chronic hyperkalemia. Abstract of a poster presented at the National Kidney Foundation virtual Spring Clinical Meetings 2021 (Abstract #271), April 9, 2021.

November 4-7, 2021

KIDNEY WEEK 2021



ASN's Kidney Week was once again a fully virtual meeting in 2021. The meeting 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 one of our coverage of Kidney Week 2021. Part two will appear in our January/February 2022 issue.

AKI in COVID-19 in Patients with and without prior Renal Function

The incidence rate of renal injury in patients with COVID-19 ranges from 3% to 9% and includes patients with urinary abnormalities to patients in critical care with acute kidney injury (AKI). The primary risk factors for COVID-19-related AKI are oncologic disease, sepsis, and heart failure. According to **Carlos Guido Musso, MD, PhD,** and colleagues, there are few data available on differences in AKI in patients with COVID-19 with previously healthy kidneys and those with chronic kidney disease (CKD).

The researchers conducted an analysis of data on patients who were treated during the first pandemic wave (2020) in Clinica de la Costa, Barranquilla, Columbia. Results of the analysis were reported during a virtual poster session at ASN Kidney Week 2021 in a poster titled *AKI Associated with COVID-19: Differences Between Previously Healthy Kidney Individuals and CKD Patients.*

The analysis included 572 patients with a diagnosis of COVID-19 confirmed by PCR test. Of the 572 patients, 188 developed AKI and had epidemiological data, serum parameters, and functional status recorded. Statistical analysis and comparison of previously kidney healthy patients with patients with previous CKD were performed.

Of 720 individuals evaluated in the emergency department for suspicion of COVID-19, 572 were admitted with confirmed SARS-CoV-2 infection. Of the 572 admitted patients, 59% were male, median age was 55 years, 36% had hypertension, 23% were obese, 18% had diabetes, 5% had heart disease, and 9% had chronic obstructive pulmonary disease (COPD). Nearly all patients (97%) were robust.

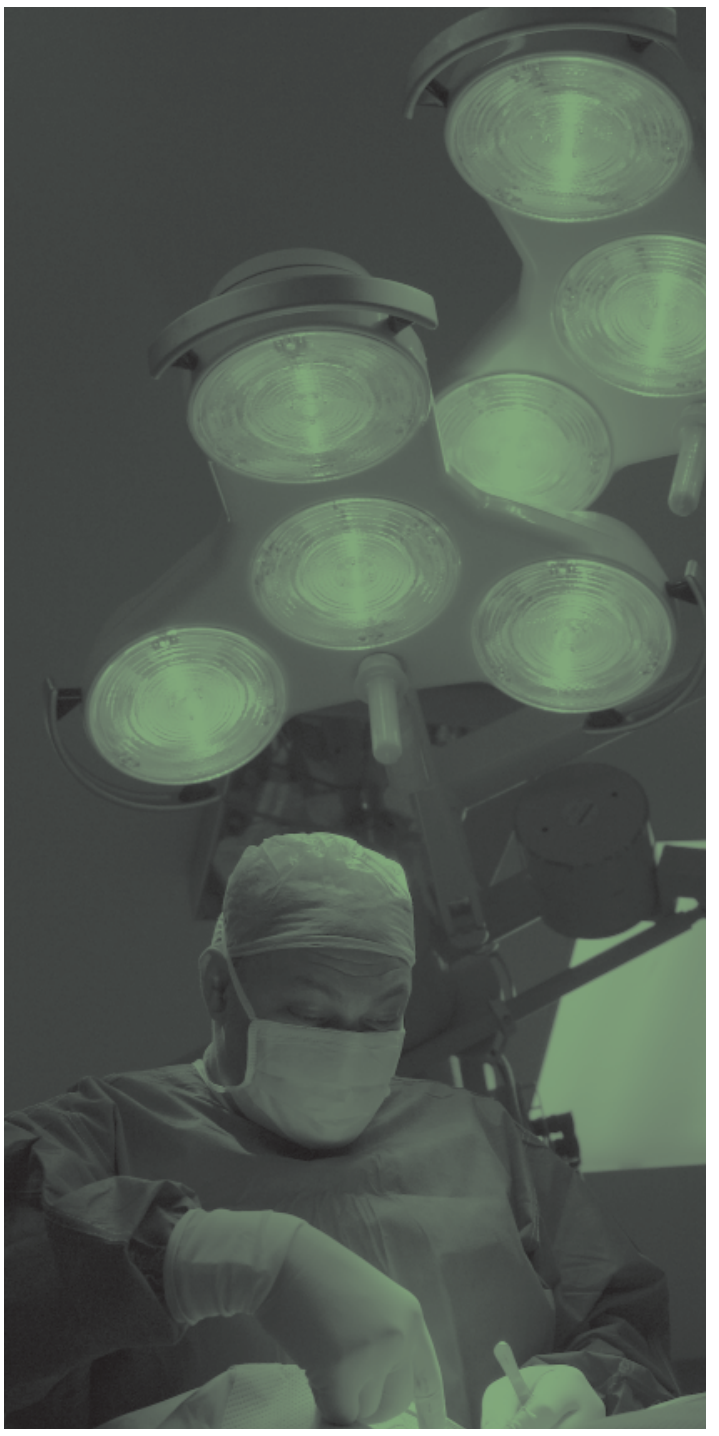
A total of 188 patients with COVID-19 developed AKI (33%). Of those, 26% (n=149) had a previous normal renal function and 7% (n=39) had CKD. Most of the patients with CKD (91%) developed AKI.

In the AKI group (both those with prior kidney health and those with CKD) , there was a greater percentage of men, participants older than 60 years, participants with Clinical Frailty Scale score ≥4, and those with diabetes mellitus, obesity, and COPD in comparison with the group without AKI. Compared with patients with prior kidney health, those with CKD had significantly higher prevalence of hypertension and cardiac disease. The prevalence of hypertension and heart disease in all patients with AKI was higher than in those without AKI.

There was a tendency of higher mortality rate in patients with prior kidney health than in those with CKD (69% vs 56%). That trend did not reach statistical significance. The trend toward higher mortality in patients with AKI compared with patients without AKI was statistically significant (P<.0001). D-dimer was significantly higher in patients with AKI with prior kidney health compared with patients with AKI with CKD (P=.06).

There was a trend to higher mortality rate and D-dimer levels in patients with AKI with prior normal renal function compared with patients with AKI and prior CKD, the authors summarized.

Source: Musso CG, Martinez A, Avendaño-Echavez, LG, et al. AKI associated with COVID-19: Differences between previously healthy kidney individuals and CKD patients. Abstract of a poster presented at the American Society of Nephrology virtual Kidney Week 2021 (Abstract P00017), November 2021.



Dialysis Modality and Heart Surgery Outcomes

Poor outcomes following cardiac surgery are more common among patients with end-stage kidney disease (ESKD) receiving dialysis than in the non-dialysis population. However, according to **Elias Bassil, MD,** and colleagues, there are few data available on the impact of dialysis modality and the type of cardiac surgery.

During a virtual poster session at ASN Kidney Week 2021, the researchers reported results of an analysis of outcomes among patients with ESKD on hemodialysis or peritoneal dialysis undergoing coronary artery bypass graft and/or valvular cardiac surgery. The poster was titled *Outcomes of ESKD Patients on Hemodialysis vs Peritoneal Dialysis Post Open Heart Surgery.*

A total of 590 patients with ESKD on hemodialysis or peritoneal dialysis who underwent coronary artery bypass graft and/or valvular cardiac surgery at the Cleveland Clinic (Ohio) from 2009 to 2019 were identified using the Electronic Health Records-based Cardio-Thoracic Surgery registry. Chi-square was used to compare baseline demographics between the hemodialysis group and the peritoneal dialysis group; t-tests for categorical and continuous variables were used to compare baseline comorbidities. Kruskal-Wallis test, Chi-square, and Fisher's exact tests were used to compare in-hospital death, hospital length of stay, intensive care unit length of stay, red blood cell transfusions required, and the incidence of postoperative complications, including pericardial effusions requiring intervention, gastrointestinal bleed, and sternal wound infections.

Of the 590 patients, 11% (n=62) were receiving peritoneal dialysis and 89% (n=528) were receiving intermittent hemodialysis; 47% (n=277) underwent valvular surgery only, 26.7% (n=158) underwent coronary artery bypass graft surgery only, and 26.3% (n=155) had combined valvular and coronary artery bypass graft surgery.

The dialysis modality groups were similar in baseline characteristics and comorbidities. Among the patients undergoing coronary artery bypass graft surgery only, patients in the peritoneal dialysis group had more pericardial effusions (12.5% vs 2.3%; P=.048) and more gastrointestinal bleeding (12.5% vs 2.2%; P=.046) than patients in the hemodialysis group.

The dialysis groups were similar in in-hospital mortality, hospital length of stay, intensive care unit length of stay, and sternal wound infections across the various surgeries. Post-surgery, 16 peritoneal patients were converted to hemodialysis; intent-to-treat analysis was applied for those patients.

In conclusion, the authors said, "In patients on maintenance dialysis, patients who underwent coronary artery bypass graft surgery, valvular surgery, and combined surgery had similar outcomes. Peritoneal dialysis patients appeared to experience more gastrointestinal bleeding and pericardial effusions requiring intervention in the coronary artery bypass graft surgery group."

Source: Bassil E, Matta M, Liaqat A, et al. Outcomes of ESKD patients on hemodialysis vs peritoneal dialysis post open heart surgery. Abstract of a poster presented at American Society of Nephrology virtual Kidney Week 2021 (Abstract P00879), November 2021.

Peritoneal Dialysis Technique Failure: Fluid-Related Risk Factors

Among patients receiving peritoneal dialysis, inadequate fluid management is associated with a higher risk of cardiovascular morbidity and mortality. There may also be an association between inadequate fluid management and shortened peritoneal technique survival. **Jennifer E. Flythe, MD, MPH,** and colleagues conducted an analysis designed to examine the associations between fluid-related clinical factors and peritoneal dialysis technique failure within 1 year of treatment initiation.

Results of the analysis were reported during a virtual oral presentation at ASN Kidney Week 2021. The presentation was titled *Fluid-Related Risk Factors of Peritoneal Dialysis Technique Failure*.

The analysis included data on adult patients with end-stage kidney disease who were newly prescribed peritoneal dialysis for ≥120 days at Fresenius Kidney Care facilities between 2017 and 2019. Deidentified data were extracted from the Fresenius Kidney Care clinical data warehouse and evaluated within 120 days of initiation of treatment. The associations between fluid-related risk factors and peritoneal dialysis technique failure were assessed using crude and case-mix adjusted Cox regression models with competing risks (patient transfer to hemodialysis, death, and loss to follow-up).

The analysis included data on 15,854 patients on automated peritoneal dialysis (APD) and 1547 patients on manual peritoneal dialysis (CAPD). Among the APD group, mean age was 58 years and renal urea clearance (K_{RU}) was 4.5 mL/min). In the CAPD group, mean age was 58 years and K_{RU} was 4.8 mL/min. Percentages of patients with peritoneal dialysis technique survival ≥1 year were 53% of APD patients and 56% of CAPD patients.

All patients with urine volume ≤100 mL, systolic blood pressure >160 mmHg, history of cardiovascular events and hospitalizations, or weight change ≥2 kg between day 1 and day 120 of peritoneal dialysis treatment had a higher risk of 1-year peritoneal dialysis technique failure.

Significant patient-reported risk factors included shortness of breath (APD only) and edema (APD and CAPD). Patients with a weekly Kt/V >2 had half the risk of peritoneal dialysis attrition at 1 year.

In conclusion, the authors said, "APD and CAPD patients with fluid-related complaints (shortness of breath and edema), history of cardiovascular morbidity and hospitalizations, hypertension, or weight change ≥2 kg within 120 days of peritoneal dialysis initiation had a higher risk of technique failure within 1 year of peritoneal dialysis initiation."

Funding for the analysis was provided by Fresenius Medical Care North America.

Source: Flythe JE, Ficociello L, Parameswaran V, et al. Fluid-related risk factors of peritoneal dialysis technique failure. Abstract of a presentation at the American Society of Nephrology virtual Kidney Week 2021 (Abstract FR-OR27), November 5, 2021.

Patients on Dialysis May Face Care Disparities

Led by Marc Turenne, PhD, researchers conducted an analysis designed to aid in understanding disparities in quality of care for patients on dialysis with an eye toward informing priorities for quality improvement as well as suggesting approaches for achieving greater health equity. The researchers also sought to determine whether disparities have been improving or worsening in recent years and whether there are geographic variations in disparities.

Results of the analysis were reported during a virtual poster session at ASN Kidney Week 2021. The poster was titled *Disparities in Quality of Care for Dialysis Patients*.

The analysis included data from Medicare and CROWNWeb to evaluate disparities based on race, ethnicity, dual eligibility, and rural-urban location. Using criteria developed by the Agency for Healthcare Research and Quality, the researchers identified disparities in 2019 based on a statistically significant regression-adjusted difference in a quality indicator and at least a 10% relative difference between groups. Generalized linear models were estimated using clustering for patients and adjustments for age, sex, cause of end-stage kidney disease (ESKD), duration of ESKD, and comorbid conditions at the time of ESKD diagnosis. National trends in disparities from 2015 to 2020 and variations in disparities by ESKD network in 2019 were examined.

The analysis examined 16 quality indicators, including use of arteriovenous fistulas, long-term catheter use, dialysis-related infection hospital admission, outpatient emergency department visits, mortality, dialysis access-related infection hospital admission, all-cause hospital admissions, and hospice use at death. Disparities involving racial minorities and dual eligible beneficiaries accounted for 13 of the 16 measured disparities. The disparities persisted over time and were found in most ESKD networks.

In summary, the authors said, "There are ongoing racial, socioeconomic, and rural-urban disparities among dialysis patients in a range of quality indicators. There may be valuable opportunities for quality initiatives in ESKD to improve health equity."

Source: Turenne M, Cogan CM, Pearson J, Huff ED. Disparities in quality of care for dialysis patients. Abstract of a poster presented at the American Society of Nephrology virtual Kidney Week 2021 (Abstract P00791), November 2021.

Disparities involving racial minorities and dual eligible beneficiaries accounted for 13 of the 16 measured disparities. The disparities persisted over time and were found in most ESKD networks.

Online Education to Improve Management of Patients with Gout

Patients with gout experience considerable negative effects on health and quality of life. There are known associations between hyperuricemia and gout and declining renal function. Results of recent studies have suggested that renal dysfunction and kidney transplant are risk factors for gout.

Nimish Mehta, PhD, MBA, and colleagues at Medscape LLC, New York, New York, recently conducted a study to determine whether online, segmented education could be used to improve knowledge, competence, and confidence among nephrologists regarding management of gout in patients with chronic kidney disease (CKD) and among recipients of kidney transplant. Results of the study were reported during a virtual poster session at ASN Kidney Week 2021 in a poster titled *Improving the Management of Gout in Patients with CKD or Kidney Transplant: Effect of Online Education*.

The educational design included a 45-minute video activity with slides, segmented into a series of five mini-lectures from different faculty. The lectures covered various aspects of gout in patients with or without CKD or kidney transplant. The effectiveness of the activity was assessed using repeated-pairs pre-/post-assessment study design with three questions related to knowledge and one related to confidence. Participants served as their own controls. Statical significance at the $P<.05$ level was assessed using a chi-squared test. The online activity launched on September 25, 2020; data were collected through December 4, 2020.

The analysis set included responses from 89 nephrologists who answered all of the assessment questions during the study period. Analysis of responses pre- and post-intervention revealed a significant improvement in overall knowledge: average correct responses increased from 52% pre-intervention to 76% post-intervention.

Specific areas of improvement included: (1) treat-to target strategy, with a target of serum uric acid level <6 mg/dL in patients treated with urate lowering therapy (20% relative improvement, $P<.05$); (2) starting low-dose allopurinol in a patient previously diagnosed with gout and stage 3 CKD presenting with painful subcutaneous tophi (25% relative improvement, $P<.01$); (3) recommending pegloticase without dose adjustment for the management of refractory gout in patients with stage 4 or 5 CKD (222% relative improvement, $P<.001$).

Following the intervention, 48% of the participants had a measurable increase in confidence in their ability to manage patients with CKD who develop gout.

In conclusion, the researchers said, "This study demonstrated the success of online, segmented mini-lectures on improving the evidence-based knowledge, competence, and confidence of nephrologists in appropriately managing gout in patients with CKD or kidney transplant."

Funding was provided by Horizon Therapeutics.

Source: Mehta N, Maeglin J, Badal K. Improving the management of gout in patients with CKD or kidney transplant: Effect of online education. Abstract of a poster presented at the American Society of Nephrology virtual Kidney Week 2021 (Abstract P01064), November 2021.

Risk of Progression to Kidney Failure in Patients with Primary Hyperoxaluria Type 1

In patients with primary hyperoxaluria type 1 (PH1), there is a positive association between the risk of kidney failure and excretion of urinary oxalate. Lumasiran is an RNA inhibitor therapeutic to lower urinary oxalate excretion in patients with PH1. During a virtual poster session at ASN Kidney Week 2021, **John C. Lieske, MD,** and colleagues reported results of an analysis estimating the risk of progression to kidney failure in patients with PH1 treated with lumasiran, compared with patients not treated with lumasiran. The poster was titled *Modeling the Risk of Progression to Kidney Failure in Patients with Primary Hyperoxaluria Type 1 Treated with Lumasiran Relative to a National History Cohort Not Treated with Lumasiran.*

A skewed-normal distribution of 24-hour urinary oxalate values for patients with PH1 was simulated based on reported urinary oxalate values from the Rare Kidney Stone Consortium (RKSC) PH Registry among patients not in kidney failure at diagnosis and who did not receive lumasiran. A loglinear model of post-lumasiran treatment steady-state urinary oxalate as a function of baseline urinary oxalate was built using data from the ILLUMINATE-A trial of lumasiran. The distribution of steady-state, on-treatment urinary oxalate values for RKSC patients was then predicted by applying this model to the stimulated 24-hour urinary oxalate excretion of the RKSC cohort, considered as baseline. The number of kidney failure events per 100 patients in the RKSC PH1 cohort who had received lumasiran was estimated using a risk model of kidney failure as a function of 24-hour urinary oxalate excretion, based on Kaplan-Meier curves of renal survival reported from the RKSC.

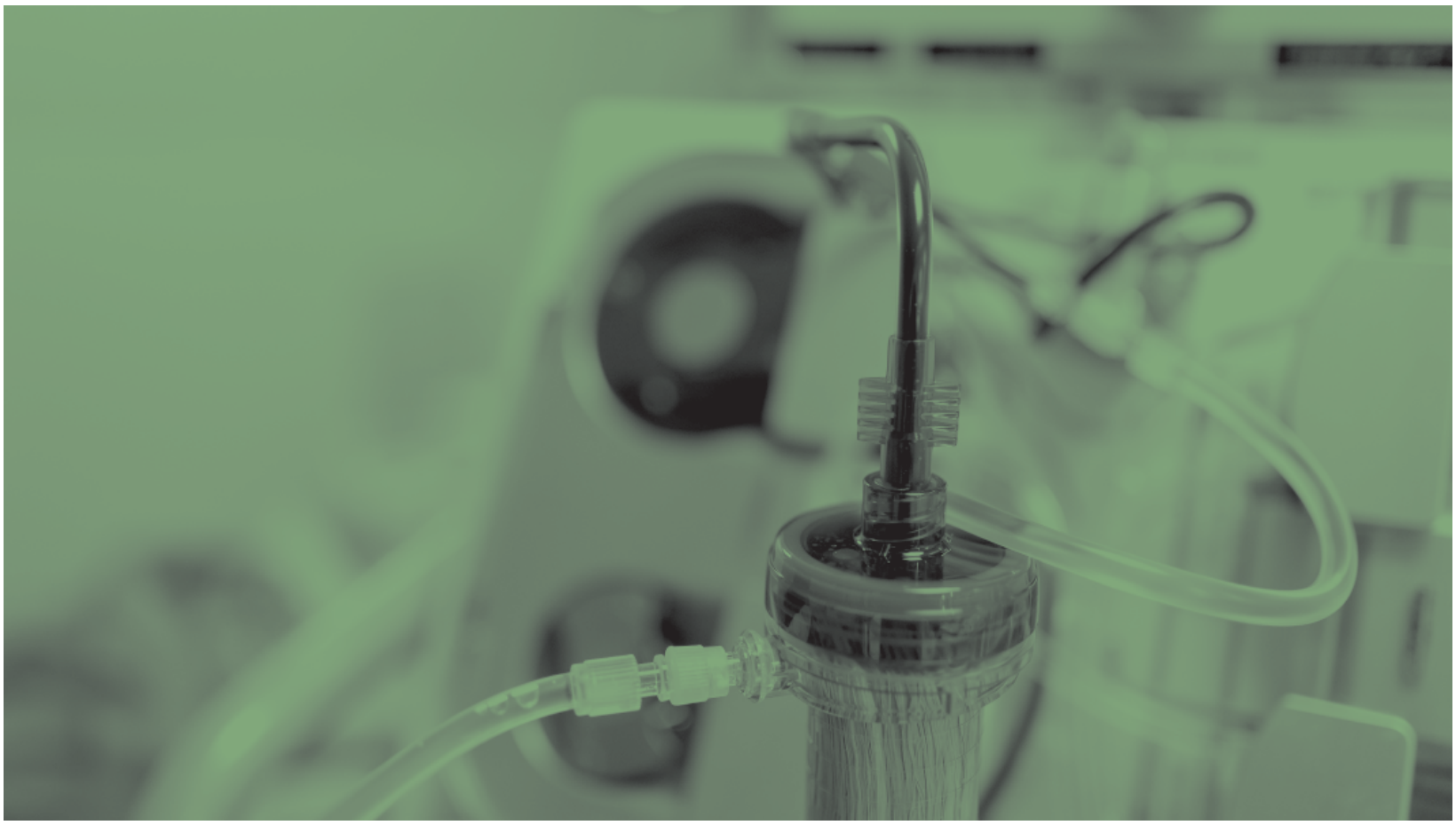
In the absence of lumasiran treatment, the mean 24-hour urinary oxalate excretion for the RKSC PH1 cohort was 2.2 mmol/24 hr/1.73 m^2, and was predicted to decrease to 0.62 mmol/24 hr/1.73 m^2 in a model simulating the effect of administration of lumasiran.

In the model for patients not treated with lumasiran, the predicted number of kidney failure events per 100 patients at 10, 20, and 30 years was 10 (95% confidence interval [CI], 4-23), 32 (95% CI, 19-50), and 42 (95% CI, 27-59), respectively. In the model of lumasiran treatment, the estimated cumulative number of kidney failure events per 100 patients was 4 (95% CI, 1-12) at 10 years and remained unchanged at 20 and 30 years.

In conclusion, the researchers said, "This analysis predicts a long-term reduction in kidney failure risk among PH1 patients treated with lumasiran, assuming prompt treatment at diagnosis."

Funding for this analysis was provided by Alnylam Pharmaceuticals.

Source: Lieske JC, Mara KC, Danese DS, et al. Modeling the risk of progression to kidney failure in patients with primary hyperoxaluria type 1 treated with lumasiran relative to a natural history cohort not treated with lumasiran. Abstract of a poster presented at the American Society of Nephrology virtual Kidney Week 2021 (Abstract P01319), November 2021.



Risk of COVID-19 among Patients Treated with RAAS Inhibitors

Researchers have hypothesized that direct viral invasion of the kidney via angiotensin converting enzyme is a mechanism of acute kidney injury (AKI) in patients with COVID-19. There are few data available on the impact of renin-angiotensin-aldosterone system inhibitors (RAASi) on the risk of AKI in COVID-19.

Bethany Birkelo, DO, and colleagues conducted a retrospective cohort study to test the hypothesis that active use of RAASi prior to admission would be associated with a greater proportional risk of AKI in COVID-19 compared with influenza. The study compared the incidence of AKI by RAASi status in 11,898 hospitalized veterans with COVID-19 or influenza between October 2, 2019, and September 30, 2020. Results were reported during a virtual poster session at ASN Kidney Week 2012 in a poster titled *RAAS Inhibition and Risk of AKI in COVID-19.*

Propensity score weighting balanced baseline conditions, laboratory results, and co-therapies in four exposure groups controlled for confounders. The four groups were RAASi users with COVID-19, non-users with COVID-19, RAASi users with influenza, and non-users with influenza. Weighted logistic regression was used to estimate the main effects of RAASi and COVID-19, and their interaction.

In the influenza groups, 7% of RAASi users had stage 2-3 AKI compared with 5% of non-users, a 2% increase (P=.03). In the COVID-19 groups, 16% of RAASi users had stage 2-3 AKI versus 12% of non-users, a 4% increase. The absolute increase in incidence of AKI for RAASi users versus non-users was greater among patients with COVID-19 than in patients with influenza; however, the difference was not statistically significant (P=.66) and the RAASi association was proportionally smaller in COVID-19. Similar absolute differences were seen in stage 1-3 AKI; that interaction was also not statistically significant (P=.66).

In summary, the authors said, "COVID-19 was associated with a greater incidence of AKI than influenza. RAASi was associated with an increased incidence of stage 2-3 AKI in patients with COVID-19 or influenza. The proportional effect of RAASi was similar in COVID-19 and influenza patients, These findings do not support a disproportionate risk of AKI among RAASi users with COVID-19."

Source: Birkelo B, Perkins A, Greevy R, et al. RAAS Inhibition and Risk of AKI in COVID-19. Abstract of a poster presented at the American Society of Nephrology virtual Kidney Week 2021 (Abstract P00037), November 2021.

Differences in Incidence of Kidney Stones in Men versus Women

Kidney stone disease is highly prevalent, and men are at higher risk of developing stones compared with women. However, according to **Pietro Manuel Ferraro, MD, MSc, PhD,** and colleagues, recent data suggest changes in epidemiology, with women becoming relatively more affected by kidney stones than in the past. There are few data available on the reasons for the differences in prevalence of kidney stones by sex and the changes over time.

During a virtual presentation at ASN Kidney Week 2021, the researchers reported results of an analysis designed to identify the associations between sex and incident kidney stones. The presentation was titled *Factors Associated with Sex Differences in the Risk of Kidney Stones.*

The analysis included data from three large cohorts. The incidence rates of kidney stones for men and women overall and across categories of age and calendar time were calculated. Age-adjusted Cox proportional hazards regression models were used to generate hazard ratios (HRs) and 95% confidence intervals (CIs). Mediation analysis was used to estimate the amount of excess risk for men explained by established risk factors (waist circumference, history of high blood pressure, history of diabetes, use of thiazides, and dietary intake). The study also examined 24-hour urine composition.

Data from 268,553 participants, representing 5,872,249 person-years of follow-up, were included in the analysis. During the follow-up, 10,302 incident stone events were confirmed. For men, the incidence rate of kidney stones was 271 per 100,000 person-years; the rate for women was 159 per 100,000 person-years. The age-adjusted HR for men compared with women was 2.32 (95%CI, 2.20-2.45).

The risk factors included in the analysis accounted for part of the difference in incidence rates, particularly waist circumference and fluid intake. The risk of stones was consistently higher across categories of age among men compared with women (HRs ranged from 2.02 to 2.76). In analysis adjusting for calendar time, the risk remained higher among men, but tended to decrease over time while it increased in women, resulting in a 48.1% decrease post-2009 compared with pre-1990.

Men had higher supersaturations for calcium oxalate and uric acid, due primarily to 26.3% higher urine oxalate, 16.3% higher urine uric acid, 23.5% higher urine phosphate, and more acidic urine. The increased risk among men was significantly influenced by urine volume, citrate, oxalate, and pH.

In conclusion, the authors said, "The risk of kidney stones is higher among men compared with women. This difference is only partly explained by modifiable lifestyle risk factors; however, differences in urine chemistries explain a substantial fraction of the excess risk."

Source: Ferraro PM, Taylor EN, Curhan GC. Factors associated with sex differences in the risk of kidney stones. Abstract of a presentation at the American Society of Nephrology virtual Kidney Week 2021 (Abstract OR30), November 4, 2021.

SARS-CoV-2 mRNA Vaccine Response in Pediatric Kidney Transplant Recipients

The mRNA SARS-CoV-2 vaccines are highly effective in the general population and recipients form an antibody to S1 subunit of the SARS-CoV-2 spike protein. Results of early studies among immunosuppressed adult recipients of solid organ transplants suggested a decreased antibody response. There are few data available on the serologic response in adolescent solid organ transplant recipients.

Clarkson Crane, MD, and **Elizabeth G. Ingulli, MD,** University of California San Diego, La Jolla, California, conducted an analysis of adolescent kidney transplant recipients at the center who received both doses of an mRNA SARS-CoV-2 vaccine. Results of the analysis were reported during a virtual poster session at ASN Kidney Week 2021 in a poster titled *Antibody Response to SARS-CoV-2 mRNA Vaccines in Pediatric Kidney Transplant Recipients.*

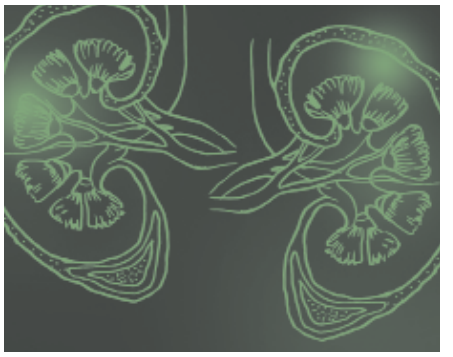
As part of routine clinical care, adolescent kidney transplant recipients who received both doses of an mRNA vaccine had the presence of SARS-CoV-2 spike protein antibodies evaluated 4 to 8 weeks following their second dose. Drs. Crane and Ingulli utilized the Abbott chemiluminescent microparticle immunoassay or Siemens Atellica IM SARS-CoV-2 IgG. Patients were characterized as vaccine responders or non-responders.

Of the 47 vaccine-eligible adolescent kidney transplant recipients in the program, 34 received both doses of an mRNA SARS-CoV-2 vaccine. Of those, 23 had spike antibody titers obtained. Median age was 21.5 years and all but one had received a transplant more than 3 years ago. Twenty-two of the 23 received Pfizer-BioNTech vaccine and one received Moderna.

Twelve patients (52%) had a positive spike antibody (responders). Of the 12, the immunosuppression of eight patients included mycophenolate (mean dose, 719 mg/m^2/day), three were treated with azathioprine, and one was not taking an antimetabolite due to Epstein-Barr virus viremia. All non-responders were treated with mycophenolate (average dose, 755 mg/m^2/day). Three patients had prior COVID-19 infection, and all had positive antibody response.

In summary, the authors said, "Our results suggest vaccine response in adolescent kidney transplant recipients is suboptimal and lower than in the general population. However, 52% response rate is similar to that previously described in adult solid organ transplant patients. While our study is limited by small sample size and lack of standardized timing for measuring antibodies, it provides further evidence of lower immunogenicity to SARS-CoV-2 vaccination in solid organ transplant. Those who did not respond tended to have a higher average dose of mycophenolate and this supports further study of alternative antimetabolite dosing strategies around the time of vaccination or the potential utility of a third vaccine dose in solid organ transplant patients. At our center, efforts to continue characterizing antibody response of pediatric kidney transplant recipients are ongoing and we anticipate additional data in the coming months as vaccine eligibility expands to younger patients."

Source: Crane C and Ingulli EG. Antibody response to SARS-CoV-2 mRNA vaccines in pediatric kidney transplant recipients. Abstract of a poster presented at the American Society of Nephrology virtual Kidney Week 2021 (Abstract PO2094), November 2021.



Discontinuation of RAS Blockade among Kidney Transplant Recipients

Recipients of kidney transplantation commonly experience cardiovascular disease and are at increased risk for morbidity and mortality. Results of recent studies have shown evidence of cardiovascular benefit with continuation of renin-angiotensin system (RAS) blockade for transplant naïve patients with CKD. However, according to **Sophie McAllister** and colleagues at the University of California San Francisco, there are few data available on whether cessation of RAS blockade among recipients of kidney transplant confers cardiovascular or survival benefits (or risks).

The researchers conducted a retrospective cohort study of kidney transplant recipients from the FAVORIT (Folic Acid for Vascular Outcome Reduction in Transplantation) study. Results of the current study were reported during a virtual poster session at ASN Kidney Week in a poster titled *Discontinuation of Renin-Angiotensin System Blockade among Kidney Transplant Recipients.*

The study included FAVORIT participants enrolled in the United States who received an angiotensin receptor blocker or an angiotensin-converting enzyme inhibitor by self-report at one or more FAVORIT visits. The risks or benefits of RAS discontinuation (versus continuation) was assessed using a propensity score weighted Cox survival analysis. Outcomes of interest were death, return to dialysis, and major adverse cardiovascular events (MACE [stroke, myocardial infarction, coronary revascularization, or heart failure]). Doubly robust estimation was also used on the propensity score weighted sample to provide conservative estimates.

A total of 2009 US participants had at least one visit where they reported taking a RAS inhibitor. Thirty percent (n=598) discontinued RAS blockade. Compared with participants who continued RAS blockade, those who discontinued RAS blockade were significantly less likely to experience mortality, return to dialysis, and MACEs.

In conclusion, the researchers said, "Kidney transplantation recipients who stopped RAS blockade had lower rates of mortality, return to dialysis, and MACEs compared with those who continued RAS blockade. These data may be useful when deciding on the risks and benefits of continuing RAS blockade for patients receiving kidney transplantation."

Source: McAllister S, Siyahian S, Seth D, Ku E. Discontinuation of renin-angiotensin system blockade among kidney transplantation recipients. Abstract of a poster presented at the American Society of Nephrology virtual Kidney Week 2021 (Abstract PO2118), November 2021.

Vadadustat for Anemia in Patients Receiving Peritoneal Dialysis

Vadadustat, an oral hypoxia-inducible factor prolyl hydroxylase inhibitor, is being investigated for the treatment of anemia in chronic kidney disease (CKD). Results of INNO$_2$VATE studies, two recently completed global phase 3 trials in patients with dialysis-dependent CKD (DD-CKD), demonstrated the noninferiority of vadadustat to darbepoetin alfa for the primary safety end point of time to first major cardiovascular event (MACE: a composite of all-cause mortality, nonfatal myocardial infarction, and nonfatal stroke) and the primary and secondary efficacy end points (correlation/maintenance of hemoglobin [Hb]).

During a virtual poster session at ASN Kidney Week 2021, **Glenn M. Chertow, MD, MPH,** and colleagues reported results of post hoc analysis of data from INNO$_2$VATE, the randomized (1:1), phase 3, global, open-label, sponsor-blind, parallel-group active controlled noninferiority trials that compared vadadustat to darbepoetin alfa to determine the safety and efficacy in patients with anemia of DD-CKD receiving either peritoneal dialysis or hemodialysis. The poster was titled *Vadadustat for Treatment of Anemia in Patients with Dialysis-Dependent CKD Receiving Peritoneal Dialysis*.

The prespecified primary safety end point was time to first MACE. The primary and key efficacy end point was the mean change in Hb from baseline to weeks 24 to 36. The key secondary efficacy end point was the mean change from baseline to weeks 40 to 52. The incidence of treatment-emergent adverse events was also examined.

A total of 3923 patients were randomized in the two INNO$_2$VATE trials. Of those, 309 were receiving peritoneal dialysis: 152 in the vadadustat arm and 157 in the darbepoetin alfa arm. Among the patients in the peritoneal dialysis population, the rates of MACE were similar in the vadadustat and darbepoetin alfa arms (25/152 [16.4%] and 27/157 [17.2%], respectively).

The least-squares mean difference in change in Hb from baseline was -0.10 g/dL (95% confidence interval [CI], -0.33 to 0.12) to weeks 24 to 36 and -0.19 g/dL (955 CI, -0.43 to 0.05) to weeks 40 to 52. The primary and key secondary efficacy end points met the prespecified noninferiority margin of -0.75 g/dL.

The incidence of overall treatment-emergent adverse events was 88.2% in the vadadustat arm versus 95.5% in the darbepoetin alfa arm. The overall incidence of serious adverse events was 52.6% in the vadadustat arm versus 73.2% in the darbepoetin alfa arm.

"Among patients receiving peritoneal dialysis in the INNO$_2$VATE phase 3 trials, safety and efficacy of vadadustat were comparable to darbepoetin alfa," the researchers said.

Funding was provided by Akebia Therapeutics, Inc., and Otsuka Pharmaceuticals Development and Commercialization, Inc.

Source: Chertow GM, Boudville N, Chowdhury P. Vadadustat for treatment of anemia in patients with dialysis-dependent CKD receiving peritoneal dialysis. Abstract of a poster presented at the American Society of Nephrology virtual Kidney Week 2021 (Abstract P00464), November 2021.

2021 ASN Lifetime Achievement Awards

Each year, the American Society of Nephrology (ASN) honors individuals who have significant accomplishments in research, education, and other areas of kidney health. The honorees for 2021 are:

The Belding Scribner Award, recognizing contributions that have direct impacts on patient care, was presented to **Jonathan Himmelfarb, MD, FASN.** Dr. Himmelfarb holds the Joseph W. Eschbach MD Endowed Chair for Kidney Research in the department of medicine, division of nephrology, University of Washington. His research and clinical achievements are internationally recognized and include areas that have inspired major advances in kidney research and care.

The Donald W. Seldin Young Investigator Award was presented to **Krzysztof Kiryluk, MD.** The award is presented to an individual with an outstanding record of achievement and creativity in basic or patient-oriented research related to the functions and diseases of the kidney. Dr. Kiryluk is associate professor of medicine at Columbia University. His research includes the genetics of IgA nephropathy, kidney transplantation, and membranous nephropathy.

The Homer W. Smith Award was presented to **Melissa H. Little, PhD.** The award recognizes contributions that affect the science of nephrology, including pathobiology, cellular and molecular mechanisms, and genetic influences on the functions and diseases of the kidney. Professor Little is the theme director of cell biology and senior principal research fellow at the Murdoch Children's Research Institute in Melbourne, Australia, and professor of medicine, dentistry and health sciences at the University of Melbourne. She is the author of more than 260 publications and helped define the genetic basis of the pediatric renal neoplasm.

Donald E. Wesson, MD, FASN, MBA, received the John P. Peters Award in recognition of his contributions improving the lives of patients and furthering the understanding of the kidney in health and disease. Dr. Wesson is professor of medicine at Texas A&M University and president of DEW Consulting. His research career has focused on the role of the kidney in maintaining acid-base and electrolyte homeostasis. He has initiated system-wide improvements in care delivery and improved care of underserved and under-resourced communities.

Joanne M. Bargman, MD, was awarded the Robert G. Narins Award that honors individuals who have made contributions to teaching and education. She is professor of medicine and director of peritoneal dialysis for the University Health Network at the University of Toronto. She is renowned for her work teaching and educating in nephrology, and has received numerous teaching awards for undergraduate, graduate, and post-graduate teaching. Dr. Bargman has also received awards for her scholarship and commitment to improving patient outcomes.

Dialysis Disequilibrium Syndrome in Patients on Hemodialysis

Patients who have missed multiple dialysis treatments, particularly those who have initiated dialysis recently, are at risk for dialysis disequilibrium syndrome (DDS), which presents as a rare neurological complication. According to **Rupesh Raina, MD, FACP, FAAP,** and colleagues at the Cleveland Clinic, Akron, Ohio, and the Akron Children's Hospital, the conceptual pathogenesis of DDS is likely a result of multiple physiological abnormalities.

The researchers explored DDS and preventive measures with a focus on effective management strategies for DDS. Results of the reviews were reported during a virtual poster session at ASN Kidney Week 2021 in a poster titled *Dialysis Disequilibrium Syndrome (DDS) in Hemodialysis Patients: A Systematic Review*.

The literature search was conducted on PubMed/Medline and Embase. Studies were included irrespective of age and sex of participating patients. Data were analyzed and a summary table was extracted with the following variables: study type, population group, age, patient characteristics, blood and dialysate flow rate, and study outcome. A descriptive analysis was performed analyzing the population size and frequency of symptoms and treatments utilizing the R software.

The search identified 49 studies that were included in the analysis. In 48 of the 49 studies, 72.4% of patients reported having DDS. The most common symptoms reported were headache (39.4%), nausea (40.4%), vomiting (39.1%), confusion (66.7%), and seizure (78.6%). In the current sample, 12 studies switched from hemodialysis to alternative modalities of dialysis, including continuous hemofiltration/hemofiltration or peritoneal dialysis, with no further reported DDS symptoms.

"We have provided comprehensive clinical practice points for both the pediatric and adolescent and young adult population," the researchers said. "Interestingly, DDS was reported more often in the early dialysis era prior to recent advances and improvements of resource allocation. Existing literature shows it is crucial to recognize symptoms of DDS and implement timely prevention to improve outcomes."

Source: Raina R, Singh SS, Chakraborty R. Dialysis disequilibrium syndrome (DDS) in hemodialysis patients: Systematic review. Abstract of a poster presented at the American Society of Nephrology virtual Kidney Week 2021 (Abstract P00928), November 2021.

Familial Clustering of CKD and Heritability of Kidney Biomarkers in the General Population

The prevalence of chronic kidney disease (CKD) in the adult population in Europe is estimated at between 3.3% and 17.3%. There are strong associations between CKD and increased risk of cardiovascular events as well as progression to kidney failure. Hypertension and diabetes are established risk factors for CKD, accounting for 50% to 70% of all cases. Familial clustering of CKD and kidney-related markers may indicate that genetic factors or shared environmental factors also play a role in the pathogenesis of CKD.

Jia Zhang, PhD, and colleagues conducted a study designed to quantify the familial aggregation of CKD and to gather heritability estimates of kidney traits and related kidney markers in the general population. Results of the study were reported in the *American Journal of Kidney Diseases* [2021;77(6):869-878].

The cross-sectional family study utilized baseline data from the Lifelines Cohort Study and Biobank, a multidisciplinary prospective population-based study conducted in the northern Netherlands. The study had a 3-generational design that included 167,648 participants, >95% with European ancestry. The primary outcome of interest was CKD, defined as estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2 measured using the CKD Epidemiology Collaboration creatinine equation (CKD_{Scr}). In a subgroup with available data on urinary albumin concentration (n=59,943), urinary albumin excretion was expressed as the rate of urinary albumin excretion (UAE) per 24 hours or urinary albumin-creatinine ratio (UACR).

Of the 167,548 Lifeline participants at baseline, the current study included 155,911 participants, within 29,703 family clusters; 39,836 singletons, who had eGFR data available at the baseline visit. A subsample with both eGFR and UACR data included 59,938 participants (including 743 juveniles), and a subsample of 59,145 adults had both eGFR and UAE data available.

In the overall cohort (n=155,911), 58.1% were female, mean age was 43.1 years, mean eGFR was 97.2 mL/min/1.73 m^2. In the subgroup with albuminuria measurements, median UAE was 3.86 mg/d and median UACR was 2.72 mg/g. Among males, the kidney risk profile (higher prevalence of smoking, hypertension, diabetes and high cholesterol) was slightly less favorable than among females. Distribution of CKD risks and kidney markers (eGFR and UAE) was similar between men and women.

Kidney profile was slightly less favorable among participants with a family history of CKD_{Scr} compared with those without a family history. The distributions of age, sex, and covariates in the subsample were similar to those in the full sample.

The crude prevalence of CKD_{Scr} was 1.19% (1,862 cases). In 5.8% of family clusters (n=1725/29,703 families), there was at least one case of CKD_{Scr}. A total of 2211 individuals had at least one first-degree relative with CKD_{Scr}. Of those, 1680 had at least one affected parent, 56 had at least one affected offspring, and 499 had at least one affected sibling.

Among participants >60 years of age, the prevalence of CKD_{Scr} increased dramatically. Mean eGFR was lower at higher age, and age-specific mean values of eGFR were lower among those with affected first-degree relatives than among the general population. Among those with a first-degree relative affected by CKD_{Scr}, the age-specific prevalence rates were significantly higher. In the subsample, the crude prevalence rates of $CKD_{Scr+UAE}$ and $CKD_{Scr+UACR}$ were 5.5% and 6.8%, respectively.

In analyses of recurrence risk ratio (RRR) for CKD_{Scr}, having a first-degree relative affected by CKD_{Scr} was generally associated with an RRR of 3.04 (95% confidence interval [CI], 2.26-4.09). There was no clear pattern in familial recurrence by kinship type or sex of the affected family member. The risk among spouses of affected individuals was higher than that of the general population (RRR, 1.56; 95% CI, 1.20-2.00).

In RRR analyses in the subsample (~60,000 participants), the prevalence of $CKD_{Scr+UAE}$ was higher than that of CKD_{Scr}. Among those with an affected first-degree relative, $CKD_{Scr+UAE}$ was more prevalent, although the trend was less pronounced than that for CKD_{Scr}. The subsample RRR for $CKD_{Scr+UAE}$ was 1.34 (95% CI, 1.14-1.58); for CKD_{Scr}, the RRR was 2.35 (95% CI, 1.74-3.17). Results were similar when albuminuria was measured using UACR rather than UAE.

In analyses using CKD_{UAE}, those with a first-degree relative affected by CKD_{UAE} had, on average, higher UAE. There was a higher prevalence of CKD_{UAE} observed among those with an affected first-degree relative. The RRR for CKD_{UAE} was 1.60 (95% CI, 1.26-2.03). The risk was elevated primarily in those with an affected mother or sibling. There was no elevated spousal risk. Results for CKD_{UACR} were similar.

Estimates of heritability were 44% for EGFR, 20% for UAE, and 18% for UACR. For the kidney markers, the estimates were 31% for serum urea, 37% for creatinine, and 48% for uric acid. Estimates for serum electrolytes ranged from 22% to 28%. In the subsample, the heritability estimates were similar but less precise. After accounting for household or spousal effects, the estimates did not change, and there was no substantial change after inclusion of additional covariates.

The researchers cited some limitations to the study findings, including 24-hour albuminuria measurements being available for only 60% of the study cohort, estimating rather than measuring GFR, lack of data on kidney biopsy, the possibility of underestimating RRRs, the low prevalence of CKD in the study population, and the inability to generalize the findings to ancestries other than European.

"In summary, we demonstrate that CKD clusters in families in the general population, given that risk of CKD was sternly elevated in those with an affected relative," the researchers said. "Considerable heritability (20-50%) of kidney traits was observed. Therefore, much of the familial clustering may be attributed to genetic factors. The data presented in this study inform future work on risk stratification based on family history, and provide a step forward in disentangling genetic and environmental risk factors in CKD." ■

TAKEAWAY POINTS

- Researchers utilized data from the Lifeline Cohort Study to quantify familial clustering of chronic kidney disease (CKD) in the general population and to examine the extent to which kidney traits could be explained by genetic and environmental factors.
- In participants with at least one first-degree relative affected by CKD, the risk of CKD was three times higher than that in the total sample.
- The heritability of kidney traits and related biomarkers ranged from moderate to high, indicating the role of genetic factors in risk of CKD.

Treating Hyperphosphatemia with Lanthanum Carbonate

Patients with chronic kidney disease (CKD) and hyperphosphatemia undergoing dialysis are at increased risk for cardiovascular events and all-cause mortality. Calcium-based phosphate binders are inexpensive and well tolerated and are commonly used to improve hyperphosphatemia. However, by increasing the calcium load, calcium-based binders may accelerate vascular calcification, a marker for cardiovascular and all-cause mortality, Updated recommendations from the Kidney Disease: Improving Global Outcomes guidelines call for restriction of the dose of calcium-based phosphate binders for patients with hyperphosphatemia.

Results of a 2018 systematic review were inconclusive regarding whether calcium-free phosphate binders reduced cardiovascular events compared with calcium-based binders. Sevelamer reduced all-cause mortality but not cardiovascular death when compared with calcium-based binders; lanthanum carbonate did not improve all-cause deaths and its effect on cardiovascular events is unknown.

Hiroaki Ogata, MD, and colleagues in Japan conducted the LANDMARK trial comparing composite events to determine whether lanthanum carbonate reduces cardiovascular events compared with calcium carbonate in patients with hyperphosphatemia undergoing hemodialysis at risk of vascular calcification. Results of the study were reported in *JAMA* [2021;325(19):1946-1954].

The primary outcome of interest was a composite of cardiovascular events: (1) death due to a cardiovascular event (myocardial infarction [MI] or stroke), including cardiac death; (2) nonfatal MI; (3) nonfatal stroke, including transient ischemic attack; (4) unstable angina; (5) hospitalization for heart failure; and (6) hospitalization for ventricular arrhythmia. Secondary outcomes were overall survival, secondary hyperparathyroidism-free survival, hip fracture-free survival, and adverse events. The study period was November 2011 to June 2018. The final analysis cohort included 1063 patients in the lanthanum carbonate group and 1072 in the calcium carbonate group (total=2135).

The two groups were well balanced in baseline characteristics, with the exception of lanthanum carbonate and statin use being more prevalent in the lanthanum carbonate group than in the calcium carbonate group. In both groups, median age was 69 years, and 40.5% were female.

Excluding patients who died, follow-up was incomplete for 13.5% of patients in the lanthanum carbonate group (n=143) and 13.2% of those in the calcium carbonate group (n=141). In the lanthanum group, median follow-up was 3.16 years; median follow-up in the calcium carbonate group was 3.16 years.

At baseline, median daily doses were 750 mg for lanthanum carbonate and 1500 mg for calcium carbonate. By month 36, lanthanum had gradually increased to 1500 mg/day; the daily dose of calcium carbonate remained virtually unchanged during the study period. In the lanthanum carbonate group, adjunctive sevelamer use was nearly unchanged in the first 36 months; in the calcium carbonate group, it gradually increased to 27.2%. In the lanthanum carbonate group, there was a consistent increase in the proportion of active vitamin D users throughout the study period; in the calcium carbonate group, active vitamin D use remained nearly flat. The two groups were similar in increase of cinacalcet use.

In the lanthanum carbonate group corrected calcium levels decreased significantly compared with the calcium carbonate group ($P<.001$ by mixed models for repeated measures analyses); serum phosphate levels increased significantly in the lanthanum carbonate group ($P<.001$) during the study period. Thus, there was no difference in calcium × phosphate products between the two groups during the study period.

PRIMARY OUTCOMES

The primary composite end point occurred in 147 of 1063 patients in the lanthanum carbonate group and 143 of 1072 patients in the calcium carbonate group (absolute difference, 0.50 per 100 person-years; 95% confidence interval [CI], –0.57 to 1.56). Following stratification according to age, sex, and diabetes status, the hazard ratio (HR) in the lanthanum carbonate group versus the calcium carbonate group was 1.11 (95% CI, 0.88-1.41). In the per-protocol set, the results were not significantly different (absolute difference, 0.48 per 100 person-years, 95% CI, –0.61 to 1.56; HR, 1.12, 95% CI, 0.86-1.45).

Across prespecified subgroups, the effect of lanthanum carbonate treatment on the primary composite end point was consistent, with no interactions observed. However, in patients undergoing hemodialysis, dialysate calcium concentrations affected the calcium load.

SECONDARY OUTCOMES

In the lanthanum carbonate group, there were 159 deaths (incidence rate, 4.96 per 100 person-years; 95% CI, 4.33-5.65), versus 158 deaths in the calcium carbonate group (incidence rate, 4.53 per 100 person-years, 95% CI, 3.93-5.19; absolute difference, 0.43 per 100 person-years, 95% CI, –0.63 to 1.49; HR, 1.10, 95% CI, 0.88-1.37). Cardiovascular mortality was significantly higher in the lanthanum carbonate group compared with the calcium carbonate group (absolute difference; 0.61 per 100 person-years, 95% CI, 0.02—1.21; HR, 1.51, 95% CI, 1.01-2.27; $P=.045$). Secondary hyperparathyroidism was more frequent in the lanthanum carbonate group, while the incidence of hip fracture during the study period was similar in the two groups.

ADVERSE EVENTS

There were 282 adverse events in the lanthanum carbonate group and 259 in the calcium carbonate group (25.7% vs 23.4%, respectively). In the lanthanum carbonate group, 63.8% of patients experienced gastrointestinal disorders, compared with 48.6% of patients in the calcium carbonate group. In the lanthanum carbonate group, hyperphosphatemia (>6.0 mg/dL) was more prevalent; hypercalcemia (>10 mg/dL) was more prevalent in the calcium carbonate group.

The researchers cited some limitations to the study, including the low incidence of cardiovascular events; the possibility that dietary calcium intake in this study population may be lower than in previous trials in Western countries; including participants from one country only; and the possibility that the results may not be generalizable to patients with overt secondary hyperparathyroidism.

In conclusion, the authors said, "Among patients undergoing hemodialysis with hyperphosphatemia and at least one vascular calcification risk factor, treatment of hyperphosphatemia with lanthanum carbonate compared with calcium carbonate did not result in a difference in composite cardiovascular events. However, the event rate was low, and the findings may not apply to patients at higher risk." ■

TAKEAWAY POINTS

- Researchers reported results of a study designed to compare composite cardiovascular events between a group of patients undergoing dialysis treated with lanthanum carbonate (a calcium-free phosphate binder) and those treated with calcium carbonate.
- The trial included patients with at least one risk factor for vascular calcification. There were no significant differences between the two groups in composite cardiovascular events.
- However, the event rates were low and the findings may not apply to patients at higher risk.

Demographic Factors and Non-Guideline-Based Treatment for Kidney Cancer

Major organizations have issued guidelines for the treatment and management of kidney cancer that favor nephron-sparing approaches such as partial nephrectomy or ablation, or active surveillance in patients with small kidney masses. According to **Jeffrey M. Howard, MD,** and colleagues, awareness of the undertreatment of clinically aggressive cancers, particularly among underserved racial/ethnic groups and those who are uninsured or underinsured, is increasing.

The researchers conducted a retrospective cohort study to examine the association between demographic factors that included sex, race/ethnicity, and insurance status, and receipt of non-guideline-based care for kidney cancer. Results of the study were reported online in *JAMA Network Open* [doi:10.10.1001/jamanetworkopen.2021.12813].

TAKEAWAY POINTS

- A retrospective cohort study was designed to determine whether demographic factors, including sex, race/ethnicity, and insurance status, are associated with receipt of non-guideline-based treatment for kidney cancer.
- In a cohort of patients identified using data from the National Cancer Database for the period 2010 through 2017, women were treated more aggressively than men, with lower odds of undertreatment and higher odds of overtreatment.
- Black and Hispanic patients had higher adjusted odds of undertreatment and overtreatment compared with White patients. There was an association between uninsured status and lower adjusted odds of overtreatment and higher adjusted odds of undertreatment.

The primary outcome of interest was receipt of non-guideline-based treatment, undertreatment or overtreatment, for kidney cancer as defined by accepted clinical guidelines. The researchers utilized data from the National Cancer Database (NCDB), a joint project of the Commission on Cancer (CoC) of the American College of Surgeons and the American Cancer Society. The database includes data from more than 1500 CoC-accredited hospitals in the United States and includes ~70% of all new cancer diagnoses in the United States.

Following application of inclusion and exclusion criteria, the final study population included 158,445 patients with cT1-2, NO, MO kidney cancer. Cancer staging was done according to the seventh edition of the American Joint Committee on Cancer TNM system.

The study population was selected to represent a comparatively young and healthy cohort, making advanced age and comorbidity unlikely to be taken into consideration in treatment decision making. Median age of the cohort was 58 years, 62.8% were men (n=99,563), 75.7% were White (n=120,001), and 57.6% had private insurance (n=91,218). A total of 36,773 (23.2%) had a Charlson Comorbidity Index (CCI) score of 0 and 121,721 (76.8%) had a CCI score of 1. Guideline-based treatment was provided to 69.4% of the cohort (n=109,901); 30.6% (n=48,544) received non-guideline-based treatment. Of the group that received non-guideline-based treatment, 3893 (2.5%) patients were undertreated and 44,651 (28.2%) were overtreated. Over the study period, the total number of patients increased, as did the proportion of patients receiving guideline-based treatment, from 11,206 of 16,934 (66.2%) in 2010 to 15,055 of 21,126 patients (71.3%) in 2017 ($P<.001$).

Results of multinominal logistic regression analyses demonstrated that in the overall study population, women were treated more aggressively than men, with statistically lower adjusted odds of undertreatment (odds ratio [OR], 0.82; 95% confidence interval [CI], 0.77-0.88; $P<.001$) and statistically significant higher odds of overtreatment (OR, 1.27; 95% CI, 1.24-1.30; $P<.001$), controlling for other demographic factors.

In subgroup analysis, the association between female sex and overtreatment was preserved for small (<2 cm) cT1a kidney masses (OR, 1.15; 95% CI, 1.06-1.24; $P<.001$) and large (2-4 cm) cT1a kidney masses (OR, 1.13; 95% CI, 1.05-1.21; $P<.001$). Women had statistically significant lower adjusted odds of undertreatment for cT1b tumors (OR, 0.79; 95% CI, 0.73-0.86; $P<.001$). There was no statistically significant association for cT2 tumors.

There were associations between Black race and statistically significant higher adjusted odds of undertreatment (OR, 1.42; 95% CI, 1.29-1.55, $P<.001$) and overtreatment (OR, 1.09; 95% CI, 1.05-1.13; $P<.001$) compared with White race, controlling for other demographic factors. The association between Black race and undertreatment remained statistically significant in subgroup analysis for cT1b and CT2 kidney masses. In the subgroup of patients with smaller masses, the adjusted odds of overtreatment were statistically significantly lower for patients with small cT1a masses.

There was an association between Hispanic ethnicity and undertreatment (OR, 1.20; 95% CI, 1.06-1.36; $P=.004$) and overtreatment (OR, 1.06; 95% CI, 1.01-1.11; $P=.01$) in the primary analysis. In subgroup analysis, the association was significant in only some tumor classifications.

There was a significant association between uninsured status and receiving less aggressive treatment when compared with private insurance status. Being uninsured was statistically significantly associated with higher adjusted odds of undertreatment (OR, 2.63; 95% CI, 2.29-3.01; $P<.001$) and lower adjusted odds of overtreatment (OR, 0.72; 95% CI, 0.67-0.77; $P<.001$). The associations remained significant in subgroup analysis for overtreatment of small cT1a masses (OR, 0.40; 95% CI, 0.33-0.49; $P<.001$) and undertreatment of cT1b masses (OR, 2.49; 95% CI, 2.10-.294; $P<.001$) and cT2 masses (OR, 2.77; 95% CI, 2.11-3.62; $P<.001$).

The authors noted some limitations to the study findings, including retrospectively applying a contemporary guideline to patients treated in the past.

In summary, the researchers said, "To our knowledge, this study represents the first attempt to assess the associations between demographic factors and receipt of non-guideline-based treatment among patients with kidney cancer. We found that female patients with kidney cancer had higher odds of receiving more aggressive treatment than men, which was associated with increased rates of overtreatment for small kidney masses and potentially increased risk for unjustified complications. Black race and Hispanic ethnicity were associated with higher odds of undertreatment and overtreatment, highlighting the bidirectional nature of inequities in treatment. Patients without insurance had markedly lower odds of overtreatment for very small kidney masses, potentially representing a rare example of a salutary association of reduced access to care. Clinicians should bear these disparities in mind when counseling individual patients, and health policy makers should take the existence of these disparities into account." ■

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Urine Citrate as Early Marker of Metabolic Acidosis in CKD

Metabolic acidosis, a common complication of chronic kidney disease (CKD), is associated with muscle wasting, bone disease, loss of kidney function, and increased mortality. Results of recent small interventional studies have shown that correction of metabolic acidosis with oral alkali supplementation, novel acid exchange resins, or lower dietary acid load may result in preservation of kidney function.

Crystal C. Tyson, MD, MHS, and colleagues conducted a randomized order, cross-over study with controlled feeding to test the hypothesis that patients with CKD and relatively preserved serum bicarbonate would be in a state of mild, subclinical acidosis compared with patients without CKD, and that the reduction in net acid excretion (NAE) after alkali supplementation would be blunted in CKD. The study aimed to compare the effects of alkali supplementation on the primary outcome of NAE in participants with and without CKD as a potential functional assay for subclinical acidosis. Results of the study were reported in the *American Journal of Kidney Diseases* [2021;78(1):38-47].

The CKD group and the non-CKD group were similar in serum concentrations of phosphorous, calcium, and bicarbonate; potassium was higher in the CKD group.

The study included 14 participants: eight with CKD (estimated glomerular filtration rate [eGFR] 30-59 mL/min/1.73 m^2 or 60-70 mL/min/1.73 m^2 with albuminuria) and six participants without CKD. At baseline, serum bicarbonate concentrations were between 20 and 28 mEq/L in all participants. No one had diabetes mellitus and none used alkali supplements at baseline.

During the study, participants were fed a mixed-acid-load diet with bicarbonate supplementation (7 days) and with sodium chloride control (7 days) in a randomized order, cross-over design. Outcomes of interest were urine NAE, 24-hour ambulatory blood pressure, and 24-hour urine and plasma metabolomic profiles, measured after each study period.

Of the total cohort, five were male, eight were White, mean age was 68 years, and mean body mass index was 29.6 kg/m^2. Eight of the 14 participants had CKD and one had serum bicarbonate <22 mEq/L. Compared with the six participants without CKD, those with CKD had lower mean eGFR (50.7 vs 85.9 mL/min/1.73 m^2) and higher mean blood pressure (121.9/68.3 mm Hg vs 116.2/64.5 mm Hg). The two groups were similar in serum bicarbonate concentrations (23.5 mEq/L for the CKD group and 23.3 mEq/L for the non-CKD group).

Participants were randomized by CKD status to the control period or the alkali period first. Twelve participants were assigned 31 mEq/d of sodium bicarbonate and one participant in each group was assigned 39 mEq/d. All participants were maintained on their baseline antihypertensive medications without dose changes during the study period, attended all on-site supervised meal visits, and maintained a weight within 2 kg of their baseline weight.

Based on data obtained from self-recorded food diaries and direct supervision at on-site meals, participants consumed ≥91% of the delivered dietary nutrients. Mean 24-hour urine sodium, potassium, phosphorous, sulfate, and urea concentrations were similar for the CKD and non-CKD groups during both the control and alkali study periods. During both periods, urine calcium was lower in the CKD group than in the non-CKD group. There were no significant within-group differences in the 24-hour urine markers.

There were no differences in the number of patients with self-reported side effects during the run-in, control, and alkali periods.

The CKD group and the non-CKD group were similar in serum concentrations of phosphorous, calcium, and bicarbonate; potassium was higher in the CKD group.

During the control period, when all participants were consuming identical diets, urine pH, ammonium, and citrate were statistically lower in the CKD group compared with the non-CKD group (all $P<.05$). After alkali, only urine ammonium remained significantly lower in the CKD group than in the non-CKD group; there were no statistically significant between-group differences in urine pH, NAE, bicarbonate, and citrate.

The effects of alkali supplementation on NAE ($P=.1$ for interaction), urine ammonium ($P=.08$ for interaction), urine pH ($P=.2$ for interaction), and citrate ($P=.1$ for interaction) were greater for participants in the CKD group than for those without CKD. Alkali was associated with a greater increase in urine pH in the CKD group (0.9; 95% confidence interval [CI], 0.6-1.3; $P<.001$) than in the non-CKD group (0.6; 95% CI, 0.2-1.0; $P=.01$) and was associated with increased urine citrate in the CKD group (63.6 mg/d; 95% CI, 11.4-115.7; $P=.02$). There was no statistically significant effect of alkali on urine citrate in the non-CKD group (9.3 mg/d; 95% CI; –51.0 to 69.5 mg/d; $P=.7$).

Both 24-hour and office blood pressure values were generally lower after alkali exposure, the difference was not statistically significant overall or by patient subgroup.

Results of metabolic analysis demonstrated that several urine organic anions were increased with bicarbonate in CKD, including 3-indoleacetate, citrate/isocitrate, and glutarate.

The researchers cited some limitations to the study, including the small sample size, the open-label design, short feeding duration, lack of a washout period between intervention periods, and lack of ambulatory blood pressure measurement at baseline.

"In summary, our results demonstrate acid-base compensations, consistent with subclinical metabolic acidosis among adults with CKD who have relatively preserved serum bicarbonate concentrations. Although increased alkali exposure further reduced NAE in adults with CKD, urine citrate excretion was partially restored by alkali supplementation among these individuals. Thus, urine citrate may identify subclinical acidosis in CKD for future targeted alkali trials," the researchers said. ■

TAKEAWAY POINTS

- Results of a study to test the hypothesis that patients with chronic kidney disease (CKD) and relatively preserved serum bicarbonate would be in a state of mild, subclinical acidosis compared with patients without CKD.
- Participants were fed a fixed-acid-load diet with bicarbonate supplementation (7 days) and with sodium chloride control (7 days) in a randomized, cross-over model.
- Participants with CKD had lower acid excretion in the form of ammonium but also lower base excretion, compared with those without CKD. Urine citrate may be an early marker of metabolic acidosis in patients with CKD.

SARS-CoV-2 Seroprevalence in US Dialysis Patients 1 Year after COVID-19 Pandemic Onset

In the United States, cases of COVID-19, hospitalizations, and deaths overwhelmed health systems. More than 25 million cases of COVID-19 and more than 500,000 deaths have been attributed to SARS-CoV-2 infections. Nearly all regions of the country dealt with threats to their hospital capacity, with the largest numbers of cases occurring between November and December 2020.

Most persons infected with SARS-CoV-2, whether asymptomatic or symptomatic, mount a specific antibody response to the infection. SARS-CoV-2 receptor-binding domain (RBD) immunoglobin antibodies persist for at least 4 to 6 months after infections. Estimates of seroprevalence are an important measure of the extent of SARS-CoV-2 community spread.

Results of a previous study suggested that patients on dialysis could provide a sentinel population for SARS-CoV-2 seroepidemiology because patients have monthly laboratory testing that facilitate surveillance. The patient population includes older adults, members of racial/ethnic minority groups, and people from low-income settings.

Based on those results, **Shuchi Anand, MD,** and colleagues conducted a cross-sectional study to estimate seroprevalence of SARS-CoV-2 antibodies in patients receiving dialysis and in adults in the United States in January 2021, prior to widespread distribution of COVID-19 vaccines. Results of the study were reported online in *JAMA Network Open* [doi:10.1001/jamanetworkopen.2021.16572].

The study was conducted from January 1 to January 31, 2021, and utilized data from US Renal Care, the third largest dialysis organization in the United States. Remainder plasma from all patients receiving dialysis at US Renal Care facilities was tested for SARS-CoV-2 antibodies. Exclusion criteria were receipt of a documented dose of SARS-CoV-2 vaccination or a missing zip code in the electronic medical record.

The researchers standardized the crude seroprevalence estimates from the sample to the US adult population using 2018 American Community Survey 1-year estimates, stratified by age group, sex, self-reported race/ethnicity, neighborhood race/ethnicity composition, neighborhood income levels, and urban or rural status. The data and rates of case detection were compared with data from a July 2020 subsample of patients who received dialysis at the same facilities.

The spike protein RBD total antibody assay was used to estimate crude SARS-CoV-2 seroprevalence in the unweighted sample, and then the estimated seroprevalence rates for the US dialysis and adult populations were calculated, adjusted for age, sex, and region.

The study sample included 21,464 patients; mean age was 63.1 years, and 57% (n=12,265) were male. The patients were disproportionally older (65-79 years of age, 7847 [37%]; ≥80 years of age, 2668 [12%]) and members of racial/ethnic minority groups (Hispanic patients, 2945 [18%]; non-Hispanic Black patients, 4875 [29%]). Patients in 43 states were included in the sample; 33 states contributed ≥30 patients to the sample. There was modest overrepresentation from the South and West regions of the United States. Neighborhood race/ethnicity composition closely matched that of the US dialysis population.

In the unweighted sample of 21,464 patients, SARS-CoV-2 assay seroprevalence estimates in January 2021 were 18.9% (95% confidence interval [CI], 18.3%-19.5%), ranging from 15.3% in the Northeast to 20.8% in the South; 18.7% (95% CI, 18.1%-19.2%) standardized to the US dialysis population; and 21.3% (95% CI, 20.3%-22.3%) standardized to the US adult population. In the unweighted sample, the subgroups with the highest seroprevalence were younger age groups (18-44 years, 25.9%; 95% CI, 24.1%-27.8%), those who self-identified as Hispanic or living in Hispanic neighborhoods (25.1%; 95% CI, 23.6%-26.4%), and those living the lowest income neighborhoods (24.8%; 95% CI, 23.2%-26.5%).

Among patients within the US Renal Care network who underwent laboratory testing in July 2020, the unweighted sample SARS-CoV-2 seroprevalence rates were 4.4% (95% CI, 4.0%-4.8%), the dialysis-adjusted rates were 4.7% (95% CI, 4.3%-5.2%), and the US population-adjusted seroprevalence rates were 5.4% (95% CI, 4.6%-6.2%). Compared with those rates, the January 2021 seroprevalence rates were 1.8-fold higher in the Northeast, 4.1-fold higher in the Midwest, 5.1-fold higher in the West, and 5.1-fold higher in the South.

There was less variation in regional and rural versus urban seroprevalences than in the earlier study. The largest regional difference was 1.2-fold higher odds of seroprevalence in residents of the South in January 2021 compared with 2.3-fold higher odds of seroprevalence in residents in the Northeast versus the West in July 2020. Seroprevalence was 1.7-fold higher among those living in neighborhoods with a majority Hispanic population compared with neighborhoods with a majority White population, and 2.0-fold higher among those living in neighborhoods with ≥30% versus <10% of residents living at the federal poverty level.

Compared with data from July 2020, the estimated SARS-CoV-2 case detection rates increased from 14% to 23% in January 2021. Infection fatality rates decreased from 0.7% in July 2020 to 0.3% in January 2021.

In citing limitations to the study findings, the researchers included the lack of data on SARS-CoV-2 reverse transcriptase-polymerase chain reaction testing or COVID-19 symptoms, and the relative undersampling from the Northeast region of the United States. Because patients on dialysis are less likely to be employed and more likely to die from SARS-CoV-2 infections, SARS-CoV-2 seroprevalence in the general population may have been underestimated.

In conclusion, the authors said, "Results of this cross-sectional study suggest that, in the United States, fewer than one in four patients receiving dialysis and adults overall had evidence of SARS-CoV-2 antibodies in January 2021, which is well below the level needed to confer herd immunity. Residents of neighborhoods with a large population of racial/ethnic minority groups, those from low-income neighborhoods, and individuals from younger age groups had a substantially higher prevalence of SARS-CoV-2 antibodies. The results suggest that, because these subpopulations overlap with people who express high levels of vaccine hesitancy in the United States, vaccination campaigns may need to engage these high-risk groups to achieve sufficient penetration and reach community-level protection against SARS-CoV-2." ■

TAKEAWAY POINTS

- Researchers conducted a cross-sectional study to estimate the seroprevalence of SARS-CoV-2 antibodies in patients on dialysis and in the overall US adult population in January 2021, prior to the widespread introduction of COVID-19 vaccine.
- Seroprevalence of SARS-CoV-2 antibodies in a cohort of 21,464 patients who were receiving dialysis within US Renal Care was 18.9%, with a seroprevalence of 18.7% standardized to the US dialysis population, and 21.3% standardized to the US adult population.
- Younger persons, those who self-identified as Hispanic or living in Hispanic neighborhoods, and those living in the lowest-income neighborhoods were among the subgroups with the highest seroprevalence.

Print-only Content

Biomarkers of Immune Activation and Risk of Kidney Failure

Worldwide, chronic kidney disease (CKD) affects approximately 697.5 million adults. Patients who progress from early stage CKD to kidney failure with replacement therapy (KFRT) are at increased risk for morbidity and mortality.

Activation of the innate and/or adaptive immune system is central to the pathogenesis of many types of kidney disease. Results of the African American Study of Kidney Disease and Hypertension (AASK) demonstrated an association between higher baseline levels of soluble urokinase-type plasminogen activator receptor (suPAR), a biomarker of immune activation, and increased risk of progression of CKD and incident KFRT.

It is unclear whether other biomarkers of immune activation are associated with incident KFRT in African American patients with nondiabetic kidney disease. **Teresa K. Chen, MD, MHS,** and colleagues conducted a prospective cohort study to test the hypothesis that higher concentrations of specific biomarkers would be associated with greater risk of KFRT, progression of CKD, and all-cause mortality. The researchers further hypothesized that the biomarkers would augment risks associated with APOL1 for KFRT and CKD progression. Results of the study were reported in the *American Journal of Kidney Diseases* [2021;78(1):75-84].

TAKEAWAY POINTS

- Researchers conducted a prospective cohort study to test the hypothesis that higher concentrations of certain biomarkers in African Americans with chronic kidney disease (CKD) attributed to hypertension would be associated with greater risks of kidney failure with replacement therapy (KFRT), progression of CKD, and all-cause mortality.
- There were associations with levels of soluble tumor necrosis factor receptor 1 (sTNFR1), sTNFR2, and TNF-a and KFRT and mortality.
- There were no associations between interferon-y and KFRT or mortality.

The biomarkers of interest were soluble tumor necrosis factor (TNF) receptors 1 (sTNFR1) and 2 (sTNFR2), TNF-a, and interferon Y (IFN-y). The primary outcome of interest was incident KFRT. Secondary outcomes were all-cause mortality and CKD progression, defined as a doubling of serum creatinine or KFRT. Cox proportional hazards models were used to assess the association of each biomarker with KFRT.

Of the 1094 participants in the AASK trial, the 500 who had baseline serum samples available for measurement of biomarkers made up the study population for the current analysis. AASK participants without available samples had slightly higher mean measured glomerular filtration rate (mGFR) (46.4 vs 44.7 mL/min/1.73 m^2) and suPAR levels (4487 vs 4417 pg/mL) than those with available samples; the two groups were similar in all other areas.

At baseline, mean age of the cohort was 54.1 years, 37% were female, mean mGFR was 44.7 mL/min/1.73 m^2, and median urinary protein-creatinine ratio (UPCR) was 0.09 g/g. Median levels of biomarkers were: sTNFR1, 2875 pg/mL; sTNFR2, 13,021 pg/mL; TNF-a, 2.92 pg/mL; and IFN-y, 5.51 pg/mL. Those in the highest sTNFR1 tertile were significantly younger and had worse kidney functions compared with those in the lower tertiles. Participants in the higher tertiles of sTNFR1 also had higher median levels of other biomarkers of immune activation, including sTNFR2, TNF-a, and suPAR.

> Each 2-fold higher baseline level of soluble tumor necrosis factor receptor 2 was associated with a 2.29-fold increase in risk of incident KFRT.

Of the 500 participants, 333 had available genotyping. Among participants with genotyping, 26% had *APOL1* high-risk status and 74% had low-risk status. Participants in the *APOL1* high-risk group were younger, had lower mean systolic blood pressure and mGFR, and had higher median UPCR, serum sTNFR1, sTNFR2, and suPAR than participants with low-risk status. At baseline, the two *APOL1* risk groups were similar with respect to TNF-a and IFN-y.

Over a median follow-up of 8.5 years, 161 of the 500 participants developed KFRT. In unadjusted analyses, there was an association between each 2-fold higher baseline level of sTNFR1 and an 8.10-fold greater risk of incident KFRT (95% confidence interval [CI], 6.15-10.66). The association was robust to adjustment for demographic and clinical factors. On further adjustment for baseline mGFR and proteinuria, the association was attenuated but remained statistically significant (hazard ratio [HR], 3.66; 95% CI, 2.31-5.80). Each 2-fold higher baseline level of sTNFR2 was associated with a 2.29-fold increase in risk of incident KFRT in fully adjusted models.

The association between TNF-a with incident KFRT was smaller, but remained significant in both unadjusted and adjusted models (HR, 1.88, 95% CI, 1.54-2.29 and HR, 1.35, 95% CI, 1.07-1.71, respectively). There was no association between IFN-y levels and incident KFRT. In comparison, there was an association between each doubling of baseline suPAR concentration and a 1.39-fold greater risk of KFRT.

During a median follow-up of 9.6 years, there were 113 deaths. In unadjusted models, there were associations between each 2-fold higher baseline level of sTNFR1, sTNFR2, and TNF-a and a 1.7- to 1.8-fold greater risk of all-cause mortality. Following adjustment for demographic and clinical factors and baseline kidney function, the associations strengthened, with each 2-fold higher baseline level of those biomarkers associated with a 2.0- to 2.2-fold higher risk of death (all $P \leq .01$). There was no association between baseline IFN-y and all-cause mortality.

Among the 333 participants with genotyping, following adjustment for *APOL1* risk status and European ancestry, each 2-fold higher baseline level of sTNFR1 was associated with a significantly increased disk of KFRT (HR, 3.83; 95% CI, 2.21-6.61), CKD progression (HR, 2.76; 95% CI, 1.68-4.54), and mortality (HR, 2.88; 95% CI, 1.31-6.35). Trends were similar for sTNFR2 and TNF-a, but not for IFN-y.

The authors cited some limitations to the study findings, including the AASK trial participants being limited to African Americans with CKD attributed to hypertension, making the findings potentially ungeneralizable to other ethnic groups or CKD causes, and the small sample size, particularly for the analyses related to *APOL1*. The researchers also noted that although the results suggest a strong association between biomarkers and adverse outcomes, they do not imply causality.

In conclusion, the researchers said, "Among African Americans with CKD attributed to hypertension, baseline serum levels of sTNFR1, sTNFR2, and TNF-a were associated with adverse kidney outcomes and mortality, with sTNFR1 appearing to have the strongest associations. Future studies are needed to determine the clinical utility of measuring and/or targeting these biomarkers in both patient care and clinical trials." ■

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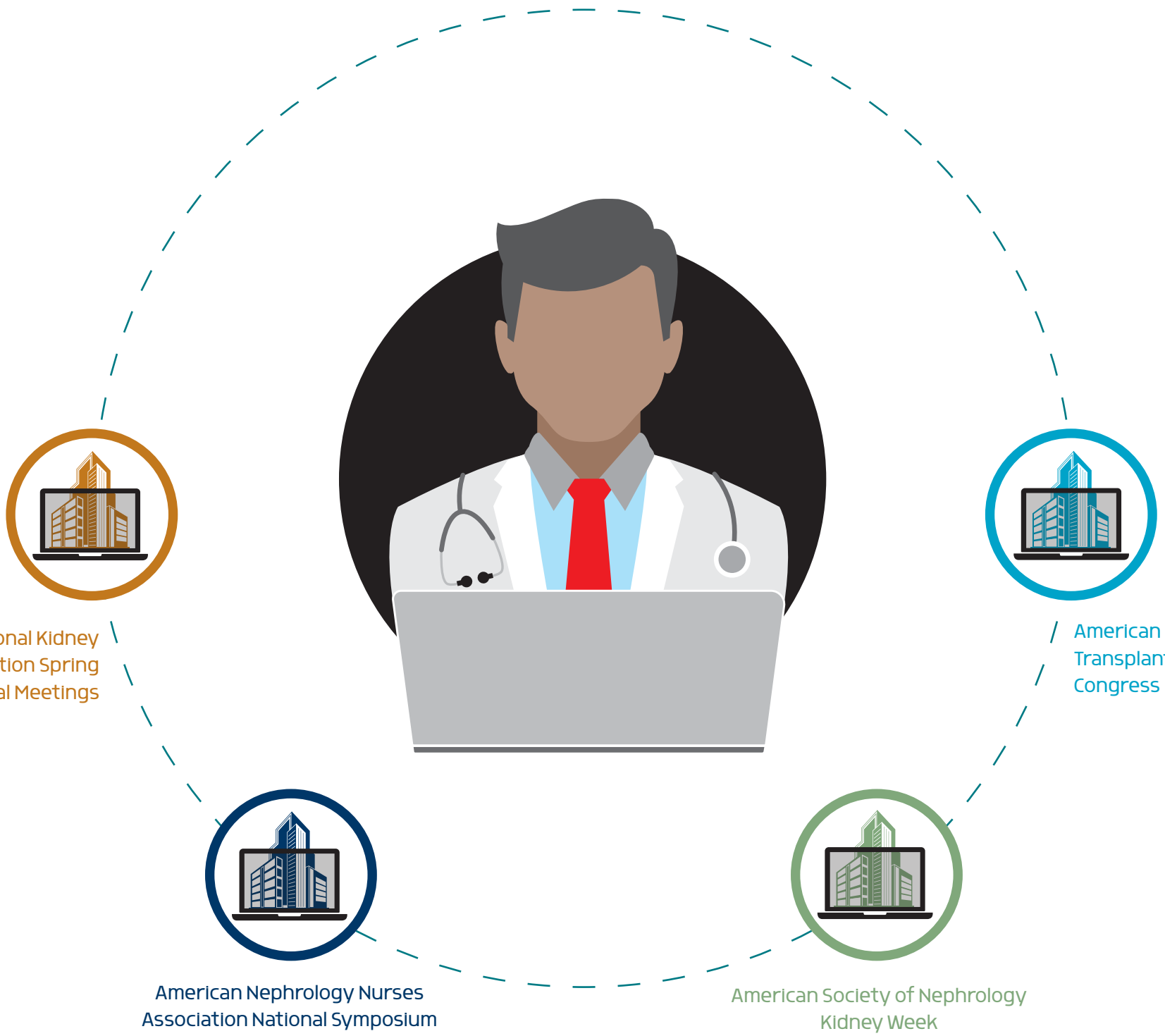


Nephrology Times goes to meetings!

Watch your inbox and mail box for coverage of posters and presentations at nephrology meetings throughout 2021.

Deceased Donor Transplant Rates with Updated US Kidney Allocation Policy

In December 2019, the Organ Procurement and Transplantation Network (OPTN) approved changes to the kidney allocation system. The changes were implemented in an effort to improve parity in organ procurement across the United States. The rationale for the changes was that, depending on the geographic location of the center for a patient on the wait list, the calculated wait time for a deceased donor kidney transplant could vary by more than 5 years. The refined policy aimed to make wait times equal regardless of geographic location.

In 2018, the United Network for Organ Sharing (UNOS) announced principles of geographic distribution that included the principle that "deceased donor organs are a national resource." **Derek A. DuBay, MD,** and colleagues proposed that if all deceased donor organs are a national resource, all patients with ESKD should be considered in the allocation policy. The researchers performed a cross-sectional population-based economic evaluation analysis to examine the impact of the 2019 OPTN kidney allocation policy using transplant rates normalized to the population burden of ESKD across the United States. Results of the analysis were reported in *JAMA Surgery* [2021;156(7):639-645].

The analysis included a merged data set containing the United States Renal Disease System (USRDS) and the Scientific Registry of Transplant Recipients (SRTR) databases. The USRDS divides the United States into networks and gathers data on all patients with ESKD and the SRTR gathers data on all patients wait-listed for solid organ transplant and all patients receiving a kidney transplant.

Participants in the analysis were patients with incident ESKD, those on the kidney transplant waiting list, and recipients of a kidney transplant. Data were collected from January 1 to December 31, 2017; the analysis was conducted in 2019.

The primary outcome of interest was the probability of a patient with ESKD being placed on the transplant waiting list or receiving a deceased donor kidney transplant. The researchers compared states and donor service areas (DSAs) for gains and losses in rates of transplanted kidneys under the new allocation system. Transplant rates were normalized for ESKD burden.

In 2017, 35,447 patients with ESKD were added to the kidney transplant waiting list and 19,694 kidney transplants were performed. Of the 19,694 transplants, 5728 were from living donors, 13,956 were from deceased donors, and 10 were from unknown donor type. A total of 15,365 wait-listed patients died or were removed from the waiting list. The kidney allocation policy pertains only to deceased kidney donors.

There were marked differences in the incidence of ESKD across the United States. The highest rates were in the District of Columbia, the Southeast, West Virginia, and New Jersey; the lowest rates were in the Mountain West states, Minnesota, and Maine, New Hampshire, and Vermont. There were also variations in the probability of a new patient with ESKD being added to the kidney transplant waitlist. The probabilities were highest in Wyoming, Colorado, Minnesota, and several New England states; the lowest probabilities were in Hawaii, Oregon, Nevada, Oklahoma, Arkansas, Louisiana, and Ohio River Valley states.

There were "stark differences" in the probability of a new patient with ESKD receiving a living or deceased donor kidney transplant across the country. The highest probability was in Minnesota, other Midwestern states, Mountain West states, Alaska, and several New England states (Massachusetts, New Hampshire, Rhode Island, and Connecticut). Probability was lowest in Nevada, West Virginia, and the Southeast.

In 2017, there was a 3-fold variation across the United States in the probability of receiving a deceased donor kidney transplant. The probability ranged from 6.36% in West Virginia to 18.68% in the District of Columbia. There was a 10-fold variation in the probability of receiving a living donor kidney transplant, from 1.21% in Alaska to 12.87% in Utah. The likelihood of a patient receiving either a deceased donor or living donor kidney transplant varied more than 3-fold, from 9.16% in Hawaii to 31.6% in Utah.

The OPTN modeling method for deceased donor allocation is based on DSAs, nonprofit agencies that coordinate deceased donation. DSAs are state based in some cases. In some heavily populated areas there may be more than one DSA per state (e.g., New York, California, and Florida); in some areas that are sparsely populated, there may be more than one state in a DSA (e.g., Washington state, Montana, and Alaska).

Based on kidney transplant frequency, the new OPTN allocation system might have been expected to result in the largest increases in deceased donor kidneys in Hawaii, West Virginia, Arkansas, Mississippi, and Nevada. However, OPTN modeling reveals that the largest increases in decreased donor allocation are likely to occur in DSAs from New York, Georgia, and Illinois; other than Georgia, those states have kidney transplant rates per incident ESKD cases above the mean. The largest decreases are likely to occur in Nevada, Ohio, and North Carolina; those states have transplant rates per incident ESKD cases significantly below the mean.

The researchers cited some limitations to the analysis, including the use of registry data, and inferring future transplant rates and outcomes based on data gathered prior to the allocation change.

In conclusion, the authors said, "The new OPTN-approved kidney allocation policy may result in worsening geographic disparities in access to transplant when measured against the burden of ESKD within a particular region of the US. Paradoxically, the largely urban areas with much higher transplant rates gain from the new allocation policy, whereas rural areas with low transplant rates, vulnerable patient populations, and a much higher ESKD burden lose access to deceased donor organs. The OPTN allocation policy may further exacerbate the inequity in these regions of the country, where patients with ESKD have a much lower probability of being wait-listed for transplant. With the updated policy, those patients who are placed on the waiting list in rural areas may have a lower probability of getting a deceased donor kidney transplant." ■

TAKEAWAY POINTS

- Researchers reported results of an analysis of the impact of the new kidney allocation system approved in 2019 by the Organ Procurement and Transplantation Network (OPTN).
- The economic evaluation of 122,659 patients with end-stage kidney disease (ESKD) demonstrated that the policy change will result in disproportionate distribution of organs across the United States.
- States with the lowest transplant rates among the population with ESKD will not see a benefit from the changes in allocation policy and may experience a decrease in allocated organs.

Measuring Risk Tolerance in Potential Living Kidney Donors

In the face of a shortage of deceased donor kidneys, coupled with the superior outcomes associated with living donor transplants, the transplant community is pursuing strategies designed to increase living donor kidney donation. The surgical risks associated with donor nephrectomy are low; nevertheless, research continues to quantify the risk of postdonation kidney failure. Transplant providers aim to limit the harms to candidates for living kidney donor (LKD) donation per the ethical principle of nonmaleficence. The cornerstone of donor evaluation is the consent of the LVD to the potential harms

The 2017 Kidney Disease Improving Global Outcomes (KDIGO) guideline for LKD evaluation and the subsequent KDIGO commentary on the guideline represent the current state of donor informed consent. The process involves disclosing extensive data required by United Network for Organ Sharing policy. According to **Carrie Thiessen, MD, PhD,** and colleagues, the policy creates a unidirectional flow of information from physician to patient.

Enhanced informed consent tools can improve patient engagement. The researchers proposed an approach that would center on the donor, and developed tools to enhance understanding of the risk among donors and facilitate discussions with providers about risk acceptance. The tools include a novel visual aid designed to measure potential donor's risk tolerance to postdonation kidney failure.

The researchers conducted a cross-sectional analysis of donor evaluations at the time of enrollment into a longitudinal mixed-methods study between November 2014 and February 2016. Results of the analysis were reported in the *American Journal of Kidney Diseases* [2021;78(2):246-258].

The analysis included data from three kidney transplant centers in the United States: Northwestern University (Chicago, Illinois); the University of Pennsylvania (Philadelphia, Pennsylvania); and Yale University (New Haven, Connecticut). Eligible participants were English-speaking adults presenting for in-person living kidney donor evaluation. The outcome of interest was participant willingness to accept postdonation kidney failure.

Willingness to accept postdonation kidney failure was measured using the Donor-Specific Risk Questionnaire (DSRQ), a dot matrix visual diagram. Associations between risk acceptance and data from social science instruments were assessed using multivariable logistic regression models.

The study enrolled a total of 312 potential LKDs (86% response rate). Following exclusion due to language comprehension barriers, insufficient time, a missing survey instrument identified following conclusion of the interview, and two difficulties related to the audio recording, the final quantitative analysis cohort included 307 participants and the final qualitative analysis included 305 participants.

Eighty-four percent of the participants were White, 61% were women, 70% were married, 85% were employed, and 57% had an annual household income of >$65,000. Self-reported scores on the 12-Item Short-Form Health Survey (SF-12) were slightly above the US adult average of 50 for both mental and physical health (54.4 and 56.5, respectively). Fourteen percent of the participants were planning to donate via a paired exchange program; the others expected to donate directly to their intended recipients. Sixteen percent had been evaluated previously at another transplant center.

Most of the participants responded they "strongly agree" or "somewhat agree" with the statements of willingness to accept a 0.9% chance of kidney failure if they donated their kidney (80% and 11%, respectively).

In multivariable analyses, participants who were older (odds ratio [OR], 0.98; 95% confidence interval [CI], 0.96-0.99), female (OR, 0.54; 95% CI, 0.31-0.93), and Black (OR, 0.25; 95% CI, 0.08-0.76) were less likely to be in the medium willingness to accept risk group than in the low willingness to accept group.

The researchers conducted semi-structured interviews with participants. Based on analysis of the interviews, six major themes emerged related to why potential donors were willing to accept risk of kidney failure and two related to preferring less risk. Reasons for accepting kidney failure risk were: (1) relationship to intended recipient; (2) benefit to the intended recipient outweighs the risk; (3) postdonation kidney failure is treatable; (4) donor is healthy; (5) risk is necessary part of donation; and (6) the risk is comparable to everyday risks. Reasons for not accepting the risk of kidney failure were: (1) health concerns and (2) caregiver responsibilities. The reasons for accepting the risk of kidney failure were expressed more frequently than those against kidney failure risk (67% vs 14%); 2% of participants expressed both views.

Participants were looking to donate to a friend (19%), sibling (18%), spouse (17%), parent (16%), other relative (16%), or child (8%). Potential donors reported a high level of perceived closeness with their intended recipient; mean Unidimensional Relationship Closeness Scale-Inclusion of the Other in the Self Scale (URCS-IOSS) composite score was 5.0 out of 7.0. Paired exchange donors reported higher levels of perceived closeness with their intended recipient than direct donors (mean of 5.6 vs 4.9 on URCS-IOSS composite scale; *P*=.008).

Ninety-four percent of participants reported using the DSRG without difficulty or adjustment to the number of dots selected. Nine participants decreased and 10 increased the chosen number of dots. The most common reason for decreasing the number of dots chosen originally was an initial misunderstanding that the dots represented certainty about willingness to accept a 0.9% change of kidney failure.

Limitations to the study cited by the authors included risk estimates not being customized to different demographic groups, and possible bias due to concerns among participants about affecting their donor eligibility.

In summary, the researchers said, "At the time of donor evaluation most potential LKDs are willing to accept at least a 0.9% chance of developing kidney failure after donation, and many would be willing to accept even higher risks. There is considerable variation in the kidney failure risk that potential donors accept. Greater relationship closeness to the intended recipient was independently associated with what most health professionals would consider as an unacceptable risk of kidney failure. Our findings provide a feasible approach for transplant centers to improve information exchange with potential LKDs, with the ultimate goal of enhancing the informed consent process with the use of personalized estimates of kidney failure risk in a shift toward greater donor-centered care." ■

TAKEAWAY POINTS

- Researchers developed a novel visual aid to measure potential donors' risk tolerance to postdonation kidney failure.
- Of the 307 participants, 96% indicated a willingness to accept a risk of kidney failure of 0.9% or greater.
- There was an independent association between the closeness of the relationship of the donor to the intended recipient and a greater willingness to accept postdonation kidney failure.

Kidney Transplants Facilitated with Voucher-Based Kidney Donation

Vouchers for future kidney transplant offer a mechanism to overcome the chronological incompatibility that occurs when the ideal time for the donor to give the kidney differs from the time when the intended recipient needs the kidney. Vouchers allow potential donors to donate a kidney and secure a voucher for their intended recipient that can be redeemed, with the kidney of a different donor, if needed in the future.

There is an acknowledged need to increase the number of kidney transplants by facilitating living donation. In July 2019, the White House announced that it would be adopting measures to expand kidney transplants, including increasing public education, decreasing the rate of discarded organs, and removing potential barriers to living donation.

kidney-paired donation. Voucher redemptions were evaluated and analyzed separately.

There has been rapid increase in the number of participating centers in the NKR family voucher program and in the number of voucher donations. At the 79 participating centers in the United States, a total of 250 family voucher donations have been facilitated. Each voucher donor identified a mean of 3.3 voucher holders (in response to the 2019 NKR Medical Board decision to allow up to five healthy voucher holders per donation), and 818 vouchers were issued. Each donation precipitated a chain with a mean length of 2.3 downstream kidney transplants, facilitating 573 total transplants. Of those, 19.4% (n=111) were performed in highly sensitized recipients, with a calculated panel of reactive antibodies of >80%.

TABLE | **Family-Based Voucher Redemptions**

Recipient No.	Recipient sex	Recipient age range, years	Recipient race/ethnicity	Recipient blood type	HLA match points	CPRA, %	Relationship of voucher holder to recipient
1	Female	60-65	White	A	25	20	Friend
2	Female	50-55	White	O	0	68	Spouse
3	Male	40-45	White	O	0	51	Spouse
4	Male	40-45	White	B	0	0	Friend
5	Male	50-55	White	O	10	92	Friend
6	Male	65-70	White	B	20	0	Spouse

Abbreviations: CPRA, calculated panel reactive antibodies; HLA, human leukocyte antigen.

The US government, including the Department of Health and Human Services, has taken actions designed to assist with accrued costs to make living kidney donation financially neutral. The use of vouchers is a program that has the potential to increase donation without the need for regulatory change or additional government spending. Further, the benefits of using a voucher program to expand living organ donation have been documented over the past 6 years. However, uncertainty regarding the actual increase in the number of living kidney donors associated with voucher programs is uncertain.

Jeffrey L. Veale, MD, and colleagues conducted a multicenter cohort study aimed at examining the consequences of voucher-based kidney donation and the capability of voucher redemptions to provide timely kidney allografts. Results of the study were reported in *JAMA Surgery* [2021;156(9):812-817].

The study was conducted at 79 transplant centers across the United States utilizing data from the National Kidney Registry (NKR) from January 1, 2104, to January 31, 2021, to identify all family vouchers and patterns in downstream kidney donations. All living kidney donors and recipients participating in the NKR family voucher program were included in the analysis.

A voucher was presented to the intended recipient at the time of donation. The vouchers had no cash value and could not be sold, bartered, or transferred to another person. When a voucher was redeemed, a living donation chain was used to return a kidney to the voucher holder. The primary study measures and outcomes were deidentified demographic and clinical data from each kidney donation, including the downstream patterns in

Median age of the kidney donors was 46 years (range, 19-78 years), and 7.6% (n=19) were ≥65 years of age. Most family voucher donors were female (157 individuals [62.8%]) and White (241 individuals [96.4%]). Prior to implementation of the family voucher program, incompatible kidney-paired donations spent a mean of 146.0 days waiting for exchange transplant. Following implementation of the program, waiting times decreased to a mean of 46.0 days, a reduction of more than 3 months.

As of publication of the report (September 2021), six vouchers had been redeemed. Of those six vouchers, three were redeemed by individuals with blood type O. One redeemer had two previous kidney transplants and was highly sensitized, with calculated panel reactive antibodies of 92%. The time from issuance of the voucher (kidney donation) to voucher redemption ranged from 167 to 867 days. Time from voucher redemption to kidney transplant ranged from 46 to 155 days.

The researchers cited some limitations to the study findings, including the retrospective design and the use of data from a single kidney exchange consortium.

In conclusion, the authors said, "The results of this study indicate that the family voucher program helped to remove a major disincentive for candidates considering living kidney donation. To date, 250 voucher donations have occurred across the United States, precipitating donation chains that produced 573 kidney transplants. All six of the patients who redeemed vouchers had timely kidney transplants, which is an indication of the family voucher program's viability." ■

TAKEAWAY POINTS

- Researchers reported results of a multicenter cohort study examining the consequences of voucher-based kidney donation and the ability of voucher redemptions to provide timely kidney allografts.
- A total of 250 voucher-based donations between 2014 and 2021 were included in the analysis; the donations facilitated a total of 573 transplants.
- To date, six vouchers have been redeemed; three of the six were among individuals with blood type O. Time from voucher redemption to kidney transplant ranged from 36 to 155 days.

Recommendations for Changes to Improve Kidney Health

The National Kidney Foundation (NKF) and OptumLabs published a set of recommendations aimed at improving kidney health and care for those with kidney disease in the United States. The recommendations were published in the *Journal of General Internal Medicine*.

The recommendations, Shared Viewpoint—Developing the Future of Kidney Care, are summarized in a late summer joint press release from NKF and OptumLabs. The recommendations focus on four key priorities: (1) improvement of screening, diagnosis, and documentation of kidney disease; (2) improvement in engagement with patients and a focus on person-centered kidney care; (3) movement of Medicare reimbursements upstream to encourage earlier interventions; and (4) increased assess to evidence-based therapies for patients with chronic kidney disease (CKD).

Joseph Vassalotti, MD, chief medical officer at NKF, said, "Lack of awareness and underdiagnosis of kidney disease leaves patients, families, and the healthcare system blind to a high population's future risk of cardiovascular events, reduced quality of life, potential kidney failure, and death. Changing this reality will require principles and solutions that get upstream of this inadequately treated disease."

OptumLabs is researching gaps in care that affect kidney health, and designing programs to leverage data and analytics to facilitate earlier identification of and treatment for patients with kidney disease. One such initiative, launched this fall, uses a risk stratification model to identify and offer in-home testing for kidney disease to UnitedHealthcare members as part of a pilot program.

David Cook, MD, chief medical officer at OptumLabs and NKF board member, said, "Kidney disease affects millions of people and it will take new approaches, corroborations, and ways of thinking to make meaningful progress against it. At OptumLabs, we're focused on improving lives and we're honored to be in the fight alongside partners like National Kidney Foundation."

The authors of the paper are Dr. Vassalotti, **Clarissa Jonas Diamantidis, MD,** of Duke University School of Medicine, and Dr. Cook.

Mount Sinai Scales Up KidneyIntelX™ Care Model

In a press release, Renalytix and the Mount Sinai Health System announced the scaled-up implementation of the KindeyIntelX™ program of early-stage testing and care management across primary care and specialty clinician networks under a real-world evidence development program for patients with diabetic kidney disease (DKD). The program signals an additional focus of care coordination efforts on patients with early stages of DKD.

Mount Sinai expects to provide KidneyIntelX testing and downstream care management at a rate of 300 patients per week by the end of 2021, with ~6000 eligible patients tested by the second quarter of 2022. In the initial rollout across seven primary care practices in Manhattan (New York City), the program demonstrated value for critical care delivery by identifying patients with DKD at low, intermediate, or high risk of declining kidney function or kidney failure early in the disease lifecycle when treatment has the potential for maximum effect.

Robert Fields, MD, MHA, executive vice president and chief population health officer at Mount Sinai Health System, said, "Our KidneyIntelX enabled diabetic kidney disease program allows us to provide a high standard of care in early-stage kidney disease patients where we have the best chance to help patients avoid significant kidney damage. Ongoing analysis and sharing of doctor and patient user experience combined with population level data insights is helping to drive systemwide access to early-stage risk assessment and treatment."

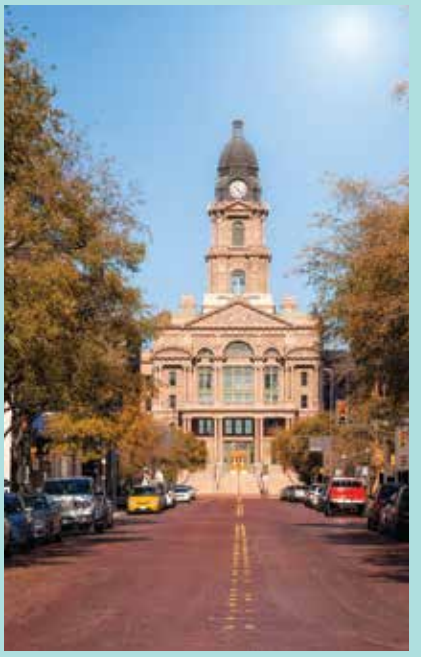
MAJOR MEETINGS 2022

National Kidney Foundation Spring Clinical Meetings 2022

April 6-10, 2022

Boston, Massachusetts

www.kidney.org/spring-clinical/general-information

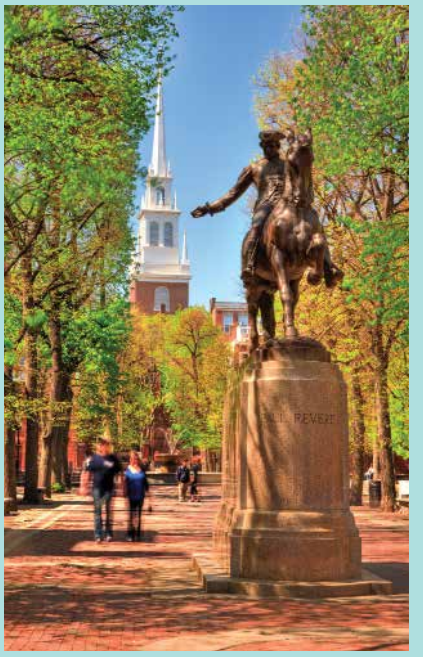


American Nephrology Nurses Association 2022 National Symposium

May 22-25, 2022

Fort Worth, Texas

www.annanurse.org/events/2022-national-symposium



American Transplant Congress 2022

June 4-8, 2022

Boston, Massachusetts

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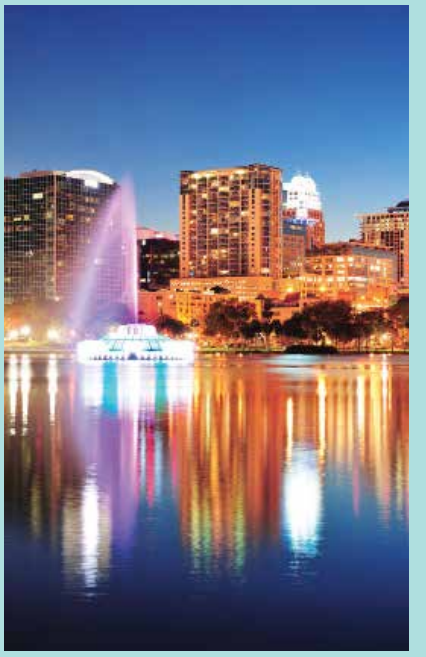

American Society of Nephrology Kidney Week 2022

November 1-6, 2022

Orlando, Florida

www.asn-online.org/education/kidneyweek/archives/future.aspx

In the press release, **David C. Thomas, MD,** professor of medicine, department of medicine, Icahn School of Medicine at Mount Sinai, said, "Systematically identifying high-risk patients with DKD under primary care at the earliest stages of their disease is essential for improving outcomes, quality of life, and reducing healthcare costs in the population with kidney disease. We now have the tools, including care navigation, and pharmacy and dietician support, in place to do more that manage the transition to dialysis or transplant. We believe this program will enable advanced support for our primary care teams to help improve the long-term outlook and quality of life for our patients with diabetic kidney disease."

FIND-CKD Phase 3 Study of Finerenone

In an early fall press release, Bayer announced the initiation of the FIND-CKD study, a multicenter, randomized, double-blind, placebo-controlled phase 3 study for an investigational new use of Kerendia® (finerenone) in addition to guideline-based therapy for the progression of chronic kidney disease (CKD) in patients with nondiabetic CKD. The study is designed to show superiority of finerenone over placebo in delaying CKD progression in that patient population. The primary outcome of interest is the mean rate of change in kidney function over time, as measured by estimated glomerular filtration rate (GFR) slope from baseline to month 32.

Hiddo L. Heerspink, PhD, PharmD, professor of clinical trials and personalized medicine and a clinical pharmacologist/trialist at the department of clinical pharmacy and pharmacology at the University Medical Center Groningen, Netherlands, and cochair of the study's executive committee said, "In 2017, an alarming 1.2 million people died from chronic kidney disease worldwide. Although diabetes is well-recognized as a leading cause of chronic kidney disease globally, a substantial proportion of the global burden is nondiabetic in origin and attributable to other causes, such as hypertension. To improve outcomes, there is an urgent need for new treatments. If successful, this study could be of great significance to those living with chronic kidney disease globally."

The planned phase 3 FIND-CKD study will examine finerenone compared with placebo in addition to standard of care in more than 1500 patients with nondiabetic CKD etiologies, including hypertension and chronic glomerulonephritis. Patients will be randomized to receive either finerenone 10 mg or 20 mg or placebo in addition to individually tolerated optimized doses of a renin-angiotensin system-blocking therapy such as an angiotensin-converting enzyme inhibitor or an angiotensin II receptor blocker."

Staff Appointments at Fresenius Medical Care North America

Fresenius Medical Care North America (FMCNA) announced three clinical leadership appointments in an early fall press release. The three positions will help drive priorities that include improvement of patient outcomes, adoption of connected health technologies supporting home dialysis, and increased access to transplant, according to the release.

Kathleen Belmonte, MS, RN, FNP-BC, MBA, has been named chief nursing officer and senior vice president of clinical services of Fresenius Kidney Care, the dialysis services division. **Benjamin Hippen, MD, FASN, FAST,** was appointed senior vice president and head of transplant medicine as part of the global medical office senior leadership team. **Shelly Nash, OD,** has been named senior vice president and chief medical information officer for FMCNA.

Bill Valle, CEO at FMCNA, said, "We welcome these exceptional clinical leaders who bring many years of deep experience working both inside and outside our company. These individuals will help us continue to be the leader in value-based care and transforming kidney care models that slow disease progression, while improving home dialysis and transplantation rates, clinical quality, and information technology to enhance experiences and affordability for the benefit of employees, physician partners, payers, and most importantly, our patients."

In her role as chief nursing officer, Ms. Belmonte will oversee efforts to ensure the delivery of clinical care along the entirety of the renal care continuum. She will also act as support to the clinical professionals who are part of patient care teams. Dr. Hippen's new role will help lead efforts to expand access to and understanding of transplant medicine as a key component of the company's patient-centric mission. Dr. Nash will work to ensure seamless communication between clinical services and information technology.

"This expansion of our executive team underscores our commitment to improving patient outcomes on a global scale by acknowledging new leadership capabilities needed in the company, " said **Franklin W. Maddux, MD, FACP,** global chief medical officer for Fresenius Medical Care. "Under their leadership in nursing care, health information technology, and organ transplantation, we will continue to drive innovation, expertise, and credibility that will enhance our ability to provide the highest quality of innovative and holistic care."

AKF Endorses Eliminating Race from GFR Estimation

In an early fall press release, the American Kidney Fund (AKF) endorsed a race-free approach to the diagnosis of kidney disease. The statement was issued in response to A Unifying Approach for GFR Estimation: Reassessing the Inclusion of Race in Diagnosing Kidney Disease, the paper published by a joint task force sponsored by the National Kidney Foundation and the American Society of Nephrology (NKF/ASN).

According to the press release, "AKF is firmly committed to reducing inequities in all phases of a patient's kidney disease journey. Consistent with the commitment, we commend the NKF/ASN Task Force for undergoing a very thoughtful, transparent and data-driven process, for gathering input from the kidney community—including AKF's Medical Advisory Committee—to develop a recommendation for GFR estimation that eliminates race, ultimately a step towards eradicating the 'othering' of people of color in medicine.

"Currently, Black Americans are four times more likely than White Americans to have kidney failure, yet are less likely to receive kidney transplants. We are hopeful the proposed change in GFR estimation will lead to earlier diagnosis of kidney disease for Black Americans particularly, and improve opportunities to slow down the progression to kidney failure.

"Operationalizing the Task Force's recommendations quickly, and adding the use of confirmatory testing, like cystatin C and other markers that are yet to be identified, must be top priorities. In addition , there is still a need to follow the research and continuously evolve GFR estimation and kidney function measurement as one step towards elimination of racial and ethnic disparities in kidney disease.

"Keeping patients at the forefront of discussions about the change in GFR estimation is paramount. A crucial next step will be to develop comprehensive transition and education materials for patients about the new GFR equation and its impact on chronic kidney disease (CKD) care. AKF stands ready to work with patients and stakeholders to integrate the GFR estimation-related changes into current programs as we partner to achieve health equity across the CKD continuum. AKF will continue to build education and awareness programs to incorporate changes that are aligned with our mission of fighting kidney disease on all fronts and helping people live healthier lives."

Corporate Support for *Know Your Kidneys*™

The nationwide education campaign conducted by the American Kidney Fund (AKF) has received new support from Otsuka America Pharmaceutical, Inc., and Boehringer Ingelheim/Lilly, according to a press release from AKF. The program, *Know Your Kidneys*™, seeks to allow individuals to prevent or slow the progression of chronic kidney disease.

One in seven Americans has kidney disease; however, of those with early CKD, 96% are undiagnosed. The campaign encourages Americans to take action to ensure early diagnosis and proper management of CKD, and of high blood pressure and diabetes, to help prevent or slow disease progression.

"We are very appreciative that our new partners understand the urgency behind our efforts to improve awareness of kidney health and increase access to educational tools that will help Americans receive an earlier diagnosis of kidney disease and even prevent it altogether, " said **LaVarne A. Burton,** president and CEO of AKF. "We've seen great engagement so far with *Know Your Kidneys* and hope to reach even more at-risk individuals, particularly people of color, who are more likely to progress to kidney failure due to persisting disparities in care that prevent them from receiving an early diagnosis.

"More than a third of US patients who receive a kidney failure diagnosis have little or no nephrology care prior to reaching the point of needing dialysis or a kidney transplant to survive. By continuing *Know Your Kidneys,* we hope more Americans can be aware of kidney function and access early intervention to help slow or stop the progression of kidney disease to kidney failure."

Jed Fulk Named Renalytix VP Sales, Government Accounts

In a recent press release, Renalytix plc announced that **Jed Fulk** has been named vice president of sales, government accounts. Mr. Fulk is developing and leading a team tasked with supporting the rollout of KidneyIntelX™ to the US Veterans Health Administration (VA) patient population. KidneyIntelX will be deployed to help VA primary care physicians identify patients with diabetic kidney disease who are at risk for disease progression and kidney failure.

The VA Health System is the largest integrated health system in the United States, providing care at 1293 healthcare facilities and serving nine million enrolled veterans each year. The prevalence of chronic kidney disease and diabetic kidney disease in the VA population is approximately one-third higher than in the general population.

In April 2021, Renalytix was awarded a 10-year Governmentwide Acquisition Contract to provide early-stage kidney disease testing services via KidneyIntelX. The contract covers KidneyIntelX laboratory testing services that can be provided through more than 140 US government departments, agencies, and affiliates, including the VA. ■

Grants Help Kidney Patients Impacted by Hurricane Ida

More than 750 low-income dialysis and kidney transplant patients affected by Hurricane Ida received emergency grants from the American Kidney Fund (AKF), according to a recent press release. Donations from public and corporate sponsors, including Horizon Therapeutics plc and Otsuka America Pharmaceutical, Inc. helped fund the grants.

Patients used the assistance to pay for lost or spoiled food needed for their strict renal diets, as well as temporary housing, transplantation to and from dialysis, home repairs, and other essentials lost in the storm and its aftermath.

LaVarne A. Burton, AKF president and CEO, said, "Disaster relief grants from the American Kidney Fund help kidney patients to cope with the devasting aftermath of a storm like Hurricane Ida. We are thankful to Horizon, Otsuka, and our many other supporters for allowing us to provide this emergency assistance, so vulnerable kidney failure patients could focus on staying as healthy as possible after this storm, particularly as we are still in the midst of a deadly pandemic."

Abstract Roundup

COVID-19

Diabetic Nephropathy and Obesity Influence COVID-19 Outcomes

Journal of Community Hospital Internal Medicine Perspectives. doi.org/10.1080/20009666.2021.1957555

Various comorbidities, including diabetes, have been recognized as risk factors for adverse outcomes among patients with COVID-19. **Martin Schiller, MD,** and colleagues conducted an analysis of data on 75 patients with COVID-19 treated at a community hospital in Germany. While focusing on diabetes mellitus, the researchers evaluated the impact of distinct comorbidities on the COVID-19 disease course.

If diabetes was present, the duration of hospital stay was prolonged. There was an association between older age and poor outcomes. In the presence of congestive heart failure or chronic kidney disease, the percentage of non-survivors increased. Among the patients with diabetes, mortality increased if any organ complication was present. By far, the most important risk factors were diabetic nephropathy or the combination of obesity plus diabetes.

In summary, the researchers said, "Taken together, an older age, congestive heart failure, and chronic kidney disease significantly influenced COVID-19 disease course and survival. Diabetic nephropathy or the combination of obesity plus diabetes had the strongest impact on patients' outcomes."

Renal Involvement in Children with COVID-19

Current Pediatric Reviews. doi: 10.2174/1573396317666210924121550

Among pediatric patients, SARS-CoV-2 infection has been associated with mild symptoms for the most part. However, renal involvement has been reported in both children and adults with COVID-19. **Yuri Márcio Campos, MD,** and colleagues, performed a review of data regarding renal involvement in COVID-19, with a focus on the pathophysiology of acute kidney injury (AKI) in pediatric inflammatory multisystem syndrome temporally associated (PIMS-TS) with SARS-CoV-2 and the potential impact of SARS-COV-2 infection on kidney function. Data on patients with history of kidney disease, including nephrotic syndrome and chronic kidney disease were included.

Results of the review of articles on renal involvement in pediatric COVID-19 patients in PubMed and Scopus suggested that with the emergence of PIMS-TS with SARS-CoV-2, pediatric patients are at risk of severe COVID-19, with multi-organ involvement and dysfunction. Several systems are affected in PIMS-TS in addition to intense inflammation, resulting in AKI. Results of some studies proposed that kidney cells, including the podocytes, may be at risk of direct infection by SARS-CoV-2; high levels of ACE2, the virus receptor, are expressed on the membrane of such cells. There have been reports of cases of glomerular diseases triggered by SARS-CoV-2 infection and relapses of previous renal diseases.

"Further studies are necessary to establish risk factors for renal involvement in pediatric COVID-19 and to predict disease outcome," the researchers said.

ACUTE KIDNEY INJURY

Baseline Serum Creatinine Level Estimated with Machine Learning Model

American Journal of Nephrology. doi.org/10.1159/00051890

Detecting acute kidney injury (AKI) relies on comparison of current serum creatinine level to baseline level. **Erina Ghosh, PhD,** and colleagues reported a regression-based machine learning model to predict baseline serum creatinine.

To predict baseline creatinine, the researchers developed and internally validated a gradient boosting model on patients admitted to the Mayo Clinic intensive care units (ICU) from 2005 to 2017. The model was externally validated on the Medical Information Mart for Intensive Care III (MIMIC III) cohort in all ICU admissions from 2001 to 2012. The researchers compared predicted baseline creatinine from the model with measured serum creatinine levels. They also compared the model's performance with that of the back-calculated estimated serum creatinine from the Modification of Diet in Renal Disease (MDRD) equation.

A total of 44,370 patients from the Mayo Clinic and 6112 individuals from the MIMIC III cohort were eligible for enrollment. The model had significantly lower error than the MDRD back calculation (mean absolute error [MAE] of 0.248 vs 0.374 in the Mayo Clinic test data; MAE of 0.387 vs 0.465 in the MIMIC III cohort) and higher correlation (intraclass correlation coefficient [ICC], 0.559 vs 0.050 in the Mayo Clinic test data; ICC of 0.357 vs 0.30 in the MIMC III cohort).

In conclusion, the researchers said, "Using machine learning models, baseline serum creatinine could be estimated with higher accuracy than the back-calculated estimated serum creatinine level."

ANEMIA

Molidustat Safe and Effective for Renal Anemia in Nondialysis Patients

American Journal of Nephrology. doi.org/10.1159/000518071

The MIYABI (molidustat once daily improves renal anemia by inducing EPO) program that included five phase 3 clinical trials, evaluated molidustat, an oral hypoxia-inducible factor prolyl hydroxylase inhibitor that induces renal production of erythropoietin, for the treatment of anemia associated with chronic kidney disease (CKD). Researchers, led by **H. Yamamoto,** reported on the MIYABI non-dialysis correction (ND-C) study examining the efficacy and safety of molidustat in patients in Japan with renal anemia not undergoing dialysis and not receiving treatment with an erythropoiesis-stimulating agent (ESA).

The 52-week randomized (1:1), open-label, active-control, parallel-group, multicenter phase 3 trial included Japanese patients with renal anemia associated with CKD stages 3-5. Molidustat or the ESA darbepoetin alfa were initiated at 25 mg once daily or 30 µg every 2 weeks, respectively. Doses were titrated regularly to correct and maintain hemoglobin (Hb) levels in the target range of ≥11.0 g/dL and <13.0 g/dL. The main efficacy outcome of interest was the mean Hb level and the change from baseline during the evaluation period (weeks 32-36). Safety outcomes included evaluation of all adverse events.

A total of 162 patients were randomized to either the molidustat group (n=82) or the darbepoetin group (n=80). At baseline, the two groups were similar. Mean baseline Hb levels were 9.84 g/dL for molidustat and 10.00 g/dL for darbepoetin. During the evaluation period, the mean for mean Hb level was 11.28 for molidustat and 11.70 for darbepoetin; both were within the target range.

Molidustat was noninferior to darbepoetin in the change in mean Hb level during the evaluation period from baseline. The proportion of patients who reported at least one treatment emergent adverse event (TEAE) was 93.9% in the molidustat group and 93.7% in the darbepoetin group. Most TEAEs were mild (54.9% for molidustat and 63.3% for darbepoetin) or moderate (22.0% for molidustat and 22.8% for darbepoetin). Three participants in the molidustat group died; one participant in the darbepoetin group died.

The researchers said, "In the MIYABI ND-C study, molidustat appeared to be an efficacious and generally well tolerated alternative to darbepoetin for the treatment of renal anemia in Japanese patients who were not undergoing dialysis and were not receiving ESA treatment."

Variations in Health Plan Coverage of ESAs for Anemia in CKD

Journal of Managed Care Specialty Pharmacy. 2021;27(9):1221-1229

NikoLetta M. Margaretos, BA, and colleagues conducted a study to examine policies among commercial health plans for coverage of erythropoiesis-stimulating agents (ESAs) for patients with anemia associated with chronic kidney disease (CKD). The secondary study objective was an examination of the evidence that the plans reviewed when formulating their coverage policies.

The researchers identified coverage policies issues for ESAs by 17 of the largest US commercial health plans using the Tufts Medical Center Specialty Drug and

Evidence and Coverage Database. Drugs indicated for anemia were darbepoetin alfa, methoxy polyethylene glycol-epoetin beta, epoetin alfa (available as two brands), and epoetin alfa-epbx. Coverage policies were current as of May 2019.

The researchers examined whether the health plans applied any restriction, such as step therapy protocols or patient subgroup restrictions in their coverage policies. The evidence cited to support the plans' policies were sorted into seven categories: (1) randomized controlled trials; (2) real-world evidence studies (studies based on data collected in a real-world setting); (3) other clinical studies (single arm trials); (4) systematic reviews and/or meta-analyses; (5) clinical or treatment guidelines; (6) health technology assessments; and (7) economic evaluations.

The researchers categorized 72.5% of coverage policies (58/80) as equivalent to the FDA label and 27.5% (22/80) as more restrictive. In the restrictive policies, the most common requirements were step therapy protocols (18/22 policies), followed by prescriber requirements (4/22 policies), and patient subgroup restrictions (3/22 policies). Five health plans applied restrictions in at least half of their coverage policies; seven did not apply restrictions in any policy.

Of the plans that cited evidence, an average of 10 citations were reviewed across ESA coverage policies (range, 1-29 studies). There was variation with regard to the types of cited studies: at least 50% of evidence cited by five health plans was randomized controlled trials; half or more of the evidence cited by four health plans was clinical or treatment guidelines.

In conclusion, the authors said, "Health plans varied on how they covered ESAs for patients with anemia due to CKD and in the evidence cited in their coverage policies. Inconsistencies in plans' coverage policies may have implications for patients' access to ESAs."

This study was funded by Otsuka Pharmaceutical Development and Commercialization.

Review and Meta-Analysis: Roxadustat for Treatment of Anemia in CKD

British Journal of Clinical Pharmacology.[doi.org/10.1111/bcp.15055].

Chronic kidney disease (CKD) is commonly associated with renal anemia. Roxadustat is the first-in-class oral hypoxia-inducible factor prolyl hydroxylase inhibitor for the treatment of anemia. **Li Zheng** and colleagues in China conducted a systematic review and meta-analysis to examine the efficacy and safety of roxadustat in the treatment of anemia in patients with CKD.

The researchers searched PubMed, Cochrane Library, Embase, and clinicaltrials.gov from inception to February 2021. The search included randomized controlled

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trials comparing the efficacy and safety of roxadustat to the efficacy and safety of an erythropoiesis-stimulating agent (ESA) or placebo in the treatment of anemia in patients with CKD.

The search revealed nine randomized controlled trials involving 2743 patients. Results of the meta-analysis demonstrated that roxadustat increased hemoglobin level by 0.91 g/dL (95% confidence interval [CI], 0.47-1.43; *P*<.05), transferrin level by 0.50 mg/dL (95% CI, 0.34-0.65; *P*<.05), and total iron-binding capacity by 50.64 µg/dL (95% CI, 36.21-65.07; *P*<.05). There were also decreases in hepcidin (mean difference [MD], –23.16; 95% CI, –37.12 to –9.19; *P*<.05) and ferritin (MD, –38.35; 95% CI, –67.41 to –9.29; *P*<.05).

The incidence of adverse events was similar between roxadustat and control groups. The incidence of adverse events was significantly higher among patients in the roxadustat group compared with those in the ESA group (odds ratio, 1.33; 95% CI, 1.06-1.68; *P*<.05).

In conclusion, the authors said, "Roxadustat can significantly improve renal anemia in CKD patients by increasing hemoglobin level and iron metabolism. However, attention must be paid to the risk of serious adverse events during treatment."

CHRONIC KIDNEY DISEASE

Metabolic Syndrome Associated with CKD Obese Patients

American Journal of Nephrology. doi.org/10.1159/000518111

The risk of chronic kidney disease (CKD) is increased in patients who are obese; however, it is unclear whether the increased risk is due to obesity itself or to the associated metabolic derangements. **S. Ciardullo** and colleagues conducted a cross-sectional study to examine the relative impact of obesity and metabolic syndrome (MS) on kidney disease. The study utilized data obtained in the 2005-2016 cycles of the National Health and Nutrition Examination Survey. Eligible patients were adults with available data on body mass index, estimated glomerular filtration rate (eGFR), urine albumin to creatinine ratio (UACR), and each of the MS components. The main outcomes of interest were eGFR <60 mL/min/1.73 m^2, UACR ≥30 mg/g, or a combination of the two.

The study included 12,335 participants. Obese participants without MS were younger and more commonly female. Following adjustment for potential confounders, compared with non-obese participants without MS, there was an increased prevalence of albuminuria and reduced eGFR among those without obesity with MS and among those with obesity and MS; there was no increase in prevalence among participants with obesity but without MS.

In separate evaluations of each MS component, there were associations between elevated blood pressure and low high-density lipoprotein cholesterol and UACR and reduced eGFR. Elevated blood glucose and triglycerides were only associated with UACR. There was no association between waist circumference and any of the renal outcomes.

In summary, the researchers said, "This large cross-sectional study suggests that MS and not obesity is associated with kidney damage and that the obesity without MS phenotype does not seem to carry an increased risk of kidney disease.

Supplementation of Dietary Fiber in Patients with CKD

Journal of Renal Nutrition. 2021;1(5):438-477

Results of previous meta-analyses found that dietary fiber could reduce the levels of p-cresyl sulfate, blood urea nitrogen, and creatinine in patients with chronic kidney disease (CKD). It has also been suggested that the dosage and duration of fiber supplementation and patient characteristics may influence the effect of dietary fiber in reducing uremic toxins, but there are few data available providing reliable evidence.

Hui-Li Yang, BSN, and colleagues conducted a literature search and meta-analysis on the effect of dietary fiber supplementation in patients with CKD. The search included PubMed, Web of Science, and Cochrane Library. Random effects models were used to pool data by the generic inverse variance method. Egger's test was used to evaluate publication bias.

The search yielded 10 randomized controlled trials involving 292 patients with CKD. Dietary fiber supplementation significantly reduced the levels of indoxyl sulfate (standard mean difference [SMD], –0.55; 95% confidence interval [CI], –1.04 to –0.07; *P*=.03), p-cresyl sulfate (SMD, –0.47; 95% CI, –0.82 to –0.13; *P*<.01), blood urea nitrogen (SMD, –0.31; 95% CI, –0.58 to –0.03; *P*=.03), and uric acid (SMD, –0.60; 95% CI, –1.02 to –0.18; *P*<.01). There was no significant difference in the reduction of creatinine (SMD, –0.31; 95% CI, –0.73 to 0.11; *P*=.14).

The reduction of indoxyl sulfate was more obvious among patients on dialysis compared with patients not on dialysis (*P* for interaction=.03) in subgroup analyses. The reduction of creatinine was more obvious among patients without diabetes than patients with diabetes (*P* for interaction <.01).

In conclusion, the researchers said, "This meta-analysis indicates that dietary fiber supplementation can significantly reduce the levels of uremic toxins in patients with CKD, with evidence for a more obvious effect of patients on dialysis and without diabetes. These findings inform recommendations for using dietary fiber to reduce the uremic toxin among CKD patients in clinical practice." ■

CONFERENCE COVERAGE SPRING CLINICAL MEETINGS

Mortality Rates in Patients with ADPKD Differ by Race

Results of previous studies have suggested racial differences among patients with autosomal dominant polycystic kidney disease (ADPKD) in access to treatment, progression of disease, and mortality. **Greg Mader, PhD,** and colleagues conducted an analysis of data on ADPKD patients ≥65 years of age to estimate race-specific mortality in patients with CKD stages 1 through 5 and patients with end-stage renal disease (ESRD).

Results of the analysis were reported during a virtual poster session at the NKF Spring Clinical Meetings 2021. The poster was titled *Racial Differences in Mortality Rates among Elderly Non-ESRD CKD and ESRD Patients with Autosomal Dominant Polycystic Kidney Disease (ADPKD): Study Findings Using Data from the USRDS.*

The analysis included data from the 2014, 2015, or 2016 United States Real Data System (USRDS) non-ESRD CKD cohort (assembled from Medicare claims data 5% sample) with at least two diagnosis codes for ADPKD. CKD stage determination was based on at least two consecutive stage diagnosis codes and age was determined at study entry. Patients with ESRD with at least one code for ADPKD diagnosis and an ESRD service date from January 2, 2104, to December 31, 2016, were also included. Mortality rates were estimated by race, sex, CKD stage, age group, and overall.

A total of 1551 elderly patients with ADPKD and non-ESRD CKD met staging criteria (0.089% of the overall non-ESRD CKD cohort). Mean age was 76.5 years, 54.4% were male, 81.3% were White, 12.5% were Black, 1.5% were Hispanic, 2.1% were Asian, and 2.6% were other or unknown race/ethnicity.

The cohort of elderly patients with ADPKD and ESRD included 14,756 patients (0.460% of the ESRD cohort). Mean age was 70.8 years, 50.4% were male, 77.3% were White, 10.9% were Black, 8.0% were Hispanic, 2.9% were Asian, and 0.8% were other or unknown race/ethnicity.

Following adjustment for age, in the non-ESRD CKD cohort the mortality rate was highest for Black patients. In the ESRD cohort, the age-adjusted morality rate was highest for White patients.

In conclusion, the researchers said, "Our results show racial differences in mortality among elderly ADPKD patients in both non-ESRD CKD and ESRD cohorts and suggest a possible survivorship effect among elderly Black ADPKD patients with ESRD."

Source: Mader G, Mladsi D, Zhou X, et al. Racial differences in mortality rates among elderly non-ESRD CKD and ESRD patients with autosomal dominant polycystic kidney disease (ADPKD): Study findings using data from the USRDS. Abstract of a poster presented at the National Kidney Foundation virtual Spring Clinical Meetings 2021 (Abstract #312), April 9, 2021.

Sarah Tolson

A Closer Look at the No Surprises Act

In the last edition of From the Field, I provided a very brief synopsis of the No Surprises Act that will be making its way to many medical practitioners in January 2022. Nephrologists, like many other specialists who round at hospitals, will likely be directly affected by this new law. While this law does present several challenges, there are also opportunities to collect reimbursement that might not have been collectable before.

It is not uncommon for the nephrologists that my company bills for to see patients during their hospital rounds whose insurance considers the hospital to be in-network but the nephrologist to be out of network. Often, these scenarios end with the nephrologist's bill to the insurance company being applied to the patient's large out-of-network deductible—and the provider is left to try and collect reimbursement from patients who are often too ill to work or respond to their bills. Under the No Surprises Act, providers have an opportunity to negotiate reimbursement at an in-network rate with the insurance company and remove the patient from the reimbursement dispute process.

NO SURPRISES ACT KEY TIMELINES

To use the No Surprises Act to your advantage, there are a few key points that your billing/administrative staff should be aware of.

- The health plan must be one that is under the jurisdiction of the No Surprises Act (see the last edition of From the Field for details).
- The health plan and the provider have 30 days to negotiate a reimbursement rate. By the end of the 30-day time frame, the health plan will issue either a payment or denial to the provider.
- In the event the provider disagrees with the reimbursement provided by the health plan, the provider has 4 days to initiate an independent dispute resolution (IDR) process to obtain a different reimbursement rate.
- There is no minimum payment threshold to initiate the IDR process, and similar claims can be batched together.
- In the IDR process for the No Surprises Act, each party submits one offer and the arbiter selects one of the offers. The arbiter's decision is final and cannot be appealed.
    - In determining the rate to select, the arbiter may consider the "qualifying payment amount"—which is based on the median in-network rate for the health plan—for the same service in the same geographical area. However, this information is provided by the insurance plan and the arbiter may not consider the usual and customary rates or the Medicare rates in their decision.
- A provider is not allowed to initiate another arbitration for 90 days against the same carrier for the same services, but all claims that occur during the 90-day cooling period are eligible for IDR after 90 days.

MAXIMIZING OPPORTUNITIES IN THE NO SURPRISES ACT

Now that we're aware of some of the key deadlines, here are some steps nephrology practices can take to maximize the opportunities presented by the No Surprises Act:

- Identify the health plans your providers most commonly encounter in scenarios that qualify for the No Surprises Act and ensure all billing staff are aware of and familiar with these plans.
- Develop an alert system to notify your key staff of the receipt of reimbursement from the plans identified in the previous step.
- Review the payments received and decide if you agree with the reimbursement. If not, initiate the negotiation process with the health plan.
- In the event the negotiation process does not result in a satisfactory outcome, initiate an IDR within the four-day time frame.
- During the 90-day cooling period, keep track of claims that come out of the provider/health plan negotiation process with an unsatisfactory outcome so they may be included in IDR at the end of the 90-day period.

The keys to maximizing opportunities in the No Surprises Act are awareness of the timelines, identification of the process your office will follow, and teamwork in following your identified process. ■

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