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Safety and Tolerability of Metformin in Patients With ADPKD

Autosomal dominant polycystic kidney disease (ADPKD) is a common familial disorder that leads to kidney failure in a majority of patients. ADPKD is caused primarily by mutation in either *PKD1* or *PKD2* (encoding polycystin 1 and 2, respectively). The disorder occurs in all races and ethnicities worldwide; the estimated prevalence is 3.3 to 4.6 per 10,000 population.

Mean age at initiation of kidney replacement therapy for patients with the more common *PKD1* mutation (80%-85%) is 53 to 58 years, resulting in substantial morbidity and mortality. According to **Godela M. Brosnahan, MD,** and colleagues, despite progress in research in ADPKD, there has been little change over the past 20 years in patient prognosis, and treatment options are limited.

To date, the only approved intervention to slow progression of kidney disease in patients with ADPKD is tolvaptan. Metformin is well tolerated and safe in other patient populations. Dr. Brosnahan et al conducted a prospective randomized controlled double-blind clinical trial to assess the safety and tolerability of metformin in patients with ADPKD and without diabetes mellitus. Results of the trial were reported in the *American Journal of Kidney Diseases* [2022;79(4):518-526].

The primary end points were the percentage of patients in each group at the end of the 12-month study period

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Outcomes Among Children With Lupus Nephritis

Up to 20% of new cases of systemic lupus erythematosus (SLE) are diagnosed in patients under 18 years of age with lupus nephritis. Lupus nephritis occurs in up to 80% of children with SLE, develops earlier, and is more aggressive in children than in adults.

In children with lupus nephritis, reduced kidney function, high-dose immunosuppression, exposure to steroids during growth and development, and chronic hypertension all contribute to increases in disease morbidity. Despite use of immunosuppression therapy, just over half of pediatric patients with lupus nephritis with proliferative glomerular lesions achieve a renal remission; those who do not achieve renal remission are at high risk for the development of kidney failure.

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Kidney and Cardiac Outcomes in Hyperkalemia

Best practice guidelines outline the emergency management of hyperkalemia. However, according to **Andrew Mclean, MCChB,** and colleagues at the University of Aberdeen, United Kingdom, the "true population burden remains unclear." Previous studies have focused on selected subsets of patients or have not completely captured the population and laboratory tests, limiting the generalizability for health policy and planning.

In addition, thresholds for defining hyperkalemia are inconsistent and are not included in the Kidney Disease: Improving Global Outcomes guidelines. Guidelines from the UK Renal Association (2020) and the European Resuscitation Council define hyperkalemia as serum potassium level ≥5.5 mmol/L (mild), ≥6.0 mmol/L (moderate), and ≥6.5 mmol/L (severe). Current guidelines define severe hyperkalemia as a clinical emergency.

Hyperkalemia is associated with both chronic kidney disease (CKD) and acute kidney disease (AKD). Acute kidney injury (AKI) was once considered an urgent transient problem with few long-term effects. However, AKI is now known to be associated with serious long-term poor health within the umbrella of AKD. An episode of hyperkalemia may worsen kidney and cardiac outcomes independent of AKI and CKD, representing an additional risk stratification tool for the evaluation of kidney reserve, need for monitoring, and long-term decision making.

Dr. McLean et al conducted a long-term population study designed to assess the

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Combination Therapy for Kidney Progression in Patients With CKD From Type 2 Diabetes

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In my April *Nephrology Times* editorial titled "Imagine Halting Progression of Kidney Disease in Patients with Type 2 Diabetes,"[1] I wrote that we could be on the cusp of halting kidney progression if we use multiple agents to target different pathophysiologic mechanisms of kidney progression. I discussed the importance of randomized clinical trials (RCTs) to test whether combination therapy is superior to using individual drugs. Indeed, post hoc analyses of large randomized controlled trials do suggest that there may be complementary benefits of treating patients in a combination of an ACE inhibitor or an angiotensin receptor antagonist, an SGLT-2 inhibitor, and a non-steroidal mineralocorticoid antagonist.[2,3]

Of course, the problem with post hoc or exploratory analyses is that they set up hypotheses to be tested rather than provide definitive evidence. Also, post hoc analyses are often insufficient when looking at the safety of a particular treatment strategy.

In an article published in May 2022 in the *Journal of the American Society of Nephrology,*[4] Michele Provenzano and colleagues conducted a pilot randomized crossover trial that examined the effects of dapagliflozin and eplerenone individually compared with in-combination in patients with CKD with or without type 2 diabetes already on maximal dose of either an ACE inhibitor or ARB.

The study was small but generated important findings that need to be urgently tested in large RCTs. A total of 46 patients were randomly assigned to the three groups: dapagliflozin, eplerenone, and dapagliflozin-eplerenone. All patients were already being maximally treated with an ACE inhibitor or ARB. At baseline, the mean estimated glomerular filtration rate (eGFR) was 58.1 mL/min/1.73 m^2, and the median level of albuminuria (UACR) was 401 mg/g of creatinine. The primary end point was the individual 24-hour UACR change from baseline during treatment with dapagliflozin, eplerenone, and their combination. The investigators also examined the change in 24-hour UACR, systolic blood pressure, eGFR, and potassium from baseline during each treatment period.

The results supported a clinically meaningful benefit of combination therapy: the UACR reduction at week 4 compared with baseline was approximately 20%, 34%, and 53% for dapa, eplerenone, and dapa+ eplerenone therapy, respectively. A ≥50% reduction in UACR at week 4 occurred in 20%, 26%, and 56% of patients on dapagliflozin, eplerenone, and dapagliflozin-eplerenone treatment, respectively. There was a nearly 5-fold and 3.6-fold higher odds of patients treated with combination therapy of achieving a ≥50% UACR reduction compared with those treated with either dapagliflozin alone or eplerenone alone, respectively. The other interesting finding was that the benefit of reducing albuminuria was more pronounced among patients with type 2 diabetes compared with those without type 2 diabetes and in patients with baseline eGFR <60 ml/min per 1.73 m^2 compared with those with eGFR ≥60 mL/min/1.73 m^2.

The important question of hyperkalemia as a side-effect was also examined in the Provenzano study. Hyperkalemia was most common among patients randomized to eplerenone alone and surprisingly was quite low in the dapagliflozin-eplerenone groups (0.9%). A lower rate of hyperkalemia was recently reported in a post hoc study of patients on SGLT-2+finererone+ACE/ARB enrolled in the FIDELIO-DKD trial compared with those who were not on those three agents.[5] The lower-than-expected rate of hyperkalemia in patients on combination therapy could be explained by increased distal sodium delivery from treatment with an SGLT-2 inhibitor, which then drives potassium secretion via principal cells in the cortical collecting duct.

So my take is that while the Provenzano study doesn't prove that combination therapy is superior to treatment with individual agents in slowing kidney progression, it does show a powerful effect on albuminuria that might be a tantalizing signal. To explore this issue more definitively, we urgently need large RCTs. Second, the lower hyperkalemia with combination MRA+ACEI/ARB+SGLT-2 inhibitor therapy suggests that concerns regarding the risk of hyperkalemia with an MRA (especially a non-steroidal MRA) like finererone may be overblown when agents are used in combination.

Disclosure: Dr. Singh consults for GSK, Bayer, and Zydus. He receives honoraria from Nephrology Times.

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Outcomes Among Children With Lupus Nephritis
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Data from the US Renal Data System show that the risk of death in patients with kidney failure secondary to lupus nephritis is significantly increased compared with patients with kidney failure from all other causes. Further, the risk of death in Black children with lupus nephritis on maintenance hemodialysis is twice that of Black children on maintenance hemodialysis due to kidney failure from other causes.

Heather Wasik, MD, MHS, and colleagues conducted a retrospective cohort study to compare outcomes among children with lupus nephritis on dialysis with children with non-lupus glomerular disease; the study also examined the risk factors for adverse outcomes among pediatric patients with lupus nephritis on dialysis. Results were reported in the *American Journal of Kidney Diseases* [2022;79(5):626-634].

Eligible study participants were children and adolescents 6 to 20 years of age enrolled in the North American Pediatric Renal Trials and Collaborative Studies (NAPRTCS) registry with lupus nephritis (n=231) and children and adolescents with non-lupus glomerular disease (n=1726) who initiated maintenance dialysis from 1991 to 2018. The outcomes of interest were hospitalization, mortality, and time to transplant.

Hospitalizations were compared using contingency tables; rates of transplantation and death in children with lupus nephritis were compared with those with non-lupus glomerular disease with multivariable cause-specific hazards models. Using data from children with lupus nephritis, multivariable logistic regression models were fit to evaluate the risk factors for hospitalization; multivariable Cox regression models were fit to evaluate factors associated with kidney transplantation.

Patients in the group with lupus nephritis were older (mean age, 15.3 years vs 13.9 years; *P*<.001), more likely to be female (78.8% vs 46.8%; *P*<.001), more likely to be Black (51.5% vs 34.0%; *P*<.001), more likely to have hemodialysis as their index dialysis modality (61.5% vs 43.8%; *P*<.001), had a lower mean hematocrit (29.7% vs 31.0%; *P*=.01), and were more likely to be taking a greater number of medications (47.4% vs 26.4% took ≥6 medications; *P*<.001) compared with patients in the non-lupus glomerular disease group. The two groups were similar in the proportion of patients with anemia and hypertension, mean height, weight, and body mass index z scores, or dialysis initiation era.

In the total study cohort, median follow-up time was 1.23 years; in the lupus nephritis group it was 1.26 years, and in the comparison group it was 1.22 years. The primary reason for loss to follow-up was lack of continued data entry in both groups. Loss to follow-up occurred in 96 patients in the lupus nephritis group and 515 patients in the comparison group. Other reasons for loss to follow-up prior to death or kidney transplantation were return of native kidney function (24 patients in the lupus nephritis group and 21 in the comparison group), administrative censoring (2 in the lupus nephritis group and 16 in the comparison group), and transfer of care to a non-NAPRTCS site (1 patient in the comparison group).

Patients in the lupus nephritis group were more likely to be hospitalized within 6 months (49.2% vs 35.1%; *P*<.001) and within 12 months (63.3% vs 48.6%; *P*<.001) of initiation of dialysis. Of the patients who were hospitalized within the 12 months after dialysis initiation, the median number of hospitalization days was 9.5 in the lupus nephritis group versus 7 days in the comparison group (*P*=.004). Reasons for hospitalization included infection, access complications, hypertension, and other cardiovascular disease.

The cumulative incidence of kidney transplantation following initiation of dialysis was significantly lower in patients in the lupus nephritis group than in the comparison group. Even after adjustment for age, race, sex, index dialysis modality, the presence of hypertension, the presence of anemia, and dialysis initiation era, the hazard of kidney transplantation was statistically significantly lower in the lupus nephritis group than in the comparison group (adjusted hazard ratio [aHR], 0.36; 95% CI, 0.23-0.57; *P*<.001) and in years 1 to 3 from dialysis initiation (aHR, 0.73; 95% CI, 0.54-0.98; *P*=.04). There were no statistically significant differences between the two groups in the hazard ratio comparison (aHR, 0.96; 95% CI, 0.55-1.66; *P*=.9) after more than 3 years from dialysis initiation.

The cumulative incidence of death following initiation of dialysis was nominally higher in patients in the lupus nephritis group than in the comparison group, but the difference did not reach statistical significance. There was no statistically significant difference in the hazard of death following initiation of dialysis after adjustment for patient age, race, sex, index dialysis modality, the presence of hypertension and anemia, and dialysis initiation era (aHR, 1.21; 95% CI, 0.47-3.11; *P*=.7). There were only six deaths in the lupus nephritis group and 25 in the comparison group. In both groups, the leading cause of death was cardiopulmonary disease (33% of deaths in the lupus nephritis group and 28% in the comparison group).

Anemia was associated with hospitalization following initiation of dialysis (adjusted odds ratio, 4.44; 95% CI, 1.44-13.66; *P*=.009). There was an association between non-White race and a lower rate of kidney transplantation (aHR, 0.47; 95% CI, 0.27-0.82; *P*=.01). There was no association between lupus nephritis and death while on dialysis (aHR, 1.21; 95% CI, 0.47-3.11; *P*=.7).

The researchers cited the lack of data on lupus disease activity and medication doses, as well as limited data on medication use in the NAPRTCS registry as limitations to the study findings.

In conclusion, the authors said, "Children with lupus nephritis who require dialysis are at high risk of adverse outcomes, including hospitalization and death in kidney transplantation. Further study must be done to identify the risk factors for adverse outcomes and to assess targeted interventions to decrease morbidity and mortality in this vulnerable population." ■

TAKEAWAY POINTS

- Researchers reported results of a study comparing outcomes among children with lupus nephritis with those among children with non-lupus glomerular disease.
- Children with lupus were more likely to be hospitalized and had a lower rate of kidney transplantation.
- There was no significant difference between the two groups in cumulative incidence of death after initiation of dialysis.

Kidney and Cardiac Outcomes in Hyperkalemia

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full population burdens of hyperkalemia, including how often it occurs, where it occurs, and the long-term implications for mortality and cardiac and kidney health. The researchers hypothesized that, controlling for AKI and CKD, mild episodes of hyperkalemia may be a complementary marker of diminished kidney or physiological reserve even when standard metrics of kidney function are otherwise normal. Results of the study were reported in the *American Journal of Kidney Diseases* [2022;79(4):527-538].

The study was conducted among the 468,594 adult residents (2012-2014) in Grampian, United Kingdom. Of those, 302,630 had at least one blood test and were followed until 2019. Hyperkalemia was defined as serum potassium ≥5.5 mmol/L. Prior to measurement of potassium, adjustments for comorbidities, demographics, measures of acute and chronic kidney function, and medications prescribed were made. The exposure of interest was the first instance of hyperkalemia for Grampian residents within each year of interest (2012, 2013, and 2014).

The primary outcome of interest was all-cause mortality followed up for at least 5 years to the end of 2019. Secondary outcomes included cardiac events (fatal or nonfatal myocardial infarction, heart failure, or stroke) and kidney failure.

Over the 3-year study period, 13,482 people experienced a first hyperkalemia event (threshold ≥5.5 mmol/L). There were 59,571 first hyperkalemia events at ≥5.0 mmol/L, 4491 at ≥6.0 mmol/L, and 2016 at ≥6.5 mmol/L. Those definitions corresponded to respective annual incidence rates per 100 person-years of 0.96 (95% CI, 0.94-0.98) at ≥5.5 mmol/L versus 4.24 (95% CI, 4.20-4.27) at ≥5.0 mmol/L, 0.32 (95% CI, 0.31-0.33) at ≥6.0 mmol/L, and 0.14 (95% CI, 0.14-0.15) at ≥6.5 mmol/L.

Expressing hyperkalemia as a proportion of the 302,630 people with blood tests, hyperkalemia represented 4099 of 182,135 (2.3%), 4044 of 188,539 (2.1%), and 3769 of 193,407 (1.9%) of those with at least one blood test in 2012, 2013, and 2014, respectively.

Most of those with hyperkalemia presented in the community and did not require hospitalization. The proportion admitted to the hospital increased when restricted to only the most severe episodes of hyperkalemia (≥6.5 mmol/L). More than half of the group with hyperkalemia had a baseline estimated glomerular filtration rate (eGFR) of ≥60 mL/min/1.73 m^2 and fewer than 20% had concurrent AKI, even among those with severe hyperkalemia.

Compared with people without hyperkalemia, in unadjusted analysis those whose blood tests did indicate hyperkalemia were 20 times more likely to have had concurrent AKI or a baseline eGFR <30 mL/min/1.73 m^2. Those with hyperkalemia were also more likely to have diabetes, heart failure, and peripheral arterial disease. Prior use of renin angiotensin aldosterone system blockers, aldosterone antagonists, and trimethoprim-containing antibiotics was greater in those with hyperkalemia. Use of thiazide diuretics was less in those with hyperkalemia.

In analysis of the primary outcome of all-cause mortality, there was an association between even a mild threshold for hyperkalemia (potassium ≥5.5 mmol/L) and substantial increased long-term mortality; excess mortality was less pronounced for hyperkalemia threshold 5.0 mmol/L.

Whereas AKI was associated with substantial short-term mortality, hyperkalemia was associated with greater long-term mortality. Following exclusion of outcomes before 90 days, a persistent long-term excess risk independent of AKI was evident up to 5 years, a finding that remained even after restricting the cohort to people who remained in the community. Regardless of AKI status, there was an excess of both cardiac and noncardiac outcomes for those with hyperkalemia.

Following adjustment for age and sex, and then all listed covariates, and controlling for baseline eGFR, outcomes for all models demonstrated an association between hyperkalemia and long-term excess mortality and both cardiac events and noncardiac death. Excess event rates after hyperkalemia also extended to the kidney failure outcome. There was a particular association between hyperkalemia and an increased relative hazard of future kidney failure among those with otherwise preserved baseline eGFR (the researchers highlighted the wide confidence intervals due to the small number of events among those without hyperkalemia [hazard ratio, 16.99; 95% CI, 9.29-31.07]).

In citing limitations to the study findings, the researchers noted the observational design that limited evaluation of causal relationship between hyperkalemia and adverse outcomes.

In conclusion, the authors said, "This analysis reports a greater incidence of hyperkalemia than has been possible to determine in previous studies. The analysis also demonstrates poorer long-term health outcomes after hyperkalemia, especially kidney outcomes, that are complementary to and not explained by existing metrics of acute and chronic kidney excretory function. Clinicians should note that even minor episodes of hyperkalemia are prognostically relevant, important to communicate, and worthy of consideration in the planning of ongoing care, monitoring, and expectations for future health." ■

TAKEAWAY POINTS

- Researchers reported results of a population-based cohort study of the incidence of hyperkalemia and its association with mortality and long-term cardiac and kidney health.
- There was a substantial burden associated with hyperkalemia in the general population.
- There were associations between hyperkalemia and poorer long-term health, particularly kidney outcomes, that were independent of other established risk factors.

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Safety and Tolerability of Metformin

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who were prescribed (1) the full randomized dose or (2) at least 50% of the randomized dose. Secondary end points included the effect of metformin compared with placebo on (1) the percentage change in total kidney volume (TKV) referenced to height (htTKV in mL/m) and (2) the change in estimated glomerular filtration rate (eGFR) over a 12-month period.

A total of 139 patients were prescreened for participation in the trial. Of those, 51 adults 30 to 60 years of age with a diagnosis of ADPKD and an eGFR of 50 to 80 mL/min/1.73 m^2 were randomized over a period of 35 months to either metformin (n=26) or placebo (n=25). Prior to the onset of the study period, one participant in the metformin group withdrew, and three participants in the metformin group and one in the placebo group were lost to follow-up evaluation before the final study visit at 12 months.

Mean age of the total cohort was 48 years, 37% were male, 98% were White, 84% had hypertension, and 65% were taking a renin-angiotensin-aldosterone system blocking drug. Mean eGFR was 70 min/mL/1.73 m^2. Sixty-nine percent of participants were in the higher risk Mayo Imaging Classes of 1C, 1D, or 1E. The two randomized groups were similar in demographic characteristics. With the exception of a higher prevalence of hypertension and larger TKV in the metformin group, the groups were similar in clinical characteristics.

Of the 22 patients in the metformin group who completed the study, 50% (n=11/22) completed the treatment phase on the full dose, including two participants who required per protocol dose reduction to 1000 mg daily for safety following a drop in eGFR to below 45 mL/min/1.73 m^2 (they did not report any significant side effects). Seven other participants completed the treatment phase on at least 50% of the full metformin dose.

More adverse symptoms were reported by participants in the metformin group. The symptoms were primarily related to the gastrointestinal tract and resolved wither spontaneously or after metformin dose reduction. Some participants in the placebo group also reported gastrointestinal symptoms, but none required dose reduction because the patients described the symptoms as tolerable.

Of the 22 patients in the metformin group who completed the study, 50% (n=11/22) completed the treatment phase on the full dose, including two participants who required per protocol dose reduction to 1000 mg daily for safety following a drop in eGFR to below 45 mL/min/1.73 m^2.

Two participants in the metformin group had safety events that required hospitalization. However, both events were unrelated to the study drug: one participant was hospitalized for acute pyelonephritis, which was successfully treated with antibiotics, and the other was hospitalized for observation for multiple symptoms with no pathologic findings on laboratory and imaging studies and was ultimately diagnosed as a viral infection.

One patient in each study group reported mild hypoglycemia episodes. Both of those patients reported lightheadedness. In the patient in the metformin group, blood glucose was 49 mg/dL; in the placebo group patient, blood glucose was 54 mg/dL. The patient in the metformin group had been fasting and was advised to eat prior to exercising and taking the study drug, and no further hypoglycemic symptoms were reported.

In analysis of the prespecified exploratory secondary end points (percentage increase in htTKV and absolute eGFR decline over 12 months) for one patient in each group it was difficult to accurately determine htTKV on the follow-up images, so those two were excluded from the secondary analyses. Of the 43 participants eligible for analyses for the secondary end points, 21 were in the metformin group and 22 in the placebo group.

The changes in htTKV and eGFR were not significantly different between the two groups. The decline in eGFR was numerically smaller in the metformin group (–0.41 vs –3.35 mL/min/1.73 m^2), although those patients had larger kidneys and more hypertension (more severe disease) than those in the placebo group; the larger decline in eGFR was therefore expected.

The short study duration, small sample size, and imbalance in baseline htTKV between treatment groups were cited by the authors as limitations to the study findings.

In conclusion, the researchers said, "Metformin at 500-1000 mg twice daily had a favorable adherence and safety profile over 12 months in participants with ADPKD with a mean eGFR of 70 ± 13 mL/min/1.73 m^2. Because of the therapeutic potential of metformin for ADPKD, further large-scale trials are warranted, using extended-release formulations and randomizing patients after a run-in period to exclude intolerant participants." ■

TAKEAWAY POINTS

- Treatments for ADPKD are limited. Researchers conducted a study to examine the safety and tolerability of metformin in patients with ADPKD and without diabetes mellitus.
- There were no cases of lactic acidosis in the metformin group and one patient in each group (metformin/placebo) experienced one episode of hypoglycemia.
- Over the 12 months of the study, 50% or more of the maximal metformin dose was safe and well tolerated in patients with ADPKD.

CONFERENCE COVERAGE **AMERICAN TRANSPLANT CONGRESS**

Deceased Donor Kidneys From Donors with AKI

One option to expand the donor pool is the use of kidneys from deceased donors with acute kidney injury (AKI). Results of previous studies have demonstrated favorable outcomes in kidney transplantations with kidneys from donors with AKI.

S. Iskhagi and colleagues at SUNY Upstate Medical University, Syracuse, New York, conducted a study designed to examine the outcomes of kidney transplantations where deceased donors developed AKI prior to organ procurement. Results were reported during a poster session at the 2022 American Transplant Congress in a poster titled *Deceased Donor Kidney Transplantation from Donors with Acute Kidney Injury: Realities and Costs.*

The retrospective study utilized medical records of kidney transplant recipients in a single center from January 2016 to November 2021. The researchers compared outcomes among recipients of a kidney graft from a donor with AKI with outcomes among recipients of a kidney graft from a donor without AKI. Donor and recipient clinical characteristics were assessed, including creatinine level, rate of delayed graft function, hemodialysis requirement post-transplant, length of hospital stay, hospital charge, and graft and patient survival rates.

A total of 372 files from consecutive deceased donor kidney transplantation recipients were examined. Of the 372 transplants, 24.7% (n=92) were from donors with AKI and 75.3% (n=280) were from donors without AKI. The two groups were similar in donor and recipient characteristics. Mean follow-up was 40 months.

There was an association between donor AKI and a higher rate of delayed graft function (45.7%, n=42 vs 30.7% n=86 in the non-AKI group, $P<.001$). The need for hemodialysis was greater in the AKI donor group than in the non-AKI group (37%, n=34 vs 26.4%, n=74, $P<.001$).

Readmission rates were higher in the AKI-donor group than in the non-AKI-donor group (42.4% vs 35.4%, $P<.001$). The two groups were similar in hospital charge (AKI, $259,267 vs non-AKI, $259,220) and in length of stay (AKI, 5.8 days and non-AKI, 6.5 days) ($P<.001$).

In summary, the researchers said, "Our study shows transplant with donor AKI is associated with increased rate of delayed graft function, hemodialysis requirements after transplant, and higher incidence of readmission. However, graft and patient survival rates, hospital charge, and length of stay were similar in both groups. Our study confirms that grafts from donors with AKI can be used safely and expand donor pool in kidney transplantation without increased cost."

Source: Iskhagi S, Shahbazov R, Ball A, et al. Deceased donor kidney transplantation from donors with acute kidney injury: realities and cost. Abstract of a poster presented at the 2022 American Transplant Congress (Abstract 737), Boston, Massachusetts, June 4, 2022.

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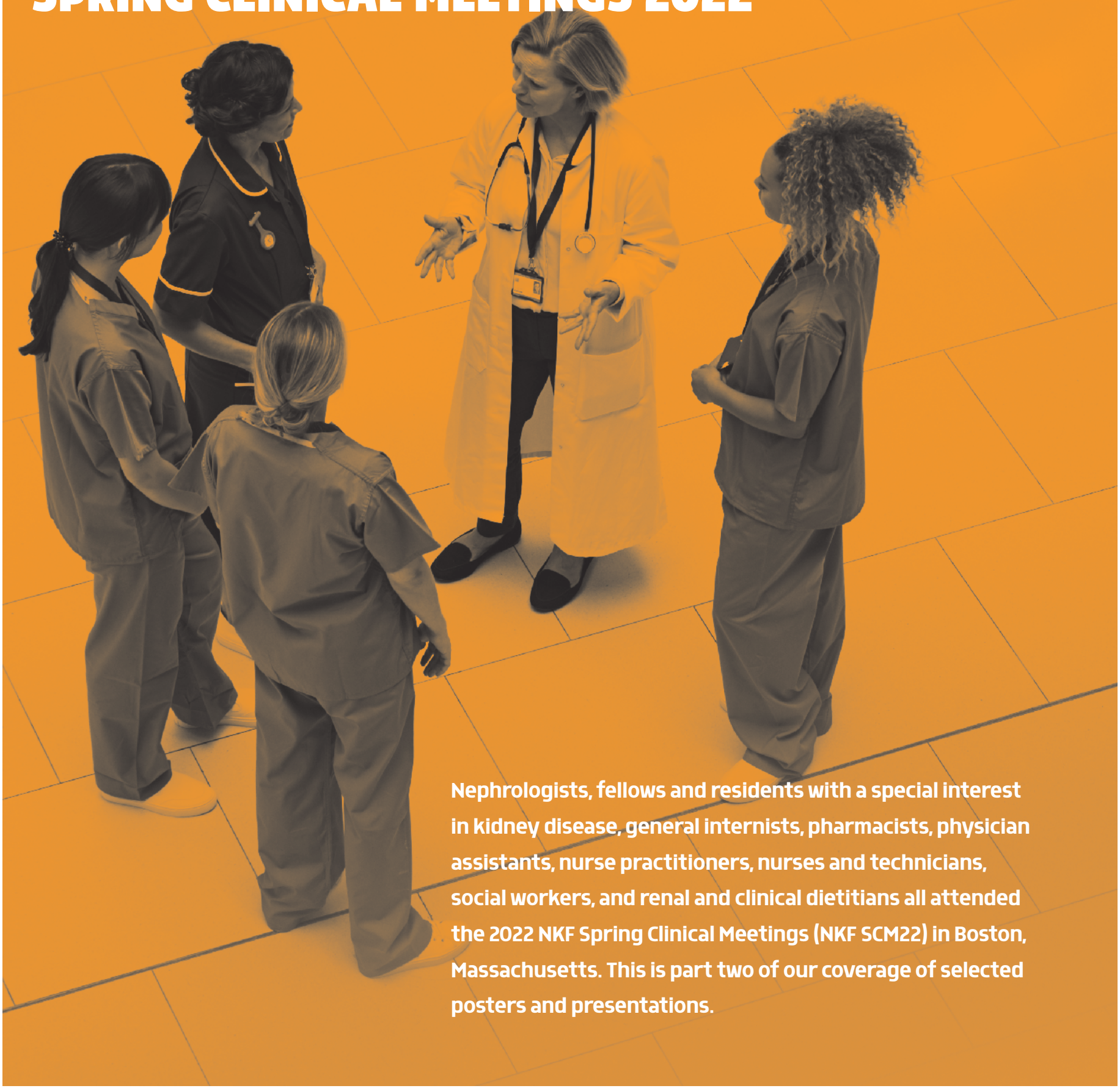

Nephrologists, fellows and residents with a special interest in kidney disease, general internists, pharmacists, physician assistants, nurse practitioners, nurses and technicians, social workers, and renal and clinical dietitians all attended the 2022 NKF Spring Clinical Meetings (NKF SCM22) in Boston, Massachusetts. This is part two of our coverage of selected posters and presentations.

Patiromer Use for Hyperkalemia Among US Veterans

The potassium binder patiromer has a favorable safety profile when compared with sodium polystyrene (SPS). **Yoshitsugu Obi, MD, PhD,** and colleagues conducted a study to examine the prevalence and characteristics of chronic patiromer users among a cohort of US veterans with hyperkalemia. Secondary objectives included an examination of the temporal association between patiromer use and use of SPS.

Results of the study were reported during a poster session at NKF SCM22. The poster was titled *Characteristics of Patiromer Users among US Veterans with Chronic Kidney Disease and Hyperkalemia.*

The cohort included 854,217 US veterans receiving care from the Veterans Administration Healthcare system. Inclusion criteria were at least one hyperkalemia event (defined as potassium >5.0 mEq/L) between January 1, 2016, and September 30, 2019. Initiation of chronic patiromer use was defined as the date of a prescription for patiromer where at least one refill was dispensed and the cumulative supply of outpatient patiromer exceeded 30 days. Characteristics of the patiromer cohort were summarized, including the use of SPS preceding chronic patiromer use.

At the first hyperkalemia event, mean levels of serum potassium and eGFR were 5.5 mEq/L and 37 mL/min/1.73 m^2, respectively. During follow-up, a total of 2004 (0.25%) of the cohort received any dose of patiromer.

At the time of the index use of patiromer, mean age was 71 years, 98% were male, 66% were White, and 31% were Black. Among those in the patiromer group, 33% (n=666) subsequently satisfied criteria for chronic patiromer use. Compared with those who did not meet those criteria, those who were chronic patiromer users on average had lower Charlson Comorbidity Index at cohort entry (4.4 vs 4.9; $P<.001$) and were more often White (71% vs 63%; $P=.003$). The two groups were of comparable age at the time of first patiromer use (71.1 years vs 71.5 years; $P=.46$).

A total of 359 (54%) patients had used SPS prior to patiromer initiation. Only 36 (5%) used SPS following chronic patiromer initiation.

In conclusion, the researchers said, "Patiromer was rarely used for treating hyperkalemia at least during this study period but appears to be replacing SPS use. Chronic patiromer users had less severe comorbidities. Further studies are needed to evaluate the effect of patiromer on clinical hard outcomes.

Source: Obi Y, Thomas F, Dashputre A, Potukuchi P, Goedecke P, Kovesdy C. Characteristics of patiromer users among US veterans with chronic kidney disease and hyperkalemia. Abstract of a poster (Poster #298) presented at the National Kidney Foundation 2022 Spring Clinical Meetings, Boston, Massachusetts, April 6-10, 2022.

Temporal Trends in Hepatorenal Syndrome In-Hospital Mortality

There have been advancements in knowledge regarding mitigation of poor outcomes in hepatorenal syndrome. However, according to **Jose Luis Zabala Genovez, MD,** and colleagues, "Specific therapeutic gaps have not been addressed effectively over the past 20 years in the United States. Mortality rates and predictors that could serve as therapeutic and preventive targets are not well established."

The researchers conducted a retrospective cohort study of patients with hepatorenal syndrome. Results were reported during a poster session at NKF SCM22 in a poster titled *Hepatorenal Syndrome in the United States: A Temporal Trend of In-Hospital Mortality and Its Predictors.*

The study utilized data from the National Inpatient Sample database and included 4938 (unweighted sample) and 23,973 (weighted sample) hospital admissions for hepatorenal syndrome from 2005 to 2014. The primary outcomes of interest were temporal trends in mortality and predictors for hospital mortality. Estimated odds ratios from multi-level mixed-effect logistic regression were used to identify patient characteristics and treatments associated with in-hospital mortality.

In 2005, the rate of in-hospital mortality was 44%; in-hospital mortality decreased to 24% in 2014. There were increased rates of liver transplantation, kidney replacement therapy, length of stay, and hospitalization cost. Following multivariable adjustment, there were associations between older age, alcohol use, coagulopathy, neurological disorder, and need for mechanical ventilation with higher mortality. There were also associations between liver transplantation, transjugular intrahepatic portosystemic shunt (TIPS), and abdominal paracentesis with lower in-hospital mortality.

"Our study shows an apparent reduction in mortality, and this reduction might explain the increased length of stay and higher resource utilization, including liver transplantation, TIPS, and kidney replacement therapy," the researchers said. "Interestingly, TIPS and abdominal paracentesis were associated with lower hospital mortality. Predictors of in-hospital mortality are similar to those found in other studies, including older age, coagulopathy, alcohol use, and neurologic disorders."

Source: Genovez JLZ, Dumancas C, Thongprayoon C, et al. Hepatorenal syndrome in the United States: A temporal trend of in-hospital mortality and its predictors. Abstract of a poster (Poster #25) presented at the National Kidney Foundation 2022 Spring Clinical Meetings, Boston, Massachusetts, April 6-10, 2022.

Social Determinants of Health and Health Care Use in Patients With ADPKD

In a poster session at NKF SCM22, **Karl Kilgore, PhD**, and colleagues reported the results of a study designed to examine the relationship between social determinants of health (SDOH) and health care resource utilization (HRU) and costs in patients with commercial and managed Medicaid health insurance with autosomal dominant polycystic kidney disease (ADPKD). The poster was titled *Impact of Social Determinants of Health (SDOH) and Specialist Care on Healthcare Resource Utilization (HRU) and Costs in Autosomal Dominant Polycystic Kidney Disease (ADPKD).*

The study used data from a national claims database. The commercial insurance group included 8766 patients, and the managed Medicaid group included 5416 patients. Eligible patients had two or more *International Classification of Diseases, Tenth Revision, Clinical Modification* codes for ADPKD between July 1, 2016, and December 31, 2018, and were continuously enrolled in a commercial or managed Medicaid insurance plan for 12 or more months.

Nine-digit ZIP codes, rather than census data, were used to link patients to SDOH. HRU included inpatient days and visits to the emergency department (ED) per 1000 patients per month and total health care costs over 1 year of follow-up. The two cohorts (commercial and managed Medicaid) were analyzed separately.

The proportion of female patients was higher in the managed Medicaid group compared with the commercial insurance group (60% vs 54%). Patients in the managed Medicaid group were, on average, 8 years younger than those in the commercial group. Managed Medicaid patients had 1.3 times higher scores on the Charlson Comorbidity Index scale, had 40% lower income, lived alone 1.3 times more often, fell below the federal poverty level 2 times more often, completed high school 1.3 times less often, and spoke English not well/at all 2.7 times more often.

There were associations between lower education level and living alone and higher inpatient days and ED utilization for both groups, and for patients in the managed Medicaid group, higher total health care costs. There was also an association between lower income and increased ED visits. There were no consistent associations between other SDOH and outcomes.

Health care resource utilization and total health care costs were significantly higher among patients with ADPKD who saw certain specialists (hematologist, cardiologist, or mental health provider) compared with those who did not. The trend was opposite among patients who saw a nephrologist.

In conclusion, the authors said, "ADPKD patients with higher rates of certain social risk factors had higher inpatient days and ED utilization and higher total health care costs than those with lower social risk factors. Managed Medicaid patients had higher rates of social risk factors than commercial patients overall. Identifying and addressing social risk factors in these patients are recommended to reduce avoidable health care resource utilization and costs and the health care disparities which are the likely cause of these disparate outcomes. In addition, patients who were seen by nephrologists had lower health care resource utilization and costs than those who were not, after controlling for SDOH and other factors. This suggests that ADPKD may present unique clinical challenges which are most effectively addressed by the appropriate medical specialist."

The study was sponsored by Otsuka Pharmaceutical Development & Commercialization, Inc.

Source: Kilgore K, Pareja K, Teigland C, et al. Impact of social determinants of health (SDOH) and specialist care in healthcare resource utilization (HRU) and costs in autosomal dominant polycystic kidney disease (ADPKD). Abstract of a poster (Poster #345) presented at the National Kidney Foundation 2022 Spring Clinical Meetings, Boston, Massachusetts, April 6-10, 2022.

RAASi Use After Hyperkalemia

Treatment with renin-angiotensin-aldosterone system inhibitors (RAASi) provides cardiorenal protection. However, due to an increased risk of hyperkalemia, the use of RAASi may be limited. **Jaejin An, PhD,** and colleagues conducted a study to examine RAASi modifications and adherence to RAASi following new-onset hyperkalemia in patients with chronic kidney disease (CKD) and/or heart failure.

Results of the study were reported during a poster session at NKF SCM22. The poster was titled *Renin-Angiotensin-Aldosterone System Inhibitor (RAASi) Use after New-Onset Hyperkalemia in a US Integrated Healthcare System.*

The retrospective cohort study utilized electronic health records at Kaiser Permanente Southern California to identify adults with hyperkalemia and CKD and/or heart failure from 2016 to 2017. Hyperkalemia was defined as potassium ≥5.0 mEq/L. Inclusion criteria were no history of hyperkalemia and two or more fills of RAASi within 12 months before the first episode of hyperkalemia (index date).

RAASi modification was classified as (1) dose reduction/discontinuation (ever filled a reduced RAASi dose or discontinuation of one or more RAASi [≥90 day gaps in refills]), (2) higher dose (ever filled an increased RAASi dose or add-on RAASi), and (3) same dose. Low adherence was defined as proportion of days covered <80% during the 3, 6, and 12 months of follow-up using outpatient pharmacy dispense records. RAASi modifications and adherence were illustrated using descriptive statistics. Stratified analyses were performed by severity of index hyperkalemia.

A total of 7875 patients had hyperkalemia. Of those, 78% had CKD only, 10% had heart failure only, and 13% had both CKD and heart failure. Within the 3 months after the index date, the proportion of patients who received a reduced RAASi dose or discontinued RAASi was 26%; within 6 and 12 months the proportion increased to 38% and 43%, respectively (RAASi discontinuation, 18%, 28%, 32% within 3, 6, and 12 months, respectively).

Among patients with borderline hyperkalemia (potassium 5.0 to 5.1 mEq/L), 37% received a reduced dose or discontinued RAASi within 12 months. Among patients with severe hyperkalemia, (potassium >6.0 mEq/L), the percentage increased to 61%.

Low adherence rates to RAASi treatment increased from 15% at baseline to 19% at 3 months, 30% at 6 months, and 35% at 12 months.

In summary, the researchers said, "Among patients with CKD and/or heart failure, RAASi dose reduction or discontinuation as well as low adherence to RAASi were common after hyperkalemia. Future studies should evaluate the effect of these modifications on risk of recurrent hyperkalemia and cardiorenal outcomes."

Source: An J, Zhou H, Sim J, et al. Renin-angiotensin-aldosterone system inhibitor (RAASi) use after new-onset hyperkalemia in a US integrated healthcare system. Abstract of a poster (Poster #184) presented at the National Kidney Foundation 2022 Spring Clinical Meetings, Boston, Massachusetts, April 6-10, 2022.

Long-Term Versus Short-Term SZC Use and Hospitalizations for Hyperkalemia

Results of a real-world study conducted by **Abiy Agiro, PhD,** and colleagues were reported during a poster session at NKF SCM22 in a poster titled *Impact on Hospitalizations of Long-Term versus Short-Term Sodium Zirconium Cyclosilicate Therapy During Routine Care for Patients with Hyperkalemia: RECOGNIZE I.* The study was designed to evaluate use of sodium zirconium cyclosilicate (SCZ) in outpatients with hyperkalemia as well as the impact of long-term versus short-term use of SZC on hospitalization for hyperkalemia.

A large US claims database was used to retrospectively identify adult outpatients ≥18 years of age with a first initiation of SZC from January 2018 to June 2020. Inclusion criteria were continuous insurance coverage 6 months before (baseline) and after (follow-up) index SZC therapy (total coverage of 12 months). Analyses were conducted for all patients and for a subgroup of patients with non-end-stage kidney disease (non-ESKD). The main objectives were to identify characteristics associated with long-term (>90 days) versus short-term (≤90 days) SZC use. Rates for hospitalization for hyperkalemia among groups were compared. Multivariate logistic regression was used to assess predictors of long- versus short-term SZC use.

Of the overall cohort of 1153 patients, 35% (n=405) received long-term SZC therapy and 65% (n=748) received short-term SZC therapy. Over 6 months of follow-up, 33% fewer patients with long-term SZC use versus short-term SZC use were hospitalized with hyperkalemia (15% vs 10%, respectively). Results were similar for the non-ESKD subgroup.

In all patients, significant predicators of long-term SZC use were baseline number of hospitalizations (lower odds) and chronic kidney disease (CKD) stage 3/unspecified (higher odds vs no CKD-ESKD). In non-dialysis patients, significant predictors of hospitalizations were liver disease (lower odds) and CKD stage 3 (higher odds vs no CKD/ESKD).

In conclusion, the authors said, "Approximately one-third of patients received long-term SZC. CKD stage 3 was a predictor of long-term SZC. Hospitalization with hyperkalemia during follow-up was lower with long-term versus short-term SZC therapy; this was also observed in the baseline period."

Funding for RECOGNIZE I was provided by AstraZeneca.

Source: Agiro A, Wirtz EL, Young JA, et al. Impact on hospitalizations of long-term versus short-term sodium zirconium cyclosilicate therapy during routine care for patients with hyperkalemia: RECOGNIZE I. Abstract of a poster (Poster #305) presented at the National Kidney Foundation 2022 Spring Clinical Meetings, Boston, Massachusetts, April 6-10, 2022.

Online CME Activity Improves Knowledge of CKD-aP

Amy Larkin, PharmD, and colleagues conducted an analysis to determine whether online continuing medical education (CME) could improve the clinical knowledge of both nephrologists and primary care physicians (PCPs) regarding the management of patients with chronic kidney disease-associated pruritus (CKD-aP). Results of the analysis were reported during a poster session at the NKF SCM22. The poster was titled *Impact of Online CME on Knowledge of CKD-Associated Pruritus.*

The CME format was an online, 30-minute, discussion with three CME-certified experts. The current analysis was designed to test the effect of the activity. Prior to and immediately following each activity, participants answered three multiple-choice knowledge/competence questions and one self-efficacy confidence question. The educational effect of the activity was assessed using a repeated pairs pre-/post-assessment study design, paired samples t-test for overall and McNemar's test at the question level (5% significance level, $P<.05$).

The analysis included all of the 514 nephrologists and 173 PCPs who answered all pre- and post-assessment questions. Overall, there were improvements seen following participation in both CME activities.

Sixty-one percent of nephrologists and 39% of PCPs improved their knowledge ($P<.01$ for both groups). Specifically, 37% of nephrologists and 18% of PCPs showed improvements at characterizing the incidence of CKD-aP ($P<.01$ for nephrologists; $P<.05$ for primary care physicians); 42% of nephrologists and 27% of PCPs demonstrated improvements at identifying new and/or emerging treatment options for CKD-aP ($P<.01$ for both groups); 8% of nephrologists and 6% of PCPs demonstrated improvements at recognizing strategies for a successful care team approach in managing CKD-aP (P=nonsignificant for both groups due to high baseline).

In response to the question relating to confidence, 44% of nephrologists and 36% of PCPs had a measurable improvement in confidence in identifying the issues as well as recognizing the signs and symptoms of CKD-aP ($P<.01$ for both groups).

Continued identified educational gaps related to CKD-aP were (1) incidence of CKD-aP (47% nephrologist; 58% PCPs) and (2) information related to new and emerging treatments for CKD-aP (19% nephrologists; 54% PCPs).

In summary, the authors said, "This study demonstrates the success of online, video-based three-expert discussion on improving knowledge of nephrologist and PCPs related to new/emerging treatment options for CKD-aP. Continued knowledge gaps were identified for future educational targets."

Source: Larkin A, Blatherwick D, Boutsalis G. Impact of online CME on knowledge of CKD-associated pruritus. Abstract of a poster (Poster #277) presented at the National Kidney Foundation Spring Clinical Meetings 2022, Boston, Massachusetts, April 6-10, 2022.

Integrating Programs for Healthy Eating and Moving with Conventional CKD Care

In nearly two-thirds of cases of chronic kidney disease (CKD) in the United States, the underlying cause is either diabetes or hypertension. In the general population, the integration of healthy eating and healthy moving (increased physical exercise) with conventional medical care improves outcomes for diabetes and hypertension. Adverse outcomes associated with CKD due to diabetes or hypertension may be reduced with the integration of healthy eating and healthy moving with conventional medical care.

The risks for CKD are disproportionately high among individuals of low socioeconomic states (SES); Medicaid is the federal government program designed to support the health needs of patients of low SES. **Donald Wesson, MD, MBA, FASN,** and colleagues conducted a study to examine whether there are offerings within Medicaid that could support the integration of healthy eating and healthy moving with traditional medical care to treat patients with CKD and diabetes and/or hypertension. Results of the study were reported during a poster session at NKF SCM22 in a poster titled *Payment Policy Support for Integrating Healthy Eating and Healthy Moving with Traditional Medical Care for Chronic Kidney Disease Care.*

Increasingly, Medicaid is going beyond the realm of conventional medical care to meet the health needs of its patients via the addition of non-medical drivers of health, such as heathy eating and healthy moving. Some state Medicaid programs address those needs with managed care products and other authorities. In some states, Medicaid utilizes flexibility within the program to enable accessibility of home delivered meals and help fund statewide infrastructure to support healthy eating. There are also grants available to support incentives for beneficiaries to take advantage of various programs designed to encourage and support increased physical exercise.

In summary, the authors said, "Medicaid provides opportunities to states to support integration of healthy eating and healthy moving with conventional medical care in the treatment of individuals with diabetes and/or hypertension associated with CKD. This integration holds promise to reduce increasing adverse outcomes in all patients with CKD and should be explored as a mechanism to reduce adverse outcomes especially in low SES populations whose health needs are supported by Medicaid."

Source: Wesson D, Mathur V, Tangri N, Hamlett S, Bushinsky D. Payment policy support for integrating healthy eating and healthy moving with traditional medical care for chronic kidney disease care. Abstract of a poster (Poster #254) presented at the National Kidney Foundation 2022 Spring Clinical Meetings, Boston, Massachusetts, April 6-10, 2022.

Predictors of Rapid Decline in Kidney Function in Patients With ADPKD

The use of creatinine measurement alone does not provide reliable data on outcomes associated with autosomal dominant polycystic kidney disease (ADPKD), according to **John Sim, MD,** and colleagues. Further, resource-intensive approaches, including Mayo Imaging Classification (MRI) or PROPKD (genetic testing) may not reflect real-world practice.

Using longitudinal data from routine clinical practice, a data-driven approach was used to identify patients with ADPKD with rapid decline in kidney function and to determine the clinical factors associated with rapid decline in kidney function. Results of a retrospective cohort study within Kaiser Permanente Southern California (2002-2018) were reported during a poster session at NKF SCM22 in a poster titled *Predictors Associated with Rapid Decline of eGFR to End-Stage Kidney Disease (ESKD) among a Diverse Autosomal Dominant Polycystic Kidney Disease (ADPKD) Population.*

The study cohort included incident ADPKD patients, identified via two or more *International Classification of Diseases* codes for ADPKD and no prior diagnoses. Patients with rapidly declining estimated glomerular filtration rate (eGFR) trajectory were identified using latent class mixed models. Predictors of rapid decline in kidney function were selected based on agreements among feature selection methods, including logistic, regularized, and random forest modeling. Selected predictors and clinically meaningful covariates were used to build the final model.

The latent class mixed models included 1744 incident ADPKD patients. Of those, 7% (n=125) were identified as rapid decline in kidney function. A total of 42 baseline measurements were included in feature selection for adaptation with multiple imputations.

Multiple imputed databases identified seven variables as important features to distinguish rapid decline in kidney function groups from non-rapid decline in kidney function groups: baseline age, serum creatinine, hemoglobin, proteinuria, hypertension, cerebrovascular disease, and liver disease. Based on a balance between clinical implications and area under the curve (AUC) assessed using non-missing data, the final model excluded serum creatinine and liver disease and included sex.

Results found 72% sensitivity, 70% specificity and accuracy, and 0.77 AUC in identifying rapid decline in kidney function. The 5-year ESKD rates were 38% among the rapid decline groups and 7% among the non-rapid decline groups.

In conclusion, the researchers said, "Using real-world data, we found that six variables highly predicted rapid decline among ADPKD patients. This clinical risk prediction model may serve as a practical screening tool to capture and manage high-risk ADPKD patients who may need earlier and more intensive management strategies."

Funding for this study was provided by Otsuka Pharmaceutical Development & Commercialization, Inc.

Source: Sim J, Shu Y-H, Harrison, T, et al. Predictors associated with rapid decline of eGFR to end-stage kidney disease (ESKD) among a diverse autosomal dominant polycystic kidney disease (ADPKD) population. Abstract of a poster (Poster #349) presented at the National Kidney Foundation 2022 Spring Clinical Meetings, Boston, Massachusetts, April 6-10, 2022.

Survey Examines Patient Preferences for Hypertension Treatments

When determining treatment plans for the management of hypertension, patient preferences are key to the shared decision-making process between patients and physicians. **David Kandzari, MD,** and colleagues conducted a discrete choice experiment (DCE) to quantify patient preferences for various attributes of hypertension treatments. The researchers also examined patient preferences for treatments for hypertension among subgroups in a post hoc analysis of a DCE.

Results were reported during a poster session at NKF SCM22. The poster was titled *Initial Subgroup Analyses of US Patient Preferences for Interventional and Pharmaceutical Hypertension Treatments.*

Using experimentally designed hypothetical hypertension treatments with varying levels of attributes and involving an interventional procedure or pills, the researchers created an online survey. Each survey respondent was given 12 questions on treatment choice, including an option for no treatment.

Random parameters logit were used to analyze survey data, and the results were used to calculate the magnitude of influence attribute variations had on patient preferences. Post hoc analyses of subgroups (sex, age, race, baseline blood pressure, and current hypertension regimen) were performed. A Wald test was used to evaluate whether there were systematic variations among subgroups in treatment choices and estimated preferences.

The study cohort included 400 patients in the United States with physician-confirmed hypertension. Of the 400, 51.5% were female, 39.0% were ≥65 years of age, 14.8% were non-Hispanic Black, 66.5% had systolic blood pressure of 140 to 160 mm Hg at baseline, 33.5% had baseline systolic blood pressure >160 mm Hg, 41.5% were taking no or one antihypertensive medications, and 58.5% were taking two or three antihypertensive pills per day.

There were no systematic differences in preferences based on patient sex, age, baseline systolic blood pressure, or pills taken per day. Black respondents were more likely to opt for hypertension treatment and more likely to select an interventional treatment than non-Black respondents.

In conclusion, the authors said, "In this post hoc subgroup analysis, patient preferences for hypertension treatments did not differ based on gender, age, baseline systolic blood pressure, or current hypertension treatment regimen, but were significantly different for Black respondents compared to non-Black respondents."

Source: Kandzari D, Weber M, Poulos C, et al. Initial subgroup analyses of US patient preferences for interventional and pharmaceutical hypertension treatments. Abstract of a poster (Poster #371) presented at the National Kidney Foundation 2022 Spring Clinical Meetings, Boston, Massachusetts, April 6-10, 2022.

Invasive Cardiac Care for Patients With CKD

Patients with chronic kidney disease (CKD) face markedly increased risk for cardiovascular morbidity and mortality. Results of previous studies have suggested underutilization of invasive cardiovascular care for the treatment of acute coronary syndrome (ACS) in patients with CKD. **Sanjana Kapoor, MD,** and **Steven Weisbord, MD,** conducted a study comparing the use of invasive cardiovascular care for ACS and the association between use of invasive cardiovascular care for ACS with 5-year mortality in a contemporary cohort of patients with and without CKD. Intensive cardiovascular care was defined as coronary angiography (CA), percutaneous coronary intervention (PCI), or coronary artery bypass grafting (CABG).

Results of the study were reported during a poster session at NKF SCM22. The poster was titled *Lower Utilization of Invasive Cardiac Care in Patients with Stage 3 and 4 Chronic Kidney Disease Admitted with Acute Coronary Syndrome in a Tertiary Healthcare System.*

Patients hospitalized with ACS (ST-elevation myocardial infarction [STEMI] or NSTEMI) between January 1, 2016, and December 31, 2019, were included in the study. Patients with CKD stage 5 or end-stage kidney disease were excluded, as were patients with DNR orders or palliative care consults. *International Classification of Diseases-Tenth Revision* (*ICD-10*) primary discharge codes were used to identify ACS, and *Current Procedural Terminology* and ICD-10-Procedure Coding System codes were used to identify CA, PCI, and CABG procedures

Multivariable logistic regression was used to compare the use of invasive care based on CKD status. Cox hazard models were used to compare mortality.

The study included 2316 NSTEMI patients and 478 STEMI patients. Of the total cohort, 540 patients had a diagnosis of CKD. Patients with CKD were more likely to be older (78 years of age vs 71 years of age; $P<.001$), and to have type 2 diabetes mellitus (67% vs 42%; $P<.001$), hypertension (98% vs 90%; $P<.001$) and a history of stroke (35% vs 21%; $P<.001$), compared with those without CKD.

Following adjustment for age, race, sex, and diagnosis of diabetes mellitus, hypertension, and history of stroke, patients with CKD were 32% less likely to undergo invasive cardiovascular procedures than those without CKD (adjusted odds ratio [aOR], 0.68; 95% CI, 0.54-0.87). The percentage of NSTEMI patients undergoing invasive cardiovascular procedures decreased with increasing CKD severity (83% vs 76% vs 68%; $P<.001$). The aOR for invasive cardiovascular procedures in patients with CKD compared with patients without CKD was 0.61 (95% CI, 0.47-0.81).

In both the CKD group and the non-CKD group, there was improved survival observed with invasive cardiovascular procedures. The adjusted hazard ratio for death at 5 years with performance of procedure was 0.63 (95% CI, 0.45-0.88) among CKD patients compared with 0.42 (95% CI, 0.33-0.53) in patients without CKD.

In summary, the authors said, "In a contemporaneous cohort of patients treated at a large, tertiary-referral hospital system, patients with CKD are less likely to undergo invasive care to treat ACS, despite a decrease in mortality with such treatment."

Source: Kapoor S, Weisbord S. Lower utilization of invasive cardiac care in patients with stage 3 and 4 chronic kidney disease admitted with acute coronary syndrome in a tertiary healthcare system. Abstract of a poster (Poster #182) presented at the National Kidney Foundation 2022 Spring Clinical Meetings, Boston, Massachusetts, April 6-10, 2022.

COVID-19 Vaccine Hesitancy in Inner-City Dialysis Patients

Researchers at SUNY Downstate Health Sciences University, Brooklyn, New York, led by **Edward Bae,** conducted a survey to assess the impact of vaccine hesitancy in underserved populations. Results of the survey were reported during a poster session at NKF SCM22 in a poster titled *Factors Affecting Decision to Receive the COVID-19 Vaccine in Inner-City Dialysis Patients.*

A random sample of 31 dialysis patients completed the survey. Questions included COVID-19 vaccination status, attitudes toward vaccines, and perception of health care/government authority. Respondents who had received two doses of the COVID-19 vaccine, one dose, or were planning on doing so were characterized as VACYES; those who were unsure or refused to receive the COVID-19 vaccine were characterized as VACNO.

Mean age of the survey cohort was 56.1 years, mean dialysis vintage was 6.2 years, 58% (n=18) were women, and 90% (n=28) identified as Black. Of the total cohort, 84% had received the vaccine.

There were no statistically significant differences between the VACYES and VACNO groups in age, time on dialysis, sex, race, education, insurance status, and presence of diabetes. Those in the VACYES group were more likely to agree with trust in the information about the vaccine (r=0.57; P<.001), felt confident about the safety and efficacy of the vaccine (r=0.75; P<.001), and trusted government guidelines regarding COVID-19 (r=0.73; P<.001).

Respondents who believed it was acceptable for the government to mandate vaccinations (r=0.52; P=.003), mandate COVID-19 vaccinations (r=0.58; P=.001), and that we should all follow government mandates to protect public health (r=0.41; P=.02) were more likely to be in the VACYES group.

Those in the VACYES group were also more likely to believe that hospitals could care for them if they fell ill with COVID-19 (r=0.62; P<.001), reported they had an active partnership with their provider (r=0.42; P=.02), and that having regular contact with their physician was the best way to avoid illness (r=0.38; P=.04).

Respondents in the VACNO group were more likely to report having less contact with medical professionals regarding dialysis-associated restrictions (r=0.63; P<.001) and felt their provider did not listen to them (r=0.38; P=.04).

In summary, the researchers said, "In our population of inner-city dialysis patients: (1) The majority are vaccinated against COVID-19; (2) patients were more likely to have received the vaccine if they had trust in the government regarding COVID-19 and in the health care system in general; (3) patients who reported more shared decision making were more likely to receive the vaccine and this should be emphasized in education efforts for vaccine acceptance in our vulnerable population."

Source: Bae E, Wei L, Gidon A, et al. Factors affecting decision to receive the COVID-19 vaccine in inner-city dialysis patients. Abstract of a poster (Poster #230) presented at the National Kidney Foundation 2022 Spring Clinical Meetings, Boston, Massachusetts, April 6-10, 2022.

Ultrafiltration Rate Changes Over Time in Hemodialysis Patients

In patients on hemodialysis, ultrafiltration rate (UFR) is associated with an increased risk of mortality. There are few data available regarding changes in UFR over time. **Mustafa Dawood, MD,** and **Jose Navarrete, MD,** renal division, Emory University, Atlanta, Georgia, conducted a study to examine changes in UFR over time in hemodialysis patients.

Results of the study were reported during a poster session at NKF SCM22. The poster was titled *Changes in Ultrafiltration Rate (UFR) Over Time in Hemodialysis Patients.*

The study cohort included all incident hemodialysis patients who were admitted to dialysis units at Emory who were alive and still receiving hemodialysis after 3 years. Ultrafiltration (UF, weight pre-dialysis minus weight post-dialysis) and UFR (UF in mL/weight post-dialysis/dialysis time in hours) were calculated and time-referenced to the beginning of hemodialysis tenure. During the observation period, the researchers also determined the proportion of patients with UFR >13 mL/kg/hour as well as the average UFR for the entire cohort.

A total of 433 patients met inclusion criteria. Of those, median age was 56 years, 95% were Black, 53% were male, 22% had a history of congestive heart failure at the time of dialysis initiation, and 12% had chronic viral disease (HIV, hepatitis C or B).

During the 3-year observation period, the percentage of patients with average UFR >13 mL/kg/hour increased. The average UFR also increased during the first year of hemodialysis tenure. Average weight decreased from 83.8 kg at the start of dialysis to 82.6 kg at 12 months and 82.3 kg at 36 months (P<.01).

During the first 3 months of dialysis, achieved dialysis duration increased from 208 minutes to 212 minutes (P<.001). It remained stable thereafter for the duration of the observation period. During the first month of dialysis, UF increased from 1.7 L to 2.2 L at 12 months (P<.001). UF remained stable thereafter.

"There was significant increase in UFR during the first year of dialysis, associated to an increase in UF and loss of weight," the researchers said. "The proportion of patients with UFR >13 mL/kg/hour also increased over time in dialysis. Achieved dialysis duration did not change significantly after 3 months of dialysis, as it is usually aimed at achieving adequate clearance and not to limit UFR. Dialysis prescription should take into consideration changes in patient weight and increased UF to limit the effect on UFR."

Source: Dawood M, Navarrete J. Changes in ultrafiltration rate over time in hemodialysis patients. Abstract of a poster (Poster #239) presented at the National Kidney Foundation 2022 Spring Clinical Meetings, Boston, Massachusetts, April 6-10, 2022.

Daprodustat for Anemia in Incident Dialysis Patients

During the first 90 days following initiation of dialysis, patients are at high risk for adverse outcomes; mortality is twice as high as in the subsequent 9 months. Patients undergoing incident dialysis, defined as dialysis initiated within 90 to 120 days, experience abrupt physiological and psychological changes that include metabolic flux from clearances of uremic mediators, correction of anemia, and changes in parameters of metabolic biome disease, blood pressure, and extracellular volume. There are few data available of the efficacy and safety of erythropoiesis stimulating agents (ESAs) and the novel hypoxia-inducible factor prolyl hydroxylase inhibitors (HIF-PHIs) during this phase of chronic kidney disease (CKD).

Daprodustat, a HIF, is being examined as an oral alternative to conventional ESA therapy. There are few data available on anemia treatment in an incident dialysis population. **Ajay K. Singh, MBBS,** and colleagues conducted a study designed to evaluate the efficacy and safety of daprodustat versus darbepoetin alfa in the treatment of CKD-related anemia in that patient population. Results of the study were reported online in *JAMA Internal Medicine* [doi:10.1001/jamainternmed.2022.0605].

TAKEAWAY POINTS

- Researchers reported results of a study designed to assess the efficacy and safety of daprodustat compared with darbepoetin alfa for 52 weeks for the treatment of chronic kidney disease (CKD)–related anemia in incident dialysis patients.
- In the daprodustat arm, the adjusted mean change from baseline was 1.02 g/dL, compared with 1.12 g/dL in the darbepoetin alfa arm, for a treatment difference of –0.10 g/dL, achieving noninferiority of daprodustat compared with darbepoetin alfa in the prespecified noninferiority margin of –0.75 g/dL.
- The results suggest that daprodustat may be a potential oral alternative to a conventional ESA.

The prospective, randomized, open-label clinical trial was conducted from May 11, 2017, through September 24, 2020, in 90 centers across 14 countries. Eligibility criteria included patients with advanced CKD who planned to initiate dialysis within 6 months of screening or who had received hemodialysis or peritoneal dialysis within 90 days prior to randomization. Additional inclusion criteria were screening hemoglobin (Hb) concentration of 8.0 to 10.5 g/dL and a randomization Hb of 8.0 to 11.0 g/dL, ESA-naïve or had received limited ESA treatment, and being iron-deplete.

Patients were randomized by dialysis modality (hemodialysis vs peritoneal dialysis) and by planned versus unplanned or urgent dialysis start (defined as no nephrology care or referral within the 4 months prior and/or a hemodialysis start with temporary vascular access with no previous planning for chronic dialysis or recent [<2 weeks] peritoneal dialysis catheter insertion). Following stratification, patients were randomized 1:1 to daprodustat or darbepoetin alfa. A protocol-specified dose adjustment algorithm to achieve and maintain Hb concentrations within 10.0 to 11.0 g/dL was applied for both treatments.

The primary objective was to demonstrate the noninferiority of daprodustat compared with darbepoetin alfa in increasing and maintaining the Hb concentration during the evaluation period. In the intent-to-treat population, the primary analysis evaluated the mean change in Hb concentration from baseline to weeks 28-52. The secondary end points included mean monthly intravenous (IV) iron dose from baseline to week 52. To assess safety and tolerability, rates of treatment-emergent and serious adverse events were compared between treatment groups.

A total of 508 patients were screened; of those, 60% (n=312) met eligibility criteria. Median age of the cohort was 55 years, and 62% (n=194) were male. At the 14 participating centers worldwide, 157 patients were randomized to daprodustat (median age, 52 years, 61% [n=96] male) and 155 were randomized to darbepoetin alfa (median age, 56.0 years, 63% [n=98] male). Forty-five patients in the daprodustat group and 39 in the darbepoetin alfa group prematurely discontinued treatment; 306 patients completed the study. Vital status was confirmed in all but one of 312 patients (99%) at week 52.

The two arms were generally similar in baseline characteristics and in dialysis type. Overall, 81% of patients (n=252) were undergoing hemodialysis and 69% (n=216) had planned initiation of dialysis.

At baseline, mean Hb concentration was 9.46 g/dL in the daprodustat group and 9.49 g/dL in the darbepoetin alfa group. The groups were similar in IV iron use (daprodustat, 67%; darbepoetin alfa, 70%). In the daprodustat group the median standardized IV iron dose at baseline (87 mg/mo) was lower than in the darbepoetin alfa group (130 mg/mo).

The two groups were similar in treatment exposure; 86% of patients (n=135) in the daprodustat arm and 90% (n=139) in the darbepoetin alfa arm received randomized treatment for more than 6 months. The median daily dose of daprodustat was 2 mg, and median dose for the four weekly doses of darbepoetin alfa was 60 mg. For both arms, the total median duration of exposure was 12 months.

During the evaluation period, mean Hb concentration in the daprodustat arm was 10.5 g/dL compared with 10.6 g/dL in the darbepoetin alfa arm. In both arms, the mean Hb concentration remained in the analysis range of 10.0 to 11.5 g/dL. In the daprodustat arm, the adjusted mean change from baseline was 1.02 g/dL, compared with 1.12 g/dL in the darbepoetin alfa arm, for a treatment difference of –0.10 g/dL (95% CI, –0.34 to 0.14 g/dL), achieving noninferiority of daprodustat compared with darbepoetin alfa in the prespecified noninferiority margin of –0.75 g/dL.

Compared with baseline, there was a reduction in mean monthly IV iron use at week 52; however, daprodustat was not superior to darbepoetin alfa in reducing use of monthly IV iron (adjusted mean treatment difference, 19.4; 95% CI, –11.0 to 49.9). The two arms were generally similar in monthly IV iron use (daprodustat, 142 mg; darbepoetin alfa, 128 mg).

The two treatment arms were generally similar in the proportion of patients experiencing treatment-emergent adverse events and serious adverse events: adverse event rates were 76% for daprodustat versus 72% for darbepoetin alfa.

The authors cited some limitations to the study, including the relatively short 52-week study treatment length and the small sample size. The small sample size limited the evaluation of major adverse cardiovascular event safety outcomes. In addition, the reporting of adverse events may have been biased due to the use of an open-label design, and because darbepoetin alfa was used in the triall, conclusions regarding noninferiority to other ESAs may be limited.

In conclusion, the researchers said, "In this randomized clinical trial, the ASCEND-ID study showed noninferiority of daprodustat to darbepoetin alfa in the treatment of anemia in incident dialysis patients. Monthly IV iron use was similar in both study arms, and although changes in iron kinetics with daprodustat were observed, the significance of these findings is not clear. Daprodustat was effective in maintaining Hb concentrations in a subgroup of patients with an unplanned dialysis start, in patients receiving peritoneal dialysis, and in patients with inflammation. The safety profile was similar between treatment groups in this 52-week study; the scientific and medical communities are still waiting for long-term safety data and recommend additional studies. Based on the efficacy and short-term safety in this study, daprodustat may represent a potential oral alternative to one of the conventional ESAs for patients with CKD who are starting dialysis." ■

Treating Type 2 Diabetes and Advanced CKD

Patients with chronic kidney disease (CKD) or end-stage kidney disease (ESKD) face increased health burdens and are at increased risk for cardiovascular events and mortality. The most common cause of CKD is type 2 diabetes, and both diabetes and CKD are associated with greater risk of all-cause mortality and increased rates of infection and cardiovascular events. The increased mortality is attributable in part to cardiovascular or infection-related events.

Both glucagon-like peptide-1 (GLP-1) receptor agonists and sodium-glucose cotransporter-2 (SGLT-2) inhibitors are associated with improved blood pressure control, greater reduction in body weight, lower mortality, and lower incidence of cardiovascular events in the general population with diabetes. Guidelines from the American Diabetes Association recommend GLP-1 receptor agonist treatment for patients with diabetes and CKD with an estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2 who are at risk for cardiovascular disease.

The Kidney Disease: Improving Global Outcomes 2020 Clinical Practice Guideline for Diabetes Management in Chronic Kidney Disease suggests GPL-1 receptor agonist treatment for patients unable to use metformin or SGLT-2 inhibitors; GLP-1 receptor agonists can be used in patients with advanced CKD or ESKD. Results of a recent meta-analysis found potentially different clinical outcomes following use of GLP-1 receptor agonists and use of dipeptidyl peptidase-4 (DPP-4) inhibitors in the general population with diabetes. In that study, there was an association between use of GLP-1 receptor agonists and improved survival compared with use of DPP-4 inhibitors.

According to **Jia-Jin Chen, MD,** and colleagues, previous randomized clinical trials have excluded or included only small numbers of patients with advanced CKD or ESKD. In addition, there are no real-world data available on comparisons of GLP-1 receptor agonists with DPP-4 inhibitors for the treatment of patients with advanced CKD or ESKD. The researchers conducted a retrospective cohort study among patients with diabetes and advanced stage CKD or ESKD to examine whether use of GLP-1 receptor agonists in that population would be associated with better outcomes compared with the use of DPP-4 inhibitors. Results of the study were reported online in *JAMA Network Open* [doi:10.1001/jamanetworkopen.2022.1169].

The study utilized data on patients with type 2 diabetes and stage 5 CKD or ESKD from the National Health Insurance Research Database of Taiwan. The study was conducted between January 1, 2012, and December 31, 2018. Data analyses were conducted from June 2020 to July 2021.

The study exposures were treatment with GFLP-1 receptor agonists compared with treatment with DPP-4 inhibitors. The outcomes were all-cause mortality, sepsis- and infection-related mortality, and mortality related to major adverse cardiovascular and cerebrovascular events (MACCE) in patients treated with GLP-1 receptor agonists compared with those in patients treated with DPP-4 inhibitors.

Covariates included age, sex, area of residence (urban or rural), income level, occupation, and 10 comorbidities (hypertension, dyslipidemia, cirrhosis, systemic lupus erythematosus, atrial fibrillation, peripheral arterial disease, coronary artery disease or ischemic heart disease, heart failure, cerebrovascular disease, and ESKD requiring dialysis). The imbalance among covariates between the groups was mitigated using propensity score weighting.

A total of 75,556 patients with type 2 diabetes and stage 5 CKD or ESKD requiring dialysis were identified during the study period. Of those, 48,277 were excluded, resulting in a study cohort of 27,279 patients. Of those, 26,578 were in the DPP-4 group (45.34% [n=14,443] were male; mean age 65 years) and 701 were in the GLP-1 receptor agonist group (49.36% male [n=346], mean age 59 years).

Prior to propensity score weighting, the DPP-4 group was older, concentrated in rural areas, and included fewer patients receiving dialysis and more patients receiving an angiotensin-converting enzyme inhibitor, diuretics, and insulin compared with the GLP-1 group. After propensity score weighting, the two groups were balanced in all analyzed covariates.

After propensity score weighting, the DPP-4 group included 26,568 patients and the GLP-1 receptor group included 603 patients. Mean age was 66 years in the DPP-4 inhibitor group and 65 years in the GLP-1 agonist group. In the DPP-4 group, 54.25% (n=14,414) were male; in the GLP-1 group 52.90% (n=319) were male. The most common comorbidity in the total cohort was hypertension (84.20% [n=22,369] in the DPP-4 inhibitor group and 83.92% [n=506] in the GLP-1 group).

The rate of all-cause mortality in the DPP-4 group was 7.95 per 100 person-years (95% CI, 7.76-8.15 per 100 person-years); in the GLP-1 group the rate was 6.10 per 100 person-years (95% CI, 4.76-7.45 per 100 person-years). Following propensity score weighting, there was an association between use of GLP-1 receptor agonists and lower all-cause mortality compared with use of DPP-4 inhibitors (hazard ratio [HR], 0.79; 95% CI, 0.63-0.98; *P*=.03).

The rate of sepsis- or infection-related mortality was 3.01 per 100 person-years (95% CI, 2.88-3.13 per 100 person-years) in the DPP-4 inhibitor group and 1.80 per 100 person-years (95% CI, 1.07-2.53 per 100 person-years) in the GLP-1 receptor group. The risk for sepsis- or infection-related mortality was lower in the GLP-1 receptor agonist group than in the DPP-4 inhibitor group (HR, 0.61; 95% CI, 0.40-0.91; *P*=.02).

The rate of MACCE-related mortality was 2.56 per 100 person-years in the DPP-4 inhibitor group and 2.64 per 100 person-years in the GLP-1 receptor agonist group. MACCE-related mortality in the GLP-1 receptor agonist group was similar to that in the DPP=4 inhibitor group (HR, 1.07; 95% CI, 0.76-1,51; *P*=.69).

In subgroup analyses, there was an association between use of GLP-1 receptor agonists with a lower risk of mortality compared with use of DPP-4 inhibitors among patients with cerebrovascular disease (HR, 0.33; 95% CI, 0.12-0.86) than among those without cerebrovascular disease (HR, 0.89; 95% CI, 0.871-1.12) (*P*=.04 for interaction).

The authors cited some limitations to the study findings, including the lack of detailed data on clinical factors and other possible confounders, the inability to examine the dose effect or to evaluate adherence to the medication, the relatively small sample size that resulted in an inability to assess the differences in treatment effects across subgroups, and pooling patients with stage CKD not receiving dialysis with those with ESKD who were receiving dialysis.

In conclusion, the researchers said, "In this cross-sectional study, in patients with type 2 diabetes and stage 5 CKD or ESKD, use of GLP-1 receptor agonists was associated with better outcomes, including all-cause mortality and sepsis- and infection-related mortality, compared with use of DPP-4 inhibitors. Additional large-scale prospective studies are needed to examine our results." ■

TAKEAWAY POINTS

- Researchers reported results of a study examining whether use of GLP-1 receptor agonists to treat patients with type 2 diabetes and CKD stage 5 or ESKD is associated with better outcomes than treatment with DPP-4 inhibitors.
- Following propensity score weighting, the rate of mortality in the GLP-1 receptor agonist group was 6.10 per 100 person-years compared with 7.95 per person-years in the DPP-4 inhibitor group.
- The risk for sepsis- or infection-related mortality was lower in the GLP-1 receptor agonist group than in the DPP-4 inhibitor group.

ESKD Cardiovascular Burden Higher in Girls Than Boys

Childhood mortality rates are declining overall. In the general population, mortality is higher in boys in most regions of the world, due in part to more accidents, prematurity, respiratory distress during infancy, and sepsis occurring post-puberty. In girls, inferior survival is associated with poverty, marginalization, and a sociocultural preference for male offspring.

Mortality in pediatric end-stage kidney disease (ESKD) is more than 30% times higher than in the general population. According to data from the United States Renal Data System on 14,024 children receiving kidney replacement therapy (KRT), girls have a higher risk of mortality (hazard ratio, 1.36; 95% CI, 1.25-1.50) due to their higher risk of cardiovascular death. Overall mortality rates in children with functioning grafts are declining; nevertheless, the proportion of cardiovascular mortality is unchanged and is ~20 % higher in girls.

Among children with ESKD, cardiovascular events are the most common causes of death, accounting for about one-third of deaths in children on dialysis and a quarter of pediatric kidney transplant recipients. Post-transplant mortality associated with cardiovascular causes is higher than that related to nonfunctioning grafts.

In adults, pulse wave velocity (PWV), a measure of vascular stiffness, is a predictor of cardiovascular mortality and is associated with a faster decline in estimated glomerular filtration rate (eGFR). Aortic PWV can be measured noninvasively and reproducibly in children. In previous studies, even after transplantation, PWV was higher in children with CKD compared with healthy peers.

Among pediatric patients, girls are less likely to undergo preemptive transplantation and show poorer graft survival compared with boys. Other data indicate a higher susceptibility among girls for cyclosporin A-associated hypertension, a possible contributor to poorer graft survival and increased cardiovascular mortality.

Rizky I. Sugianto, PhD, and colleagues conducted a study to examine the course of arterial stiffness in children with ESKD who underwent kidney transplantation, either preemptively or following prior dialysis. The study outcome of interest was potential differences between boys and girls. Results were reported online in *Kidney International* [doi.org/10.1016/j.kint.2021.11.032].

The current study, 4C-T (Cardiovascular Comorbidity in Children and Chronic Kidney Disease—Transplantation), is a substudy of the 4C study, a prospective observational study that included 704 patients 6 to 17 years of age with CKD, with an eGFR <60 mL/min/1.73 m² who were not yet receiving KRT enrolled between 2009 and 2011.

The substudy included 235 children undergoing preemptive transplantation (n=150) or following prior dialysis (n=85). Of the 235, 34% (n=80) were girls. Of the total cohort, 196 had observations prior to and following transplantation, 36 only before transplantation, and three only after transplantation. Longitudinal analyses (median/maximum follow-up time of 6/9 years) were performed using linear mixed regression models and further stratified by the categories of time: pre-kidney replacement therapy and post-transplantation. The analyses for PWV z scores (PWVz) were performed in three analysis steps: all data comprising the whole observation time and then divided into two separate analyses according to transplantation: pre-transplantation and post-transplantation.

There were no differences between girls and boys in eGFR at inclusion and the last visit pre-transplantation, age at inclusion and transplantation, time from eGFR ≥30 mL/min/1.73 m² to transplantation, and time on dialysis. At the time of the last visit prior to transplantation, girls showed significantly lower height, systolic blood pressure, hemoglobin, sodium, calcium, uric acid, and higher high-density lipoprotein than did boys.

PWVz increased by 0.095 per year since inclusion ($P<.0001$), independent of the underlying kidney disease ($P=.64$). In the mixed model, PWVz was 0.295 higher in girls ($P=.045$) than in boys.

In a comparison between the study population and a cohort of healthy children with comparable height, the healthy children demonstrated considerably lower PWVz (median –0.28) at study inclusion. PWVz did not increase with time in the healthy children (PWVz –0.048 per year; $P=.27$) and did not differ between girls and boys.

A total of 230 patients were included in an analysis of the effect of sex on PWV prior to transplantation. Compared with boys, girls showed a higher PWVz increase of 0.15 per year ($P=.039$). In a final covariate model of 158 patients, delta eGFR was a strong predictor for PWVz in girls. A decline in eGFR of –4 mL/min/1.73 m² per year prior to transplantation was associated with a higher PWVz of 0.16 in girls ($P=.017$) compared with boys. In both sexes, there were associations between higher diastolic blood pressure z score and higher low-density lipoprotein and a higher PWVz.

There were 199 patients included in an analysis of the effect of sex on PWV following transplantation. PWVz for girls was 0.44 higher than that for boys ($P=.02$). For both sexes, PWVz increased by 0.12 per year post-transplantation and by 0.25 per year on dialysis ($P=.006$). There was no interaction detected between time and sex.

In an additional analysis of 195 patients screened for potential covariates using the basic model, PWVz increased by 0.13 per year post-transplantation ($P<.0001$) and by 0.19 per year on dialysis ($P=.03$). There was an association between a one-point higher PWVz at the last pre-transplantation visit and a post-transplantation PWVz increase of 0.36 ($P<.0001$). The association of female sex and higher PWVz persisted ($P=.01$).

In girls, a decline of 4 mL/min/1.73 m² in eGFR per year pre-transplantation was associated with a PWVz increase of 0.22 after transplantation ($P=.039$). There was also a significant association between a longer time to transplantation (>12 months) and a higher PWVz of 0.57 in girls ($P=.017$). In both sexes, PWVz increased further after transplantation and was positively associated with time on dialysis and diastolic blood pressure.

The researchers cited a potential selection bias as a limitation to the study findings, as well as a possible limit to the generalizability of the findings due to the study population being predominantly White.

In conclusion, the authors said, "The observed higher susceptibility of girls for cardiovascular organ damage in conjunction with kidney disease progression highlights the importance of a closer attention to cardiovascular and kidney function parameters early in the disease course in female patients. Importantly, girls are more vulnerable toward eGFR decline and when exposed to a longer waiting time to transplantation. Early interventions and a faster access of girls to transplantation are crucial to tackle the sex differences in cardiovascular and mortality risk. Strict blood pressure control and management of dyslipidemia are of importance for both sexes." ■

TAKEAWAY POINTS

- Girls with kidney failure face higher mortality rates than do boys, with cardiovascular complications representing the most common causes of death in both sexes.
- Increased aortic pulse wave velocity (PWV) is highly predictive for cardiovascular events and mortality. To uncover potential differences between girls and boys, researchers conducted a study to examine the course of arterial stiffness in children with end-stage kidney disease who underwent kidney transportation.
- The study revealed that girls with advanced chronic kidney disease are more susceptible to develop vascular stiffening compared with boys, a difference that persists after kidney transplantation and may contribute to the higher mortality rates in girls with kidney failure.

Outcomes for Living Kidney Donors: Results of the SOLKID Study

Successful kidney transplantation enables patients with end-stage kidney disease (ESKD) to regain renal function, enjoy improved quality of life (QoL), and have enhanced life expectancy. Due to organ shortages, living kidney donation has gained considerable importance in most health systems. With an increased use of living donors, the physical and psychological health of the donors has become an important facet of kidney transplantation.

Until recently, the long-term health of donors was assumed to be comparable or even better than that of the general population. However, findings from recent studies suggest donors may experience declines in kidney function and QoL, and increased fatigue.

Barbara Suwelack, MD, and colleagues conducted a prospective, multicenter, interdisciplinary designed study to detect clinically relevant changes in kidney function, QoL, or fatigue as well as the underlying influencing factors following living kidney donation if those conditions are seen and lasting. Results of the study (SOLKID [Safety of the Living Kidney Donor]) were reported online in *Kidney International* (doi.org/10.1016/j.kint.2021.12.007).

Twenty transplant centers in Germany participated in the study. In addition to the primary outcomes of interest (kidney function, QoL, and fatigue), secondary end points were blood pressure, hemoglobin A1c, body mass index, depression, and somatization.

Donors were examined and data were collected predonation (T0), and 2 (T1), 6 (T2), and 12 months (T3) postdonation. All participants completed paper-based questionnaires to assess psychosocial factors and QoL. The short-form 36-item Health Survey (SF-36) was used for QoL. Fatigue was measured using the Multidimensional Fatigue Inventory (MFI-20). The five dimensions of the MFI-20 (general fatigue, physical fatigue, mental fatigue, reduced activation, and reduced motivation) were interpreted separately.

The study cohort included 336 living donors. Mean age was 52 years, 59.8% were female, and the majority had a vocational training and were full-time or part-time employed.

Prior to living kidney donation, mean arterial pressure values were in the normal range. Seventy-five percent of donors had no antihypertensive medication, 16% took one, 6% took two, and 3% took more than two antihypertensives. Median hemoglobin A1c value was 5.5% and mean estimated glomerular filtration rate (eGFR) was >90 mL/min/1.73 m^2. Five donors had predonation eGFR of <60 mL/min/1.73 m^2. At TO, body mass index suggested slight overweight.

Scores on the SF-36 physical (median Physical Component Scale score, 58.26) and mental (median Mental Component Scale score, 55.36) component scores were in the upper range of the standard normal population. The Patient Health Questionnaire (PHQ) showed no major depressive or somatization symptoms (PHQ-9 score 1.00 and PHQ-15 score 3.00, respectively). The cohort showed no increased fatigue levels prior to donation compared with the healthy population.

During follow-up, with the exception of eGFR, there was little or no change observed in most of the physical variables after living kidney donation. There was no significant increase in the number of donors on antihypertensive medication (25.1%-26.3%, TO vs T3).

There was significant decrease in kidney function, a decrease that remained during follow-up. Serum creatinine increased significantly from a median value of 0.8 mg/dL to 1.1 mg/dL (T3), and eGFR decreased from 96 mL/min/1.73 m^2 (T0) to 60 mL/min/1.73 m^2 (T1) and remained decreased. Total loss of eGFR was 32 mL/min/1.73 m^2 (38%) from T0 to T1 and 30 mL/min/1.73 m2 from T0 to T3.

There was a significant decline in Physical Component Scale scores (T1), which did not fully recover during the subsequent follow-up. Mental Component Scale scores were nearly unaffected. In results of SF-36 dimension scores, at T1 there was a decline for bodily function, physical role, pain, general health, and vitality, which also did not fully recover. Vitality was notably impaired after 12 months.

At T3, donors had a slight but significant increase in depressive symptoms but a larger increase in somatization. At 8 weeks postdonation, there was a detectable increase in fatigue. The increase in fatigue remained in four of the five domains (general fatigue, physical fatigue, mental fatigue, and reduced activity). During the 12 months postdonation, there were significant changes in kidney function (serum creatinine and eGFR), SF-36 QoL (vitality), PHQ-15, and general and mental fatigue.

The proportion of donors with decreased eGFR CKD stage 3 increased from 1.5% predonation to ~50%; none showed ESKD. The proportion of donors with impaired vitality increased and remained increased at T3. The percentage of donors with clinically relevant somatization increased from 3.8% to 12.9%.

In multivariate linear mixed model regression, kidney function (after decreasing between T0 and T1) continually increased from T1 to T3 (P=.0167), with higher eGFR at T2 and at T3 compared with T1. Higher eGFR at T0 resulted in higher eGFR a follow-up. Older age at baseline resulted in a lower eGFR during follow-up, with a decrease of 0.31 per year of life.

The primary influencing factors for decreased kidney function and increased fatigue were their respective predonation levels and donor age for kidney function and subject stress level in fatigue.

The authors cited not addressing a living kidney donor's lifetime risk of an adverse outcome >12 months postdonation and limited availability of data on the course of kidney function in older healthy donors as limitations to the findings.

In conclusion, the researchers said, "The large prospective study on physical and psychosocial outcomes of donors shows that although living kidney donation seems to be a safe procedure, impairment in kidney function and increased fatigue occurs in a significant number of donors. Our study underlines the need to inform future donors about these potential medical and psychosocial risks of living kidney donation. Noteworthy, half of the donors developed renal impairment, but this was not correlated to changes in QoL. At this time, it is not possible to conclude whether impaired kidney function will improve or might influence the morbidity and mortality of donors. Special attention should be given to the evaluation of elderly donors because renal outcome is mainly influenced by donor age and baseline GFR.

"Our data show an increase of fatigue in subjects with signs of fatigue and stress predonation. Because it is not known a priori which donor will experience relevant fatigue, we should feel obliged to inform donors about the postdonation risk of fatigue, which might influence their QoL. If we could characterize the risk of negative consequences for each donor, we might be able to provide individually tailored risk information and prevention strategies for donors on risk. More work on the individual risk of a negative physical and psychosocial health outcome in living donors should be the focus of future studies." ■

TAKEAWAY POINTS

- Results of the Safety of the Living Kidney Donor cohort study examining the physical and psychosocial outcomes in living donors in relation to their predonation health status were reported.
- There was little or no change in depression and quality of life; those values regained their predonation level.
- There was significant decline in kidney function and an increase in the proportion of donors with fatigue and somatization.

Sugar-Sweetened Beverages and Risk of Mortality in CKD

Beverages represent a substantial contributor to sugar intake in the modern diet. Sugar-sweetened beverages (SSBs) are the largest single source of added sugar in the American diet, including sodas, soft drinks, sugary coffees and teas, fruit-flavored drinks, vitamin-water drinks, and energy drinks that contain added caloric sweeteners such as fruit juice concentrates, sucrose, and high fructose corn syrup.

There are 140 to 150 calories and 35 to 38 grams of sugar in a characteristic 12-ounce serving of soda. Approximately 21% of the total energy in the American diet was consumed as beverages in 2021. While consumption of SSBs has declined over the past 10 years, a recent survey revealed a slight rebound in consumption.

There are abundant data on the positive correlation between SSBs and weight gain, diabetes, and coronary heart disease. However, according to **Xiao-Yu Cai, MD,** and **Nan-Hui Zhang, MD,** and colleagues, there are few data on the relationship between intake of SSBs and the risk of mortality in patients with chronic kidney disease (CKD). The researchers conducted an analysis to examine the association between SSBs and subsequent overall death in patients with CKD. Results were reported in *Clinical Kidney Journal* [2022;15(4):718-726].

and 42% had stage 3 CKD. The participants in the group with higher SSB intake were more likely to be younger, male, and non-Hispanic White, unmarried, less physically active, have a lower household poverty-to-income ratio, and lower education level. Consumption of SSBs was associated with a higher intake of total energy, dietary acid load, red and processed meat, and lower consumption of whole grains.

During average follow-up of 8.3 years, there were 1137 deaths of all causes (28%). Following adjustment for demographic and life-style factors and dietary factors, participants who consumed ≥2 servings per day had a hazard ratio (HR) of 1.80 (95% CI, 1.27-2.55) for all-cause mortality compared with those who did not consume SSBs. The association was further strengthened after adjustment for baseline estimated glomerular filtration rate, high total to high-density lipoprotein cholesterol level, hypertension, diabetes, cardiovascular disease, and cancer (HR, 1.90; 95% CI, 1.36-2.66; *P* for trend <.001).

In the continuous analysis, the risk of all-cause mortality was 18% higher for each additional serving of SSB intake per day (HR, 1.18; 95% CI, 1.08-1.28). Restricted cubic splines (RCSs) indicated a linear relationship between SSB intake and all-cause mortality.

In the continuous analysis, the risk of all-cause mortality was 18% higher for each additional serving of SSB intake per day (HR, 1.18; 95% CI, 1.08-1.28).

The analysis utilized data from the US National Health and nutrition Examination Survey (NHANES), 1999-2014. The total NHANES population included 82,091 people. Following application of inclusion and exclusion criteria, the final analysis cohort included 3996 participants with CKD and complete data.

In all of the NHANES cycles, individual dietary intakes were assessed via 24-hour dietary recall questionnaires. In the first two cycles (1999-2002), only one in-person 24-hour dietary recall was conducted. Beginning in 2003, the cycles included two dietary recalls. The primary recall was conducted by trained investigators at a mobile examination center and the second was a follow-up by telephone 3 to 10 days later. The beverages, nutrients, and energy intakes were calculated using the results of the recall from the 1999-2002 cycles and the average of nutritional data from both recalls in the 2003-2014 cycles.

SSBs were defined as sodas, sugary fruit juices, fruit-flavored drinks, sport and energy drinks, sweetened coffee and tea, and other sugary drinks. One serving was defined as 12 ounces.

The study outcome of interest was all-cause mortality during follow-up. Prior to December 31, 2015, NHANES data were linked to National Death Index records. The cause of death was determined according to the 10th edition of the *International Statistical Classification of Diseases.*

Patients were divided into four groups based on SSB consumption: (1) none; (2) >0 to <1 serving per day; (3) 1 to <2 servings per day; and (4) ≥2 servings per day. Participants were then divided into five groups based on the intake of added sugars in SSBs. Analysis of variance and Rau-Scott X^2 test with adjusted sample weights for baseline continuous variables and categorical variables, respectively, were used to assess the differences between groups. Following adjustment for potential confounders, a multivariate Cox regression model was used to estimate the relationship between SBB intake and all-cause mortality in patients with CKD.

Of the 3966 patients in the analysis cohort, median age at baseline was 67 years, 22% were Black, 54% were female,

Compared with the quintile with the lowest added sugar intake from SSBs, the highest quintile was associated with higher all-cause mortality (HR, 1.69; 95% CI, 1.2-2.36). The RCSs indicated a linear association between added sugar in SSBs and all-cause mortality (HR, 1.14; 95% CI, 1,05-1.24) for each increased 20 grams of added sugar per 1000 kilocalories of total energy intake.

There was no association with mortality when replacing one serving of SSBs with an equivalent amount of artificially sweetened beverages or pure juice or sweetened milk. However, substituting SSBs with an equivalent amount of unsweetened coffees (HR, 0.82; 95% CI, 0.74-0.91), unsweetened teas (HR, 0.86; 95% CI, 0.76-0.98), plain water (HR, 0.79; 95% CI, 0.71-0.88), or non- or low-fat milk (HR, 0.75; 95% CI, 0.60-0.93) was related to a 14% to 25% reduced risk of all-cause mortality.

The authors cited some limitations to the study, including not updating the baseline 24-hour dietary recall information during the follow-up period, not including other variables that could influence renal function (blood pressure, blood glucose status, salt intake, and other dietary information), and possible residual confounders even after adjustment for sociodemographic, lifestyle-related factors, diet-related factors, and comorbidities.

In conclusion, the researchers said, "We found that in the CKD population, increased SSB intake was associated with a higher risk of mortality and indicated a stratified association with dose. Plain water and unsweetened coffee/tea might be possible alternatives for SSBs to avert untimely deaths, which could be a simple, economical, clinically safe and effective choice for CKD patients. In future studies, researchers should take advantage of the latest dietary information to further investigate the life-course relationship between SSB consumption and mortality, as well as to discover the mechanism of SSB damage to the kidney." ■

TAKEAWAY POINTS

- Researchers reported results of an analysis of NHANES data to assess the association between intake of sugar-sweetened beverages (SSBs) and the risk of death in patients with CKD.
- Among the 3996 participants, during an average follow-up of 8.3 years, there were a total of 1137 deaths from any cause (28%).
- Following adjustment, those who consumed ≥2 servings per day of SSBs had a hazard ratio for all-cause mortality of 1.80, compared with those who did not consume SSBs.

Fresenius Launches Kidney-Focused Genomics Registry

The Global Medical Office of Fresenius Medical Care has launched the My Reason® campaign, a program designed to promote patient enrollment in the company's kidney-focused genomics registry, introduced in 2021. According to a recent press release, the campaign's goal is enrollment of more than 100,000 participants within 5 years.

The data collected by My Reason will provide a research tool linking genomic and clinical data of chronic kidney disease and end-stage kidney disease participants, enabling scientists to better understand genetic variations in patients.

Franklin W. Maddux, MD, global chief medical officer at Fresenius Medical Care, said, "My Reason will help us build a groundbreaking registry of people with advanced kidney disease from diverse ethnic and cultural backgrounds. Pulled from such a large population of patients, when paired with existing clinical data, this data set at scale will help scientists untangle the complex interactions that lead to kidney injury and use genetic sequencing to better understand pathways of injury in kidney disease."

Patients and their family members who reside in the United States are eligible to participate in the My Reason campaign that launched in the spring.

AKF Supports Home Equity and Accountability Act

The American Kidney Fund (AKF) issued a press release in support of the Home Equity and Accountability Act (HEAA) of 2022 introduced by Rep. Robin L. Kelly (D-IL) and the Congressional Tri-Caucus. The bill is aimed at achieving health equity in the United States and addresses kidney disease research, surveillance, prevention, and treatment.

LaVarne A. Burton, AKF president and CEO, said, "AKF strongly supports the HEAA and applauds Rep. Robin Kelly and the Congressional Tri-Caucus for reintroducing this landmark legislation that tackles longstanding health disparities seen in every part of our country. This bill provides clear, actionable steps designed to advance health equity, one of AKF's top priorities.

"Kidney disease is an urgent public health problem that currently affects 37 million Americans. At this moment, about 810,000 people in the United States are living with kidney failure and need dialysis or a transplant to survive.

"While people of all races and ethnicities are equally likely to develop kidney disease, people of color are more likely to reach kidney failure and require dialysis or a transplant to survive. Black Americans represent 35% of those with kidney failure, but only 13% of the US population, and Hispanic/Latino people are 1.5 times more likely to progress to kidney failure than non-Hispanic people. This is unacceptable.

"The intersection of systemic racism and social determinants of health create unequal opportunities for Black patients and other patients of color to best manage their kidney disease before it's too late.

"The Health Equity and Accountability Act contains important provisions that address kidney disease, such as increasing research into kidney disease in minority populations and inclusion of people of color in clinical trials, improving research by focusing on data sharing, genetic mapping and gene therapy; creating a national action plan to address kidney disease; expanding public health programs; increasing use of home dialysis in communities of color; increasing transplants for people of color and expanding Medigap access for people with kidney failure.

"These are lifesaving measures that will benefit millions of Americans, and we look forward to continuing to work with Rep. Kelly on efforts to pass this critically important legislation."

Versi™PD Cycler System Cleared by US FDA

In late spring, the US FDA awarded 510(k) clearance to the Versi™PD Cycler System. The system is a portable automated peritoneal dialysis system from Fresenius Medical Care North American. According to a press release, the system is the lightest, smallest, and quietest dialysis cycler in the United States.

Fresenius Medical Care is developing innovative technologies designed to accelerate the growth of home therapies, making home dialysis systems that are smarter, more intuitive, and easier to use for patients with kidney failure. VersiPD is designed to improve health equity by making home therapy a more feasible option for a broader population of dialysis patients.

Joe Turk, president of the Renal Therapies Group at Fresenius Medical Care, said, "The clearance of VersiPD is another important step in our effort to make home therapies easier for patients and more efficient for clinicians. We have listened closely to what patients and clinicians want in a home dialysis experience and have brought those ideas into the heart of this innovative system."

VersiPD is supported by the Kinexus™ Therapy Management Platform, a connected health system that works to improve patient outcomes and nurse productivity through remote therapy monitoring and programming capabilities. The platform is also available with the Liberty® Select Cycler and is designed to be fully compatible with the company's future portfolio of home dialysis machines.

Mike Anger, MD, chief medical officer for the Renal Therapies Group at Fresenius, said, "We believe that our new VersiPD will empower more patients to reclaim their freedom and independence, while further enabling care teams to better support patients and intervene more quickly when necessary. We know most patients can be successful dialyzing at home with the right technology and support, and this new cycler is an important milestone in our journey to truly transform dialysis care."

Strive and NANI Announce Expanded Partnership

In a recent press release, Strive Health announced an expansion of its relationship with Nephrology Associates of Northern Illinois and Indiana (NANI). Building on the partnership launched in 2021, Strive and NANI have established a risk-bearing platform that places the nephrologists at the center of global risk contracts with an increasing number of government and commercial payers.

According to the press release, the expanded partnership "unlocks the ability to extend care to as many as 20,000 patients with chronic kidney disease (CKD) and end-stage kidney disease (ESKD) throughout Illinois and Indiana."

Strive CEO and cofounder, **Chris Riopelle,** said, "Our approach to kidney care has yielded compelling results, helping to delay the progression of the disease, reducing costs, and improving the patient experience. Given our success, it only makes sense to broaden our scope to reach more patients who we know will benefit from a value-based model."

Strive and NANI will manage the financial risk and governance of risk contracts with Medicare and Medicare Advantage plan members with CKD and ESKD. As part of the expanded partnership, NANI is increasing its equity investment in Strive. Strive and NANI will also conduct outcomes-oriented clinical research on the effectiveness of interventions in reducing costs in value-based contracting models. The research aims to help further the nephrology industry's understanding of which interventions can improve outcomes and drive down costs.

Brian O'Dea, CEO of NANI, said, "Strive's solution is integrated into our members' practices, giving them the tools and infrastructure needed to succeed in a value-based contract. NANI's mission has always been to put the patient at the center of the care model and make it as easy as possible for each patient to receive what they need to manage their condition effectively and achieve better health outcomes. Our partnership with Strive makes it possible to achieve that goal."

NFK Joins the AST Living Donor Circle of Excellence

The National Kidney Foundation (NFK) has announced its membership and strategic partnership with the American Society of Transplantation's (AST) Living Donor Circle of Excellence program. By recognizing employers that provide lost wages to living donors while they recover from surgery, the program works to achieve its of goal increasing the number of living organ donors. By participating in the Circle of Excellence, NKF is demonstrating its commitment to making living donation more accessible.

There are nearly 100,00 patients waiting for a life-saving kidney. Lost wages are a barrier for potential donors; of the 24,670 transplants performed in 2021, only 5971 involved a living donor. The typical leave of absence needed by a living kidney donor ranges from 2 to 8 weeks; living liver donors require longer leaves. The minimum proportion of wage support by members of the AFT program is 80%; companies may elect to provide more than 80%.

Kevin Longino, CEO of NFT and a kidney transplant recipient, said, "Every day 12 people die on the waitlist. We need to rip down every possible barrier to becoming a living donor, and employers who join the Circle of Excellence are doing just that. By supporting those willing to help others struggling with life-threatening illness and helping to reduce any financial burden from living donation, employers can actively promote access to transplantation for all."

Membership in the Circle of Excellence requires employers to take actions that support living organ donation, including implementation of policies that provide salary support for employees who choose to be a living organ donor. Member employers may also offer financial support to employees in need or an organ transplant, but whose living donor faces a loss of income during the recovery period.

John Gill, MD, AST predicant, said, "The Circle of Excellence gives employers the opportunity to be heroes to their employers. A living donor's gift is life-saving for patients in need of a kidney or liver transplant and has a huge positive impact on society. Patients facing life-threatening disease can live normal lives, raise their families, and participate in their communities. By supporting living donors, we are also building stronger communities."

Georgia Living Donor Protection Bill

The American Kidney Fund (AKF) has issued a press release praising Georgia governor, Brian Kemp, for signing into law the Giving the Gift of Life Act (H.B. 275). The new law provides protections for living organ donors in Georgia by prohibiting life insurers from discriminating against living donors by denying or canceling coverage. The law also increases available tax credits for living donors to a maximum of $25,000.

AKF worked closely with state Sen. Jon Albers (District 56), the bill's sponsor, to advance the legislation through the Georgia General Assembly. Senator Albers is himself a kidney donor.

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Print-only Content

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LaVarne A. Burton, AKF president and CEO, said, "Living donor protections, like those in the Giving the Gift of Life Act, save lives by removing barriers to living organ donation and making more transplants possible. We are grateful to Gov. Kemp, the Georgia General Assembly, and the AKF Ambassadors who provided written testimony on behalf of the legislation. By prohibiting discriminatory practices against living organ donors and increasing incentives for both individuals and their employers to donate, there will be more organs available for the nearly 4000 Georgians on the organ transplant waiting list, including more than 3500 who are waiting for a kidney."

Increasing protections for living donors is a cornerstone of AKF's policy agenda. The Fund's State of the States: Living Donor Protection Report Card measures seven types of legislation states should enact to provide protection for living donors and encourage living organ donation. Signing the Giving the Gift of Life Act into law moves Georgia's report card grade up from a C to a B. Overall, the grade average for the United States is now a C.

Strive Health and Bon Secours Mercy Health Announce Collaboration

In a recent press release, Strive Health and Bon Secours Mercy Health announced a collaborative relationship designed to deliver high-quality, whole-person care for patients with kidney disease. Strive Health (Denver, Colorado) will work with Ohio-based Bon Secours Mercy Health to provide care for the nearly 8000 patients with chronic kidney disease (CKD) and end-stage kidney disease in Ohio to help patients preserve kidney function and delay the progression of kidney disease.

The collaboration aims to deliver a new care model to kidney patients, leveraging Strive's proprietary technology platform and Strive Kidney Heroes™ interdisciplinary clinical care teams.

Jean Haynes, chief population and community health officer at Bon Secours Mercy Health, said, "With Strive, we have found an organization that enables us to enhance our ability to deliver whole-person care to our patients with kidney disease anywhere anytime. Together, we bring a proven innovative clinical model to our communities that integrates with our current model of care."

The Strive clinical care team includes nurse practitioners, dietitians, pharmacists, care coordinators, and licensed clinical social workers. The team members act as an extension of the patient's physician to help manage kidney disease and comorbid conditions, such as diabetes, that can impact a patient's overall health.

"The Strive team is honored to have the opportunity to work alongside one of the largest and most strategic health systems in the US to provide care to kidney disease patients in Ohio," said **Chris Riopelle,** co-founder and CEO of Strive Health. ■

COVID-19

AKI in COVID-19: A Systematic Review

Frontiers in Medicine. doi.org/10.3389/fmed.2022.705908

Patients hospitalized with COVID-19 who develop acute kidney injury (AKI) are at increased risk for mortality. **Tahereh Sabaghian, MD,** and colleagues conducted a systemic review designed to assess the symptoms, complications, and treatments performed to manage AKI in patients with COVID-19. The search included PubMed, Medline, Web of Science, and EMBASE relevant scientific literature published up to February 1, 2022. The keywords used were "COVID-19," "SARS-CoV-2," and "acute kidney injury."

The review included 44 studies representing 114 COVID-19 patients with AKI; mean age of the participants was 53.6 years. The most common comorbidities in the patients with COVID-19 and AKI were history of diabetes, hypertension, and hyperlipidemia. In 12 of the 44 studies, participants had a history of AKI.

The most common pathological evidence of AKI was focal segmental glomerulosclerosis and acute tubular necrosis. The average length of stay in the hospital was 19 days, and the average duration of need for mechanical ventilation was 3 days.

In conclusion, the researchers said, "The current systemic review shows that AKI frequently complicates the course of COVID-19 hospitalizations and is associated with increased severity of illness, prolonged duration of hospitalization, and poor prognosis. Given the extent of the adverse impact of AKI, early detection of comorbidities and renal complications is essential to improve the outcomes of COVID-19 patients."

Extended KDIGO Definition to Diagnose Early AKI in COVID-19

PLOS Medicine. doi.org/10.1371/journal.pmed.1003969

Acute kidney injury (AKI) is a common and significant complication in patients with COVID-19. According to **Marina Wainstein, MBBS,** and colleagues, there are few data available on the incidence and impact of AKI occurring in the community or early in the hospital admission. The traditional Kidney Disease Improving Global Outcome s(KDIGO) definition of AKI may not identify patients whose hospitalization coincides with recovery of AKI as manifested by a decrease in serum creatinine.

Dr. Wainstein et al. conducted a study to test the hypothesis that more cases of AKI in patients with COVID-19 would be identified using an extended KDIGO definition (eKDIGO), adapted from the International Society of Nephrology (ISN) Oby25 studies, and that the cases may correspond to community-acquired AKI with similarly poor outcomes as previously reported in that patient population.

The study included patients who were admitted to 1609 hospitals in 54 countries with SARS-CoV-2 infection from February 15, 2020, to February 1, 2021. The incidence, staging, and timing of AKI were evaluated using a traditional KDIGO definition and an eKDIGO definition. The eKDIGO definition incorporated a commensurate decrease in serum creatinine.

Patients with eKDIGO outcomes, i.e., admission to the intensive care unit (ICU), invasive mechanical ventilation, and in-hospital death, were compared for all three groups of patients (those identified with KDIGO definition, those identified with eKDIGO definition, and those without AKI). Following adjustment for disease severity and AKI susceptibility, survival curves and logistic regression were used to assess the relationship between eKDIGO AKI and in-hospital death.

The final analysis cohort included 75,670 patients. Median length of stay was 12 days. There were twice as many patients with AKI identified by eKDIGO than by traditional KDIGO (31.7% vs 16.8%). Patients in the eKDIGO group had a greater proportion of stage 1 AKI (58% vs 36% in KDIGO patients). Peak AKI occurred early in the admission more frequently among patients in the eKDIGO group than among those in the KDIGO group.

Compared with patients without AKI, patients in the eKDIGO group had worse renal function on admission, more in-hospital complications, higher rates of admission to the ICU and invasive ventilation, and increased mortality. Mortality and rate of ICU admission were lower among patients in the eKDIGO group than among those in the traditional KDIGO group, but were significantly higher when compared with patients in the group without AKI.

In conclusion, the authors said, "An extended KDIGO definition of AKI resulted in a significantly higher detection rate in this population. These additional cases of AKI occurred early in the hospital admission and were associated with worse outcomes compared with patients without AKI."

DIABETIC NEPHROPATHY

SAA and 25(OH)VD Potential Diabetic Nephropathy Markers

Journal of Clinical Laboratory Analysis. doi.org/10.1002/jcla.24283

Qian Liu, PhD, and colleagues conducted a cross-sectional study to examine the relationships between serum amyloid A (SAA), 25-hydroxyvitamin D (25(OH)VD), and diabetic nephropathy. The researchers sought to provide evidence for the prevention and management of diabetic nephropathy.

The study cohort included 182 patients with type 2 diabetes mellitus (T2DM). The researchers measured and analyzed patients' levels of SAA, 25(OH)VD, and other conventional indictors. Binary logistic regression was used to evaluate risk factors for diabetic nephropathy, and receiver operating characteristic curve analysis was applied for the combined measurement of SAA and 25(OH)VD.

Compared with healthy controls, the levels of SAA in patients with T2DM were significantly higher, and there was significant increase in the SAA level as diabetic nephropathy progressed ($P<.05$). Conversely, the level of 25(OH)VD in patients with diabetic nephropathy was significantly lower than in healthy controls ($P<.05$).

Patients with diabetic nephropathy were distinguished from those with T2DM more consistently using the combined measurement of SAA and 25(OH)VD than with measurement of SAA or 25(OH)VD alone. SAA was an independent risk factor for diabetic nephropathy, and 25 (OH)VD was an independent protective factor for diabetic nephropathy.

In conclusion, the researchers said, "SAA and 25(OH)VD might be used as potential markers to identify patients at increased risk of developing diabetic nephropathy."

KIDNEY STONES

Changes in Diet After Kidney Stone Formation

Clinical Journal of the American Society of Nephrology. 2022;17(1):83-89

Diet is a key contributor to the formation of kidney stones. However, there are few data on the association of long-term changes in dietary factors after a kidney stone. **Pietro Manuel Ferraro, MD, MSc, PhD,** and colleagues conducted a data analysis to compare changes in dietary factors in patients with and without kidney stones during follow-up.

The analysis utilized data from three longitudinal cohorts, the Health Professionals Follow-Up Study and Nurses' Health Studies I and II. Repeat food frequency questionnaires were used to assess daily intake of dietary calcium, supplemental calcium, animal protein, caffeine, fructose, potassium, sodium, oxalate, phytate, vitamin D, vitamin C, sugar-sweetened beverages, fluids, net endogenous acid production, and Dietary Approaches to Stop Hypertension score.

The analysis cohort included 184,398 participants with no history of kidney stones; of those, 7095 became confirmed stone formers. In the stone formers, there were significant changes in several intakes over time, with some showing a relative increase up to 8 years later. The intakes with changes included caffeine (difference in differences, 8.8 mg/d; 95% CI, 3.4 to 14.1), potassium (23.4 mg/d; 95% CI, 4.6 to 42.3), phytate (12.1 mg/d; 95% CI, 2.5 to 21.7), sodium (43.1 mg/d; 95% CI, 19.8 to 66.5), and fluids (47.1 mg/d; 95% CI, 22.7 to 71.5).

There were significant decreases in other dietary factors, including oxalate (–7.3 mg/d; 95% CI, –11.4 to –3.2), vitamin C (–34.2 mg/d; 95% CI, –48.8 to –19.6), and vitamin D (–18.0 IU/d; 95% CI, –27.9 to –8.0). There was significant reduction in intake of sugar-sweetened beverages of –0.5 servings per week and –1.4 servings per week in Nurses' Health Study I and II, respectively. There were also reductions in intake of supplemental calcium of –105.1 mg/d and –69.4 mg/d for women in the two Nurses' Health studies.

There were no significant changes in animal protein, dietary calcium, fructose, Dietary Approaches to Stop Hypertension score, and net endogenous acid production.

In summary, the authors said, "After the first episode of a kidney stone, mild and inconsistent changes were observed concerning dietary factors associated with kidney stone formation."

TRANSPLANTATION

Recurrent IgA Nephropathy and Allograft Survival

Allograft Glomerular Diseases. doi:org/10.1159/00519834

According to researchers, while IgA nephropathy (IgAN) is the most common recurrent glomerulonephritis encountered in the kidney allograft, the clinical and immunogenetic characteristics of IgAN are not well understood. **Catherine R. Kavanagh, MD,** and colleagues conducted a study to assess the determinants and prognosis of recurrent IgAN with a focus on human leukocyte antigens (HLAs).

The study cohort included 282 transplant recipients between 2005 and 2019 from two North American and one European medical centers with failure secondary to IgAN and 202 without recurrence. The prevalence of HLAs was compared with external healthy controls of European ancestry. The Kaplan-Meier method and log rank test were used to assess graft survival, and Cox proportional hazards were used for multivariable analyses.

Compared with the external controls of European ancestry, the frequency of HLA-DQ5 was higher (42% vs 30%; odds ratio [OR], 1.68; $P=.002$) and the frequency of

CONFERENCE COVERAGE **AMERICAN TRANSPLANT CONGRESS**

Dose Reduction in ATG During COVID-19 Pandemic

Many transplant centers modified induction immunosuppression regimens during the COVID-19 pandemic. Beginning in December 2020, the UC Davis, Sacramento, California, transplant center reduced anti-thymocyte globulin (ATG) protocol dosing by up to 33% compared with pre-pandemic doses (7.5, 4.5, and 3 mg/kg per immunologic risk) for all recipients; there was no change in maintenance immunosuppression.

P. A. Than and colleagues at the center conducted an analysis to assess the impact of reduced ATG dose on kidney allograft and transplant recipient outcomes. Results were reported during a poster session at the 2022 American Transplant Congress in a poster titled *Impact of ATG Dose Reduction on Kidney Transplant Outcomes during the COVID-19 Pandemic*.

The retrospective review included adults who received a kidney transplant between December 2020 and March 2021 (pandemic) with at least 6 months of follow-up post-transplant and adults who received a kidney transplant between January 2019 and December 2019 (pre-pandemic). 2019 was selected as a comparable pre-pandemic cohort because transplant recipients were treated without influence from the COVID-19 pandemic. Electronic health records were used to extract patient demographic and laboratory data. Multi-organ transplant recipients were excluded from the analysis.

A total of 79 adult kidney transplants were performed during the pandemic era and 211 were performed during the pre-pandemic era. There was no increase during the pandemic in the rate of biopsy proven rejection (including surveillance and for-cause biopsies) compared with the pre-pandemic era (6.3% vs 8.0%, respectively; $P=.8$).

The rate of BK viremia (>1000 copies/mL) at 3 months was lower in the pandemic era than in the pre-pandemic era, but the difference did not reach statistical significance (6.4% vs 8.7%, respectively; $P=.6$). The rate of delayed graft function (DGF) was significantly higher in the pandemic era compared with the pre-pandemic era (42.3% vs 22.9%, respectively; $P=.002$). None of the participants tested positive for COVID-19 within 1 month of transplant.

In conclusion, the researchers said, "Despite reduction in ATG dose, we found no significant change in the rate of rejection or infections. We did however find a significant increase in the rate of DGF during the pandemic era. Further studies are needed to assess the long-term effects of reduced induction immunosuppression regimen on kidney transplant recipients."

Source: Than PA, De Leon F, Jen K, Goussous N, Perez RV, Wang AX. Impact of ATG dose reduction on kidney transplant outcomes during the COVID-19 pandemic. Abstract of a poster presented at the 2022 American Transplant Congress (Abstract 1379), Boston, Massachusetts, June 6, 2022.

PEDIATRIC KIDNEY DISEASE

Sleep Disorders in Pediatric CKD

Pediatric Nephrology . doi.org/10.1007/s00467-022-05536-y

There are substantial variations in the reported prevalence of sleep disorders in children with chronic kidney disease (CKD). **Kun-Tai Kang, MD, MPH,** and colleagues conducted a quantitative meta-analysis to estimate the prevalence of sleep disorders among pediatric patients with CKD. The study protocol was registered on PROSPERO (registration number CRD42021268378).

The search included PubMed, MEDLINE, EMBASE, and Cochrane review databases up to June 2021. Eligible studies included data on the prevalence of sleep disorders in children with CKD. The meta-analysis included 12 studies with 595 children (mean age, 12.9 years; 55.6% boys; mean sample size, 49.6 patients).

A random-effects model was used to estimate the prevalence of restless legs syndrome, sleep-disordered breathing, pediatric obstructive sleep apnea (eg, apnea-hypopnea index >1 event/hour in polysomnography), excessive daytime sleepiness, and insomnia/insufficient sleep. The prevalence of sleep disorders among children on dialysis and those not on dialysis was compared with subgroup analyses.

The prevalence of restless legs syndrome in children with CKD was 21% (95% CI, 14%-30%). The prevalence of sleep-disordered breathing, pediatric obstructive sleep apnea, excessive daytime sleepiness, and insomnia/insufficient sleep was 22% (95% CI, 12%-36%), 34% (95% CI, 19%-53%), 27% (95% CI, 17%-41%), and 14% (95% CI, 7%-27%), respectively.

Results of subgroup analyses demonstrated that the pooled prevalence of excessive daytime sleepiness was significantly higher in children on dialysis compared with those not on dialysis (43.3% vs 11.2%; *P*=.018). The subgroup of children on dialysis also had a high prevalence of other sleeping disorders; however, the differences did not reach statistical significance. Compared with controls, children with CKD exhibited a 3.9-fold increased risk of restless legs syndrome and a 9.6-fold increased risk of excessive daytime sleepiness.

"Sleep disorders are common in children with CKD," the researchers said. "Our results indicate that while the prevalence rates of various sleep disorders were higher in children on dialysis than in children not on dialysis, the prevalence of excessive daytime sleepiness was statistically significant in children on dialysis."

HAL-DR15 and HLA-DQ6 was lower (15% vs 28%; OR, 0.46; *P*<.001 and 32% vs 45%; OR, 0.59; *P*=.003, respectively) in kidney transplant recipients of European ancestry with kidney failure secondary to IgAN. The frequency of those HLAs were similar in recurrent versus nonrecurring IgAN.

Younger recipient age at the time of transplant was an independent predictor of recurrence of IgAN. HLA matching was an independent predictor for recurrent IgAN only in recipients of living-related but not in deceased or living-unrelated transplants. Recurrent IgAN was an independent predictor for allograft failure and for acute rejection. There were associations with serum creatinine at biopsy, degree of proteinuria, and concurrent acute rejections and inferior allograft survival in patients with recurrent IgAN.

In conclusion, the authors said, "Recurrent IgAN negatively affects allograft survival. Younger recipient age at transplantation is an independent predictor of recurrent IgAN, while the presence of HLAs associated with IgAN in the native kidney and HLA matching in recipients of deceased or living-unrelated transplants are not."

Changes in Bone Turnover and Mineralization After Kidney Transplant

Journal of the American Society of Nephrology. 2022;33(3):638-652

There are few data available of the effect of kidney transplantation on bone. **Hanne Skou Jørgensen, MD, PhD,** and colleagues conducted a prospective, observational cohort study to describe the evolution of bone disease in the first year following kidney transplantation.

The study cohort included patients refered for kidney transplantation under a steroid-sparing immunosuppressive protocol. Bone phenotyping (bone histomorphometry, bone densitometry by dual-energy x-ray absorptiometry, and biochemical parameters of bone and mineral metabolism) was done before or at the time of transplant and repeated at 12 months following transplant.

Ninety-seven patients had paired data available (median age, 55 years, 72% male, 21% with diabetes). In the majority of patients (65%), bone turnover remained normal or improved. Bone histomorphometry revealed decreases in bone resorption (eroded perimeter, mean 4.6% pre- to 2.3% post-transplant; *P*<.001) and disordered bone formation (fibrosis, 27% pre- versus 2% post-transplant, *P*<.001).

Bone mineralization was normal in all but one patient pretransplant; however, at 1 year post-transplant, delayed mineralization was seen in 15% of patients. There was an association between hypophosphatemia and deterioration in histomorphometric parameters of bone mineralization. Changes in bone mineral density varied from –18% to +17% per year. There was a relationship between cumulative steroid dose and bone loss at the hip; resolution of hyperparathyroidism was related to bone gain at both the spine and the hip.

In conclusion, the authors said, "Changes in bone turnover, mineralization, and volume post-transplant are related both to steroid exposure and ongoing disturbances of mineral metabolism. Optimal control of mineral metabolism may be key to improving bone quality in kidney transplant patients." ■

Sarah Tolson

Tips for Selecting a Medical Billing Solution

One commonality between most dialysis programs and nephrology practices is that both must submit claims to insurance companies to collect reimbursement for services provided. The three most common billing solutions I have encountered are an in-house billing team, electronic health records (EHR) company billing, and third-party billing services. I have observed pros and cons of each in my 14 years in the renal billing industry. In this issue, we will examine the challenges and benefits of these billing solutions to consider when choosing a billing solution for a nephrology office or dialysis program.

IN-HOUSE BILLING TEAM

Having an in-house biller or billing department is likely the most popular solution. Most of the people I work with at Sceptre Management have experience working in a medical office as an in-house biller or billing department manager. Having someone in your office managing the revenue cycle and collecting on outstanding accounts receivables can be convenient because you're able to interact with them daily, and they understand internal processes and can handle other duties.

However, it can be a challenge to cover time an in-house biller is unable to work, such as vacation and sick time. It is not a role that is easy to cover, as it can require at least several months of training. While some practices are fortunate to have long-term billers on their payroll, many practices and dialysis programs are plagued by turnover in their billing staff. Hiring new billers often results in a slowdown in billing and collections while the new hire is trained. My experience has been that it usually takes a minimum of 6 months for billers to have a basic understanding of dialysis billing and reimbursement. Having to hire a new biller frequently can really put a strain on cash flow.

EHR COMPANY BILLING

With this solution, maintaining clinical and patient demographic data in the same system is convenient and efficient when the work performed each day is automatically converted into billing data. If the EHR company's billing department performs well, this may be a good option for a practice that prioritizes consolidating their vendors.

When considering this solution, think about the following:

- How much experience does the EHR's billing team have with your specialty?
- What options do you have if you love the EHR but aren't happy with the billing services?
- Will the EHR let you bring your billing in-house if you aren't satisfied with their performance or would they require you to switch to a different EHR?
- What are the checks and balances in place to assist you in monitoring the performance of the billing services?

THIRD-PARTY BILLING SERVICE

Third-party billing services vary; some require you to use their EHR, while others are EHR agnostic. Some break tasks up into accounts receivables, charge entry, and payment posting teams, or may assign specific representatives that only work on your account.

Working with a reputable third-party billing service that specializes in your practice specialty may help your reimbursement to be better optimized due to the service's in-depth knowledge of that specialty's billing requirements. Working with a third-party billing service helps to alleviate the turnover and headache related to training billing staff.

While third-party solutions can be a great option, keep the following in mind when considering it:

- How will they charge you based on what is collected or what has been billed out?
- Will they invoice your practice at an all-inclusive rate or are there separate charges for things such as submitting secondary claims, sending appeals, or mailing patient statements?
- How often does the billing service meet with you to review your practice's accounts receivables?
- What access will you have to the billing data?

Once you decide on the billing solution that seems like the best fit for your practice, it may be beneficial to interview several different companies or individual billers. After identifying those that seem like good fits, it can be helpful to check their references as well. ■

Sarah Tolson is the director of operations for Sceptre Management Solutions, Inc., a company specializing in billing for outpatient ESRD dialysis programs, nephrology practices, and interventional nephrology. Your questions are welcome, and she can be reached at stolson@sceptremanagement.com, 801.775.8010, or via Sceptre's website, www.sceptremanagement.com.

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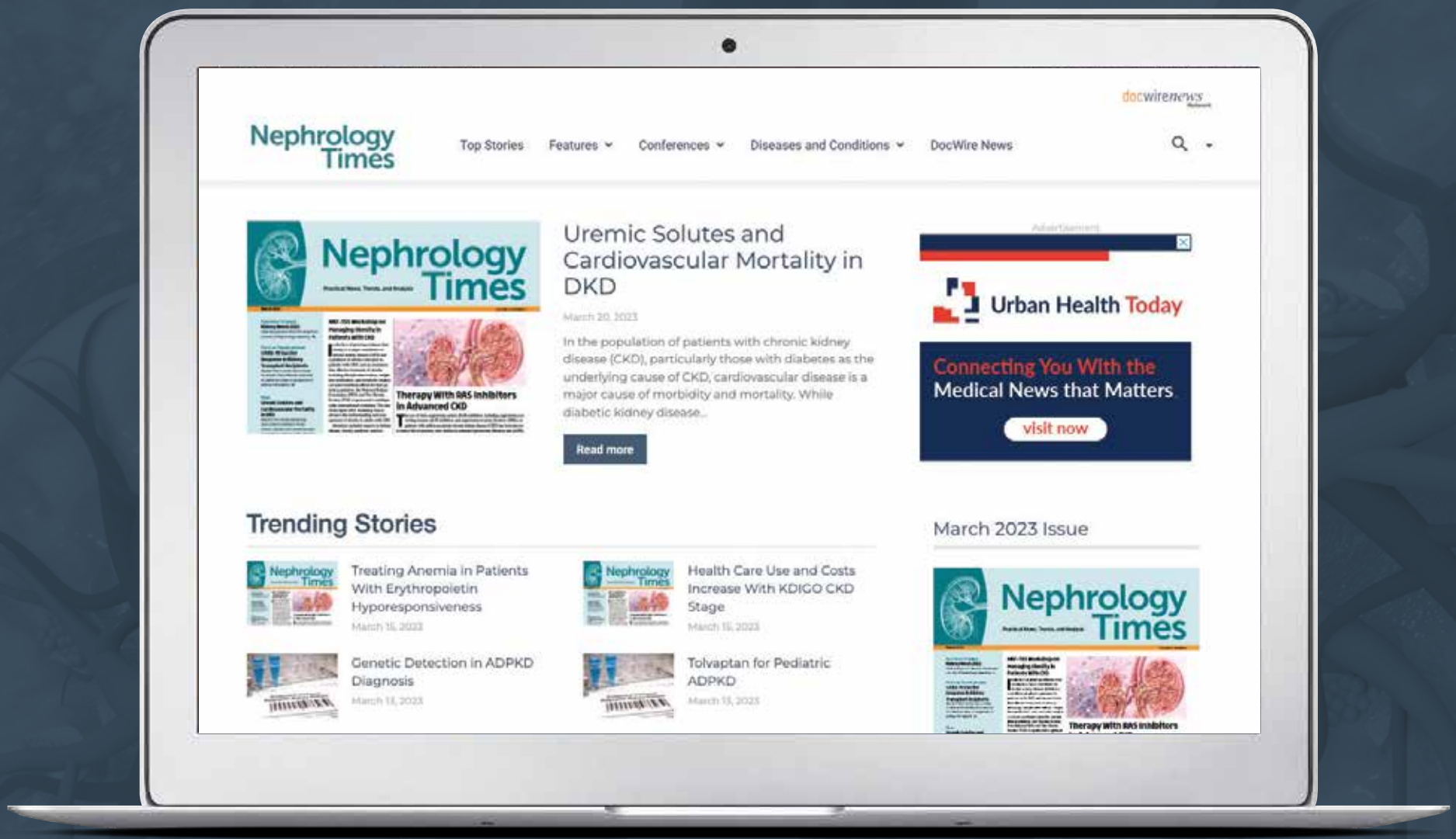

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