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Practical News, Trends, and Analysis

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Outcomes Vary in Peritoneal Dialysis-Related Peritonitis

Peritonitis associated with peritoneal dialysis is associated with substantial morbidity and adds to hospitalizations and treatment costs. While the rates of peritonitis associated with peritoneal dialysis have decreased due to advances in peritoneal dialysis connectology as well as other evidence-based preventative strategies, peritonitis remains the leading cause of transition to hemodialysis.

Compared with the limited preventive efforts designed to reduce enteric microorganisms, the most successful efforts for preventing peritonitis associated with peritoneal dialysis have focused on reducing the incidence of Gram-positive infections by improving aseptic technique, reducing exit-site and peritoneal dialysis catheter colonization, and reducing touch-contamination events.

The PDOPPS (Peritoneal Dialysis Outcomes and Practice Patterns Study) and OPPUS (Optimizing the Prevention of Peritoneal Dialysis-Associated Peritonitis Study in the United States) were established to identify various peritoneal dialysis treatment practices and peritonitis characteristics that are associated with a reduction in the risk of peritonitis and peritonitis-related adverse events.

Muthana Al Sahlawi, MD, and colleagues conducted an observational prospective cohort study designed to describe regional differences in peritonitis cure rates across a diverse group of countries enrolled in PDOPPS and assess the impact of various patient,

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Coffee and Caffeine Consumption May Reduce Kidney Stones

Approximately 15% of the population is affected by kidney stones. Evidence from a large body of observational studies has suggested an associated between habitual consumption of coffee and caffeine and a reduction in the risk of kidney stones. However, it is unclear whether the associations are causal due to the possibility of confounding in observational studies and the lack of data from randomized controlled trials.

Using genetic variants as instrumental variables for an exposure (e.g., coffee

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Mortality Risk following Home Hemodialysis Treatment Failure

For the majority of people with kidney failure worldwide, dialysis remains the long-term treatment despite advances in prevention and treatment of chronic kidney disease (CKD). The limited availability of organs for transplant as well as risks associated with transplantation for some patients contribute to the continued use of dialysis for patients with end-stage kidney disease.

The goal of dialysis treatment is to provide the optimal quality of life for patients with kidney failure. Compared with in-center hemodialysis, home hemodialysis has been shown to provide superior quality of life and has at least equal if not superior mortality rates. While home hemodialysis can be performed for many years, there are patients who eventually experience treatment failure and return to in-center treatment. In Australia and New Zealand, median time to treatment failure is between 5 and 8 years, depending on patient age.

Drivers for a return to in-center treatment may include clinical, technical, or psychosocial reasons. **David J. Semple, PhD,** and colleagues conducted a retrospective cohort study to determine the early and late mortality of all patients in Australia and New Zealand who returned to in-center hemodialysis following home hemodialysis compared with patients who remained on home hemodialysis and those on in-center hemodialysis who were never on home hemodialysis. Results were reported in the *American Journal of Kidney Diseases* [2022;79(1):15-23].

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Print-only Content

Consumption of Coffee and Caffeine

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consumption), the Mendelian randomization (MR) design can strengthen the causal inference, according to researchers **Shuai Yuan, BMed, MMedSc,** and **Susanna C. Larsson, PhD.** The random allocation of effect allele in the MR design resembles the randomization process in randomized controlled trials, and the method can diminish reverse causation because genetic variants used to proxy the effect of the exposure cannot be modified by the onset and progression of the outcome.

The researchers conducted a MR study designed to examine the potential causal associations of coffee and caffeine consumption with the risk of kidney stones. Results of the study were reported in the *American Journal of Kidney Diseases* [2022;79(1):9-14].

MR analysis is an instrumental variable analysis using genetic variants as instrumental variables. The analysis is based on three important assumptions: (1) there should be robust associations between the genetic variants proposed as instrumental variables and the exposure; (2) the used genetic variants should not be associated with any confounders; and (3) the selected genetic variants should affect the risk of the outcome merely through the risk factor rather than via alternative pathways. The reported study was based on publicly available summary-level data from large genome-wide association studies and consortia.

A meta-analysis of four genome-wide association studies (GWAS) on coffee consumption with up to 375,833 individuals of European ancestry (~89% from the UK Biobank study) yielded 15 single-nucleotide polymorphisms (SNPs) associated with coffee consumption at the genome-wide significance level ($P < 5 \times 10^{-8}$).

Twelve independent SNPs were used as instrumental variables for coffee consumption. The effect sizes for the SNP-coffee associations were scaled to a 50% increase (an increase from 1 cup to 1.5 cups). A meta-analysis of six GWAS on caffeine consumption with 9876 individuals of European ancestry yielded two variants associated with caffeine consumption at $P < 5 \times 10^{-8}$. Summarized statistics for SNPs associated with caffeine consumption were derived from a GWAS on 4460 women and scaled to an 80-mg increase (equivalent to the caffeine dose from 1 cup of coffee). Responses on a self-reported questionnaire were used to measure caffeine consumption from coffee, tea, and cola consumption. Selected SNPs explained around 0.5% and up to 1.3% phenotypic variance on average for coffee and caffeine consumption, respectively.

Summary data from the UK Biobank study and the FinnGen consortium were used to determine associations of coffee- and caffeine-associated SNPs with kidney stones. In the UK Biobank, cases with kidney stones were identified by codes from the *International Classification of Diseases, Tenth Revision (ICD-10),* as well as codes from the Office of Population and Censuses Surveys, and self-reported operation codes. Following adjustment for sex, age, and the genotyping platform, GWAS was performed on 6536 cases and 388,508 controls of European ancestry. In FinnGen, cases were defined by N20 in *ICD-10* and 592 in *ICD-8* and *ICD-9*. The fourth release of the FinnGen consortium data was used with 3856 cases and 172,757 noncases, following removal of individuals with ambiguous gender, high genotype missingness (>5%), excess heterozygosity (±4 SD), and non-Finnish ancestry.

In the UK Biobank, the F statistic for the association for coffee consumption was 159. There was an inverse association between genetically predicted consumption of coffee and caffeine and a risk of kidney stones. In the FinnGen consortium, the associations were directionally similar.

Following meta-analysis of the two data sources, the odds ratio of kidney stone disease was 0.57 (95% confidence interval [CI], 0.39-0.82; *P*=.003) per genetically predicted 50% greater coffee consumption and 0.86 (95% CI, 0.77-0.96; *P*=.008) per genetically predicted 80-mg greater caffeine consumption. The combined odds ratio of kidney stones was 0.60 (95% CUI, 0.46-0.79; *P*<.001) per a genetically predicted 50% increase in coffee consumption and 0.81 (95% CI, 0.69-0.94; *P*=.005) per a genetically predicted 80-mg increase in caffeine consumption. In sensitivity analyses, the results for coffee consumption in relation to kidney stones remained constant.

In MR-Egger regression sensitivity analysis, there was mild heterogeneity but no evidence of pleiotropy (*P* for the intercept >0.2). In MR-PRESSO analyses, there were two outliers in the FinnGen consortium. Following removal of outliers, the association remained.

The researches cited some limitations to the study findings, including possible horizontal pleiotropy, meaning that genetic instruments influence risk of kidney stones not via coffee or caffeine consumption but via other pathways. However, the researchers noted, traits that are genetically correlated with coffee consumption, such as obesity and smoking, appear to increase risk of kidney stone disease, and are therefore unlikely to bias inverse associations between coffee consumption and formation of kidney stones. Daily fluid intake is another pleiotropic factor and it is likely to be positively correlated with coffee and caffeine consumption and inversely associated with risk of kidney stone disease. The genetic variants used for caffeine consumption are involved in caffeine metabolism and have been shown to be associated with caffeine metabolites in previous studies.

In conclusion, the authors said, "This MR study provides genetic evidence in support of causal inverse associations of coffee and caffeine consumption with kidney stones. Increasing coffee and caffeine consumption may be a prevention strategy for kidney stones." ■

TAKEAWAY POINTS

- Researchers conducted a Mendelian randomization analysis to examine the causal nature of associations between consumption of coffee and caffeine and lower risk of kidney stones.
- In the UK Biobank data analysis, genetically predicted coffee and caffeine consumption was associated with a lower risk of kidney stone disease.
- In analyses using data from the FinnGen consortium, the associations between coffee and caffeine consumption and the lower risk of kidney stones were directionally similar to those in the UK Biobank analysis.

CONFERENCE COVERAGE AMERICAN TRANSPLANT CONGRESS 2021

Treating Antibody-Mediated Rejection in Kidney Transplant Recipients

The optimal regimen for the treatment of acute and chronic antibody-mediated rejection (AMR) in kidney transplant recipients is unclear. **A. Al Jurdi** and colleagues conducted a single-center retrospective study to examine the outcomes among kidney transplant recipients with acute and chronic AMR who were managed with varying treatment regimens. Results of the study were reported during a virtual presentation at the 2021 American Transplant Congress. The presentation was titled *Outcomes of Kidney Transplant Recipients with Antibody-Mediated Allograft Rejection: A Retrospective Study.*

The study cohort included all kidney transplant recipients at the center with biopsy-proven acute or chronic AMR between January 2017 and September 2020. The primary outcome of interest was allograft loss at last follow-up. Secondary outcomes were differences in allograft survival between treatment regimens, and changes in estimated glomerular filtration rate (eGFR) and urine protein-creatinine ratio (UPCR) at last follow-up.

The study included 53 kidney transplant recipients with AMR. Mean age of the cohort was 51 years, and 50% were female. The most common cause of end-stage kidney disease was glomerular disease, and 57% received living donor kidney transplants. The median number of HLA ABDR mismatches was four, and 38% had pre-transplant donor-specific antibodies. Immunosuppression regimens were anti-thymocyte globulin (61%), basiliximab (35%), and alemtuzumab (4%). Thirty-five percent of participants had acute AMR and 65% had chronic-active AMR. At the time of biopsy, mean eGFR was 32 mL/min/1.73 m^2 and UPCR was 3.0 g/g.

Treatment regimens included pulse steroids (72%), intravenous immunoglobulin (64%), plasma exchange (51%), bortezomib (43%), and rituximab (4%). Some patients received more than one treatment.

At a median follow-up of 23 months, patient survival was 94% and death-censored allograft survival was 74%, mean eGFR was 28 mL/min/1.73 m^2, and UPCR was 0.96 g/g. The risk of allograft loss was greater in patients with UPCR >3 g/g at time of biopsy compared with patients with UPCR <3 g/g (relative risk [RR], 4.3; 95% confidence interval [CI], 1.6-11.6). There was no difference in the risk of allograft loss in patients who received plasmapheresis compared with those who did not (RR, 0.97; 95% CI, 0.4-2.4). There was also no significant difference in the risk of allograft loss among patients who received bortezomib than in those who did not (RR, 0.8; 95% CI, 0.3-2.0). The risk of allograft loss was similar in patients with chronic AMR compared with those with acute AMR (RR, 1.3; 95% CI, 0.5-3.6).

"Proteinuria above 3 g/day is associated with increased risk of allograft failure in patients with AMR. Use of plasmapheresis or bortezomib was not associated with lower risk of allograft failure in kidney transplant recipients with AMR. Novel treatment regimens are needed to improve the outcomes of kidney transplant recipients with acute and chronic AMR," the researchers said.

Source: Al Jurdi A, Goldfarb L, Lafargue M, Azzi A, Riella L V. Outcomes of kidney transplant recipients with anti-body mediated allograft rejection: A retrospective study. Abstract of a presentation at the virtual 2021 American Transplant Congress (Abstract 1025), June 5, 2021.

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Mortality Risk following Home Hemodialysis

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The study cohort included all patients in the Australia and New Zealand Dialysis and Transplant Registry who initiated hemodialysis during 2005-2015 and were treated for >90 days. The outcomes of interest were mortality and cause of death.

The cohort was stratified into four states: state 1, in-center hemodialysis, no home hemodialysis; state 2, first home hemodialysis episode; state 3, in-center hemodialysis, prior home hemodialysis; state 4, home hemodialysis, prior in-center hemodialysis and home hemodialysis. Individual patients moved between states over time but were only ever in one state at a time. Of the 19,158 patients initiating in-center hemodialysis (state 1), only 2309 transitioned to home hemodialysis.

The association between patient treatment states and mortality was examined using a time-varying multivariate Cox proportional hazards analysis with shared frailty. Patients were censored at the time of transplantation or change in treatment modality to peritoneal dialysis.

Of the 23,358 patients who initiated hemodialysis between 2005 and 2015, 19,306 remained alive on hemodialysis for >90 days. Median follow-up time was 2.2 years. At initiation of dialysis, mean age was 60.8 years, 62.1% were male, and nearly 49% had diabetes. Of the total cohort, 87% (n=16,752) never experienced home hemodialysis, and 13% (n=2554) received home hemodialysis during the study period. Of those 2554,2457 either moved from in-center hemodialysis to home hemodialysis (n=2309) or initiated home hemodialysis directly (n=148). An additional 97 patients transferred to home hemodialysis from transplant or peritoneal dialysis and were not included in the survival analysis.

Compared with the group who never experienced home hemodialysis, those who did were younger, more likely to be male, and more likely to be Maori or Pacific Islander. They were also more likely to have obesity (defend as body mass index >30 kg/m^2), more likely to have polycystic kidney disease or reflux as their primary kidney disease, and more frequently had an arteriovenous fistula as their first dialysis access. They were less likely to be a late referral to renal services, have major associated major comorbidities, or have an central catheter as first dialysis access.

Overall, 23.5% (n=577) of home hemodialysis patients transitioned from state 2 to state 3; of those 29.6% (n=171) then restarted home hemodialysis during the study period (state 4). Of the patients entering state 4, 61 subsequently transferred back to in-center home dialysis, when they were censored from the analysis.

During the 2.2 years of follow-up, 6972 patients died. The crude death rate was highest in state 1 (crude rate, 14.9 [95% confidence interval [CI], 14.5-15.2] per 100 patient years) and state 3 (14.4 [95% CI, 12.1-16.8] per 100 patient years) and lowest in state 2 (4.4 [95% CI, 3.9-5.0] per 100 patient years) and state 4 (5.9 [95% CI, 3.6-9.0] per 100 patient-years. During the first 30 days, 30 to 90 days, and >90 days, mortality rates in state 3 were 20.6 (95% CI, 9.9-37.9), 17.5 (95%CI, 9.8-28.8), and 13.6 (95% CI, 11.3-16.3) per 100 patient-years, respectively.

Results of both univariate and multivariate analyses demonstrated that home hemodialysis treatment failure (transition from home hemodialysis to in-center hemodialysis) was associated with an increased risk of death in the first 30 days (hazard ratio [HR], 3.93; 95% CI, 2.09-7.40; P<.001), between 30 and 90 days (HR, 3.34; 95% CI, 1.98-5.62; P<.001), and beyond 90 days (HR, 2.29; 95%cI, 1.84-2.85; P<.001)

> At initiation of dialysis, mean age was 60.8 years, 62.1% were male, and nearly 49% had diabetes.

Patient age, late referral, smoking status, cause of kidney failure, and the presence of major comorbidities (coronary artery disease, cerebrovascular disease, peripheral vascular disease, chronic lung disease, and diabetes) were also significant independent covariates for death. There were associations between Caucasian ethnicity and the use of an arteriovenous fistula for dialysis access and a reduced risk of death. Only patient age was associated with a similar magnitude of risk for mortality as home hemodialysis treatment failure.

During the study period, the most common causes of death were withdrawal from treatment (n=2500; 4.9 [95% CI, 4.7-5.1] per 100 person-years) and cardiovascular events (n=2246; 4.4 [95% CI, 4.2-4.6] per 100 person-years). Less common causes of death were infection, malignancy, and other causes.

The retrospective design of the study was cited as a limitation to the findings. The researchers also listed the lack of patient-level data on causes or intention of dialysis modality change or medical events before dialysis modality change as study limitations.

In conclusion, the researchers said, "Our study highlights high mortality rates in patients returning to in-center hemodialysis from home hemodialysis, at both early and late time points, and supports the need for further investigation into causes and implications of dialysis modality changes." ■

TAKEAWAY POINTS

- Researchers conducted a retrospective cohort study to assess the early and late mortality of patients utilizing home hemodialysis in Australia and New Zealand who returned to in-center hemodialysis compared with those who stayed on home hemodialysis and those who remained on in-center hemodialysis.
- Following home hemodialysis treatment failure, adjusted mortality was increased compared with continued home hemodialysis.
- The increased risk of mortality was seen in both early (first 30 days and 30-90 days) and late (beyond 90 days) periods after home hemodialysis failure.

Outcomes Vary In Peritoneal Dialysis- Related Peritonitis
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treatment, and peritonitis characteristics on the likelihood of a cure following an episode of peritonitis. Secondary objectives included exploration of the impact of those factors on individual peritonitis-related events, including death, removal of the peritoneal dialysis catheter, transfer to hemodialysis, and relapse/repeat peritonitis episode. Results were reported in the *American Journal of Kidney Diseases* [2022;79(1):45-55].

Compared with Gram-positive peritonitis, a nominally lower odds of cure was seen with culture-negative peritonitis. Gram-negative polymicrobial and fungal peritonitis all had significantly lower odds of cure.

TAKEAWAY POINTS

- Researchers analyzed data from the PDOPPS (Peritoneal Dialysis Outcomes and Practice Patterns Study) to determine the likelihood of cure after an episode of peritoneal dialysis-associated peritonitis.
- The analysis cohort included 1190 patients at 126 facilities in Australia, New Zealand, Canada, Japan, Thailand, the United Kingdom, and the United States.
- Outcomes varied by patient characteristics, peritonitis characteristics, and modifiable peritonitis treatment practices.

The analysis utilized mixed-effects logistic models to estimate associations (odds ratios [ORs], with 95% confidence interval [CI]) of peritonitis outcomes by organism category. Data from the United States, Australia, New Zealand, Canada, Japan, Thailand, and the United Kingdom were included.

During the study observation period of PDOPPS phase 1, from among 7075 sample peritoneal dialysis patients at 126 peritoneal facilities, 5440 patients did not experience peritonitis during follow-up, leaving 1635 patients. Following application of exclusion criteria, the final analysis cohort included 1190 patients who had at least one peritonitis episode (1631 peritonitis episodes in total). Median patient ages were 59 years in Thailand and the United States, 62 years in Canada, 65 years in the United Kingdom, and 67 years in Japan and Australia/New Zealand.

There were no differences in adjusted odds of cure by age (adjusted OR [aOR] per 5 years older, 1.00; 95% CI, 0.96-1.04), male sex (aOR, 0.80; 95% CI, 0.63-1.03), years on peritoneal dialysis (aOR per each additional year, 1.01; 95% CI, 0.95-1.07), or diabetes (aOR, 0.80; 95% CI, 0.63-1.01).

Overall, peritonitis cure was achieved in 65% of episodes (range, 66% to 68% in Japan, Canada, the United States, and Australia/New Zealand; 56% in the United Kingdom; and 54% in Thailand). There was, however, substantial variation across facilities in each country. Following adjustment for patient and facility characteristics, the between-country differences were not statistically significant (P=.1).

Compared with Gram-positive peritonitis, a nominally lower odds of cure was seen with culture-negative (aOR, 0.73; 95% CI, 0.54-1.01) peritonitis. Gram-negative (aOR, 0.41; 95% CI, 0.30-0.57), polymicrobial (aOR, 0.30; 95% CI, 0.20-0.47), and fungal (aOR, 0.01; 95% CI, 0.00-0.07) peritonitis all had significantly lower odds of cure.

SECONDARY OUTCOMES

Death within 50 days occurred in 6% of peritonitis episodes overall (Japan, 2%; Thailand, 15%; others, 4%-5%). Relapsing/recurring peritonitis occurred in 9% of episodes overall (range, 8%-14%), removal of peritoneal catheter in 21% of episodes overall (United Kingdom, 30%; others, 17%-24%), and transfer to hemodialysis in 16% of episodes overall (Thailand, 10%, others, 15%-19%).

In general, compared with Gram-positive peritonitis, fungal peritonitis was associated with a higher risk of death (aOR, 8.32; 95% CI, 2.94-23.57), transfer to hemodialysis (aOR, 15.05; 95% CI, 6.88-32.92), and removal of peritoneal dialysis catheter (aOR, 92.46; 95% CI, 26.22-325.99). Compared with Gram-positive peritonitis, the aOR for death, transfer to hemodialysis, and removal of peritoneal dialysis catheter was also elevated for Gram-negative peritonitis and polymicrobial peritonitis.

There was an association between use of automated peritoneal dialysis and a greater likelihood of cure (aOR, 1.36; 95% CI, 1.02-1.82) when compared with continuous ambulatory peritoneal dialysis; the association remained after removal of Thailand (where use of continuous ambulatory peritoneal dialysis is nearly uniform) from the analysis (aOR, 1.38; 95% CI, 1.03-1.85). The odds of cure were also higher in facilities with greater icodextrin use (aOR per 10% greater icodextrin use, 1.06; 95% CI, 1.01-1.12), and with the same OR seen in analyses excluding Thailand where there is no use of icodextrin. Empirical aminoglycoside use (aOR, 3.95; 95% CI, 1.23-12.68), and ciprofloxacin use versus ceftazidime use for Gram-Negative peritonitis (aOR, 5.73; 95% CI, 1.07-30.61) also resulted in higher odds of cure.

There were associations between prior peritonitis episodes (aOR, 0.85; 95% CI, 0.74-0.99) and concomitant exit-site infection (aOR, 0.41; 95% CI, 0.26-0.64) and lower odds of cure.

Study limitations cited by the authors included the possibility of biased sample selection and limiting of the generalizability of the findings; the use of facility-level treatment variables may not have captured patient-level treatments.

In conclusion, the researchers said, "We have described regional differences in peritonitis outcomes across seven participating countries enrolled in the PDOPPS and have identified potentially modifiable practices that may impact peritonitis cure and adverse events. The high hemodialysis transfer in all countries suggests that novel interventions to prevent and treat peritonitis are needed. Given that outcomes are mostly related to the microbiology of peritonitis, better organism identification methods and more tailored treatment strategies that are organism specific may help reduce the morbidity associated with peritonitis. The association of aminoglycosides with higher cure rates for Gram-negative peritonitis warrants further investigation." ■

CONFERENCE COVERAGE **AMERICAN TRANSPLANT CONGRESS 2021**

Intrarenal Immune Response to BKV Infected Cells

BK-virus associated nephropathy (BKVAN) is associated with acute renal allograft injury as well as chronic allograft disease and, in some patients, allograft failure. The intrarenal mechanisms involved in the resolution of BKVAN are not well understood at present. **D. M. Okamura** and colleagues conducted a study aimed at investigating the intrarenal immune responses to BKV infected tubular cells. Results were reported during a virtual session at the American Transplant Congress in a presentation titled *Dissecting the Intrarenal Immune Response to Viral Infected Cells in Pediatric BK Virus-Associated Nephropathy (BKVAN).*

The study included three pediatric patients who were diagnosed with BKVAN: one with progressive BKVAN leading to graft failure and two with resolution of BK viremia, but with either new donor-specific antibodies or new interstitial fibrosis/tubular atrophy. Each patient had a biopsy prior to the BKVAN diagnosis: two normal and one with Banff 1A rejection. Regions of interest with BK polyoma infected tubular cells in BKVAN biopsy samples were identified and compared with normal tubular regions of interest from baseline biopsy, n=8-12 regions of interest per biopsy.

Results of digital spatial profiling revealed upregulated proteins with significant differences between normal (n=24), rejection (n=12), and BKVAN biopsy groups (n=32) (P<.0001). CD8 levels were approximately 13 times higher in BKVAN compared with normal. There was a significant, 7.8-fold increase in CK20 levels that distinguished BKVAN from normal and rejection kidneys (P<.0001). In addition, activated macrophage markers such as CD44 and CD68 distinguished BKVAN from normal kidneys (P<.0001 and P=.002, respectively), and were associated with progressive BKVAN (P<.01).

In conclusion, the researchers said, "Although this study is limited by the low number of patients, it more accurately represents the intrarenal immune microenvironment of BK infected tubular cells compared to whole tissue investigations and needs further study. These results represent the first step to devise improved treatment strategies."

Source: Okamura D.M., Jackson S. W., Dharnidharka V. R., Smith J. M. Dissecting the intrarenal immune response to viral infected cells in pediatric BK virus-associated nephropathy (BKVAN). Abstract of a presentation at the virtual 2021 ANNA National Symposium (Abstract 806), June 5, 2021.

Tolvaptan Patients with ADPKD: Post Hoc Analysis of the TEMPO 3:4 Trial

The principal function of vasopressin is decreasing urinary output. The effects of vasopressin are facilitated by the V1a, V1b, and V2 receptors. The V2 receptor is responsible for the antidiuretic effect and is activated by a minimal change in vasopressin signal. The V1a receptor is responsible for vasoconstriction and requires higher vasopressin levels.

Activation of the V2 receptor is crucial for water hemostasis, but can also be harmful in various kidney disorders, including autosomal dominant polycystic kidney disease (ADPKD). Patients with ADPKD are treated with tolvaptan, a selective V2 receptor antagonist, which has been shown to slow the rate of disease progression in patients at risk of rapid decline in kidney function.

According to **Judith E. Heida, MD,** and colleagues, tolvaptan could theoretically have effects on blood pressure, including an increase in vascular resistance via increase V1a receptor activation and a resulting increase in blood pressure. Conversely, preventing vasopressin binding to the V2 receptor could result in a decrease in blood pressure. In the long-term, tolvaptan ameliorates the rate of disease progression, and may reduce the development of secondary symptoms of kidney disease, including hypertension.

The researchers conducted a post hoc analysis of data from the TEMPO 3:4 trial to examine the magnitude and time course of the effect of tolvaptan on blood pressure expressed as a continuous variable, taking into account measured values as well as use of blood pressure-lowering medication. Results of the analysis were reported in the *Journal of the American Society of Nephrology* [2021;32(7):1801-1812].

The TEMPO 3:4 trial was a prospective, multicenter, double-blind, randomized, controlled trial assessing the efficacy of tolvaptan in patients with early-stage ADPKD. The trial included 1445 patients with ADPKD who were randomized 2:1 to tolvaptan or placebo for 3 years. The post hoc analysis included evaluations of systolic and diastolic blood pressure, mean arterial pressure, hypertension status, and use and dosing of antihypertensive drugs over the course of the trial.

Of the 1445 patients, 916 were randomized to tolvaptan and 484 to placebo. The two groups were similar in baseline characteristics. Baseline blood pressures were comparable in the two study arms: 129 mm Hg systolic and 82.5 mm Hg diastolic blood pressure in the tolvaptan arm; 128 mm Hg systolic blood pressure and 82.4 mm Hg diastolic blood pressure in the placebo arm. In the tolvaptan arm, 81% of patients had hypertension compared with 84% in the placebo arm. In both study arms, 77% of patients were taking antihypertensive medications at baseline; the majority of medications were renin-angiotensin-aldosterone system (RAAS) inhibitors. The two arms were similar in dosages of the antihypertensives.

In patients with normotension at baseline, there was no difference between the two arms in baseline blood pressure, although body mass index in patients in the tolvaptan arm (n=179) was significantly higher than in patients in that subgroup of the control arm (n=79). Patients in the tolvaptan arm also used a cholesterol-lowering drug more often and had a higher height-adjusted total kidney volume than those in the control arm. Among patients with hypertension at baseline, there were no significant differences in blood pressure or other baseline characteristics between the tolvaptan arm (n=782) and the control arm (n=405).

Following 3 weeks of study treatment, copeptin was significantly higher in the tolvaptan arm than in the control arm. There were no significant differences between the two arms in patient characteristics related to blood pressure, including systolic and diastolic blood pressure or number and dose of antihypertensive drugs. Tolvaptan use resulted in a decrease in mean body weight from 79.7 kg to 78.8 kg and an increase in mean plasma sodium from 140.4 mmol/L to 142.6 mmol/L, suggesting a decrease in circulating volume. There were significant associations between changes in copeptin levels and the changes in body weight (R=0.08; P=.02) and plasma sodium (R=0.16; P<.001), but not with blood pressure. In the placebo arm, there was a significant increase in weight (P=.007) and plasma sodium remained stable (P=.85).

Over time, a small difference in blood pressure between the two arms occurred: a significant decrease in systolic blood pressure after 28 months and in diastolic blood pressure after 32 months. At the end of the study period, both systolic and diastolic blood pressure were lower in the tolvaptan arm than in the control arm (systolic blood pressure, 126 vs 129 mm Hg, respectively, P=.002 and diastolic blood pressure, 81.2 vs 82.6 mm Hg, respectively, P=.01). Average number of antihypertensive drugs was given at a similar dose in the two arms. After 28 months of treatment, average mean arterial pressure was also significantly lower in the tolvaptan arm than in the control arm (99.7 vs 100.9 mm Hg, respectively; P=.04).

After long-term use of tolvaptan, approximately 3 weeks after withdrawal of study medication, data were available for 734 patients in the tolvaptan arm and 407 patients in the control arm. Differences that were observed at month 36 had leveled off between the two study arms. In the tolvaptan arm, there was a significant increase in systolic blood pressure from 125 to 127 mm Hg (P<.001) as well as in diastolic blood pressure (from 80.4 to 81.0 mm Hg; P=.04). The number and dose of antihypertensive medications used in the two arms remained similar. There was no change in the placebo arm in systolic blood pressure or diastolic blood pressure.

The authors acknowledged some limitations to the study including the post hoc design, the possibility of variability in outcomes due to differences in choice of blood pressure therapy, blood pressure being measured during outpatient clinic visits rather than at home, and not measuring vasopressin directly.

In conclusion, the researchers said, "This study demonstrates that start of tolvaptan treatment in patients with ADPKD does not have a clinically significant long-term effect on blood pressure, perhaps due to simultaneously occurring blood pressure-increasing and blood pressure-lowering effects that cancel out. During prolonged use, however, gradually blood pressure becomes lower in patients on tolvaptan compared with patients on placebo. This observation can likely be attributed to a sustained natriuretic effect, possibly in combination with the beneficial effect of tolvaptan on disease progression. When after 3 years of treatment, tolvaptan is stopped, there is an increase in blood pressure in tolvaptan-treated patients up to a level that is again similar to that of the placebo-treated subjects. This increase is likely caused by the sudden recovery of the V2-mediated antidiureris and sodium reabsorption, resulting in an excess of circulating volume. This acute effect of stopping tolvaptan is expected to disappear in the long term." ■

The TEMPO 3:4 trial was funded by Otsuka Pharmaceutical and Otsuka Pharmaceutical Development and Commercialization, Inc. (Rockville, Maryland).

TAKEAWAY POINTS

- Researchers reported results of a post hoc analysis of data from the TEMPO 3:4 trial to examine the magnitude and time course of the effect of tolvaptan use on blood pressure in patients with autosomal dominant polycystic kidney disease.
- TEMPO 3:4 included two arms: patients receiving tolvaptan (n=916) and patients receiving a placebo (control, n=484). Baseline blood pressure was similar in the two arms.
- After 3 years of treatment, mean systolic and diastolic blood pressure were significantly lower in the tolvaptan arm than in the control arm; at 3 weeks after discontinuation of the study medication, the differences leveled off.

Burden of Financial Hardship Associated with CKD

In the United States, approximately 37 million adults are affected by chronic kidney disease (CKD), and are at increased risk for morbidity and mortality. The prevalence of CKD is expected to increase in The United States in the coming years due to an aging population and a rise in the prevalence of risk factors for CKD, including hypertension, diabetes, and obesity.

Patients, families, and the healthcare system incur a substantial burden associated with CKD. In 2017 annual Medicare spending related to CKD, including kidney failure requiring kidney replacement therapy, was more than $120 billion; advancing CKD severity was associated with escalating costs. In 2019, individuals with CKD constituted 9.8% of the Medicare population but contributed 27.6% of the cost. While those costs cannot be attributed solely to CKD, due to the interaction with other chronic conditions such as hypertension and diabetes, there remains a high economic burden associated with CKD.

According to **Isaac Acquah, MD, MPH,** and colleagues, there are few data available on the extent of the burden and determinants of financial hardship associated with CKD. The researchers conducted a cross-sectional study in a large, nationally representative sample of nonelderly adults with CKD to examine the extent of financial hardship from medical bills and the association of the financial hardship with major sociodemographic and clinical predictors. Results of the study were reported in the *American Journal of Kidney Diseases* [2021;78(5):658-668].

The study cohort included nonelderly adults with CKD identified from the 2014-2018 National Health Interview Survey (NHIS). The outcomes of interest were financial hardship based on medical bills and the consequences of financial hardship, including high financial distress, food insecurity, cost-related medication nonadherence, and delayed or forgone care due to cost. Financial hardship was categorized into three levels: (1) no financial hardship; (2) financial hardship but able to pay bills; and (3) financial hardship and unable to pay bills. The researchers modeled financial hardship two ways: (1) any financial hardship regardless of ability to pay versus no financial hardship and (2) inability to pay bills versus no financial hardship and financial hardship but able to pay bills.

The associations of sociodemographic and clinical factors with the outcomes of financial hardship based on medical bills were examined using multivariable logistic regression models. Nationally representative estimates of financial hardship were computed using medical bills.

The final study sample included 1425 individuals with CKD, accounting for 1.1% of the total nonelderly (<65 years of age) population not covered by Medicare in the NHIS, and representing approximately 2.1 million adults with CKD annually. Mean age of the study cohort was 48.6 years, approximately 50% lived in a low-income household (representing an estimated 970,000 Americans), 43.3% had private insurance coverage (representing nearly 890,000 individuals), 36.1% had Medicaid coverage (representing ~740,000 individuals), and 12.3% were uninsured (representing ~250,000).

Annually, financial hardship from medical bills was reported by 46.9% (95% confidence interval [CI], 43.7%-50.2%) of the study population (representing an estimated 964,000 nonelderly adults with CKD). Inability to pay medical bills at all was reported by 20.9% (95% CI, 18.5%-23.6%) (representing an estimated 430,000). The prevalence of inability of pay medical bills at all was highest in those from low-income households (26.4% vs 15.6% in middle/high-income households; $P<.001$) and in the uninsured (50.2% vs 15.1% for those with private insurance; $P<.001$).

The nonelderly adults with CKD who experienced financial hardship from medical bills were mostly older, non-Hispanic White females, pertaining to larger families, who were insured, had a suboptimal cardiovascular risk factor profile, and a higher comorbidity count.

Independent predictors of financial hardship were identified in multivariable analyses. The lack of insurance was most strongly associated with any financial hardship from medical bills (odds ratio [OR], 4.06; 95% CI, 2.18-7.56; referent: private insurance). There were associations between higher odds of financial hardship from medical bills and suboptimal cardiovascular risk factor profile (poor cardiovascular risk factor profile: OR, 1.87; 95% CI, 1.19-2.95; average profile: OR, 1.63; 95% CI, 1.06-2.51; referent: optimal profile) and a higher comorbidity count (one comorbid condition: OR, 1.73; 95% CI, 1.14-2.63; two or more comorbid conditions: OR, 1.68; 95% CI, 1.10-2.58; referent: zero comorbid conditions).

The strongest predictor of inability to pay medical bills at all was the lack of insurance (OR, 4.63; 95% CI, 2.59-8.29: referent: private insurance). There were also associations between low household income (OR, 1.85; 95% CI, 1.14-3.01) and high comorbidity count (one comorbid condition: OR. 1.94; 95% CI, 1.16-3.25; two or more comorbid conditions: OR, 2.10; 95% CI, 1.33-3.33; referent: zero comorbid conditions) and higher odds of inability to pay medical bills at all.

There was a graded increase in high financial distress (48.7% and 74.9% vs 31.5%; $P<.001$), cost-related medication adherence (30.9% and 48.0% vs 7.4%; $P<.001$), and delayed/forgone medical care due to cost (9.8% and 16.5% vs 4.1%; $P<.001$) by financial hardship status (financial hardship but able to pay and unable to pay, respectively, vs no financial hardship).

Following adjustment for possible confounders, those with CKD who experienced financial hardship from medical bills but were able to pay had higher odds of high financial distress (OR, 2.68; 95% CI, 1.84-3.91), cost-related medication nonadherence (OR, 5.94; 95% CI, 3.48-10.14), and forgone/delayed medical care due to cost (OR, 2.18; 95% CI, 1.11-4.30) compared with individuals without financial hardship from medical bills. For those with inability to pay medical bills, that relationship was stronger.

In citing limitations to the study findings, the authors included use of a self-reported definition of CKD, basing the definition of financial hardship on survey data, the inability to establish causality due to the cross-sectional design, and the possibility of residual confounding.

In conclusion, the researchers said, "Nonelderly adults with CKD have a high prevalence of financial hardship from medical bills and its consequences. Lack of insurance may be a strong determinant of financial hardship from medical bills. Our findings highlight the need for further examination of financial hardship in this population using additional study designs, including evidence from prospective studies. Future efforts must focus on exploring financial hardship in both early and advanced CKD, as well as the temporal relationship between CKD and financial hardship. Our results may inform policy-making to improve existing financial coverage for CKD treatment in order to reduce the burden of financial hardship in the nonelderly population." ■

TAKEAWAY POINTS

- Researchers conducted a cross-sectional study to examine financial hardship due to medical bills among nonelderly adults with chronic kidney disease.
- Results of the study suggest that one in two nonelderly adults with CKD in the United States either have difficulty paying their medical bills or cannot pay them at all.
- Those without insurance coverage were more likely to report financial hardship due to medical bills; however, those with insurance also faced that challenge.

Optimal FBG levels and Progression of Diabetic Kidney Disease

Worldwide, the prevalence of end-stage kidney disease (ESKD) is increasing; the leading cause of ESKD is diabetes. The incidence of diabetic kidney disease has been shown to decrease with decreases in blood glucose levels in patients with diabetes. However, according to **Hae Hyuk Jung, MD, PhD,** there are few data available on the optimal blood glucose target associated with slowed progression of diabetic kidney disease.

Dr. Jung conducted a retrospective cohort study to examine the appropriate on-treatment glycemic levels associated with slowing diabetic kidney disease progression. Results were reported online in *JAMA Network Open* [doi:10.1001/jamanetworkopen.2021.27387].

The study exposure was on-treatment fasting blood glucose (FBG) level. The primary outcome of interest was a composite of doubling of serum creatinine, ESKD, or death from chronic kidney disease (CKD).

The study was conducted among retrospective cohorts generated from data from the National Health Information Database in Korea; patients with CKD were identified from a cohort of adults 40 to 74 years of age in the nationwide health screening survey in 2009 or 2010, when the survey initially included data on serum creatinine.

> The primary outcome of interest was a composite of doubling of serum creatinine, end-stage kidney disease, or death from chronic kidney disease.

Following application of inclusion and exclusion criteria, the study cohort included 183,049 participants using antihyperglycemic agents; mean age was 61.7 years and 54.1% (n=99,110) were men. Of those, 131,401 individuals had CKD (mean age, 62.4 years; 54.2% men [n=71,280], and 51,648 individuals without CKD (mean age, 59.6 years; 53.9% [n=27,830] men). Among the 183,049 participants, 72,268 had CKD with dipstick albuminuria, 74,717 had estimated glomerular filtration rate (eGFR) of 15 to less than 60 mL/min/1.73 m^2, and 64,861 were from the general population.

The distribution of follow-up FBG levels was widespread. The rate of inadequately decreased FBG level was higher among participants in the albuminuria group, and the rate of excessively decreased FBG level was higher in the population with decreased eGFR, compared with the general population.

During 9 years of follow-up, the primary composite outcome of major kidney events was found in 15.4% (n=11,120) of participants in the albuminuria population, 10.8% (n=8048) in the decreased eGFR population, and 4.3% (n=2787) in the general population.

Overall, on-treatment FBG level had a J-shaped cure for hazard ratios of major kidney events; the HR was lowest at FBG levels between 110 mg/dL and 160 mg/dL. In the albuminuria population, there was an association between FBG levels of 126 mg/dL to less than 140 mg/dL (HR, 0.87; 95% confidence interval [CI], 0.81-0.94) and 140 mg/dL to less than 160 mg/dL (HR, 0.90; 95% CI, 0.84-0.96) and decreased risk of the composite outcome. Levels of 160 mg/dL to less than 180 mg/dL were associated with increased risk (HR, 1.10; 95% CI, 1.03-1.18) compared with FBG levels of 110 mg/dL to less than 126 mg/dL.

In the decreased eGFR population, there were associations with FBG levels of 80 mg/dL to less than 100 mg/dL (HR, 1.30; 95% CI, 1.20-1.42) and levels of 160 mg/dL to less than 180 mg/dL (HR, 1.13; 95% CI, 1.04-1.23) and increased risk of the primary composite outcome compared with levels of 110 mg/dL to less than 126 mg/dL.

Among patients without CKD, FBG levels of 80 mg/dL to less than 100 mg/dL (HR, 1.29; 95% CI, 1.01-1.65) and levels of 126 mg/dL to less than 140 mg/dL (HR, 1.23; 95% CI, 1.03-1.47) were associated with increased risk compared with FBG levels of 110 mg/dL to less than 126 mg/dL.

In patients without albuminuria at baseline, there were associations between FBG levels of 140 mg/dL to less than 160 mg/dL (HR, 1.14; 985% CI, 1.09-1.20) and increased risk of new-onset albuminuria. There were no associations between levels of 100 mg/dL to less than 110 mg/dL compared with FBG levels of 110 mg/dL to less than 126 mg/dL.

In analyses of all-cause mortality, levels of FBG of 160 mg/dL to less than 180 mg/dL (HR, 1.20; 95% CI, 1.12-1.28) were associated with increased risk among patients with albuminuria, and FBG levels of 140 mg/dL to less than 160 mg/dL were associated with increased risk among patients with decreased eGFR (HR, 1.10; 95% CI, 1.04-1.16) and among those with no CKD (HR, 1.10; 95% CI, 1.00-1.21) compared with levels of 110 mg/dL to less than 126 mg/dL.

Limitations to the study findings included the lack of data on hemoglobin A1c necessitating use of FBG level only to assess glycemic status, not distinguishing between type 1 and type 2 diabetes, and limiting the study population to Korean adults 40 to 74 years of age with no known cardiovascular or cancer disease, possibly limiting the generalizability of the findings to other populations.

In conclusion, Dr. Jung said, "This study's findings suggest that timely blood glucose control is important for preventing diabetic kidney disease and that intensive versus standard glycemic control may not be associated with greater protection for the progression of established diabetic kidney disease. An individualized and comprehensive approach is necessary for treating patients with diabetes and CKD. Nonetheless, careful glycemic control may still be associated with decreasing overall health risks among patients with CKD, particularly those with no albuminuria." ■

TAKEAWAY POINTS

- Results of a Korean study designed to examine the optimal on-treatment glycemic levels associated with slowing progression of diabetic kidney disease.
- Among participants with albuminuria, there was an association between a fasting blood glucose (FBG) level of 126 mg/dL to less than 140 mg/dL and 140 mg/dL to less than 160 mg/dL and decreased risk of the composite outcome of serum creatinine doubling, end-stage kidney disease, or death from chronic kidney disease.
- In patients without albuminuria at baseline, there were associations between FBG levels of 140 mg/dL to less than 160 mg/dL (HR, 1.14; 985% CI, 1.09-1.20) and increased risk of new-onset albuminuria.

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Models to Predict Risk after Acute Kidney Injury

Among the one in seven hospitalized patients who develop acute kidney injury (AKI) during hospital admission, many continue to experience poor health outcomes following discharge, including a one in three risk of unplanned readmission within 90 days, as well as incomplete recovery of kidney function associated with new or progressive chronic kidney disease during the year after the initial discharge. There are few data available on which discharged hospital patients should receive follow-up care after AKI and for which reasons.

Current guidelines recommend follow-up of all individuals with AKI after 90 days. According to **Simon Sawhney, MBChB, PhD,** and colleagues, for some patients, an early period of increased surveillance and care may be beneficial; for others, additional monitoring and follow-up interventions may not be of benefit and may unnecessarily increase healthcare costs.

Two risk prediction models for outcomes of AKI after hospital discharge have been developed recently. The Grampian- Aberdeen (United Kingdom) tool predicts death or hospital readmission for all individuals (with and without AKI) in the early postdischarge period. The model, that includes AKI as a key predictor, could be used by primary care physicians to target those who may benefit from early surveillance. A second focused risk prediction model, Alberta (Canada), has been developed to predict the risk of progression to new CKD glomerular filtration rate (GFR) categories 4 and 5 (G4-G5) among survivors of AKI and can be used to identify patients who would benefit from referral to a nephrologist.

Dr. Sawhney et al. conducted a validation study of the two risk models of AKI outcomes to compare the net benefit of risk model-based clinical decisions following AKI. The outcomes of interest were death or readmission within 90 days for all hospital survivors, and progression to new CKD G4-G5 for patients who survived at least 90 days following AKI. Results were reported in the *American Journal of Kidney Diseases* [2021;78(1):28-37].

In both cohorts, AKI was defined and staged for severity using Kidney Disease Improving Global Outcomes (KDIGO) AKI criteria. The Aberdeen readmissions model established AKI using a validated KDIGO-based algorithm: AKI was present if there was (1) an increase in creatinine of >0.3 mg/dL within 48 hours; or (2) a 50% rise from the lowest creatinine in the past 7 days; or (3) a 50% rise from the median creatinine in the past 8-90 days, or 91-3265 days if no closer samples existed. In the Alberta CKD G4-G5 model, AKI was established based on a rise in creatinine during hospitalization of >0.3 mg/dL or >50% of the most recent outpatient prehospital baseline 7-365 days prior to admission.

The Aberdeen death or readmissions model was temporally validated in a cohort of all adult Grampian, North Scotland, residents admitted to hospital in Grampian in 2012 (with or without AKI). The Alberta CKD G4-G5 model was geographically validated using all adult Grampian residents admitted to hospital with AKI between 2011-2013 who had a baseline estimated GFR >45 mL/min/1.73 m^2 and survived at least 90 days postdischarge.

The validation cohort for the Aberdeen death or readmissions model included 26,575 individuals (mean age, 66.1 years) and 2927 events. The validation cohort for the Alberta CKD G4-G5 model included 9382 individuals (mean age, 60.9 years) and 140 events.

Both models discriminated well in the external validation cohorts: area under the curve (AUC) of 0.77 for the Aberdeen death or readmissions model and AUC of 0.86 for the Alberta G4-G5 model. In both models, risks were overpredicted; following recalibration, that measure improved. The odds ratios were similar for refitted models with the exception of albuminuria in the CKD G4-G5 model, for which an unmeasured value of albuminuria had a protective effect in the external validation cohort.

For predicting death or readmission among all hospital survivors using the Aberdeen model, there was a positive net benefit of follow-up of those with AKI; a model-guided approach led to the greatest net benefit at the relevant risk thresholds. In decision curve analysis of the net benefit for predicting death or readmission where the analysis was restricted to people with AKI, the greatest net benefit occured by following the risk model, with limited benefit or potential net harm from following only those with severe AKI.

For predicting CKD G4-G5 progression at 1 year using the Alberta model among those who survived to hospital discharge, a model-guided approach provided a small gain in net benefit that remained superior to a strategy guided by discharge eGFR <30 mL/min/1.73 m^2 at the prespecified 10% risk threshold. The superiority of a model-guided approach was consistent for both models regardless of whether the original, recalibrated, or refitted model was used.

In process mining of all hospital discharges, of the 105,461 individuals discharged from a hospital admission in Grampian between 2011-2014, 9% (n=9220) died or were readmitted within 90 days. Of the 9220, 41% (n=3776) were recovering after an episode of AKI.

Of 13,232 individuals discharged after AKI, 29% (n=3776) were readmitted or died within 90 days. Most of the monitoring of kidney function between 30 and 90 days postdischarge was conducted in primary care. An additional 10% (1369/13,232) patients were assessed in an outpatient specialty clinic within 90 days, and 10% (1325/13.232) attended an emergency department. A lack of any postdischarge monitoring between discharge and readmission was evident in 42% (1101/2401) of deaths/readmissions within 30 days, and 39% (1464/3776) of deaths or readmission within 90 days after AKI. Median times to the unmonitored adverse outcomes were 9 and 13 days.

In citing limitations, the researchers noted that both original models overstated risks, indicating the need for regular updating.

In conclusion, the authors said, "We have shown that risk prediction models for death or readmission and CKD have the potential to assist in prioritizing people who have had AKI within follow-up care planning and may be superior to alternative strategies such as prioritizing on AKI severity or kidney recovery alone. Further, many people with poor outcomes after AKI receive little or no postdischarge monitoring. A necessary next step is to design and trial risk model-assisted decisions that triage people into appropriate models of postdischarge care that provide the most appropriate level of specialist/nonspecialist input at the most appropriate timepoint." ■

TAKEAWAY POINTS

- There are few data available to guide prioritizing care following hospital discharge among patients who experiences acute kidney injury (AKI) during the hospital stay.
- Results of an external validation of two risk models for outcomes following AKI were reported. The models were the Grampian-Aberdeen readmission model and the Alberta model that predicts the risk of progression to chronic kidney disease stage 4-5.
- Both models provided net benefit superior to any other decision strategy.

Mortality and Pediatric Peritoneal Dialysis

Children with kidney failure are commonly treated with maintenance peritoneal dialysis, performed at home by the patient's adult caregivers. Peritoneal dialysis is the preferred modality in children due to its applicability across the pediatric age range and compatibility with schooling and social life. However, according to **Sophie Ploos van Amstel, MD,** and colleagues, the successful implementation of maintenance peritoneal dialysis is a challenging therapy, one that is subject to significant patient morbidity and mortality.

To date, research on pediatric kidney replacement therapy (KRT) has focused primarily on Europe and North America. Survival rates appear to have improved over the past 30 years, yet annual mortality rates for children on dialysis are at least 30 times higher than in the general population. Five-year patient survival for pediatric dialysis patients is ~84% in North America and ~90% in Europe.

The International Pediatric Peritoneal Dialysis Network (IPPN) collects patient outcome data and comprehensive clinical, biochemical, and treatment information from a large cohort of children undergoing maintenance peritoneal dialysis worldwide. Results of previous studies based on the IPPN database have identified associations of patient survival with clinical and laboratory findings, and with macroeconomic factors. The researchers in the current study used IPPN data to describe (1) the current global and regional mortality risk of children treated with maintenance peritoneal dialysis, (2) the main causes of death, and (3) the macroeconomic factors that are associated with mortality risk and/or the distribution of death causes around the globe. Results were reported in the *American Journal of Kidney Diseases* [2021;78(3):380-390].

The prospective cohort study included patients who were <19 years of age at inclusion into the IPPN registry who initiated maintenance peritoneal dialysis between 1996 and 2017. The primary exposure of interest was region (Asia, Western Europe, Eastern Europe, Latin America, North America, and Oceania). The primary outcome of interest was all-cause maintenance peritoneal mortality.

The researchers also examined other demographic, clinical, and macroeconomic factors. They divided countries into four income groups based on gross national income (GNI): low income (<$12,000), lower-middle income ($12,000 to <$16,000), upper-middle income ($16,000 to <$45,000), and high-income (≥$45,000).

Patients were observed for 3 years and the mortality rates in the regions and income groups were calculated. Cause-specific hazards models with random effects were fit to calculate the proportional change in variance for factors that could explain variation in mortality rates.

The study included 2956 patients. Most Asian countries (56.4%) fell in the lowest GNI quartile; Latin American countries tended to have a slightly higher GNI. All countries in Western Europe fell in the higher GNI quartiles; Eastern European countries clustered within the middle quartiles. All countries in North America were classified as having a high GNI.

Median age at initiation of KRT was 7.8 years and varied between 4.9 years in Western Europe and 9.3 years in Asia. Median age at inclusion in the IPPN was 8.3 years, ranging from 5.3 years in Western Europe to 9.8 years in North America. In general, patients treated in Europe were younger than those in Asia and North America ($P<.001$).

CAKUT (congenital anomalies of the kidney and urinary tract) was the most frequent primary kidney disorder (46.2%), followed by glomerulopathies (27.6%). Percentages of patients with a defined syndrome were higher in North America and Eastern Europe (17.7% and 17.6%, respectively), compared with other regions. Confirmed genetic disorders were significantly less common in Latin America (4.1% vs 12.4% overall). The more frequent comorbidities were cardiac abnormalities (14.1%), cognitive dysfunction (13.8%), and motor dysfunction (11.7%). The percentages of all comorbidities, with the exception of hearing dysfunction, were markedly higher in North America ($P<.001$).

Overall, approximately one-third of patients had received KRT prior to initiating their current maintenance peritoneal dialysis treatment. Of those, 20.1% had received a kidney transplant and 79.9% had undergone dialysis treatment (hemodialysis, previous peritoneal dialysis, or both). Time on KRT prior to inclusion in the IPPN Registry was a median 3.0 months. On registry entry, the majority of patients were treated with automated peritoneal dialysis (75.7%), followed by continuous ambulatory peritoneal dialysis (23.5%), and other peritoneal dialysis treatment (1.6%). There were significant differences in the distribution of peritoneal dialysis among regions ($P<.001$); the percentage of automated peritoneal dialysis was highest in North America (95.1%).

Oceania was excluded from the survival analyses due to limited number of patients. Median follow-up duration in the IPPN Registry was 1.68 years. During follow-up, maintenance peritoneal dialysis was stopped in 1969 patients, of whom 9% (n=177) died. Other reasons for stopping maintenance peritoneal dialysis were kidney transplantation, switch to hemodialysis, and loss to follow-up assessment.

The mortality rate in North America was significantly lower than in other regions. Following adjustment for region, mortality rates were highest in low-income countries, followed by the lower-middle-income countries.

After 3 years, the probability of death in the overall cohort was 5%, ranging from 2% in North America to 9% in Eastern Europe. Results of analysis by GNI quartile demonstrated that after 3 years of follow-up assessment, patients in countries with a low GNI tended to have a higher mortality risk and a lower probability of receiving a kidney transplant.

The variance among regions was examined using cause-specific hazards models with random effects. Results demonstrated that country differences in GNI explained 50.1%, choice of modality explained 22.5%, and body mass index explained 11.1% of the variance. Other minor factors included KRT vintage (9.3%) and sex (2.4%).

Limitations to the study cited by the authors included the possibility of problems with the accuracy and quality of the data in the IPPN Registry, and the possibility of selection bias.

In conclusion, the researchers said, "This study shows that the overall 3-year patient survival on pediatric maintenance peritoneal dialysis is high, and that country income is associated with patient survival. On the other hand, the interpretation of interregional survival differences as found in this study remains complicated due to selection bias working in different directions. To reduce such bias, population-based registries are warranted." ■

TAKEAWAY POINTS

- Researchers reported results of a study examining the mortality risk of children on maintenance peritoneal dialysis worldwide, as well as factors associated with patient survival.
- At 3-years of assessment, the probability of mortality in the overall cohort was 5%, ranging from 2% in North America to 9% in Eastern Europe.
- Mortality rates adjusted for region were highest in low-income countries, followed by lower-middle-income countries.

Thiazide Diuretics in Patients with Varying Levels of Kidney Function

Worldwide, hypertension remains the greatest contributor to morbidity and mortality. The prevalence of hypertension increases with age; much of the morbidity and mortality associated with hypertension occurs in older individuals. Effective pharmacotherapy has eased the health burden of uncontrolled hypertension. The efficacy of thiazide diuretics in lowering blood pressure and reducing cardiovascular events is well documented. According to **Cedric Edwards, MD,** and colleagues, there are few data available on whether a specific thiazide is preferable in terms of safety and efficacy.

The most widely prescribed thiazide in North American is hydrochlorothiazide, which is shorter-acting and less potent per milligram than chlorthalidone. Head-to-head studies of those two agents have demonstrated mixed results. Older studies indicated that chlorthalidone was superior in blood pressure control and reduction of cardiovascular events. However, more recent studies have shown equivalency in cardiovascular risk reduction but an increased risk of adverse kidney outcomes and hypokalemia with chlorthalidone.

Patients with chronic kidney disease (CKD) have high rates of hypertension, more than 80%, including 50% who require three or more antihypertensive medications. Results of recent studies of thiazides have suggested effectiveness in this patient population. There are few data available on comparisons of chlorthalidone and hydrochlorothiazide in individuals with CKD. Dr. Edwards et al. conducted a large population-based cohort retrospective study of older adults to compare the safety and clinical outcomes associated with chlorthalidone versus hydrochlorothiazide use across levels of kidney function. Results were reported online in *JAMA Network Open* [doi:10.1001/jamanetworkopen.2021.23365].

The study was conducted on Ontario, Canada, from 2007 to 2015, and included adults ≥66 years of age who initiated chlorthalidone or hydrochlorothiazide during the study period. Data analysis was conducted from December 2019 through September 2020.

New chlorthalidone users were matched 1:4 with new hydrochlorothiazide users by a propensity matched score. The associations between use of chlorthalidone versus use of hydrochlorothiazide and the outcomes of interest overall and within estimated glomerular filtration rate (eGFR) categories (≥60, 45-59, and <45 mL/min/1.73 m^2) were examined using time-to-event models accounting for competing risks.

The outcomes of interest were adverse kidney events (≥30% decline in eGFR, dialysis, or kidney transplantation), cardiovascular events (composite of myocardial infarction, coronary revascularization, heart failure, or atrial fibrillation), all-cause mortality, and electrolyte anomalies (sodium or potassium levels outside reference ranges).

Following high-dimensional propensity score (HDPS) matching, the analysis cohort included 12,722 adults, mean age 74 years, 56% of whom were women (n=7063), and mean eGFR was 60 mL/min/1.73 m^2. Of the 12,722, 2936 had a newly dispensed prescription for chlorthalidone and 9786 had a newly dispensed prescription for hydrochlorothiazide. Rates of angiotensin-converting enzyme inhibitors were higher among participants in the chlorthalidone group, as were rates of use of calcium channel blockers and nephrological care. Participants in the hydrochlorothiazide group had higher rates of angiotensin receptor blocker use. Both chlorthalidone and hydrochlorothiazide were more commonly prescribed as add-on therapy (chlorthalidone: 90% [n=2647]; hydrochlorothiazide: 93% [n=9050]) rather than as monotherapy.

There was an association of a higher risk of decline in eGFR of ≥30% with chlorthalidone use compared with hydrochlorothiazide use (128 events per 1000 person-years [95% confidence interval (CI), 118-138] versus 93.7 events per 1000 person-years [95% CI, 89.3-98.1]; hazard ratio [HR], 1.24; 95% CI, 1.13-1.36). There was no modification associated with eGFR category in the association of chlorthalidone or hydrochlorothiazide use with decline in eGFR ≥30%. There was no significant difference in the risk for dialysis or kidney transplantation between chlorthalidone and hydrochlorothiazide use (4.75 events per 1000 person years [95% CI, 3.08-6.42] vs 2.29 events per 1000 person-years [95% CI, 1.69-2.90]; HR, 1.44; 95% CI, 0.88-2.36). There was no modification of association by eGFR category.

There was an association between chlorthalidone use and a higher risk of cardiovascular events compared with hydrochlorothiazide use (160 events per 1000 person-years [95% CI, 150-171] vs 128 events per 1000 person-years [95% CI, 123-133]; HR, 1.12; 95% CI, 1.04-1.22). The association was not modified by eGFR category.

The groups were statistically similar in all-cause mortality: 30.5 events per 1000 person-years (95% CI, 26.3-34.8) in the chlorthalidone group and 24.7 events per 1000 person-years (95% CI, 22.8-26.7). However, among patients with eGFR of ≥60 mL/min/1.73 m^2, there was an association between chlorthalidone use and higher all-cause mortality risk: 23.5 events per 1000 person-years (95% CI, 19.1-28.0) vs 17.8 events per person-years (95% CI, 15.9-19.7); HR, 1.27 (95% CI, 1.02-1.58). There was no significant difference in all-cause mortality risk in participants with eGFR ≤60 mL/min/1.73 m^2.

There was a greater risk of hypokalemia with chlorthalidone use compared with hydrochlorothiazide use (133 events per 1000 person-years [95% CI, 123-142] vs 73 events per 1000 person-years [95% CI, 70-77]; HR, 1.70; 95% CI, 1.55-1.87), with no modification of the association by eGFR category. The increased risk was more pronounced in patients with higher baseline kidney function. There were no differences observed between the two treatment groups for dialysis or kidney transplantation (HR, 1.44; 95% CI, 0.88-2.36), all-cause mortality (HR, 1.10; 95% CI, 0.93-1.29), hyperkalemia (HR, 1.05; 95% CI, 0.79-1.39), or hyponatremia (HR, 1.14; 95% CI, 0.98-1.32).

Limitations cited by the authors included the observational design of the study, the lack of blood pressure measurement, the study index period from 2007 to 2015 contributing to the possibility of an element of historical bias, and the possible limitation of the generalizability of the findings resulting from the inclusion and exclusion criteria.

In conclusion, the researchers said, "In this population-based cohort study of older adults, we found that chlorthalidone use was associated with a higher risk of EGFR decline, cardiovascular events, and hypokalemia compared with hydrochlorothiazide use. The excess risk of hypokalemia associated with chlorthalidone was attenuated in participants with reduced kidney function. Placed in context with prior observational studies comparing the safety and clinical outcomes associated with thiazide diuretics, these results suggest that there is no clear reason to prefer chlorthalidone over hydrochlorothiazide." ■

TAKEAWAY POINTS

- Results of a population-based cohort study examining the safety and clinical outcomes of chlorthalidone or hydrochlorothiazide use among older adults with varying levels of kidney function.
- There was an association between chlorthalidone use and a higher risk of decline in estimated glomerular filtration rate, cardiovascular events, and hypokalemia compared with hydrochlorothiazide use.
- In participants with reduced kidney function, the excess risk of hypokalemia with chlorthalidone was attenuated.

Changes in Body Composition and Muscle Strength Following Kidney Transplantation

Patients with advanced chronic kidney disease (CKD) commonly experience low muscle mass (sarcopenia) as well as decreased muscle oxidative capacity, strength, and physical function, contributing to decreased quality of life and increased morbidity and mortality. Possible mechanisms for sarcopenia associated with CKD include decreased protein synthesis, activation of catabolic pathways, and specific proteases by metabolic acidosis, defects in insulin/insulin-like growth factor 1 signaling, inflammation, abnormal appetite regulation, and impaired microRNA responses.

Many of the underlying risk factors of sarcopenia are corrected with kidney transplantation. However, according to **Thomas Dienemann, MD, MSCE,** and colleagues, immunosuppressive medications, infection, and poor allograft function may serve as impediments to recovery of muscle mass and function.

There are associations between low muscle mass relative to fat mass (relative sarcopenia) and mortality and disability, but there are few data available on the associations following kidney transplantation. Dr. Dienemann et al. conducted a prospective longitudinal cohort study to examine how measures of body composition change following receipt of a kidney allograft. Results of the study were reported in the *American Journal of Kidney Diseases* [2021;78(6):816-825].

The study objectives were to characterize dual-energy x-ray absorptiometry measures of appendicular lean mass index (ALMI), fat mass index (FMI), fat distribution, and ALMI relative to FMI ($ALMI_{FMI}$), peripheral quantitative computed tomography measures of calf muscle density as an index of intramuscular adipose tissue, isokinetic leg muscle strength, and physical activity at the time of kidney transplantation, compared with healthy concurrent controls, (2) describe changes in these parameters in transplant recipients over a 24-month interval, and (3) identify correlates of changes, including allograft function and glucocorticoid exposure.

The study cohort included kidney transplant recipients, aged 20 to 60 years, at the University of Pennsylvania. Exclusion criteria included prior transplantation, systemic inflammatory disease, glucocorticoid therapy within the prior 6 months, prior malignancy, and dual-organ transplantation. A total of 152 kidney transplant recipients met eligibility requirements and 60 were enrolled. Reasons for non-participation included lack of interest and the burden of study visits.

There were no differences in age and body mass index between those that enrolled and those that did not enroll. Prevalence of pretransplant diabetes (18% vs 41%; *P*=.002) and delayed graft function were lower in the group that enrolled than in those who did not enroll (13% vs 29%; *P*=.008). Demographics were similar in the control and transplant recipient groups. At enrollment, transplant recipients reported less intentional exercise compared with controls.

Of the 60 kidney transplant recipients enrolled in the study, 58 completed the 12-month visit and 53 completed the 24-month visit. Three moved out of state, one had a myocardial infarction, and three withdrew. Those seven were younger than the remaining participants (31 vs 43 years; *P*=.009); however, there were no other differences in baseline characteristics or body composition results.

Six participants had delayed graft function, and three had an acute rejection during follow-up. Of the 49 patients who did not have diabetes at baseline, six developed post-transplant diabetes.

At baseline, the ALMI z scores in transplant recipients were significantly lower than in the controls. The scores were nominally lower among those on dialysis prior to transplantation than among recipients of preemptive transplants (–0.58 vs –0.30), a difference that was not statistically significant. Over the first 6 months, the ALMI z scores increased and were not statistically different compared with the controls from 6 months onward. Among participants on dialysis, the gains in AMLI z scores over 24 months were marginally greater (*P*=.05), adjusted for the baseline value. Increases in FMI z score were associated with increases in the ALMI z score. There were no associations between laboratory parameters, estimated glomerular filtration rate (eGFR), and intentional exercise and changes in AMLI z score.

Over 24 months, the prevalence of obesity increased from 18% to 45%, representing an average weight gain of 10.1 kg. The FMI z scores were comparable between the transplant recipients and the controls at baseline, and increased significantly over 23 months. There was no association between intentional exercise and changes in FMI z scores.

At baseline, $ALMI_{FMI}$ z scores were lower in transplant recipients than in controls. The scores increased over the first 6 months, but remained lower than the controls over the study interval. Changes in FMI z score were inversely associated with changes in $ALMI_{FMI}$ z score (ß, –0.31; 95% confidence interval, –0.59 to –0.02; P=.04). There were no associations between laboratory parameters, eGFR, and intentional exercise and $ALMI_{FMI}$ z scores.

At the time of transplantation, muscle strength z scores in transplant recipients were significantly lower than in controls and were comparable in pre-emptive and non-pre-emptive transplant recipients (–0.76 vs –0.85). Overall, muscle strength relative to ALMI improved (*P*=.04) but remained low compared with controls.

In the early months following transplantation, intentional exercise increased significantly (*P*<.05), but remained significantly lower than in controls across study duration (*P*=.002). In longitudinal models, there were no associations between changes in intentional exercise and laboratory parameters, eGFR, and ALMI *z* scores.

Limitations to the study findings cited by the authors included the lack of muscle biopsies, which precluded assessment of muscle histology and metabolism, the lack of measures of dietary intake, lifestyle habits, or energy expenditure, and the possibility of selection bias.

In summary, the researchers said, "The 2-year interval after kidney transplantation was characterized by gains in muscle mass and strength that were outpaced by gains in fat mass, resulting in persistent sarcopenia." ■

TAKEAWAY POINTS

- Researchers reported results of a prospective longitudinal cohort study designed to examine how measures of body composition change after kidney transplantation.
- In the 24-months following transplantation, the prevalence of obesity increased from 18% to 45%; fat mass index (FMI) also increased.
- Despite gains in FMI, muscle density improved after transplantation.

SARS-CoV-2 Antibody Response in Kidney Transplant Recipients

Kidney transplant recipients who contract COVID-19 are at high risk for severe disease, and were among the group prioritized for early vaccination. In immunocompromised individuals, including kidney transplant recipients, immune response to vaccination is reduced. There are two classes of SARS-CoV-2 vaccines available in the United States and Europe: (1) mRNA)mRNA-1273 [Moderna] and BNT162b2 [PfizerBioNTech]) and (2) viral vector (ChAdOx1 [AstraZeneca] and Ad26COVS1 [Janssen]). Of those, Ad260VS1 is the only vaccine that has been shown to induce a positive immune response following a single dose.

Results of early studies from Israel and the United States demonstrated that only 54% and 38% of kidney transplant recipients developed antibodies against the spike protein following vaccination with two doses of an mRNA vaccine. Proposed strategies to improve response to SASR-CoV-2 vaccination include additional dosing and heterologous booster vaccination.

Recent reports of a third dose of a SARS-CoV-2 vaccine in individuals with low or no response had promising results; more than one in three patients developed antibodies against SARS-CoV-2. **Roman Reindl-Schwaighofer, MD, PhD,** and colleagues reported on results of a single center, 1:1 randomized clinical trial of a third dose of vaccine against SARS-CoV-2 infection *[JAMA Internal Medicine.* doi:10.1001/jamainternmed.2021.7372].

The study was designed to examine the effectiveness of a third dose of an mRNA vaccine compared with a vector vaccine in kidney transplant recipients who did not have antibodies against the SARS-CoV-2 spike protein following two doses of an mRNA vaccine. The primary study end point was seroconversion after 4 weeks (29-42 days) following the third vaccine dose. Secondary outcomes included neutralizing antibodies and T-cell response assessed by interferon-y release assays (IGRA).

Patients were randomized 1:1 to receive a third dose of the same, previously administered, mRNA vaccine (mRNA-1273 or BNT162b2) or a single dose of the vector vaccine (Ad26COVS1). Antibody response was evaluated using the Elecsys® Anti-SARS-CoV-2 enzyme immunoassay (Roche Diagnostics), which tests for the receptor-binding domain of the SARS-CoV-2 spike protein (cutoff, ≥0.8 U/mL; per manufacturer's instructions).

The study cohort included 197 kidney transplant recipients. Mean age was 61.2 years, 58% (n=115) were men, and 42% (n=82) were women (race and ethnicity were not recorded). Eligible participants had not experienced an antibody response to two prior mRNA vaccination. Of the 201 patients who had been enrolled and randomized to receive a third dose of a homologous (mRNA) vaccine (n=100) or a heterologous (Ad-26COVSI) vaccine (n=100), two in the mRNA group were lost to follow-up, one in the vector group withdrew consent prior to vaccination, and another in the vector died of a myocardial infarction 4 weeks after vaccination.

At baseline, there were no statistically significant differences between the two study groups.

PRIMARY END POINT

Four weeks after the third vaccination, 76 patients had developed antibodies against the SARS-CoV-2 spike protein (>0.8 U/mL), representing an overall response rate of 39%. There was no statistically significant difference between the homologous and heterologous vaccination strategies; the response rate for mRNA vaccine was 35% compared with 42% for the vector vaccine (odds ratio [OR], 1.31; 95% confidence interval [CI], 0.71-2.44; *P*=.38).

SECONDARY END POINTS

At 4 weeks, applying the antibody cutoff levels (>15 U/mL; >100 U/mL; >141 BAU/mL; and >264 BAU/mL), the overall response rate was 22%, 8%, 6%, and 3%, respectively. There were no statistically significant differences between the groups. Following the third vaccination with mRNA and vector vaccines, mean antibody levels were 22 and 33 U/mL, respectively. Only 22% of the positive antibody responses (>0.8 U/mL) showed functional neutralizing capacity. Regarding antibodies with neutralizing capacity, there was no statistically significant difference between the mRNA and vector vaccine groups: 6% for mRNA and 11% for vector vaccine (OR, 1.95; 95% CI, 0.63-6.72; *P*=.22).

The overall T-cell response assessed by IGRA was low; only 17 kidney transplant recipients showed a positive reactivity against the SARS-CoV-2 spike protein (nine in the mRNA group and eight in the vector group [OR, 0.86; 95% CI, 0.27-2.64; P=.80]). After the third vaccination, there was no statistically significant difference between groups in reactivity (mean, 0.049 IU/mL and 0.037 IU/mL for mRNA and vector groups, respectively). There was an increase in reactivity between the screening and follow-up points (mean, 0.028 IU/mL and 0.043 IU/mL, respectively; *P*=.02).

There was no association between type of vaccine received as the third dose and development of antibodies after vaccination (OR, 1.32; 95% CI, 0.74-2.35; *P*=.35). There were associations between vaccine response and receiving nontriple immunosuppression (OR, 3.59; 95% CI, 1.33-10.75), longer time after kidney transplant (OR, 1.44; 95% CI, 1.15-1.83, per doubling of years), and torque teno virus plasma levels (OR, 0.92; 95% CI, 0.88-0.96, per doubling of levels).

Compared with the vector vaccine, there was an association between a third dose of an mRNA vaccine and a higher frequency of local pain at the injection site; systemic symptoms were comparable between the two groups.

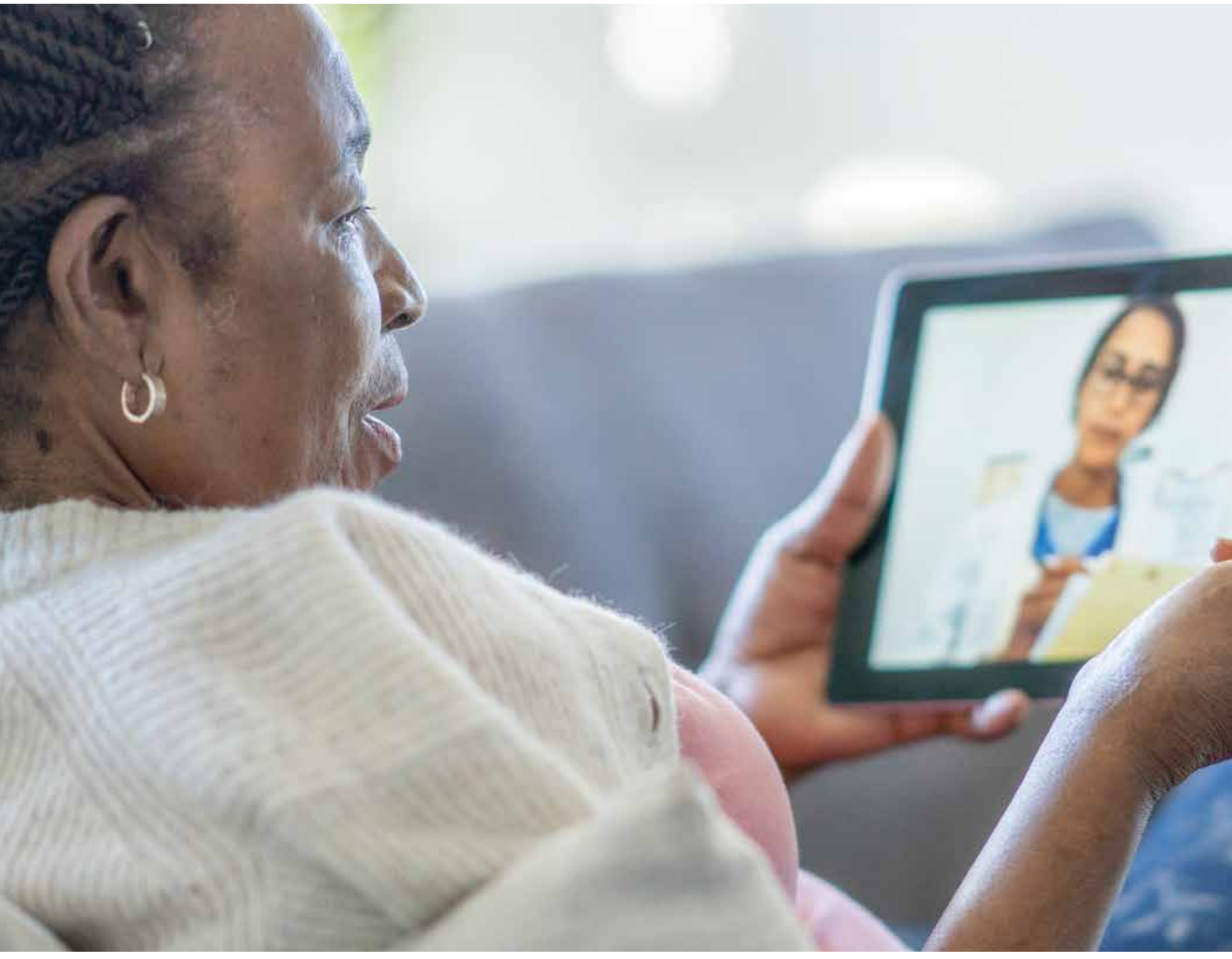
The researchers cited some limitations to the study, including the small sample size and the inclusion of only kidney transplant recipients without a detectable immune response after two doses of an mRNA vaccine, which created a high-risk population with severely impaired immune response to vaccination.

In conclusion, the authors said, "This randomized clinical trial found that more than one in three kidney transplant recipients without an immune response against SARS-CoV-2 after two doses of an mRNA vaccine developed antibodies against the spike protein after the third dose However, only 22% of those showing seroconversion had antibodies with neutralizing capacity. The heterologous vaccination strategy was safe and well tolerated but did not result in a statistically significant difference in the humoral immune response to a third dose of SARS-CoV-2 vaccine after 4 weeks.

"Strategies to improve the immune response in solid organ transplant recipients are urgently needed. Further research is required to determine if additional doses (ie, fourth dose or more) increase the proportion of kidney transplant recipients developing protective immunity, as observed among initial nonresponsers to the hepatitis B vaccine. Other immunization strategies may include temporarily reducing maintenance immunosuppression or prophylaxis with long-acting recombinant neutralizing antibodies that successfully reduce viral load in patients without protective immunity and which may convey passive immunity for several months." ■

TAKEAWAY POINTS

- Researchers reported results of a randomized clinical trial designed to assess the effectiveness of a third dose of an mRNA versus a vector vaccine in kidney transplant recipients without antibodies against the SARS-CoV-2 spike protein after two doses of an mRNA vaccine.
- Of the 197 study participants, 39% developed antibodies against the SARS-CVoV-2 spike protein 4 weeks after a third dose of an mRNA vaccine.
- The heterologous vaccination strategy with a vector-based vaccine was well tolerated and safe but not significantly better than the homologous mRNA-based strategy.



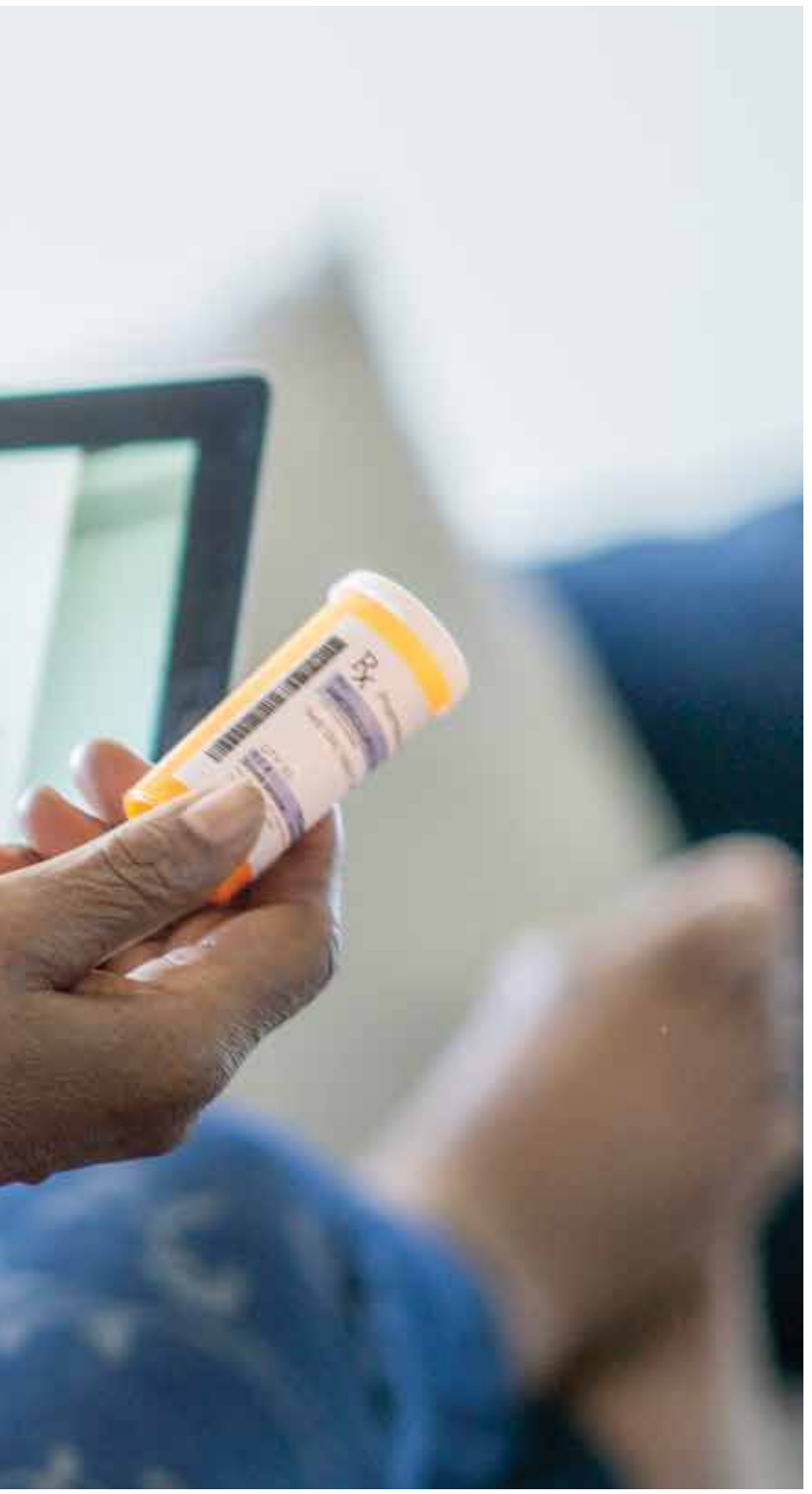
Perceptions of Telehealth among Older Adults with CKD

During the pandemic, use of telehealth increased dramatically among older adults with chronic conditions, including chronic kidney disease (CKD). Approximately 38% of adults >65 years of age in the United States have CKD, corresponding to 20% of traditional Medicare payments ($114 billion annually). Due to the Advancing American Kidney Health Initiative and the 2018 Bipartisan Budget Act, telehealth is likely to remain significant to CKD care.

Prior to the pandemic, telehealth was seen as a cost-effective strategy to improve access to care for patients with chronic illnesses. However, according to **Keren Ladin, PhD, MSc,** and colleagues, there are few data available on whether and how telehealth promotes patient-centered care among older adults with complex conditions such as CKD.

Telehealth may improve access to patient-centered care, particularly for populations with challenges with transportation or caregiving. Some patients are willing to use telehealth and results of small observational studies suggest similarities in outcomes between patients receiving telehealth and those receiving in-person care.

Previous studies of the impact of telehealth on engagement and experience of older, critically ill adults have relied on surveys or claims data that were insufficient for understanding telehealth



experiences of older adults with chronic conditions. Dr. Ladin et al. conduced a qualitative study at four sites to address those gaps by identifying factors affecting telehealth experiences of older adults with CKD, their care partners, and kidney clinicians to improve patient-centered telehealth. Results were reported online in *JAMA Network Open* [doi:10.1001/jamanetworkopen.2021.37193].

The study utilized semi-structured interviews that were conducted from August to December 2020 with purposively sampled patients, caregivers, and clinicians in Boston, Massachusetts; Chicago, Illinois; Portland, Maine; and San Diego, California. Eligible patients were ≥70 years of age with CKD stages 4 to 5. The participants described experiences with telehealth, including the factors that contributed to and impeded engagement, satisfaction, and quality of care. Data were analyzed using thematic analysis.

The researchers conducted a total of 60 interviews: 19 clinicians; 30 patients; and 11 care partners. Of the patients, 43% (n=13) were non-Hispanic Black, 67% (n=20) were women, and 73% (n=22) were ≥75 years of age. Sixteen of the 19 clinicians were nephrologists. Mean interview time was 30 minutes.

QUALITY OF CARE

Most clinicians felt that, due to the inability to conduct physical examinations and laboratory test, telehealth compromised care quality. One clinician said, "It's not good medicine to...not see people in person. The physical exam is really a part of what we do and not being able to examine the patient is a problem." Another said, "I'm always worried I'm missing something." Another said, "Our [telehealth] assessment is not as good. There's a lot of holes. You're going to get in trouble if you do [telehealth] too many times sequentially." Another said, "I just really hate [telehealth]...So it saves maybe a bit of [COVID-19] exposure, but unfortunately [we] need labs. I don't know how much we're really saving them in terms of keeping them safe."

Concerns of patients centered around the quality of care and home diagnostics.

A few clinicians did value the holistic understanding of patients' home environment and self-management. One clinician said, "When you're going through the medications, [patients]...can actually hold the bottle up and show you. There are some things that you can do better [with telehealth}. It does give you a little bit of a view of the setting in which the patient lives." Some clinicians noted that telehealth can empower patients to participate in their care. One said, "We're learning [patients are] able to check their blood pressures, knowing that they can show me...[what] I need in order to make a good assessment."

Concerns of patients centered around the quality of care and home diagnostics. One patient said, "I don't think it's a good idea to try to diagnose people over the telephone...Your machine may not be as good as the ones at the doctor's office, and you may be getting a wrong result." Another said, "I'm not good at doing the blood pressure at home.

PATIENT-CLINICIAN ENGAGEMENT

Patients, care partners, and clinicians all described telehealth as more convenient, less costly, and more efficient than visits to the clinic. One patient said, "I actually prefer [telehealth] rather than have to hike...to the medical center." Patients reported appreciating the relaxed home environment and the reduction in COVID-19 risks. One patient said, "You're more comfortable when you're not sitting on a stool in some doctor's office waiting room. You don't have to dress up."

Care partner engagement was facilitated with telehealth, particularly while visitation restrictions were in place. A care giver said, "If [I] wasn't at the appointment, then I would worry, 'Did [they] tell her everything?' Telehealth has been very helpful." A patient said, "My sister's got a computer...She contacts the doctors, it's working out wonderful."

The challenges to patient engagement cited by the participants included technical issues and a lack of a quiet, private place. One clinician said, "The technology's not perfect. Sometimes there are sound issues...internet connection issues. There's not really a lot of real-time help for the patient." Another said there were "lots of technical challenges...which are dumped on the provider and the patient and which we have to solve without a lot of technical support." Other concerns centered on harms to the patient-clinician relationship, limited ability to comfort patients in virtual settings, and reduced patient trust.

Study limitations cited by the researchers included the possibility of recall bias as well as the underrepresentation of Hispanic patients and non-English speakers.

In conclusion, the authors said, "The findings of this study suggest a spectrum of telehealth satisfaction among older patients with CKD and care partners and found nephrologists tended to be less satisfied with telehealth. Training clinicians in virtual physical examinations, interspersing in-person visits, and interventions to mitigate disparities is needed." ■

TAKEAWAY POINTS

- Results of a qualitative study using semi-structured interviews conducted in 2020 to examine patient, care partner, and clinician perceptions of the benefits and drawbacks of telehealth compared with in-person visits.
- Benefits of telehealth included convenience, greater care partner engagement, and clinician understanding of patients' home environments.
- Drawbacks reported were concerns about care quality due to limited physical examination and laboratory tests and loss of social connection.

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NFK Announces 2022 Awards

Garabed Eknoyan Award

In a press release in early winter, the National Kidney Foundation (NKF) announced the winner of the Garabed Eknoyan Award. The prestigious award is given in recognition of an individual whose work promotes the mission of NKF in making lives better for people with kidney disease. The winner for 2022 is **Bernard Jaar, MD,** of the Nephrology Center of Maryland and Johns Hopkins University, Baltimore. The award will be presented during the NKF 2022 Spring Clinical Meetings, April 6-10, 2022.

Bernard Jaar, MD

Dr. Jaar is a practicing nephrologist on the part-time faculty in the Division of Nephrology, Department of Medicine at the Johns Hopkins School of Medicine, with a joint appointment in the Department of Epidemiology at the Johns Hopkins Bloomberg School of Public Health. He holds a master of public health degree and is a fellow of the American College of Physicians, the American Dubiety of Nephrology, and the National Kidney Foundation.

Paul Palevsky, MD, president of NKF, said, "Dr. Jaar lives the mission of NKF and is an example in our profession worth emulating. It is our honor to recognize his years of work educating nephrologists on kidney care through manuscripts, book chapters, editorial work, and of course his work on the Kidney Disease Outcomes Quality Initiative Guidelines."

Dr. Jaar said, "It is an extraordinary privilege to be recognized with this award in honor of Dr. Eknoyan, a giant in the field of nephrology. I am very thankful to the NKF for this recognition. I would like to dedicate this award to my mentors—people who have helped shape my career and opened doors to new opportunities. But I also want to thank my colleagues at the Nephrology Center of Maryland who have enthusiastically supported my academic 'escapades' over the years. Finally, and most importantly, I thank my spouse, Dora, for her unwavering support and without whom I would not be here today."

Carol Mattix Award

The Carol Mattix Award was created by the Council of Nephrology Nurses and Technicians to honor Carol Mattix who was a home dialysis training nurse whose tireless work improved the lives of kidney patients. In a press release, NKF announced that the winner for 2022 is **Cheyenne Fasce, BSN, RN.** Ms. Fasce is a pediatric hemodialysis and peritoneal dialysis nurse and nurse trainer DCI at Upstate University Hospital, Syracuse, New York.

Cheyenne Fasce, BSN, RN

"I am passionate about kidney health and kidney disease simply because I have seen how devastating its effects can be on patients and their families," Ms. Fasce said. "Pediatrics have a special place in my heart because I am a mother and imagining how difficult it must be to have a child with a life-altering, incurable illness drives me to do all that I can to help. This award is also very meaningful to me because it will bring awareness to the special population that I serve, which is pediatric end-stage renal disease patients. There is little awareness in the general public and in healthcare that children can suffer from this condition, or that it may occur suddenly and without much warning."

NKF president, **Paul Palevsky, MD,** said, "Cheyenne's relentless drive to make the world a better place for dialysis patients is apparent in everything she does. She has played an integral part in developing and growing the outpatient pediatric dialysis programs and the upstate New York community is all the better because of her work. It is clear that Cheyenne is always thinking ahead for the next best way she can advocate for patients."

Fresenius Kidney Care Receives Excellence in Technology Awards

In a recent press release, Fresenius Kidney Care announced it had been awarded two Brandon Hall Group Bronze Awards for Excellence in Technology. Fresenius Kidney Care is the dialysis services division of Fresenius Medical Care North America. The awards recognized the home dialysis digital training platform recently launched by Fresenius Kidney Care.

The platform for peritoneal dialysis patients, the PD Patient Education Experience, won in two categories: (1) best advance in content management technology and (2) best advance in mobile learning technology. The home therapy training program platform is accessible through the Fresenius Kidney Care PatientHub and complements the in-person training between a nephrology nurse and the patient. Currently available in English, a version in Spanish will be available soon.

Dinesh Chatoth, MD, associate chief medical officer of Fresenius Kidney Care, said, "Through this new PD Education Experience, patients receive detailed and consistent training that is customized to their individual needs. This is vital to improving their confidence and ability to perform PD at home, while reducing the risk of infections and adverse complications, Ultimately, this means greater patient safety at home and success in long-term PD treatment."

As of early February, more than 8500 patients had registered to use the PD Education Experience platform, and as many as 6000 new users are being added each week. The platform, along with other patient resources in PatientHub, allows peritoneal dialysis patients to document their treatment outcomes, complications, vital signs, and laboratory results. The platform also allows care teams to train patients with more consistency across the company.

Ascend Expands Relationship with Siemens Healthineers

Ascend, a leading dialysis testing laboratory in the United States, has announced an expansion of its strategic relationship with Siemens Healthineers. According to a press release from Ascend, the new agreement will increase the testing capacity at Ascend's laboratory in Sunnyvale, California, opening in the second quarter of 2022.

The new lab will be outfitted with more than 40 Atellica Solution analyzers. **Paul F. Beyer,** Ascend CEO, said, "We are committed to staying ahead of the industry while providing impeccable service and quality results. Our new laboratory needs the most advanced instrumentation and automation. After evaluating different solutions, Ascend chose Siemens Healthineers because it offered the best combination of innovation, service, and precision."

According to the press release, the Atellica Solution integrates immunoassay and clinical chemistry analyzers with sample-management technology to enable laboratory professionals to focus on driving better outcomes. The automation-ready solution is flexible, scalable, and features patented bidirectional magnetic sample-transport technology, with more than 300 customizable configurations and a broad assay menu.

Jennifer Zinn, executive vice president and head of diagnostics, North America, at Siemens Healthineers, said, "With Atellica Solution, Siemens Healthineers delivers a best-in-class solution for the leading laboratories in the United States. We are excited to support Ascend in the growth of their new Sunnyvale megalab by delivering a highly scalable offering with a broad assay menu and proven performance."

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Vantage Health and Fresenius Announce Partnership

In a dual press release, Vantage Health Plan and Fresenius Medical Care North America (FMCNA) announced a value-based care agreement designed to slow the progression of late-stage chronic kidney disease (CKD), reduce unnecessary hospitalizations, improve outcomes, and lower the total cost of care for people with kidney failure or end-stage kidney disease (ESKD).

The collaboration will improve alignment of healthcare reimbursement with quality performance to provide value to Vantage HealthPlan members. Members will have access to more than 2600 dialysis centers and to home dialysis options.

Gary Jones, MD, CEO of Vantage Health Plan, said, "The collaboration between Vantage and Fresenius Medical Care North America was developed to improve the quality of life for Vantage members living with renal disease. By working together, we can better coordinate care and expand access to treatment for our members. This will allow us to provide the right care in the right setting with the added benefits of lowering costs, achieving member health goals, and improving the whole experience for members and providers. That's our aim at Vantage, Making Healthcare Work. We are excited about the partnership."

The agreement will provide members of Vantage Health Plan with access to education, support, and care management through KidneyCare:365 Health Programs, including initiatives to slow progression of CKD, support optimal starts on dialysis, and ensure treatment compliance among patients transiting to dialysis. The program also offers education and empowerment allowing patients to choose transplantation or home dialysis therapies.

David Pollack, president of FMCNA's Integrated Care Group, said, "This partnership will help us deliver more coordinated care and personalized treatments for people living with late-stage kidney disease. Our growing partnerships with InterWell Health, a renal network of high-performing nephrologists who are focused on value-based care, is an important component of our ability to drive improved health outcomes and cost savings for payors like Vantage. We are dedicated to creating an integrated approach to fully address the complex needs of this vulnerable population."

Positive Results for AlloSure® Kidney in ADMIRAL Study

In a press release, CareDx, Inc. announced results of a study of AlloSure® Kidney, a measurement of allograft injury in routine organ transplant surveillance. Results of the ADMIRAL (Assessing AlloSure Dd-cfDNA Monitoring Insights of Renal Allografts with Longitudinal Surveillance [NCT04566055]) study were reported in *Kidney International*. The real-world study monitored 1092 kidney transplant recipients at seven transplant centers for up to 3 years using the AlloSure Kidney donor-derived cell-free DNA (dd-cfDNA) as part of standard care.

According to a press release, study results demonstrate that AlloSure Kidney can be used in both subclinical and clinical rejection, as a predictor of de novo donor-specific antibody formation, as a leading indicator of donor-specific antibodies, is superior to serum creatinine, and can be used to identify estimated glomerular filtration rate decline.

Reg Seeto, CEO and president of CareDx, said, "We are proud to continue to bring transplant innovation for patients, where AlloSure is now the first donor-derived cell-free DNA test to demonstrate clinical utility in prediction of de novo donor-specific antibody, and both subclinical and clinical rejection in a long-term study. ADMIRAL continues CareDx's 20-year commitment to setting scientific standards through the investment in a prospective, multi-center study that followed over 1000 patients that included a diverse sample set."

Matthew R. Weir, MD, director of the Division of Nephrology in the Department of Medicine at the University of Maryland Hospital, Baltimore, said, "The results of the ADMIRAL study confirm that AlloSure Kidney is fundamentally changing transplant care by being an effective noninvasive service that can be used routinely in the surveillance setting to assess organ health. The predictive value of the test along with its improvement over standard of care serum creatinine for rejection surveillance, makes AlloSure Kidney an invaluable tool for renal transplant physicians working to preserve donated kidneys and keep patients healthy and off dialysis."

CONFERENCE COVERAGE KIDNEY WEEK 2021

Diagnosing Acute Hepatic Porphyria with Renal Injury Biomarkers

Defects in enzymes in the heme biosynthesis pathway are associated with acute hepatic porphyria (AHP), a group of rare genetic diseases. The most common subtype of AHP is acute intermittent porphyria (AIP), associated with accumulation of heme pathway intermediates, delta-aminolevulinic acid (ALA), and porphobilinogen (PBG), leading to acute attacks. Long-term complications include hypertension and chronic kidney disease, which is present in 30% to 60% of patients with biochemically active AIP. Patients who carry a genetic mutation and have elevated levels of ALA and PBG but are not experiencing acute attacks are classified as chronic high excreters (CHE).

During a virtual poster session at ASN Kidney Week 2021, **Simina Ticau, PhD,** presented results of an analysis of proteins in plasma of patients with AHP with recurrent acute attacks (>90% AIP). The poster was titled *Renal Injury Biomarkers Are Elevated in Acute Hepatic Porphyria*.

Proteomic analysis (Olink® platform) was used to measure 1196 proteins in plasma from consenting patients from the EXPLORE natural history study, the ENVISION phase 3 study, and patients with CHE in the ALN-AS1-001 phase 1 study at baseline. A separate cohort of healthy controls were age- and sex-matched to EXPLORE patients was also analyzed. The proteins that were significantly different between patients with AHP or CHE patients and controls were identified using linear regression accounting for age and sex.

A total of 212 plasma proteins were significantly different between healthy controls and patients with AHP. Two proteins with the largest effect sizes, kidney injury molecule-1 (KIM1; 3.4-fold; P=8.0e-13) and matrix metalloproteinase-7 (MMP7; 5-fold; P=1.5e-25) were previously described as biomarkers of kidney injury. Three additional kidney injury biomarkers (neutrophil gelatinase-associated lipocalin, cystatin C [CST3], and chitinase-3-like protein 1) showed significant elevations in patients with AHP.

There were moderate to strong correlations observed between each of those biomarkers and estimated glomerular filtration rate. Patients with AHP with a diagnosis of renal disease demonstrated significantly higher levels of each of those biomarkers compared with patients without a diagnosis of AHP (P<.01). In addition, KIM1, MMP7, and CST3 were significantly elevated in CHE patients compared with controls.

In conclusion, the researchers said, "Renal injury biomarkers may aid in diagnosing and managing kidney disease in patients with AHP suffering from recurrent acute attacks as well as chronic high excreters.

Funding for the analysis was provided by Alnylam Pharmaceuticals.

Source: Ticau S, Yucius K, Karras A, et al. Renal injury biomarkers are elevated in acute hepatic porphyria. Abstract of a poster presented at the American Society of Nephrology virtual Kidney Week 2021 (Abstract P00467), November 2021.

MAJOR MEETINGS 2022

National Kidney Foundation Spring Clinical Meetings 2022

April 6-10, 2022
Boston, Massachusetts
www.kidney.org/spring-clinical/general-information

American Nephrology Nurses Association 2022 National Symposium

May 22-25, 2022
Fort Worth, Texas
www.annanurse.org/events/2022-national-symposium

American Transplant Congress 2022

June 4-8, 2022
Boston, Massachusetts
bit.ly/2YCuf8a

Renal Research Institute 24th International Conference on Dialysis

September 20-23, 2022
Chicago, Illinois
https://renalresearch.com/conference

American Society of Nephrology Kidney Week 2022

November 1-6, 2022
Orlando, Florida
www.asn-online.org/education/kidneyweek/archives/future.aspx

CONFERENCE COVERAGE
KIDNEY WEEK 2021

Daprodustat for Anemia in Patients on In-Center Hemodialysis

Researchers, led by Daniel W. Coyne, MD, recently conducted a study designed to examine the efficacy and safety of daprodustat, a hypoxia-inducible factor prolyl hydroxylase inhibitor being investigated for the treatment of anemia in patients with chronic kidney disease (CKD). The study evaluated daprodustat administered three times weekly versus recombinant human erythropoietin (rhEPO) for patients receiving in-center hemodialysis.

Results of the study, ASCEND-TD, were reported during a virtual poster session at ASN Kidney Week 2021. The poster was titled *ASCEND-TD: A Randomized, Double-Blind, Active-Controlled Study of Daprodustat Administered Three Times Weekly in Hemodialysis Patients.*

The study (NCT034000334) randomized 2:1 in-center hemodialysis patients with a baseline hemoglobin (Hb) of 8 to 11.5 g/dL already on rhEPO to the daprodustat arm (n=270) or to the rhEPO arm (n=137) for 52 weeks. A dosing algorithm sought to maintain Hb between 10 and 11 g/dL.

The primary endpoint of interest was mean change in Hb in the evaluation period (weeks 28-52). The key secondary endpoint was average monthly intravenous (IV) iron dose; other secondary endpoints were blood pressure and variability in Hb.

Baseline characteristics in the overall study cohort (n=407) were balanced between the two arms. Daprodustat was non-inferior to rhEPO for mean change in Hb (model-adjusted mean treatment difference [daprodustat-rhEPO] -0.05; 95% confidence interval [CI], -0.21 to 0.10).

During the evaluation period, mean Hb was 10.45 g/dL and 10.51 g/dL for the daprodustat arm and rhEPO arm, respectively. However, 80% of the daprodustat group were responders (defined as mean Hb during the evaluation period in the analysis range [10-11.5 g/dL]) compared with 63.6% in the rhEPO group, with a difference of 16.5% (one-sided nominal P=.0007 after adjustment for region).

Mean monthly IV iron dose was not statistically significantly lower with daprodustat versus rhEPO. There were fewer blood pressure elevations with daprodustat versus rhEPO (one-sided nominal P=.0093); the overall effect of daprodustat on blood pressure was similar to rhEPO.

Safety findings were comparable between the treatment arms. The incidence of treatment-emergent adverse events was similar: 75% in the daprodustat arm and 79% in the rhEPO arm.

In summary, the authors said, "Daprodustat was non-inferior to rhEPO in Hb response and was well tolerated. Daprodustat administered three times weekly using the protocol employed in this study is a viable alternative to rhEPO in prevalent hemodialysis patients with anemia of CKD."

Funding for this study was provided by GlaxoSmithKline.

Source: Coyne DW, Singh AK, Lopes RD, et al. ASCEND-TD: A randomized, double-blind, active-controlled study of daprodustat administered three times weekly in hemodialysis patients. Abstract of a poster presented at the American Society of Nephrology virtual Kidney Week 2021 (Abstract PO0487), November 2021.

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Fresenius Kidney Care Partners with Biim Ultrasound

Fresenius Kidney Care and Biim Ultrasound AS have established a partnership to expand use of Biim's ultrasound system for assessing needle cannulation prior to dialysis treatment. In 2020, Fresenius Kidney Care piloted the use of the system at more than 24 dialysis centers to help improve patient experience and reduce assess failures.

According to a recent press release, Fresenius Kidney Care will expand the rollout of use of the Biim system to involve hundreds of additional centers throughout the United States in 2022. Often used in the hospital setting, to date ultrasound has not been widely or routinely used in outpatient dialysis clinics.

"Our expanded use of Biim's technology reflects our commitment to offering the highest level of care for people living with kidney failure and in need of life-sustaining dialysis treatment," said **Mike Asselta,** president of Fresenius Kidney Care. "The use of ultrasound is a tool we hope will enable our dedicated care teams to further improve the patient experience. In addition, this agreement further supports our commitment to creating value for patients and payors."

Rune Nystad, CEO of Biim, said, "We are proud and of course very pleased that Fresenius Kidney Care has put its trust in Biim and our products by implementing our ultrasound system as part of their patients' treatments. For Biim, this agreement represents a major milestone, and we look forward to our continued partnership."

According to the press release, Fresenius Kidney Care will continue to evaluate the impact of using ultrasound to assess with cannulation as the technology is made available to more patients, including home patients during training. Following additional evaluation of the program, a broader distribution of Biim's ultrasound system is possible. ■

NFK Supports KDIGO Guidelines on Diabetic Kidney Disease

The National Kidney Foundation's (NKF) professional workgroup charged with reviewing the KDIGO 2020 Clinical Practice Guideline for Diabetes Management in Chronic Kidney Disease has endorsed the latest guideline from Kidney Disease Improving Global Outcomes (KDIGO). KIDGO is a nonprofit, international organization working to improve the care and outcomes of patients with kidney disease through development of clinical guidelines.

The NKF's Kidney Disease Outcomes Quality Initiative (KDOQI) produces its own evidence-based guidelines for US practitioners in addition to reviewing KDIGO guidelines for applicability in US practice. According to a recent press release, the workgroup reviewing the KDIGO diabetes guidelines was "particularly pleased that in addition to addressing the emergence of SGLT2 inhibitors as a treatment for diabetic kidney disease and the nuances of renin-angiotensin system inhibition, KDIGO provided a thorough review and recommendations on comprehensive management of nutrition, exercise, and multidisciplinary collaboration as a central component of care."

Amy K. Mottl, MA, MPH, FASN, and KDOQI workgroup co-chair, said, "The discovery of multiple, effective therapies for diabetic kidney disease has brought about renewed hope and a transformative change for the care of patients. This has reinvigorated the diabetes community to explore optimal approaches to clinical care, education of patients and providers, and to carry on in the quest for individualized treatments at all stages of kidney disease. There is still so much to be done in the realms of research, public policy, and education, but this renewed energy, together with dedication and continued collaboration, will hopefully bring about a day when end-stage kidney disease from diabetes in a rarity."

Michael V. Rocco, MD,MSCE, KDOQI chair, said, "KDIGO is to be commended for the development of their first guideline on the management of diabetes mellitus in chronic kidney disease. The incorporation of recently published results from the randomized clinical trials of SGLT2 inhibitors and long-acting GLP-1RAs will be invaluable to clinicians navigating the care of kidney disease patients in this rapidly changing field. These clinical trials build upon the work done by the National Kidney Foundation, in partnership with the Food and Drug Administration, to develop new surrogate end points for clinical trials in patients with chronic kidney disease."

CONFERENCE COVERAGE KIDNEY WEEK 2021

Economic Burden of CKD Progression in Type 2 Diabetes

Progression of chronic kidney disease (CKD) adds substantial economic burden in type 2 diabetes. **C. Daniel Mullins, PhD,** and colleagues conducted a study to evaluate the medical costs associated with progression of CKD, defined by Kidney Disease: Improving Global Outcomes (KDIGO) risk categories in patients with type 2 diabetes and CKD.

Results of the study were reported during a virtual poster session at ASN Kidney Week 2021. The poster was titled *Economic Burden Associated with CKD Progression Based on Kidney Disease: Improving Global Outcomes (KDIGO) Risk Categories in Type 2 Diabetes.*

The Optum electronic health records database (January 2007 to December 2019) was used to identify a prevalent cohort of adult patients with type 2 diabetes or CKD who had measures of estimated glomerular filtration rate and urine albumin-to-creatinine ratio indicating moderate or high KDIGO risk categories.

Progression of CKD was defined as an increase in KDIGO risk category. The index date was defined as the first record indicating CKD progression for progressors; the later of the first record indicating the patient's risk category or 2 years before the end of follow-up for non-progressors. Annualized costs for inpatient admissions, visits to the emergency department, and outpatient visits were evaluated for up to 2 years after the index date.

There were 218,624 patients with moderate risk at baseline; of those, 19% (n=41, 986) progressed to high risk and 1% (n=3102) progressed to very high risk. Among 50,461 patients with high risk at baseline, 28% (n=14,241) progressed to very high risk.

Compared with non-progressors, the annual incremental costs for patients who progressed from moderate risk to high risk were $5193; for those who progressed from moderate risk to very high risk, $18,168; and for high risk to very high risk, $15,280. The main driver of incremental costs was inpatient costs. Medical costs related to CKD contributed to 28%, 34%, 42%, and 44% of total medical costs in the four groups; highest in patients who progressed to very high risk.

In conclusion, the researchers said, "Patients with type 2 diabetes and CKD in KDIGO moderate or high risk categories had significantly higher medical costs when they progressed to a higher KDIGO risk category compared to those without progression. Preventing progression could bend the cost curve in patients with type 2 diabetes and CKD."

Funding for the study was provided by Bayer.

Source: Mullins CD, Pantalone K, Betts KA, et al. Economic burden associated with CKD progression based on Kidney Disease: Improving Global Outcomes (KDIGO) risk categories in type 2 diabetes. Abstract of a poster presented during the American Society of Nephrology virtual Kidney Week 2021 (Abstract P00774), November 2021.

COVID-19

AKI in Pediatric Patients with COVID-19

Therapeutic Apheresis and Dialysis. doi.org/10.1111/1744-9987.13793

Since December 2019, COVID-19 has challenged the global healthcare system due to the rapid proliferation and lack of treatment, resulting in more than 180 million cases and 3.8 million deaths. Pediatric patients comprise only 1% to 2% of diagnosed cases of COVID-19; however, the incidence of acute kidney injury among pediatric COVID-19 patients ranges from 8.2% to 18.2%, compared with 49% in adults.

In a recent review, **Rupesh Raina, MD,** and colleagues focused on the use of various blood filters approved for use in pediatric kidney replacement therapy to mitigate adverse effects of severe illness. These blood filters have a range of therapeutic effects, including cytokine removal, endotoxin removal, both cytokine and endotoxin removal, and non-specific removal of proteins that have been established and can be used to mitigate the varying effects of the cytokine storm syndrome in COVID-19.

Risk Factors for AKI in Patients with COVID-19

Therapeutic Apheresis and Dialysis. doi.org/10.1111/1744-9987.13790

The kidneys are frequently affected in patients with COVID-19, **Nergiz Bayrakci, MD,** and colleagues conducted a multicenter study designed to examine the incidence of and risk factors for acute kidney injury (AKI) in patients with COVID-19 in the intensive care unit (ICU); the researchers also sought to examine the association between AKI in that patient population and mortality.

The study cohort included 328 patients diagnosed with COVID-19 admitted to the ICU. The outcomes of interest were risk factors associated with AKI and mortality.

Of the 328 patients, 27.9% (n=88) were diagnosed with AKI. Development of AKI was significantly associated with older age, higher baseline creatinine level, lower albumin level, and coexistence of cardiovascular disease and chronic obstructive pulmonary disease. In the total cohort, there were significant associations between mortality and AKI, older age, requirement of intermittent mandatory ventilation, higher neutrophile level, and lower lymphocyte and albumin levels.

In conclusion, the researchers said, "AKI is frequently seen during the course of COVID-19 and is associated with high mortality. Identifying AKI-related risk factors appears essential in the management of COVID-19 patients."

CHRONIC KIDNEY DISEASE

Phosphate-Lowering Agents in Non-Dialysis-Dependent CKD

Journal of the American Society of Nephrology. 2022;33(1):59-76

There are few data available on the benefits of phosphate-lowering interventions on clinical outcomes in patients with chronic kidney disease (CKD); previous studies have focused on patients on dialysis. **Nicole M. Lioufas, MBBS, BmedSci, FRACP,** and colleagues conducted a systematic review and meta-analysis to summarize evidence from randomized controlled trials of the benefits and risks of noncalcium-based phosphate-lowering treatment in patients with non-dialysis-dependent CKD.

The studies included in the meta-analysis involved noncalcium-based phosphate-lowering therapy compared with placebo, calcium-based-binders, or no study medication in adults with CKD not on dialysis or post-transplant. Outcomes included biomarkers of mineral metabolism, cardiovascular parameters, and adverse events. The Sidik-Jonkman method for random effects was used to determine meta-analysis outcomes. The certainty of the evidence was determined using Cochrane risk of bias and GRADE assessment.

A total of 20 trials, representing 2498 participants (median sample size, 120 participants; median follow-up, 9 months) met inclusion criteria. Overall, the risk of bias was low. Compared with placebo, noncalcium-based phosphate binders reduced serum phosphate (12 trials, weighted mean difference –0.37; 95% confidence interval [CI], –0.58 to –0.15 mg/dL, low certainty evidence) and urinary phosphate excretion (eight trials, standardized mean difference [SMD], –0.61; 95% CI, –0.90 to –0.31, low certainty evidence), but resulted in increased constipation (nine trials; log odds ratio [OR] 0.93; 95% CI, 0.02-1.83, low certainty evidence)and greater vascular calcification score (three trials, SMD, 0.47; 95% CI, 0.17 to 0.77, very low certainty evidence). The data for the effects of phosphate-lowering therapy on cardiovascular events and mortality were scant.

In conclusion, the researchers said, "Noncalcium-based phosphate-lowering therapy reduced serum phosphate and urinary phosphate excretion, but there was an unclear effect on clinical outcomes and intermediate cardiovascular end points. Adequately powered randomized controlled trials are required to evaluate benefits and risks of phosphate-lowering therapy on patient-centered outcomes."

DIABETES

Diabetes and Mortality in Patients on Hemodialysis

Journal of Renal Nutrition. 2022;32(1):94-101

In a recent retrospective cohort study, **Eiji Ishimura, MD, PhD,** and colleagues examined the association of diabetes with mortality in patients on hemodialysis with regard to obesity, sarcopenia, and sarcope-

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nic obesity. The study also examined the prevalence of each group and diabetes.

A hand dynamometer and dual-energy x-ray absorptiometry were used to evaluate muscle strength, muscle mass, and fat mass in 308 chronic hemodialysis patients. Mean age was 58 years, mean duration of hemodialysis was 6.5 years, 60.1% were male, and 32.8% had diabetes. New criteria established by the Asian Working Group were used to define sarcopenia. Percent body mass was used to define obesity (males ≥25%; females ≥35%).

Participants were divided into four groups: normal (38.7%); obesity (18.8%); sarcopenia (26.9%); and sarcopenic obesity (15.6%). The prevalence of diabetes was significantly skewed across the four groups, being higher in the sarcopenic obesity group compared with the other three groups. Results of multivariate regression analysis revealed that diabetes was significantly and independently associated with sarcopenic obesity (odds ratio, 3.495; 95% confidence interval, 1.683-7.255; *P*=.008). There was no significant association between diabetes and sarcopenia.

During follow-up of 76 months, 100 patients died. The rates of all-cause mortality were significantly higher in the sarcopenia and sarcopenic obesity groups compared with patients in the normal and obesity groups (*P*=.004). Further, results of multivariate Cox proportional hazards analysis demonstrated that the presence of diabetes was significantly associated with higher all-cause mortality in all 308 patients.

"Sarcopenic obesity is highly prevalent in chronic hemodialysis patients," the researchers said. "Diabetes was found to be a significant and independent contributor to the presence of sarcopenic obesity. Diabetes was shown to be a significant predictor of all-cause mortality, independent of the present normal, obesity, sarcopenia, and sarcopenic obesity groups."

DIALYSIS

PEW Assessment in Patients on Peritoneal Dialysis

Journal of Renal Nutrition. 2021;31(6):679-686

There are few data available regarding the extent to which protein-energy wasting (PEW) contributes to increased risk of mortality among patients receiving peritoneal dialysis. PEW is defined as the loss of body protein and energy reserves associated with kidney disease.

Piyawan Kittiskulnam, MD, and colleagues reported results of a retrospective cohort study conducted from 2012 to 2020. PEW was diagnosed by application of one of four criteria: (1) altered serum biochemistry indicated by a serum albumin level of <3.5 g/L; (2) decreased body mass status, defined as body mass index of <23 kg/m2 or <10% total body fat; (3) muscle wasting, defined by lean tissue index, calculated as a lean tissue mass normalized to the height-squared in the <10th percentile of the reference population; and (4) low dietary protein intake determined by the normalized protein equivalent of a total nitrogen appearance of <0.8 g/kg/day. The researchers also used the Malnutrition Inflammation Score (MIS) as an alternative tool for assessing PEW.

The cohort included 555 participants with average age of 57.5 years. Prevalence of PEW was 27.3% and 196 participants died during the mean follow-up of 25.5 months. In the unadjusted model, the risk of death was higher among participants with PEW with at least three of the four criteria (hazard ratio, 1.61; 95% confidence interval, 1.19-2.18; *P*=.02). Following adjustment for potential confounders, the associations were attenuated.

In multivariable models, there were significant associations between two of the four criteria (decreased serum albumin and low muscle mass) and mortality. There were no significant associations between higher risk of death and decreased body mass or low protein intake. In both unadjusted and adjusted models, both high MIS (≥5 points) and each one-point increase in MIS were significantly associated with higher risk of death.

In summary the researchers said, "Among peritoneal dialysis patients, the presence of PEW was not a better predictor of all-cause mortality than either the altered serum biochemistry (albumin) or low muscle mass criteria. The MIS performed well as an independent predictor of death and might be an option for assessment of PEW status in the peritoneal dialysis population."

CONFERENCE COVERAGE **KIDNEY WEEK 2021**

Renal Flares and Missed Appointments in Lupus Nephritis

Clinical outcomes among African American and Hispanic patients with lupus nephritis have been shown to be worse than among White patients. African American and Hispanic patients with lupus nephritis have higher prevalence of severe inflammatory nephritis, and higher rates of doubling creatinine, end-stage kidney disease, and death, compared with White patients.

Loulwa Alsharhan, MD, and colleagues conducted a study designed to examine the frequency and severity of renal flares of patients treated at a lupus nephritis clinic at a safety-net hospital in Boston, Massachusetts. The number of renal flares and the number of missed appointments were determined using Chi-square tests. Results were reported during a virtual poster session at ASN Kidney Week 2021 in a poster titled *The Relationship Between Renal Flares and Continuity of Medical Care in Patients with Lupus Nephritis.*

A total of 116 patients with lupus nephritis who were treated at the clinic between 2005 and 2019 were included in the study. Of those, 27 (23.3%) self-identified as White or Asian and non-Hispanic (group 1) and 89 (76.7%) self-identified as Black, African American, and/or Hispanic (group 2). The two groups were similar in demographics and disease characteristics.

During the study period, 69 patients (59.5%) did not experience any flare and 47 (40.5%) experienced one or more flares. Of the 47 patients who experienced one or more flares, 42 (89%) missed one or more appointments over the course of the study. In group 2, the rate of missed appointments was significantly higher than the rate of missed appointments in group 1 (85.4% vs 48.1%, respectively; *P*<.001).

In summary, the authors said, "This study represents one of the largest cohorts of patients with lupus nephritis with consistent, longitudinal, long-term follow-up. We found that in our Black, African American, and/or Hispanic patient population, there was a significant association between renal flares and missed appointments. In our safety-net hospital setting, missed appointments frequently represent patients' inability to access care due to various challenges, including lack of sick days at work, transportation challenges, access to certain technologies, and language barriers. When looking to reduce racial and ethnical healthcare disparities, we should design interventions that are aimed at removing key barriers to healthcare access."

Source: Alsharhan L, Schmidt IM, Bonegio R, et al. The relationship between renal flares and continuity of medical care in patients with lupus nephrites. Abstract of a poster presented at the American Society of Nephrology virtual Kidney Week 2021 (Abstract P01599), November 2021.

PEDIATRIC NEPHROLOGY

Nocturnal Dipping in Children with CKD

Clinical Journal of the American Society of Nephrology. 2022;17(1):75-82

In patients with chronic kidney disease (CKD), the physiologic nocturnal decalin in blood pressure is often blunted. However, according to **Christine Y. Bakhoum, MD, MAS,** and colleagues, there are few data available on the consequences of blood pressure nondipping in children. The researchers conducted a cross-sectional analysis of ambulatory blood pressure monitoring and echocardiographic data in participants in the Chronic Kidney Disease in Children study.

The analysis was designed to determine risk factors for nondipping and to examine whether nondipping is associated with higher left ventricular mass index in children with CKD. The relationship of risk factors with dipping and nondipping with left ventricular mass index was evaluated using multivariable linear and spline regression analysis.

The analysis included data on 552 children; mean age was 11 years, mean estimated glomerular filtration rate was 53 mL/min/1.73 m^2, and 41% were classified as nondippers. In those with nonglomerular CKD, there were significant associations between female sex and higher sodium intake and less systolic and diastolic dipping ($P \leq .05$). In participants with glomerular CKD, Black race and greater proteinuria were significantly associated with less systolic and diastolic dipping ($P \leq .05$).

There were no significant associations between systolic dipping and diastolic dipping with left ventricular mass index. However, in spline regression plots, there did seem to be a nonlinear relationship between diastolic dipping and left ventricular mass index. Compared with diastolic dipping of 20% to 25%, dipping of <20% was associated with 1.41-g/$m^{2.7}$-higher left ventricular mass index (95% confidence interval [CI], –0.47 to 3.29), and dipping of >25% was associated with 1.98-g/$m^{2.7}$-higher left ventricular mass index (95% CI, –0.77 to 4.73); those associations did not reach statistical significance.

In conclusion, the authors said, "Black race, female sex, and greater proteinuria and sodium intake were significantly associated with blunted dipping in children with CKD. We did not find a statistically significant association between dipping and left ventricular mass index."

TRANSPLANTATION

Dietary Intake and Serum Uric Levels in Transplant Recipients

Journal of Renal Nutrition. 2021;31(6):637-647

Larissa S. Limirio, MSc, and colleagues reported results of a study designed to examine the association between dietary intake and uric level acids in kidney transplant patients. The cross-sectional study included 113 kidney transplant recipients. Assessment of dietary intake included two 24-hour dietary recalls using the 5-step multiple pass method.

The study examined intake of energy, carbohydrate, total protein, animal protein, vegetable protein, total fat, saturated fat, trans fat, monounsaturated fat, polyunsaturated fat, omega-3 and omega-6 fatty acids, total sugar, added sugars, total fiber, insoluble fiber, soluble fiber, alcohol, caffeine, fructose, glucose, lactose, sucrose, vitamin A, vitamin C, vitamin E, and calcium. The researchers also examined the intake of several food groups (portions). Hyperuricemia was defined as >7.0 m/dL for men and >6.0 m/dL for women.

Results of odds ratio analyses suggested that kidney transplant recipients who ingested more vegetable protein (g/kg) and caffeine (mg) had lower risk of hyperuricemia. In linear regression models there was a positive association between animal protein intake (g) (ß=0.011; P=.048) and serum uric acid. There was an inverse association between vegetable intake (g/kg) (ß=–2.45; P=.047) and serum uric acid. However, following a multiple linear regression analysis that included both vegetable and animal protein, the association with uric acid remained with vegetable protein intake only.

There were no associations between uric acid and other nutrients and portions of food groups.

All analyses were adjusted for sex, age, hypertension, body mass index, glomerular filtration rate, use of medications, and misreporting of caloric intake.

"Vegetable protein and caffeine intakes were inversely associated with uric acid in kidney transplant patients," the researchers summarized.

Survival with Second Transplant versus Remaining on Waitlist after Graft Loss

Clinical Journal of the American Society of Nephrology. 2022;17(1):90-97

The median kidney transplant half-life is 10 to 15 years. According to **Alexander Kainz, PhD,** and colleagues, the scarcity of donor organs and immunologic sensitization of candidates for retransplantation create a need for quantitative data on if and when a second transplantation is no longer associated with a lower risk of mortality compared with waitlisted patients treated by dialysis. The researchers conducted a retrospective study to examine the association between time on waiting list with patient survival in patients who received a second transplant versus remaining on the wait list.

The study used target trial emulation to analyze data from 2346 patients from the Austrian Dialysis and Transplant Registry and Eurotransplant with a failed first graft. Eligible patients were >18 years of age and were waitlisted for a second kidney transplantation in Austria from 1980 to 2019. Differences in restricted mean survival time and hazard ratios for all-cause mortality comparing the treatment strategies *retransplant* versus *remain waitlisted with maintenance dialysis* were examined for different waiting times after the first graft loss.

Compared with remaining on the waitlist, restricted mean survival time at 10 years of follow-up was longer with second kidney transplantation (5.8 life months gained; 95% confidence interval, 0.9-11.1). In patients with longer waiting time after loss of the first allograft, the survival difference was diminished. For patients with waiting time for retransplantation of <1 year and 8 years, restricted mean survival time differences at 10 years were 8.0 life months (95% CI, 1.9-14.0) and 0.1 life months gained (95% CI, –14.3 to 15.2), respectively.

In conclusion, the authors said, "Second kidney transplant is associated with patient survival compared with remaining waitlisted and treatment by dialysis, but the survival difference diminishes with longer waiting time." ■

Sarah Tolson

Understanding Acronyms and Payment Adjustments

If you have worked in the healthcare industry for any length of time, you have probably heard conversations taking place almost entirely in acronyms. We use acronyms for body parts, anatomical locations, diseases and disorders, insurance companies, claim forms, and many other things. My personal favorite grouping of acronyms is those used by Medicare to represent claim payment adjustments. This year we are fortunate enough to have two payment adjustments with fun acronyms that can apply to dialysis facility billing. The first is Transitional Drug Add-on Payment Adjustment, or TDAPA, and my favorite is Transitional Add-on Payment Adjustment for New and Innovative Equipment and Supplies, or TPNIES, pronounced *tip knees*.

Prior to TPNIES and TDAPA, Medicare's reimbursement model for dialysis, the ESRD Prospective Payment System (PPS), provided reimbursement for the medications, supplies, labor, lab work, etc. that comprised the average dialysis treatment. Each year the ESRD PPS is adjusted to account for several factors, and there are several patient and facility-level adjustments intended to increase or decrease the reimbursement relative to the increase or decrease in the presumed costs associated with a patient's dialysis treatment. However, the ESRD PPS is based largely on historical data from dialysis facilities as there were no avenues for reimbursement for new and innovative medications, supplies, or supplies that came to market for the treatment ESRD.

TPNIES

TPNIES, finalized as part of the 2020 ESRD PPS final rule, is a pathway for reimbursement under the ESRD PPS for new equipment and supplies that improves the diagnosis or treatment of Medicare beneficiaries. To qualify for reimbursement under TPNIES, the equipment or supply should meet the following criteria:

- Has been designated by CMS as a renal dialysis service
- Is new (within 3 years of the date of the FDA marketing authorization)
- Is commercially available by January 1st of the year the payment adjustment would take effect
- Has a complete HCPCS level II code application, submitted in the required time frame
- Meets the predefined criteria for innovative as it pertains to TPNIES
- Is not a capital-related asset, with the exception of home dialysis machines

For the first time, in calendar year 2022, CMS will be providing reimbursement for renal dialysis equipment under TPNIES. The Tablo® System has been awarded TPNIES beginning in 2022. In the 2022 ESRD PPS Final Rule, CMS finalized a payment adjustment of $9.50 per treatment for TPNIES-eligible home dialysis machines when they are used in the home for a single patient. CMS estimates that in calendar year 2022, reimbursement under TPNIES will be approximately $2.5 million, $490,000 of which will be attributed to beneficiary coinsurance amounts.

TDAPA

Beginning in 2018, CMS issued reimbursement for the first medications covered under TDAPA, etelcalcetide and oral cinacalcet. For me personally, it was a time of excitement and learning as there had not been a major change to dialysis reimbursement since the inception of the ESRD PPS in 2011. The readers of this column who are involved in the financial side of a dialysis facility may remember the challenging, up-hill battle that was obtaining appropriate reimbursement for the TDAPA drugs from commercial payers, Medicare Advantage Plans, and Medicaid.

This year there is an antipruritic, difelikafalin, indicated for use during hemodialysis that will be reimbursed by CMS under TDAPA for the next 2 years. At the time of this writing, CMS has yet to release information regarding the specifics of how to bill and obtain reimbursement for the new pruritis medication. Dialysis facilities that plan to utilize difelikafalin may benefit from reviewing their payer agreements to identify which payers should reimburse separately for difelikafalin and which payers likely will not provide separate reimbursement. Once these payers are identified, it may be helpful to compare the list of payers that will reimburse for the TDAPA medication to the insurance coverage held by the facility's patients. This type of analysis may be beneficial for determining the potential financial impact of utilizing the new TDAPA medication. ■

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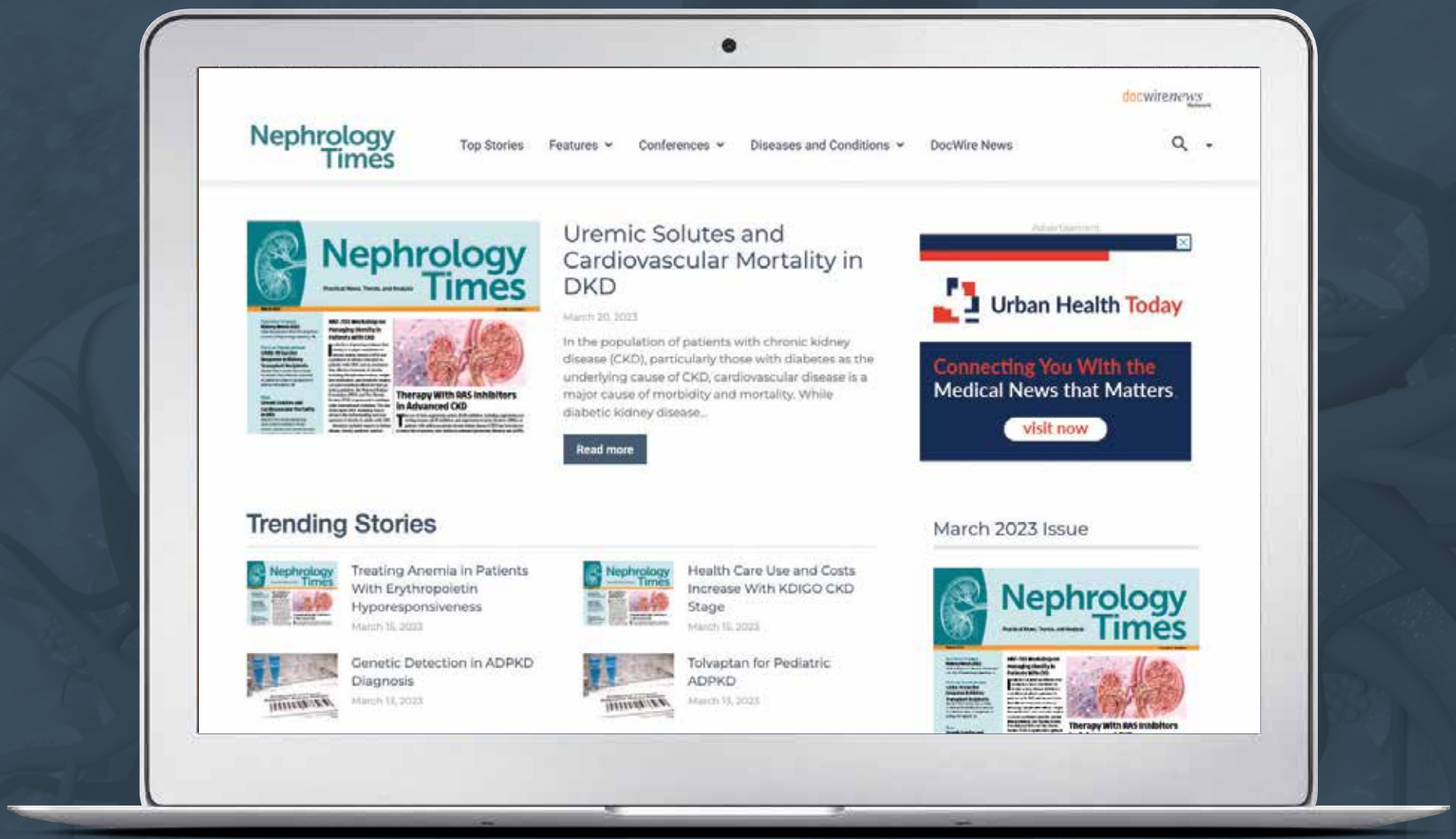

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