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COVID-19 Related AKI and Discharge Kidney Function

Patients hospitalized with severe COVID-19 infection commonly develop acute kidney injury (AKI). There are wide variations in the reported incidence of AKI among that patient population; results of recent studies from the United States suggest an incidence rate of as high as 37% to 40%. Patients hospitalized with COVID-19 who experience AKI face poor prognosis, increased length of stay, and increases in healthcare costs. Further, patients with COVID-19 who survive AKI appear to be at increased risk of death and incident chronic kidney disease (CKD).

Researchers, led by **Jia H. Ng, MD, MSCE,** updated results from a previous study on AKI in COVID-19 among 5449 patients. The current study, reported in the *American Journal of Kidney Diseases* [2021; 77(2):204-215], included 9657 patients with COVID-19, >99% of whom have completed outcomes. The study was designed to provide analysis of in-hospital mortality and kidney outcomes among patients with COVID-19 and AKI.

The primary outcome of interest in the retrospective observational cohort study was in-hospital death. Secondary outcomes were requiring dialysis at discharge and recovery of kidney function. The study was conducted in a large New York health system. Data were obtained from 13 hospitals using the enterprise inpatient electronic health record Sunrise Clinical Manager (Allscripts).

The cohort included all adult pa-

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Patients with COVID-19 and CKD Face Increased Risk of In-Hospital Mortality

Emerging data on COVID-19 caused by SARS-CoV-2 suggest that patients with underlying kidney dysfunction have worse COVID-19–related outcomes than patients without underlying kidney dysfunction. There have been similar outcome differences across cohorts with and without kidney dysfunction in other illness states such as general critical illness and influenza. The differences may be related to innate immunity impairment, vascular dysfunction, and heightened inflammatory state associated with advanced chronic kidney disease (CKD).

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Hospitalization Risk among Dialysis Patients Varies with Community Racial Composition

In-hospital admissions among individuals receiving kidney replacement therapy account for up to 33% of Medicare expenditures for that patient population and are a risk factor for high morbidity and mortality. Data from the US Renal Data System (USRDS) reveal risk factors for hospitalization are female sex, Black race, and young age. However, according to **Ladan Golestaneh, MD, MS,** and colleagues, there are substantial variations in hospitalization rates by health service area, and risks for hospitalizations are not consistent across varying types of communities, as defined by racial composition and rural/urban continuum, in the United States.

Results of previous observational studies have demonstrated disparities in predialysis care, quality of dialysis care, and access to transplantation in patients residing in Black communities. The risk of hospitalization has been shown to be higher in Black patients on hemodialysis, but it is not known whether the higher risk is related to the risks inherent in living in communities with a high percentage of Black residents.

Dr. Golestaneh et al. conducted a retrospective analysis of prospectively collected data from a cohort of patients receiving hemodialysis to test the hypothesis that patients receiving hemodialysis being treated at facilities in communities with more Black residents have a higher risk for hospitalization and that this association accounts, in part, for the higher risk for hospitalization attributed to

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Beauty and the Beast: Terlipressin for the Treatment of Hepatorenal Syndrome

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The hepatorenal syndrome (HRS) is one of the most dreaded and tragic illnesses to manage in nephrology. Patients are sick and mortality is very high, because treatment absent a liver transplant generally doesn't work.[1,2]

HRS was first recognized in 1877 by Friedrich Theodor von Frerichs, a German pathologist, who reported the presence of oliguria in patients with ascites. In later years, others substantiated the link between liver disease and acute kidney injury. In a classic paper in the *Lancet* in 1956, Hecker and Sherlock described the cardinal features of HRS: renal failure with progressive oliguria, a very low urinary sodium excretion, hyponatremia, and the absence of proteinuria.

In HRS, the traditional teaching has been that the kidneys are "innocent" bystanders to a vasoconstrictive humoral factor generated by the failing liver (usually cirrhotic liver).[1] Furthermore, the kidney failure is "functional and reversible" once the diseased liver is replaced by a healthy liver allograft.

HRS is classified as type 1 or type 2. Type 1 HRS (or HRS-1) is more fulminant and is characterized by a very rapid decline in renal function (doubling of serum creatinine over less than 2 weeks). Median survival for HRS-1 is less than 2 weeks. In contrast, type 2 HRS (HRS-2) runs a more chronic course and is characterized by a diuretic-resistant ascites, and a less rapid decline in renal function.

Treatment of HRS-1 is challenging.[2] Different strategies, including transjugular intrahepatic portosystemic shunt (TIPS) to decompress the portal decompression and dialysis, have been tried with variable success. Both generally are viewed as temporizing measures while awaiting liver transplantation.

Among medical therapies, the most promising is the use of the vasopressin analogue terlipressin in combination with albumin. Terlipressin is widely used outside of the United States for the treatment of HRS-1[1,2] for more than 10 years. However, the FDA has so far not approved terlipressin in the United States, because the global trial experience has been limited (only in a few hundred patients in aggregate),[2,3] and because two prior phase 3 trials have been inconclusive.

The publication on March 4, 2021, of the CONFIRM trial by Florence Wong and colleagues in the *New England Journal of Medicine*[4] provides exciting and important evidence in favor of terlipressin in combination with albumin for the treatment of HRS-1. An accompanying editorial by Garcia-Tsao is also very positive.[5] This is welcome news for an illness that, short of liver transplantation, is usually fatal. The strengths of the CONFIRM trial are its design (randomized double-blind, placebo, control), the careful reporting of clinical outcomes and safety outcomes, and its size (the largest trial conducted so far).

The details of the CONFIRM trial are as follows. Sixty sites in the United States and Canada recruited 300 subjects (199 received terlipressin and 101 received placebo). Eligible patients had HRS-1, cirrhosis, ascites, and rapidly progressive kidney failure, with a doubling of the serum creatinine level to at least 2.25 mg/dL within 2 weeks prior to randomization. Patients were randomly assigned to either terlipressin plus albumin or placebo plus albumin. Terlipressin 1 mg or placebo was administered intravenously over 2 minutes every 5.5 to 6.5 hours.

Across the board, HRS-1 patients treated with terlipressin demonstrated benefit compared with placebo. For the primary endpoint, reversal of HRS was reported in 32% in the terlipressin group and 17% in the placebo group (P=.006). Although there was no difference in mortality between the two groups, the trial was not powered for this.

But here is the kicker—*the beauty and the beast aspect* of terlipressin. While adverse effects were similar in patients treated with terlipressin compared with placebo, respiratory failure and death from respiratory failure was much higher in the terlipressin group compared with placebo-treated patients (11% versus 2%).

How is terlipressin used in practice? The experience is mostly outside the United States. Terlipressin can be administered either as IV boluses or as a continuous infusion. The IV bolus approach was used in the CONFIRM trial, but a continuous intravenous infusion is also popular and has been used in other trials (from 2 mg/day to 12 mg/day).[2] In a study in 2016 by Cavallin and colleagues[6], administration of terlipressin by bolus was compared with continuous infusion. Similar efficacy with both means of administration was reported, but there was a much lower rate of adverse events using the infusion approach as compared to administering by bolus (35.29% vs 62.16%, P<.025).

What's my take on the CONFIRM trial? First of all, this trial was very well conducted and in a sizable number of patients in a population that is very hard to recruit. Bravo to the investigators. Second, the trial demonstrated clear benefit and should amply reassure the FDA that this therapy works; an approval for terlipressin for HRS-1 may now be on the cards. Third, CONFIRM introduces yet another challenge in managing patients with HRS-1, which should make us think hard about using it once approved—namely the risk of acute respiratory failure. Additional trials will be needed to tease out the ideal HRS-1patient to treat with terlipressin. ■

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Patients with COVID-19 and CKD

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Patients with underlying CKD may be particularly vulnerable to COVID-19 critical illness, characterized by multisystem organ failure, thrombosis, and a heightened inflammatory response. Approximately 10% of patients hospitalized with COVID-19 develop critical illness; the mortality rate in that patient population is exceedingly high. Data from the United States suggest that patients with critical COVID-19 illness accompanied by acute kidney injury (AKI) have worse outcomes than those without AKI. Results of other studies suggest that similarly poor outcomes are seen in patients with critical COVID-19 and pre-existing CKD; patients with kidney failure receiving maintenance hemodialysis are at particular risk.

The sample size in those studies were limited and most lacked comparator populations. **Jennifer E. Flythe, MD, MPH,** and colleagues conducted a retrospective cohort study to describe the clinical courses of critically ill patients with COVID-19 with and without pre-existing CKD. The study also examined the association between degree of underlying kidney disease and the occurrence of in-hospital mortality and other outcomes (respiratory failure, shock, and thromboembolic events).

The study utilized data from STOP-COVID. Results were reported in the *American Journal of Kidney Diseases* [2012;77(2):190-203]. STOP-COVID is a multicenter cohort study that enrolled consecutive adults ≥18 years of age with laboratory-confirmed COVID-19 who were admitted to ICUs at 68 geographically diverse hospitals in the United States between March 4, 2020, and May 10, 2020. Patients were followed forward in historical time from admission to the ICU to in-hospital death, hospital discharge, or June 6, 2020, the date of database locking.

The study predictors were the presence (vs absence) of pre-existing kidney disease. The primary outcome of interest was in-hospital mortality. Secondary outcomes were respiratory failure, shock, ventricular arrhythmia/cardiac arrest, thromboembolic events, major bleeds, and acute liver injury.

The study cohort included 4264 patients with COVID-19 critical illness. Of those, 3% (n=143) had pre-existing kidney failure requiring maintenance hemodialysis, 12% (n=521) had pre-existing non–dialysis-dependent CKD, and 85% (n=3600) had no pre-existing CKD. Most (58%) were treated in ICUs located in the northeastern United States.

Patients with non-dialysis–dependent CKD were older than dialysis patients (median, 69 vs 65 years) and patients without pre-existing CKD (median, 69 vs 61 years). Comorbid conditions (diabetes and cardiovascular conditions) were more common in patients with pre-existing CKD (both those on maintenance dialysis and non–dialysis-dependent CKD) compared with patients without CKD.

Of the 143 patients receiving maintenance dialysis, 90% (n=128) were receiving in-center hemodialysis, 6% (n=9) peritoneal dialysis, 1% (n=2) home hemodialysis, and 3% (n=4) had undocumented modality prior to hospital admission. Of the 128 patients on in-center hemodialysis with a known access type, 64% (n=82) dialyzed via a fistula, 27% (n=35) via catheter, and 9% (n=11) via graft prior to admission.

Median time from onset of symptom of COVID-19 to admission to the ICU was 4 days among patients on maintenance dialysis, 7 days among non-dialysis–dependent CKD patients, and 7 days among patients without pre-existing CKD. In general, dialysis patients reported COVID-19-related symptoms prior to ICU admission at a lower frequency than those without CKD; the exception was the percentage of dialysis patients reporting altered mental status being more than twice that of patients in the non-CKD group (25% vs 12%) and slightly more than that of patients with non-dialysis–dependent CKD (25% vs 20%). Respiratory symptoms were less frequent in dialysis patients compared with the other two groups.

Compared with patients receiving maintenance dialysis, a higher percentage of patients without pre-existing CKD were mechanically ventilated (74% vs 80%). Prone positioning was used in a higher percentage of patients in the group without pre-existing CKD (42%) compared with patients in the non-dialysis–dependent CKD group (27%) and those in the dialysis group (24%). Patients without pre-existing CKD were more commonly treated with remdesivir than patients with non-dialysis–dependent CKD. Remdesivir was not administered to any maintenance dialysis patients.

Across all three patient groups, respiratory failure was the leading contributing cause of death. Compared with patients with no pre-existing CKD, those with non-dialysis–dependent CKD and those in the maintenance dialysis group had higher risks of 14- and 28-day in-hospital mortality. In models examining the association between in-hospital mortality and pre-existing kidney disease status, independent of other comorbid conditions, the associations were slightly attenuated but remained statistically significant: fully adjusted hazard ratios for 28-day in-hospital mortality were 1.25 (95% confidence interval [CI], 1.08-1.44) for non-dialysis–dependent CKD and 1.41 (95% CI, 1.09-1.81) for maintenance dialysis-dependent kidney failure. Results were similar in models assessing 14-day in-hospital mortality.

Patients in the maintenance dialysis group had nominally higher risks of shock, ventricular arrhythmia or cardiac arrest, major bleeding events, and acute liver injury during the 14 days following ICU admission; those findings were not statistically significant. Across all three patient groups, the occurrence of thromboembolic events was similar.

The researchers cited some limitations to the study findings, including the observational design and the possibility of residual confounding, defining pre-existing kidney disease based on the presence of prior assessments of eGFR or documentation of CKD in the medical record of the admitting hospital, capturing data for organ injury and organ support during the first 14 days following ICU admission only, the lack of data on inflammatory markers, the lack of data for 14- and 28-day vital status for patients who were discharged prior to those time points, and the limited numbers of secondary outcomes.

In conclusion, the researchers said, "In this multicenter, nationally representative cohort of US adults with COVID-19 critical illness, we found that both non-dialysis–dependent CKD patients and kidney failure patients receiving maintenance dialysis had a 28-day in-hospital rate of ~50% and patients with underlying kidney disease had higher in-hospital mortality than patients without pre-existing CKD, with maintenance dialysis patients having the highest risk in adjusted analyses. As evidenced by differences in symptoms and clinical trajectories, patients with pre-existing kidney disease may have unique vulnerability to COVID-19–related complications that warrant additional study and special consideration in the pursuit and development of targeted therapies." ■

TAKEAWAY POINTS

- Researchers reported results of a retrospective cohort study designed to examine the clinical courses of critically ill COVID-19 patients with and without pre-existing chronic kidney disease (CKD) as well as the association between the degree of underlying kidney disease and in-hospital mortality.
- Approximately 50% of patients with underlying kidney disease died within 28 days of admission to the intensive care unit, compared with 35% of patients without pre-existing CKD.
- Compared with patients without CKD, those receiving maintenance dialysis had higher risk for 28-day in-hospital death; patients with non-dialysis-dependent CKD had an intermediate risk.

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tients ≥18 years of age with positive results by polymerase chain reaction testing of a nasopharyngeal sample for SARS-CoV-2 who were hospitalized from March 1, 2020, to April 27, 2020. AKI was defined according to Kidney Disease: Improving Global Outcomes criteria as an increase in serum creatinine level by 0.3 mg/dL within 48 hours or 1.5 to 1.9 times increase in serum creatinine level from baseline within 7 days (stage 1); 2 to 2.9 times increase in serum creatinine level within 7 days (stage 2); and 3 or more times increase in serum creatinine level within 7 days or initiation of dialysis (stage 3).

During the study period, 11,635 patients were admitted to 13 health system hospitals with a diagnosis of COVID-19. Of those patients, 9657 patients were included in the final cohort. Follow-up continued until June 4, 2020, the day of death, or the day of discharge, whichever came earlier. A total of 2409 patients were admitted to an intensive care unit (ICU), 2033 were treated with mechanical ventilation, and 2075 required vasopressor support during the hospital stay. Within the study cohort, 2418 patients died (25.0%), 7149 (74.0%) were discharged home, and 90 (0.9%) were still admitted at study end. Complete hospital disposition data were available for 99.6% of patients without AKI, 98.1% of patients with AKI stage 1 to 3, and 96.2% of patients with AKI stage 3 requiring dialysis (AKI 3D).

Of the 9657 patients in the study cohort, 39.9% (n=3854) developed AKI: 33.3% (n=3216) had AKI stages 1 to 3 (1644 with stage 1, 840 with stage 2, and 732 with stage 3) and 6.6% (n=638) had AKI 3D. Following accounting for follow-up time, the incidence rate of AKI was 38.3 per 1000 patient-days (32.0 per 1000 patient-days for AKI 1-3 and 6.3 per 1000 patient-days for AKI 3D). The group of patients who developed AKI had a higher proportion with comorbid conditions (diabetes mellitus, coronary artery disease, heart failure, and chronic kidney disease [CKD]). The AKI 3D group had the highest levels of inflammatory markers (D-dimer, C-reactive protein, and serum ferritin), followed by the AKI stage 1-3 group and the non-AKI group.

Of the 3216 patients in the AKI 1-3 group, 40.8% (n=1313) required mechanical ventilation and 42.1% (n=1354) required vasopressors. In the group with AKI 3D (n=638), 91.0% (n=581) required mechanical ventilation and 91.5% (n=584) required vasopressors.

Median time to AKI diagnosis was 10.3 hours following initiation of mechanical ventilation and 7.3 hours after initiation of vasopressor therapy. Among patients who required mechanical ventilation and had AKI, 74.7% (n=1415/1894) developed AKI following initiation of mechanical ventilation; among patients with AKI who required vasopressor therapy, 70% (n=1357/1938) developed AKI following vasopressor therapy initiation.

Among patients without AKI (n=5801), 7.3% (n=421) experienced in-hospital death, a rate of 10.8 deaths per 1000 patient-days. Among the 3216 patients with AKI 1-3, 46.4% (n=1491) died, for a rate of 31.1 deaths per 1000 patient-days. Using the non-AKI group as reference, the unadjusted hazard rate (HR) for in-hospital mortality was 5.6 (95% confidence interval [CI], 5.0-6.3) among patients with AKI 1-3. Following adjustment for baseline demographics, comorbidity, and severity of illness, the risk for in-hospital mortality remained significant. Of the patients with AKI 3D, 79.3% (n=506) died (37.5 deaths per 1000 patient-days). Using the non-AKI group as reference, the unadjusted HR for in-hospital mortality was 11.3 (95% CI, 9.6-13.1).

There were significant differences based on AKI status in median length of stay in patients who survived to discharge. Patients with AKI 3D had the longest median length of stay (29.2 days), followed by patients with AKI 1-3 (11.6 days), and those in the non-AKI group (5.2 days).

Among the 3854 patients who developed AKI, 83.4% (n=3216) developed AKI 1-3 during their admission; of those, 51.7% (n=1663) survived and 74.1% (n=1233/1663) regained kidney function. Median serum creatinine level on discharge was lower than median admission and peak serum creatinine levels across all stages of AKI.

For patients with AKI 3D, 16.9% (n=108/638) survived and 3.7% (n=24) remained hospitalized at the end of the study period. Among the survivors, 66.7% (n=72) had recovery of kidney function (not requiring dialysis at discharge) and a minimum of 33% decline in discharge serum creatinine from peak serum creatinine level. Among the patients who recovered kidney function, 75% (n=54) had a discharge serum creatinine level lower than the admission and peak levels. Among patients with AKI 3D who survived, the remaining 33.3% (n=36/108) did not achieve recovery of kidney function. Of those patients, 33 required dialysis at discharge and three were discharged off dialysis but did not have at least 33% decline in discharge serum creatinine level from peak level. Median time off dialysis prior to hospital discharge was 17.0 days.

Prehospitalization chronic kidney disease was the only independent risk factor associated with needing dialysis at discharge (odds ratio, 9.3; 95 % CI, 2.3-37.8).

Limitations to the study cited by the researchers were the observational retrospective design and limiting the cohort to patients admitted to centers in the New York metropolitan area during the initial peak of the pandemic.

In conclusion, the researchers said, "We found that the development of AKI during hospitalization with COVID-19 was associated with a substantial increase in risk for death. This risk was amplified when AKI resulted in dialysis. Most surviving patients with COVID-19 and AKI experienced substantial kidney recovery before discharge. In contrast, among those who had AKI 3D and survived, 30.6% still needed dialysis at discharge, a group of patients whose subsequent outcomes will require further study." ■

TAKEAWAY POINTS

- Researchers conducted an observational retrospective cohort study in patients in 13 hospitals in metropolitan New York who were hospitalized with COVID-19 between March and April 2020 to examine outcomes of patients who developed acute kidney injury (AKI) while hospitalized.
- The AKI incidence rate was 38.4 per 1000 patient-days. Incidence rates of in-hospital mortality for patients without AKI, those with AKI stages 1-3, and those with AKI requiring dialysis (AKI 3D) were 10.8, 31.1, and 37.5 per 1000 patient-days, respectively.
- Among patients with AKI 1-3 who survived to discharge, 74.1% recovered kidney function. Among those with AKI 3D who survived to discharge, 30.6% remained on dialysis at discharge.

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Hospitalization Risk among Dialysis Patients

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Black patients by the USRDS. Results of the study were reported in the *American Journal of Kidney Diseases* [2020;76(6):754-764].

The study cohort included 4567 patients who were treated at 154 dialysis facilities in 127 unique zip codes and were enrolled in US DOPPS (Dialysis Outcomes and Practice Patterns Study) phases 4 to 5 (2010-2015). The outcome of interest was the rate of hospitalizations during the study period.

Mean follow-up time was 1.35 years. Of the 4567 study participants, 53% were White, 27% were Black, 10% were Hispanic, and 4% were Asian. Thirteen percent were ≤45 years of age and 45% were women. The zip codes were stratified into tertiles based on the percentage of Black residents in sampled zip codes of dialysis facilities: median percentage for tertiles 1, 2, and 3 were 1.0% (range, 0%-1.8%), 5.5% (range, >1.8% -14.4%), and 34.2% (range, >14.4%-92.6%), respectively.

Most facilities in tertile 3 were in poor urban areas, with a higher percentage of households headed by women and lower percentages of households with a higher education and with an active internet subscription compared with tertiles 1 and 2. Facilities in tertile 3 were also more frequently for-profit and had a higher patient census.

Compared with patients treated at facilities in tertile 1, those treated in facilities in tertile 3 were younger, more commonly Black, had lower educational level attainment, more commonly lived in poverty, and more frequently had an arteriovenous graft or catheter rather than an arteriovenous fistula. Mean Charlson scores were also lower in tertile 3 compared with tertile 1.

Fewer patients at tertile 3 centers had a diagnosis of psychiatric disorder, coronary or other cardiac/cerebrovascular diseases, diabetes, or lung disease; a higher proportion had hypertension, heart failure, and HIV, and reported substance abuse. There were also clinically relevant differences in the cause of kidney failure: Black patients receiving dialysis in zip codes with the lowest tertile of Black residents had a diagnosis of glomerulonephritis more commonly as the cause of kidney failure and a diagnosis of hypertension less commonly than Black patients treated at facilities in tertiles with the highest proportion of Black residents (12.3% vs 8.8% for glomerulonephritis; 33.3% vs 44.0% for hypertension; *P*=.07).

The overall hospitalization incidence rate among all patients was 1.19 per person-year. Crude hospitalization rates per person-year for tertile 1, tertile 2, and tertile 3 were 1.05, 1.20, and 1.37, respectively. Compared with the lowest tertile, the unadjusted model incidence rate ratio (IRR) for hospitalizations was 1.11 (95% confidence interval [CI], 0.96-1.30) in tertile 2 and 1.28 (95% CI, 1.08-1.51) in tertile 3.

Following adjustment for categories of variables, the association remained robust. For tertile 3, the IRR was 1.32 (95% CI, 1.12-1.56) in fully adjusted models compared with tertile 1.

The researchers also examined effect modification of the association between community racial composition tertile and hospitalization with a priori-specified patient (including sex, race, and comorbid conditions) and facility characteristic (profit status and patient census). There was no significant 2-way interaction between community racial composition tertile and age (*P*=.5), sex (*P*=.1), diabetes status (*P*=.1), race/ethnicity (*P*=.2), Charlson comorbidity score (*P*=.1), facility profit status (*P*=.9), or facility patient census (*P*=.3). The variables did not modify the effect of community racial composition tertile on hospitalizations IRR.

In community racial composition tertiles 1, 2, and 3, crude mortality rates were 0.19, 0.15, and 0.14 deaths per patient-year, respectively. In Cox analysis, following adjustment for age and facility clustering, the hazard ratio (HR) for mortality was 0.92 (95% CI, 0.77-1.11) for tertile 3 compared with tertile 1 and 0.85 (95% CI, 0.71-1.01) for tertile 2 compared with tertile 1. Results of fully adjusted Cox models had similar HRs for mortality within tertiles.

The researchers cited some limitations to the study findings, including the possibility of residual confounding due to unmeasured patient- or community-level variables. In addition, the use of community racial composition may have overlooked socioeconomic factors and their role in outcomes.

In conclusion, the researchers said, "This study found that patients treated in dialysis facilities located in communities with a high percentage of Black residents are at higher risk for hospitalization than patients treated in communities with a lower percentage of Black residents, despite similar quality of dialysis care and adherence and after adjustment for individual comorbid conditions and individual- and community-level sociodemographic factors, including individual-level race/ethnicity. To eliminate healthcare disparities while at the same time reducing cost, the medical community should focus on addressing drivers of higher hospital/emergency department use in communities with a higher percentage of Black residents." ■

TAKEAWAY POINTS

- Researchers conducted a retrospective analysis of prospectively collected data to examine whether living in communities with predominantly Black residents is associated with risk for hospitalization among patients receiving hemodialysis.
- The study stratified patients based on tertiles of percentage of Black residents within the zip codes of patients' dialysis facility.
- Residents in facilities in tertile 3 (higher proportion of Black patients) had higher adjusted rate of hospitalization (hazard ratio, 1.32; 95% confidence interval, 1.12-1.56) compared with those treated in communities in tertile 1.

Urate-Lowering Treatment with Allopurinol and CKD Progression

Patients with elevated serum urate levels are at increased risk for the onset and progression of chronic kidney disease (CKD) and end-stage renal disease (ESRD). Results of observational studies have shown a linear association between serum urate levels and outcomes that include onset of CKD, progression to ESRD, cardiovascular events, and death. As a result of reduced excretion, serum urate level increases linearly with decreasing glomerular filtration rate (GFR). It is unknown whether elevated serum urate levels have a causative role in kidney disease progression, or are an indirect marker of decreased kidney function, or both.

Sunil V. Badve, PhD, and colleagues conducted the CKD-FIX (Controlled Trial of Slowing of Kidney Disease Progression from the Inhibition of Xanthine Oxidase) study to test the hypothesis that urate-lowering therapy with allopurinol would attenuate the decline in estimated GFR (eGFR) over a period of 104 weeks in a population of patients with CKD. Results of the study were reported in the *New England Journal of Medicine* [2020;382(26):2502-2513].

The investigator-initiated, randomized, double-blind, placebo-controlled trial was conducted at 31 centers in Australia and New Zealand. Eligible patients were adults with stage 3 or 4 CKD, defined as eGFR 19 to 59 mL/min/1.73 m^2 who were at increased risk for CKD progression. An increased risk for CKD progression was defined as a urinary albumin:creatinine ratio of ≥265 (with albumin measured in milligrams and creatinine in grams) (≥30 with albumin measured in milligrams and creatinine in millimoles) or a decrease in eGFR of at least 3.0 mL/min/1.73 m^2 in the preceding 12 months. Exclusion criteria were history of gout, allopurinol hypersensitivity, clinical indication for allopurinol, and unresolved acute kidney injury in the previous 3 months.

The primary outcome of interest was the change in eGFR from baseline to 104 weeks, using the Chronic Kidney Disease Epidemiology (CKD-EPI) creatinine equation. Secondary outcomes included a composite of 40% reduction from baseline in eGFR or death from any cause; a composite of a 30% reduction in eGFR from baseline, ESRD, or death from any cause; individual components of the composite kidney outcomes; blood pressure, albuminuria and serum urate level; cardiovascular events; hospitalization for any cause; and quality-of-life scores on the 36-Item Short Form Survey. Patients were randomized to receive allopurinol (100 to 300 mg daily) or placebo.

A total of 369 patients (60% of the target number) were randomly assigned to either the allopurinol group (n=185) or the placebo group (n=184) from March 2014 through December 2016. The researchers stopped enrollment due to slow recruitment. Immediately after randomization, three patients in each group withdrew consent. The remaining 363 patients were included in the assessment of the primary outcome.

At the end of the 12-week dose escalation phase, 69% (n=126), 9% (n=17), and 5% (n=9) of the 182 patients in the allopurinol group were taking three tablets, two tablets, and one tablet daily, respectively; in the placebo group, the corresponding percentages were 70% (n=126), 15% (n=27), and 6% (n=10) of 181 patients.

During the 104-week follow-up period, 54 patients (30%) in the allopurinol group and 45 patients (25%) in the placebo group discontinued the assigned regimen. A total of 132 patients (73%) in the allopurinol group and 144 patients (80%) in the placebo group completed the 104-week follow-up period. Patients in the allopurinol group took allopurinol for a mean of 75.8 weeks; patients in the placebo group received placebo for a mean of 83.0 weeks.

With the exception of the primary cause of kidney disease, baseline characteristics were balanced between the groups. Mean eGFR was 31.7 mL/min/1.73 m^2 and median urinary albumin-creatinine ratio was 716.9. Mean serum urate level was 8.2 mg/dL.

There was no significant difference in change in eGFR between the allopurinol group and the placebo group: –3.33mL/min/1.73 m^2 per year and –3.23 mL/min/1.73 m^2 per year, respectively; mean difference, –0.10 mL/min/1.73 m^2 per year. Results were similar in additional analyses and sensitivity analyses, and the results for the primary outcome were consistent across a wide range of prespecified subgroups.

The secondary composite outcome of a 40% decrease in eGFR, ESRD, or death from any cause occurred in 35% (n=63) of patients in the allopurinol group and in 28% (n=51) of patients in the placebo group (risk ratio [RR], 1.23; 95% confidence interval [CI], 0.90-1.67; hazard ratio [HR], 1.34; 95% CI, 0.92-1.93). Results were similar for the composite outcome of a 30% decrease in eGFR, ESRD, or death from any cause (RR, 1.13; 95% CI, 0.89-1.44; HR, 1.23; 95% CI, 0.90-1.69).

In the allopurinol group, mean serum urate level decreased to 5.1 mg/dL (95% CI, 4.8-5.3) at 13 weeks and remained at 5.3 mg/dL (95% CI, 5.1-5.6) up to 104 weeks. In the placebo group, mean serum urate level at 12 weeks was 8.2 mg/dL (95% CI, 7.9-8.5) and remained at 8.2 mg/dL (95% CI, 7.9-8.4) for the duration of follow-up.

Overall, the mean differences in the serum urate level, following adjustment for baseline values, was –2.7 mg/dL (95% CI, –3.0 to –2.5). There were no significant differences between the two groups in urinary albumin:creatinine ratio, systolic blood pressure, diastolic blood pressure, or health-related quality of life.

The rates of serious adverse events were similar in the two groups: 170 events among 84 participants in the allopurinol group and 167 events among 79 participants in the placebo group (46% and 44%, respectively). There were no significant differences in the risk of nonserious adverse drug reactions, including rash, between the two groups.

Limitations to the findings cited by the authors included insufficient power due to incomplete enrollment, a high percentage of patients who discontinued the regimen, the use of a serum creatinine-based equation for the calculation of eGFR, and the use of a surrogate outcome.

In conclusion, the researchers said, "In the present trial, which was stopped early, we did not find that allopurinol was more effective than placebo in slowing the decline in eGFR over a period of 104 weeks in patients with stage 3 or 4 CKD and an elevated risk of disease progression." ■

TAKEAWAY POINTS

- Researchers conducted a randomized, controlled trial to determine whether urate-lowering treatment with allopurinol would attenuate decline in estimated glomerular filtration rate (eGFR) in patients with chronic kidney disease at risk for disease progression.
- Adults with stage 3 or 4 CKD and no history of gout were randomly assigned to receive allopurinol or placebo; the primary outcome of interest was the change in eGFR from baseline to week 104.
- Compared with placebo, among patients with CKD and a high risk of progression, urate-lowering treatment with allopurinol did not slow a decline in eGFR.

Consistent Gap in CKD Awareness among US Adults at Risk for Kidney Failure

Chronic kidney disease affects an estimated 15% of the US population, and nine of 10 adults with CKD are unaware they have it. Previous studies between 2009 and 2016 have suggested some increase in patient awareness of CKD in adults with CKD stage 4; however, other studies have found low overall CKD awareness across populations that are racially/ethnically and geographically diverse.

Patient awareness is a key component of CKD management and preventive care. Knowledge of CKD diagnosis reinforces adherence to lifestyle changes and treatments for cardiovascular and renal risk factors. It is unknown whether prevention of CKD progression is associated with greater awareness of the presence of CKD.

Chi D. Chu, MD, and colleagues conducted a serial cross-sectional study on behalf of the Centers for Disease Control and Prevention Chronic Kidney Disease Surveillance Team to estimate CKD awareness in a nationally representative population sample according to the risk for progression to kidney failure. The research team also sought to determine whether awareness of CKD has changed over time among patients most at risk for progression to kidney failure. Results of the study were reported in the *American Journal of Kidney Diseases* [2020;76(2):174-183].

The study utilized data from the National Health and Nutrition Examination Survey (NHANES) from 1999 to 2016. Of the 92,062 NHANES participants during that time period, eligible participants were ≥20 years of age, not pregnant, and had complete data on age, sex, race, serum creatinine level or urinary albumin-creatinine ratio (UACR). Exclusion criteria were not having CKD glomerular filtration rate (GFR) categories 3 or 4 (G3-G4), as defined by estimated GFR (eGFR) ≥15 mL/min/1.73 m^2 and <60 mL/min/1.73 m^2; patients with eGFR <15 mL/min/1.73 m^2 were excluded due to small sample size. Participants who did not answer "yes" or "no" to the question on awareness of CKD were also excluded.

The study predictor was 5-year risk of kidney failure, estimated using the Kidney Failure Risk Equation (KFRE). Predicted risk was categorized as minimal (<2%), low (2% to <5%), intermediate (5% to <15%), or high (≥15%). The outcome of interest was CKD awareness, defined by a "yes" answer to the question "Have you ever been told by a doctor or other health professional that you had weak or failing kidneys?"

Following application of exclusion criteria, the analysis included 3713 survey participants. In the study population, higher KFRE risk was more common among men, persons of nonwhite race/ethnicity, those with diabetes, and those with hypertension. Mean eGFR ranged from 52 mL/min/1.73 m^2 in the group with minimal KFRE risk to 26 mL/min/1.73 m^2 in the group with highest KFRE risk. Median UACR across the four groups of KFRE risk ranged from 9 to 934 mg/g.

Overall, the proportion of patients with any type of health insurance was high (~96%) and was similar across all groups. In the higher risk groups, Medicaid was more common (14.4% in the highest risk group vs 6.6% in the lowest risk group) and private insurance was less common (48.9% in the highest risk group vs 61.2% in the lowest risk group).

Of participants with CKD G3-G4 and <2% KFRE risk (minimal risk), 7.0% were aware of their CKD (95% confidence interval [CI], 5.9%-8.3%); of those in the low risk group, 18.7% were aware (95% CI, 14.0%-23.4%); of participants in the intermediate risk group, 43.4% were aware (95% CI, 36.4%-50.5%); and of those in the high risk group, 49.6% were aware (95% CI, 41.1%-58.2%).

Consistently over time, crude prevalence of CKD awareness was higher with higher KFRE risk group. In analyses of awareness over time, results of unadjusted analyses showed a borderline statistically significant trend only among those at minimal KFRE risk: 6.3% (95% CI, 4.3%-8.3%) in 1999-2004 and 9.6% (95% CI, 7.4%-11.8%) in 2011-2016; P_{trend}=.03). No statistically significant trends were seen in the other KFRE risk groups. CKD awareness estimates were numerically higher in the low KFRE risk group in 2011-2016 than in 1999 to 2004 (22.6%; 95% CI, 14.7%-30.4% vs 14.6%; 95% CI, 6.6%-22.5%, respectively); however, the trend was not statistically significant. In higher KFRE risk groups, awareness ranged from 42% to 50%.

Results were similar in analyses adjusted for sex, age, race/ethnicity, presence of hypertension, and presence of diabetes. There were no statistically significant trends seen in any KFRE risk group.

Multivariable logistic regression was used to examine the association between KFRE risk and CKD awareness. In unadjusted and adjusted models, the odds of CKD awareness were greater with each category of higher KFRE risk. In the two highest risk groups, the odds were similar. All of the associations between CKD awareness and each KFRE risk group were statistically significant (P<.01 for each).

In comparisons of CKD awareness with awareness of diabetes and hypertension, from 1999 to 2016, awareness of diabetes and hypertension were consistently higher in all CKD G3-G4 and in high-risk CKD. Both hypertension and diabetes exhibited an increase in prevalence of disease awareness during that time period (P_{trend}<.001 for both).

The researchers noted that the primary limitation to the study was the imperfect sensitivity of the question used in NHANES to ascertain awareness of kidney disease. Other limitations included the small numbers of patients with advanced CKD, basing the diagnosis of CKD on a single measurement of creatinine and albuminuria, and the cross-sectional design.

"In summary we found in a nationally representative sample that approximately half the persons with CKD and high risk for progression to kidney failure (≥15% within 5 years) were unaware of having kidney disease, and among those with minimal (<2%) risk, <10% were aware. The heterogeneity of kidney failure risk also likely contributes to difficulty demonstrating the effects of CKD awareness in the overall CKD population. Future studies of CKD awareness should present risk-stratified results because this may better direct public health efforts," the researchers said. ■

TAKEAWAY POINTS

- Researchers conducted a cross-sectional study to estimate awareness of chronic kidney disease (CKD) in a nationally representative sample stratified according to risk of progression to kidney failure.
- Among persons with the lowest risk estimated with the Kidney Failure Risk Equation (KFRE), unadjusted CKD awareness from 2011 to 2016 was 9.6%, compared with 49.0% among those with highest risk.
- In adjusted analyses, there was no change in CKD awareness over time. In all groups of KFRE risk, awareness of CKD remained below that of hypertension and diabetes; awareness of hypertension and diabetes increased over time.

Association of Biomarkers NT-proBNP and BNP with Clinical Outcomes in ESKD

In the general population in the United States, the leading cause of death is cardiovascular disease, accounting for nearly 25% of deaths. Among patients with end-stage kidney disease (ESKD), the prevalence of cardiovascular disease is approximately 10 to 20 times that in the general population. However, there are few data available regarding a consensus on estimating future cardiovascular risk in patients with ESKD.

There is an increase in the use of cardiac biomarkers to predict cardiovascular morbidity and mortality in asymptomatic patients. The biomarkers brain natriuretic peptide (BNP) and the inactive cleavage fragment N-terminal pro-BNP (NT-proBNP) are released upon ventricular stretch or ischemia, and have been shown to be associated with death in patients with heart failure, stable and active coronary artery disease, sepsis, and in high-risk non-cardiac surgery patients.

Kidney function has been shown to have an inverse correlation with peptide concentrations. Recent studies have suggested significant associations between elevated baseline NT-proBNP and BNP levels and cardiovascular morbidity and mortality in patients with ESKD. However, according to **Tyrone G. Harrison, MD,** and colleagues the utility of the biomarkers in patients with ESKD has been limited by heterogeneous relationships between biomarker level elevations and outcomes. The researchers conducted a systematic review and meta-analysis to examine associations between different threshold elevations of NT-proBNP and BNP and clinical outcomes in patients with ESKD. Results of the review were reported in the *American Journal of Kidney Diseases* [2020;76(2):233-247].

The search included MEDLINE via Ovid (1946 to September 10, 2019) and EMBASE (1974 to September 10, 2019), using medical subject headings and text words with analogous terms for end-stage kidney disease, renal replacement therapy, brain natriuretic peptide, and N terminal pro-brain natriuretic peptide. The search was limited to observational studies and observational analyses of trials without restriction on intervention type or language. Studies of pediatric patients, transplant recipients, pregnant patients, and those with acute kidney injury were excluded. The EMBASE search also included relevant conference abstracts from the past 5 years.

Of the 4960 nonduplicate studies identified, 4734 were excluded at title and abstract level. A total of 226 studies underwent full-text review. Of those, 61 were included in the systematic review, and 49 in the meta-analysis.

The 61 studies were published from 2001 to 2019; 18 examined BNP, 40 examined NT-proBNP, and three investigated both. The type of peptide assays varied and most BNP assays were completed with frozen samples. Study size ranged from 44 to 2990 patients, for a total of 19,688 patients. The study cohorts were predominantly men and average age was 46.0 to 75.4 years. Forty-four of the studies included only patients receiving hemodialysis; 10 included only patients receiving peritoneal dialysis, five included patients receiving either hemodialysis or peritoneal dialysis, and one included patients with kidney failure without kidney replacement therapy. Time on maintenance dialysis therapy ranged on average from 0.25 to 9.4 years and study follow-up ranged on average from 0.9 to 8 years. When reported, baseline prevalence of cardiovascular disease, diabetes, and hypertension ranged from 7% to 100%, 0% to 100%, and 22% to 96%, respectively.

Quality of the studies was assessed using the Newcastle Ottawa Scale, designed for nonrandomized studies. Quality assessment also utilized the Outcome Reporting Bias in Trials II (ORBIT II) tool by applying it to the exposure groups in the observation studies in place of interventions from trials. The ORBIT II tool assesses the risk for outcome reporting bias, characterized as high/low/none for each outcome.

The Newcastle Ottawa Scale includes a total of nine potential points. Of the 61 studies included in the review, 87% (n=53) received seven or more points (high quality); the median score was eight (interquartile range, 7-9). Most of the studies (79%, n=48) included adjusted estimates. Risk for outcome reporting bias was identified as being generally low for the cardiovascular events (high risk in 6 studies), but high for the cardiovascular mortality outcome (high risk in 35 studies).

Of the 61 studies, 31 (51%) provided data for cardiovascular mortality, with a total of 1533 events (range of 4-238 cardiovascular deaths per study). Twenty-one studies examined the relationship between NT-proBNP and CV mortality. Nine provided unadjusted effect estimates, and nine provided adjusted effect estimates to enable meta-analysis. Threshold-specific unadjusted hazard ratios (HRs) were progressively greater with greater level of NT-proBNP threshold: from 1.45 (95% confidence interval [CI], 0.91-2.32) at level >2000 pg/mL to 5.95 (95% CI, 4.23-8.37) at >15,000 pg/mL. BNP levels >550 pg/mL were associated with increased risk for cardiovascular mortality (HR, 2.54; 95% CI, 1.49-4.33).

Data for all-cause mortality were reported by 56 studies (91.8%), for a total of 4712 events (range, 9-612 deaths per study). The risk for all-cause mortality were significantly higher at all NT-proBNP thresholds, ranging from >1000 to <2000 pg/mL (HR range, 1.53-4.00). The risks for all-cause mortality at BNP levels >100 pg/mL were 2.04 and 2.07 at BNP levels >550 pg/mL.

Results of adjusted analyses demonstrated similarly greater risks for both cardiovascular and all-cause mortality with greater NT-proBNP concentrations.

Limitations to the findings cited by the authors included incomplete reporting of outcomes and the possibility of outcome reporting bias, and poor precision in estimations of the risk for cardiovascular events for specific thresholds of both peptides.

"These limitations notwithstanding, our study provides new and potentially clinically useful information on the relationships of various thresholds of NT-proBNP and BNP levels with outcomes in patients with ESKD including increased risk for cardiovascular mortality, all-cause mortality, and cardiovascular events. Further work is warranted to identify how to incorporate the use of natriuretic peptides to stratify and reduce cardiovascular risk for patients with ESKD," the researchers said. ■

TAKEAWAY POINTS

- In a systematic review and meta-analysis, researchers examined associations between various thresholds of the brain natriuretic peptide (BNP) and N-terminal pro-BNP (NT-proBNP) and clinical outcomes in patients with end-stage kidney disease (ESKD).
- Pooled unadjusted hazard ratios for cardiovascular mortality were progressively greater for greater thresholds of NT-proBNP; the risk for all-cause mortality was also significantly higher at all NT-proBNP thresholds.
- There was an increased risk for cardiovascular mortality with BNP levels >550 pg/mL; the risk for all-cause mortality was 2.07 at BNP levels >550 pg/mL.

Calcimimetic Agents for Treatment of Adults with Secondary Hyperparathyroidism

Complications of chronic kidney disease (CKD) include hyperphosphatemia, impaired vitamin D activation, hypocalcemia, and increased parathyroid hormone (PTH) synthesis and secretion. Secondary hyperparathyroidism and other factors that include hyporesponsiveness to PTH and fibroblast growth factor 23 biology lead progressively to bone pain, fracture, and deformity; accelerated valvular and vascular calcification; myopathy; and itch. There is also an association between secondary hyperparathyroidism and all-cause and cardiovascular mortality. International clinical practice guidelines call for serum PTH levels being lowered toward a target range.

Calcimimetic drugs mimic the action of calcium on calcium-sensing receptors in the parathyroid gland and suppress PTH synthesis and secretion. Cinacalcet is associated with adverse effects including frequent nausea and vomiting. Newer agents, etelcalcetide and evocalcet, reduce PTH levels compared with placebo and may have fewer gastrointestinal adverse events.

There are few data available on the comparative effectiveness and acceptability of these agents. **Suetonia C. Palmer, Mb ChB, PhD,** and colleagues conducted a systematic review of randomized controlled trials and a network meta-analysis to compare the effectiveness of the three calcimimetic agents: cinacalcet, etelcalcetide, and evocalcet. Results were reported in the *American Journal of Kidney Diseases* [2020; 76(3):321-330].

The study population included adults with CKD enrolled in a clinical trial of a calcimimetic agent. The researchers searched MEDLINE (February 7, 2013, through November 21, 2019), EMBASE (February 7, 2013, through November 21, 2019), and the Cochrane Central Registry of Controlled Trials (through CENTRAL Issue 11 of 12, November 2019). Randomized controlled trials and quasi-randomized controlled trials that compared a calcimimetic agent alone or in combination with another agent, vitamin D compound, parathyroidectomy, placebo, or standard care as treatment for adults with secondary hyperparathyroidism due to CKD were included. Studies in children and those in adults with primary hyperparathyroidism were excluded.

The primary review outcomes of interest were achievement of a target reduction in serum PTH levels and hypocalcemia. Secondary outcomes included nausea, vomiting, serious adverse events, all-cause mortality, cardiovascular mortality, heart failure, and fracture.

The search yielded 412 unique records; of those, 17 records reporting 18 studies met inclusion criteria. Those 18 were added to a previous published systematic review of 18 studies involving 7446 participants, resulting in a final analysis total of 36 studies involving 11,247 participants. The included trials included two in which there were two or more treatment strata using different routes or different doses of intervention; in one publication two trials were reported.

Thirty-two of the 36 trials (involving 10,601 patients) involved patients being treated with long-term dialysis. Two trials included 46 recipients of a kidney transplant who had persistent secondary hyperparathyroidism and two trials (458 patients) examined treatment in patients with early stages of CKD. The trials conducted in the earliest years (from 2000 onward) principally evaluated cinacalcet versus standard care. Trials of etelcalcetide and evocalcet were published in 2015 and 2018, respectively. One study compared a calcimimetic agent with surgical parathyroidectomy in 30 kidney transplant recipients.

Mean study age for participants ranged from 47.2 years to 69 years; median age was 55.0 years. The proportion of men ranged from 33% to 86% of participants; median was 60.6%. Treatment time ranged from 1 week to 21.2 months; median was 5.5 months.

Twenty-four trials (6521 participants) examined the efficacy of calcimimetic agents in achieving target PTH levels. Compared with placebo, calcimimetic agents had higher odds of achieving target PTH levels. Etelcalcetide had the highest odds of achieving PTH target levels compared with evocalcet (odds ratio [OR], 4.93; 95% confidence interval [CI], 1.33-18.2) and cinacalcet (OR, 2.78; 95% CI, 1.19-6.67).

Hypocalcemia was examined in 29 trials (10,528 participants). The trials had varying definitions of hypocalcemia. All examined interventions were associated with hypocalcemia to a greater extent than placebo. Etelcalcetide had the highest odds of incurring hypocalcemia (ORs, 2.30 [95% CI, 1.35-3.92] versus evocalcet and 1.47 [95% CI, 1.08-2.00]) versus cinacalcet.

A total of 28 trials (10,827 participants) analyzed nausea. Nausea was experienced to a greater degree with cinacalcet and etelcalcetide than with placebo. Cinacalcet was ranked worst for nausea and increased the odds, compared with evocalcet (OR, 2.02; 95% CI, 1.21-3.34). In comparison with placebo, there was no detectable increase in nausea with evocalcet.

In 24 trials (10,646 participants) analyzing vomiting, cinacalcet and etelcalcetide were associated with vomiting to a greater extent than was placebo. Cinacalcet ranked worst for vomiting; however, there was no detectable difference in odds compared with etelcalcetide (OR, 1.11; 95% CI, 0.08-1.55) or evocalcet (OR, 1.47; 95% CI, 0.89-2.45).

Study limitations cited by the authors were not including the full range of trials evaluating vitamin D compounds other than those simultaneously evaluating calcimimetic agents, the lack of longer-term data for comparisons of the agents, and the variations across the trials in definitions of end points.

The researchers said, "In conclusion, this network meta-analysis provides comparisons of all available calcimimetic agents for treatment of secondary hyperparathyroidism. At present, the benefits of calcimimetic agents are limited to lowering serum PTH levels during short-term follow-up. Longer-term effects of treatment on cardiovascular and bone complications are uncertain. Etelcalcetide was the most efficacious calcimimetic agents for lowering serum PTH levels, but incurred hypocalcemia, nausea, and vomiting. Cinacalcet ranked worst for nausea and had somewhat lower effectiveness. Evocalcet had lower effectiveness for achieving target PTH levels while incurring fewer adverse effects." ■

TAKEAWAY POINTS

- Researchers conducted a systematic review and network meta-analysis to compare the effectiveness of three calcimimetic agents: cinacalcet, etelcalcetide, and evocalcet.
- Etelcalcetide had the highest odds of achieving a parathyroid hormone (PTH) target level compared with the other two agents; however, etelcalcetide appeared to cause more hypocalcemia compared with the other two.
- Cinacalcet was ranked worst for nausea and had somewhat lower effectiveness for achieving PTH target levels; evocalcet had lower effectiveness for achieving target PTH levels but was associated with fewer adverse effects.

AKI in Patients Using SKLT2 Inhibitors versus Other Glucose-Lowering Drugs

Of the approximately one in 11 adults worldwide with diabetes, 90% have type 2 diabetes mellitus. Globally, the prevalence of type 2 diabetes has nearly quadrupled since 1980 and it is expected to continue to increase. Up to 25% of patients with type 2 diabetes also have comorbid chronic kidney disease (CKD), heart failure, or cardiovascular disease.

Cardiovascular disease is the leading cause of mortality associated with type 2 diabetes. Sodium/glucose cotransporter 2 (SGLT2) inhibitors, oral glucose-lowering drugs, effectively lower hemoglobin A1c levels via inhibition of sodium/glucose cotransporters in the kidney proximal convoluted tubule, leading to glucosuria. Currently available SGLT2 inhibitors in North America and Europe include empagliflozin, canagliflozin, and dapagliflozin. Clinical trials have demonstrated benefits beyond the glucose-lowering effects of those agents, including lowering of the risk of major cardiovascular events, promotion of weight loss, decreases in blood pressure, decreases in all-cause and cardiovascular-related mortality, and slowing of the progression of CKD. Recent consensus guidelines recommend SGLT2 inhibitors as add-on therapy to metformin in patients with atherosclerotic CKD, clinical heart failure, and CKD, assuming adequate kidney function.

However, according to **Christie Rampersad, MD,** and colleagues, the use of SGLT2 inhibitors may increase the risk for acute kidney injury (AKI). The researchers conducted a retrospective cohort study designed to examine whether SGLT2 inhibitors, compared with all other glucose-lowering drugs, are associated with increased risk of AKI. Results of the study were reported in the *American Journal of Kidney Diseases* [2020;76(4):471-479].

The primary outcome of interest was the incidence of AKI, identified as a composite of documented AKI through either hospital discharge codes or laboratory data. Serum creatinine values, but not urine output, were used to identify and stage AKI as defined by Kidney Disease: Improving Global Outcomes criteria. The study population included adults in Manitoba, Canada, with type 2 diabetes mellitus followed up from June 2014 until March 2017.

In the study's incident user design (first prescription of an SGLT2 inhibitor or all other glucose-lowering drugs [oGLDs]), there were 6017 patients whose incident prescription during the study period was for an SGLT2 inhibitor and 42,758 patients whose incident prescription was for an oGLD. Patients who began treatment with an SGLT2 inhibitor were older, had more microvascular disease, and were more likely to already be taking a resin-angiotensin-aldosterone system (RAAS) inhibitor, or additional oGLD at baseline.

TAKEAWAY POINTS

- Researchers conducted a retrospective cohort study to examine whether sodium/glucose cotransporter 2 (SGLT2) inhibitors are associated with acute kidney injury (AKI) compared with all other glucose-lowering drugs (oGLDs).
- The primary outcome of interest was incident AKI, defined by either an increase in serum creatinine level and/or hospital discharge codes for AKI while taking glucose-lowering drugs.
- In comparison of 4778 incident users of SGLT2 inhibitors with 4778 incident users of oGLDs, there were no differences observed in the primary outcome (hazard ratio, 0.64; 95% confidence interval, 0.40-1.03; *P*=.06).

> There was no risk difference in the primary outcome in the SGLT2 inhibitor group compared with the oGLD group: hazard ratio, 0.64; 95% CI, 0.40-1.03; *P*=.06.

Following propensity matching, the groups each included 4778 patients. A total of 1239 patients were not matched due to propensity scores outside the caliper distance of any remaining eligible oGLD initiation episodes. After matching, standardized differences between SGLT2 inhibitors and oGLDs for all variables were <10%. Mean age of study participants was ~59 years, ~45% were women, ~27% had cardiovascular disease, ~71% were taking an RAAS inhibitor, and ~87% received metformin at baseline.

In on-treatment analysis, dapagliflozin contributed more patient-years (50.9%) than canagliflozin (42.5%) and empagliflozin (6.6%). In the oGLD group, the most common index medications were dipeptidyl peptidase 4 inhibitors, insulin, and sulfonylureas.

The on-treatment analysis included 117 AKI events in 7745 patient-years. In the SGLT2 inhibitor group, there were 4226 patient-years of follow-up, compared with 3519 patient-years of follow-up in the oGLD group. There were 47 AKIs in the SGLT2 inhibitor group and 70 in the oGLD group. In patients receiving SGLT2 inhibitors, there were lower event rates of AKI per 100 patient-years than in patients receiving oGLDs: 1.11 (95% confidence interval [CI], 0.79-1.43) versus 1.99 (95% CI, 1.52-2.46). Most of the AKI events occurred >90 days following initiation of the drug.

There was no risk difference in the primary outcome in the SGLT2 inhibitor group compared with the oGLD group: hazard ratio [HR], 0.64; 95% CI, 0.40-1.03; *P*=.06. HRs were consistent across all methods of identification of AKI. There was no effect modification by either RAAS inhibitor (*P*=.9) or diuretic (*P*=.8) use.

The researchers conducted four sets of sensitivity analysis. There were no associations between use of SGLT2 inhibitors and increased risk for AKI in any of the four analyses.

There were some limitations to the findings cited by the authors, including residual unmeasured confounding effects, particularly if patients at lower risk for AKI were more likely to be prescribed SGLT2 inhibitors for reasons not captured in the propensity matching. There may have been biases in prescribing, monitoring of blood work, and reporting of adverse events due to the 2016 FDA warning. Finally, the data were insufficient to compare individual SGLT2 inhibitors.

"In conclusion, our study found that SGLT2 inhibitors are not associated with increased risk for AKI. Our findings should be considered complementary to the growing body of evidence including clinical trials and prospective and retrospective studies that now show kidney-protective effects of SGLT2 inhibitors. Further, avoiding SGLT2 inhibitors due to the fear of short-term adverse effects risks missing their substantial long-term benefits for heart failure and kidney failure," the researchers said. ■

Managing Acute Complications with Outpatient Interventions: A Scoping Review

Rates of use of emergency departments (ED) and hospital admission are high among patients with chronic kidney disease (CKD), particularly among patients with CKD requiring dialysis. Patients receiving maintenance dialysis have, on average, three visits to the ED per year, a rate that is three to eight times higher than among the general population. Of those ED visits, a significant proportion result in hospital admission. Further, ED and in-patient care are drivers of medical costs for patients with CKD, and are associated with significant emotional burden for patients and their caregivers.

Meghan J. Elliott, MD, MSc, and colleagues posit that outpatient care may provide an alternative to ED and inpatient care in patients with CKD. The researchers conducted a scoping review of quantitative and qualitative studies to examine the scope of outpatient interventions used to manage acute complications of chronic diseases and highlight places to adapt and test interventions in patients with CKD. Results of the review were reported in the *American Journal of Kidney Diseases* [2020;76(6):794-805].

The review identified studies of outpatient interventions for adults experiencing acute complications related to one of five chronic disease (CKD, chronic respiratory disease, cardiovascular disease, cancer, and diabetes). The researchers searched MEDLINE, EMBASE, CINAHL, Cochrane Central Register of Controlled Trials, grey literature, and conference abstracts to December 2019.

The search yielded 16,621 unique citations. Of those, the researchers retrieved 218 articles for full-text review. Following the review, 137 were excluded; reasons for exclusion were setting ineligibility (n=17), intervention ineligibility (n=72), population (n=24), study design (n=21), or other (n=3). The final review included 77 studies (with four companion reports). The 77 studies reported on 57 unique interventions for adults with acute complications of one of the five chronic diseases of interest.

Most of the 77 included studies were observational (n=29) or randomized controlled trials (n=25). Other study designs were uncontrolled before-after (n=12), quasi-experimental (n=5), qualitative (n=4), and mixed-methods (n=2). The studies were conducted in the United States (n=29), the United Kingdom (n=14), and Spain (n=14), as well as nine other countries. More than a third of the studies were published within the past 6 years. There were no identified studies describing outpatient management strategies for acute complications of CKD or kidney failure.

The researchers categorized the 57 interventions as: hospital at home (n=16); observation unit (n=9); ED-based specialist service (n=4); ambulatory program (n=18); and telemonitoring (n=10). The interventions were most commonly used for patients experiencing acute exacerbations of chronic obstructive pulmonary disease (COPD) or congestive heart failure (CHF) and complications related to cancer. There were no interventions identified for management of acute complications of CKD or kidney failure. The home setting was the most common setting for the interventions; interventions were conducted by healthcare providers, including specialist physicians and nurses.

Twenty-six published reports described 16 unique hospital-at-home interventions designed to provide hospital-level care in the patient's home setting. Most treated patients with COPD (n=11) and/or CHF (n=6). Nine hospital-at-home interventions had home visits provided by physicians; all 16 had home visits provided by nurses. Nearly half were operational 7 days a week, mostly during daytime hours. Four specified after-hours nursing or physician telephone support. All 16 provided standard medical therapies in the home for patients who met eligibility criteria; only four studies indicated patient education as part of the program.

Thirteen studies described nine observation unit interventions that were most commonly provided to patients with decompensated CHF (n=5) or asthma exacerbations (n=3). The observation unit was a designated area within or next to the ED and was staffed by ED physicians and nurses. Eight of the interventions specified a maximum length of stay in the observation unit between 8 and 48 hours prior to a decision regarding hospital admission or discharge.

Among cancer patients, there were four unique interventions based on ED-based specialist services. This intervention reflected either a specialty ED or a model of care where a specialist physician was embedded as a consultant to the general ED.

Twenty studies described 18 ambulatory care interventions. Most were specialist-run day hospitals or rapid access clinics in cancer and chronic respiratory disease populations. Other ambulatory care interventions were outpatient treatment pathways and scheduled follow-up for chemotherapy-related febrile neutropenia and telephone hotline services.

Ten interventions providing telemonitoring were described in 14 studies. The interventions aided in prompt identification of acute complications of respiratory conditions. The intervention included daily self-monitoring of physiologic parameters such as oxygen saturation or peak expiratory flow using a device that transmitted data to the patient care team remotely.

The researchers classified outcomes as improved, unchanged, or worsened in the intervention group versus a control or comparator group. Based on those classifications, 160 outcomes were reported: 34% improved, 17% no change, 1% worsened, and 19% mixed results. The studies most commonly reported comparative outcomes on domains of healthcare use (e.g., hospital admissions; 62%) and patient outcomes (e.g., disease control and mortality; 45%).

When assessed in between-group comparisons, cost savings were reported (87%), including all of the hospital-at-home studies; use and patient outcomes improved in 44% and 21% of the studies, respectively. Fewer than half of the studies reported on those outcomes.

The researchers said, "In summary, we identified and described five main types of interventions for managing acute complications of common chronic disease in the outpatient setting. The lack of studies on identified interventions for those with advanced CKD highlights an important knowledge gap and opportunity for evaluating novel outpatient strategies for management of acute complications in this population." ■

TAKEAWAY POINTS

- Researchers conducted a scoping review of outpatient interventions for the management of acute complications of chronic diseases to examine opportunities to adapt and test interventions among patients with chronic kidney disease.
- The review included 77 studies that described 57 unique interventions, including hospital at home, ED-based specialist service, ambulatory programs, and telemonitoring.
- Most of the interventions delivered cost savings; however improvements were not consistently observed in other outcome domains.

Screening for Primary Hyperparathyroidism among US Veterans with Kidney Stones

TAKEAWAY POINTS

- Researchers conducted a study to assess the prevalence of parathyroid hormone (PTH) testing in US veterans with kidney stones and hypercalcemia; the study also sought to identify the characteristic of veterans who were more and less likely to receive PTH testing.
- Of the final cohort of veterans with kidney stones and hypercalcemia (n=7561), 24.8% (n=1873) completed a serum PTH level measurement.
- Testing rates across the 130 US Veterans Health Administration facilities varied widely, ranging from 4% to 57%.

Kidney stones affect approximately one in 11 persons in the United States and up to 50% those who experience a kidney stone develop a recurrent stone within 10 years of their first stone episode. Primary hyperparathyroidism (PHPT) is present in 3% to 5% of patients with kidney stones; screening for PHPT is a possible strategy for reducing the kidney stone recurrence rate. There are few data available on the rate of screening for PHPT in patients with kidney stones.

The American Urological Association and European Association of Urology recommend measurement of serum calcium concentration in patients with kidney stones followed by measurement of serum parathyroid hormone (PTH) if there is clinical suspicion of PHPT.

Calyani Ganesan, MD, MS, and colleagues conducted a cohort study to test the hypothesis that the frequency of PTH testing remains low despite current clinical practice guidelines and that a wide variation in screening practices is not adequately explained by patient-specific or facility-level factors. Results of the study were reported in *JAMA Surgery* [2020;155(9):861-868].

The study utilized data from a large national cohort of patients receiving care within the Veterans Health Administration (VHA) healthcare system to examine the prevalence of PTH testing in veterans with kidney stones and hypercalcemia. The researchers also sought to identify the demographic, geographic, and clinical characteristics of veterans who were more or less likely to receive PTH testing.

The data included VHA health records from the Corporate Data Warehouse for veterans who received care in one of 130 VHA facilities in the United States from January 1, 2008, through December 31, 2013. Patients with kidney stones were defined as those with one or more inpatient *International Classification of Diseases, Ninth Revision (ICD-9)* codes for kidney or ureteral stone procedures within 1 year. Exclusion criteria included previous screening for PHPT.

There were 157,539 unique veterans with a *ICD-9* code for a kidney or ureteral stone procedure during the study period. Of those, 139,115 had a serum calcium determination withing 6 months of their index stone diagnosis. Following application of exclusion criteria, the final study cohort comprised 7561 patients with kidney stones and measured hypercalcemia (n=3938) or albumin-corrected hypercalcemia (n=3623).

Mean age of the cohort was 64.3 years, 94.5% (n=7139) were men, and 75.0% (n=5673) were White. Patients with hypercalcemia were more likely than those with normocalcemia (n=124,173) to have diabetes (39.8% [n=3013] vs 29.5% [n=36,655]), impaired kidney function, defined as estimated glomerular filtration rate <45 mL/min/1.73 m^2 (36.1% [=2731] vs 15.1% [n=18,775]), osteoporosis (4.4% [n=331] vs 2.1% [n=2626]), and fractures (7.1% [n=535] vs 4.2% [n=5264]).

Of the 7561 eligible patients, 24.8% (n=1873) completed a serum PTH level measurement near the time of their initial stone diagnosis. Among the 3938 patients with measured hypercalcemia, 34.8% (n=1369) completed a serum PTH measurement; only 13.9% (n=504) of the 3623 patients with albumin-corrected hypercalcemia did so.

Of 2624 patients with a Charlson Comorbidity Index score lower than three, 33.6% (n=882) completed a serum PTH level measurement. Patients with measured hypercalce-

CONFERENCE COVERAGE KIDNEY WEEK 2020

Need for RRT Reduced with Terlipressin for HRS-1 after Liver Transplant

Patients with cirrhosis may develop hepatorenal syndrome type 1 (HRS-1), a severe but reversible acute kidney injury. Patients with HRS-1 who require renal replacement therapy (RRT) are at risk for prolonged intensive care unit stays and mortality. Results of the CONFIRM study (NCT02770716), a randomized, placebo-controlled trial of terlipressin, demonstrated the efficacy of terlipressin for inducing reversal of HRS-1 and reducing the cumulative need for RRT.

Juan Carlos Q. Velez, MD, and colleagues conducted a study to examine whether terlipressin reduces the rate of RRT following liver transplantation. Results of the current study were reported during a virtual poster session at ASN Kidney Week 2020 in a poster titled *Treatment of Hepatorenal Syndrome Type 1 with Terlipressin Reduces Need for Renal Replacement Therapy after Liver Transplantation.*

The CONFRIM trial was conducted in North America and included 300 participants. The trial was designed to compare HRS-1 reversal rates between treated patients 2:1 with albumin plus terlipressin (n=199) or albumin plus placebo (n=101). Dr. Velez and colleagues conducted a post hoc analysis of data from CONFIRM to examine the rate of renal replacement therapy following liver transplantation by intention-to-treat analysis through 90 days of follow-up. The researchers also conducted a poled analysis of three phase 3 randomized controlled trials of terlipressin in HRS-1 (OT-0401 [NCT00089570], REVERSE [NCT01143246], and CONFIRM) to examine 90-day overall and RTT-free survival rates in patients who underwent liver transplantation.

Of the 199 patients in the terlipressin group in the CONFIRM trial, 46 (23.1%) underwent liver transplant. In the placebo group, 29 of the 101 patients (28.7%) underwent liver transplantation. Following liver transplantation, the rate of post-operative renal replacement therapy in patients in the terlipressin group was significantly lower than in patients in the placebo group (19.6% [9/46] vs 44.8% [13/29], respectively; P=.036). The overall survival rate among liver transplant recipients in the terlipressin group was 100% (46/46) compared with 93.1% (27.29) in the placebo group. The difference was not statistically significant.

In the pooled analysis of data from the three phase 3 studies, the 90-day survival rates were 98.9% (93.94) and 91.0% (7.178) in the terlipressin group and the placebo group, respectively (P=.014). In pooled analyses of data from REVERSE and CONFIRM, for transplant-listed patients, 50.0% of the terlipressin group were alive without RRT at day 90, compared with 32.2% (19/59) of patients in the placebo group (P=.032).

In conclusion, the researchers said, "Treatment with terlipressin added to albumin for patients with HRS-1 significantly decreased the need for RRT following liver transplantation."

Source: Velez, JCQ, Sclair S, Sanchez, A. et al. Treatment of hepatorenal syndrome type 1 with terlipressin reduces need for renal replacement therapy after liver transplantation. Abstract of a poster presented at the virtual American Society of Nephrology Kidney Week 2020 (Abstract P00052), October 22, 2020.

mia with PTH testing versus those with albumin-corrected hypercalcemia were more likely to have had an elevated PTH level (40.8% [n=558] vs 31.5% [n=159]) above the population reference range (*P*<.001), and a higher median level of 24-hour urine calcium excretion (221 mg vs 104.5 mg; *P*<.001). Of the 1873 patients with PTH testing, 38.3% (n=717) had an elevated PTH consistent with biochemical PHPT.

Results of multivariable logistic regression models revealed that the odds of PTH testing in patients with kidney stones and hypercalcemia were lower with older age (odds ratio [OR], 0.95 per decade; 95% confidence interval [CI], 0.90-1.00) and among patients with a history of metastatic cancer (OR, 0.63; 95% CI, 0.49-0.81).

Patients with albumin-corrected hypercalcemia were less likely to complete PTH testing compared with patients with measured hypercalcemia (OR, 0.32; 95% CI, 0.28-0.37). There was a direct association between PTH testing and the magnitude of elevation of calcium concentration (OR, 1.07 per 0.1 mg/dL >10.5 mg/dL; 95% CI, 1.05-1.08) and the number of elevated serum calcium concentration measurements (OR, 1.08 per measurement >10.5 mg/dL; 95% CI, 1.06-1.10).

Rates of PTH testing varied among patients who received care in specialty clinics. The odds of PTH testing were higher for patients who visited either a nephrologist or a urologist (OR, 1.56; 95% CI, 1.35-1.81). The odds were much higher for patients who were seen by both a nephrologist and a urologist (OR, 6.57; 95% CI, 5.33-8.10) compared with patients who did not visit a stone specialty clinic during the observation period. Patients seen by an endocrinologist were nearly 5-fold more likely to undergo PTH testing (OR, 4.93; 95% CI, 4.11-5.93).

There was wide variation in the prevalence of PTH testing across the 130 VHA facilities in the United States (range, 4.0%-57.0%).

Limitations to the study findings cited by the authors included the percentage of men in the study population, defining PHPT as the presence of an elevated serum calcium concentration with an elevated serum PTH level measurement and not considering alternative criteria for diagnosing PHPT, the inability to determine whether patients with chronic kidney disease and HPT had primary or secondary HPT with overzealous treatment using oral calcium and/or calcitriol or active vitamin D analogs, and not capturing medical care for veterans with kidney stones who received treatment outside the VHA.

In conclusion, the researchers said, "In this cohort study, a generally low rate of PTH testing was found in veterans with kidney stones and hypercalcemia, and extensive variation in PTH testing rates was found across VHA facilities in the US. More awareness of the level or frequency of elevated serum calcium concentration may be associated with higher rates of PTH testing in patients with kidney stones. Improved screening for PHPT could increase the rates of detection and treatment of PHPT and decrease stone recurrence associated with missed or untreated PHPT." ■

Physical Performance and Clinical Outcomes in Kidney Transplant Candidates

Among patients on the kidney transplant waitlist, frailty is a common and consequential risk factor, and is associated with lower waitlist access and higher risk for removal from the waitlist or death. However, use of frailty assessment in pretransplantation assessment is not common. How to incorporate frailty and poor physical function into clinical practice is uncertain.

Xingxing S. Cheng, MD, MS, and colleagues conducted a prospective observational cohort study designed to examine the association between measured physical performance and clinical outcomes among patients on kidney transplant waitlists. Results of the study were reported in the *American Journal of Kidney Diseases* [2020;76(6):815-825].

The cohort included consecutive patients who were evaluated at the researchers' Transplant Readiness Assessment Clinic from May 2017, when they implemented physical performance testing, through December 2018. The center measures physical performance rather than frailty. The center utilized the 60-second sit-to-stand (STS; also known as chair-stands) test and the 6-minute walk test (6MWT). The STS is a subcomponent of the Short Physical Performance Battery measuring lower-extremity strength. The 6MWT incorporates elements of lower-extremity strength and gait speed, as well as an assessment of cardiorespiratory fitness.

The primary outcome of interest was time to adverse waitlist outcomes, defined as removal from the waitlist or death. Secondary outcomes were time to transplantation and time to death.

The relationship between clinical characteristics and results of physical performance tests was examined using linear regression. The association between physical performance test results and outcomes was examined using subdistribution models.

The cohort included 305 patients; of those, 305 had 6MWT results and 304 had STS test results. The researchers divided each physical performance test into tertiles. Measures of physical function, including Karnofsky score at listing, were positively correlated with 6MWT and STS test results and negatively correlated with Estimated Post-Transplant Survival (EPTS) score.

The median 6MWT result was 393 m, corresponding to 2.9 metabolic equivalence of tasks, and a physical activity between the "physical care for children," and a "brisk walk." The median STS test result was 17 repetitions. There was a direct correlation between the two physical performance test results, with R2 values of 0.49 for the STS test and 6MWT.

Thirty-four percent (n=103) of the 305 patients had at least one instance of repeat testing. In results of repeat testing, 6MWT was unchanged (defined as within 50 m of initial result) in 60% of patients, 22% experienced an increase of >50 m, and 18% experienced a decrease of >50 m. In repeat STS testing, results in 63% of patients were unchanged (defined as 5 repetitions of initial result), 28% experienced an increase of more than five repetitions, and 9% experienced a decrease of more than five repetitions.

Median follow-up was 362 days. During follow-up, 58 patients were removed from the waitlist for comorbid conditions, 15 patients on the waitlist died, 104 underwent transplantation, and 128 were alive on the waitlist with survival time censored. The 58 patients were removed from the waitlist for cardiopulmonary disease (59%), noncardiovascular disease (52%), frailty and poor physical function (48%), and vascular disease (41%).

Median 6MWT scores were 305 m for patients who died, 244 m for patients removed from the waitlist, 419 m for transplant recipients, and 403 m for patients alive on the waitlist with survival time censored. Median STS test results were 14 repetitions for patients who died, 10 repetitions for patients removed from the waitlist, 20 repetitions for transplant recipients, and 18 repetitions for patients alive on the waitlist with survival time censored.

There were negative associations between results of the 6MWT and STS test and waitlist removal or death; there was a positive association between the test results and kidney transplantation. Relative risks for death or removal from the waitlist for patients in the lower and middle tertiles of physical performance were significantly higher than those in the top tertile; the likelihood of transplantation was significantly lower for patients in the low and middle tertile compared with patients in the top tertile of physical performance. There was no attenuation in the effect size following adjustment for covariates.

There was an association between each 50 m lower 6MWT result and an increased risk for death or waitlist removal (adjusted subdistribution hazard ratio [sHR], 1.42; 95% confidence interval [CI], 1.30-1.56) and decreased likelihood of transplantation (adjusted sHR, 0.80; 95% CI, 0.72-0.88). There was an association between each 5 repetiton lower STS test result and an increased risk for death or waitlist removal (adjusted sHR, 1.53; 95% CI, 1.33-1.75) and decreased likelihood of transplantation (adjusted sHR, 0.80; 95% CI, 0.71-0.89).

When clinical characteristics were approximated by EPTS categories, there was an inverse relationship between the 6MWT and STS test and EPTS. A second model, approximating clinical characteristics by demographics and comorbid conditions (age, sex, dialysis vintage, diabetes mellitus, and known atherosclerotic disease) performed better that the model containing only EPTS.

The researchers cited some limitations to the study, including the single-center, observational design, and limiting physical performance testing to two operators.

In summary, the researchers said, "We report our experience in applying two physical performance tests to risk-stratify patients at the top of the deceased donor kidney transplant waitlist. Our results demonstrate that the physical performance testing yields valuable information beyond clinical characteristics or EPTS score. Given their ease of implementation and quantitative nature, we suggest that 6MWT and/or STS test be incorporated for patient counseling and preparation pretransplantation and as an intermediate outcome of prehabilitation programs." ■

TAKEAWAY POINTS

- Researchers conducted a prospective observational cohort study to examine the association between measured physical performance and clinical outcomes among patients on kidney transplant waitlists.
- Physical performance was assessed using the 6-minute walk test and the sit-to-stand test; the tests were incorporated into routine clinical assessments.
- Of the 305 patients in the study, those who did better on the two tests were less likely to be removed from the waitlist and more likely to receive a kidney transplant.

Outcomes among Transplant Recipients Hospitalized Due to COVID-19

Due to chronic immunosuppression as well as the presence of numerous comorbidities, the risk of developing severe COVID-19 may be high in kidney transplant recipients. Researchers in the United States, Italy, and Spain conducted a retrospective cohort study to examine the clinical outcomes among kidney transplant recipients to identify predictors of poor clinical outcomes. Results of the study were reported in the *American Journal of Transplantation* [2020;20(11):3140-3148].

The study was led by **Paolo Cravedi, MD, PhD,** division of nephrology, department of medicine, Icahn School of Medicine at Mount Sinai, New York, New York. The cohort included 144 kidney transplant recipients who were hospitalized due to COVID-19 at 12 transplant centers in North America and Europe. The 12 centers were participating in the TANGO International Transplant Consortium. All kidney transplant recipients ≥18 years of age with a functioning allograft who were admitted to a hospital between March 2 and May 15, 2020, were included.

Of the 144 patients, 66% (n=95) were male, median age was 62 years; 40% were Hispanic, 31% were White, and 25% were Black. The most common comorbidity was hypertension (95%), followed by diabetes (52%), obesity (49%), heart disease (28%), and lung disease (19%). Twenty-eight percent of the cohort had a prior or current history of smoking, 15% had a history of cancer, 17% (n=24) were receiving angiotensin II receptor antagonists at the time of diagnosis, and 14% (n=20) were taking angiotensin-converting enzyme (ACE) inhibitors.

The time to COVID-19 diagnosis following transplant ranged from <1 year to 31 years (median 5 years); 16% of the patients in the study cohort were diagnosed during the first year post-transplant. Causes of original kidney disease were diabetes (30%), glomerular disease (17%), hypertension (14%), and polycystic disease (9%). Seventy-eight percent of the cohort had undergone deceased-donor kidney transplant and 62% received induction therapy with T cell depletion at the time of transplant. Maintenance immunosuppression regimens included tacrolimus (91%), antimetabolite (mycophenolate) (77%), mTOR inhibitor (7.5%), and steroids (86%).

On admission, the most common symptoms were fever and dyspnea (67%), followed by myalgia (53%), and diarrhea (38%). Median follow-up was 52 days following the diagnosis of the first COVID-19 patient. During follow-up, 51% of the cohort (n=74) developed acute kidney injury, 29% (n=42) required mechanical ventilation, and 46 patients died, totaling 32% mortality. Of the patients who entered the intensive care unit, 51% (n=22) died. Median time from onset of illness (prior to admission) to discharge was 22 days; the median time to death was 15 days. Three patients were treated with extracorporeal membrane oxygenation; none of the three survived.

> There was no significant association between immunosuppression withdrawal and mortality.

There was no difference in mortality across the 12 transplant centers. Patients who died were older than survivors (66 vs 60 years of age; $P<.001$); 71% of the patients >60 years of age were among those who died. There were no significant differences in outcomes between recipients of organs from living or deceased donors or between patients with <1 year since transplant compared with those with longer time since transplant. Among the patients who died, the time from onset of symptoms to admission was slightly shorter. There were no significant differences between survivors and nonsurvivors in race, comorbidities, induction therapy with depleting agents, maintenance immunosuppression, or therapy with renin angiotensin system inhibitors.

At admission, the respiratory rate was significantly higher in nonsurvivors compared with survivors, and diarrhea was less frequent in nonsurvivors (23.9% vs 44.9%). There were no significant differences between the two groups in other clinical characteristics at presentation.

Major laboratory markers were tracked from illness onset. Lymphopenia was present in 42% of patients. Baseline lymphocyte count was significantly higher in survivors compared with nonsurvivors (1.2 vs 0.7; $P=.004$), as was estimated glomerular filtration rate (eGFR; 53 vs 38 mL/min/1.73 m^2). There were no significant differences between the groups in white blood cell, hemoglobin, platelet, alanine aminotransferase, and creatine phosphokinase levels.

In 68% of the cases, mycophenolate (MMF/MPA) or everolimus was reduced or discontinued; calcineurin inhibitor was discontinued in 23% of the cohort (n=32). There was no significant association between immunosuppression withdrawal and mortality. Most patients received hydroxychloroquine (71%) and antibiotics (74%) and a smaller subset of patients received tocilizumab (13%) or antivirals (14%). With the exception of a slightly greater use of antibiotics in nonsurvivors, there was no significant difference in mortality among different treatments of COVID-19.

In univariable analysis, the odds of in-hospital mortality was higher in older patients and patients with higher respiratory rates, LDH, interleukin 6 (IL-6), and procalcitonin levels. In patients with diarrhea or higher eGFR levels, mortality risk was lower. Those variables were used for multivariable logistic regression models. In addition to age, there were associations between higher respiratory rate, lower eGFR, and higher IL-6 at admission and increased odds of death.

The researchers cited some limitations to the study, including differences in approaches and access to medications for the treatment of COVID-19, focusing on a homogenous cohort of hospitalized kidney transplant recipients, and the small sample size and retrospective design of the study.

"Kidney transplant recipients should be closely monitored as they appear to have a high mortality and acute kidney injury rate. Investigation of the best strategy of immunosuppression adjustment on COVID-19 will be needed," the researchers said. ■

TAKEAWAY POINTS

- Researchers in the TANGO International Transplant Consortium conducted a retrospective cohort study to examine the clinical outcomes of a cohort of 144 kidney transplant recipients who were hospitalized due to COVID-19 at 12 transplant centers in North America and Europe.
- During a median follow-up of 52 days, 52% of the patients developed acute kidney injury, 29% required intubation, and 32% died.
- The patients who died were older, and had lower lymphocyte counts and glomerular filtration rate levels compared with survivors.

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Results of BRIDGE and BRIGHT Trials of Pegunigalsidase Alfa for Fabry Disease

Final results from the phase 3 BRIDGE clinical trial of pegunigalsidase alfa were presented at the 17th Annual WorldSymposium 2021, according to a press release from Protalix BioTherapeutics, Inc, and Chiesi Global Rare Diseases. The conference that focused on lysosomal disease was held virtually February 8-12, 2021. Pegunigalsidase alfa is an investigational therapy in development for the potential treatment of Fabry disease.

Ales Linhart, MD, Charles University, Praha, Czech Republic, a principal investigator in the trials, reported the results in oral and poster sessions. The BRIDGE trial was a 12-month open label, single arm switch over study designed to evaluate the safety and efficacy of pegunigalsidase alfa, 1 mg/kg infused every 2 weeks, in up to 22 patients with Fabry disease previously treated with agalsidase alfa (marketed by Takeda Pharmaceutical Company as Replagal®) for at least 2 years and on a stable dose for at least 6 months. Replagal is not approved in the United States.

The data presented at the conference showed substantial improvement in renal function measured by mean annual estimated glomerular filtration rate (eGFR slope) in both men and women who were switched from agalsidase alfa to pegunigalsidase alfa. The mean annualized eGFR slope improved from –5.90 mL/min/1.73 m^2 per year while on agalsidase alfa to –1.19 mL/min/1.73 m^2 per year on pegunigalsidase alfa in all patients. Men improved from –6.36 mL/min/1.73 m^2 per year to –1.73 mL/min/1.73 m^2 per year and women improved from –5.03 mL/min/1.73 m^2 per year to –0.21 mL/min/1.73 m^2 per year. There was a decrease in patients with progressing or fast progressing kidney disease following the switch to pegunigalsidase alfa, and the majority of patients achieved stable status post-switch.

Of the 22 patients, 20 completed the 12-month treatment duration; 18 of those opted to roll over to a long-term extension study and continue treatment with pegunigalsidase alfa.

"The final analysis of the BRIDGE study in Fabry patients previously treated with agalsidase alfa demonstrates a potential benefit of pegunigalsidase alfa on renal function," Dr. Linhart said.

Topline results from the BRIGHT phase 3 clinical trial were also announced in February. The BRIGHT trial was designed to evaluate pegunigalsidase alfa, 2 mg/kg administered every 4 weeks, for the potential treatment of Fabry disease.

Among patients with Fabry disease previously treated with commercially available enzyme replacement therapy for a minimum of 3 years and on a stable dose administered every 2 weeks, topline results of the BRIGHT trial found that pegunigalsidase alfa administered by intravenous infusion every 4 weeks was well tolerated and stable clinical presentation was maintained. No new patients developed treatment-induced anti-drug antibodies following the switch to treatment with pegunigalsidase alfa.

In a press release, **Einat Brill Almon, PhD,** senior vice president and chief development officer at Protalix, said, "We are excited to share these topline results from the BRIGHT study, our third consecutive positive clinical trial of pegunigalsidase alfa following the phase 1/2 and the BRIDGE clinical studies. The results indicate that this investigational therapy is well tolerated and potentially an effective treatment for adult patients living with Fabry disease. We are encouraged to see that all of the patients who completed this study chose to enroll in the long-term extension study. Currently, 80% of the patients enrolled in the BRIGHT study have been treated with this treatment regimen for over 2 years. We look forward to advancing this study and further evaluating the results."

John Bernat, MD, PhD, University of Iowa, principal BRIGHT investigator, said, "Patients participating in the BRIGHT study have expressed their satisfaction with the once every 4 weeks regimen. Infusions of 2 mg/kg once every 4 weeks has the potential to enable patients to maintain their clinical status while reducing their number of treatments by half."

Dr. Almon added, "Of the 30 patients enrolled, 29 remained negative for anti-drug antibodies throughout the course of treatment. Of the 10 patients who were initially positive for anti-drug antibodies, four became negative for neutralizing antibodies at 12 months, suggesting tolerization by these patients. We find these immunogenicity data very encouraging and supportive to the positive benefit-risk profile of pegunigalsidase alfa." ■

AOPO Sets Annual Transplant Goal

The Association of Organ Procurement Organizations (AOPO) has announced an initiative to reach 50,000 organ transplants annually by 2026. The goal is a 50% increase over current annual figures, and it puts AOPO on a path to meet and exceed the expectation from the Centers for Medicare & Medicaid Services of 41,000 annual transplants by 2026.

In a press release from AOPO, **Joe Ferreira,** president, said, "Fifty thousand organ transplants mean many loved ones will have a chance of living better, longer lives. We recognize that organ procurement organizations (OPOs) are a vital component of a larger system and true success comes from OPOs, donor hospitals, transplant programs, and other stakeholders working together toward this common goal of increased organ transplants. We believe the four initiatives we have outlined will challenge our members, as well as other stakeholders, to collaboratively improve overall system performance which makes the goal of 50,000 organ transplants annually very achievable."

The four initiatives are: (1) expand collaboration; (2) reduce health inequality; (3) maximize organ utilization; and (4) drive innovation.

AOPO CEO **Steve Miller** said, "AOPO is committed to improving the organ donation and transplantation process to optimize every opportunity to pursue, recover, and transplant organs. By taking these steps to improve the system, we are honoring donors and donor families who made the selfless gift to donate and ensuring those waiting for a life-saving transplant receive organs as soon as possible."

Lupus Nephritis Often Diagnosed in Late Stages

According to a press release from GlobalData, more than 60% of diagnosed prevalent cases of lupus nephritis in the United Kingdom are seen in class IV and V, indicating a delay in the diagnosis of lupus nephritis.

Nneoma Okeke, MD, epidemiologist at GlobalData, said, "This could be due to an initial misdiagnosis of the disease, which results in late diagnosis or treatment beginning at a more advanced stage. According to GlobalData, diagnosed cases are increasing annually in the United Kingdom, with an annual growth rate of 0.47% highlighting the importance for an increase in awareness.

"Rare diseases such as lupus nephritis are continually being discovered. As such, COVID-19 could play a role in the development of a new rare disease. While the COVID-19 pandemic is still ongoing, it is difficult to predict what residual effects will be seen in populations affected by the virus. However, there have already been reports of 'long COVID-19' where symptoms persist for over three months after a patient is diagnosed. Those with long COVID-19 will need to be monitored and evaluated further to get a better understanding of this disease, which may evolve into a rare disease."

There are more than 6000 identified rare diseases affecting more than 300 million people worldwide. While most rare diseases are genetic, nearly 30% are the result of infections, allergies, and other environmental causes.

"Rare diseases affect millions of people worldwide, and increased awareness could lead to more timely diagnoses and treatment, improving the quality of life for those affected," Dr. Okeke said.

Strive Health Names Board Member

Rich Whitney, chairman and CEO of Radiology Partners, has been named to the board of directors of Strive Health, a leader in value-based kidney care. In a press release, **Chris Riopelle,** CEO at Strive Health, said, "Rick is a deeply experienced healthcare leader and entrepreneur who has been at the forefront of changing many areas of healthcare delivery, including kidney care. He brings outstanding depth and market knowledge that complements our innovative approach to value-based kidney care.

Rich will be an asset to our board and instrumental in our next phase of growth."

At Radiology Partners, Mr. Whitney has led the company from startup to nearly $2 billion in revenue. "Treating kidney disease is expensive and holds many opportunities to improve the patient journey," he said. "Strive Health is transforming the traditional approach to kidney care with advanced technology, and high-touch care teams that lower costs and help patients lead better lives. I am excited to join the board and work with the team."

Accolades and Awards for American Kidney Fund

Throughout the second half of 2020, the American Kidney Fund (AKF) received recognition for several of its resources and initiatives. Notable achievements were highlighted in a press release from AKF.

The fund received a Silver from the Digital Health Awards for the COVID-19 series on AFK's Advocacy Blog, and a Merit for the COVID-19 series on the fund's Kidney Today blog. Both blogs were launched to provide timely and accurate information about COVID-19 to patients with kidney disease.

The Kidney Kitchen website received a Gold from the dotcom Awards and a Silver from the Digital Health Awards. The site is a resource for the strict renal diet adhered to by patients with kidney disease. A Gold from the MarComm Awards, Silver from the Digital Health Awards, and two Bronze from the Omni Awards were presented for the YouTube video, How Well Do You Know Your Kidneys?

LaVarne A. Burton, AKF president and CEO, said, "Living with kidney disease is never easy, but 2020 presented an especially great challenge for kidney patients. Through our two blog series providing important updated information throughout the pandemic and resources like Kidney Kitchen easing the everyday burden of managing the strict renal diet, kidney patients across the nation turned to AKF and our resources to help manage one of the most difficult years in recent memory. Putting patients first is one of the values that drive our organization, and we are honored to have received this recognition for our work."

RenalytixAI and University of Utah Announce Partnership

RenalytixAI and the University of Utah announced a partnership to improve kidney health and reduce the risk of kidney failure for patients in the earliest stages of kidney disease. RenalytixAI is an artificial intelligence-enabled in vitro diagnostic company.

The partnership will implement the company's diagnostic platform, KidneyIntelX, in combination with advanced clinical management solutions to optimize patient care and improve outcomes among patients at University of Utah Health. KidneyIntelX is designed to aid identification of adults with early-stage chronic kidney disease and diabetes who are at risk for progression decline in kidney function or kidney failure.

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The partnership will enable the implementation of care navigation and pharmacy programs, behavioral and health economic assessments, in combination with data-driven analytics. KidneyIntelX will be deployed directly into the electronic health records system to enable access to more than 1700 clinicians for seamless test ordering and patient risk score reporting as part of standard clinical workflow.

In a press release from RenalytixAI, **John Inadomi, MD,** chair of the department of internal medicine at the University of Utah School of Medicine said, "Working with RenalytixAI to improve kidney disease management yields the University of Utah new avenues to innovate approaches to translational research, health informatics, and clinical care. This partnership is exciting because it is so forward looking."

James McCullough, CEO of RenalytixAI, said, "University of Utah's clinical and translational expertise presents an ideal opportunity to interrupt the devasting and costly effects of progressive chronic kidney disease from its earliest stages to help prevent irreversible late-stage kidney disease and dialysis. This partnership is enabling RenalytixAI to address a major health problem, help build the life sciences sector in Utah, and show the economic value of such a robust public private collaboration . We look forward to being able to announce additional innovative partnerships of this type in the future."

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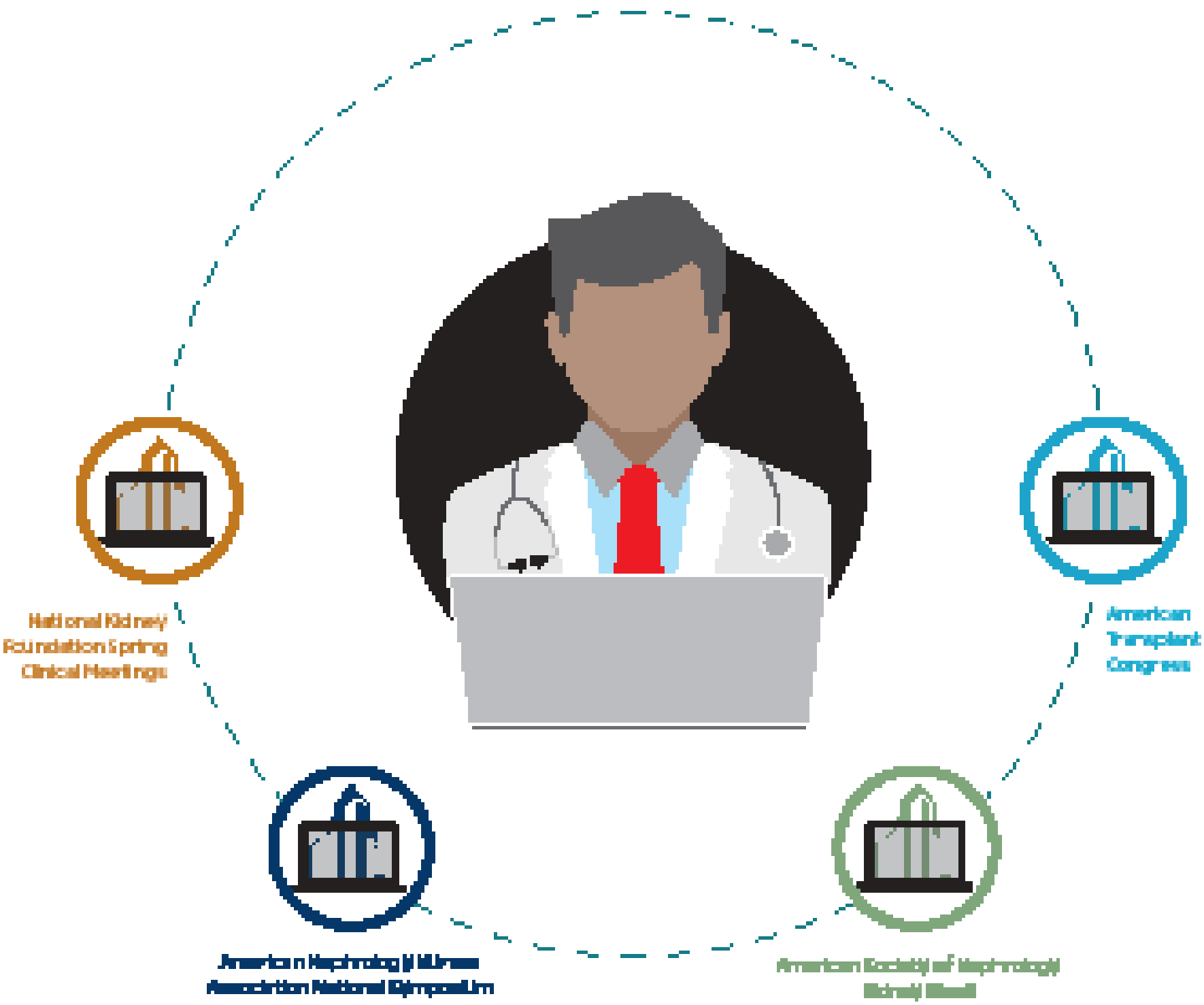
Education Campaign on Primary Hyperoxaluria Launched by AKF

In observance of Rare Disease Day on February 28, the American Kidney Fund (AKF) announced an awareness and education campaign focused on primary hyperoxaluria (PH), a disorder associated with recurrent kidney stones that commonly results in kidney failure. The campaign aims to increase awareness and understanding of PH types 1, 2, and 3, with particular emphasis on PH1, the most prevalent and severe type. The PH campaign was developed with support from Alnylam Pharmaceuticals, Inc. Campaign content was developed in partnership with the nonprofit Oxalosis & Hyperoxaluria Foundation (OHF).

"People living with primary hyperoxaluria need access to credible information and resources about the disease, and people who are undiagnosed but suffering from symptoms need to be aware that they could be at risk," said **LaVarne A. Burton,** president and CEO of AKF, in a recent press release. "We are grateful to Alnylam and the Oxalosis & Hyperoxaluria Foundation for their support in helping us to expand our educational resources on this vital topic and to provide people with PH the tools they need to encourage their family members to get tested for PH before kidney damage occurs."

Kim Hollander, executive director of OHF, said, "The OHF is dedicated to making sure that no one is missed in diagnosis, treatment, and care for PH. We are excited about these new resources, which will help give those living with the disease the opportunity to learn more. We are incredibly excited to partner with AKF to help expand awareness and outreach for PH." ■

Whether in person or virtual, we have you covered.



Nephrology Times goes to meetings!

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

Nephrology Times

Home Blood Pressure Treatment among Hemodialysis Patients Feasible and Safe

In the general population blood pressure is an important modifiable risk factor for cardiovascular events and mortality. Rates of those events are high in patients with kidney failure being treated with maintenance hemodialysis. However, management of blood pressure in that patient population is challenging due to U-shaped associations of systolic blood pressure measured at the dialysis unit prior to the start of dialysis with cardiovascular disease and death found in multiple observational studies.

The mortality risk is higher in hemodialysis patients with predialysis systolic blood pressure <140 mm Hg than in those with systolic blood pressure >140 mm Hg. The adjusted risk for mortality in patients with predialysis systolic blood pressure of 150 to 179 mm Hg is comparable, if not lower, than in patients with predialysis systolic blood pressure of 140 to 149 mm Hg, even after accounting for case-mix. Those data have led to uncertainty regarding management of blood pressure in dialysis patients among providers and guideline committees.

Many opinion leaders feel that measuring and targeting out-of-dialysis-unit blood pressure may not be feasible. **Nisha Bansal, MD, MAS,** and colleagues hypothesized that there would be more widespread measuring and targeting of home blood pressure if studies revealed the practicality of that approach. They conducted a pilot clinical trial (BOLD [Blood Pressure Lowering in Dialysis]) to test the feasibility, adherence to, safety, and tolerance of home blood pressure measurement and treatment. Results of the study were reported in the *American Journal of Kidney Diseases* [2021;77(1):12-22].

The nonblinded 4-month, parallel-group, randomized, controlled trial included 50 participants in the greater Seattle, Washington, and San Francisco, California, areas, and compared a strategy of targeting home systolic blood pressure <140 mm Hg versus predialysis systolic blood pressure <140 mm Hg. The primary outcomes of interest were feasibility, adherence, safety, and tolerability.

The 50 participants were treated by 10 different primary nephrologists at eight different dialysis units (seven nephrologists at the University of Washington and three at the University of California, San Francisco). Patients were randomly assigned to home blood pressure treatment or predialysis blood pressure treatment (25 in each group). Home and predialysis systolic blood pressures were ascertained every two weeks.

Mean age of the overall cohort was 56.6 years, 40% were female, 8% were Hispanic, 40% were Black, 28% were White, 22% were Asian, 6% were Pacific Islander, and 6% were other race. The primary kidney disease diagnosis was diabetes mellitus in 44%, hypertension in 18%, polycystic kidney disease in 2%, and other or unknown in 36%.

Of the 25 patients in the home dialysis group, home systolic blood pressure was 4.6 mm Hg lower on average than predialysis blood pressure at baseline. The correlation between home systolic blood pressure and predialysis blood pressure was modest ($r=0.61$; $P=.001$).

Overall, 49 of the 50 participants completed the study successfully. The participant who withdrew did so because she received a deceased donor kidney transplant.

During the 4-month intervention period, among participants in the home blood pressure group 97.4% of study visits had at least one home blood pressure measurement completed and transmitted to the research team. Throughout the 16-week study period, adherence to home blood pressure measurements was high and consistent. All participants in the home blood pressure treatment arm were able to complete at least one blood pressure measurement during weeks 1 to 4; 96% of participants completed one home measurement in weeks 5 to 16.

Of the 25 participants in the home blood pressure group, 84% (n=21) completed a survey on the experience; 95% of those (20/21) strongly agreed or agreed that it was "easy using the home blood pressure device to measure blood pressure," 86% (18/21) strongly agreed or agreed that "remembering to measure blood pressure using the home blood pressure device twice over 2 weeks was easy," and 100% (21/21) said they "would recommend patients with [end-stage kidney disease] use this home blood pressure device to measure their blood pressure at home."

The percentage of dialysis treatments with either excessively low or high pre- or post-dialysis systolic blood pressures was small and similar in the two groups. The rates of syncope, falls, and flash pulmonary edema were also comparable between the two groups.

Among participants in the home blood pressure treatment group the frequency of intradialytic hypotension was lower than among those in the predialysis treatment group, although the difference was not statistically significant (8.3% vs 13.4%; *P*=.3). The two groups were similar in the frequency of reported cramping, dizziness, and lightheadedness during the 4-month intervention period.

Those in the home blood pressure group reported more symptoms of fatigue compared with those in the predialysis treatment group (32% vs 16%); the number of participants reporting fatigue were similar in the two groups (15/25 vs 16/25). The groups were similar in the proportion of dialysis treatments shortened for reasons of cramping, low blood pressure, or symptoms of low blood pressure. Self-reported time to recovery from dialysis was similar in the two groups.

Limitations to the findings cited by the authors included the small sample size and the short duration of the intervention.

In summary, the researchers said, "In this pilot trial we found that measuring and treating home blood pressure was feasible and well tolerated. Further, we did not observe any strong signals to suggest any safety concerns. Our data support the notion that repeat measurement of home blood pressure is a pragmatic way to obtain out-of-dialysis unit blood pressure in many dialysis patients in the real world. A larger trial with more participants and longer follow-up will be needed to understand the value of home blood pressure measurements as a guide to antihypertensive therapies among hemodialysis patients." ■

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COVID-19

AKI among Hospitalized COVID-19 Patients

Journal of the American Society of Nephrology. 2021;32(1):151-160

Early reports have indicated that patients with COVID-19 often develop acute kidney injury (AKI), associated with poor outcomes. There are limited data on AKI among patients hospitalized with AKI in the United States.

Lili Chan, MD, and colleagues conducted a retrospective, observational study of a review of data from electronic health records of adults 18 years of age with laboratory-confirmed COVID-19 admitted to the Mount Sinai Health System from February 27 to May 30, 2020. The review examined the frequency of AKI as well as dialysis requirement, AKI recovery, and adjusted odds ratios (aORs) with mortality.

A total of 3993 patients were hospitalized with COVID-19 during the study period. Of those, 46% (n=1835) developed AKI, and 19% (n=347) of those patients required dialysis. Proportions of AKI requiring dialysis with stages 1, 2, or 3 were 39%, 19%, and 42%, respectively. Twenty-four percent of patients (n=976) were admitted to the intensive care unit and 76% of those (n=745) experienced AKI.

Results of urine studies were available for 435 patients with AKI. Of those, 84% had proteinuria, 81% had hematuria, and 60% had leukocyturia. Independent predictors of AKI were chronic kidney disease, male sex, and higher serum potassium level at admission.

Among patients with AKI, in-hospital mortality was 50%, compared with 8% among patients without AKI (aOR, 9.2; 95% confidence interval, 7.5-11.3). Of patients with AKI who survived to discharge, 35% had not recovered to baseline kidney function at time of discharge. An additional 28 of 77 patients who had not recovered kidney function at discharge did so on posthospital follow-up.

"AKI is common among patients hospitalized with COVID-19 and is associated with high mortality. Of all patients with AKI, only 30% survived with recovery of kidney function by the time of discharge," the researchers said.

COVID-19 Outcomes among Patients on RRT

Journal of the American Society of Nephrology. 2021;32(2):385-396

Frail, elderly patients and those with multiple chronic comorbidities are disproportionally affected by SARS-CoV-2. It is unclear whether patients receiving renal replacement therapy (RRT) face an additional risk due to their specific exposure and complex immune dysregulation.

Johan De Meester, MD, and colleagues in Belgium conducted a prospective, multicenter, region-wide registry study designed to define the incidence, characteristics, and outcomes of SARS-CoV-2 infection in adult patients on RRT versus the general population from March 2, 2020, to May 25, 2020. The study included all patients undergoing RRT in the Flanders region of Belgium.

At the end of the initial epidemic wave, the crude and age-standardized cumulative incidence rates of SARS-CoV-2 infection were 5.3% versus 2.5%, respectively, among 4297 patients on hemodialysis, and 1.4% versus 1.6%, respectively, among 3293 kidney transplant recipients (compared with 0.6% in the general population). Crude and age-standardized cumulative mortality rates were 29.6% versus 10.9%, respectively, among the hemodialysis patients, and 14.0% versus 23.0%, respectively, among the kidney transplant recipients (compared with 15.3% in the general population).

When compared with mean mortality rates during the same 12-week period in 2015-2019, there was no excess mortality in the hemodialysis population because COVID-19 mortality was balanced by lower than expected mortality among uninfected patients. Only 0.18% of kidney transplant recipients died of SARS-COV-2 infection.

In conclusion, the researchers said, "Morality associated with SARS-CoV-2 infection is high in patients on RRT. Nevertheless, the epidemic's overall effect on the RRT population remained remarkably limited in Flanders. Calculation of excess mortality and age standardization provide a more reliable picture of the mortality burden of COVID-19 among patients on RRT."

AKI in COVID-19 Positive Patients

PLOS Medicine. doi.org/10.1371/journal.pmed.1003406

Initial data show a high incidence of acute kidney injury (AKI) in patients with COVID-19. However, it is unclear whether COVID-19 is an independent risk factor for AKI. There are also few data on differences between AKI associated with COVID-19 and AKI due to other causes. **Nitin V. Kolhe, MBBS, MD,** and colleagues conducted a retrospective cohort study to examine the relationship between COVID-19, AKI, and outcomes in patients admitted to two acute hospitals in Derby, United Kingdom.

The analysis included electronic data from 4759 hospitalized patients who were tested for COVID-19 between March 5, 2020, and May 12, 2020. Data were linked to electronic patient records and laboratory information management systems. The primary outcome of interest was AKI; secondary outcomes included in-hospital mortality, the need for ventilatory support, admission to the intensive care unit, and length of stay.

Compared with patients in the COVID-19 negative group (n=3374), those with COVID-19 (n=1161) were older (72.1 vs 65.3 years; $P<.001$), were more likely to be male (56.6% vs 44.9%; $P<.001$), were more likely to be of Asian ethnicity (8.3% vs 4.0%; $P<.001$), and less likely to be White (75.5% vs 82.5%; $P<.001$).

A total of 304 COVID-19 positive patients (26.2%) developed AKI, compared with 420 (12.4%) of COVID-19 negative patients (AKI controls).

The odds of developing AKI were higher among COVID-19 positive patients 65 to 84 years of age (odds ratio [OR], 1.67; 95% confidence interval [CI], 1.11-2.50), those needing mechanical ventilation (OR, 8.74; 95% CI, 5.27-14.77), those with congestive heart failure (OR, 1.72; 95% CI, 1.18-2.50), chronic liver disease (OR, 3.43; 95% CI, 1.17-10.00) and chronic kidney disease (OR, 2.81, 95% CI, 1.97-4.01). Mortality was higher in COVID-19 patients with AKI compared with COVID-19 patients without AKI (60.5% vs 27.4%; $P<.001$. AKI was an independent predictor of mortality (OR, 3.27; 95% CI, 2.39-4.48).

Mortality was higher in COVID-19 positive patients with AKI than in the AKI control group (60.5% vs 27.6%; $P<.001$).

In conclusion, the researchers said, "We observed a high incidence of AKI in patients with COVID-19 that was associated with a 3-fold higher odds of death than COVID-19 without AKI and a 4-fold higher odds of death than AKI due to other causes. These data indicate that patients with COVID-19 should be monitored for the development of AKI and measures taken to prevent this."

DIABETES

Gaps in Care for Hemodialysis Patients with Diabetes

Kidney360. doi.org/10.34067/KID.0007082020

Patients with diabetes and end-stage kidney disease requiring chronic hemodialysis face numerous healthcare challenges. **Kristin K. Clemens, MD,** and colleagues in Canada, conducted a population-based retrospective study in that patient population to determine the prevalence of gaps in diabetes care, explore regional differences in care, and define predictors of care gaps.

The study included adults with prevalent diabetes mellitus who were receiving in-center hemodialysis as of January 1, 2018. The researchers examined the proportion of patients with (1) insufficient or excessive glycemic monitoring; (2) suboptimal screening for diabetes-related complications (retinopathy and cardiovascular screening); (3) hospital encounters for hypo- or hyperglycemia; and (4) hospital encounters for hypertension in the 2 years prior (1/1/2016-1/1/2018). Patient, provider, and health system factors associated with more than one care gap were identified, and multivariable logistic regression was used to determine predictors. Geographic Information Systems were used to examine spatial variation in gaps.

The study identified 4173 patients with diabetes who were receiving in-center hemodialysis. Mean age was 67 years, 39% were female, and the majority were of lower socioeconomic status. More than one care gap was identified in approximately 42% of the cohort; the most common care gap was retinopathy screening (53%). Significant predictors of more than one gap in care were younger age, female sex, shorter duration of diabetes, dementia, fewer visits to a specialist, and not receiving care from a physician for diabetes. There was evidence of spatial variation in care gaps across the study region.

In conclusion, the researchers said, "There are opportunities to improve diabetes care in patients receiving in-center hemodialysis, particularly screening for retinopathy. Focused efforts to bring diabetes support to high-risk individuals might improve their care and outcomes."

END-STAGE KIDNEY DISEASE

Taste Changes in Patients with ESKD

Journal of Renal Nutrition. 2021;31(1):80-84

Patients with end-stage kidney disease (ESKD) often have gastrointestinal symptoms, leading to reduced health-related quality of life as well as malnutrition. **Jessica Dawson, MNutDiet,** and colleagues conducted a study to describe the prevalence of taste changes among patients with ESKD and examine whether there is an association between taste changes and the presence or severity of other nutrition-related symptoms and malnutrition.

The retrospective audit included 298 patients with ESKD on conservative, nondialysis management or renal replace-

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ment therapy with available results on an assessment of taste changes. A Likert scale was used to assess taste change, from none to overwhelming. Patients also provided descriptions of taste changes. Other outcomes of interest were gastrointestinal symptoms collected using the iPOS-renal symptom inventory, nutritional status, and biochemical parameters.

Of the 298 patients in the study cohort, 38% reported taste changes. There were significant associations between taste changes and upper gastrointestinal symptoms (nausea, vomiting, anorexia, and dry/sore mouth) and malnutrition.

"Our findings indicate that taste changes are highly prevalent and probably underrecognized in ESKD. Further investigation of the association with malnutrition is needed. Future trials are needed to evaluate strategies to manage taste changes in this population," the researchers said.

HEPATITIS C

DAA-Based Treatments in Patients with Renal Impairment

Nephrology. 2020;25(11):829-838

Hongling Yang, PhD, and colleagues conducted a study designed to further determine the efficacy and safety of direct-acting antiviral (DAA)-based treatments in patients with hepatitis C virus (HCV) infection. The researchers searched MEDLINE, EMBASE, and the Cochrane Library for relevant studies.

Studies examining the efficacy and safety of DAA-based treatments against HCV infection in patients with renal impairment and HCV infection were eligible for inclusion in the analysis. Outcomes included efficacy and safety. An inverse-variance weighted random effect model and Freeman-Tukey double arcsine transformation were used to obtain summary estimates. The final review included 27 studies representing 1048 participants. The majority of included studies were of fair quality with Newcastle-Ottawa scale scores between 4 and 6.

The pooled virologic response rates at the end of treatment or 4, 12, and 24 weeks of treatment were 97.0% (95% confidence interval [CI], 94.0%-99.0%), 80.9% (95% CI, 49.3%-98.7%), 94.1% (95% CI, 91.6%-96.3%), and 89.6% (95% CI, 75.5%-98.1%), respectively. The pooled relapse rate was 6.4% (95% CI, 3.4%-10.4%).

The pooled incidence of adverse events and serious adverse events leading to discontinuation were 47.6% (95% CI, 35.0%-60.4%), and 2.9% (95% CI, 1.4%-5.0%), respectively. There was high heterogeneity among studies for rates of sustained virologic response at 4 and 24 weeks. With the exception of relapse rate, formal statistical testing did not identify the presence of publication bias for all measured outcomes.

In conclusion, the researchers said, "The results support the efficacy and safety of DAA-based treatments in this population. Future studies with better design, larger sample size, and longer follow-up will be the next step."

HYPERKALEMIA

Risk of Recurrence of RAASi-Related Hyperkalemia

Clinical Journal of the American Society of Nephrology. doi.org/10.2215/CJN.12990820

There are few data available on the optimal ambulatory management of renin-angiotensin-aldosterone system inhibitor (RAASi)-related hyperkalemia to reduce the risk of recurrence. **Gregory L. Hundemer, MD,** and colleagues conducted a study to examine the risk of recurrence of hyperkalemia on the basis of outpatient pharmacologic changes following an episode of RAASi-related hyperkalemia.

The population-based, retrospective cohort study included 49,571 older adults (mean age, 79 years) who developed hyperkalemia (defined as potassium ≥5.3 mEq/L) while on a RAASi. The patients were grouped as: (1) no intervention; (2) discontinuation of RAASi; (3) decrease in RAASi dose; (4) new diuretic; (5) diuretic dose increase; or (5) sodium polystyrene sulfonate within 30 days.

The primary outcome of interest was recurrence of hyperkalemia. Secondary outcomes were cardiovascular events and all-cause mortality within 1 year.

Twenty-three percent of the cohort received a pharmacologic intervention. Of those, the most commonly prescribed strategy was RAASi discontinuation (74%), followed by decrease in RAASi (15%), increase in diuretic (7%), new diuretic (3%), and sodium polystyrene sulfonate (1%).

Within 1 year, a total of 16,977 recurrent hyperkalemic events occurred. Compared with no intervention (35%, reference group), the cumulative incidence of recurrent hyperkalemia was lower in the RAASi discontinuation group (29%; hazard ratio [HR], 0.82; 95% confidence interval [CI], 0.78-0.85). There was no difference with RAASi dose decrease (36%; HR, 0.94; 95% CI, 0.86-1.02), new diuretic (32%; HR, 0.95; 95% CI, 0.78-1.17), or diuretic increase (38%; HR, 0.99; 95% CI, 0.87-1.12), and a higher incidence with sodium polystyrene sulfonate (55%; HR, 1.30; 95% CI, 1.04-1.63).

There was no association between RAASi discontinuation and a higher risk of 1-year cardiovascular events (HR, 0.96; 95% CI, 0.91-1.02) or all-cause mortality (HR, 1.05; 95% CI, 0.96-1.15) compared with no intervention.

In conclusion, the researchers said, "Among older adults with RAASi-related hyperkalemia, RAASi discontinuation is associated with the lowest risk of recurrent hyperkalemia, with no apparent increase in short-term risks for cardiovascular events or all-cause mortality."

TRANSPLANTATION

Racial Disparities in Accruable Time on Transplant Wait List

Journal of the American Society of Nephrology. doi.org/10.1681/ASN.2020081144

Patients whose estimated glomerular filtration rate (eGFR) is ≤20 mL/min/1.73 m^2 may accrue wait time for kidney transplantation. However, progression of kidney disease is faster in Black patients than in White patients, potentially leading to disparities in accruable time on the kidney transplant waitlist prior to initiation of dialysis.

Elaine Ku, MD, MAS, and colleagues conducted an analysis to compare differences in accruable wait time and transplant preparation by CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) estimating equations in participants in the Chronic Renal Insufficiency Cohort (CRIC), using estimates of kidney function by creatinine ($eGFR_{cr}$), cystatin C ($eGFR_{cy}s$), or both ($eGFR_{cr\text{-}cys}$). Weibull accelerated failure time models were used to determine the association between race (non-Hispanic Black or non-Hispanic White) and time to end-stage kidney disease (ESKD) from an eGFR of ≤20 mL/min/1.73 m^2. The researchers then estimated how much higher the eGFR threshold for waitlisting would be required to achieve equity in accruable preemptive wait time for the two groups.

Based on $eGFR_{cr}$, 444 CRIC participants were eligible for waitlist registration. However, the potential time between eGFR ≤20 mL/min/1.73 m^2 and ESKD was 32% shorter for Black patients than for White patients. By $eGFR_{cys}$, 435 participants were eligible, and Black participants had 35% shorter potential wait time compared with White participants. By $eGFR_{cr\text{-}cys}$, 461 participants were eligible and Blacks had a 31% shorter potential wait time than Whites.

The researchers estimated that registering Black patients on the waitlist as early as an eGFR of 24 to 25 mL/min/1.73 m^2 might improve racial equity in accruable wait time prior to onset of ESKD.

"Policies allowing for waitlist registration at higher GFR levels for Black patients compared with White patients could theoretically attenuate disparities in accruable wait time and improve racial equity in transplant access," the researchers said. ■

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Sarah Tolson

Audits: Friend, not Foe

Around 20 years ago I took a course from a local college that was designed to teach students to be medical office specialists. At the time, this meant I would be able to work at a front desk, as a certified medical coder or as a medical biller. When I began working as a medical biller, I realized that the course I had taken only gave me a comprehensive medical terminology overview, a better understanding of anatomy, and not a whole lot about how to be a successful medical biller. One thing our billing instructor drilled into our heads was that audits were terrible, scary, heartburn-inducing events that we should avoid at all costs. I carried that phobia of audits around with me until I began performing internal audits for my employer, where I learned what a helpful tool a proactive audit could be.

One of the tenets of medical billing is that you only bill for services rendered. Related to this tenet is "if it is not documented, it did not happen." These two tenets (along with many related rules and regulations that govern medical documentation and coding standards) guided the internal audits I performed. Reviewing billing entries and comparing them to medical records is incredibly tedious work, and it can be difficult to sit down with the individual you have audited and review their errors. The best part of an audit is using it as a tool to identify areas for process improvement and potential increases in revenue.

WHY PERFORM AN AUDIT?

During my time at Sceptre Management, I have been fortunate to have the opportunity to hone my auditing skills on internal employee audits as well as many diverse types of audits for our clients. Aside from being well prepared for an audit by Medicare or another entity, there are many ways practices and dialysis facilities can benefit from an internal or third-party audit.

Audits help analyze coding and documentation to provide feedback of the practice's current work to revenue capture ratio. An audit may determine that a practice's documentation and code selection is adequate, leaving the practice with confidence that they would do well in a payer audit. An audit may also reveal opportunities for providers to improve their code selection based on their documentation to maximize revenue.

TYPES OF AUDITS

There are many types of audits that are relevant to nephrology practices and dialysis facilities. Here are some of the most common:

General Audit

- General audits provide an overview of the documentation and code selection for the entire practice. These audits can be either prospective (before billing takes place) or retrospective (after billing takes place). Performing a general audit retrospectively helps to identify problems with payer reimbursement and denials. General audits provide an overview of the entire practice and may identify areas of potential education.

Provider Comparison Audit

- Provider comparison audits are helpful to ensure all providers in the practice are complying with documentation and coding requirements as well as capturing all available revenue.

Service Specific Audit

- A service specific audit is a great tool to use when a nephrology practice begins providing a new therapy or service to its patients. This type of audit focuses on the relationship between the diagnosis, service, documentation, and resultant claims, ensuring medical necessity is demonstrated and billing is compliant.

Focused Audit

- Focused audits are usually performed after a general audit or provider comparison audit identifies an area of potential improvement. Focused audits are designed to hone in on a particular area of concern and help identify effective corrective measures.

Audit Frequency and Auditor

- The best practice for general audits is to conduct them annually. However, depending on the specific nephrology practice or dialysis facility, bi-annual audits may be more beneficial. In the event an audit uncovers a concern with a provider or service, regular audits should be used to verify the efficacy of education and corrective actions taken to address the concern.

In the event you opt to perform an internal audit using your existing staff, the individual selected as the auditor should have familiarity with documentation requirements and coding guidelines. It is also helpful for your selected auditor to be detail oriented and possess organizational skills. There are companies a nephrology practice or dialysis program can hire to perform these types of audits. When deciding on a company to audit your practice, it is helpful to look for a company that not only has staff who are licensed coders and medical auditors but also experience in your practice's specialty and good references. ■

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

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