Nephrology Times

Practical News, Trends, and Analysis

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GFR Estimations without Current Race-Based Equations

The use of indicators for Black race in equations commonly used to estimate glomerular filtration rate (GFR) from the level of serum creatinine has come under scrutiny and criticism of late.

Adults who identify as Black have, on average, higher levels of serum creatinine, independent of age, sex, and GFR, compared with those who do not identify as Black. Equations developed to estimate GFR from serum creatinine level have incorporated information on race, a practice that should, it has been argued, be eliminated. The inclusion of race suggests that race is a biologic rather than primarily a social construct. Nonetheless, concerns have been raised regarding possible misclassification of estimated GFR resulting from the removal of the race coefficient from current equations.

Chi-yuan Hsu, MD, and colleagues conducted an analysis of data from a large, national study involving adults with chronic kidney disease (CKD). The researchers sought to gain insights into the relationships among race, genetically derived ancestry, serum creatinine level, and serum cystatin C level to identify strategies for the accurate estimation of GFR without reliance on racial classifications. Results were reported online in the *New England Journal of Medicine* [doi:10.1056/NEJMoa2103753].

The study cohort was comprised of participants enrolled in the CRIC

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Immune Response Rate In Dialysis Patients after SARS-CoV-2 Vaccination

Risk of mortality among adults on dialysis who are infected with SARS-CoV-2 is higher than that among adults not receiving dialysis. The majority of clinical trials of patients with SARS-CoV-2 infection have not included patients with end-stage kidney disease (ESKD); in patients in that population, the efficacy of SARS-CoV-2 vaccines is assessed using immunogenicity.

To date, there have been few systematic reviews of the immunogenicity rates of patients receiving dialysis. **Ja-Jen Chen, MD,** and colleagues conducted a systematic

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Pulmonary Hypertension in CKD and Risk of Adverse Events and Mortality

Pulmonary hypertension (PH) affects up to 10% of individuals more than 65 years of age and is more common among those with chronic kidney disease (CKD), due in part to the high prevalence of heart failure, volume overload, and vascular calcification in that population. Results of previous studies have found a prevalence of PH of 20% to 15% at various stages of CKD.

Even after accounting for underlying cardiovascular and other comorbidities, the mortality risk in patients with PH is amplified in the presence of CKD. Associations of elevated pulmonary artery pressure and PH with adverse cardiovascular events and mortality have also been consistently noted in CKD. Most of those prior studies of PH in CKD included relatively younger patients; there are few data available on the associations between PH and outcomes among elderly patients with CKD.

Sankar D. Navaneethan, MD, MS, MPH, and colleagues conducted a retrospective, observational study with a matched cohort design to examine the associations of PH with morality, kidney failure, and hospitalization (both cardiovascular and non-cardiovascular) in a cohort of Medicare beneficiaries with diagnosed CKD. Results were reported in the *American Journal of Kidney Diseases* [2021;78(5):700-708].

The primary outcome measure of interest was time to all-cause mortality

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Prolyl Hydroxylase Inhibitors for Anemia Treatment in CKD Patients: What's the Unmet Need?

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Prolyl hydroxylase inhibitors (PHIs) stimulate the erythropoietin gene to produce endogenous erythropoietin and represent a potentially exciting alternative class of agents over conventional parenterally administered erythropoiesis-stimulating agents (ESA) in treating anemia of chronic kidney disease (CKD). Unlike ESAs, PHIs are oral rather than injectable. And, unlike conventional ESAs, appear to modulate iron homeostasis in the body. Thus, PHIs represent an oral agent that corrects anemia of kidney disease. The primary mechanism for this is activating the erythropoietin gene, but a potential collateral benefit could be also favorably influencing iron metabolism.

Three PHIs are under clinical development. The first in class, roxadustat, recently failed to receive approval by the US FDA, but is approved in Europe. The other two agents, vadadustat and daprodustat, will likely be reviewed by the US FDA in the spring and fall of 2022, respectively *[disclosure: I am the academic lead for the Ascend Clinical Trial program for daprodustat].*

We recently published two papers in the *New England Journal of Medicine*[1,2] [see page 24] that randomly assigned either dialysis or non-dialysis patients to daprodustat or conventional ESA. The two coprimary outcomes were hemoglobin efficacy and a cardiovascular composite (MACE or all-cause mortality, non-fatal myocardial infarction, and non-fatal stroke). In each of the trials, daprodustat was non-inferior or no worse than conventional ESA for MACE, and for correction of hemoglobin; daprodustat was also well tolerated.

Even with approval, however, the biggest question that most nephrologists will ask about PHIs is, "Why use them?"

The obvious advantage of PHIs over conventional ESAs is that an oral medication is generally more convenient for patients compared to an injectable agent, even if it is self-administered as a subcutaneous injection. Still, perhaps more important than this is that the widespread availability of an oral agent (once approved) is likely to increase accessibility to anemia treatment especially among CKD patients not undergoing dialysis. This is because patients often need to jump through hoops to receive anemia treatment. In dialysis patients a conventional ESA is administered three times each week and dialysis unit staff administer the drug in a very controlled and regulated manner. In patients not on dialysis (but also those on who are on peritoneal dialysis and/or home dialysis), an oral drug such as PHI is easy for patients to take and there are no logistical hoops once the drug is dispensed.

As the awareness about PHIs as a new class of anemia drugs increases after their approval, many nephrologists are going to ask: "What are the benefits for patients with respect to hard end points, like mortality or cardiovascular complications?" Of course, this is an important point and the phase 3 PHI trials, including for daprodustat, have not demonstrated superiority over conventional ESA for hard end points. But they weren't designed to, although if there were a major favorable signal, it would have been observed. That said, it is conceivable that using moderate doses of ESA has similar safety to using an orally administered PHI agent, and that no signal being observed is because at lower doses to incompletely correct anemia, conventional ESAs are quite safe. A question that hasn't been answered is whether PHIs might end up being safer when the goal of treatment is to achieve a normal hemoglobin.

PHIs induce endogenous production of erythropoietin, and erythropoietin levels are at a fraction of peak levels compared with those observed after administration of intravenous or subcutaneous epoetin alfa. A randomized trial using a PHI in both arms, one arm probably at a lower and the other at higher dose of PHI that aims for a normal Hb in one arm versus the FDA standard of 10-11 g/dL in the other has not been done.

In patients not on dialysis (but also those who are on peritoneal dialysis and/or home dialysis), an oral drug such as PHI is easy for patients to take and there are no logistical hoops once the drug is dispensed.

So, my take is that there are still some ways to go to truly understanding the potential of PHIs in treating the anemia of CKD. There is no question that PHIs represent a major development and have much promise. They do meet an unmet need. The next step is for the FDA to approve one or more PHI agents. After that, or in parallel, additional studies are needed, including those that explore the effect of PHIs on iron metabolism. It's likely that phase 4 studies will need to be considered to tease out the potential for beneficial effects and/or evaluate safety in subgroups of patients. And the experiment of evaluating whether a PHI can be used to normalize the Hb in CKD patients will need to be considered. ■

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2. Singh AK, Carroll K, McMurray JJV, et al. Daprodustat for the Treatment of Anemia in Patients Not Undergoing Dialysis. *N Engl J Med.* 2021 Dec 16;385(25):2313-2324. doi: 10.1056/NEJMoa2113380. Epub 2021 Nov 5. PMID: 34739196.

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review and meta-analysis to investigate immunogenicity rates among patients with ESKD following receipt of SARS-CoV-2 vaccines. The study also examined potential risk factors for vaccine nonresponse and significant differences in antibody response rates between adults receiving dialysis and those not receiving dialysis. Results were reported online in *JAMA Network Open* [doi:10.1001/jamanetworkopen.2021.31749].

The search included the PubMed, Embase, and Medline databases. The researchers searched for relevant articles published between January 1, 2020, and July 30, 2021. Keywords used to retrieve preprint articles from the medRxiv server included dialysis, end-stage renal disease, SARS-CoV-2 vaccine, ChAdOx1 nCoV-19, Oxford-AstraZeneca, mRNA vaccines, BNT162b2, and mRNA-1273.

Inclusion criteria were studies on patients with ESKD receiving hemodialysis or peritoneal dialysis, adult populations and those that reported postvaccination antibody response rates. The search was limited to clinical trials, letters, commentaries, and preprint articles published in English after 2019.

The primary outcome of interest was postvaccination immunogenicity rates among patients with ESKD. The secondary outcome was the immunogenicity rates of patients with ESKD receiving dialysis compared with those of people without ESKD, not receiving dialysis.

A total of 669 potentially eligible studies were identified. Following exclusion of irrelevant studies and those not addressing the outcome of interest or those only based on ESKD with kidney transplant population, the final meta-analysis included 32 studies, including six preprint articles.

The 32 studies represented 4917 participants, and four vaccines were administered (JNJ-78436735 [Janssen], mRNA-1273 [Moderna], BNT162b2 (Pfizer-BioNTech], and AZD1222 [AstraZeneca]). Most of the participants received the BNT162b2 vaccine. None of the participants received a mixture of different SARS-CoV-2 vaccines.

The six preprint articles from the medRxiv server and another five from enrolled studies only reported the immunogenicity rates of patients receiving dialysis who did not complete vaccination protocol (e.g., only received one dose of the BNT162b2 vaccine). Other articles reported an antibody response after the second dose with or without reporting the response rate after the first dose. Three studies included immunogenicity rates following the booster shot.

Mean age of participants ranged from 60.5 years to 76 years. The predominant dialysis modality was hemodialysis. Five studies included patients receiving a mix of hemodialysis and peritoneal dialysis, and one study enrolled patients only receiving peritoneal dialysis. Mean dialysis vintage ranged from 1.7 years to 7 years. All included studies had a low-to-moderate risk of bias.

Results of the meta-analysis demonstrated that the overall immunogenicity rate in patients receiving dialysis was 86% (95% confidence interval [CI], 81%-89%), with high heterogeneity (I^2=90.6%).

A second meta-analysis was performed to assess whether there was a significant difference in antibody response rate between patients receiving dialysis and individuals not receiving dialysis (control). Immunogenicity rates in the dialysis group after both the first and second dose were significantly lower than in the control group (relative risk [RR], 0.61; 95% CI, 0.47-0.79; I^2=70.2% and RR, 0.88; 95% CI, 0.82-0.93; I^2=72.2%, respectively). The lower response rate of patients in the dialysis group relative to those in the control group was less apparent in the second dose than that in the first dose (P=.007).

Results of a sensitivity analysis that excluded the preprinted and unpublished articles were highly consistent with the primary analysis results; the pooled immunogenicity rate was 85% (95% CI, 79%-90%), with high heterogeneity (I^2=89.8%).

To identify the potential source of heterogeneity, subgroup analysis was performed. The antibody response rate was lowest in patients lacking complete vaccination protocols and was highest in those with third booster vaccine protocols. The postvaccination immune rate of participants with a history of SARS-CoV-2 infection was significantly higher than that of participants without prior SARS-CoV-2 infection. There was no significant difference in response rate between those receiving hemodialysis and those receiving peritoneal dialysis.

There was significant correlation between a higher prevalence of diabetes and a lower immune response rate. There were no significant associations between mean age, proportion of women, dialysis vintage, and response rate.

The researchers cited some limitations to the study findings, including measuring vaccination efficacy based on the immuobridging approach that relies on humoral immunity.

In conclusion, the authors said, "This systematic review and meta-analysis found that patients with ESKD had a pooled postvaccine immune response rate of 86%. Compared with the nondialysis group, patients receiving dialysis had a lower probability of producing an antibody response after receiving the first dose and the second dose of a COVID-19 vaccine. Furthermore, this difference between nondialysis and dialysis populations became statistically smaller after the second dose. Scheduling the second vaccine dose without delay might be preferable in patients receiving dialysis. Prevalence of diabetes had an inverse linear association with the immune response rate. Further investigations of immune response and side effects of SARS-CoV-2 vaccines in patients receiving dialysis, as well as the benefits and real world clinical efficacy of different vaccine protocols, different types of vaccine, are warranted." ■

TAKEAWAY POINTS

- Researchers conducted a systematic review and meta-analysis to examine the immune response after SARS-CoV-2 vaccination of people receiving dialysis. The review included 32 studies.
- In the dialysis group, the overall response rate was 86%. The response rate after the first and second vaccine doses was lower in the dialysis group than that in the non-dialysis group.
- The prevalence of diabetes had an inverse linear association with immunogenicity rate.

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(Chronic Renal Insufficiency Cohort) study, a multicenter, prospective, observational study that included racially and ethnically diverse patients. The current analysis included a randomly selected subgroup of 1423 CRIC participants. Of those, 1248 participants had data available on race as reported by the participant, genetic ancestry markers, as well as serum creatinine, serum cystatin C, and 24-hour creatinine levels and were included in the final analysis.

Of the 1248 participants in the current study, 37% (n=458) identified as Black or Black and multiracial; the median percentage of African ancestry was 82.6% in those who identified as Black and 0.2% in those who identified as non-Black. Standardized differences between Black and non-Black participants in regard to age, sex, and measured eGFR were low. Mean serum creatinine levels were higher in Black participants; mean cystatin C levels were not higher in Black participants.

In the validation data set, among the Black participants estimated GFR calculated on the basis of level of serum creatinine, age, and sex alone underestimated measured GFR by a median of 3.99 mL/min/1.73 m^2 (95% confidence interval [CI], 2.17-56.2). Among non-Black participants, the median difference between measured and estimated GFR was –0.92 mL/min/1.73 m^2 (95% CI, –2.29 to 0.55), an indication of statistical bias in Black participants when a race or ancestry term was not used.

There were no systematic differences between measured and estimated GFR when race as reported by participants (Black and non-Black) or percentage of African ancestry were included in the models. Models that included a race or ancestry term were correspondingly more accurate for Black participants with respect to P_{10} (proportion of estimated GFRs within 10% of measured GFR) (42%; 95% CI, 34 to 50) compared with models that did not include such a term (31%; 95% CI, 24 to 39).

Independent of age, sex, and measured GFR, there was an association between Black race and a 10.7% (95% CI, 8.8 to 12.7) higher serum creatinine level than among participants of non-Black race. Further, there was an association between every 10% increase in the percentage of African Ancestry and an increase of 1.3% (95% CI, 1.1 to 1.6) in the serum creatinine level in the full study sample.

The inclusion of non-GFR determinants of serum creatinine level such as metrics of body composition and urinary excretion of creatinine did not eliminate the misclassification introduced by the removal of race or ancestry from GFR estimating equations based on serum creatinine. Non-GFR determinants of serum creatinine that differed according to Black (as opposed to non-Black) rage and higher percentage of African ancestry included higher body mass index, body-surface area, height , weight, bioelectrical impedance analysis phase angle, bioelectrical impedance analysis-quantified fat-free mass, and 24-hour urinary excretion of creatinine. There was no association between Black race or a higher percentage of African ancestry and tubular secretion of creatinine. There were associations between Black race or higher percentage of African ancestry and lower dietary protein as assessed by the Diet History Questionnaire.

In the final model that included several of the non-GFR determinants of serum creatinine, the race coefficients were not fully attenuated and there was 8.7% (95% CI, 5.8 to 11.7) higher measured GFR in Black participants compared with non-Black participants and 1.1% (95% CI, 0.8 to 1.5) higher measured GFR per 10% increase in the percentage of African ancestry.

Following adjustment for age, sex, and measured GFR, there was no association between Black race and cystatin C level. The difference comparing Black participants with non-Black participants in the full study sample was 0.03% (95% CI, –2.12 to 2.11). In addition, there was no independent association between African ancestry and cystatin C level (0.2% per 10% increase in the percentage of African ancestry; 95% CI, –0.25 to 0.28).

Models with cystatin C, age, and sex alone derived from the development data set resulted in estimates of GFR that were very close to the measured GFR in Black participants (median difference, 0.33 mL/min/1.73 m^2; 95% CI, –1.43 to 1.92). The GFR estimates in Black participants when cystatin C-based equations were used were accurate (P_{10}, 41%; 95% CI, 34% to 49%) as compared with equations using the serum creatinine level, age, sex, or race or percentage of African ancestry. The model had no meaningful improvement in the statistical bias or accuracy when a race term or an ancestry term was included in an equation based on cystatin-C.

Study limitations included the use of only research volunteers, small sample sizes, and the inability to generalize results to those with higher levels of GFR or populations outside the United States.

"Our study showed that the use of serum cystatin C rather than serum creatinine for GFR estimation produced estimates of similar validity while eliminating the negative consequences of race-based approaches," the researchers said. ■

TAKEAWAY POINTS

- Results of an analysis of data from a large national study to examine the relationships among race, ancestry, serum creatinine level, and serum cystatin C level to develop strategies for accurate estimation of glomerular filtration rate (GFR) without inclusion of racial classifications.
- The researchers considered three alternatives: replacement of race with a quantitative measure of ancestry in estimation of GFR; replacement of race with non-GFR determinants of serum creatinine that vary by race; and elimination of the need to consider race by use of cystatin C as the glomerular filtration marker.
- The use of cystatin C generated accurate results that eliminated the negative consequences of current race-based approaches.

Pulmonary Hypertension in CKD

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as reported in the Centers for Medicare & Medicaid Services files. Secondary outcomes were time to kidney failure (determined by the US Renal Data System from the date of initiation of dialysis or kidney transplantation), and hospitalizations extracted from Medicare claims. The researchers also categorized hospitalizations into cardiovascular and non-cardiovascular hospitalizations (data identified from primary *International Classification of Diseases (ICD), Ninth Edition and ICD-Tenth Edition* diagnosis codes at discharge).

The association between PH and mortality was assessed using Cox proportional hazards models, adjusting for age, sex, race, and comorbidities. The association between PH and kidney failure was assessed with death as a competing event in Fine-Gray models. The relationship between PH and all-cause, cardiovascular, and non-cardiovascular hospitalizations using a negative binomial model.

Following application of inclusion and exclusion criteria, the study cohort included 30,052 patients with PH and CKD and 150,260 CKD stage-matched patients without diagnosed PH. Participants were 67 to 95 years of age.

Patients in the group with PH were older (median, 80.7 years vs 79.9 years) and more likely to be female (57.8% vs 51.7%) than those in the group without PH. More than one-third of the study population had CKD stage 3; CKD stage was unknown for 44.3% of the study population. In the PH group, the proportion of participants with coronary artery disease, heart failure, obesity, interstitial lung disease, and chronic obstructive pulmonary disease was higher than that in the non-PH group. Of those with Medicare Part D data available, 86% of those in the PH group were prescribed diuretics compared with 60% of those in the non-PH group.

TAKEAWAY POINTS

- Pulmonary hypertension (PH) is highly prevalent among patients with chronic kidney disease (CKD). Researchers reported results of a study among Medicare beneficiaries with CKD ≥67 years of age to examine associations between PH and mortality, kidney failure, and hospitalization.
- At the end of year 1 of follow-up, years 2 to 3, and years 4 to 5, there was an association between PH and higher mortality in both unadjusted and adjusted models.
- Those with PH also had a higher rate of all-cause, cardiovascular, and non-cardiovascular hospitalizations and higher rate of kidney failure than those without PH.

During year 1 of follow-up, years 2 to 3, and 4 to 5, in both unadjusted and adjusted models, there were associations between PH and higher mortality. The highest hazard was seen in follow-up year 1 (hazard ratio [HR], 2.87; 95% confidence interval [CI], 2.79-2.95). In the two later follow-up periods, the association was attenuated but remained statistically significant: HR, 1.56; 95% CI, 1.51-1.61 in years 2 to 3, and HR, 1.47; 95% CI, 1.40-1.53 in years 4 to 5.

> At the end of year 1, the rate of kidney failure occurrence was 35.5 per 1000 person-years in the group with PH compared with 12.8 per 1000 person-years in the group without PH.

At the end of year 1, the rate of kidney failure occurrence was 35.5 per 1000 person-years in the group with PH compared with 12.8 per 1000 person-years in the group without PH. In both unadjusted and adjusted models, the risk for kidney failure was higher in patients with PH (adjusted HR, 2.18; 95% CI, 1.98-2.39). In the time periods after follow-up year 1, the rate of kidney failure was lower in those with PH: 16.1 per 1000 person-years in years 2 to 3 and 14.2 per 1000 person-years in years 4 to 5.

The risk of kidney failure among those with PH was significantly higher in years 2 to 3 but not 4 to 5 in multivariable models. Higher rates of acute kidney injury (AKI) events and AKI requiring dialysis support within 30 to 90 days of the AKI event were seen among those in the PH group compared with those without PH.

There was an association between the presence of PH and a higher rate of all-cause, cardiovascular, and non-cardiovascular hospitalization, particularly in the follow-up year 1. The rate between PH and cause-specific hospitalizations was higher for cardiovascular hospitalization than for non-cardiovascular hospitalization(4.61 vs 2.62).

The association of PH with mortality or kidney failure in follow-up year 1 was not modified by sex, race, and the presence of diabetes. The association of PH with hospitalization was modified by sex and diabetes in follow-up year 1; the association was stronger among men than among women and stronger among those without diabetes than among those with diabetes. In follow-up years 2 to 3, there was a stronger association of PH with mortality among men than among women and the association of PH with kidney failure was stronger among those with diabetes than those without diabetes. In follow-up years 4 to 5, the association between PH and mortality was stronger among those without diabetes than among those with diabetes.

Reliance on billing codes and lack of data on echocardiogram or right heart catheterization were cited as limitations to the study.

In summary, the authors said, "The presence of PH was associated with increased risks of mortality, kidney failure, and cardiovascular and non-cardiovascular hospitalization among Medicare beneficiaries previously diagnosed with CKD. Further studies are warranted to explain the mechanisms underpinning the observed associations and to test the potential utility of current and novel therapeutic agents to treat PH in those with CKD." ■

CONFERENCE COVERAGE AMERICAN TRANSPLANT CONGRESS

Kidney Paired Donation in Pediatric Recipients

Kidney paired donation allows for ABO-mismatched or HLA-incompatible pairs to receive a living donor kidney transplant. Among the pediatric kidney transplant population who will likely require multiple transplants in their lifetime, the superior graft survival among recipients of living donor kidneys is of particular importance. According to **J. Smith** and colleagues, kidney paired donation represents a strategy to increase living donation among pediatric kidney transplant candidates. The use of kidney paired donation is on the increase among adults; the use of the strategy in the pediatric population is not well outlined.

The researchers utilized data from the Scientific Registry of Transplant Recipients to examine the population of pediatric living donor transplant recipients from 2014 to 2019 by kidney paired donation status. The researchers performed chi-squared tests for difference by kidney paired donation status, and compared the proportion of pediatric and adult kidney paired donation recipients during the study period. Results were reported during a virtual session at the 2021 American Transplant Congress in a presentation titled *Kidney Paired Donation in Pediatrics: An Underused Opportunity?*

The number of kidney paired donation kidney transplants has increased from 8 (3.3% of living donor recipients) in 2014 to 18 (7.5%) in 2019, with a peak of 25 (9.1%) in 2018. Use of kidney paired donation is higher in adults and has been steadily increasing since 2014.

Characteristics that were more common to pediatric kidney paired donation recipients than to other pediatric living donor recipients were: Black race (18.0% vs 8.3%); previous transplant (15.7% vs 6.5%), panel reactive antibodies >20% (33.7% vs 13.8%), and donor <10 years older than the recipient (6.7% vs 2.7%).

In conclusion, the researchers said, "Participation in kidney paired donation presents logistical and financial challenges for pediatric kidney programs, but an increasing number have been performed in recent years. This program could provide increased transplant opportunities for pediatric recipients, especially for disadvantaged groups."

Source: Smith J, Skeans M, Engen R, Bartosh S. Kidney paired donation in pediatrics: An underused opportunity? Abstract of a presentation at the virtual 2021 American Transplant Congress (Abstract 77), June 5, 2021.

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Conference Coverage

November 4-7, 2022

KIDNEY WEEK 2021

ASN's Kidney Week was once again a fully virtual meeting in 2021. The meeting included presentations and posters highlighting the latest findings in kidney health research, as well as sessions on advances in the care of patients with kidney and related disorders.

This is part two of our coverage of Kidney Week 2021.

Mortality Risk in COVID-19-Related AKI versus ESRD

Risks for development of acute kidney injury (AKI) and rates of mortality are high among patients hospitalized with COVID-19. Independent risk factors for COVID-19 disease severity and mortality include chronic kidney disease (CKD) and end-stage renal disease (ESRD). **Karela B. Herrera-Enriquez, MD,** and colleagues conducted a study comparing mortality rates of patients hospitalized with COVID-19 disease who (1) developed AKI with baseline normal renal function, defined as glomerular filtration rate >60 mL/min/1.73 m^2, (2) developed AKI with baseline moderate-to-severe CKD (stages 3 or 4), and (3) had ESRD.

Results of the study were reported during a virtual poster session at ASN Kidney Week 2021. The poster was titled *Comparison of Mortality in Hospitalized COVID-19 Patients with AKI vs ESRD.*

The study included consecutive patients admitted with COVID-19 disease who were referred to nephrology with AKI or ESRD on dialysis. Collected retrospective data included demographics, medical history including CKD stage, laboratory results, O_2 therapy, AKI diagnosis based on Kidney Disease: Improving Global Outcomes criteria, and renal replacement therapy (RRT). The unadjusted association between CKD stage and mortality was examined using chi-square test. The associations between CKD stage and morality were estimated using multivariate logistic regression models, adjusting for potential confounders.

The analysis included 166 patients. Of those, 87 had AKI with normal baseline function (AKI-N), 41 had AKI in CKD stage 3 or 4 (AKI-CKD 3/4), and 38 had ESRD. Mechanical ventilation was used in 33 of the patients in the AKI-N group (37.9%), 20 of those in the AKI-CKD 3/4 group (48.8%), and 10 of those in the ESRD group (26.3%) (P=.069).

Three patients in the AKI-N group (3.5%) received intermittent hemodialysis and nine (10.3%) received continuous RRT (CRRT)/prolonged intermittent RRT (PIRRT). In the AKI-CKD 3/4 group, six patients (14.6%) received intermittent hemodialysis and seven (17.1%) received CRRT/PIRRT. Of all patients with AKI, 55.5% had AKI stage 3. A total of 34 patients with ESRD (89.5%) received intermittent hemodialysis and two (5.3%) received peritoneal dialysis. Patients in the AKI-CKD 3/4 group were more likely to receive RRT than those in the AKI-N group (P=.035).

In the AKI-N group, 36 patients (41.4%) died, compared with 26 patients (63.4%) in the AKI-CKD 3/4 group and nine (23.7%) in the ESRD group (P=.001). Following adjustment for age, race, sex, diabetes mellitus, hypertension, obesity, and congestive heart failure, the odds of mortality were increased for AKI-CKD 3/4 (odds ratio [OR], 2.59; P=.006) and decreased for ESRD (OR, 0.5; P=.001), compared with AKI-N.

In summary, the researchers said, "COVID-19 patients with ESRD had less mortality than AKI-N, while AKI-CKD 3/4 had higher mortality than both ESRD and AKI-N patients. Prospective studies to determine specific criteria for early indication of RRT in COVID-19 AKI patients are warranted, as it may decrease mortality especially in those with baseline CKD 3/4."

Source: Herrera-Enriquez KB, D'Adamo C, Alhamdan N, Ranich T. Comparison of mortality in hospitalized COVID-19 patients with AKI vs ESRD. Abstract of a poster presented at the American Society of Nephrology virtual Kidney Week 2021 (Abstract P00016), November 2021.

FIDELITY Analysis: Finerenone and SGLT-2i Use

During a virtual oral session at ASN Kidney Week 2021, **Peter Rossing, MD, DMSc,** and colleagues reported results of the FIDELITY analysis, conducted to assess the efficacy and safety or finerenone in patients with chronic kidney disease (CKD) and type 2 diabetes. The presentation was titled *Finerenone in Patients with CKD and Type 2 Diabetes by SGLT-2I Treatment: The FIDELITY Analysis.*

Finerenone is a novel nonsteroidal, selective mineralocorticoid receptor antagonist; it was tested across the spectrum of patients with CKD and type 2 diabetes in the FIDELIO-DKD and FIGARO-DKD trials. To reduce the risk of progression of CKD, sodium-glucose cotransporter-2 inhibitors (SGLT-2is) are recommended for patients with CKD and type 2 diabetes, making their combined use with finerenone of interest. The FIDELITY analysis examined the use of finerenone in patients by SGLT-2i use.

The prespecified analysis combined patient-level data from the FIDELIO-DKD (NCT02540993) and FIGARO-DKD (NCT02545049) phase 3, randomized, double-blind, placebo-controlled multicenter clinical trials. In both trials, patients were randomized 1:1 to receive oral finerenone or placebo.

Eligibility criteria were type 2 diabetes and either a urine albumin-to-creatinine ratio [UACR] ≥30 to <300 mg/g and estimated glomerular filtration rate (eGFR) ≥25 to ≤90 mL/min/1.73 m^2 or UACR ≥300-<5000 mg/g and eGFR ≥25 mL/min/1.73 m^2 with optimized renin-angiotensin system blockade. Efficacy outcomes included a cardiovascular composite end point to time to cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for heart failure, and a kidney composite endpoint of time to kidney failure, sustained ≥40% decline in eGFR from baseline, or renal death.

A total of 13,026 patients were included in the FIDELITY analysis. Of those, 877 (approximately 7%) received an SGLT-2i at baseline: 438 (6.7%) in the finerenone arm and 439 (6.7%) in the placebo arm. Compared with placebo, the risk of the cardiovascular composite endpoint was reduced with finerenone irrespective of SGLT-2i use at baseline: with SGLT-21, hazard ratio (HR), 0.63; 95% confidence interval [CI], 0.40- to <1.00; without SGKT-2I, HR, 0.87; 95% CI, 0.79 to 0.96; P for interaction, 0.41).

In conclusion, the researchers said, "FIDELIO-DKD and FIGARO-DKD comprise the largest cardiorenal outcomes program to date; therefore, combining the data for the SGLT-2i subgroup in the FIDELITY analysis may provide further insights into the effects of receiving both finerenone and an SGLT-2i."

Funding for the analysis was provided by Bayer AG.

Source: Rossing P, Filippatos G, Bakris GL, et al. Finerenone in patients with CKD and type 2 diabetes by SGLT-2i treatment: The FIDELITY analysis. Abstract of a presentation at the American Society of Nephrology virtual Kidney Week 2021 (Abstract SA-OR22), November 6, 2021.

Kidney Outcomes in FIGARO-DKD Trial

Results of the FIDELIO-DKD trial demonstrated that finerenone reduced the risk of kidney outcomes in patients with predominantly advanced chronic kidney disease (CKD) and type 2 diabetes. The FIGARO-DKD trial assessed the effects of finerenone in patients with less advanced CKD and type 2 diabetes. The primary outcome in FIGARO-DKD was a composite of cardiovascular events.

The key secondary outcomes were sustained decrease in estimated glomerular filtration rate (eGFR) of ≥40% from baseline, time to kidney failure, or renal death. A similar kidney composite end point was exchanging a sustained ≥40% decrease in eGFR with a ≥57% decrease, and change in urine albumin-to-creatinine ratio [UACR] from baseline to month 4 (prespecified outcomes in the hierarchical testing strategy).

During an oral session at the ASN virtual Kidney Week 2021, **George L. Bakris, MD,** and colleagues reported results of the secondary kidney outcomes. The presentation was titled *Finerenone and Kidney Outcomes in Patients with CKD and Type 2 Diabetes: Results from FIGARO-DKD.*

FIGARO-DKD (NCT02545049) was a randomized, double-blind, placebo-controlled phase 3 trial. Patients were randomized to either finerenone or placebo. Eligibility criteria included type 2 diabetes, UACR ≥30 to <300 mg/g and eGFR ≥25 to ≤90 mL/min/1.73 m^2 or UACR ≥300 to ≤5000 mg/g and eGFR ≥60 mL/min/1.73 m^2, optimized renin-angiotensin system blockade, and screening potassium level of ≤4.8 mEq/L.

A total of 7352 patients were included in the current analysis. Of those, 62% had baseline eGFR of ≥60 mL/min/1.73 m^2 and 49% had baseline UACR <300 mg/g. Median follow-up was 3.4 years, during which 9.5% of patients (n=350) in the finerenone arm and 10.8% (n=395) of patients in the placebo arm had a 40% eGFR composite endpoint event (hazard ratio [HR], 0.87; 95% confidence interval [CI], 0.76-1.01; P=.069).

There was a clinically meaningful prolongation of the time to the 57% eGFR composite end point with finerenone (HR, 0.77; 95% CI, 0.60-0.99). At month 4, there was greater reduction in UACR in the finerenone arm than in the placebo arm (ratio of least-squares means 0.68; 95% CI, 0.65-0.70).

The incidence of adverse events was similar between the two trial arms.

"In FIGARO-DKD, patients with stage 1-4 CKD and type 2 diabetes, finerenone induced a pronounced reduction in albuminuria," the authors said. "Kidney composite outcomes observed were directionally similar to that seen among patients with more advanced kidney disease in the FIDELIO-DKD trial."

Funding was provided by Bayer AG.

Source: Bakris GL, Ruilope LM, Rossing P, et al. Finerenone and kidney outcomes in patients with CKD and type 2 diabetes: Results from FIGARO-DKD. Abstract of a presentation at the American Society of Nephrology virtual Kidney Week 2021 (Abstract SA-OR21), November 6, 2021.

Gout in Patients on Dialysis: Risk Factors and Outcomes

There are few data available regarding gout among patients with dialysis-dependent end-stage renal disease. **Anthony J. Bleyer, MD**, and colleagues conducted a study designed to examine the epidemiology, risk factors, and outcomes among dialysis patients with gout.

Results of the study were reported during a virtual poster session at ASN Kidney Week 2021. The poster was titled *Risk Factors and Outcomes of Gout in Dialysis Patients: A Cohort Study of the United States Renal Data System (USRDS).*

The study utilized 2017 USRDS data to identify adult patients ≥18 years of age with Medicare as the primary payer. Baseline characteristics and comorbidities for dialysis-dependent patients with gout were assessed at initiation of dialysis and at 3-months prior to the gout diagnosis, and were compared with dialysis patients without gout. The researchers estimated risks of all-cause hospitalization and mortality and compared the risks between those with gout and those without gout.

Of 275,651 dialysis patients in 2017, 15% (n=41,312) had one or more claims for gout following initiation of chronic outpatient dialysis. More than a third of the diagnoses of gout were made by internal and family medicine physicians.

Patients with gout were more likely to be older (mean 64.5 years vs 56.8 years), male (62% vs 54%), of Asian race (6.2% vs 3.7%), and obese (31.4 kg/m^2 vs 30.2 kg/m^2), compared with patients without gout. Patients with gout were also more likely to undergo hemodialysis via central venous catheter (15% vs 13%) than those without gout.

Those with gout had higher comorbidity prevalence of diabetes (67% vs 62%), hypertension (93% vs 74%), heart failure (49% vs 30%), ischemic heart disease (49% vs 30%), peripheral vascular disease (32% vs 22%), stroke (12% vs 8%), acute myocardial infarction (7% vs 3%), and angina (4% vs 2%), compared with patients without gout.

In adjusted regression analysis, the three most significant factors associated with a diagnosis of gout were older age (odds ratio [OR], 4.23 for ≥65 years vs <65 years; 95% confidence interval [CI], 4.03-4.43), previous transplant (OR, 2.37; 95% CI, 2.24-2.50), and comorbid hypertension (OR, 2.71; 95% CI, 2.59-2.83). In multivariate analysis, in the year after diagnosis of gout, the risk of hospitalization was higher by 11% (95% CI, 8% to 13%), and the risk of mortality was higher by 9% (95% CI, 5% to 12%).

In conclusion, the researchers said, "The prevalence of gout was 15% in the US Medicare dialysis-dependent population. Gout patients had a higher comorbidity burden especially for cardiovascular conditions and higher risk of hospitalization and mortality. Future studies are needed to elucidate whether improved recognition and management of gout may reduce the risk for worse cardiovascular outcomes."

Funding for this study was provided by Horizon Therapeutics.

Source: Bleyer AJ, Zhang Y, Kshirsagar OS, Marder B, LaMoreaux B. Risk factors and outcomes of gout in dialysis patients: a cohort study of the United States Renal Data System (USRDS). Abstract of a poster presented at the American Society of Nephrology virtual Kidney Week 2021 (Abstract PO0792), November 2021.

Markers of Disease Severity in COVID-19: Hospital versus Community Acquired AKI

There are strong correlations between the etiology of acute kidney injury (AKI) in COVID-19 and age, comorbidities, and laboratory markers of severity of disease. Outpatients with COVID-19 have different exposure that may be the cause of AKI compared with hospitalized patients with COVID-19. The etiology of community-acquired (CA) AKI may vary from the etiology of AKI among patients with hospital-acquired (HA) AKI.

Shashank Kailash, MD, and colleagues at Emory University School of Medicine, Atlanta, Georgia, conducted an analysis of data from all COVID-19 PCR-confirmed cases admitted to four hospitals from March 1, 2020, to May 31, 2020. Results of the analysis were reported during a virtual poster session at ASN Kidney Week 2021 in a poster titled *Increased Markers of Disease Severity in COVID-19 Patients with Hospital-Acquired vs Community-Acquired AKI.*

Data were collected electronically through July 31, 2020, including readmissions. Chart review was used to determine baseline C-EPI estimated glomerular filtration rate for the period of 6 months prior to admission to 5 months post-admission. Kidney Disease: Improving Global Outcomes criteria were used to score AKI and recovery from AKI.

CA was defined as AKI with the highest level of creatinine on admission, rising creatinine on admission, or renal replacement therapy within 48 hours of admission without a subsequent AKI event after recovery. All AKI occurring more than 48 hours after admission was considered HA. A model adjusted for demographics, body mass index, Elixhauser comorbidity index (ECI), and chronic kidney disease stage was used to assess which laboratory values correlated with CA or HA.

Patients in the two groups were similar in demographics; the only significant difference was in ECI. Patients in the CA group had less severe AKI, improved recovery to baseline, and lower mortality compared with those in the HA group. The lower mortality among patients with CA was directly related to lower AKI stage. Within a given stage of AKI, there was no difference in mortality between the two groups. Recovery of renal function was significantly better in CA stage 1 versus HA (8% vs 26%; P=.001); there were no differences for stage 2 or 3.

Following adjustments, there were significant associations between higher maximum dimers, alanine aminotransferease, aspartate aminotransferease, Bili, B-type natriuretic peptide (BNP), lactic acid, C-reactive protein (CRP), ferritin, lactate dehydrogenase, neutrophils, troponin, and lower minimum lymphocyte count and HA, compared with CA. On admission, only higher BNP, higher CRP, lower creatine phosphokinase (CPK), and higher total CO2 were associated with HA versus CA.

In summary, the authors said, "Compared to patients with CA, patients with HA had higher stages of AKI that correlated with higher mortality. They also had worsened recovery from stage 1 AKI and increased markers of COVID severity (except for CPK) in-hospital and on admission. We propose that factors other than COVID-19 disease severity led to CA, with volume and rhabdomyolysis as possible contributors."

Source: Kailash S, Navarrete JE, Hosein D, Rahbari-Oskoui FF, French HA. Increased markers of disease severity in COVID-19 patients with hospital-acquired vs community-acquired AKI. Abstract of a poster presented at the American Society of Nephrology virtual Kidney Week 2021 (Abstract PO0026), November 2021.

Intradialytic Hypertension and Risk of Long-Term Mortality

Hypertension is a common comorbidity among patients receiving maintenance dialysis. Increases in systolic blood pressure from pre- to post-hemodialysis (intradialytic hypertension) occur in a subset of hemodialysis patients. Results of previous studies in patients with intradialytic hypertension have shown adverse short- and long-term outcomes. However, according to **Anika T. Singh, MD, MMSc,** and colleagues, there is little consensus on an evidence-based definition.

During a virtual poster session at ASN Kidney Week 2021, the researchers reported results of a retrospective cohort study designed to examine the association of various definitions of intradialytic hypertension with all-cause mortality. The poster was titled *Association of Different Definitions of Intradialytic Hypertension with Long-Term Mortality in Hemodialysis*.

Intradialytic hypertension was defined as ≥30% of baseline sessions with an increase in pre- to post-hemodialysis systolic blood pressure of (1) ≥0 mmHg (Hyper0); (2) ≥10 mmHg (Hyper10); or (3) ≥20 mmHg increase (Hyper20). Unadjusted and adjusted Cox proportional hazards models were used to examine the association of the three definitions with all-cause mortality. Interaction terms were used to assess for effect modification according to pre-specified variables, including demographic (age, sex), hemodialysis-related (pre-hemodialysis systolic blood pressure, ultrafiltration rate), and comorbidities (diabetes, heart failure, and peripheral artery disease [PVD]).

The cohort included 3198 participants. At baseline, mean age was 62 years, 57% were male, and 14% were Black. The average change in blood pressure from pre- to post-hemodialysis was 13 mmHg.

During the baseline period, 47% of participants met the Hyper0 definition and were at 29% higher adjusted risk of death (HR, 1.29; 95% confidence interval [CI], 1.03-1.62), compared with those with no increase in systolic blood pressure. Twenty-one point two percent of participants met the definition of Hyper10, which was associated with a 21% higher adjusted risk of death (HR, 1.21; 95% CI, 0.96 to 1.51). Hyper20 was present in 6.8% of participants and was associated with a 5% higher risk of death (HR, 1.05; 95% CI, 0.76-1.46).

There was evidence of effect modification by age and PVD (*P* for interaction = .02 for both). The risk of death was higher in participants 45 to 70 years of age and in those without PVD.

"Individuals with any increase in systolic blood pressure from pre- to post-hemodialysis experienced the highest adjusted risk of mortality, compared with other threshold-based definitions with effect modification by age and PVD," the researchers said.

Source: Singh AT, Waikar SS, McCausland F. Association of different definitions of intradialytic hypertension with long-term mortality in hemodialysis. Abstract of a poster presented at the American Society of Nephrology virtual Kidney Week 2021 (Abstract P00878), November 2021.

Predictors of Non-Recovery of Kidney Function after COVID-19-Related AKI

Results of studies of patients hospitalized with COVID-19 have suggested associations between hospitalization for COVID-19 and severe acute kidney injury (AKI). However, according to **Sahitya Allam, MD,** and colleagues, there are few data available on the determinants of recovery of kidney function for patients with COVID-19-related AKI.

The researchers conducted a retrospective analysis of patients hospitalized at a single center from March 2020 to April 2021 with diagnoses of COVID-19 and AKI. Results of the analysis were reported during a virtual poster session at ASN Kidney Week 2021 in a poster titled *Predictors of Recovery of Kidney Function Following AKI During Hospitalization for COVID-19*.

The analysis defined recovery of kidney function as a discharge creatinine <0.3 mg/dL above baseline. Chart review yielded data on patients' demographics, comorbidities, AKI stage, admission to the intensive care unit (ICU), and laboratory values. Factors associated with kidney function recovery were identified using univariate analysis and a multivariate logistic regression model.

The analysis included data on 216 patients. Of those, average age was 66.3 years and 56.0% were men. Recovery of kidney function by discharge was seen in 62% of the cohort.

In univariate analysis, correlates of non-recovery of kidney function by discharge were congestive heart failure (CHF) (P=.063), AKI requiring dialysis (P<.001), AKI stage (P<.001), admission to the ICU (P<.001), and lower albumin (P=.040). In the multivariate logistic regression model, the associations of CHF (P=.010), AKI stage 2 (P=.011), AKI stage 3 (P=.001), and admission to the ICU (P=.006) with non-recovery remained.

At a median of 64 days post-discharge, follow-up data was available for 131 patients (61% of the cohort). Of those patients, 14% had no new recovery after discharge, and 18% had no improvement compared with discharge. At 60 days after discharge, 8.4% had new CKD. At discharge, 3% of all patients were dependent on dialysis. Non-recovery at 60 days post-discharge was associated with baseline CKD (P=.03) and CHF (P=.037).

"History of CHF, severity of AKI, and ICU admission are predictors of non-recovery of kidney function in patients with COVID-19 and AKI," the authors said.

Source: Allam S, Wisner BW, Ravindran A, Kalantari K. Predictors of recovery of kidney function following AKI during hospitalization for COVID-19. Abstract of a poster presented at the American Society of Nephrology virtual Kidney Week 2021 (Abstract P00023), November 2021.

Frequency of Deceased Donor Kidneys Allocated Out of Sequence

Allocation of deceased donor kidneys follows a ranked match-run list of potential recipients. The frequency of deviation by organ procurement organizations (OPOs) from the mandated match-run in exceptional circumstances is unknown.

Kristen L. King and colleagues conducted an analysis to examine the frequency of exceptions to the standard allocation policy. Results of the analysis were reported during a virtual poster session at ASN Kidney Week 2021 in a poster titled *Increasing Frequency of Kidneys Allocated Out of Sequence by Organ Procurement Organizations.*

The researchers utilized Scientific Registry of Transplant Recipients data on all deceased donor kidney transplants in the United States from 2015 to 2019 to identify cases where an OPO-initiated allocation exception occurred (operational-OPO, Donor Medical Urgency, or Expedited Placement). The analysis was designed to examine the frequency of deceased donor kidney transplants from exceptions over time as well as the characteristics of donors with kidneys placed out-of-sequence.

During the study period, 981 kidneys from 673 donors were transplanted via OPO-initiated allocation exception. During that same time period, transplants with allocation exceptions (median kidney donor profile index [KDPI] 67, age 47 years) nearly doubled, from 153 kidneys in 2015 (1.5% of all deceased donor kidney transplants) to 291 in 2019 (2.1%).

The process of allocation exception was used at least once by 52 of 58 OPOs (median ≤1 per year). However, two outlier OPOs accounted for 54% all the exceptions over 5 years (426 [43%[and 110 [11%]). Only 56% of any transplant centers received any allocation-exception deceased donor kidney transplants, with two centers receiving 26% (129 [13%] and 132 [13%]).

Characteristics of donor kidneys placed via allocation exception were less favorable, but only 25% had KDPI ≥85%. Allocation exemption kidneys went to recipients with two fewer priority points (median score: 4.3 vs 6.3 in-sequence), the equivalent of 2 fewer years of waiting time.

In conclusion, the researchers said, "Two OPOs and a few kidney transplant centers are driving an increase in OPO-initiated exceptions in kidney allocation. Although kidneys placed out-of-sequence were lower quality, the majority did not meet the traditional threshold for marginal kidneys. Without monitoring, increasing pressure to improve organ utilization risks increasing out-of-sequence allocation potentially exacerbating disparities in access to transplantation."

Source: King KL, Husain SA, Mohan S. Increasing frequency of kidneys allocated out of sequence by organ procurement organizations. Abstract of a poster presented at the American Society of Nephrology virtual Kidney Week 2021 (Abstract PO2104), November 2021.

Increasing Prevalent Peritoneal Dialysis Population

Compared with in-center hemodialysis, patients who require renal replacement therapy may experience improved quality of life with peritoneal dialysis. However, according to **Hari Dukka, MBBS, FASN,** and colleagues at the University Hospitals of Derby and Burton NHS Foundation Trust, Derby, United Kingdom, it can be challenging to increase the prevalent patient population on peritoneal dialysis after a certain number is reached.

The researchers conducted a retrospective analysis designed to examine the turnover of patients on peritoneal dialysis over an 8-year period. They also sought to understand the reasons for a stagnant prevalent peritoneal dialysis population in the renal unit in Royal Derby Hospital. Results of the analysis were reported during a virtual poster session at ASN Kidney Week 2021 in a poster titled *Increasing the Prevalent Peritoneal Dialysis Patient Population Can Be Challenging.*

The number of patients starting and stopping peritoneal dialysis each year from 2013 to 2020 was documented using an electronic database (Vital data, ICM). Reasons given for stopping peritoneal dialysis and the duration of technique survival were noted. If technique failure resulted in conversion to hemodialysis for more than 3 months, the cause of the failure was also noted. Patients who converted to hemodialysis for less than 3 months were excluded from the analysis.

The number of patients starting peritoneal dialysis (324) and stopping peritoneal dialysis (322) was similar for each year during the study period. Reasons for stopping peritoneal dialysis were switching to hemodialysis (40% to 60%), death (15% to 30%), and receipt of renal transplantation (10% to 35%).

Switching modality to hemodialysis was due primarily due to infection (60% to 80%), poor clearances and ultrafiltration rates (10% to 30%), and social reasons (10% to 15%). Of patients who changed modality to hemodialysis due to infection, peritonitis accounted for 75% to 85% of the cases, followed by exit site and tunnel infections (15% to 25%).

The introduction of a kidney quality improvement project in 20218 resulted in a reduction of numbers of patients switching from peritoneal dialysis to hemodialysis. However, there was no impact on the prevalent patient population, due to a decrease in the incident patient population.

In summary, the authors said, "Increasing the prevalent population on peritoneal dialysis can be challenging even with a high incident peritoneal population. Having mechanisms which prevent infections, early identification, and treatment of infections may help improve prevalent peritoneal dialysis population."

Source: Dukka H, Edwards E, Jain A, Arora D. Increasing the prevalent peritoneal dialysis patient population can be challenging. Abstract of a poster presented at the American Society of Nephrology virtual Kidney Week 2021 (Abstract P00951), November 2021.

Predicting CKD in Patients with Diabetes Using Machine Learning

Chronic kidney disease (CKD) develops in approximately half of patients with type 2 diabetes. Patients with diabetes and CKD are at increased risk of mortality. Increases in the frequency of screening for CKD have resulted in fewer missed diagnoses; however, increases in screening frequency have not been uniformly implemented.

During a virtual poster session at ASN Kidney Week 2021, **Angier O. Allen, MA,** and colleagues at Dascena Inc., Houston, Texas, reported on a machine learning algorithm (MLA) to predict CKD following a diagnosis of type 2 diabetes mellitus. The poster, describing the development and retrospective validation of the MLA, was titled *Using Machine Learning to Predict CKD upon Type 2 Diabetes Mellitus Diagnosis.*

Development of the MLA included extraction of electronic health records (EHRs) from a proprietary diabase of more than 700 healthcare sites in the United States between 2007 and 2020. Data on 171,201 adults ≥18 years of age who were recently diagnosed with type 2 diabetes mellitus were included. To assess the risk of stage 3+ CKD in patients with diabetes, a random forest MLA was developed using EHR data collected in the year prior to the diagnosis of diabetes. Patients with type 2 diabetes mellitus and CKD stage 3+ were identified using *International Classification of Diseases, Ninth Edition (ICD-9) and ICD, Tenth Edition*, codes.

The MLA was tested on a hold-out test set of 42,801 patients in addition to a separate external validation dataset. The Centers for Disease Control and Prevention (CDC) CKD risk score was used as a comparator. The performance of the MLA and the CDC CKD risk score was assessed on the hold-out test set and the external validation dataset via area under the receiver operating characteristic curve.

When analyzed for prediction of CKD stage 3+ in patients recently diagnosed with type 2 diabetes mellitus, the MLA outperformed the CDC CKD risk score on both the hold-out test set and the external validation dataset.

In conclusion, the authors said, "This retrospective study shows that a MLA can provide timely predictions of CKD among recently diagnosed type 2 diabetes mellitus patients. Early detection of CKD in diabetic patients may enable therapeutic interventions, lifestyle changes, prevention of progression, and reduction of dialysis dependency, as well as healthcare costs."

Source: Allen AO, Iqbal Z, Green-Saxena A, Das R. Using machine learning to predict CKD upon type 2 diabetes mellitus diagnosis. Abstract of a poster presented at the American Society of Nephrology virtual Kidney Week 2021 (Abstract P00762), November 2021.

AURORA 1 Post Hoc Analysis: Voclosporin in Patients with Severe Lupus Nephritis

Results of the AURORA 1 phase 3 trial demonstrated that compared with mycophenolate mofetil (MMF) and low-dose steroids, the addition of voclosporin significantly increased rates of complete renal response in patients with lupus nephritis. Voclosporin is a novel calcineurin inhibitor with a favorable metabolic profile and a consistent dose-concentration relationship.

During an oral presentation at the ASN virtual Kidney Week 2021, **Hanni Menn-Josephy, MD,** and colleagues presented results of a post-hoc analysis assessing whether the efficacy of voclosporin in patients with severe lupus nephritis is similar to that in the overall study population in AUORA 1. The presentation was titled *Voclosporin Is Effective in Achieving Complete Renal Response in Severe Lupus Nephritis*.

AURORA 1 enrolled patients with systemic lupus erythematosus, biopsy-proven active lupus nephritis (Class III, IV, or V), and proteinuria of ≥1.5 mg/mg (≥2 mg/mg for Class V). Of the enrolled patients, 179 were randomized to the voclosporin arm (23.7 mg twice a day) and 178 were randomized to the control arm. All patients received MMF (1 g twice a day) and low-dose oral steroids.

Severe lupus nephritis was defined as baseline urine protein to creatinine ratio (UPCR) ≥3 mg/mg with Class III or IV biopsy (±Class V) with active lesions. To ensure the population was representative of severe disease in clinical practice, renal function and serology was evaluated. Complete renal response was defined as UPCR ≥0.5 mg/mg with stable renal function, use of low-dose steroids, and no use of rescue medication.

Severe disease was present in 76 patients in the voclosporin arm and 72 in the control arm. At baseline, mean UPCR was 5.9 mg/mg. At 1 year, complete renal response was 34.2% in the voclosporin arm and 11.1% in the control arm (odds ratio, 4.43; *P*=.001).

In summary, the researchers said, "In patients with severe lupus nephritis, adding voclosporin to MMF and steroids results in statistically significant higher complete renal response rates. This is clinically meaningful given that patients with severe disease are at higher risk of worse long-term outcomes and development of ESKD."

Funding for this analysis was provided by Aurinia Pharmaceuticals, Inc.

Source: Menn-Josephy H, Truman M, Palmen M, Mina-Osorio P. Voclosporin is effective in achieving complete renal response in severe lupus nephritis. Abstract of an oral presentation at the American Society of Nephrology virtual Kidney Week 2021 (Abstract SA-OR31), November 6, 2021.

Disparities in SDOH and Healthcare Resource Utilization in Patients with ADPKD

Health disparities in chronic kidney disease (CKD) are attributed, in part, to social determinants of health (SDOH). **Karl M. Kilgore, PhD,** and colleagues conducted a study designed to compare SDOH and healthcare resource utilization in commercially insured patients with autosomal dominant polycystic kidney disease (ADPKD) with a lower income population managed with Medicaid.

Results of the study were reported during a virtual poster session at ASN Kidney Week 2021. The poster was titled *Social Determinants of Health (SDOH) and Healthcare Resource Utilization (HRU) in Autosomal Dominant Polycystic Kidney Disease (ADPKD) by CKD Stage*.

The study population included 8766 patients with commercial insurance and 5416 patients with Medicaid who were identified using a national claims database. Eligible patients had two or more ADPKD diagnoses between July 1, 2016, and December 31, 2018, and were continuously enrolled in either a commercial plan or Medicaid for a minimum of 12 months. Patients were linked to SDOH via 9-digit ZIP address providing a precise assignment that was compared to census data. Healthcare resource utilization included inpatient days and emergency department (ED) visits per 1000 patients per month (PPPM) over 1 year of follow-up.

Patients in the Medicaid group were more likely to be female (60% vs 54%) and on average 8 years younger than those in the commercial insurance group. In the Medicaid group, Charlson Comorbidity Index (CCI) scores were 1.3 times higher, income was 40% lower, patients were two times more likely to live below the federal poverty level, 1.3 times less likely to complete high school, 2.7 times more likely to speak English not well or at all, 2.6 times less likely to own a vehicle, 53% more likely to be unemployed, and lived in an area with shortage of primary and mental healthcare 6.8%/6.4% more often.

The differences in the two payer groups were consistent across CKD stages, with the exception of increases in CCI scores with higher CKD stage for both groups. There were also tendencies toward increases in disparities in income, rates of unemployment, and provider shortages with CKD stage.

Mean bed days ranged from 34.6 (stage 1) to 402 (for patients with end-stage kidney disease) PPPM for commercial payer patients, and were three to four times higher for Medicaid patients (range, 112 to 874 across CKD stages). Visits to the ED PPPM ranged from 38 to 114 for commercially insured patients and 154 to 376 for patients in the Medicaid group.

In both groups, hospital readmission for post-acute care was high: 15% of patients in the commercial insurance group and 20% of those in the Medicaid group were readmitted within 30 days of inpatient stay. Utilization of healthcare resources increased with CKD stage.

In summary, the authors said, "ADPKD patients have large variation in SDOH by type of insurance. Lower social status of Medicaid managed patients may be associated with higher healthcare resource utilization, and these disparities appear to increase as CKD stage progresses. In the clinical care of this vulnerable population, consideration of SDOH such as language barriers, transportation insecurity, and poverty is recommended."

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

Source: Kilgore KM. Mohammadi I, Japes H. Social determinants of health (SDOH) and healthcare resource utilization (HRU) in autosomal dominant polycystic kidney disease (ADPKD) by CKD stage. Abstract of a poster presented at the American Society of Nephrology virtual Kidney Week 2021 (Abstract PO1252), November 2021.

Blood Pressure and Risk of Adverse Kidney Outcomes

The most common comorbidity among patients with chronic kidney disease (CKD) is hypertension. Uncontrolled hypertension can result in adverse clinical outcomes, including myocardial infarction, acute coronary syndrome, ischemic stroke, heart failure, and death. High blood pressure also affects the kidney itself, and uncontrolled hypertension is a key factor in the loss of kidney function. Blood pressure control is an important therapeutic strategy in patients with CKD to prevent hypertension-related complications.

At present, optimal blood pressure targets are undetermined. The American College of Cardiology/American Heart Association suggest lowering target systolic blood pressure to <130 mm Hg. However, the effect of a lower blood pressure target on kidney function remains a concern. Results of previous studies and meta-analyses of randomized controlled trials have not shown that intensive blood pressure control is effective in reducing the risk of kidney failure. All clinical trials had cardiovascular outcomes and mortality as primary outcomes; adverse kidney events were analyzed a secondary outcomes.

The optimal blood pressure control for preventing progression of CKD is unclear. **Jee Young Lee, MD,** and colleagues in the Republic of Korea conducted a prospective observational cohort study to examine the association between blood pressure and adverse kidney outcomes among participants in the Korean Cohort Study for Outcome in Patients with CKD (KNOW-CKD). Results were reported in the *American Journal of Kidney Diseases* [2021;78(2):236-244).

The primary outcome of interest was a composite kidney outcome of a ≥50% decline in estimated glomerular filtration rate (eGFR) from baseline or incident kidney replacement therapy. The study participants were 2044 patients in the KNOW-CKD trial in Korea.

At study entry, 32.4% (n=663) of participants had diabetes mellitus and 15.6% (n=318) had cardiovascular disease. During follow-up, there were a median of four measurement of blood pressure and four of creatinine. In general, the patients with higher systolic blood pressure were older, more likely to have diabetes and cardiovascular disease, and had lower kidney function than those with lower systolic blood pressure.

During 7472 years of follow-up over a median of 3.66 years, the primary composite outcome occurred in 23.1% (n=473) of participants, for an incidence rate of 63.3 (95% confidence interval [CI], 57.9-69.3) per 1000 patient-years. All-cause deaths occurred in 74 patients; of those 31 died before reaching the composite kidney outcome. Compared with systolic blood pressure of <120 mm Hg, event rates for the composite kidney outcome were greater at higher baseline levels of systolic blood pressure. In analyses with categories of diastolic blood pressure, rates of the composite kidney outcome events were higher in the 70-79 and 80-89 mm Hg categories compared with diastolic blood pressure of <70 and ≥90 mm Hg.

Using cause specific hazards model, the researchers examined the association between systolic blood pressure levels and the risk of the composite kidney outcome. In the fully adjusted model, using baseline systolic blood pressure as a categorical measure, there was a weak but graded association of baseline systolic blood pressure with the risk of the composite kidney outcome. Compared with systolic blood pressure <120 mm Hg, the hazard ratios (HRs) for 120-129, 130-139, and ≥140 mm Hg were 1.10 (95% CI, 0.84-1.44), 1.20 (95% CI, 0.93-1.59), and 1.43 (95% CI, 1.07-191), respectively. There was no significant difference in the risk of the composite kidney outcome among systolic blood pressure categories <140 mm Hg.

The researchers conducted an analysis of the association of systolic blood pressure with the composite kidney outcome using a marginal structural model while accounting for changes in systolic blood pressure over time and for potential confounding of other time-dependent covariates. In this analysis, the graded association of time-updated systolic blood pressure levels with the composite kidney outcome was more apparent. Compared with systolic blood pressure <120 mm Hg, the HRs for 120-129, 130-139, and ≤140 mm Hg were 1.31 (95% CI, 0.98-1.75), 1.59 (95% CI, 1.16-2.16), and 2.29 (95% CI, 1.69-3.11), respectively. In the time-updated model, the risk of the composite kidney outcome began to increase when systolic blood pressure was >130 mm Hg.

In analyses with diastolic blood pressure, there was no association between baseline diastolic blood pressure and the risk of the composite kidney outcome. In the adjusted model using baseline diastolic blood pressure, using diastolic blood pressure <70 mm Hg as the reference group, the HRs for 70-79, 80-89 and ≥90 mm Hg were 1.19 (95% CI, 0.91-1.56), 1.16 (95% CI, 0.88-1.54), and 1.23 (95% CI, 0.88-1.17), respectively. In the time-updated diastolic blood pressure model, the corresponding HRs were 1.18 (95% CI, 0.89-1.56), 1.31 (95% CI, 0.99-1.75), and 1.74 (95% CI, 1.24-2.46), respectively. This association was consistent in an additional time-updated model using averaged diastolic blood pressure.

Compared with patients with systolic blood pressure <120 mm Hg, those with higher systolic blood pressure had steeper slopes of eGFR decline. In the model that included both systolic blood pressure and diastolic blood pressure, only systolic blood pressure was significantly associated with the composite kidney outcome.

Limitations to the study cited by the authors included the observational design, not examining other outcomes such as mortality and cardiovascular events in defining optimal blood pressure, performing blood pressure measurements at the clinic office rather than collecting ambulatory or home blood pressure measurements, the possibility of residual confounding, and including only Korean patients in the cohort.

In conclusion, the authors said, "Analyses with KNOW-CKD data confirm previous findings of a significant association of higher blood pressure levels with CKD progression. The stronger association with time-updated blood pressure suggests that a single measured baseline blood pressure is not a reliable predictor and underscores the importance of prolonged and sustained blood pressure control. However, determining an optimal blood pressure target in patients with CKD remains a future challenge." ■

TAKEAWAY POINTS

- Researchers in Korea conducted a prospective observational study using data from the KNOW-CKD study to examine the association between blood pressure and adverse kidney outcomes.
- The outcome of interest was a composite kidney outcome of a ≥50% decline in eGFR from baseline or incident kidney replacement therapy.
- There were associations between systolic blood pressure and diastolic blood pressure and a higher risk of the composite kidney outcome. The association was greater with systolic blood pressure than diastolic blood pressure.

Print-only Content

Efpeglenatide Lowers CV, Renal Events in Type 2 Diabetes–associated CKD

Individuals with diabetes are at increased risk of adverse cardiovascular events compared with those without diabetes. People with diabetes are also at increased risk of adverse rental events. The risk of adverse cardiovascular events in patients with type 2 diabetes have been shown to be reduced with use of glucagon-like peptide-1 (GLP-1) receptor agonists that are structurally similar to human GLP-1.

Efpeglenatide, an exendin-based GLP-1 receptor agonist, administered weekly via subcutaneous injection, lowers glucose levels without causing hypoglycemia. There are few data available on the effect of efpeglenatide on cardiovascular and renal outcomes in patients with type 2 diabetes who are at high risk for adverse cardiovascular events.

Hertzel C. Gerstein, MD, and colleagues, conducted an international, randomized, controlled trial (the AMPLITUDE-O trial) at 344 sites in 28 countries to evaluate efpeglenatide in participants with type 2 diabetes and either a history of cardiovascular disease or current kidney disease (defined as estimated glomerular filtration rate [eGFR] of 25.0 to 59.9 mL/min/1.73 m^2) plus at least one other cardiovascular risk factor. The trial was designed by the sponsor (Sanofi) in conjunction with an independent international steering committee. Sanofi also managed the trial sites and collected the data. Study results were reported online in the *New England Journal of Medicine* [doi:10.1056/NEJMoa2108269].

Participants were randomized in a 1:1:1 ratio to (1) receive efpeglenatide at a weekly dose of 2 mg for 4 weeks and then 4 mg per week until the end of the trial; (2) efpeglenatide at a dose of 2 mg per weeks, then 4 mg per week for 4 weeks, and then 6 mg per week until the end of the trial; or (3) placebo. The treatment period was defined as the time of randomization until the end of the trial, death, or discontinuation of the assigned regimen.

The primary outcome of interest was the first occurrence of a major adverse cardiovascular event (MACE; a composite of nonfatal myocardial infarction, nonfatal stroke, or death from cardiovascular or undetermined causes). Secondary outcomes of interest included an expanded MACE composite outcome (MACE, coronary revascularization, or hospitalization for unstable angina) and a composite renal outcome (incident macroalbuminuria [defined as a urinary albumin-to-creatinine ratio of >300, as measured in milligrams of albumin to grams of creatinine, or >33.9, as measured in milligrams of albumin to millimoles of creatinine], plus an increase in the urinary albumin-to-creatinine ratio of ≥30% from baseline, a sustained decrease in eGFR of ≥40% for ≥30 days, renal replacement therapy for ≥90 days, or a sustained eGFR of <15 mL/min/1.73 m^2 for ≥30 days).

Between May 11, 2018, and April 25, 2019, 5732 patients underwent screening. Of those, 4076 met eligibility requirements and subsequently underwent randomization: 1359 to receive the 4-mg dose of efpeglenatide, 1358 to receive the 6-mg dose of efpeglenatide, and 1359 to receive placebo. After a median follow-up period of 1.81 years, follow-up ended on December 10, 2020, (total follow-up: 7395.4 person years). As of the end of follow-up, primary outcome status was known for 96.7% (n=3941) of the 4076 participants, and the vital status was known for 99.9% (n=4073) of the participants.

At baseline, mean age of study participants was 64.5 years; 47.9% (n=1954) were <65 years of age; and 33.0% (n=1344) were female. A total of 3650 participants (89.6%) had a history of cardiovascular disease, 1287 (31.6%) had eGFR <60 mL/min/1.73 m^2, 888 (21.8%) had both cardiovascular disease and low eGFR, and 618 (15.2%) were using a sodium-glucose cotransporter 2 (SGLT2) inhibitor. Usage of various glucose-lowering or cardioprotective drugs was similar among the three groups at baseline. At the last trial visit, a greater percentage of participants in the placebo group than in the two efpeglenatide groups (pooled data) were taking a dipeptidyl peptidase 4 inhibitor (1.9% vs 0.9%, *P*=.005) or an SGLT2 inhibitor (21.2% vs 17.5%, *P*=.004).

During follow-up, at least one MACE occurred among 7.0% (189/2717) of participants in the efpeglenatide groups and 9.2% (n=125/1359) of those in the placebo group (3.9 vs 5.3 events per 100 person-years; hazard ratio [HR], 0.73; 95% confidence interval [CI], 0.58-0.92; *P*<.001 for noninferiority at both the 1.8 and 1.3 margins and *P*=.007 for superiority).

Participants in the efpeglenatide groups also reported a significantly lower incidence of at least one expanded MACE composite event (HR, 0.79; 95% CI, 0.65-0.96; *P*=.02), a renal composite outcome event (HR, 0.68; 95% CI, 0.57-0.79; *P*<.001), and a MACE or death from noncardiovascular causes (HR, 0.73; 95% CI, 0.59-0.91; *P*=.004).

In predefined, clinically relevant subgroups of participants, analysis of the evident effect of efpeglenatide on the primary outcome did not vary with sex, age, race, duration of diabetes, glycated hemoglobin level, body mass index, eGFR, history of cardiovascular disease, use of SGLT2 inhibitors, or use of metformin.

A higher percentage of participants in the efpeglenatide groups reported severe gastrointestinal adverse effects compared with the placebo group (*P*=.009). The percentage of participants reporting constipation, diarrhea, nausea, vomiting, or bloating was also higher among those in the efpeglenatide groups than in the group receiving placebo. Other prespecified safety outcomes and other adverse effects were similar among the three groups.

Limitations to the study cited by the authors included the short follow-up period, the occurrence of the primary outcome in fewer participants than anticipated, and selection for previous cardiovascular disease and kidney disease, limiting the power of the trial and its generalizability to individuals at lower-risk with type 2 diabetes.

In conclusion, the researchers said, "The results of our trial show that efpeglenatide reduces the risk of serious adverse cardiovascular and renal events among persons with type 2 diabetes and either a history of cardiovascular disease or current kidney disease." ■

TAKEAWAY POINTS

- The AMPLITUDE-O trial was designed to assess the effects of efpeglenatide, an exendin-based glucagon-like peptide-1 receptor agonist, in patients with chronic kidney disease associated with type 2 diabetes.
- A composite renal outcome (a decrease in kidney function or macroalbuminuria) occurred in 13.0% of participants randomized to receive efpeglenatide compared with 18.4% of participants in the placebo group (hazard ratio, 0.68; 95% confidence interval 0.57-0.79; *P*<.001).
- The risk of cardiovascular events was lower among those in the efpeglenatide groups than in the placebo group (hazard ratio, 0.73; 95% confidence interval, 0.58-092; *P*<.001).

Employment Rates Are Low among Kidney Transplant Recipients

Worldwide, approximately 0.1% of the population is affected by kidney failure with a need for renal replacement therapy. According to statistics from the National Kidney Foundation, more than 2 million people globally receive chronic dialysis treatment or are living with a functional kidney transplant. Patients with kidney failure experience reduced quality of life, increases in psychosocial problems, and difficulties in maintaining normal employment, due, in part, to time-consuming dialysis treatments.

In recent decades, there have been improvements in replacement therapy in kidney failure such as modalities with automated peritoneal dialysis and home hemodialysis. Further, the number of kidney transplants is increasing as is the survival rate following transplantation.

However, results of studies have demonstrated that many patients with kidney failure remain unemployed. Previous studies have reported rates of employment and predictors of employment during dialysis or after kidney transplantation; the results have never been summarized in a systematic review of patients with kidney failure receiving dialysis or having a kidney transplant.

Lilli Kirkeskov, MD, and colleagues in Denmark and Norway conducted a systematic review and meta-analysis to establish the rate of employment before and after initiation of dialysis and kidney transplantation. The researchers also sought to identify predictors of employment during dialysis and post-transplant. Results were reported online in *BMC Nephrology* [doi.org/10.1186/s12882-021-02552-2].

The literature search included the period from January 1966 to August 2020. The researchers searched the PubMed, Embase, and Cochrane Library databases for articles in English. The search terms used were (chronic kidney disease OR chronic renal disease OR kidney transplant OR renal transplant OR dialysis OR hemodialysis OR peritoneal dialysis) AND (unemployment OR work ability OR disability pension). Data on employment rate, study population, age, sex, educational level, duration of dialysis, kidney donor, ethnicity, dialysis modality, waiting time for transplantation, diabetes, and depression were extracted.

A total of 2310 references addressing kidney failure and employment were identified. Based on titles, 133 studies were potentially relevant for evaluation; of those, 58 met inclusion criteria. Twenty-seven of the 58 studies described employment in kidney failure patients during dialysis, 25 addressed employment post-transplant, and six addressed both dialysis and kidney transplantation. The final analysis included 33 studies regarding dialysis and 31 regarding kidney transplantation, representing 162,059 and 137,742 participants, respectively. The studies were published from 1981 to 2020 (median: 2013), and most (81%) were cross-sectional and analyzed data at a specific point in time. The cross-sectional studies were small to medium sized; the cohort studies were mainly larger population studies. More than half of the studies were single center and were mainly from high-income countries.

The average age of patients on dialysis was 52.6 years and the average age of the kidney transplant recipients was 46.7 years. More than half of both groups were male: 60.3% and 59.8%, respectively.

The weighted mean for the employment rate during dialysis was 26.3%. In the 16 studies that excluded patients ≥65 years of age, the weighted mean employment rate was 21.6%. The United States generally appeared to have a lower employment rate among patients on dialysis. Removing studies conducted in the United States from the analysis resulted in a weighted mean of 44.4% compared with 24.8% in the United States. In 23 cross-sectional studies, the employment rate was 24.9%; in the three cohort studies, the employment rate was 51.7%.

In general, after the initiation of dialysis, the employment rate dropped. Nine studies included data before and after dialysis initiation; in those studies, the employment rate decreased by 16.4% (weighted mean) (range: 5.2% to 58.5% within and between countries). Overall, the employment rate was higher in patients receiving peritoneal dialysis compared with patients on hemodialysis (58.8% vs 39.5%).

The pre-transplant employment rate was 36.9% (weighted mean), ranging from 25% to 86% between continents. Post-transplant, the employment rate was 38.2% (weighted mean, all studies), ranging between 14.2% and 85% within and between continents. When including only the 18 studies that excluded patients ≥65 years of age, the employment rate was 34.4%.

Both pre- and post-transplant data were available in 14 studies: the change in the employment rate from pre- to post-transplant ranged from a decrease of 30% to an increase of 3.5%. The employment rate was assessed at 1 year post-transplant in most studies. One study assessed employment rates (full-time work) 1 and 5 years post-transplant (38.1% and 35.6%, respectively).

Twelve studies included information on normative comparison data to use for meta-analysis of predictors for employment during dialysis, but only for some of the predictors (dialysis modality (peritoneal dialysis vs hemodialysis), diabetes versus being without diabetes, educational level (more than high school vs high school or less), sex, and age. Predictors for employment during dialysis were not having diabetes, educational level greater than high school, peritoneal dialysis, and male sex. Young age was also a predictor for employment.

Fifteen studies that included post-transplant employment rates also had information on normative comparison data to use for meta-analysis for employment post-transplant. The predictors for post-transplant employment with low heterogeneity were having a living donor, educational level more than high school, peritoneal dialysis, male sex, younger age, being White, waiting time for transplantation, and depression. Predictors with moderate heterogeneity were pre-transplant employment, being without diabetes, and shorter time in dialysis.

Limitations to the study included the lack of a control group in nearly all of the studies, the cross-sectional design of the majority of the studies, and lack of all relevant risk factors for unemployment.

In conclusion, the authors said, "Kidney failure patients have a low employment rate during dialysis and pre- and post-transplant. Predialysis employment, a higher education, not having diabetes or depression, being younger, male, White, receiving a living donor kidney, and a short waiting time before transplantation were all predictors for post-transplant employment. It is important to support kidney failure patients through a combination of clinical and social measures to ensure that they remain in work." ■

TAKEAWAY POINTS

- Patients with kidney failure, either on dialysis or recipient of a kidney transplant, face difficulties maintaining employment.
- Results of a systematic review and meta-analysis revealed low rates of employment for patients on dialysis and for kidney transplant recipients.
- Predictors for employment in both groups included younger age, being without diabetes, use of peritoneal dialysis, transplantation with a living donor kidney, and higher education level.

Food Literacy and Adherence to Mediterranean-Style Diet in Kidney Transplant Recipients

The optimal treatment for end-stage kidney disease is kidney transplantation, providing improved quality of life and longer life expectancy compared with maintenance dialysis. However, compared with the general population, life expectancy of kidney transplant recipients is still lower, due primarily to high cardiovascular morbidity and mortality. Kidney transplant recipients commonly have an unfavorable cardiovascular profile, characterized by post-transplantation weight gain, obesity, metabolic syndrome, post-transplantation diabetes mellitus, and hypertension.

As in the general population and in other high risk groups, there is an association between a healthy diet, including a variety of wholegrain products, fruit and vegetables, nuts, legumes, lean meats and fish, and an avoidance of high sodium intake and lower cardiovascular risks in kidney transplant recipients. Results of previous studies have shown an association between adherence to a Mediterranean-style diet and a lower risk of post-transplantation diabetes and all-cause mortality in addition to improved kidney function outcomes. Dietary sodium restriction has also been proven effective in lowering blood pressure in kidney transplant recipients.

As part of the TransplantLines Cohort and Biobank study at the University Medical Center Groningen in the Netherlands, **Karin Boslooper-Meulenbelt** and colleagues conducted a cross-sectional study to examine levels of food literacy among kidney transplant recipients and assess its association with adherence to a Mediterranean-style diet and with dietary sodium intake. Results of the study were reported in the *Journal of Renal Nutrition* [2021;31(6):628-636].

A total of 148 kidney transplant recipients 1 year or more post-transplantation who completed a Food Frequency Questionnaire (FFQ) were invited to complete the Self-Perceived Food Literacy (SPFL) questionnaire and All Aspects of Health Literacy Scale (AAHLS). The collection of data occurred between June 2019 and January 2020.

Mean age of the study cohort was 56 years, 66% were male, mean estimated glomerular filtration rate was 53.7 mL/min/1.73 m^2, and mean plasma potassium level was 4.02 mmol/L. One participant had end-stage kidney failure requiring dietary restrictions. Mean consumption of fruit and vegetables was 129 g/day and 127 g/day respectively. Mean SPFL score was 3.63. The majority of participants reported maximum scores at the functional and communicative domain of the AAHLS.

Results of univariable linear regression analysis demonstrated an association between higher mean SPFL scores and a higher Mediterranean Diet Score, reflecting better adherence to a Mediterranean-style diet (*P*<.001). Following adjustment for age and sex, cardiometabolic parameters, transplant-related parameters, employment status, level of education, smoking status, and alcohol use, the associations remained significant.

In both unadjusted and adjusted linear regression analyses, there were no significant associations between sodium intake and SPFL score.

Results of univariable linear regression analysis demonstrated an association between higher mean SPFL scores and a higher Mediterranean Diet Score, reflecting better adherence to a Mediterranean-style diet (*P*<.001).

Participants with higher food literacy levels (SPFL score ≥3.41) were more often female, were older, had higher level of education, and were less often an active smoker than those with lower food literacy levels. There were no significant differences in transplant-related and cardiometabolic parameters across levels of food literacy with the exception of time since transplantation: those with lower food literacy levels had longer time since transplantation.

Mediterranean Diet Score was significantly higher among participants with higher food literacy levels as well as higher fruit, vegetable, and fish consumption compared with those with lower food literacy levels. Participants in the group with higher food literacy generally limited salt intake to <6 g/day more often than did those in the group with lower food literacy (*P*=.08). However, the majority of participants in both groups exceeded the advised salt consumption of 6 g/day. Participants with lower food literacy were involved in meal preparation less often than those with higher food literacy.

Limitations to the study cited by the authors included the use of the SPFL that has subjective, self-reported questions to determine the level of food literacy, the possibility of selection bias, and the inability to correct for changes in dietary intake over time.

In conclusion, the researchers said, "Higher levels of food literacy, measured with the SPFL questionnaire, are associated with better adherence to a Mediterranean-style diet in kidney transplant recipients. The association between food literacy and sodium intake is less consistent. Further studies are needed to determine if interventions focused on improving food literacy may contribute to a healthier diet and better long-term outcomes in kidney transplant recipients." ■

TAKEAWAY POINTS

- Researchers in the Netherlands conducted a cross-sectional study to examine food literacy levels in kidney transplant recipients and the association with adherence to a Mediterranean-style diet and restriction of sodium intake.
- Those with higher food literacy level were more likely to have better adherence to a Mediterranean-style diet. The associations between higher food literacy and a higher Mediterranean Diet Score were significant in unadjusted and adjusted linear regression analyses.
- There were no significant associations between higher food literacy and dietary sodium intake.

Print-only Content

Daprodustat for Treatment of CKD–Related Anemia

Anemia related to chronic kidney disease (CKD) is associated with reduced quality of life, more frequent blood transfusions, and increased risk of cardiovascular events. Results of previous trials among patients with CKD have raised safety concerns regarding the use of conventional erythropoiesis-stimulating agents (ESAs) for the treatment of anemia. When treatment is targeted a normal hemoglobin (Hb) level (13.0 to 14.0 g/dL), potential risks associated with the use of recombinant human erythropoietin and its derivatives include increases in the risk of stroke, myocardial infarction, vascular access thrombosis, tumor progression, or death.

Results of more recent trials have suggested that hypoxia-inducible factor (HIF) prolyl hydroxylase inhibitors (PHIs) are as effective as ESAs in increasing levels of Hb. **Ajay K. Singh, MBBS, FRCP, MBA,** and colleagues reported results of the ASCEND-D (Anemia Studies in Chronic Kidney Disease: Erythropoiesis via a Novel Prolyl Hydroxylase Inhibitor Daprodustat–Dialysis) and the ASCEND-ND (Anemia Studies in Chronic Kidney Disease: Erythropoiesis via a Novel Prolyl Hydroxylase Inhibitor Daprodustat—non-Dialysis) trials [*New England Journal of Medicine*; doi:10.1056/NEJMoa2113379 and doi:10.1056/NEJMoa2113380].

ASCEND-D: DAPRODUSTAT IN PATIENTS RECEIVING DIALYSIS

ASCEND-D was a randomized, open-label, phase 3 trial among patients who were undergoing maintenance dialysis, including patients with ESA hyporesponsiveness. The researchers sought to examine the hematologic efficacy, cardiovascular safety, and iron kinetics of the oral HIF-PHI daprodustat compared with conventional therapy with ESAs.

Eligible patients were adults with CKD who were undergoing dialysis and had a Hb level of 8.0 to 11.6 g/dL. Patients were required to have a serum ferritin level of >100 ng/mL and a transferrin saturation above 20%. Exclusion criteria included anemia unrelated to CKD, recent cardiovascular event, or current or recent cancer.

The trial consisted of four periods: screening, placebo run-in, treatment, and follow-up. Patients were evaluated at least every 4 weeks during the first year of the trial and at least every 12 weeks thereafter. Patients were randomized in a 1:1 ratio to receive either oral daprodustat or an injectable ESA (epoetin alfa if they were receiving hemodialysis or darbepoetin alfa if they were receiving peritoneal dialysis). The primary outcomes were the mean change in the Hb level from baseline to weeks 28 through 52 (noninferiority margin, –0.75 g/dL) and the first occurrence of a major cardiovascular event (MACE), defined as a composite of death from any cause, nonfatal myocardial infarction, or nonfatal stroke (noninferiority margin, 1.25).

A total of 2964 patients underwent screening at 431 centers in 35 countries from November 23, 2016, through August 10, 2018. At baseline, the two trial groups (daprodustat, n=1487 and ESA, n=1477) were well balanced in demographic and clinical characteristics, including history of cardiovascular disease, previous ESA dose, and use of intravenous iron. Of the total cohort, 88.5% were undergoing hemodialysis and 12.2% were considered to have ESA hyporesponsiveness on the basis of ESA-resistance index or receipt of an epoetin dose of at least 450 U per kilogram of body weight per week. Mean baseline Hb level was 10.4 g/dL across the two groups.

In the daprodustat group, the mean change in Hb level from baseline to weeks 28 through 52 was 0.02 g/dL, compared with 0.10 g/dL in the ESA group, for a difference of 0.18 g/dL (95% confidence interval, 0.12-0.24), meeting the prespecified noninferiority margin for daprodustat.

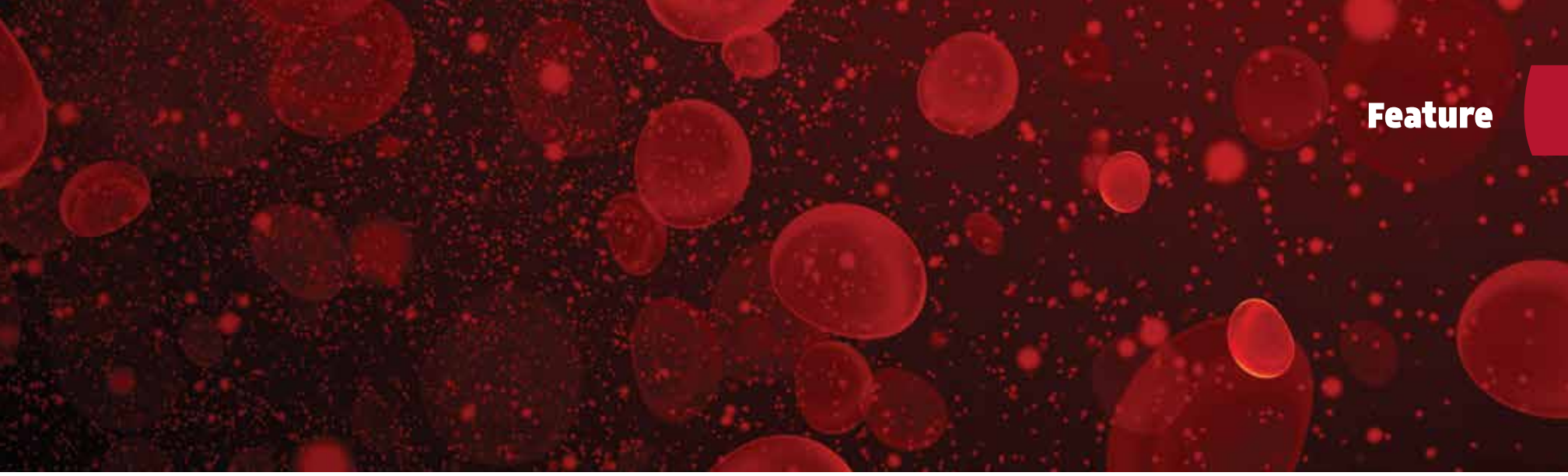
In the daprodustat group, the mean change in Hb level from baseline to weeks 28 through 52 was 0.28 g/dL, compared with 0.10 g/dL in the ESA group, for a difference of 0.18 g/dL (95% confidence interval [CI], 0.12-0.24), meeting the prespecified noninferiority margin for daprodustat. Results of supplementary analysis provided findings that were consistent with the primary analysis. The effect of daprodustat compared with ESA therapy was generally consistent across prespecified subgroups.

In the daprodustat group a first MACE occurred in 25.2% of patients (n=374/1487), compared with 26.7% of patients (n=394/1477) in the ESA group (hazard ratio [HR]; 0.93; 95% CI, 0.81-1.07), meeting the prespecified noninferiority margin of 1.25. In general, treatment effect was consistent across prespecified subgroups, and the results were consistent with other supplementary intention-to-treat and on-treatment analyses.

Results of superiority testing for daprodustat compared with ESA were not significant regarding the three cardiovascular principal secondary outcomes: the first occurrence of MACE (HR, 0.93; 95% CI, 0.81-1.07), the first occurrence of MACE or a thromboembolic event (HR, 0.88; 95% CI,

Daprodustat is an oral hypoxia-inducible factor prolyl hydroxylase inhibitor that stimulates endogenous erythropoietin production but also influences iron metabolism. The results from our ASCEND-ND and ASCEND-D trials support daprodustat as an effective and safe oral alternative to conventional ESAs. While daprodustat hasn't been approved by either the US or European regulatory authorities as yet, I am hopeful that it will be approved by the end of the year.

Ajay K. Singh, MBBS, FRCP, MBA



0.78-1.00), and the first occurrence of MACE or hospitalization for heart failure (HR, 0.97; 95% CI, 0.85-1.11). The incidence of death from any cause was similar in the two groups.

A total of eight patients (five in the daprodustat group and three in the ESA group) were excluded from the safety analyses because they did not receive the randomized treatment. The percentages of patients with serious adverse events were similar between the two groups (52.2% in the daprodustat group vs 50.7% in the ESA group).

The researchers cited some limitations to the findings, including the open-label design, the possibility that the observation time for the trial was insufficient to characterize the full risks, and the use of epoetin alfa as the comparator, possibly limiting the generalizability of the conclusions regarding the noninferiority of daprodustat to other ESAs.

In summary, the authors said, "In this trial, we found that daprodustat was noninferior to conventional ESAs in the treatment of anemia among patients with CKD who were undergoing dialysis and in the incidence of cardiovascular outcomes."

ASCEND-ND: DAPRODUSTAT IN PATIENTS NOT RECEIVING DIALYSIS

ASCEND-ND was a randomized, open-label, phase 3 trial with blinded adjudication of cardiovascular outcomes among patients with CKD not undergoing dialysis comparing daprodustat with darbepoetin alfa for the treatment of anemia. The primary outcomes were the mean change in hemoglobin level from baseline to weeks 28 through 52 and the first occurrence of a major adverse cardiovascular event (MACE), defined as a composite of death from any cause, nonfatal myocardial infarction, or nonfatal stroke.

Adult patients were eligible for the trial if they had CKD stage 3 to 5 and were not currently receiving dialysis or scheduled to initiate dialysis within 90 days, met hemoglobin and ESA criteria, and had a serum ferritin level of >100 ng/mL and a transferrin saturation above 20%. Exclusion criteria were anemia not associated with CKD, a recent cardiovascular event, or current or recent cancer.

The trial had four periods: screening, placebo run-in, treatment, and follow-up. Eligible patients were randomized in a 1:1 ratio to receive either oral daprodustat or subcutaneous darbepoetin alfa.

A total of 3872 patients were randomized to receive daprodustat (n=1937) or darbepoetin alfa (n=1935) at 506 centers in 39 countries; randomization occurred from December 5, 2016, through December 7, 2020. At baseline, the two groups (daprodustat, n=1937; darbepoetin alfa, n=1935) were well balanced in demographic and clinical characteristics, including estimated glomerular filtration rate, coexisting conditions, history of cardiovascular disease, and previous ESA does in those who had received an ESA. Mean baseline Hb level was 9.9 g/dL across the two groups.

In the daprodustat group, mean change in Hb level from baseline to weeks 28 through 52 was 0.74 g/dL, compared with 0.66 g/dL in the darbepoetin alfa group; difference 0.08 g/dL (95% CI, 0.03-0.13), meeting the prespecified noninferiority margin. Findings in supplementary analyses were consistent with those in the primary analysis. In general, the effect of daprodustat compared with darbepoetin alfa was consistent across the prespecified subgroups.

A rapid increase in Hb level was defined as an increase of >2 g/dL during any 4-week period from randomization through the first year, and was observed in ≤2% of patients in both trial groups. Adherence to the trial regimen was 97% of patients in the daprodustat group and 98% in the darbepoetin alfa group.

In the daprodustat group, a first MACE occurred in 19.5% of patients (n=378/1937) compared with a first MACE in 19.2% (n=371/1935) in the darbepoetin alfa group (hazard ratio, 1.03; 95% CI, 0.89-1.19), meeting the prespecified noninferiority margin of 1.25.

In the daprodustat group, a first MACE occurred in 19.5% of patients (n=378/1937) compared with a first MACE in 19.2% (n=371/1935) in the darbepoetin alfa group (HR, 1.03; 95% CI, 0.89-1.19), meeting the prespecified noninferiority margin of 1.25. Analysis in prespecified subgroups yielded generally consistent results. The results were also consistent with those in other supplementary intention-to-treat analyses. The on-treatment MACE analysis that censored data on patients at 28 days following the date of the last dose, revealed a higher incidence of a first MACE during the treatment period in the daprodustat group compared with the darbepoetin alfa group (14.1% vs 10.5%, respectively, HR, 1.40; 95% CI, 1.17-1.68).

Results of superiority testing were not significant for the four principal secondary outcomes: the first occurrence of MACE in the daprodustat group as compared with the darbepoetin alfa group (HR, 1.03; 95% CI, 0.89-1.19), MACE or thromboembolic events (HR, 1.06; 95% CI, 0.93-1.22), MACE or hospitalization for heart failure (HR, 1.09; 95% CI, 0.95-1.24), and progression of CKD (subdistribution HR, 0.98; 95% CI, 0.84-1.13). The incidence of death from any cause was similar in the two groups.

Two patients in the darbepoetin group were excluded from the safety analyses because they did not receive the assigned treatment. Serious adverse events that started or worsened after initiation of trial treatment were reported in 43.9% of patients (n=850/1937) in the daprodustat group and 36.4% of patients (n=703/1933) in the darbepoetin alfa group. There was no notable excess of any event in the daprodustat group relative to the darbepoetin alfa group.

The open-label design of the study and patient awareness of treatment assignment were cited as limitations to the study findings, Other limitations included the possible insufficiency of the observation time for the trial, the use of darbepoetin alfa possibly limiting generalizability of the conclusions regarding noninferiority to other ESAs, and not taking into account the different dosing frequencies.

In summary, the researchers said, "In this trial, we found that daprodustat was noninferior to darbepoetin alfa, both in the treatment of anemia in patients with CKD who were not undergoing dialysis and with respect to cardiovascular outcomes. This trial showed that daprodustat and darbepoetin alfa had similar efficacy."

Both trials were supported by GlaxoSmith Kline. ■

TAKEAWAY POINTS

- Researchers reported results of ASCEND-ND, a trial comparing the safety and efficacy of daprodustat with conventional therapy with the erythropoiesis-stimulating agent (ESA), darbepoetin alfa, for the treatment of anemia in patients with CKD not receiving dialysis.
- The primary efficacy outcome of interest was mean change in hemoglobin level from baseline to weeks 28 through 52. The difference of 0.08 g/dL between the two groups met the prespecified noninferiority margin of -0.75 g/dL.
- The two groups were similar in percentages of patients with a first MACE event (19.5% in the daprodustat group vs 19.2% in the darbepoetin alfa group), meeting the prespecified noninferiority margin for daprodustat.

The Liver Meeting 2021

SCr ≥5 mg/dL Tipping Point in Treatment of HRS-AKI with Terlipressin

The importance of prompt treatment of hepatorenal syndrome-acute kidney injury (HRS-AKI) with vasoactive medications and albumin is highlighted in guidelines from the European Association of the Study of the Liver. For every 1 mg/dL increase in serum creatinine (SCr) at the time of treatment initiation, the odds of HRS reversal and survival decrease by >30%.

Results of clinical trials of terlipressin have suggested that SCr ≥5 mg/dL is a possible tipping point for clinical outcomes. **Andrew S. Allegretti, MD, MSc,** and colleagues conducted a post hoc analysis of a medical chart review study to describe the efficacy and safety outcomes in patients with an SCr ≥5 mg/dL at the time of vasopressor initiation.

The analysis included data from 203 hospitalized adult patients treated with terlipressin collected across 26 hospitals in the United Kingdom between January 1, 2013, and December 31, 2017. Results were reported during a virtual poster session at the AASLD Liver Meeting in a poster titled *Serum Creatinine ≥5 mg/dL Is Associated with Decreased Safety and Efficacy in Patients Treated with Terlipressin for Hepatorenal Syndrome-Acute Kidney Injury (HRS-AKI) in the United Kingdom (UK).*

Data were collected up to 90 days post-discharge. HRS treatment response was measured by the change in SCr from 1 day before initiation of terlipressin to the last day of vasopressor treatment or day 14, whichever came first. Treatment response was categorized as complete response if SCr decreased to ≤1.5 mg/dL, as partial response if SCr decreased ≥20% but >1.5 mg/dL, and as no response if SCr decreased <20%.

A total of 203 patients received terlipressin. Of those, 89% (n=181) had a SCr <5 mg/dL at presentation and 11% (n=22) had a SCr ≥5 mg/dL. The two groups were similar in baseline characteristics.

Patients who presented with SCr <5 mg/dL were significantly more likely to achieve complete response compared with patients who presented with SCr ≥5 mg/dL (54.7% vs 13.6%, respectively; *P*<.001). Conversely, patients who presented with SCr ≥5 mg/dL were significantly more likely to achieve partial response (50.0% vs 21.2%, respectively; *P*<.001).

In patients who presented with SCr <5 mg/dL, median duration of terlipressin treatment was 6.0 days; in patients presenting with SCr ≥5 mg/dL, median duration of treatment was 6.5 days.

The two groups were not significantly different in the proportion of patients who received antibiotics (SCr <5 mg/dL, 53.0%; SCr ≥5 mg/dL, 68.2%; *P*=.178) or albumin (SCr <5 mg/dL, 72.4%, ≥5 mg/dL, 68.2%; *P*=.870). Patients presenting with SCr <5 mg/dL were less likely to develop fluid overload or pulmonary edema (14.4%) and multi-organ failure (6.1%) compared with patients with presenting SCr ≥5 mg/dL (27.3% and 31.8%, respectively). In patients with presenting SCr <5 mg/dL overall, survival was significantly longer than in patients with presenting Scr ≥5 mg/dL.

In conclusion, the authors said, "The results of the study confirm those of previous trials linking higher presenting SCr to poorer efficacy in patients with HRS-AKI. Importantly, patients with SCr ≥5 mg/dL also were significantly more likely to develop adverse events compared to those with a presenting SCr <5 mg/dL. Survival data from this post hoc analysis support the importance of earlier initiation of vasoconstrictors to optimize patient outcomes."

The study was supported by Mallinckrodt Pharmaceuticals.

Source: Allegretti A, Jamil K, Verleger K, et al. Serum creatinine ≥5 mg/dL is associated with decreased safety and efficacy in patients treated with terlipressin for hepatorenal syndrome-acute kidney injury (HRS-AKI) in the United Kingdom (UK). Poster presented at the American Association for the Study of Liver Disease virtual Liver Meeting, November 12-15, 2021.

Characteristics and Outcomes of Patients Hospitalized with HRS-AKI

Hepatorenal syndrome-acute kidney injury (HRS-AKI) is characterized by rapid deterioration in renal function in patients with cirrhosis. HRS-AKI is the result of portal hypertension that leads to decreased effective circulating arterial volume and renal vasoconstriction. Patients with HRS-AKI face poor prognosis; results of studies in multiple cohorts demonstrated ~50% survival at 1 month.

Other previous studies have shown associations between vasoconstrictors and improvement in outcomes in patients with HRS-AKI. In the United States, treatment primarily involves use of vasoactive medications such as midodrine with octreotide, norepinephrine, and vasopressin, in combination with albumin. Critical factors that can aid in predicting clinical outcome and treatment response among patients with HRS-AKI include Model of Endstage Liver Disease (MELD) score that incorporated serum bilirubin, creatinine, and the international normalized ratio, along with acute-on-chronic liver failure (ACLF).

Arun J. Sanyal, MD, and colleagues conducted a retrospective, observational study designed to identify characteristics of patients with HRS-AKI in the United States and to assess treatment patterns and clinical outcomes based on disease severity. Results of the study were reported during a virtual poster session at the AASLD Liver Meeting in a poster titled *Hepatorenal Syndrome Patient Characteristics, Treatment, and Clinical Response by Disease Severity: Real-World Practice Patterns from 11 US Hospitals.*

The study utilized medical chart data extracted by physicians from adult patients hospitalized at 11 tertiary care centers in the United States. Data were collected from hospital admission up to 90 days post-discharge or until death.

International Classification of Diseases (ICD), Ninth Revision, and ICD-Tenth Revision codes were used to identify eligible patients; patient eligibility was also determined using chart documentation of diagnosis of HRS-AKI. Patients were selected based on a random number generated by the study sponsor.

Inclusion criteria were age >18 years, alive, or deceased at the time of data collection, and first hospital admission for HRS-AKI episode between January 1, 2016, and June 30, 2019. Patients were excluded if they were enrolled in any clinical trial during hospitalization, had incomplete laboratory data for assessment of treatment response (defined as a serum creatinine [SCr] on the day of vasopressor initiation and discontinuation), or had hospital stay ≤2 days.

The analysis included data on 132 patients at 11 tertiary care centers. Of the total cohort, 49.2% (n=65) had standard disease severity (baseline SCr <5 mg/dL, ACLF grade 0-2, and MELD score <35) and 50.8% (n=67) had severe disease (baseline SCr ≥5 mg/dL or ACLF >2 or MELD score ≥35). At admission, mean patient age was 57 years, 45.5% were female, and 68.2% were White. The most common precipitating events were treatment with diuretics (42.4%) and large-volume paracentesis (41.7%). The primary underlying cause of cirrhosis was acute alcoholic cirrhosis (55.3%), which was more common in the group with severe disease at presentation than in the standard disease group (67.2% vs 43.1%; *P*=.005).

The two groups were similar in initial vasopressor therapies: midodrine/octreotide monotherapy (89.2% vs 82.1%), norepinephrine monotherapy (1.5% vs 6.0%), and other combination therapies (9.2% vs 11.9%). Median duration of treatment was norepinephrine, 3 days in the standard presentation group and 6.5 days in the severe disease group; midodrine/octreotide, 5 days in the standard group and 6 days in the severe disease group; and other therapy, 12 days in the standard group and 5.5 days in the severe group. Nearly all (99%) patients received concurrent treatment with albumin (100% of patients in the standard presentation group and 98.5% of those in the severe disease presentation group).

Mean change in SCr from baseline to day 14 was -0.2 mg/dL in the standard presentation group and +0.7 in the severe presentation group (*P*=.006). Overall response was 23.0% (complete response [CR], 13.8% and partial response [PR], 9.2%) in the standard disease presentation group and 34.3% (CR, 17.9% and PR, 16.4%) in the severe disease presentation group (*P*=.3). Median time from initiation of vasopressor treatment to response was 14 days in both groups.

In the standard group, median overall survival from initiation of vasopressor treatment was 1.5 months compared with 0.6 months in the severe disease group.

In conclusion, the authors said, "Midodrine/octreotide was the most prescribed vasopressor for HRS-AKI in the United States. The results of the study do not support a link between disease severity at presentation and response to vasopressor treatment or mortality. Overall response rate was low in patients initiating existing treatment regimens irrespective of disease severity, indicating an unmet need in HRS-AKI patients and need for alternate therapies that will improve response and survival outcomes."

The study was supported by Mallinckrodt Pharmaceuticals.

Source: Sanyal AJ, Reddy R, Brown KA, et al. Hepatorenal syndrome patient characteristics, treatment, and clinical response by disease severity: Real-world practice patterns from 11 US hospitals. Poster presented at the American Association for the Study of Liver Disease virtual Liver Meeting, November 12-15, 2021.

Strive Health Announces Strive Care Partners

In late fall, Strive Health announced the debut of Strive Care Partners (SCP), a dedicated platform to enable "nephrologists to share and succeed in global risk contracts with payors." The platform is designed to benefit patients with chronic kidney disease and end-stage kidney disease through a comprehensive, patient-centered approach to enhance lives and local communities.

Strive's partnerships encompass 500 nephrology providers; represented payor agreements include Medicare's Comprehensive Kidney Care Contracting program and Medicare Advantage global risk contract. Strive supports nephrologists through transformative care delivery, proprietary technology, and value-based contracting resources. Under the SCP platform, the suite of services will support existing nephrologist partnerships as well as future relationships.

Chris Riopelle, CEO and founder of Strive Health, said, "Our value-based kidney care platform was built from day one for nephrologist integration and enablement. Nephrologists have responded to our solution with excitement beyond our wildest expectations, demonstrating the momentum of new value-based payment models in the kidney space. We are proud to launch a dedicated platform that serves nephrologists as they transform their practices from volume to value."

St. Joseph's Health and Renalytix Partner to Advance Kidney Health

St. Joseph's Health and Renalytix announced a partnership to implement an advanced clinical care model designed to improve kidney health in patients with type 2 diabetes and early-stage chronic kidney disease. According to a press release from Renalytix, the KidneyIntelX™ platform will be integrated with care management at St. Joseph's to help prevent patients with diabetes and early-stage kidney disease from progressing to significant disease and/or kidney failure. KidneyIntelX enables primary care and specialist physicians to identify risk and implement St. Joseph's Health management, nutrition, and education intervention protocols in a timely manner.

St. Joseph's Health is part of Trinity Health, a large multi-institutional Catholic healthcare delivery system in the United States, serving communities that include more than 30 million individuals in 25 states. KidneyIntelX test risk assessment will be available through St. Joseph's Hospital's electronic health record system, providing access to primary care physician, endocrinologists, nephrologists, and care teams.

Paul Fiacco, MD, medical director, Trinity Health Integrated Care ACO and president of CNY AIM (a clinically integrated network affiliated with St. Joseph's Health), said, "This risk assessment allows primary care clinicians to provide early intervention to their identified high-risk patients to prevent future disease progression to kidney failure. This partnership with Renalytix is motivated by our common desire to expand our value proposition to larger populations and further strengthen our population health management capabilities."

Christine Loftsgaarden, vice president, commercial partnerships at Renalytix, added, "St. Joseph's Health shares our forward-thinking, patient-centric approach to changing the standard of care in kidney health. St. Joseph's Health's early-stage chronic kidney disease care model, powered by KidneyIntelX, is expected to drive improved clinical and cost outcomes to make healthier kidneys both attainable and sustainable."

Fresenius Named One of *Newsweek*'s Most Loved Workplaces

Fresenius Medical Care North American (FMCNA) has been named one of *Newsweek's* Most Loved Workplaces for 2021. FMCNA came in at #42 among the top 100 companies rated for employee happiness and satisfaction at work, and was one of the top three healthcare companies on the list. *Newsweek* cited the company's work around diversity, equity, and inclusion.

In a recent press release, **Bill Valle,** CEO of FMCNA, said, "The dedication of our employees throughout the pandemic has demonstrated our commitment to providing superior care to our patients and is a testament to the true heart of our invaluable workforce. Receiving this honor is especially meaningful this year, as our employees have been working tirelessly in challenging circumstances to ensure our patients have access to the life-sustaining care they rely on us for. 'The Most Loved Workplace' honor is a tribute to the love that our employees have always shown to our patients, their work, and each other, and validates who we are—a team of caring people that treats all others with empathy, compassion, and respect. I am especially humbled by the recognition of our efforts around diversity, equity, and inclusion. We know we are better together and stronger when everyone is truly valued and cherished."

The *Newsweek* list was created in collaboration with the Best Practice Institute. The results were determined following surveys of more than 800,000 employees from businesses with workforces that varied in size from 50 to more than 10,000.

"In the wake of the pandemic, business hit hurdles in terms of retaining and attracting employees—but the companies that made this list are delivering the respect, care, and appreciation that it takes to create a positive workplace that nurtures talent," said **Nancy Cooper,** global editor in chief, *Newsweek*.

AKF Summit on Unknown Causes of Kidney Disease Project

In December, the American Kidney Fund (AKF) held a working session summit as part of AKF's Unknown Causes of Kidney Disease (UCKD) Project, aimed at convening thought leaders in the renal community to address four areas critical to improving diagnosis and treatment of kidney disease.

In a recent press release, **LaVarne A. Burton,** AKF president and CEO, said, "Too many patients fall into late-stage kidney disease or kidney failure, without a clear understanding of why. This can have dire consequences, such as delayed treatment, additional comorbidities, and even the loss of a transplanted kidney. We are working to bring together a thoughtful, dedicated collaboration among the kidney care community, resulting in steady progress toward making systematic changes that will help reduce the number of patients unaware of the origins of their kidney disease."

During the December meeting, the summit participants discussed key goals, current progress, anticipated barriers, and next steps on three areas of interest: (1) public policy, ensuring equitable insurance coverage for patients seeking an accurate diagnosis; (2) patient and caregiver empowerment, creating a suite of resources and tools to empower patients to work with their clinicians to secure an accurate diagnosis; and (3) healthcare professional awareness and education, including conducting research with primary care physicians, nephrologists, urologists, endocrinologists, nurse practitioners, and physician assistants.

Sponsors of the UCKD Project include Sanofi Genzyme, Natera Inc., Vertex Pharmaceuticals, Inc., Alexion Pharmaceuticals, Otsuka America Pharmaceutical, Inc., and Travere Therapeutics.

Three Top Executives Named to NFK National Board of Directors

The National Kidney Foundation (NKF) has named three top executives to the foundation's board of directors. In a late fall press release, **Anthony Tuggle,** chair of NKF's national board and a kidney transplant recipient, said, "We're so excited for these three incredibly talented executives to join the NFK board of directors and share their extensive knowledge in the areas of expertise."

Hubert L. Allen, JD, is the executive vice president, general counsel, and secretary at Abbott, the global healthcare company. He leads a global team of more than 250 lawyers who interact with legal systems in more than 100 countries in support of Abbott around the world. He dealt with the challenges faced by patients with kidney disease when he developed acute kidney injury due to rhabdomyolysis. He regained full kidney function after being on dialysis for a few months.

"It's an honor to join the largest kidney patient organization in the country and pay it forward to help others dealing with a difficult diagnosis like kidney disease," Mr. Allen said.

Renee Richardson Gosline, PhD, is senior lecturer in the Management Science group at the MIT Sloan School of Management and a principal research scientist at MIT's Initiative on the Digital Economy. She said, "In general, most Americans know very little about the kidneys: the signs of kidney disease, how an early diagnosis can save your life, or how to support a patient. I'd like to change that. People who live with this invisible illness should not feel invisible themselves; yet many of the millions of Americans living with kidney disease do... Joining the NKF national board is an honor and I am grateful to contribute to this important cause."

Alison Steiber, PhD, RDN, is a registered dietitian nutritionist and chief science officer at the Academy of Nutrition and Dietetics. She said, "Nutrition plays a huge role in maintaining optimal health throughout each stage of your life, and good kidney health actually keeps you alive. I am passionate about the impact that nutrition can have on the health outcomes of patients with CKD, so I'm absolutely honored to join the NKF board of directors and share my decades of expertise in the field of renal nutrition."

AKF Lauds Build Back Better Act Provisions to Help Patients with Kidney Disease

In a recent press release, the American Kidney Fund (AKF) praised the US House of Representatives for including provisions in the Build Back Better Act aimed at helping Americans with chronic kidney disease (CKD) and kidney failure (end-stage kidney disease [ESKD]).

LaVarne A. Burton, president and CEO of AKF, said, "Access to affordable, comprehensive health insurance and primary care physicians is the first step to ensuring that CKD is found early, which can provide kidney patients with early interventions that can slow or halt progression of the disease. Expansion of Medicaid and enhanced Affordable

Care Act (ACA) tax credits so more people in the United States can afford health insurance has been a longstanding policy priority of AKF. We are so pleased to see these provisions in the Build Back Better Act, as they will help kidney patients who rely on Medicaid, Medicare, and private insurance."

The Build Back Better Act includes a provision that would provide Medicaid coverage to those who live in states where there is a coverage gap due to lack of expansion of Medicaid. Those patients have incomes too high to qualify for Medicaid, but too low for ACA tax subsidies. The Build Back Better Act would expand ACA tax credits to the lower income threshold, allowing those patients to gain access to health insurance. The Act would also expand the Federal Medical Assistance Percentage from 90% to 93% from 2023 to 2025, allowing patients to retain access to needed healthcare services.

Positive Topline Results from AURORA 2

In a recent press release, Aurinia Pharmaceuticals, Inc., announced positive topline results from the AURORA 2 continuation study examining long-term safety and tolerability of Lupkynis™ (voclosporin) for the treatment of adults with active lupus nephritis, a complication in

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News Briefs

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patients with systematic lupus erythematosus. Aurinia is a biopharmaceutical company working to deliver therapeutics to treat autoimmune disease.

Neil Solomons, MD, chief medical officer at Aurinia, said, "We are pleased by the final results of the AURORA 2 continuation study evaluating Lupkynis for the treatment of lupus nephritis, which supports the long-term safety and tolerability for up to 3 years. Furthermore, we observed that efficacy was maintained in combination with MMF and low-dose steroids.

Amit Saxena, MD, assistant professor, department of medicine at NYU Langone Medical Center and an AURORA 2 investigator, said, "Up to half of patients with systemic lupus erythematosus will develop lupus nephritis that can result in severe and permanent damage to the kidneys and, in some cases, renal failure. These highly anticipated long-term results of voclosporin in adult patients with lupus nephritis show consistent safety with the phase 3 AURORA 1 study and a benign impact on eGFR even after up to 3 years of treatment while maintaining the impressive reductions in proteinuria seen in AURORA 1."

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Patent Issued for Saghmos Therapeutics ST-62516

In a late fall press release, Saghmos Therapeutics announced the issuance of a US patent for its lead product, ST-62516 (trimetazidine). Saghmos Therapeutics is a privately held biopharmaceutical company developing therapies for life-threatening cardiovascular and renal diseases

Saghmos plans to initiate a phase 3 study of ST-62516 for the reduction of cardiorenal complications associated with contrast-induced kidney injury in patients with chronic kidney disease undergoing contrast procedures. Trimetazidine is a mitochondrial metabolic modulator with clinical evidence of cardiorenal benefits, as well as a favorable safety and tolerability profile as demonstrated published studies.

Anna Kazanchyan, MD, CEO of Saghmos, said, "We are very pleased to announce the issuance of the '345 patent, which will enhance the long-term value of ST-62516. This patent lays the foundation for Saghmos' growing intellectual property estate, including pending international patents as well as additional patent applications that are in preparation."

Contrast-induced kidney injury has a disproportionate impact on Black patients, with a 3.4-fold higher prevalence of end-stage renal disease requiring dialysis. Dr. Kazanchyan added, "ST-62516 will have broad societal impact by helping achieve health equity." ■

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Abstract Roundup

CHRONIC KIDNEY DISEASE

Serum Magnesium and Risk of Cardiovascular Events

Journal of Renal Nutrition. 2021;31(5):494-502

In the general population there are associations between hypomagnesemia and cardiovascular events and between hypermagnesemia and overall mortality. However, according to **Isabel Galán Carrillo, MD,** and colleagues, the data in patients with chronic kidney disease (CKD) are not as strong. The researchers conducted an observational study to examine the relationship between serum magnesium (SMg) concentration and cardiovascular morbidity and mortality, all-cause mortality, and progression to kidney failure in a population of patients with CKD.

The study included 746 patients with CKD. Baseline characteristics and analytical profile were collected at the first study visit. Patients were followed for a mean of 42.6 months. Mean age was 70 years, 62.9% of the cohort were male, 45.2% had CKD stage 3, and 35.9% had CKD stage 4. Mean SMg concentration was 2.09 mg/dL, with a close correlation between SMg concentration and serum creatinine, phosphorus, and intact parathyroid hormone (iPTH) values.

There was an association between use of calcitriol and higher SMg concentration; calcium supplements and proton pump inhibitors were associated with lower SMg concentration.

In both unadjusted and adjusted analysis, pa-

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tients with hypermagnesemia had an overall higher risk of cardiovascular events (adjusted hazard ratio [aHR, 1.34; 95% confidence interval [CI], 1.02-1.77; *P*=.037). Patients with hypermagnesemia also had a higher risk of all-cause mortality (HR, 1.54; 95% CI, 1.00-2.31; *P*=.049).

Following a propensity score matching for SMg concentration, the researchers identified two comparable groups of 287 patients each. Again, the group with hypermagnesemia had higher all-cause mortality, that persisted in the Cox model adjusted for calcium, phosphorus, and iPTH. There was no association between SMg concentration and initiation of kidney replacement therapy.

In conclusion, the authors said, "Magnesium concentration increases with decreasing kidney function. Hypermagnesemia predicts cardiovascular events and all-cause mortality in this same population, Thus, magnesium supplementation should be used with caution in these patients."

DIALYSIS

Physical Activity and Outcomes in Patients on Hemodialysis

Journal of Renal Nutrition. 2021;31(4):380-388

Patients receiving maintenance hemodialysis have different patterns of physical activity on hemodialysis days and non-hemodialysis days. However, it is unknown whether there is an association between those differences and clinical outcomes. **Shohei Yamamoto, PT, MSc,** and colleagues conducted an analysis to assess the association of physical activity levels on dialysis and non-dialysis days with cardiovascular hospitalizations and mortality. The outcomes of interest were all-cause mortality and a composite of cardiovascular hospitalizations and mortality.

Patients undergoing hemodialysis at outpatient centers from 2002 to 2019 were retrospectively enrolled. Accelerometry was used to record the number of steps over 3 hemodialysis days and 4 non-hemodialysis days. Patients were divided into two groups, each according to the median number of steps performed on hemodialysis days (2371 steps/day) and non-hemodialysis days (3752 steps/day). The cohort was then categorized into four groups according to each median value: (1) more active on hemodialysis/more active on non-hemodialysis days (MM); (2) more active on hemodialysis/less active on non-hemodialysis days (ML); (3) less active on hemodialysis/more active on non-hemodialysis days (LM); and (4) less active on hemodialysis/less active on non-hemodialysis days (LL).

The analysis included data on 512 patients; median follow-up was 3.4 years. There were associations between higher physical activity on hemodialysis and non-hemodialysis days and lower risk of mortality (hazard ratio [HR], 0.59; 95% confidence interval [CI], 0.54-0.65 and HR, 0.84; 95% CI, 0.80-0.88, respectively). Mortality risks were greater in the ML group (HR, 1.20; 95% CI, 1.13-1.28), the LM group (HR, 1.82; 95% CI, 1.53-2.17), and the LL group (HR, 1.83; 95% CI, 1.65-2.02) compared with the MM group. Associations between physical activity with multiple cardiovascular hospitalizations and mortality were similar to those between physical activity and mortality.

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In conclusion, the researchers said, "Higher physical activity on hemodialysis and non-hemodialysis days was associated with lower risks of cardiovascular hospitalizations and mortality. However, higher physical activity levels on either hemodialysis or non-hemodialysis days alone did not improve clinical outcomes."

POLYCYSTIC KIDNEY DISEASE

Blood Pressure and Tolvaptan in Patients with ADPKD

Journal of the American Society of Nephrology. 2021;32(7):1801-1812

Tolvaptan, a V2 receptor antagonist, is prescribed for the treatment of patients with autosomal dominant polycystic kidney disease (ADPKD) to slow progression. According to **Judith E. Heida, MD,** and colleagues there may be alterations in blood pressure in patients treated with tolvaptan via various acute and chronic effects.

The researchers conducted a post hoc analysis of data from the TEMPO 3:4 trial, a study that included 1445 patients with ADPKD. Patients were randomized 2:1 to receive tolvaptan or placebo for 3 years. The current analysis examined systolic and diastolic blood pressure, mean arterial pressure, hypertension status, and use and dosing of antihypertensive drugs during the course of the study.

The two study arms were similar in blood pressure at baseline. Following 3 weeks of treatment with tolvaptan, mean body weight had decreased from 79.7 to 78.8 kg, and mean plasm sodium increased from 140.4 to 142.6 mmol/L (both $P<.001$), suggesting a decrease in circulating volume. Blood pressure remained similar in the two groups.

Following 3 years of treatment, mean systolic blood pressure was significantly lower in the tolvaptan group than in the placebo group (126 vs 129 mm Hg, respectively; $P=.002$). Mean diastolic blood pressure was also lower in the tolvaptan arm than in the placebo arm (81.2 vs 82.6 mm Hg, respectively; $P=.01$). At follow-up 3 weeks after discontinuation of the study medication, the differences leveled off. The two study arms were similar in use of antihypertensive drugs throughout the study period.

In conclusion, the authors said, "Long-term treatment with tolvaptan gradually lowered blood pressure compared with placebo, which may be attributed to a beneficial effect on disease progression, a continued natriuretic effect, or both."

TRANSPLANTATION

Mortality Rates among Transplant Recipients with Diabetes

BMJ Open Diabetes Research & Care. doi:10.1136/bmjdrc-2020-001962

There are few data available on the role diabetes type 1 and type 2 play in modifying prognosis in kidney transplant recipients. **Jessica Harding, MD,** and colleagues conducted a study to compare mortality among kidney transplant recipients with type 1 diabetes, type 2 diabetes, and non-diabetes-related end-stage kidney disease (ESKD).

The study included 254,188 first-time single kidney transplant recipients ≥18 years of age who were identified from the US Renal Data System database (2000-2018). *International Classification of Diseases, 9th* and *10th Clinical Modification* codes were used to define diabetes status as primary cause of ESKD. The risk of death associated with type 1 and type 2 diabetes relative to non-diabetes was calculated using multivariable Cox regression models (right-censored). Trends in standardized mortality ratios (SMRs) (2000-2017), relative to the general US population, were assessed using Joinpoint regression.

Median survival time was 14.6 years, over which 72,175 (28.4%) deaths occurred. Five-year survival probabilities were 88% for non-diabetes, 85% for type 1 diabetes, and 77% for type 2 diabetes. Following adjustment, mortality was highest in the type 1 diabetes group (hazard ratio [HR], 1.95; 95% confidence interval [CI], 1.88-2.03) and then type 2 diabetes (HR. 1.65; 95% CI, 1.62-1.69), as compared with non-diabetes.

SMRs declined for all three groups. The SMRs in 2017 were 2.38 (95% CI, 2.31-2.45) for non-diabetes, 6.55 (95% CI, 6.07-7.06) for type 1 diabetes, and 3.82 (95% CI, 3.68-3.98) for type 2 diabetes.

The researchers said, "In the USA, diabetes type is an important modifier in mortality risk among kidney transplant recipients, with highest rates among people with type 1 diabetes-related ESKD. Development of effective interventions that reduce excess mortality in transplant recipients with diabetes is needed, especially for type 1 diabetes." ■

COVID-19

Adverse Outcomes in Kidney Transplant Recipients with COVID-19

Journal of Clinical Medicine. 2021;10(21):51-62

COVID-19 has an adverse impact on kidney function, as has been widely reported since the start of the global pandemic. However, according to **Jia-Jin Chen, MD,** and colleagues, there are few data available on the burden of COVID-19 on kidney transplant recipients.

The researchers conducted a systematic review and meta-analysis with a random-effect model to examine the rate of mortality, admission to the intensive care unit (ICU), and graft loss in the adult kidney transplant population with COVID-19. Sensitivity analysis, subgroup analysis, and meta-regression were also performed.

Results demonstrated a pooled mortality rate of 21% (95% confidence interval [CI], 19%-23%), an ICU admission rate of 26% (95% CI, 22%-31%), an invasive ventilation rate of those who required ICU care of 72% (95% CI, 62%-81%), a rate of acute kidney injury of 44% (95% CI, 39%-49%), a rate of kidney replacement therapy of 12% (95% CI, 9%-15%), and a rate of graft loss of 8% (95% CI, 5%-15%).

The authors added, "The meta-regression indicated that advancing age is associated with higher mortality; every increase in age by 10 years was associated with an increased mortality rate of 3.7%. Regional differences in outcome were also detected. Further studies focused on treatments and risk factor identification are needed."

Nursing Solutions for Patients with COVID-19-Related AKI

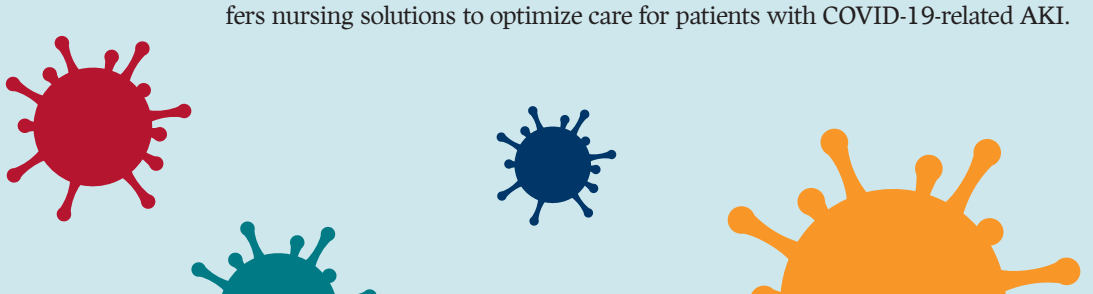
Nephrology Nursing Journal. 2021;48(5):493-498

Patients who develop acute kidney injury (AKI) during SARS-CoV-2 infection face increased risk of morbidity and mortality. AKI can occur at any stage of infection with COVID-19; clinical judgment and awareness of AKI risk factors in combination with early detection and diagnosis are key in preventing short- and long-term complications in patients with AKI related to COVID-19.

Chantal Fortin, MScN, NNP, BScN, and **Anne Boucher, MD, FRCPC,** conducted a literature review to identify risk factors for AKI in patients with COVID-19. Primary risk factors were pre-existing chronic kidney disease, obesity, and presentation with severe COVID-19. Patients who developed AKI during acutely severe disease had slightly worse outcomes than those with AKI without COVID-19. Certain genetic susceptibilities may also play a role in developing AKI in COVID-19.

Nurses can play a role in the detection, prevention, and treatment of AKI in patients with COVID-19. Care for patients and families in the context of COVID-19 and kidney injury can be optimized with the implementation of nursing interventions. Healthcare facilities can plan for resources needed due to the increased healthcare burden of survivors of AKI related to COVID-19.

The review includes recent data on how the virus causes kidney injury and offers nursing solutions to optimize care for patients with COVID-19-related AKI.



Sarah Tolson

Care Management Services

Each year, as part of the service my company provides to our clients, I review the CMS physician fee schedule for the upcoming year as well as the ESRD PPS final rule. I also provide summaries to our clients outlining the changes and updates that are pertinent to their day-to-day business. This year, our nephrology practice clients were most interested in learning about the additional reimbursement opportunities possible via care management service that Medicare covers and the additional codes that have been added for care management services. Many of the nephrologists I speak with find they are already performing some of the elements of care management, and with a little effort, they can obtain reimbursement for care they are already providing to their patients. In this column, we will review the three types of care management covered by Medicare: Transitional Care Management, Chronic Care Management and Principal Care Management.

TRANSITIONAL CARE MANAGEMENT

Nephrologists who round in hospitals are likely already providing some of the elements of Transitional Care Management (TCM) services. TCM services are designed to support the transition of a patient who has been hospitalized back to the community setting, accepting responsibility for patient care at post-facility discharge without a service gap where moderate or high complexity medical decision making is beneficial to minimize the likelihood of hospital readmission. This care management category contains two procedure codes.

TCM services do require a face-to-face visit within a specified time frame from the patient's discharge and there are non-face-to-face services that can be provided by non-physician practitioners (NPP) such as nurse practitioners and physician assistants as well as auxiliary personnel under the supervision of the physician or NPP. TCM services are a great fit for many nephrology practices because they can be billed in the same month as the Medicare Capitated Payment (MCP) for ESRD patients.

CHRONIC CARE MANAGEMENT

CMS began reimbursing for Chronic Care Management (CCM) and Complex Chronic Care Management (CCCM) services to promote better health outcomes for individuals with multiple chronic conditions. CCM and CCCM services have several similarities to MCP services in that they are charges that cover services rendered for an entire month, and the provider billing for CCM and CCCM services is responsible for overseeing the patient's care and coordinating with other specialists the patient may need to see. This category of care management contains six procedure codes, one of which is new for 2022.

CCM and CCCM services are only reimbursable to one provider each month. To alleviate multiple providers rendering CCM and CCCM services at the same time, patient consent to receive CCM or CCCM services and acknowledgement they will be responsible for some cost sharing are required elements for coverage.

Several of the practices my company bills for have begun providing CCM and CCCM services to their level three and level four chronic kidney disease (CKD) patients as members of that patient population often have at least one other chronic condition.

CCM and CCCM services do have several required elements that may be time prohibitive for some practices to undertake. For practices that feel CCM and CCCM services would be a great service to offer patients but need assistance in doing so, there are third-party services that can help with different aspects of CCM and CCCM services.

PRINCIPAL CARE MANAGEMENT

Principal Care Management (PCM) services are similar to CCM services yet are different in that the patient is only required to have one chronic condition that the provider is managing. PCM services require either thirty minutes of healthcare professional time or clinical staff time where the staff are directed by a qualified healthcare professional each month. Acute kidney failure and CKD are both eligible conditions for PCM services. All procedure codes for PCM services are new in 2022.

As of the time of this writing, there are 12 codes for care management services covered by Medicare. Each procedure code has its own guidelines and requirements for coverage that providers, ancillary staff, and billers should be familiar with to ensure all guidelines for coverage and reimbursement are met. Another important note is that not all insurance carriers cover care management services. ■

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