Nephrology Times

Practical News, Trends, and Analysis

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Cardiovascular Risk Increased in Healthy Individuals with GHF

Chronic kidney disease (CKD) is a risk factor for cardiovascular morbidity and mortality. Among individuals with supranormal estimated glomerular filtration rate, glomerular hyperfiltration (GHF), the risk of cardiovascular disease may also be increased. In high risk conditions such as diabetes, metabolic syndrome, hypertension, and smoking-related disorders, GHF may be a marker of vascular dysfunction and is associated with increased rates of cardiovascular events. The definition of GHF is highly variable, making interpretation of studies in this patient population complex. Further, it is unknown whether GHF is associated with abnormal vascular dysfunction in apparently healthy individuals.

Marie-Eve Dupuis, MD, and colleagues conducted a population-based cohort study to determine whether there is an association between GHF and increased cardiovascular risk in healthy individuals. The researchers used an epidemiologic definition of hyperfiltration with stratification for age and sex. Results of the study were reported in *JAMA Network Open* [2020;3(4):e202377].

The study utilized longitudinal follow-up data from the CARTaGENE population cohort. Enrollment occurred from August 2009 to October 2010, with follow-up available through March 31, 2016. Data analysis occurred in October 2019. The cohort

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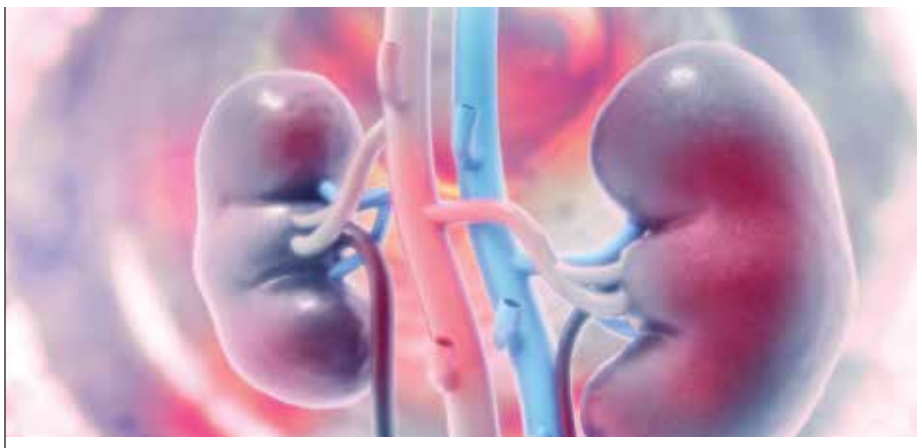

Trajectory of Kidney Function after AKI and Long-Term Clinical Outcomes

Acute kidney injury (AKI) is common among hospitalized patients, is associated with poor outcomes, and accounts for $10 billion in healthcare costs each year. The Kidney Disease Improving Global Outcomes (KDIGO) consensus group defines AKI as an increase in the concentration of serum creatinine (SCr) of ≥0.3 mg/dL or ≥50% of the baseline value within a 48-hour period or within 7 days after hospitalization or a decrease in urine output. KDIGO severity classification of AKI ranges from 0 (no AKI) to stage 3; the classification is based

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Pulmonary Hypertension Associated with Poor Survival in Patients with CKD

Approximately 21% to 41% of patients with chronic kidney disease (CKD) are diagnosed with pulmonary hypertension (PH); in patients with kidney failure requiring dialysis, the percentage is 60%. There are no targeted treatments available for PH in patients with CKD. In previous studies of PH in this patient population, diagnosis and quantification of PH severity has relied on transthoracic echocardiography. Right heart catheterization can provide more detailed insight into potential underlying mechanisms of PH.

PH is defined as mean pulmonary artery pressure ≥25 mm Hg on right heart catheterization at rest. PH can be stratified into subtypes, including precapillary PH, isolated postcapillary PH, and combined pre- and postcapillary PH. There are few data available on how CKD affects PH subtypes. Among patients with CKD with PH, the combined pre- and postcapillary subtype may contribute to the overall PH burden due to a combination of: (1) chronic volume overload; (2) pulmonary vascular remodeling due to increases in vasoactive factors such as nitric oxide, prostacyclin, and endothelin; (3) inflammation; and (4) comorbid lung disease.

Daniel L. Edmonston, MD, and colleagues conducted an observational retrospective study designed to examine the prevalence and consequences of subtypes of PH in patients with CKD. Results of the study were reported in the

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Print-only Content

Print-only Content

Dialysis Moonshot Revisited: A Funding Idea

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In the July/August 2019 issue of *Nephrology Times*[1] I published an article on the idea of a dialysis moonshot, based on the Obama/Biden cancer initiative the "Beau Biden Cancer Moonshot." Ryan Murray and Molly O'Neill followed up on my article by writing in the *Kidney News*[2] on behalf of the ASN about the importance of a "Kidney Moonshot" and this has been more recently reinforced by both John Sedor, who chairs the steering committee for *KidneyX*[3], and John Butler, chair of Kidney Care Partners and CEO of Akebia Therapeutics.[4] So the idea has some legs.

The basic point that I made was as follows:

> *"What the dialysis world needs is a "shot in the arm." It needs the equivalent of the Cancer Moonshot, a $1.8 billion initiative approved in December 2016 to find a cure for cancer. The Dialysis Moonshot could focus on strategies to improve the quality of life and clinical outcomes in dialysis patients. A focused effort that is well funded could make the difference."*

Still, how to fund the initiative has not been resolved.

In an article in the June issue of the *Journal of the American Society of Nephrology,* Tom Hostetter proposes a novel and potentially workable idea.[5] The premise for his funding proposal is that the large dialysis organizations—Fresenius and DaVita—in aggregate generate over $4 billion in annual profits. Yet, they seem to spend little on research. Of the money that is allocated, most is restricted to funding research ideas that are generated locally by dialysis clinics in their network.

Hostetter proposes that the government assess the dialysis chains and charge a fee of $3.00 for each dialysis treatment reimbursed by a commercial payor and $0.50 for each treatment paid by Medicare. He estimates that this would generate more than $58 million/year.

What could be done with this money? Hostetter proposes that at least one possible model is the Patient-Centered Outcomes Research Institute (PCORI). PCORI has well-established procedures to review proposals that include a diverse panel of patients, their advocates, experts, researchers in the field, and commercial entities.

Dialysis does need a shot in the arm in funding. The federal government spends a fraction of money on kidney disease compared to what it spends on cancer, cardiovascular, or HIV research.[6] Increases in kidney funding especially earmarked for dialysis have been quite modest, at least to date, and have not led to any meaningful innovation in dialysis care. The status quo is unacceptable.

Therefore, identifying an alternative source of funding is welcome and needed. That it comes from a small assessment on commercial and Medicare reimbursed treatments is reasonable. Still, expect the dialysis providers and their shareholders to push back. They will view it as a burdensome tax. But they have had their chance to spend money on research and improve outcomes. Progress has been spotty.

Tom Hostetter should be applauded for coming up with an innovative idea that might have a transformative effect on outcomes in dialysis patients. It's the right thing to do.

Follow me on Twitter @DoctorAjaySingh

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Trajectory of Kidney Function

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on the maximum change in SCr concentration or the minimum urine output throughout the hospital stay.

The KDIGO definition does not stratify patients based on differences in patterns of AKI recovery. According to **Pavan K. Bhatraju, MD, MSC,** and colleagues, combining patients with varying patterns of recovery may hide subgroups that are more closely associated with clinical outcomes and may also hide pathophysiological processes unique to certain populations with AKI. The researchers conducted a prospective, multicenter cohort study designed to determine whether the trajectory of recovery of kidney function within 72 hours after AKI is associated with long-term risk of clinical outcomes. Results were reported in *JAMA Network Open* [2020;3(4):e202682].

The primary outcome of interest was a composite of major adverse kidney events, defined as incident or progressive chronic kidney disease, long-term dialysis, or all-cause death during study follow-up. The cohort included 1538 adults with or without AKI 3 months following hospital discharge between December 1, 2009, and February 28, 2015. Statistical analyses were completed November 1, 2018. Participants with or without AKI were matched based on demographic characteristics, site, comorbidities, and prehospitalization estimated glomerular filtration rate. Resolving AKI was defined as a decrease in SCr of ≥0.3 mg/dL or ≥2 from maximum in the first 72 hours following AKI diagnosis. Nonresolving AKI was defined as not meeting the criteria for resolving AKI.

A total of 1538 hospitalized patients were included in the cohort; of those, 964 were men, and mean age was 64.6 years. Fifty percent (n=769) had no AKI, 31% (n=475) had a resolving AKI pattern, and 19% (n=294) had a nonresolving AKI pattern. In the first 72 hours following diagnosis of AKI, mean maximum SCr concentration was 1.1 mg/dL in the non AKI population, 2.4 mg/dL in the resolving AKI group, and 2.4 mg/dL in the nonresolving AKI group. There were no significant differences between patients with resolving AKI and those with nonresolving AKI at baseline and within 72 hours after diagnosis.

Compared with participants with resolving AKI, those with nonresolving AKI were more likely to be male (70% vs 66%), have diabetes (53% vs 49%), and have preexisting CKD (41% vs 39%). Conversely, compared with patients with nonresolving AKI, those with resolving AKI were more likely to have sepsis (18% vs 11%), and KDIGO stage 2 AKI (18% vs 12%) or stage 3 AKI (11% vs 10%). Of the 769 patients with AKI, 74% (n=566) had KDIGO stage 1 AKI.

At the time of hospital discharge, only 54% (n=257) of the patients with resolving AKI had full AKI recovery (SCr concentration that returned to prehospitalization baseline level). At 3 months post-hospitalization, slightly fewer (51%) of the resolving group had recovered to baseline kidney function. Among the nonresolving AKI group, a smaller percentage of patients had an SCr concentration that returned to baseline at discharge or at 3 months post-discharge. Only 16% of patients in the nonresolving group had AKI recovery at hospital discharge, and 38% had AKI recovery at 3 months post-discharge.

The primary outcome (major adverse kidney event) occurred in 36% (n=550) of participants. For participants without AKI, the unadjusted incidence rate was 5.9 events per 100 patient-years; for those with resolving AKI, the rate was 11.9 events per 100 patient-years; and for those with nonresolving AKI, the rate was 16.6 events per 100 patient-years.

Following adjustment for baseline demographic characteristics, diabetes, cardiovascular disease, CKD, sepsis, and site of enrollment, the adjusted hazard ratio (aHR) for the primary outcome was higher in both participants with resolving AKI (aHR, 1.95; 95% confidence interval [CI], 1.58-2.40; $P<.001$) and those with nonresolving AKI (aHR, 2.80; 95% CI, 2.26-3.46; $P<.001$) than in those without AKI. The associations remained following additional adjustment for KDIGO AKI stage at 72 hours after diagnosis, shock, mechanical ventilation, and major surgery.

In the groups with AKI, there was an association between nonresolving AKI and a 51% greater risk of a major adverse kidney event (95% CI, 22%-88%; $P<.001$) compared with those without AKI. In patients with nonresolving AKI, the higher risk was due to a higher risk of incident CKD (aHR, 2.40; 95% CI, 1.65-3.49; $P<.001$) and progressive CKD (aHR, 1.58; 95% CI, 0.94-2.64; $P=.07$), compared with those in the resolving AKI group. There were no significant differences in the risk of incident dialysis and death between the AKI recovery patterns.

The researchers cited some limitations to the study, including enrolling patients who survived at least 90 days after hospitalization, potentially limiting generalizability to a patient population at higher risk of inpatient mortality; possible confounding; and the relatively small number of eligible patients with KDIGO AKI stage 2 or 3.

In conclusion, the researchers said, "We defined two AKI recovery subgroups (resolving and nonresolving) that exhibited differences regarding risk for long-term kidney-specific outcomes after hospitalization. In the future, AKI recovery subgroups may allow for improved risk stratification, facilitate prognostic enrichment of AKI clinical trials, and assist in targeting resources for follow-up and early detection of CKD in high-risk populations with AKI." ■

TAKEAWAY POINTS

- Researchers conducted a prospective, multicenter cohort study to examine whether there is an association between the trajectory of kidney function recovery with 72 hours after acute kidney injury (AKI) and long-term risk of kidney-specific outcomes.
- The study included a total of 1538 participants: 50% (n=769) had no AKI; 31% (n=475) had a resolving AKI pattern; and 19% (n=294) had a nonresolving AKI pattern.
- The adjusted hazard ratio for major adverse kidney events was higher for those in the two AKI groups than for participants without AKI. In the population with AKI, those in the nonresolving group had a 51% increased risk of a major adverse kidney event compared with those in the resolving AKI group.

Glomerular Hyperfiltration
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included 9515 healthy individuals, defined as those without hypertension, diabetes, cardiovascular disease, estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2, or statin and/or aspirin use. The 9515 eligible patients 40 to 69 years of age were identified using health information accessed through the CARTaGENE research platform.

The primary outcome of interest was the risk of cardiovascular events, defined as a composite of cardiovascular mortality, myocardial infarction, unstable angina, heart failure, stroke, and transient ischemic attack (TIA). Cox and fractional polynomial regressions and propensity score matching were used to identify the risk of adverse cardiovascular events. Following stratification for sex and age, individuals with eGFR >95th percentile were compared with those with normal filtration rate, defined as eGFR in the 25th to 75th percentiles.

Of the 9515 healthy individuals, 42.6% (n=4050) were male, and median age was 50.4 years. A total of 473 had GHF (median eGFR, 112 mL/min/1.73 m^2) and 4761 had normal GFR (control group; median eGFR, 92 mL/min/1.73 m^2). There were wide variations in the ranges of eGFR for those with GHF or normal filtration rates according to each age decade and sex. Those with GHF were slightly younger, and more often African American or smokers.

With the exception of a slightly higher heart rate and augmentation index with GHF, hemodynamic parameters were similar between the GHF group and controls. Data on dietary habits were available in 45% (n=213) of those with GHF and 50% (n=2387) of controls; median daily protein and sodium were similar between the groups (61 g vs 63 g and 2.2 g vs 2.3 g, respectively).

Median follow-up was 70 months. During follow-up, there were 245 cardiovascular events overall (three cardiovascular deaths, 67 myocardial infarctions, 69 unstable angina episodes, 52 heart failure episodes, 34 strokes, and 20 TSAs). In the GHF group, there were 35 events in 473 individuals, for an incidence rate of 13.2 per 100 person-years; in the control group, there were 210 events in 4761 individuals, for an incidence rate of 7.7 per 100 person-years.

In both unadjusted and adjusted Cox regression analyses, there was an association between GHF and an increased risk of cardiovascular events compared with normal GFR (unadjusted hazard ratio [HR], 1.71; 95% confidence interval [CI], 1.20-2.44; *P*=.003; adjusted HR, 1.88; 95% CI, 1.30-2.74; *P*=.001). In sensitivity analyses where GHF was defined following stratification for age decade, sex, and (1) race, (2) active smoking status, or (3) obesity, the association between GHF and CVE remained significant. Following exclusion of individuals with a cardiovascular event in the first 6 months and 12 months and after exclusion of TIA from the composite outcome, GHF remained significantly associated with cardiovascular events.

Using propensity score, 406 healthy individuals with GHF were matched with 406 controls of similar age and baseline characteristics. In that cohort, those with GHF had median eGFR of 112 mL/min/1.73 m^2 compared with 94 mL/min/1.73 m^2 in the control group. Results of unadjusted Cox regression analysis demonstrated an association between GHF and higher risk of cardiovascular events compared with normal filtration (HR, 2.20; 95% CI, 1.44-4.24; *P*=.02).

The researchers identified a subset of 597 CARTaGENE participants with stage 3a CKD to examine the cardiovascular event risk association with GHF compared with CKD. In unadjusted Cox regression analysis, healthy individuals with GHF had a cardiovascular event risk similar to that of participants with stage 3a CKD (HR, 0.90; 95% CI, 0.56-1.42; *P*=.64). This association was seen despite the healthy individuals with CKF having a more favorable hemodynamic and metabolic profile and a lesser burden of comorbidities at baseline.

In citing limitations to the study, the researchers included the possibility of selection bias; limiting the cohort to those 40 to 49 years of age; using estimated GFR rather than measured GFR; the availability of data on albuminuria in only a small subset of CARTaGENE participants; and the sample size that was insufficient to adequately assess the association between occurrence of individual types of cardiovascular events and GHF.

"Using data from the prospective CARTaGENE cohort, GHF was shown to be associated with a higher risk of cardiovascular events in healthy middle-aged individuals. Glomerular hyperfiltration could be an easily identifiable marker of an unfavorable milieu and vascular dysfunction. Therefore, identification of GHF in healthy individuals may provide an opportunity to implement preventive strategies to reduce the global burden of cardiovascular diseases," the researchers said. ■

TAKEAWAY POINTS

- Researchers conducted a prospective population-based cohort study to examine whether glomerular hyperfiltration (GHF) is associated with increased risk for cardiovascular events in healthy individuals.
- Compared with participants with normal filtration rate, those with GHF had an increased cardiovascular risk: hazard ratio, 1.88; 95% confidence interval, 1.30-2.74; *P*=.001.
- The risk of cardiovascular events among the healthy individuals with GHF was similar to that of participants with stage 3a chronic kidney disease.

CONFERENCE COVERAGE KIDNEY WEEK 2019

Proton Pump Inhibitor Use Associated with Increase in CKD Progression

Washington, DC–Patients with gastroesophageal reflux disease and peptic ulcer disease are commonly treated with proton pump inhibitors (PPIs) that block hydrogen potassium ATPase (H_+, K_+ -ATPase). H_+, K_+ ATPase is present in other organs, including the kidneys.

The progression of kidney disease can be hastened by metabolic acidosis. Researchers at Tulane University, led by **Sixto G. Giusti, MD,** conducted a study to examine the relationship between chronic PPI use in patients with chronic kidney disease (CKD) stages G3a to G4 and the development of metabolic acidosis and rate of kidney function decline. The study was designed to test the hypothesis that patients with CKD who have been on PPI therapy for at least 1 year would have a higher prevalence of metabolic acidosis and faster progression of CKD compared with patients not on PPI therapy.

Results of the study were reported during a poster session at Kidney Week 2019 in a poster titled *The Effect of Proton Pump Inhibitor Use on the Development of Metabolic Acidosis and Decline in Kidney Function in Patients with CKD Stages G3a to G4.*

The researchers utilized data from the Veterans Administration Informatics and Computing Infrastructure national database system. The study included adult patients with CKD (defined as estimated glomerular filtration rate [eGFR] <60 mL/min/1.73 m^2) and a record of receiving care for a minimum of 5 years at the VA from January 1, 1999, through May 31, 2018. Exclusion criteria were dialysis, renal transplant, or death. Outcome measures of interest were mean serum bicarbonate and progression of CKD, measured by decline in GFR determined by the Modification of Diet in Renal Disease study equation.

The PPI group was matched to a control group using Propensity Score Matching on age, sex, race, and Charlson Comorbidity Index. The associations of PPI use with metabolic acidosis, dialysis, all-cause mortality, and progression of CKD were analyzed using Kaplan-Meier curve and Cox regression models. Progression of CKD was defined as a 10 unit decrease of eGFR from baseline eGFR.

In the final sample, the PPI cohort included 1406 patients; mean age was 62.07 years and 62.02% were white. Median follow-up was 4.7 years. The control cohort (no PPI use) included 573 patients; mean age was 63.25 years and 70.33% were white. Median follow-up was 4.2 years.

Compared with the control group, the PPI group had a significantly increased risk of CKD progression and dialysis (adjusted hazard ratio [aHR], 1.43; 95% confidence interval [CI], 1.17-1.74 and aHR, 1.69; 95% CI, 1.03-2.77, respectively). The risk of metabolic acidosis and all-cause mortality were also higher in the PPI group than in the control group, but the differences did not reach statistical significance (aHR, 1.83; 95% CI, 0.88-3.82 and aHR, 1.25; 95% CI, 0.96-1.64, respectively).

In summary, the researchers said, "The data suggest that chronic PPI accelerates progression of kidney disease in CKD patients. Chronic PPI use should be discouraged in this population."

Source: Giusti SG, Lin Y, Liu S, Nakhoul NL, Shi L, Batuman V. The effect of proton pump inhibitor use on the development of metabolic acidosis and decline in kidney function in patients with CKD stages G3a to G4. Abstract of a poster presented at the American Society of Nephrology Kidney Week 2019 (Abstract TH-P0452), November 7, 2019, Washington, DC.

Pulmonary Hypertension

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American Journal of Kidney Diseases [2020; 75(5):713-724].

The outcome of interest was all-cause mortality. The researchers hypothesized that combined pre-and postcapillary PH would be the most common PH subtype and would be predictive of the highest mortality risk in the CKD patient population.

Patients were stratified by CKD severity at baseline using the Kidney Disease Improving Global Outcomes glomerular filtration rate (GFR) categories: CKD G3a (estimated GFR [eGFR], 45 to 49 mL/min/1.73 m^2); G3b (eGFR, 30 to 44 mL/min/1.73 m^2); G4 (eGFR, 15 to 29 mL/min/1.73 m^2), and G5/G5D (<15 mL/min/1.73 m^2 or on hemodialysis). Patients with eGFRs ≥60 mL/min/1.73 m^2 were classified as not having CKD.

The researchers utilized the Duke Databank for Cardiovascular Disease to identify all right heart catheterizations performed at Duke University Hospital from January 1, 2000, to December 31, 2014. Following application of exclusion and inclusion criteria, the study cohort included 12,618 patients.

The average age for patients with CKD was 69 years compared with 57 years in patients without CKD. In the CKD cohort, patients without PH tended to be older; age did not differ among PH subtypes. Within the CKD G5/G5D group, 70.5% were on dialysis. Regardless of CKD status, African American patients were disproportionately affected by PH; African American patients represented the highest proportion of patients with the combined pre- and postcapillary PH subtype (31.7% of patients with combined pre- and postcapillary PH and CKD, 33.9% of patients with combined pre- and postcapillary PH but no CKD).

Compared with other PH subtypes, precapillary PH predominantly affected women in both the CKD and non-CKD cohorts: 59.7% of precapillary PH in the CKD cohort and 60.7% of precapillary PH in patients in the non-CKD cohort. Chronic obstructive pulmonary disease and scleroderma were over-represented in the precapillary PH subtype; heart failure and diabetes mellitus were more prominent in the isolated postcapillary and combined pre- and postcapillary PH subtypes. In the CKD cohort, GFR tended to be worse in the isolate postcapillary PH and combined pre- and postcapillary PH subtypes.

In the CKD cohort, the prevalence of PH was 73.4%; in the non-CKD cohort, the prevalence was 56.9%. In all patients with CKD, the most common PH subtypes were isolated postcapillary PH (39.0%) and combined pre- and postcapillary PH (38.3%). In the non-CKD cohort, the most prevalent PH subtype was precapillary PH (35.9%).

In the CKD group, patients with the combined pre- and postcapillary PH subtype had the poorest survival; in the non-CKD group, the worst survival was in the patients with precapillary PH subtype. The association of PH subtype with mortality was modified but the presence or absence of CKD (*P* for interaction <.001), but severity of CKD did not modify the association within those with CKD (*P* for interaction =.3). In both unadjusted and adjusted analyses, among patients with no CKD and compared with no PH as the reference group, precapillary PH had the highest hazard ratio (HR) for mortality (HR, 2.27; 95% confidence interval [CI], 2.00-2.57). Isolated postcapillary PH and combined pre- and postcapillary PH also had significantly greater mortality.

Compared with no PH as the reference group, within each CKD GFR category, the highest HR of mortality was associated with combined pre- and postcapillary PH. For patients in the G5/G5D cohort, only the combined pre- and postcapillary PH subtype had higher risk for mortality compared with the reference group (HR, 1.63; 95% CI, 1.12-2.36).

There were some study limitations cited by the authors, including the single-center design perhaps limiting the generalizability of the findings; variations in operator technique for the right heart catheterizations that may have affected the uniformity of certain catheterization parameters; not excluding patients on peritoneal dialysis; and lack of data for vascular access in the hemodialysis patients in the study.

In summary, the researchers said, "PH remains an under-recognized yet significant cardiovascular complication for patients with CKD. Unlike other cardiovascular diseases in patients with CKD, the exact mechanism of this association remains largely unknown and no targeted treatment exists. Our study suggests that processes that increase pulmonary vascular resistance and/or remodeling represent a prominent mechanism and potential therapeutic target for patients with CKD that is complicated by PH. In addition, patients with combined pre- and postcapillary PH are a particularly vulnerable subgroup with the highest risk for mortality. As demonstrated by trials of vasodilator therapy in patients with heart failure and combined pre- and postcapillary PH, the recognition of this large combined pre- and postcapillary PH cohort in CKD may present new therapeutic options." ■

TAKEAWAY POINTS

- In patients with chronic kidney disease (CKD), pulmonary hypertension (PH) is associated with increased risk for cardiovascular disease and mortality. Researchers conducted a study to examine the prevalence and outcomes of PH subtypes in patients with CKD.
- The most common subtypes of PH in the CKD cohort were isolated postcapillary (39.0%) and combined pre- and postcapillary PH (38.3%). In the non-CKD cohort, precapillary PH was most common.
- In the CKD cohort, compared with no PH, combined pre- and postcapillary PH was associated with the highest risk for mortality in adjusted analyses.

CONFERENCE COVERAGE KIDNEY WEEK 2019

Patiromer Safe and Effective in Mild/Moderate and Severe Hyperkalemia

Washington, DC–Researchers, led by **Matthew Weir, MD,** conducted a post hoc analysis to examine the efficacy and safety of patiromer based on the severity of baseline hyperkalemia. Patiromer, a sodium-free nonabsorbed potassium binder, uses calcium as the counter-exchange ion. Results were reported during a poster session at Kidney Week 2019 in a poster titled *Efficacy and Safety of Patiromer by Baseline Serum Potassium Level <6.0 vs ≥6.0 mEq/L: Pooled results of Three Studies.*

The analysis included pooled data from trials of patiromer, including AMETHYST-DN, OPAL-HK, and TOURMALINE. Participants of the three trials were patients treated with patiromer with a starting dose of up to 25.2 g/day. Included in the post hoc analysis were patients who took one or more dose of patiromer and had one or more serum potassium measurement post baseline. Eligible participants were stratified according to serum potassium level: ≥6.0 mEq/L and <6.0 mEq/L. Outcomes of interest were change in serum potassium from baseline at week 4, serum potassium level over time, and the percentage of participants with any serum potassium measurement in the target range (3.8-5.0 mEq/L).

A total of 623 patients were included in the evaluation. Of those, 53 had baseline serum potassium ≥6.0 mEq/L and 570 had baseline serum potassium <6.0 mEq/L. At baseline, mean estimated glomerular filtration rate (eGFR) was 33.0 mL/min/1.73 m^2 in those with serum potassium ≥6.0 mEq/L and 40.2 mL/min/1.73 m^2 in those with serum potassium <6.0 mEq/L. In both groups, >90% of patients were taking renin-angiotensin-aldosterone system inhibitors. At day 3 (48 hours after taking first dose), mean serum potassium was reduced to 5.5 mEq/L in both groups.

Through week 4, 97% of patients in the serum potassium <6.0 mEq/L group and 93% of patients in the serum potassium ≥6.0 mEq/L group achieved any serum potassium measurement in the target range. At week 4, mean reductions from baseline were -0.67 (95% confidence interval [CI], -0.71 to -0.63) and -1.67 (95% CI, -1.91 to -1.43) in the serum potassium <6.0 mEq/L and serum potassium ≥6.0 mEq/L groups, respectively.

In the serum potassium <6.0 mEq/L group, 31% of patients reported adverse events versus 43% in the serum potassium ≥6.0 mEq/L group. Adverse events related to patiromer (most commonly constipation and diarrhea) were reported in 13% and 19%, respectively.

In summary, the researchers said, "Patiromer was effective and well-tolerated in patients with mild/moderate hyperkalemia and severe hyperkalemia. Regardless of the severity of hyperkalemia, treatment with patiromer lowered serum potassium to 3.8-5.0 mEq/L in 93% of patients in 4 weeks. A higher rate of constipation occurred in the serum potassium ≥6.0 mEq/L subgroup and may be related to the fact that these patients appear to have worse overall health (e.g., lower eGFR)."

Source: Weir MR, Mayo M, Yuan J, Conrad A, Rafique Z. Efficacy and safety of patiromer by baseline serum potassium level <6.0 vs ≥6.0 mEq/L: Pooled results of three studies. Abstract of a poster presented at the American Society of Nephrology Kidney Week 2019 (Abstract FR-P0254), November 8, 2019, Washington, DC.

Funding for this study was provided by Relypsa, Inc.

NATIONAL KIDNEY FOUNDATION

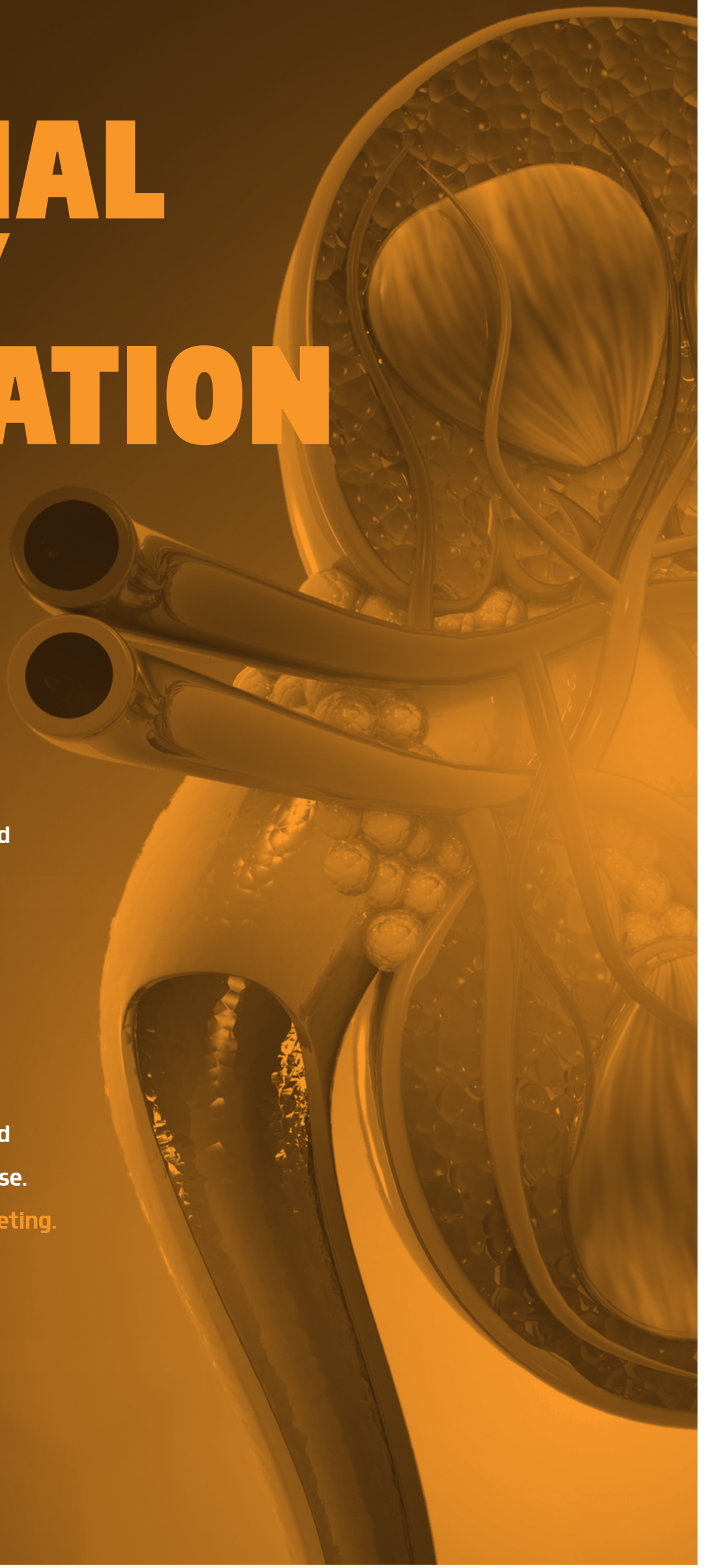
SPRING CLINICAL MEETINGS 2020

March 25-29

Nephrologists, fellows and residents with a special interest in kidney disease, general internists, pharmacists, physician assistants, nurse practitioners, nurses and technicians, social workers, and renal and clinical dietitians all benefit from the NKF Spring Clinical Meetings.

Presenters reported the latest insights into chronic kidney disease care and participants were informed about new and evolving concepts related to kidney disease.

This is Part Two of our coverage of the meeting.



Pooled Analysis of Roxadustat for Anemia in Non-Dialysis-Dependent CKD Patients

In phase 3 studies examining the efficacy of roxadustat for the treatment of anemia in patients with chronic kidney disease (CKD), the therapy improved iron absorption and bioavailability. Roxadustat is a hypoxia-inducible factor prolyl hydroxylase inhibitor. At the NKF 2020 spring Clinical Meetings, **Robert Provenzano, MD,** and colleagues presented results of an analysis of data from the phase 3 studies in non-dialysis-dependent (NDD) CKD patients with iron repletion or depletion at baseline. The presentation was titled *Roxadustat Treatment of Anemia in Non-Dialysis-Dependent Chronic Kidney Disease Is Not Influenced by Iron Status.*

The researchers analyzed data from three completed studies individually and in the pooled population by iron status. Patients were randomized to receive roxadustat or placebo for up to 4 years. Baseline hemoglobin and change from baseline were summarized overall as well as in patients with iron repletion (defined as ferritin ≥100 mg/L and transferrin saturation ≥20%) or iron depletion. The study allowed use of oral iron and intravenous iron was allowed as rescue.

Across the three studies, 2391 patients were in the roxadustat group and 1886 patients were in the placebo group. Mean baseline hemoglobin was 9.10 g/dL in the roxadustat group and 9.10 g/dL in the placebo group. At baseline, 60% (n=1433) of patients were iron replete for roxadustat and 60% (n=1127) were iron replete for placebo. The mean change from baseline in hemoglobin was similar in iron-replete and iron-depleted patients receiving roxadustat. Roxadustat dose and iron use in subgroup will be explored in additional data analyses.

The mean change from baseline in hemoglobin in the roxadustat patients was summarized by study and iron status:

1. OLYMPUS (study one): adjusted least squares mean change from baseline overall (n=1384), 1.75; iron-replete (n=782), 1.71; iron depleted (n=552), 1.76.
2. ANDES (study two): adjusted least squares mean change from baseline overall (n=616), 2.02; iron-replete (n=366), 1.98; iron-depleted (n=241), 2.10.
3. ALPS (study three): adjusted least squares mean change from baseline overall (n=391), 1.99; iron-replete (n=204), 1.97; iron-depleted (n=187), 1.99.
4. Pooled: adjusted least squares mean change from baseline overall (n=2391), 1.94; iron-replete (n=1433), 1.94; iron-depleted (n=956), 1.94.

"Roxadustat corrected and maintained hemoglobin in patients with NDD-CKD and anemia regardless of iron status at baseline," the researchers said.

Source: Provenzano R, Fishbane S, Coyne D, et al. Roxadustat treatment of anemia in non-dialysis-dependent chronic kidney disease is not influenced by iron status. Abstract of a presentation at the National Kidney Foundation 2020 Spring Clinical Meetings; abstract #192.

Dose Effect Post Hoc Analysis of DIALYZE Study Data

Results of the DIALIZE trial (NCT03303521) demonstrated that sodium zirconium cyclosilicate (SZC) reduced predialysis serum potassium after the long interdialytic interval. Further, SZC is well tolerated in hemodialysis patients with hyperkalemia. **Bruce Spinowitz, MD,** and colleagues conducted a post hoc analysis to examine the dose effect of SZC on predialysis body weight, blood pressure, and ultrafiltration rate during dialysis. They reported results during the NKF Spring Clinical Meetings in a presentation titled *Dose Effect Analysis of Sodium Zirconium Cyclosilicate (SZC) in Hyperkalemic Hemodialysis Patients in the DIALYZE Study.*

The DIALYZE study cohort included 196 patients who were randomized 1:1 to placebo (n=99) or SZC (n=97); the safety analysis included 195 of the 196 patients. The starting dose was 5 g once daily on non-dialysis days for a 4-week dose titration (titrated in 5 g increments to 15 g maximum) to achieve predialysis potassium 4.0 to 5.0 mmol/L, and a 4-week stable dose evaluation phase (SZC 0, 5, 10, or 15 g).

The post hoc analysis examined change from baseline (visit 4, day 1) to the end of treatment (visit 15, day 57) in interdialytic weight gain, diastolic blood pressure, systolic blood pressure, and ultrafiltration rate, stratified by final SZC dose in the dose titration phase. Dialysis ultrafiltration rate was calculated as actual ultrafiltration (mL)/dialysis duration (h)/ predialysis weight (kg).

During the dose evaluation phase, 38, 41, and 17 patients received SZC 5, 10, and 15 g, respectively. There was no consistent pattern in changes from baseline in interdialytic weight gain, diastolic blood pressure, systolic blood pressure, and ultrafiltration rate. There was no relationship between changes and SZC dose.

"Findings of no increases in blood pressure, interdialytic weight gain, or ultrafiltration rate with higher SZC doses suggest that dose adjustments based on patients' serum potassium resulted in comparable safety," the researchers said.

Source: Spinowitz B, Fishbane S, McCafferty K, et al. Dose effect analysis of sodium zirconium cyclosilicate (SZC) in hyperkalemia hemodialysis patients in the DIALYZE study. Abstract of a presentation at the National Kidney Foundation 2020 Spring Clinical Meetings; abstract #260.

Albumin and Hemoglobin Increased with Optiflux® Dialyzer Use for 6 Months

Optiflux® dialyzers, single-use, high-flux dialyzers, are available in four sizes: F160 NR (1.5 m^2), F180NR (1.7 m^2), F200NR (1.9 m^2), and F250NR (2.5 m^2). The dialyzers are designed to enhance small and middle molecule clearance without increasing loss of albumin. Epidemiologic studies among patients on dialysis have suggested that low levels of serum albumin are markers of increased risk of mortality.

In patients with low serum albumin levels, albumin loss should be avoided. **Meijiao Zhou, PhD,** and colleagues at Fresenius Medical Care Renal Therapies Group and Fresenius Medical Care North America, Waltham, Massachusetts, conducted a retrospective study to examine changes in biomarkers of patients dialyzed with Optiflux dialyzers for 6 months. The analysis included a subset of patients with low serum albumin levels at baseline. Results of the study were reported online in a presentation at NKF 2020 Spring Clinical Meetings. The presentation was titled *Evaluation of Biomarkers in Chronic Hemodialysis (HD) Patients Dialyzed with Optiflux High-flux Dialyzers.*

The study included data from 976 in-center hemodialysis patients treated exclusively with Optiflux dialyzers for 6 months. Exclusion criteria included liver disease, cancer, HIV, or history of drug abuse. Paired t-test was used to compare pre-hemodialysis laboratory results at the first month of data collection (month 1) with those at month 6. A subanalysis of patients with hypoalbuminemia, defined as serum albumin ≤3.5 mg/dL, at month 1 was also conducted. For each dialyzer, all analyses were performed separately. Patients dialyzed with F200NR and F250NR were combined into one group.

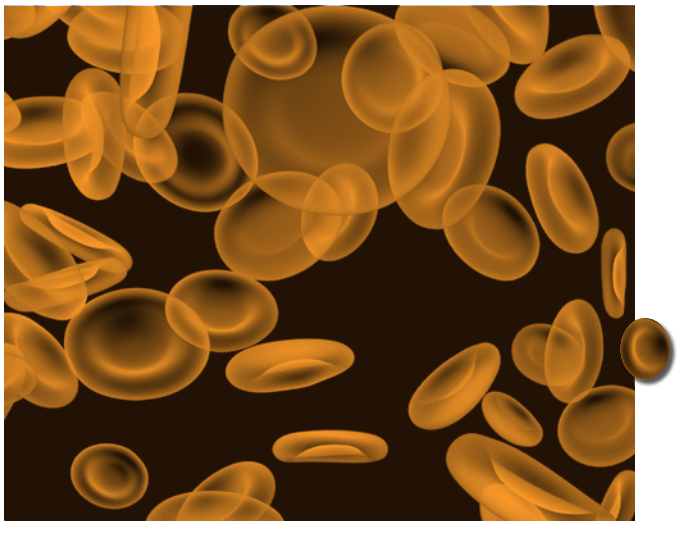
In all groups, there were significant increases in mean serum albumin and hemoglobin. For patients dialyzed with F160NR (n=310), mean albumin levels at month 1 and month 6 were 3.80 and 3.89 g/dL, respectively; difference, 0.09; $P<.001$. Mean albumin levels at month 1 and month 6 for patients dialyzed with F180NR (n=634) were 3.86 and 3.91 g/dL, respectively; difference; 0.05; $P<.0001$. Mean albumin levels at month 1 and month 6 for patients dialyzed with F200NR and F250NR (n=32) were 3.82 and 3.93 g/dL, respectively; difference, 0.11; $P=.02$.

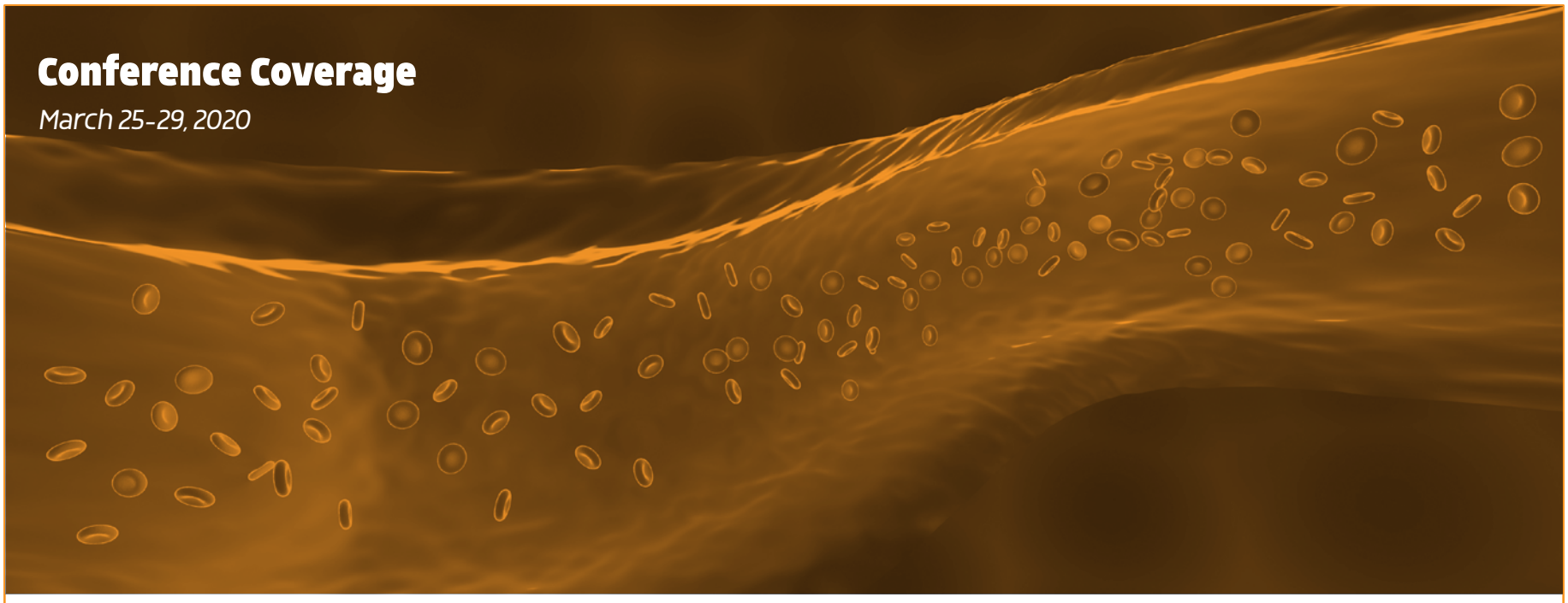
Hemoglobin levels in patients in the F160NR group increased from 10.66 g/dL to 11.095 g/dL (difference, 0.39; $P<.0001$). Hemoglobin levels in the F180NR group increased from 10.82 g/d to 11.08 g/dL (difference, 0.26; $P<.0001$). Hemoglobin levels in the F200NR/F250NR group increased from 10.91 g/dL to 11.28 g/dL (difference, 0.37; $P=.03$).

In the subanalysis (n-156), 87% of patients had increases in serum albumin by month 6: 48 of 59 patients in the F160NR group (81.4%); 82 of 92 in the F180NR group (89/1%); and 5 of 5 in the F200NR/F250NR group (100%).

"During a 6-month follow-up, hemodialysis patients dialyzed with Optiflux dialyzers showed increases in serum and hemoglobin while maintaining dialysis adequacy," the researchers said.

Source: Zhou M, Ficociello L, Costanzo M, Mullon C, Kossman R. Evaluation of biomarkers in chronic hemodialysis (HD) patients dialyzed with Optiflux high-flux dialyzers. Abstract of a presentation at the National Kidney Foundation 2020 Spring Clinical Meetings; abstract #282.





Worsened Outcomes Associated with Anemia in CKD

Anemia is a common comorbidity in patients with chronic kidney disease (CKD); however, there are few data available on the long-term clinical burden of anemia in that patient population. **Eric Wittbrodt, PharmD, MPH,** and colleagues conducted an analysis to examine selected cardiovascular and renal outcomes in non-dialysis CKD patients with and without anemia at baseline. Results of the retrospective observational study were reported during the NKF Spring Clinical Meetings in a presentation titled *Clinical Outcomes in Patients with Anemia in CKD Using Linked US Claims and Electronic Health Records Data.*

The cohort included patients in a real-world practice in the United States. The researchers utilized the integrated Limited Claims and Electronic Health Record data (IBM Health, Armonk, New York). Patients were ≥18 years of age with two or more estimated glomerular filtration rate (eGFR) measurements <60 mL/min/1.73 m^2 ≥90 days apart. The study defined anemia as the presence of any observed hemoglobin <10 g/dL within 6 months of confirmatory eGFR (anemia baseline period). The baseline period for disease history was defined as the start of patient data + 6 months; baseline for laboratory measures and medication use was defined as the date of the second confirmatory eGFR + 6 months.

Exclusion criteria were active bleeding, chronic dialysis, and iron deficiency anemia. The study examined baseline patient characteristics and clinical outcomes during follow-up for the period January 1, 2012, to September 30, 2017. Descriptive data were summarized and no inferential statistics were performed.

The total study cohort included 22,720 patients. Of those, 5283 (23%) had baseline hemoglobin <10 g/dL. In the CKD with anemia group, 60% were female, mean age was 70 years; 50% had CKD stage 3a, 27% CKD stage 3b, 15% CDK stage 4, and 9% CKD stage 5. Mean follow-up was 2.9 years. In the CKD without anemia group, 56% were female, mean age was 70 years; 68% had CKD stage 3a, 24% CKD stage 3b, 6% CKD stage 4, and 1% CKD stage 5. Mean follow-up was 3.8 years.

During follow-up, acute coronary syndrome (ACS) events occurred in 2.3% of patients with and without baseline anemia, heart failure hospitalizations occurred in 6.0% and 3.7%, and stroke hospitalizations and emergency visits occurred in 2.8% and 3.7% of those with and without anemia at baseline, respectively. In the groups with and without anemia at baseline, total event (initial and recurrent) rates per 100 patients per year were 0.86 and 0.70 for ACS, 2.84 and 1.43 for heart failure hospitalizations, and 0.84 and 0.78 for stroke hospitalizations and emergency visits, respectively.

In the with and without anemia-at-baseline groups, end-stage renal disease occurred in 44% and 25%, respectively. Progression of CKD stage occurred in 67% and 59% of patients in the with and without anemia at baseline groups, respectively. The median change in eGFR slope in the groups with and without anemia at baseline was -0.6 and -0.3 mL/min/1.73 m^2, respectively.

"This analysis highlights worsened outcomes associated with anemia in CKD, particularly hospitalization for heart failure and eGFR decline, in patients of a large US cohort," the researchers said.

Source: Wittbrodt E, James G, Kumar S, et al. Clinical outcomes in patients with anemia in CKD using linked US claims and electronic health records data. Abstract of a presentation at the National Kidney Foundation 2020 Spring Clinical Meetings; abstract #196.

Long-Acting Anemia Treatment May Stabilize Hemoglobin Levels

There are few scientific-based data comparing clinical outcomes of erythropoiesis-stimulating agents (ESAs) in patients on dialysis. **Roberta Lugo-Robles, MPH,** and colleagues in Puerto Rico conducted a retrospective comparative effectiveness study designed to evaluate anemia management effectiveness through the conversion of short-acting ESA to long-acting ESA in a population of Latino hemodialysis patients.

Outcomes of interest included treatment effectiveness and hemoglobin variability. Results were reported in a presentation submitted to NKF Spring Clinical Meetings and published in the *Journal of Renal Nutrition* [2020;30(2):173]. The presentation was titled *Conversion from Epoetin Alfa to Darbepoetin Alfa in Hemodialysis Patients: Effectiveness and Variability in Anemia Treatment.*

Two parameters were used to evaluate effectiveness: (1) the percentage of patients reaching target hemoglobin levels and (2) comparison of average hemoglobin levels between treatments. A variability panel was used to assess fluctuations in hemoglobin. The panel consisted of the following measurements: (1) standard deviation, (2) residual standard deviation, (3) repeated measures ANOVA (analysis of variance), (4) hemoglobin absolute change, (5) hemoglobin absolute change, and (6) linear regression of hemoglobin values over time.

The final analysis included 504 hemodialysis patients. In temporal trends, short-acting treatment tended to decrease hemoglobin levels by 0.015 g/dL and long-term tended to have a minimal increase of 0.035 g/dL. Variability was similar with both treatments (±0.98 g/dL).

There was a statistically significant two-way interaction between treatment and time, indicating hemoglobin concentration changes differently over time depending on the type of treatment undertaken. Comparisons of the second month of treatment yielded the most significant difference in hemoglobin levels, with a mean difference of -0.344 g/dL (95% confidence interval, 0.23-0.46).

The difference in mean hemoglobin levels decreased across the study period. During the 6-month study period, there was no statistically significant difference among the hemoglobin levels. During the final 3 months of the study, hemoglobin levels tended to increase significantly, suggesting that the levels began to stabilize. However, the researchers noted, due to the short duration of the study, they were not able to observe the maximum increase and stability of hemoglobin during the long-acting treatment.

In conclusion, the researchers said, "From the data collected, we concluded that long-acting treatment is potentially a better treatment option for hemodialysis patients. Research findings suggested long-acting treatment induced less hemoglobin variability (results based on the six months of follow-up). The hemodialysis patients will benefit from the new treatment in terms of hemoglobin stability with less doses administration with the possibility of reducing adverse health outcomes."

Source: Lugo-Robles R, Vazquez D, Santos AR, Irizarry J. Conversion from epoetin alfa to darbepoetin alfa in hemodialysis patients: effectiveness and variability in anemia treatment. Abstract of a presentation at the National Kidney Foundation 2020 Spring Clinical Meetings; *Journal of Renal Nutrition* [2020;30(2):173].

Pre-ESRD Nephrology Care Aids in Patient Coping Strategies

More than one-third of patients diagnosed with end-stage renal disease (ESRD) were not receiving care from a nephrologist at the time of the diagnosis. **Megan Urbanski, PhD,** and colleagues conducted a study to examine the coping styles and strategies used by patients when diagnosed with ERSD; comparisons were made among patients with varying amounts of pre-ESRD nephrology care. Results of the study were reported at the NKF Spring Clinical meetings in a presentation titled *Coping with an ESRD Diagnosis: Differences among Patients According to Presence of Pre-ESRD Nephrology Care.*

The researchers utilized a mixed-methods study design. Patients with varying amounts of pre-ESRD nephrology care participated in semi-structured interviews that examined coping styles and strategies relating to the ESRD diagnosis and initiation of renal replacement therapy. Patients were grouped according to amount of pre-ESRD nephrology care they had received.

Applied thematic analysis was used to analyze interview results to deductively and inductively create codes. Transcripts of interviews conducted to date were coded independently by two members of the research team. The researchers also collected relevant sociodemographic data and administered three coping-related validated measures. Data collection is ongoing.

To date, 40 patients with varying amounts of pre-ESRD nephrology care have participated in the study. Results of interim analyses indicate that there are variations in the coping styles and strategies used by diagnosed patients according to the amount of pre-ESRD nephrology care. Four qualitative themes have been identified; 1) psychological distress; (2) adjustment to illness issues; (3) influences on primary appraisal of the stressor; and (4) secondary appraisal of the stressor.

There are variations between groups in mean scores on the Denial, Acceptance, and Active Planning subscales of the Brief COPE measure and on the Coping Strategies Index-Short Form Emotion-Focused Disengagement subscale. Patients with no history of pre-ESRD nephrology care have the highest mean scores.

In summary, the researchers said, "The qualitative and quantitative differences in coping with the ESRD diagnosis and renal replacement therapy initiation according to amount of pre-ESRD care suggest further exploratory and targeted intervention research is necessary to help all patients optimally adjust to this life-altering illness."

Source: Urbanski M, Dumenci L, Gadegbeku C, Siminoff L, Waterman A, Gardiner H. Coping with an ESRD diagnosis: differences among patients according to presence of pre-ESRD nephrology care. Abstract of a presentation at the National Kidney Foundation 2020 Spring Clinical Meeting; abstract #296.

Medication Problems in High-Risk CKD Patients

Due to high medication burden and the presence of multiple comorbidities, patients with chronic kidney disease (CKD) are at high risk for experiencing medication therapy problems (MTPs). However, the frequency of MTPs in pre-dialysis CKD patients is unclear.

Melanie R. Weltman, PharmD, and colleagues reported on a project that is part of the Kidney Coordinated Health Management Partnership, an ongoing National Institutes of Health funded, pragmatic randomized controlled trial that is testing an electronic health record-based population health management approach to improve CKD care. Results were reported at the NKF Spring Clinical Meetings in a presentation titled *Frequency of Medication Therapy Problems in a High-Risk Chronic Kidney Disease Population.*

Patients in the project are 18 to 85 years of age with CKD, at a high risk of progression to end-stage renal disease, and are not being followed by a nephrologist. Participants in the intervention arm receive nephrology recommendations (electronic consult), pharmacist-led telephone medication therapy management (MTM), and nurse-led CKD/dietary education. The Pharmacy Quality Alliance MTP Categories Framework is used to identify and categorize MTPs. The recommendations are included in the electronic health record for the patient's primary care physician to review at an upcoming office visit.

Enrollment began in July 2019. To date, 47 patients have received MTM and a total of 82 MTPs have been identified. Most patients (94%) experienced at least one MTP. The most common MTP was 'unnecessary medication therapy' (28%), due in large part to long-term use of proton pump inhibitors without clear indication, followed by 'dosage too low' (26%), and 'dosage too high' (23%).

Renin-angiotensin-aldosterone system inhibitors were frequently dosed too low, as suggested by uncontrolled blood pressure and/or significant proteinuria. Thirteen percent of patients reported recent prescription or over-the-counter nonsteroidal anti-inflammatory drug use.

In conclusion, the researchers said, "Preliminary data from this ongoing trial suggest that patients with high-risk CKD experience a high frequency of MTPs. Interdisciplinary care of CKD patients may facilitate early identification, resolution, and prevention of MTPs and thereby improve CKD care and slow CKD progression."

Source: Weltman M, Chen H, Abdel-Kader K, Jhamb M, Nolin TD. Frequency of medication therapy problems in a high-risk chronic kidney disease population. Abstract of a presentation at the National Kidney Foundation 2020 Spring Clinical Meetings; abstract #276.

Improving the Rate of Fistula Access at a VA Hospital

Guidelines from Kidney Disease Improving Global Outcomes recommend that all patients with end-stage renal disease (ESRD) receiving dialysis use a fistula for access. More than 90-day catheter rate prevalence at dialysis centers are tracked by the Centers for Medicare & Medicaid (CMS). The Veterans Health Administration (VA) is not required to abide by CMS guidelines; however, the VA uses them for guidance, resulting in expected rates of catheter use of less than 12.1%.

Sylvester Barnes, MD, reported on a VA quality improvement project at the NKF Spring Clinical Meetings in a presentation titled *Dialysis CVC Improvement Rate: A VA Quality Improvement Project.* The project was conducted at the Hines VA (HVA) hospital. Approximately 85 patients receive regular hemodialysis at HVA at the outpatient dialysis unit. In 2018, the 90-day catheter prevalence rate was above 35% consistently, far above the goals of the VA.

In response to the consistently high rate of catheter use, HVA established a multidisciplinary committee that included the dialysis attending rounding for that month, vascular surgery, and interventional radiology. New hires included a dedicated dialysis access nurse and an interventional nephrologist. The committee met biweekly and discussed in detail each patient with a catheter for dialysis access. A personalized access plan was created for each patient.

Following access creation, regular interventions were scheduled to manage access-related maturation issues, identified by routine surveillance. Following two weeks of stable access cannulation, catheters were removed. The committee met to discuss any patient with arteriovenous fistula or arteriovenous graft access who required more than one intervention in 90 days or was on the verge of failure (based on interventional nephrology or interventional radiology opinion). Those patients were placed on an unstable access list.

With the project in place, as of September 2019, the more than 90-day catheter rate decreased to 13%; projections for October 2019 indicated the rate would be less than 12%, in accordance with VA guidelines.

The authors said, "It is felt that the two biggest factors that have helped our catheter rate include forming our multidisciplinary committee, interventional nephrology hires to help provide more endovascular procedure access time, and the hiring of a dedicated access advanced nurse practitioner to help identify access-related problems and regularly schedule these patients for intervention with interventional nephrology, interventional radiology, or referral for surgical revision of the access."

Source: Barnes S, Wadhwa A. Dialysis CVC improvement rate: a VA quality improvement project. Abstract of a presentation at the National Kidney Foundation 2020 Spring Clinical Meetings; abstract #302.

Projections for October 2019 indicated the more than 90-day catheter rate would be less than 12% in accordance with the VA guidelines.

Association between Folic Acid Treatment and CKD Progression Varies by Vitamin B_{12} Level

Compared with the general population, patients with chronic kidney disease (CKD) have a substantially increased risk for kidney failure, cardiovascular disease, and mortality despite standard interventions for the management of traditional risk factors associated with CKD. According to **Youbao Li, MD,** and colleagues, new treatment approaches are needed.

Hyperhomocysteinemia is prevalent and significantly related to decline in kidney function among patients with CKD. Homocysteine is a sulfur-containing acid. The remethylation pathway of homocysteine metabolism is regulated by folate and vitamin B_{12} (B12). In populations with fortification or supplementation of folic acid, the main nutritional determinant of total homocysteine (tHcy) level is B12 status.

Results of the renal substudy of the China Stroke Primary Prevention Trial (CSPPT) suggest that treatment with folic acid can significantly delay CKD progression by 55% among hypertensive patients with mild-to-moderate CKD. There are few data on the effect of naturally occurring serum B12, without supplements, on the association between folic acid treatment and CKD progression. Dr. Li et al. conducted a post hoc analysis of the renal substudy of the CSPPT. Results were reported in the *American Journal of Kidney Diseases* [2020;75(3):325-332].

Of the 20,702 hypertensive adults enrolled in the CSPPT trial, 15,104 were enrolled in the renal substudy. Results of the renal substudy found no significant difference in the odds of progression to CKD in the enalapril-folic acid group compared with the enalapril-alone group in the total population. However, among participants with CKD at baseline (estimated glomerular filtration rate [eGFR] <60 mL/min/1.73 m^2 and/or proteinuria), the odds of CKD progression (primary outcome) were reduced by 55% with folic acid treatment. The odds of the composite outcome of the primary outcome and all-cause death were reduced by 35%.

For the current analysis, only patients with CKD at baseline were included. A total of 1374 participants with CKD and B12 measurements at baseline were included in the analysis of the primary outcome, and 1445 participants with CKD and B12 measurements at baseline were included in the analysis of the composite outcome analysis.

The primary outcome, progression of CKD, was defined as a decrease in eGFR of ≥30% and to a level of <60 mL/min/1.73 m^2 at the exit visit if baseline eGFR was ≥60 mL/min/1.73 m^2; or a decrease in eGFR ≥50% at the exit visit if the baseline eGFR was <60 mL/min/1.73 m^2; or kidney failure (eGFR <15 mL/min/1.73 m^2 or the need for dialysis). Secondary outcomes were (1) a composite outcome of the primary outcome and all-cause death; (2) rapid decline in eGFR (average decline ≥5 mL/min/1.73 m^2 per year; and (3) the annual rate of relative decline in eGFR.

Participants were stratified by tertiles of B12. Overall, mean eGFR at baseline was 86.1 mL/min/1.73 m^2. Those with higher levels of B12 were less likely to be carriers of MTHFR 677 TT (the gene encoding methylenate-trahydrofolate reductase); had higher levels of fasting glucose, total cholesterol, and folate; and had higher living standards. They also tended to consume more red meat; but had lower tHcy levels and lower prevalence of proteinuria at baseline. Within each baseline B12 stratum, nearly all baseline characteristics were comparable between the two treatment groups (enalapril-folic acid group and enalapril-alone group).

Median duration of treatment was 4.4 years. Mean treatment adherence (percentage of the study medication actually taken during the trial) was approximately 80% in both treatment groups within each baseline B12 stratum. Patient withdrawal was defined as discontinuing the use of study drugs for any reason more than 180 days prior to termination of the study; the rates of patient withdrawal ranged from 6.0% to 11.7% within treatment groups among each baseline B12 stratum. All participants were included in the analysis irrespective of treatment withdrawal. The two treatment groups were similar in use of concomitant medication use during the trial.

There were no associations between baseline B12 levels and the primary or secondary renal outcomes. Among participants with higher baseline B12 levels (≥248 pmol/L), compared with enalapril alone, enalapril-folic acid treatment was associated with an 83% reduction in the odds of the primary renal outcome (1.6% in the enalapril-folic acid group vs 7.8% in the enalapril alone group; odds ratio [OR], 0.17; 95% confidence interval [CI], 0.07-0.40). Among those with metabolic B12 deficiency (B12 levels <248 pmol/L), there was no significant difference in the primary outcome between the two groups (OR, 1.21; 95% CI, 0.51-2.85).

Among participants with baseline B12 levels in tertiles 2 or 3 (≤244 pmol/L), there was an association between treatment with enalapril-folic acid and an 80% reduction in the odds of the primary outcome (OR, 0.20; 95% CI, 0.09-0.45) compared with enalapril alone. Among those in the lowest tertile of B12 level (<244 pmol/L), there was no significant difference between the two groups in the primary outcome (OR, 1.07; 95% CI, 0.45-2.57).

Following exclusion of participants with B12 levels >555 pmol/L or exclusion of participants who withdrew from the study treatment, similar results were observed. Similar trends were also seen in participants with eGFRs of 30 to <60 mL/min/1.73 m^2.

The researchers cited some limitations to the findings, including the possibility of residual confounding due to the post hoc analysis design; only assessing participants' eGFR at baseline and the exit visit; the study cohort being limited to Chinese hypertensive patients with low baseline folic acid levels; and the relatively small sample size.

In conclusion, the researchers said, "Compared with enalapril alone, enalapril-folic acid treatment was associated with an 83% reduction in the odds of CKD progression among patients with mild-to-moderate CKD with B12 levels ≥248 pmol/L. The potential benefits of B12 (in the form of methylcobalamin) with a higher dosage of folic acid on CKD outcomes warrants further investigation, especially in those with low B12 levels." ■

TAKEAWAY POINTS

- Researchers conducted a post hoc analysis of data from an interventional trial to assess the modifying effects of vitamin B_{12} (B12) levels on the association between treatment with folic acid and progression of chronic kidney disease (CKD).
- Compared with treatment with enalapril alone, treatment with enalapril + folic acid was associated with an 83% reduction in the odds of CKD progression among patients with higher baseline B12 levels.
- Among patients with baseline B12 levels <248 pmol/L, there was no significant difference between the group treated with enalapril alone and the group treated with enalapril + folic acid.

QIP Scores and Rates of Mortality among Incident Dialysis Patients

Kidney failure is irreversible and patients with kidney failure require renal replacement therapy or kidney transplantation for survival. Due to the shortage of kidney donors, incompatible blood and tissue type, not being a good candidate for transplantation, or other social barriers, the majority of patients with kidney failure remain on dialysis therapy.

In 1972, the Centers for Medicare & Medicaid Services (CMS) included end-stage renal disease (ESRD) as the first disease-based eligibility; ERSD remains the only disease with such designation. In 1972, the dialysis population was 10,000 patients; in 2014, the number of patients on maintenance dialysis was 399,455. Costs have followed a similar increasing trend in that time period, and CMS has continued to encourage reforms to increase efficiency in care for patients with ESRD.

In the 2011 payment reform, CMS proposed an expanded bundle payment program, recommending a fixed payment per dialysis treatment. As part of the bundle payment reform, CMS implemented a Quality Incentive Program (QIP). In the QIP, care at dialysis facilities is rated on a scale of 0 to 100.

The impact of the QIP program on health outcomes is unknown; the program has been criticized for including laboratory indicators while limiting data on patient health outcomes. Noting that survival rates of patients on dialysis have remained less than optimal, **Fozia Ajmal, MD, PhD,** and colleagues conducted a study to examine the association between dialysis facility QIP performance scores and patient survival following initiation of dialysis. The researchers sought to test the hypothesis that mortality among incident dialysis patients would be higher among poor-performing facilities compared with those performing well. Results of the study were reported in the *American Journal of Kidney Diseases* [2020;75(2):177-186].

The retrospective cohort study included 84,493 incident dialysis patients from January to December 2013. Inclusion criteria were survival, no receipt of a kidney transplant, and no loss to follow-up within 90 days of dialysis initiation. Average follow-up was 5 months.

The independent variable was facility QIP scores (ranging from 0 to 100) for calendar year 2013. Facility covariates included chain affiliation, for-profit and low-volume status, dialysis treatments per facility per year, registered nurses per 10,000 treatments, technicians per 10,000 treatments, and services including home hemodialysis, peritoneal dialysis, and late shift.

Five different options were used to identify membership in a chain of dialysis facilities. For the three largest chains, each chain was assigned a number (1-3); facilities affiliated with the smaller or regional chains were consolidated into a single category (chain 4); and the remaining facilities were grouped into an independent category.

County covariates reflected the characteristics of counties where patients resided. The analysis included the proportion of Hispanics, blacks, unemployed, and those living in poverty. Median household income was also a county covariate.

Mean age of the cohort was 63.8 years, 57.3% were men, 51.4% were non-Hispanic white, 29.8% were unemployed, 60.7% were retired, and 40.9% were obese. Comorbidities included hypertension (88.4%); 48.1% had diabetes as the most common cause of kidney failure, followed by hypertension (31.4%). Approximately 7% of the participants were uninsured. Central venous catheter was the most common access modality at dialysis initiation (72.9%).

Most facilities (77.1%) operated 11 to 25 dialysis stations, provided more than 10,000 treatments (45.3%), were affiliated with large chains (chain 1, 33.7%; chain 2, 4.0%; chain 3, 32.4%), and were for profit (92.1%). All centers provided access to hemodialysis; 49.2% provided peritoneal dialysis, 27.6% provided home hemodialysis, and 19.2% offered late-night dialysis.

Of the 2983 counties represented in the analysis, most patients resided in urban areas (81.6%) and the South (44.6%). Average proportions of Hispanics and blacks per county were 15.4% and 17.9%, respectively. The average rate of unemployment was 7.7%.

Following exclusion of patients who died during the first 90 days of the first ESRD service, 11.8% of patients died within 1 year of follow-up. The hazard ratios (HR) of death varied by QIP scores. Compared with mortality rates at facilities with the highest QIP scores (≥90), mortality was higher in patients at facilities with scores <45 (HR, 1.60; 95% confidence interval [CI], 1.37-1.86); 45 to <60 (HR, 1.41; 95% CI, 1.29-1.55); 60 to <70 (HR, 1.09; 95% CI, 1.02-1.16) and 70 to <80 (HR, 1.08; 95% CI, 1.02-1.14). There was no statistically significant difference for patients at facilities scoring 80 to <85 and 85 to <90 compared with patients at facilities scoring ≥90 (reference category).

In fully adjusted models, there was a higher mortality rate among patients at facilities with QIP scores <45 (HR, 1.39; 95% CI, 1.15-1.68) and 45 to <60 (HR, 1.21; 95% CI, 1.10-1.33), compared with facilities with QIP scores ≥90.

In analyses of associations between patient, facility, and county covariates and patient mortality, there were associations between unemployment (HR, 1.76; 95% CI, 1.54-2.00), being retired (HR, 1.84; 95% CI, 1.62-2.09), being underweight (HR, 1.28; 95% CI, 1.17-1.40), being uninsured (HR, 1.63; 95% CI, 1.43-1.87), having ≥2 comorbid conditions (HR, 1.25; 95% CI, 1.16-1.35), and central venous catheter access (HR, 1.45; 95% CI, 1.27-1.65) and increased likelihood of death. There was also an association between each 1-year older age and living ≥10 miles from the dialysis facility and increased mortality risk.

Lower mortality risk was seen in facilities affiliated with chain 3 and those offering home dialysis. Facilities with 11 to 25 dialysis stations and those with >25 dialysis stations also had lower patient mortality risk.

Study limitations cited by the researchers included using the latest available data (2015), potentially limiting the generalizability of the findings to years other than those studied; the inability to adjust for the number of transitions for patients who visited multiple dialysis facilities or for changes in treatment modality; and not adjusting for baseline laboratory markers such as serum albumin level and residual kidney function.

"In conclusion, we show that higher scores using the QIP criteria of 2015 robustly predicted higher patient survival in incident dialysis patients. Our findings support the metrics as used in QIP for monitoring quality and suggest more research to further improve risk prediction of clinical and patient-reported outcomes in dialysis patients using the recent QIP data," the researchers said. ■

TAKEAWAY POINTS

- Researchers conducted a retrospective cohort study to test the hypothesis that mortality rates among incident dialysis patients would be higher among dialysis facilities with lower CMS Quality Incentive Program (QIP) scores compared with facilities with higher QIP scores.
- In a cohort of 84,493 patients who initiated dialysis from January to December 2013, 11.8% died during an average follow-up of 5 months.
- Rates of patient mortality were higher at facilities with QIP scores <45 and 45 to <60, compared with facilities with QIP scores ≥90.

Antioxidant Vitamins for Patients with Diabetes and Albuminuria

Due to the increasing prevalence of diabetes worldwide, diabetic kidney disease (DKD), a major cause of end-stage renal disease (ESRD), has become a public health issue. Guidelines recommend the use of renin-angiotensin-aldosterone system (RAAS) blockers in patients with DKD. However, according to **Jinxia Chen, MD, PhD,** and colleagues, due to the large number of patients with DKD who progress to ESRD, more interventions in this patient population should be investigated.

Dietary antioxidants, such as vitamins C and E, are important antioxidants in the human body. Supplementation of antioxidant vitamins have been shown to be effective in preventing cardiovascular and microvascular complications in experimental diabetic animal models, but not in diabetic patients. More recent clinical trials have demonstrated that higher doses of vitamins C and E (administered either separately or in combination) can reduce microalbuminuria and restrict the progress of DKD. However, the effect of vitamins C and E remains unclear.

The researchers conducted a meta-analysis designed to evaluate the effect of vitamins C and E in patients with diabetes and albuminuria. Results of the meta-analysis were reported in the *Journal of Renal Nutrition* [2020;30(2):101-110].

Two independent investigators performed searches of PubMed, Embase, CENTRAL (the Cochrane Central Register of Controlled Trials in the Cochrane Library), Web of Science, OVID, and www.clinicaltrials.gov. The initial search was conducted on December 5, 2017, and updated several times; the last update was December 10, 2018.

The search identified 2383 articles. Following exclusion of duplicate and irrelevant articles, 509 remained. A further 432 articles were excluded after review of the titles and abstracts of the 509 articles. Application of inclusion and exclusion criteria for this meta-analysis yielded a final count of 10 eligible articles.

Study sample size in the 10 studies ranged from 10 to 108 participants; the meta-analysis represents a total of 445 individuals. The duration of interventions in the studies ranged from 4 to 48 weeks. Two of the studies had a crossover design, and the remaining eight were parallel-designed. All of the 445 participants were patients with diabetes and albuminuria. All study interventions included vitamin E; four of the studies also included vitamin C.

> All study interventions included vitamin E; four of the studies also included vitamin C.

Seven of the 10 studies included assessment of albuminuria or proteinuria. Among 347 patients with diabetes, supplementation with vitamin C or E did not have a significant effect on albuminuria or proteinuria (standardized mean difference [MD]=-0.18, 95% confidence interval [CI], -0.40 to 0.03; *P*=.09). Three studies avoided the administration of RAAS blockers (33.3% of the results); two studies used RAAS blockers (44.0% of the results). RAAS blockers were not mentioned in the other studies.

Three of the studies reported post-treatment serum creatinine levels. There was an association between vitamin C and E supplementation and a reduction in serum creatinine levels in patients with diabetes and albuminuria (MD=-0.11 mg/dL; 95% CI, -0.19 to -0.03; *P*=.007).

Blood pressure was measured in five studies following implementation of the intervention. The effects of antioxidant vitamins on systolic blood pressure were significant (MD=-6.02 mm Hg; 95% CI, -9.65 to -2.40; *P*=.001). Those findings indicated an association between antioxidant vitamins and reduced systolic pressure; however, there was little effect on diastolic pressure.

Five studies reported hemoglobin A1c (HbA1c) results and three reported fasting glucose levels following intervention. Supplementation with antioxidants had significant effect on HbA1c or fasting plasma glucose levels (MD=-0.22%; 95% CI, -0.43 to 0; *P*=.05 and MD=-1.12 mg/dL; 95% CI, -13.24 to 10.99; *P*=.86, respectively).

Four studies reported total cholesterol. There was no significant association between antioxidant vitamins and total cholesterol levels (MD=-0.33; 95% CI -8.33 to 7.67; *P*=.94). Three studies reported on high-density lipoprotein cholesterol (HDLC) levels and two reported on low-density lipoprotein cholesterol (LDLC) and triglyceride levels. There was no significant effect of antioxidant vitamins on HDLC (MD=0.18 mg/dL; 95% CI, -3.80 to 4.16; *P*=.40) or LDLC (MD=–5.83 mg/dL; 95% CI -19.40- to 7.74; *P*=.08).

Six of the studies did not report any adverse events and two randomized controlled trials reported there were no adverse events or side effects. One randomized controlled trial reported that two participants withdrew due to adverse side effects in the first week of the study; no details were provided.

One randomized controlled trial was excluded due to low quality; the exclusion did not significantly affect the main outcomes of albuminuria or proteinuria, serum creatinine, or blood pressure.

Limitations to the study cited by the researchers included the difficulty in estimating publication bias; the single-center design and relatively small sample size of the studies included in the analysis; and the short treatment time in the analyzed studies.

The effect of antioxidant vitamins, including vitamins C and E, on diabetic kidney disease remains controversial, and a meta-analysis on this is still lacking. Our study indicates that the administration of antioxidant vitamins, specifically vitamins C and E, can benefit patients with diabetes and albuminuria in terms of kidney function and systolic blood pressure; however, more robust evidence is needed to confirm the effect of antioxidant vitamins," the researchers said. ■

TAKEAWAY POINTS

- A meta-analysis to examine the effect of antioxidant vitamins, specifically vitamins C and E, on patients with diabetes and albuminuria was conducted recently.
- The analysis included 10 studies representing 445 participants. Patients with diabetes and albuminuria were included regardless of diabetic type, and patients had to have received treatment with vitamins C or E.
- Treatment with antioxidant vitamins had significant effects of serum creatinine levels and systolic blood pressure; antioxidant vitamins had no effect on albuminuria or proteinuria, diastolic blood pressure, glucose, or lipid metabolism.

IgAN Progression Prediction Improved with Urinary Matrix Metalloproteinase 7 Level

The most common primary glomerulonephritis is immunoglobin A (IgA) nephropathy (IgAN), a leading cause of kidney failure. Among patients with IgAN, approximately 10% to 60% progress to kidney failure within 10 to 20 years. IgAN is heterogeneous and carries a highly variable risk for disease progress, making prediction of prognosis in individual patients a challenge in clinical practice.

Currently, the risk for disease progression in patients with IgAN relies on clinical data including proteinuria, blood pressure, and estimated glomerular filtration rate (eGFR at biopsy, or a histologic score (MEST-C) based on mesangial hypercellularity, the presence of endocapillary proliferation, segmental glomerulosclerosis/adhesion, and severity of tubular atrophy/interstitial fibrosis. Results of a previous study suggested that a combination of clinical data with histologic score improved risk stratification in IgAN; integrating the most validated risk factors may be the best strategy for a clinically relevant method of stratifying risk in this patient population.

Efforts to develop biomarkers for early prediction of disease progression in IgAN produced several biomarkers in serum (such as galactose-deficient IgA1 [Gd-IgA1], autoantibodies against Gd-IgA1, fibroblast growth factor 23 [FGF-23), and matrix metalloproteinase 7 [MMP-7]) and urine (such as angiotensinogen [AGT], epidermal growth factor [EGF], and kidney injury molecule 1 [KIM-1]). Most of the testing of these biomarkers has been conducted in studies with relatively small sample size; results to date have shown only modest improvement in prediction.

MMP-7 expression may not be detected in the normal adult kidney; however, levels are markedly induced in the presence of IgAN. Urinary MMP-7 levels reflect renal Wnt/b-catenin signaling, which is activated in IgAN. **Xiaobing Yang, MD,** and colleagues conducted a prospective multicenter 2-stage cohort study in China to test the hypothesis that urinary MMP-7 level may be useful as a noninvasive biomarker for early prediction of IgAN progression. Results of the study were reported in the *American Journal of Kidney Diseases* [2020;75(3):384-393].

The outcome of interest was IgAN progression, defined as a composite of either a permanent reduction ≥40% in eGFR (confirmed by a second measurement at least 30 days later) over baseline, kidney failure (eGFR to <15 mL/min/1.73 m^2 or the need for renal replacement therapy), or death, whichever occurred first.

The study enrolled a total of 946 patients. Of those, 554 patients participated in a training cohort to create a reference Cox proportional hazard model for IgAN progression. The remaining 392 patients were enrolled in a validation cohort to externally validate the prediction models that incorporated urinary MMP-7 derived from the training set. The training cohort was used as the comparator of the performance of urinary MMP-7 level with those of the other seven biomarkers (urinary AGT, EGF, KIM-1; serum Gd-IgA1, MMP-7, KIM-1, and FGF-23) as predictors of the risk for progression of IgAN.

Median follow-up was 40 months in the training set and 28 months in the validation set. Sixty-one patients (event rate, 3.3% per year) in the training set reached the composite end point of 40% decline in eGFR (n=35) or kidney failure (n=26). In the validation set, 37 patients reached the composite renal outcome (event rate, 4.1% per year): 25 experienced a 40% decline in eGFR and 12 had kidney failure. There were no participant deaths in either cohort.

Prior to biopsy, <20% of patients in the training set were treated with renin-angiotensin system (RAS) inhibitors and <10% received immunosuppression agents. There was no significant difference in drug use between those with and those without disease progression. Following biopsy, most patients in both cohorts received RAS inhibitors regardless of progression status. Use of immunosuppression agents was more common in patients with disease progression than in patients without disease progression.

In univariable models, there were significant associations with IgAN progression with levels of each of the eight biomarkers (P<.05 for all). However, following adjustment for clinical variables and MEST-C score, the associations with serum levels of FGF-23, KIM-1, and MMP-7 were no longer significant.

Of the eight biomarkers, the association with IgAN progression was strongest with urinary MMP-7 level. In the adjusted model, patients in the highest tertile of urinary MMP-7 (>3.9 mg/g) at biopsy had a 2.7-fold higher risk of IgAN progression compared with patients in the lower two tertiles combined.

When assessed as a continuous variable in a multivariable model, there was an association between higher urinary MMP-7 and a higher risk of IgAN progression (hazard ratio per 1-standard deviation greater, 3.2; 95% confidence interval [CI], 19-5.6; P<.001).

Urinary MMP-7 was a stronger predictor of IgAN progression in patients with early stage (eGFR ≥60 mL/min/1.73 m^2) disease (P for interaction=.02). In a subgroup with eGFR ≥60 mL/min/1.73 m^2 at biopsy, there was an association between urinary MMP-7 levels >3.9 mg/g and a 3.4-fold higher risk for progression compared with those for whom this biomarker was below this threshold. In patients with baseline eGFR <60 mL/min/1.73 m^2, those with urinary MMP-7 levels >3.9 mg/g has 2.3-fold increased risk.

In the training set, urinary MMP-7 level outperformed the other seven biomarkers in progression risk in IgAN, producing a C statistic of 0.85 (95% CI, 0.72-0.83) in the multivariable Cox model. Baseline MMP-7 level predicted the 3-year risk for the composite renal outcome, with a C-statistic of 0.82 (95% CI, 0.75-0.89).

The addition of urinary MMP-7 level to the model using clinical data at biopsy and MEST-C score resulted in a significant improvement in the risk prediction of IgAN progression compared with the reference model.

The lack of validation in other ethnic populations was a study limitation.

"In conclusion, we have identified urinary MMP-7 level as an independent and strong predictor for the progression of IgAN," the researchers said. "The addition of urinary MMP-7 level to the clinical data at time of biopsy and MEST-C score significantly improved the 3-year risk prediction of the composite renal outcome and risk reclassification of disease progression in IgAN." ■

TAKEAWAY POINTS

- Early and accurate prediction of disease progression in patients with immunoglobulin A nephropathy (IgAN) is a clinical challenge.
- Researchers in China conducted a prospective observational cohort study to test the hypothesis that the addition of urinary matrix metalloproteinase 7 (MMP-7) level to clinical data at time of biopsy would be a promising predictor of IgAN progression.
- In this cohort, urinary MMP-7 was an independent predictor of progression of IgAN; risk prediction was significantly improved with the addition of MMP-7 level to the current approach.

AMERICAN TRANSPLANT CONGRESS 2020

The American Transplant Congress is the joint annual meeting of the American Society of Transplant Surgeons and the American Society of Transplantation. The Congress provides a forum for the exchange of new scientific and clinical information related to solid organ and tissue transplantation. Presentations and posters provide information on advances in research and care to transplant physicians, scientists, nurses, organ procurement professionals, pharmacists, and other transplant professionals.

Due to the coronavirus, the 2020 American Transplant Congress was held virtually, providing a showcase for the latest research and advances made by the transplant community in the past year.

Cell-Free DNA (AlloSure®) Testing in Recipients of SODQ Kidneys

Researchers at the University of Southern California, led by **Y. A. Qazi,** conducted a study to examine the role of cell-free DNA testing (AlloSure®, CareDx, Brisbane, California) during graft dysfunction in kidney transplant recipients who received kidneys from donors with Sub-Optimal Donor Quality (SODQ). Results of the study were reported during a virtual poster session at the American Transplant Congress 2020 in a poster titled *Role of Cell-free DNA (AlloSure) Testing in Recipients of Kidneys with Sub-Optimal Donor Quality.*

The study defined SODQ kidneys as kidneys that had undergone a biopsy by the Organ Procurement Organization (OPO) at the time of procurement. The most common indications for biopsy by the OPO were donor history of hypertension, diabetes mellitus, and acute kidney injury. The current analysis included all SODQ kidneys that had subsequently undergone a for-cause kidney biopsy and AlloSure testing (ASt). The researchers collected data regarding the final diagnosis of the for-cause biopsy and the results of the ASt.

A total of 60 patients underwent a procurement biopsy, a for-cause biopsy, and an ASt. Twenty of the 60 had ASt testing performed within the month prior to the for-cause biopsy; the remaining 40 had testing performed more than 4 months prior to or after the biopsy and were not included in the analysis.

Sixty-five percent (13/20) of the analysis cohort had rejections. Of those seven were borderline (BL)/early allogeneic T-cell receptor (TCR), two scored 1a on the ASt, one scored 1b, and three had antibody-mediated rejection (AMR). Three of the 20 patients had an ASt result of <0.15% (one was BL/early TCR rejection, one had diabetic changes, and one had mild acute tubular necrosis). Five of the 20 patients had ASt >1% (two AMRs, one 1b, one 1a, 1 BL).

ASt identified 1a or greater rejections in four of six patients (67%) with a 1% cutoff. The mean ASt for BL/early TCR rejection was 0.42% (95% confidence interval [CI], 0.15%-1.5%). ASt for biopsies with moderate IF without rejection trended higher at 0.58% (95% CI, 0.35%-0.80%).

In conclusion, the researchers said, "SODQ kidneys are more prone to graft dysfunction necessitating evaluations and biopsies. Our results demonstrate the following regarding ASt in SODQ kidneys: Over 85% of patients who underwent a for-cause biopsy have AST >0.15%. While ASt was able to identify higher grades of rejection, a threshold of <1% is warranted to identify BL rejections. Levels of >0.50% may suggest the presence of higher grades of tubular atrophy due to donor quality and should be confirmed by evaluating the results of procurement biopsy. In the absence of moderate IF in baseline biopsies, AST levels of >0.15% to 1% should raise concerns for borderline rejections and be followed with a biopsy or empiric but careful adjustment in immunosuppression."

Source: Qazi YA, Mon W, Smogorzewski M. Role of cell-free DNA (AlloSure®) testing in recipients of kidneys with sub-optimal donor quality. Abstract of a poster presented at the virtual American Transplant Congress 2020 (Abstract D-277), May 30, 2020.

Outcomes Following Listing Policy Change for Simultaneous Liver-Kidney Transplantation

The listing policy for simultaneous liver-kidney transplantation issued on July 10, 2017, imposed more stringent criteria on recipient renal function. Data on recipient outcomes following the change are scarce. **M. L. Samoylova** and colleagues at Duke University Hospital, Durham, North Carolina, conducted an analysis to examine outcomes prior to and following the policy change.

Results of the analysis were reported during a virtual presentation at the American Transplant Congress 2020. The presentation was titled *Utilization and Outcomes of Simultaneous Liver-Kidney Transplants after Change in Allocation Policy.*

Data from the United Network for Organ Sharing database were used to identify adult recipients of simultaneous liver-kidney transplant from 2007 to 2018. The patients were stratified into three eras: 2007 to 2011; 2012 to July 10, 2017, (policy change); and July 11, 2017, to July 2018. The researchers used Chi-squared test and multivariable Cox proportional hazard models to compare patient and graft survival at 1 year.

During the three eras, a total of 5809 patients received simultaneous liver-kidney transplantation: 1892 in the 2007 to 2011 era, 3004 in the 2012 to July 10, 2017, era, and 913 in the July 11, 2017, to July 2018 era. Median donor age and Kidney Donor Profile Index were similar among the three eras (35 years, 33 years, and 34 years, respectively, P=.33 and 1.05, 1.04.and 1.06, respectively; P=.01).

Over time, the number of Expanded Criteria Donors decreased (10%, 8%, and 7%, respectively). There was no change in the proportion of patients on hemodialysis while on the transplant waitlist over time (72.5% vs 72.6% vs 73,0%, respectively, P=.96). There was also no change in mean estimated glomerular filtration rate at transplant among those not on hemodialysis (21.7 mL/min/1.72 m^2 vs 21.2 mL/min/1.73 m^2 vs 21.2 mL/min/1.73 m^2, respectively, P=.83).

Between the first two eras, 1-year survival improved and then remained unchanged following the policy change (85% vs 90% vs 91%, respectively, P=.37). Trends for liver and kidney graft survival were similar.

In multivariable models, there was no difference in survival at 5 years pre-policy versus post-policy (hazard ratio [HR], 1.24; 95% confidence interval, [CI] 0.96-1.60; P=.10). The models did suggest an increased hazard of liver graft failure within the first year (HR, 1.28; 95% CI, 1.01-1.63; P=.047).

In conclusion, the researchers said, "Recipient renal function at transplant appears unchanged after the change in simultaneous liver-kidney transplantation listing policy. Despite concern that the policy change would select for sicker recipients and result in poor outcomes, short-term outcomes are similar to prior. Further attention is necessary to the factors affecting outcomes of liver grafts and center-level differences in practice."

Source: Samoylova ML, Shaw BI , Kesselli SJ, et al. Utilization and outcomes of simultaneous liver-kidney transplants after changes in allocation policy. Abstract of a presentation at the virtual American Transplant Congress 2020 (Abstract 580), May 30, 2020.

Postdonation Systolic Blood Pressure in Older Donors with Hypertension

Reduced nephrons is one of the mechanisms underlying predonation hypertension in living kidney donors ≥50 years of age. The 50% nephron mass reduction associated with donor nephrectomy may exacerbate predonation, controlled hypertension. Guidelines regarding hypertension in organ donors are evolving. **F. Al Ammary** and colleagues at Johns Hopkins University, Baltimore, Maryland, designed a study to examine the trajectory of systolic blood pressure in older donors with and without hypertension.

The researchers reported results of the study during a virtual presentation at the American Transplant Congress 2020. The presentation was titled *Predonation Hypertension and Early Postdonation Systolic Blood Pressure among Older Living Kidney Donors.*

Using data from the Scientific Registry of Transplant Recipients, the researchers examined postdonation systolic blood pressure in the first 2 years after nephrectomy among 11,969 older living kidney donors form 2010 to 2018. A mixed linear model with donor-level random intercept adjusting for age, sex, race, predonation systolic blood pressure, body mass index, and year of donation were used to model the association between hypertension and postdonation systolic blood pressure. The odds of having 6-month postdonation systolic blood pressure >130 mmHg and >140 mmHg were modeled using multivariable logistic regression.

Of 11,969 older donors identified, 9.7% (n=1161) had hypertension. Median predonation systolic blood pressure was 130 mmHg among donors with hypertension versus 124 mmHg among donors without hypertension. Following adjustment for baseline characteristics including predonation systolic blood pressure, there was an association between hypertension and $a_{1.8}2.4_{3.0}$ mmHg increase in postdonation systolic blood pressure (P<.001). Hypertension was associated with 39% higher odds of having 6-month postdonation systolic blood pressure >130 mmHg (adjusted odds ratio [aOR], $_{1.20}1.39_{1.61}$; P<.001) and 50% higher odds of having 6-month postdonation systolic blood pressure >140 mmHg (aOR, $_{1.25}1.50_{1.82}$; P<001).

In conclusion, the researchers said, "Predonation hypertension was associated with higher risk of uncontrolled 6-month postdonation systolic blood pressure among older donors, even after adjusting for predonation systolic blood pressure. Our findings call for programs to monitor postdonation systolic blood pressure in donors with hypertension to ensure adequate blood pressure control following nephrectomy."

Source: Ammary FAI, Muzzale AD, Brennan DC, Segev DL, Massie AB. Predonation hypertension and early postdonation systolic blood pressure among older living kidney donors. Abstract of a presentation at the virtual American Transplant Congress 2020 (Abstract 361), May 30, 2020.

Conference Coverage

March 25-29, 2020

Early Hospital Discharge after Kidney Transplantation

Improvements in perioperative care following kidney transplantation include reduction in length of operative stay to as low as 2 days. However, according to **E. Calderon** and colleagues at the Mayo Clinic, Phoenix, Arizona, there are few data available on the effect of reductions in length of stay on post-transplant healthcare utilization.

The researchers conducted a retrospective study to examine the association between reduced length of stay and healthcare utilization following kidney transplantation in a cohort of 1001 consecutive kidney transplant patients at the Phoenix Mayo Clinic. Results of the study were reported during a virtual presentation at the American Transplant Congress 2020. The presentation was titled *Outcomes and Healthcare Utilization after Early Hospital Dismissal in Kidney Transplantation: An Analysis of 1001 Consecutive Cases.*

The analysis included a prospectively collected kidney transplant database that was merged with healthcare utilization administrative data from the center from 2011 to 2015. Patients were stratified into early dismissal (≤2 days), normal dismissal (3-5 days), and late dismissal (>5 days).

Of the 1001 patients, 19.8% were in the early dismissal cohort, 79.4% were in the normal dismissal cohort, and 3.8% were in the late dismissal cohort. The proportion of living donor transplants was highest in the early dismissal cohort: early, 51%; normal, 31.4%, late, 18.4%; $P<.001$. The early discharge group had lower delayed graft function (early, 19.2%; normal, 32%; late, 73.7%; $P=.001$).

There was no difference among the three groups in readmission rate or emergency department visits at 30 and 90 days. Glomerular filtration rate was similar among the groups and there was no difference in biopsy proven rejection rate. Patients in the early and normal discharge cohorts had improved graft and patient survival compared with the late discharge cohort ($P=.05$). Risk adjusted models showed no difference in readmission, graft survival, or patient survival.

"Discharging patients 2 days after kidney transplant is feasible. It does not increase hospital utilizations and provides similar patient and graft survival when compared to patients that are discharged later," the researchers said.

Source: Calderon E, Chang Y, Chang JM, et al. Outcomes and healthcare utilization after early hospital dismissal in kidney transplantation: An analysis of 1001 consecutive cases. Abstract of a presentation at the virtual American Transplant Congress 2020 (Abstract 177), May 30, 2020.

Risk of New-Onset Diabetes after Kidney Transplantation and Proportion of Veillonella

Patients undergoing kidney transplantation are at risk for new-onset diabetes after transplantation (NODAT). NODAT is a common complication after kidney transplantation; however, according to researchers in the Republic of Korea, the mechanism of NODAT is not fully understood. Results of recent studies suggest that in the general population gut bacteria play a key role in diabetes.

The researchers, led by **K. Ji Eun,** conducted a study designed to examine the gut microbiota on NODAT in kidney transplant recipients. Results of the study were reported during a session at the virtual American Transplant Congress 2020 in a poster titled *Proportion of Veillonella and the Risk of New-Onset Diabetes Mellitus after Kidney Transplantation.*

Stool samples were collected from 46 transplant recipients at three time points: prior to transplantation, 3 months following transplantation, and 12 months following transplantation. Stool DNA extraction and 16s DNA metagenome sequencing were performed. The development of post-transplantation diabetes mellitus was defined as hemoglobin A1c level ≥6.5% or initiation of the use of diabetes medications.

Of the 46 transplant recipients, 11 were diagnosed with pre-transplant diabetes mellitus. During follow-up of 2.1 years, 15 of the remaining 35 patients were diagnosed with NODAT.

Results of the 16s DNA analysis showed significant differences among patients without diabetes, those with NODAT, and those with pre-transplant diabetes in change of abundance in genus Veillonella according to the time after transplant. In patients without diabetes, there was a significant increase in the proportion of Veillonella at 3 months post-transplant; there was no increase in patients with NODAT or pre-transplant diabetes.

In unadjusted analysis, patients with reduced abundance of Veillonella at 3 months post-transplant compared with 3 months pre-transplant had a 6.0-fold increased risk of developing NODAT compared with those without reduced abundance of Veillonella (hazard ratio [HR], 6.00; 95% confidence interval [CI], 1.87-19.2; $P=.003$). Following adjustment for age, sex, body mass index, dialysis duration, and desensitization, the adjusted HR was 5.85 (95% CI, 1.62-21.28), $P=.007$.

"The reduction of Veillonella at 3 months after transplantation is significantly associated with NODAT," the researchers said.

Source: Eun KJI, Kim H, Cho H, et al. Proportion of Veillonella and the Risk of New-Onset Diabetes Mellitus after Kidney Transplantation. Abstract of a poster presented at the virtual American Transplant Congress 2020 (Abstract B-047), May30, 2020.

Outcomes among Recipients of Kidney Allografts from Donors with Hypertension

Allografts from living kidney donors may carry subclinical pathological abnormalities to the recipient, increasing the risk for adverse clinical outcomes. Diminished number of nephrons is one mechanism associated with hypertension. Recipients of allografts from donors with hypertension may have insufficient number of nephrons, leading to adverse outcomes associated with hyperfiltration injury.

Researchers at Johns Hopkins, Baltimore, Maryland, led by **F. Al Ammary,** conducted an analysis to examine change in estimated glomerular filtration rate (eGFR) over time and survival in recipients of allografts from donors with versus without hypertension, stratified by donor age. Results were reported during a virtual poster session at the American Transplant Congress 2020 in a poster titled *Long-Term Outcomes in Recipients of Allografts from Living Kidney Donors with Hypertension.*

The researchers utilized a national cohort of adult living-donor kidney transplantation recipients from January 1, 2005, to June 30, 2017, to identify 49,990 recipients from donors ≤50 years of age (younger), including 597 whose donors had hypertension and 21,130 recipients from donors ≥50 years of age (older), including 1441 whose donors had hypertension. Mixed models with random intercepts and random slopes and Cox regressions models adjusting for recipient, donor, and transplant characteristics were used in the analyses.

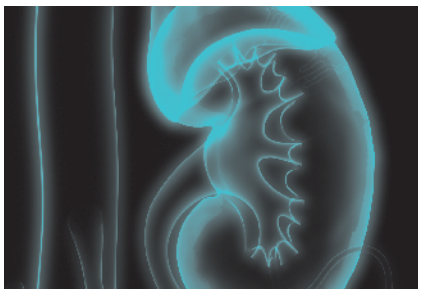
Median follow-up was 5.4 years. In the cohort of recipients from younger donors with versus without hypertension, the annual decline in eGFR was -1.10 mL/min/1.73 m^2 versus -0.50 mL/min/1.73 m^2, respectively ($P<.01$). The 12-year all-cause graft survival was 50.3% versus 56.0%, respectively (graft failure hazard ratio [HR] 1.21; 95% confidence interval [CI], 1.03-1.43; $P=.02$).

Among recipients from older donors with versus without hypertension, the annual decline in eGFR was -0.68 mL/min/1.73 m^2 versus -0.64 mL/min/1.73 m^2, respectively ($P=.7$). The 12-year graft survival was 50.7% versus 50.0%, respectively (graft failure HR, 1.04; 95% CI, 0.93-1.17; $P=.5$).

"Hypertension in younger, but not in older, donors was associated with worse recipient outcomes," the researchers said.

Source: Ammary FAI, Yu S, Muzaale A. et al. Long-Term Outcomes in Recipients of Allografts from Living Kidney Doors with Hypertension. Abstract of a poster presented at the virtual American Transplant Congress 2020 (Abstract C-081), May 30, 2020.

> "Hypertension in younger, but not in older, donors was associated with worse recipient outcomes."



Outcomes in HCV Positive and Negative Recipients of HCV Positive Kidney

Previously, hepatitis C positive (HVC+) donor kidneys were only transplanted into recipients who were HCV infected (D+/R+). The emerging availability of direct acting anti-viral (DAA) medications has enabled the transplantation of an HCV positive kidney into a non-infected recipient (D+/R-).

J. Torabi and colleagues at Montefiore Medical Center, Bronx, New York, conducted an analysis to compare center waitlist times and total waitlist allocation days between a cohort of HCV positive patients who were transplanted with donor positive kidneys (D+/R+) (n=29) with a cohort of patients who were HCV negative and received a donor positive kidney (D+/R-) (n=40). Following transplantation, D+/R- recipients were treated with DAAs.

Results of the analysis were reported during a virtual poster session at the American Transplant Congress 2020 in a poster titled *Transplantation of HCV Positive Kidneys Confers Excellent Outcomes for HCV Infected and Uninfected Recipients.*

The D+/R- cohort had older recipient and donor age compared with the D+/R+ cohort: 66.9 years vs 60.8 years (*P*=.02) and 35.1 years versus 29.9 years (*P*=.01), respectively. The Kidney Donor Profile Index was also significantly higher in the D+/R- group than in the D+/R+ group (60.9 vs 44.9; *P*=.01).

There were no statistically significant differences in waitlist times between the two groups in either total allocation time (1340 days in the D+/R- group vs 1209 days in the D+/R+ group; *P*=.61) or center waitlist days (745 days in the D+/R- group vs 543 days in the D+/R+ group; *P*=.28). All D+/R- patients developed HCV viremia following transplantation, but with DAA treatment achieved sustained virologic response within 12 weeks.

There were no significant differences in length of stay between the D+/R- group and the D+/R+ group (5.1 vs 6.1; *P*=.33) or incidence of delayed graft function (28% vs 38%; *P*=.36). Creatinine and estimated glomerular filtration rate at 1 and 6 months were similar in both groups. All patients tolerated DAA treatment with no adverse effects from treatment.

In summary, the researchers said, "Transplantation of HCV positive kidneys offers excellent outcomes in both HCV positive and negative recipients."

Source: Torabi J, Muhdi N, Montal A,et al. Transplantation of HCV positive kidneys confers excellent outcomes for HCV infected and uninfected recipients. Abstract of a poster presented at the virtual American Transplant Congress 2020 (Abstract A-044), May 30, 2020.

Obesity and Outcomes of Simultaneous Kidney-Pancreas Transplantation

In patients with type 1 diabetes as well as, more recently, type 2 diabetes, pancreas transplantation has proven effective in normalizing glucose control with equivalent patient and graft survival rates. However, according to researchers at Temple University School of Medicine, Philadelphia, Pennsylvania, there are few data available on outcomes of simultaneous kidney-pancreas transplantation in overweight and obese recipients.

Patients with type 2 diabetes are often overweight, increasing the risk of graft rejection, infections, and surgical complications. The researchers, led by **S. Karhadkar,** conducted a study to examine short- and long-term outcomes of simultaneous kidney-pancreas transplantation in overweight and obese recipients. Results were reported during a poster session at the virtual American Transplant Congress 2020 in a poster titled *Effect of Obesity on Short- and Long-Term Outcomes on Simultaneous Kidney-Pancreas Transplantation.*

The study utilized data from the United Network for Organ Sharing database to examine outcomes of simultaneous kidney-pancreas transplantation in the United States from 1998 to 2017. Recipients of simultaneous kidney-pancreas transplant were stratified into four groups: (1) overweight type 2 diabetes; (2) normal weight type 2 diabetes; (3) overweight type 1 diabetes; and (4) normal weight type 1 diabetes.

To determine the effects of body mass index on post-transplant patient outcomes, the researchers compared the groups regarding the causes of kidney and pancreas graft failure, graft survival times, and total deaths due to pancreas-related complications. Univariate analyses were performed using Chi2 for categorical and Mann-Whitney U/Kruskal-Wallis as appropriate for continuous variables. Subset analyses were also performed.

During the study period, 8507 patients with type 1 diabetes underwent simultaneous kidney-pancreas transplantation; of those patients, 4408 were overweight. The most common cause for renal graft failure was chronic and acute rejection; the most common cause for pancreas allograft failure was allograft thrombosis (31%). In non-obese recipients, the most common cause for graft loss was chronic rejection. In the overweight population there were a total of 1165 graft failures due to rejection or surgical procedure: 469 kidney graft failures and 696 pancreas graft failures.

A total of 874 patients with type 2 diabetes underwent simultaneous kidney-pancreas transplantation during the study period. Of those, 550 were overweight and 324 were classified as normal weight. In analysis of the cause of kidney graft failure, recurrent diseases were seen only in the overweight cohort, followed by primary failure and rejection. For pancreas graft failure, rejection and bleeding were seen in high frequency in the overweight cohort.

In both the type 1 and type 2 cohorts, graft survival times were higher and the percentage of deaths due to pancreas-related complications in relation to the total patient population was lower in the normal weight groups compared with the overweight groups.

In conclusion, the researchers said, "Overweight diabetic patients carry more risk of rejection and presence of surgical procedure complications than the non-overweight counterparts. Non-overweight patients also had longer survival times, and had less mortality due to pancreas-related complications in both types of diabetes."

Source: Karhadkar S, Lau K, Singh P, Di Carlo A. Effect of obesity on short- and long-term outcomes on simultaneous kidney-pancreas transplantation. Abstract of a poster presented at the virtual American Transplant Congress 2020, (Abstract A-260), May 30, 2020.

Opioid-Free Pain Management Following Kidney Transplant

The opioid epidemic in the United States is a national health crisis that had devasted patients and their families. A major contributor to narcotic exposure and harm has been high levels of unnecessary prescribing of opioids in the post-operative setting. In May 2019 the University of Illinois at Chicago shifted its post-operative pain management strategy from opioid minimization to opioid avoidance and instituted a Surgical Opioid Avoidance Protocol (SOAP).

J. Benken and colleagues at the University of Illinois at Chicago conducted an evaluation to assess the impact of SOAP on pain control following renal transplant. Results of the evaluation were reported during a virtual presentation at the American Transplant Congress 2020 in a presentation titled *Opioid-Free Pain Control? Surgical Opioid Avoidance Protocol (SOAP) Following Kidney Transplant.*

In the pre-SOAP pain management strategy, pain scores of 7 to 10 triggered prescription of morphine 2 mg IV push every 2 hours as needed; the interval was increased daily with the goal of discontinuation by post-operative day 2. The SOAP strategy calls for acetaminophen, followed by lidocaine topical patch and tramadol for moderate pain. Two consecutive pain scores of >7 despite intervention trigger notification of the physician.

The primary end point of the protocol assessment was average pain score. A sample size calculation was performed to determine the number of patients needed in each group, pre-SOAP and post-SOAP, to detect a difference of 1 in the average pain score. Baseline characteristics were collected for each group and the average pain score throughout the renal transplant admission was calculated. Previous minimization strategies at the center significantly shortened length of stay; length of stay was a secondary end point in the current analysis.

Overall, power was met and 103 adult renal transplant recipients were included. Demographics were similar in age, sex, race, and body mass index between the two groups. Compared with the pre-SOAP strategy for pain management, the average pain score was significantly lower in renal transplant recipients utilizing SOAP (2.6 vs 1.7; *P*=.002). Length of stay was similar between the two groups.

"Opioid avoidance post-operatively with SOAP is feasible and even significantly reduced average pain score within an adult renal transplant population," the researchers said.

Source: Benken J, Campara M, Vellis E Votta, Tzvetanov I, Benedetti E. Opioid-free pain control? Surgical Opioid Avoidance Protocol (SOAP) Following Kidney Transplant. Abstract of a presentation at the virtual American Transplant Congress 2020 (Abstract 547), May 30, 2020.

Conference Coverage

March 25-29, 2020

Outcomes among Recipients of Older Hypertensive Living Donor Kidneys

There have been data reported supporting the long-term safety of nephrectomy in donors with hypertension. However, according to **A. Sharfuddin** and colleagues at Indiana University School of Medicine, Indianapolis, there are few long-term data on outcomes among recipients of kidneys from donors with hypertension. The use of older hypertensive donors, those ≥60 years of age, is rare and there are only minimal data on outcomes among recipients of kidneys from hypertensive donors >60 years of age.

The researchers conducted a study to examine the demographics of older living donors and their recipient outcomes in the United States. Results of the study were reported during a virtual poster session at the American Transplant Congress in a poster titled *Kidney Transplant Recipient Outcomes from Older (60+) Hypertensive Living Donors*.

The retrospective review utilized the United States United Network for Organ Sharing database for the period January 2000 through December 2016. Pediatric and multiorgan transplant recipients were excluded and the time period was limited to minimum 1-year follow-up.

Of the 111,483 living donors during the study period, 5.1% (n=5695) were ≥60 years of age and met study criteria. Of the 5695, 9.3% (n=531) were hypertensive. Median follow-up was 4.6 years.

There were no statistically significant differences between recipients with older hypertensive versus older non-hypertensive donors in all-cause unadjusted graft survival (P=.57), death-censored graft survival (P=.79), or patient survival (P=.52). There were no differences between the two groups in race, sex, dialysis, delayed graft function, or acute rejection. In the hypertensive living donor group, there was no difference in graft survival between recipient race, sex, donor race, and acute rejection. Compared with donors 60 to 64 years of age, graft survival was inferior in donors >65 years of age (P=.0005) in both hypertensive and non-hypertensive donors (P=.035).

In conclusion, the researchers said, "Transplant recipient outcomes from older hypertensive living donors are favorable and comparable to those donors without hypertension. Careful selection of such donors and matching to appropriate recipients should not be discouraged when such donors are available."

Source: Sharfuddin A, Taber T, Adebiyi O, Panezai M, Mishler D, Yaqub M. Kidney transplant recipient outcomes from older (60+) hypertensive living donors. Abstract of a poster presented at the virtual American Transplant Congress 2020 (Abstract A-079), May 30, 2020.

Pulmonary Hypertension and Patient Outcomes after Kidney Transplantation

The increase in the prevalence of pulmonary hypertension in patients with chronic kidney disease is driven by left heart failure, high cardiac output, hypoxic lung diseases, and metabolic derangements. Those physiologic factors can affect outcomes following kidney transplant. **M.C. Nguyen** and colleagues at Johns Hopkins Hospital. Baltimore, Maryland, conducted a study to examine post kidney transplant graft and patient survival and to determine the association between donor type and outcomes in patients with pretransplant pulmonary hypertension.

The researchers reported results of the study during a virtual presentation at the American Transplant Congress 2020. The presentation was titled *Pulmonary Hypertension Is Associated with Inferior Graft and Patient Survival after Kidney Transplantation*.

The researchers utilized data from the United States Renal Data System from 2000 to 2018 to identify 92,721 adult deceased-donor kidney transplant and living-donor kidney transplant recipients. Pretransplant pulmonary hypertension was identified using one inpatient claim, two outpatient claims at least 30 days apart, and right heart catherization procedure codes within 1 year of diagnosis of pulmonary hypertension. Cox regression and inverse-probability weighting were used to compare delayed graft function, patient survival, and death-censored graft failure between recipients with and without pulmonary hypertension.

Of the 92,712 kidney transplant recipients, 2570 (2.8%) had pretransplant pulmonary hypertension. In a weighted standardized population, median patient survival following kidney transplantation among patients with pulmonary hypertension was 9.0 years compared with 12.8 years for patients without pulmonary hypertension. There was an association between pulmonary hypertension and higher risk of delayed graft failure (odds ratio [OR], 1.28; 95% confidence interval [CI], 1.15-1.41; P<.01), death-censored graft failure (hazard ratio [HR], 1.18; 95% CI, 1.06-1.30; P<.01), and patient mortality (HR, 1.54; 95% CI, 1.42-1.66; P<.01).

Among patients with pulmonary hypertension, recipients of a living-donor kidney transplant had substantially decreased risk of delayed graft function compared with deceased-donor kidney transplant recipients (OR, 0.12; 95% CI, 0.05-0.30; P<01). The survival benefit of living-donor kidney transplant compared with deceased-donor kidney transplant was comparable in both the group with pulmonary hypertension and the group without pulmonary hypertension (P for interaction=.2).

"Pretransplant pulmonary hypertension is associated with inferior graft and patient survival post kidney transplantation. These data inform risk stratification and transplant selection process," the researchers said.

Source: Nguyen N, Chiang P, Motter J, et al. Pulmonary hypertension is associated with inferior graft and patient survival after kidney transplantation. Abstract of a presentation at the virtual American Transplant Congress 2020 (Abstract 341), May 30, 2020.

Use of dd-cfDNA to Stratify Risk of Allograft Loss in African American Recipients

Despite advances in the modern era of kidney transplantation, the rates of allograft loss remain disproportionately higher among African American transplant recipients than among non-African American recipients. According to **A. Langone** and colleagues, biologic and socioeconomic risk factors are associated with the persistent racial disparities in outcomes. Donor derived-cell free DNA (dd-cfDNA), as a marker of cellular injury, has been shown to have value in risk stratification.

The researchers conducted a study designed to compare the distribution of dd-cfDNA, stratified by self-reported race, to ascertain whether dd-cfDNA is a predictor of increased risk for allograft failure. Results of the study were reported during a virtual poster session at the American Transplant Congress in a poster titled *Value of dd-cfDNA When Considering Recipient Ethnicity to Further Help Risk Stratify Transplant Recipients*.

Patients in the DART (Diagnosing Active Rejection in Kidney Transplant Recipients) study were followed for 2 years. During the first year following kidney transplantation, dd-cfDNA (AlloSure®, CareDx, Brisbane, California) was measured up to seven times. A total of 676 samples from African American patients were compared with 1307 samples from patients of other race/ethnicity. The researchers examined the cumulative distribution of dd-cfDNA in both cohorts.

Compared with the non-African American cohort, patients in the African American cohort had significantly higher cumulative distribution of dd-cfDNA: mean 0.69 among African Americans versus 0.45 among non-African Americans, P=.0006. Events of allograft rejection were more frequent among African Americans than in the non-African American cohort (P=.0159).

When considering the dd-cfDNA cumulative distribution function for the percentage change in estimated glomerular filtration rate (eGFR) stratified by race, African American patients had a significant improvement in eGFR compared with the non-African American patients following the clinical care intervention.

In summary the researchers said, "African American [ethnicity] is a significant risk factor for transplant recipients and is associated with an increase in dd-cfDNA. The regular use of dd-cfDNA as part of post-transplant surveillance may assist in the assessment and quantification of risk, and help allow earlier intervention to improve the overall outcomes and eGFR when events occur."

Source: Langone A, Fischbach B, Cohen D. Value of dd-cfDNA when considering recipient ethnicity to further help risk stratify transplant recipients. Abstract of a poster presented at the virtual American Transplant Congress (Abstract B-323), May 30, 2020.

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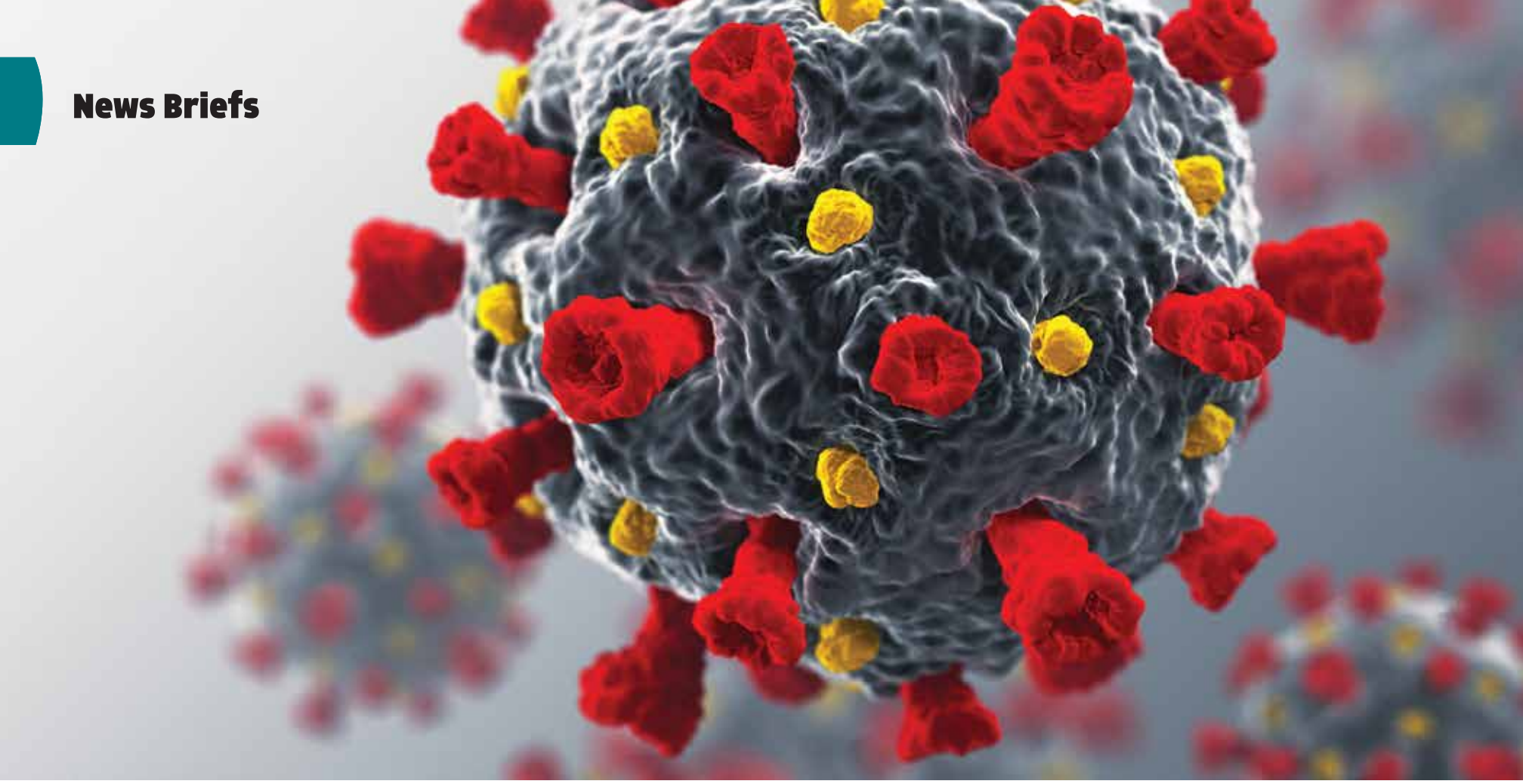

Study: KidneyIntelX™ to Predict COVID-19 Renal Complications

In a press release, RenalytixAi announced that investigators at the Icahn School of Medicine at Mount Sinai, New York, New York, would use the KidneyIntelX™ platform to assess the risk of adverse kidney effects in patients diagnosed with COVID-19. The platform will be used in a cohort of patients with COVID-19 admitted to Mount Sinai in a study called Pred-MAKER (Prediction of Major Adverse Kidney Events and Recovery).

The study will examine clinical factors and biomarkers, including multiple plasma biomarkers and urine proteomics and RNA sequences, to predict major adverse renal events in that patient population.

Steven Coca, MD, cofounder of RenalytixAI and co-investigator in PRED-MAKER, said, "Given the evidence that there is extensive systemic inflammation as well as kidney tubular injury in patients with COVID-19, the KidneyIntelX platform is well positioned to play a prominent role in understanding which patients are more likely to experience longer-term detrimental effects of COVID-19 infection."

The goal of the study is to improve understandings of the mechanisms of COVID-19 associated with kidney disease and to stratify patients into low-, medium-, and high-risk categories for major adverse renal events.

Corporate and Foundation Donations to the AKF Emergency COVID-19 Fund

The American Kidney Fund (AKF) announced that Fresenius Medical Care North America, the Greater Cincinnati Foundation, the Sozosei Foundation, and GSK have donated to the AKF Coronavirus Emergency Fund. The US-based Sozosei Foundation was established in late 2019 by Otsuka American Pharmaceutical, Inc.

The AKF emergency fund was established in late March to provide financial assistance to low-income dialysis and post-transplant patients who are struggling with medical expenses. Nearly 9000 patients had applied for assistance by mid-May.

LaVarne A. Burton, AKF president and CEO, said, "We are very grateful for the generosity of these companies and foundations in joining us in the critical effort to help patients during this emergency. Because of these generous gifts, hundreds of low-income dialysis and post-transplant patients will receive desperately needed grants to help them at a time when they are struggling and vulnerable."

In a press release in June, Ms. Burton announced that AstraZeneca's gift of $1.1 million to the Fund wiped out the waiting list for 4000 patients. Because of the AstraZeneca contribution, every patient on the Fund's waiting list received assistance.

"AstraZeneca's donation to the Coronavirus Emergency Fund is an act of profound generosity that will allow us to help 4000 kidney patients who are facing incredibly difficult economic circumstances in the middle of this public health emergency," Ms. Burton said.

The press release from AKF noted that contributions to the emergency fund may be made at KidneyFund.org/emergency, with 100% of all contributions going directly to patients in need.

Rockwell Medical Names Russell Ellison, MD, President and CEO

Russell H. Ellison, MD, MSc, has been appointed president and chief executive officer at Rockwell Medical, Inc. Rockwell Medical is a biopharmaceutical company working to inform anemia management and improve outcomes for patients. According to a press release, Dr. Ellison will continue to serve as a member of the company's board.

"We are pleased to appoint Russell as chief executive officer to lead our company through its important next phase of growth, which will focus on leveraging the medical attributes of our ferric pyrophosphate citrate technology," **John P. McLaughlin,** chairman of the Rockwell board of directors, said. "Russell's extensive medical expertise, deep understanding of the renal and anemia space based on his experience developing therapeutic products, experience as a CEO of public and private companies, and capital markets knowledge make him an ideal candidate to drive our strategic direction."

In the press release, Dr. Ellison said, "Through my work to date with Rockwell Medical as a consultant and a member of the board, I have gained an increased appreciation for the unique medical attributes of Triferic and the various opportunities we have to help patients with iron deficiency and create value for Rockwell Medical shareholders. I am honored to lead the company and look forward to continuing to work with my colleagues and other Rockwell stakeholders to advance and deliver on the Company's strategy."

Positive Top-Line Results from INNO2VATE

In a press release, Vifor Pharma announced that its partner, Akebia Therapeutics, Inc., reported positive top-line results from the INNO2VATE trial examining the efficacy and safety of vadadustat versus darbepoetin alfa for the treatment of anemia due to chronic kidney disease (CKD) in adult dialysis-dependent patients (DD-CKD). Vadadustat is an investigational oral hypoxia-inducible factor prolyl hydroxylase inhibitor (HIF-PHI). INNO2VATE is a global, phase 3 cardiovascular outcomes study. Akebia plans to submit a New Drug Application for vadadustat to the FDA for the treatment of anemia due to CKD in both dialysis dependent and non-dialysis dependent patients.

Stefan Schulze, Vifor Pharma president of the executive committee and chief operating officer, said, "We are delighted with the positive top-line data from Akebia's INNO2VATE global phase 3 study of vadadustat for the treatment of anemia due to CKD in dialysis patients. By successfully meeting its primary efficacy and cardiovascular end points, we believe the INNO2VATE data positions vadadustat as a potential new oral standard of care for treating all populations of dialysis patients, including both incident and prevalent dialysis patients with anemia due to CKD, subject to its approval. We look forward to working with Akebia to bring vadadustat, upon approval, to our dialysis patients."

BLA Submitted for Fabry Disease Treatment

In a May press release, Protalix BioTherapeutics, Inc. announced the submission of a Biologics License Application (BLA) to the US FDA for pegunigalsidase alfa (PRX-102) for proposed treatment of adult patients with Fabry Disease; the BLA was submitted via the FDA's Accelerated Approval Pathway. In January 2018, the FDA granted Fast Track designation to PRX-102, a long-acting recombinant, PEGylated, cross-linked α-galactosidase-A investigational product candidate. Protalix is working with Chiesi Global Rare Diseases, a unit of Chiesi, an international research-focused healthcare group.

The BLA submission includes preclinical, clinical, and manufacturing data compiled from a completed phase 1/2 clinical trial, as well as data from the phase 3 BRIDGE switch-over study and safety data from ongoing clinical studies of PRX-102.

"We are grateful for the assistance the FDA provided leading up to the submission of this BLA via the Accelerated Approval pathway, and we look forward, together with Chiesi, to working with the FDA as we seek marketing approval for PRX-102," said **Dror Bashan,** president and CEO at Protalix. "Together with Chiesi, we thank our investigators and study participants who have made reaching this milestone possible and have supported Protalix in our commitment to bringing this new treatment option to the Fabry patient community."

Giacomo Chiesi, head of Chiesi Global Rare Diseases, said, "The submission of this BLA to the FDA represents a significant milestone for our Global Rare Diseases division that was established earlier this year to strengthen Chiesi's focus in making a difference for patients living with rare diseases around the world. Our partnership and active collaboration with Protalix are a great example showing how we can leverage Chiesi's global reach and decades of experience in drug development to support patients and their families living with Fabry disease and many other devasting rare diseases."

FDA Accepts NDA for Terlipressin for Hepatorenal Syndrome Type 1

The US FDA has accepted the New Drug Application (NDA) submitted by Mallinckrodt for terlipressin, an investigational agent being evaluated for the treatment of hepatorenal syndrome type 1 (HRS-1). On March 17, 2020, Mallinckrodt, an international biopharmaceutical company, announced the completion of its rolling submission of the NDA for terlipressin. The FDA assigned a Prescription Drug User Fee Act (PDUFA) target date of September 12, 2020.

HRS-1 is an acute and life-threatening syndrome involving acute kidney failure in patients with cirrhosis. HRS-1 has a median survival time of approximately 2 weeks and a greater than 80% mortality within 3 months if left untreated. There are currently no approved drug therapies for HRS-1 in the United States.

In a press release from Mallinckrodt, **Steven Romano, MD,** executive vice president and chief medical officer, said, "We are pleased that we received filing acceptance of our NDA submission. This is an important milestone in our clinical development program for terlipressin to address a critically high unmet need for patient with HRS-1 and their physicians, who historically have had limited treatment options. We look forward to working with the agency during their review of our regulatory package."

Phase 2 Study Announced by Alkahest, Inc.

Alkahest Inc. has announced the initiation of a phase 2 study (AKST1210-201) designed to explore the treatment of cognitive impairment in patients with end-stage renal disease (ESRD). Alkahest is a clinical stage biotechnology company focused on discovering and developing therapies to treat age-related diseases. The phase 2 study announced in a press release will examine the use of an extracorporeal medical device to remove excess Beta-2 microglobulin (B2M) from circulation to treat cognitive impairment in patients undergoing hemodialysis.

Karoly Nikolich, PhD, CEO of Alkahest, said, "A large proportion of individuals with end-stage renal disease who receive hemodialysis have cognitive impairment, which may be associated with reduced ability for self-care, poor adherence to dietary and fluid restrictions, and poor outcomes. Alkahest's preclinical research has demonstrated that Beta-2 microglobulin, which is present at higher levels in older individuals, is drastically elevated in patients undergoing dialysis and may contribute to the higher prevalence of cognitive impairment in these individuals. By reducing the amount of B2M in the plasma, we hope to introduce an effective way to lessen this impairment and allow patients on hemodialysis for ESRD to achieve improved treatment outcomes and quality of life."

AKST1210-201 is a randomized, double-blind, feasibility and tolerability study.

Top-Line Data from KALM-2 Phase 3 Trial

Positive top line data from the KALM-2 phase 3 trial of KORSUVA™ (CRb45/difelikefalin) Injection in hemodialysis patients with moderate-to-severe chronic kidney disease-associated pruritus (CKD-aP) were announced in the spring. The announcement was made by Cara Therapeutics, Inc. and Vifor Fresenius Medical Care Renal Pharma. The therapy achieved its primary end point, a key secondary end point, and was well tolerated with a safety profile consistent with that seen in KALM-1 and in the KORSUVA clinical program in patients with CKD-aP.

The primary end point was the proportion of patients on 0.5 mcg/kg KORSUVA Injection who achieved a three-point or greater improvement from baseline in the weekly mean of the daily 24-hour Worst Itching Intensity Numeric Rating Scale (WI-NRS) score at week 12. The results demonstrated that 54% of patients in the treatment group met the end point compared with 42% of those in the placebo group. In addition, 41% of patients in the treatment group had a four-point or greater improvement from baseline in the weekly mean of the daily 24-hour WI-NRS score at week 12 compared with 28% of those in the placebo group.

At present, there are no approved treatments for CKD-aP in the United States or Europe. Cara Therapeutics will submit a New Drug Application for KORSUVA Injection to the FDA in the second half of 2020 and will work with VFMRCP to submit for marketing approval to the European Medicines Agency shortly thereafter.

TRULO Registry Study Begins Patient Enrollment

Eurofins-Transplant Genomics had announced patient enrollment in the TRULO (TruGraf long-term clinical outcomes) registry study. TRULO is a prospective, multicenter observational registry study to evaluate post-transplant clinical outcomes in kidney transplant recipients who are undergoing serial TruGraf testing. Study results will provide long-term data, beyond 2 years post-transplant, on the benefits of non-invasive surveillance of stable kidney transplant recipients to identify silent subclinical rejection.

The post-transplant registry will include 2000 transplant patients from up to 50 transplant centers and will incorporate both TruGraf patient monitoring and TRAC™ donor-derived cell-free DNA measurements. The study aims to focus on long-term outcomes in kidney transplant recipients.

Fresenius Ships Acute Care Dialysis Solutions Under EUA

In a press release, Fresenius Medical Care North America's Renal Therapies Group announced the first shipment of multiBic dialysate solutions for use in continuous renal replacement therapy (CRRT) to support hospitals faced with CODIV-19 related increases in acute kidney injury (AKI). The US FDA granted Emergency Use Authorization (EUA) to the solutions and to the multiFiltrate PRO system for use in acute care settings during the COVID-19 pandemic.

Emerging evidence suggests that COVID-19 leads to multi-organ failure, including AKI, creating demands for CRRT far above normal levels. Fresenius has provided a supply of dialysis machines and solutions to hospitals nationwide.

Bill Valle, CEO of Fresenius Medical Care North America (FMCNA) said, "We appreciate the FDA's quick action in order to get these needed supplies and equipment into the US for emergency use to provide CRRT to treat more patients with acute kidney injury and to help save more lives. This is just one part of a larger effort to support continuous supply of critical care machines and dialysis solutions for our nation's hospitals."

Joe Turk, president of home and critical care therapies at FMCNA, added, "Since we first became aware of the increasing demand for dialysis due to COVID-19, we have been working diligently to support hospitals with the needed critical care equipment and supplies. While the early experiences in other geographies appear to be less challenging than in the New York metropolitan area, the option to support our nation's hospitals with these systems brought in under EUA will allow us to even better serve patients during this pandemic."

Fresenius Medical Care North America Donates to Food Is Medicine Coalition

Fresenius Medical Care North America (FMCNA) announced a $250,000 donation to the Food Is Medicine Coalition (FIMC). The coalition supports organizations across the United States that deliver medically tailored meals to individuals living with kidney disease. The COVID-19 pandemic has resulted in an increase in demand from patients struggling to manage their illness by attaining nutritious meals. The meals are delivered through a referral from a medical professional or healthcare plan.

Bill Valle, chief executive officer at FMCNA, said, "During the COVID-19 pandemic, many people living with chronic disease are feeling even more strained and unable to access the food they need to thrive. We are committed to addressing the growing demand for healthy food by helping provide medically tailored meals for people living with kidney failure."

Karen Pearl, president and CEO of God's Love We Deliver and chair of the Food Is Medicine Coalition, said, "The Food Is Medicine Coalition is deeply grateful to Fresenius Medical Care North America for their much needed and generous support during the COVID-19 pandemic. The nutritious meals the FIMC organizations provide are critical to all of our clients' health and well-being, and help them stay at home and out of the hospital where they are safest and most comfortable." ■

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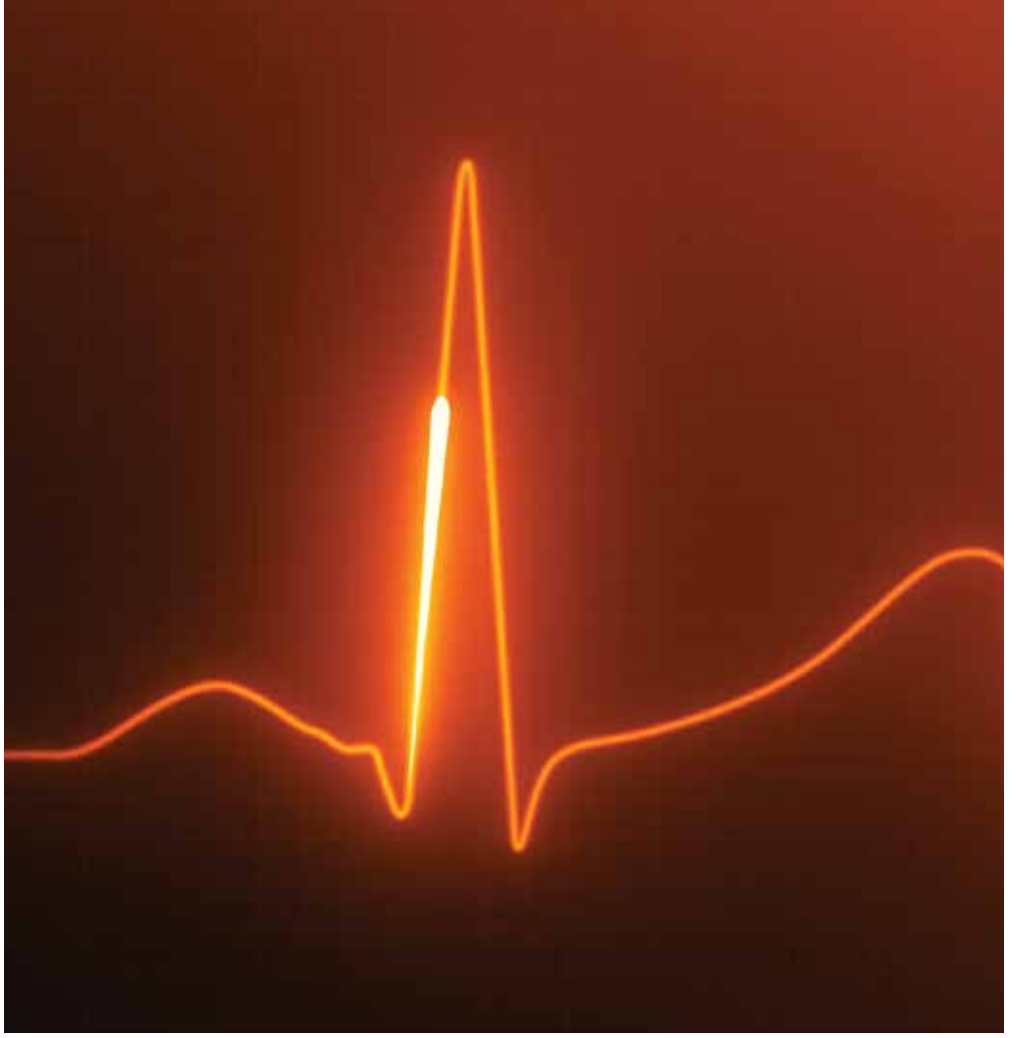
Abstract Roundup



CHRONIC KIDNEY DISEASE

CKD Progression and Clearance of Secretory Solutes

Journal of the American Society of Nephrology. 2020;31(4):817-827

The secretion of organic solutes by the proximal tubules is an essential intrinsic kidney function; however, the clinical significance of the kidney's clearance of tubular secretory solutes is unclear. **Yan Chen, PhD,** and colleagues conducted a prospective cohort study to examine that significance.

The cohort included 3416 participants with chronic kidney disease (CKD) from the Chronic Renal Insufficiency Cohort (CRIC) study. At baseline, the researchers measured plasma and 24-hour urine concentrations of endogenous candidate secretory solutes. CKD progression was defined as a ≥50% decline in estimated glomerular filtration rate (eGFR), initiation of maintenance dialysis, or kidney transplantation. Associations of secretory-solute clearances with CKD progression and mortality were tested using Cox proportional hazards regression following adjustments for eGFR, albuminuria, and other confounding characteristics.

Mean age of the participants was 58 years, 41% were black, and median eGFR was 43 mL/min/1.73 m^2. Following adjustment, there were associations between lower kidney clearances of six solutes (kynurenic acid, pyridoxic acid, indoxyl sulfate, xanthosine, isovalerylglycine, and cinnamoylglycine) with significantly increased risk of CKD progression. The strongest association of increased risk of disease progression was with kynurenic acid, a highly protein-bound solute. There were significant associations between lower clearances of isovalerylglycine, tiglylglycine, hippurate, and trimethyluric acid and all-cause mortality.

In conclusion, the researchers said, "We found lower kidney clearances of endogenous secretory solutes to be associated with CKD progression and all-cause mortality, independent of eGFR and albuminuria. This suggests that tubular clearance of secretory solutes provides additional information about kidney health beyond measurements of glomerular function alone."

Blood Pressure Patterns and Cognitive and Physical Functioning in CKD

Clinical Journal of the American Society of Nephrology. 2020;15(4):455-464

Patients with chronic kidney disease (CKD) commonly experience hypertension as well as cognitive impairment and frailty; however, there are few data available on the link between those complications. **Lama Ghazi, PhD,** and colleagues conducted a study to assess the association between ambulatory blood pressure patterns, cognitive function, physical function, and frailty among patients with nondialysis-dependent CKD.

The cohort included 1502 participants of the Chronic Renal Insufficiency Cohort (CRIC). Ambulatory blood pressure readings were obtained on the 1502 individuals. Blood pressure patterns (white coat, masked, sustained versus controlled hypertension) and dipping patterns (reverse, extreme, nondippers versus normal dippers) were evaluated.

Outcomes of interest were (1) cognitive impairment scores from the Modified Mini Mental Status Examination of <85, <80, and <75 for participants <65 years of age, 65 to 79 years of age, and ≥80 years of age, respectively, (2) physical function, measured by the short physical performance battery (SPPB), with higher scores (0-12) indicating better functioning, and (3) frailty measured by meeting three or more of the following: slow gait speed, muscle weakness, low physical activity, exhaustion, and unintentional weight loss.

Of the 1502 participants, mean age was 63 years, 56% were male, and 39% were black. At baseline, 129 had cognitive impairment and 275 were frail. Median SPPB score was 9. In the fully adjusted model, at baseline, participants with masked hypertension had 0.41 lower SPPB scores compared with those with controlled hypertension.

Over 4 years of follow-up, 529 participants had incident frailty and 207 had incident cognitive impairment. Following multivariable adjustment, there was no association between blood pressure or dipping patterns and incident frailty or cognitive impairment.

"In patients with CKD, dipping and blood pressure patterns are not associated with incident or prevalent cognitive impairment or prevalent frailty," the researchers said.

Effects of Phosphate Binders on Metabolism of Vitamin D

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Patients with chronic kidney disease with hyperphosphatemia are commonly treated with phosphate binders to lower phosphate levels. The effects of specific phosphate binders on vitamin D are unknown. **Charles Ginsberg, MD,** and colleagues conducted a secondary analysis of data from the Phosphate Normalization Trail.

The trial included patients with moderate to advanced CKD who were randomized to receive either placebo, sevelamer carbonate, lanthanum carbonate, or calcium acetate for 9 months. The current analysis was designed to examine changes in serum concentrations of vitamin D metabolites including 24,25-dihydroxyvitamin D3 [24,25(OH)2D3], 1,25-dihydroxyvitamin D3 [1,25(OH)2D3], the ratio of 24,25(OH)2D3 to 25-hydroxyvitamin D [the vitamin D metabolite ratio (VMR)] and the ratio of serum 1,25(OH)2D to 25-hydroxyvitamin D.

Compared with placebo, there was an association between randomization to calcium acetate and a 0.6 ng/mL (95% confidence interval [CI], 0.2-1) and 13.5 pg/ng (95% CI, 5.5-21.5) increase in 24,25(OH)2D3 and VMR, respectively, as well as a 5.2 pg/mL (95% CI, 1.1-9.4) reduction in 1,25(OH)2D. In the sevelamer carbonate arm, randomization was associated with a 0.5 ng/mL (95% CI, –0.9 to –0.1) and 11.8 pg/ng (95% CI, –20 to –3.5) reduction in 24,25(OH)2D3 and VMR, respectively. There was no association with the change in 1,25(OH)2D3. There was no association between randomization to lanthanum carbonate and a change in any of the vitamin D metabolites.

"Administration of different phosphate binders to patients with moderate to severe CKD results in unique changes in vitamin D metabolism," the researchers said.

DIALYSIS

Primary Care Physician Continuity of Care During Transition to Dialysis

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There are few available data on whether there is an association between primary care physician (PCP) continuity of care and a lower risk of death and hospitalization in a population of patients with end-stage renal disease transitioning to dialysis. **Samuel A. Silver, MSc, MD, FRCPC,** and colleagues conducted a population-based study of incident patients who initiated maintenance dialysis between 2005 and 2014 and survived for at least 90 days.

High PCP continuity of care was defined as (1) a high usual provider of care index (where >75% of PCP visits occurred with the same PCP) in the 2 years prior to dialysis initiation and (2) at least one visit with the same PCP in the 90 days following dialysis initiation. The primary outcome of interest was all-cause mortality; secondary outcomes included all-cause and disease-specific hospitalization during the 2 years following dialysis initiation.

Using provincial-linked administrative databases in Ontario, Canada, the researchers identified 19,099 eligible patients. Of those, 6612 patients had high PCP continuity; from that cohort, 97% (n=6391) were matched to 6391 patients with low PCP continuity. There was no association between high PCP continuity and a lower risk of mortality (14.5 deaths per 100 person-years vs 15.2 deaths per 100 person-years). There was no difference in the rate of all-cause hospitalization between the two groups. With the exception of hospitalizations related to diabetes, there was no association between high PCP continuity and a lower risk of any disease-specific hospitalization.

In conclusion, the researchers said, "High primary care physician continuity before and during the transition to maintenance dialysis was not associated with a lower risk of mortality of all-cause hospitalization."

Screening Tests for Cognitive Impairment in Dialysis Patients

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Results of neurocognitive testing suggest that cognitive impairment is common among patients receiving maintenance hemodialysis. Researchers, led by **David A. Drew, MD, MS,** sought to identify a well performing screening test for cognitive impairment to allow for broader assessment in dialysis facilities, leading to optimal delivery of education and medical management.

In a cohort of 150 patients on hemodialysis from 2015 to 2018, the researchers performed a set of comprehensive neurocognitive tests that included the domains of

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memory, attention, and executive function. The tests were designed to classify patients with normal cognitive function versus mild, moderate, or severe cognitive impairment. The predictive ability of the Mini Mental State Examination, the Modified Mini Mental State Examination, the Montreal Cognitive Assessment, the Trail Making Test Part B, the mini-Cog test, and the Digit Symbol Substitution Test was assessed using area-under-the-curve (AOC) analysis to determine the ability of each test to identify severe cognitive impairment.

Mean age of the cohort was 64 years, 61% were men, 39% were black, and 94% had at least a high school education. Of the 150 participants, 21% had normal cognitive function, 17% had mild cognitive impairment, 33% had moderate impairment, and 29% had severe impairment. The highest overall predictive ability for severe impairment was seen in the Montreal Cognitive Assessment (AUC, 0.81); a score of ≤21 had a sensitivity of 86% and specificity of 55% for severe impairment, with a negative predictive value of 91%.

The Trails B and Digit Symbol tests also performed reasonably well (AUC, 0.73 and 0.78, respectively). The predictive performances of the remaining tests were lower.

In summary, the researchers said, "The Montreal Cognitive Assessment, a widely available and brief cognitive screening tool, showed high sensitivity and moderate specificity in detecting severe cognitive impairment in patients on maintenance hemodialysis."

Print-only Content

HYPERTENSION

Prevalence of Blood Pressure Phenotypes among Hypertensive Adults

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Out-of-clinic blood pressure measurements are recommended in recent guidelines. **Stanford E. Mwasongwe, MPH, MDiv,** and colleagues performed an analysis to compare the prevalence of blood pressure phenotypes between 51 black patients, with and without chronic kidney disease (CKD), taking antihypertensive medications. Patients who underwent ambulatory blood pressure monitoring at baseline (between 2000 and 2004) in the Jackson Heart Study were eligible.

CKD was defined as an albumin-to-creatinine ratio ≥30 mg/g or estimated glomerular filtration rate (eGFR) ≤60 mL/min/1.73 m^2. Sustained controlled blood pressure was defined by blood pressure goal both inside and outside the clinic, and sustained uncontrolled blood pressure was defined as blood pressure above goal both inside and outside of the clinic. Masked uncontrolled hypertension was defined by controlled clinic-measured blood pressure with uncontrolled out-of-clinic blood pressure.

There was an association between CKD and a higher multivariable-adjusted prevalence ratio for uncontrolled versus controlled clinic blood pressure (prevalence ratio, 1.44; 95% confidence interval [CI], 1.02-2.02) and sustained uncontrolled blood pressure versus sustained controlled

blood pressure (prevalence ratio, 1.66; 95% CI, 1.16-2.36). Following multivariable adjustment, there were no statistically significant differences between the group with CKD and the group without CKD in the prevalence of uncontrolled daytime or nighttime blood pressure, nondipping blood pressure, white-coat effect, and masked uncontrolled hypertension.

There was an association between reduced eGFR and masked uncontrolled hypertension versus sustained controlled blood pressure (prevalence ratio, 1.42; 95% CI, 1.00-2.00). There was an association between albuminuria and uncontrolled clinic blood pressure (prevalence ratio, 1.76; 95% CI, 1.20-2.60) and sustained uncontrolled blood pressure versus sustained controlled blood pressure (prevalence ratio, 2.02; 95% CI, 1.36-2.99).

In summary, the authors said, "The prevalence of blood pressure phenotypes defined using ambulatory blood pressure monitoring is high among adults taking antihypertensive medication."

PEDIATRIC NEPHROLOGY

Elevated Blood Pressure Load as Predictor of Adverse Outcomes

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Elevated blood pressure load is part of the criteria for ambulatory hypertension in pediatric, but not adult, guidelines. **Jason Lee, MD,** and colleagues conducted a study to examine the prevalence of isolated blood pressure load elevation and the associated risk with adverse outcomes in children with chronic kidney disease (CKD). The researchers also sought to determine whether blood pressure load offers risk determination independently or in conjunction with mean ambulatory blood pressures.

The study included 533 children in the CKD in Children (CKiD) study. Blood pressure load elevation was defined as ≥25% of all readings elevated but mean blood pressure normal. The analysis examined the prevalence of normotension, isolated blood pressure load elevation, and ambulatory hypertension.

Isolated blood pressure load elevation was present in 23% of the cohort. There was no statistically significant association between isolated blood pressure load elevation and left ventricular hypertrophy (LVH) in cross-section (odds ratio, 1.8; 95% confidence interval [CI], 0.8-4.2) or time to end-stage renal disease (ESRD) (hazard ratio, 1.2; 95% CI, 0.7-2.0). In unadjusted cross-sectional analysis, there was an association between every 10% higher systolic blood pressure load and 1.1-times higher odds of LVH but discrimination for LVH was poor. In unadjusted longitudinal analysis, there was an association between every 10% higher systolic blood pressure load with a 1.2-times higher risk of ESRD, but discrimination for ESRD was also poor.

There was no statistically significant association between systolic blood pressure load and either LVH or ESRD after accounting for mean systolic blood pressure load. Findings were similar with diastolic blood pressure load.

"Blood pressure load does not provide additive value in discriminating outcomes when used independently or in conjunction with mean systolic blood pressure in children with CKD," the authors said.

TRANSPLANTATION

Vitamins D and K Status and Long-Term Outcomes in Transplant Recipients

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Compared with dialysis, kidney transplantation confers substantial survival benefits to patients with end-stage renal disease. However, the risk of mortality and graft failure remains high. Recipients of kidney transplant may be deficient in micronutrient status, including vitamins D and K. **Adriana J. van Ballegooijen, PhD,** and colleagues conducted a study to examine the association between vitamins D and K status and vitamin D treatment with all-cause mortality and death-censored graft failure.

The study included 461 kidney transplant recipients at a single center at a median of 6.1 years following transplantation. Baseline concentrations of vitamins D and K were measured by 25-hydroxyvitamin D [25(OH)D] and dephosphorylated uncarboxylated matrix gla protein (dp-ucMGP). Patients were stratified into 25(OH)D <50/≥50 nmol/L and median dp-ucMGP <1057/≥1057 pmol/L.

Mean age of the study cohort was 52 years. Of the 461 kidney transplant recipients, 26% (n=122) had low vitamins D and K status. During a median of 9.8 years of follow-up, 28% of patients (n=128) died and 10% (n=48) developed death-censored graft failure.

There was an association between low vitamins D and K status with increased mortality risk (hazard ratio [HR], 2.33; 95% confidence interval [CI], 1.26-4.30) and increased risk of graft failure (HR, 3.25; 95% CI, 1.17-9.08) compared with kidney transplant recipients with 25(OH)D ≥50 mmol/L and dp-ucMGP <1057 pmol/L, respectively.

There was a strong association between dp-ucMGP and mortality (per 500 pmol/L increase): HR, 1.41, 95% CI, 1.08-1.41 for vitamin D treatment versus HR, 1.07; 95% CI, 0.97-1.18 for no vitamin D treatment, and graft failure (HR, 1.71; 95% CI, 1.17-2.49 for vitamin D treatment vs HR, 1.19; 95% CI, 1.05-1.36 for no vitamin D treatment).

In conclusion, the researchers said, "Combined vitamins D and K deficiency are highly prevalent and are associated with increased mortality and graft failure risk compared with high vitamins D and K status. Low vitamin K status was strongly associated with increased risk of premature mortality and graft failure for patients treated with vitamin D versus no vitamin D treatment." ■

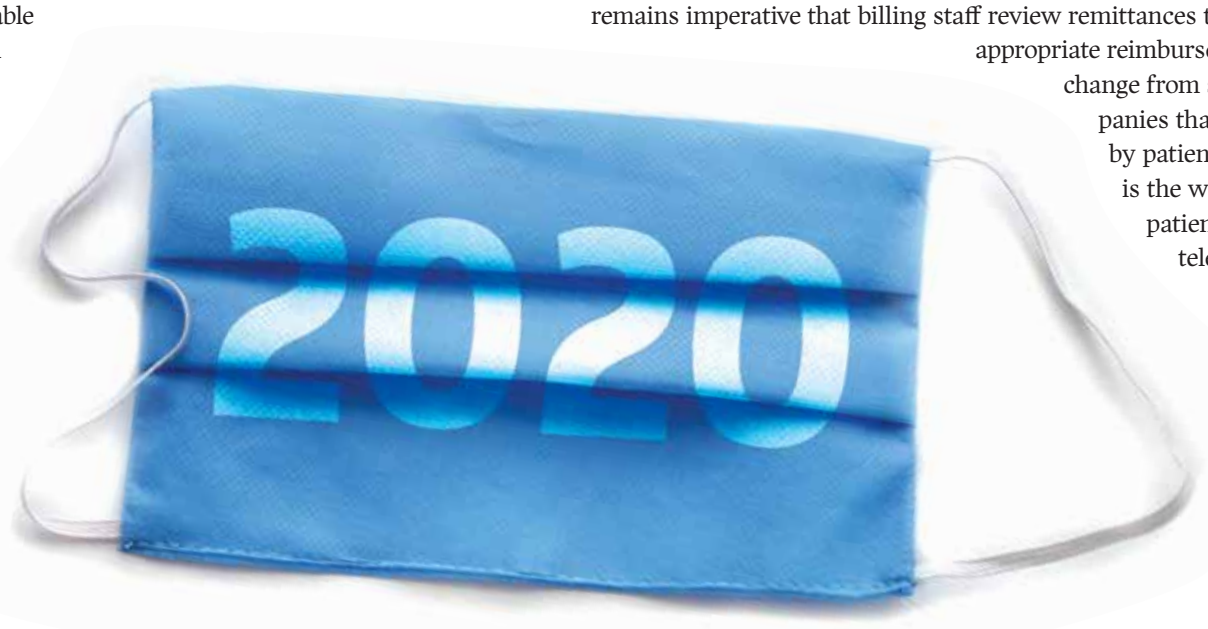
Print-only Content

Sarah Tolson

A Year of Change

The year 2020 has been a year of fast, sweeping changes. At the time of this writing, many places in the United States are seeing spikes in COVID-19 cases and considering reverting to stringent lockdown protocols. Since the last column, the company I work for, Sceptre Management Solutions, along with many other billing companies, has transitioned from a traditional brick and mortar workplace to employees working from home. This change has allowed Sceptre Management and other billing companies continue to maximize revenue for our clients while complying with state health department guidelines.

Physician offices and dialysis facilities alike have been scrambling to provide their patients with the best possible care, minimize the risk of exposure to COVID-19 for both patients and caregivers, and comply with ever-changing state and federal safety guidelines during this public health emergency. Insurance companies have also made changes to facilitate contact-free access to healthcare for their members. Medicare released a list of 239 Current Procedural Terminology (CPT) codes that are payable under the Medicare Physician Fee Schedule when they are furnished via telehealth. Most insurance companies have followed Medicare's lead and expanded their list of covered telehealth services to allow patients more flexibility in accessing healthcare. Now, more than any time in our history, people are receiving healthcare via telehealth.



Along with all the changes in covered services, there have been changes in the billing requirements for telehealth services. Now, it is critical to stay up to date on billing regulations and requirements. Not only has the number of patient visits dwindled in many practices, but staff being unfamiliar with current telehealth billing requirements can result in a loss of revenue. There are three steps that can be followed by billing staff to ensure maximum reimbursement is obtained for telehealth services during this time of change.

STEP 1. STAY CURRENT ON BILLING REQUIREMENTS

The first step to obtaining maximum reimbursement for telehealth services is to stay up to date on the billing requirements for all the insurance companies you submit claims to. Many payers send updates via email while others maintain bulletin boards on their website. Whatever the distribution method, read all the updates released by the payers you submit claims to as the updates become available.

STEP 2. COMMUNICATE BILLING AND COVERAGE INFORMATION WITH ALL BILLING STAFF

When it comes to billing and reimbursement, knowledge is power. Ensuring a more cohesive approach to capturing reimbursements requires educating all team members who deal with telehealth billing regarding the services covered via telehealth and coverage requirements for each insurance company. For example, some insurance companies are waiving copays for telehealth visits. Educating your patient collection team about which insurance companies are waiving copays and which ones are not will help them collect copays when needed and avoid unnecessary overpayments from patients.

STEP 3. REVIEWING REMITTANCES FOR CORRECT REIMBURSEMENT

While most insurance companies have made sweeping policy changes to allow for more flexibility for patients and providers in regard to telehealth services as well as some increases in reimbursement for certain telehealth services, it remains imperative that billing staff review remittances to ensure receipt of appropriate reimbursement. One coverage change from some insurance companies that has been welcomed by patients and providers alike is the waiver of copays and patient liabilities for some telehealth services. The challenge billing staff encounter with this reimbursement change is that when the payer processes the claims, although the payer's policy states copays have been waived, the remittance may show that the patient was assessed a copay. To correct the error, the biller must call the payer and request the claim be processed according to the payer's updated policy. Copays are so commonplace that it would be easy for a biller to overlook a claims processing error such as this. Knowledge of and familiarity with each payer's policies and a process to review remittances for accuracy are imperative to ensure billing staff are capturing all available reimbursement for your practice. ■

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