Nephrology Times

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Cardiovascular Outcomes in CKD: Women versus Men

Cardiovascular disease is the leading cause of death among individuals with chronic kidney disease (CKD). Results of previous epidemiologic studies of non-CKD populations demonstrated that the incidence of cardiovascular events is lower in women than in men, and that women have longer survival compared with men. Those results have been attributed to a more favorable cardiovascular risk profile among women and to other biological differences including sex hormone levels, estrogen in particular. Thus, sex-specific guidelines for prevention of cardiovascular disease have been in place for the past 20 years.

However, according to **Stephanie M. Toth-Manikowski, MD, MHS,** and colleagues, among a population of patients in the United States receiving maintenance dialysis, women have only a slightly lower risk of death compared with men. The researchers conducted a prospective cohort study to assess sex-related differences (women vs men) in different types of cardiovascular events and death in the CRIC (Chronic Renal Insufficiency Cohort) study. Results were reported in the *American Journal of Kidney Diseases* [2021;78(2):200-209].

The outcomes of interest were an atherosclerotic composite (myocardial infarction, stroke, or peripheral artery disease), incident heart failure, cardiovascular death, and all-cause death. Cox proportional hazards regression

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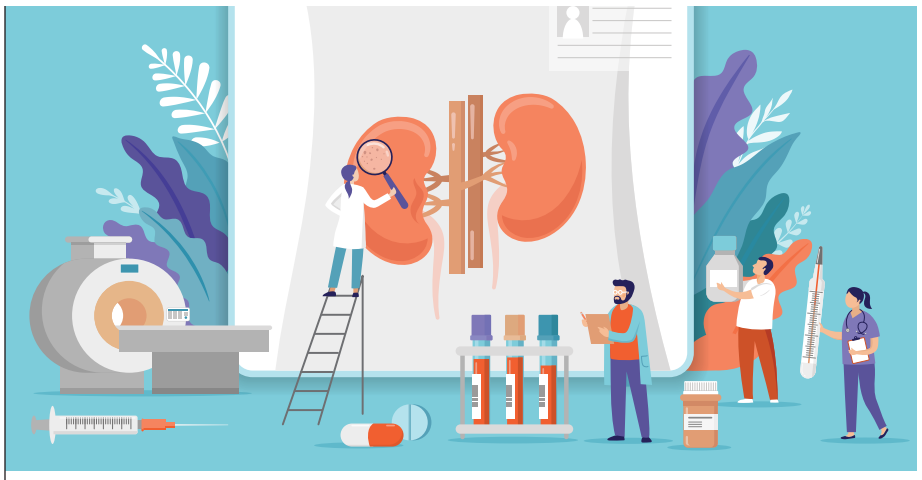

Combination of Changes in UACR and eGFR as Predictor of Kidney Outcomes

Because kidney failure commonly develops over a long period of time, researchers designing and conducting randomized trials in nephrology face specific challenges; studies that seek to examine effects on the outcome of kidney failure require substantial follow-up time.

Previous kidney trials have used changes in estimated glomerular filtration rate (eGFR) and albuminuria separately as alternative outcomes. However, there are few data available on the utility of combining change in albuminuria and change

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Socioeconomic Status and Markers of Subclinical Cardiovascular Disease in Children with CKD

Adult and pediatric patients with chronic kidney disease (CKD) are at high risk for cardiovascular disease-related morbidity and mortality. Results of previous studies indicate that African American adults with CKD are at higher risk of cardiovascular disease-related morbidity and mortality than White adults with CKD. In children with CKD, lower socioeconomic status may worsen patient and family stress, anxiety, and depression, making it difficult to adhere to medical regimens, In addition, socioeconomic factors such as low household income have been associated with other adverse health indicators such as poorer growth in children with CKD. African Americans face chronic stress associated with systemic racism, affecting health through changes in psychological, physiological, and behavioral pathways.

There are few data available on the association between race and social determinants of subclinical cardiovascular health among children with CKD. **Kristen Sgambat, PhD,** and colleagues conducted a study to examine differences in socioeconomic factors and subclinical cardiovascular disease markers by race among participants in the CKiD (Chronic Kidney Disease in Children) study and whether differences in cardiovascular disease markers persist following adjustment for socioeconomic factors. The researchers also sought to test the hypothesis that racial differences in CKD may vary according to CKD diagnosis due to risk factors

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CKD and the Long-COVID Syndrome

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Approximately 221 million people worldwide have been diagnosed with infection from SARS-CoV-2, the virus that causes COVID-19.[1] In the United States alone there have been over 40 million cases and nearly 650 thousand deaths (as of September 2021).[1] The Centers for Disease Control and Prevention (CDC) uses the term "post-COVID conditions" to describe health issues that persist >30 days after a person is first infected with SARS-CoV-2.[2] These CDC post-infection categories include long COVID, multiorgan effects of COVID, and longer-term effects of COVID-19 treatment or hospitalization.

Long COVID is a syndrome of lingering health effects of COVID. It is characterized by varied symptoms, including fatigue, sleep disorder, difficulty concentrating (brain fog), headache, loss of smell or taste, palpitations, chest pain, cough and shortness of breath, joint or muscle pain, and mental health issues such as depression and anxiety. The causes of long COVID are still unclear, although there are several hypotheses, including long-term effects of endothelial cell damage, ongoing infection, and autoimmune effects. Estimates from the UK's Office of National Statistics (ONS), point to a prevalence of long COVID of about 21% at 5 weeks and 10% at 12 weeks from onset of COVID-19.[3]

While kidney involvement is a well-recognized complication of acute COVID-19, kidney sequelae as a component of the long COVID syndrome has not been previously reported. A recent publication by **Benjamin Bowie** and colleagues in the *Journal of the American Society of Nephrology (JASN)*[4] has skillfully documented a significant burden of kidney disease among survivors after 30 days of infection with the SARS-CoV-2 virus. This study should set off alarm bells for both clinicians and policy workers.

Alarm bells for clinicians because there could be a staggering clinical burden for nephrologists in the wake of the COVID pandemic, and for policy makers because resources will need to be rapidly identified to expand kidney services and funding at a health system, and, more broadly, at a country level, if millions need care for complications of kidney disease, including dialysis and transplantation.

The paper by Bowie and colleagues assembled a large cohort of subjects (89,216 30-day COVID-19 survivors and 1,637,467 non-infected controls). They examined the risks of acute kidney injury (AKI), decline in estimated glomerular filtration rate (eGFR), end-stage kidney disease (ESKD), and major adverse kidney events (MAKE), defined as eGFR decline ≥50%, ESKD, or all-cause mortality in the 30 days post-acute COVID infection (the long COVID phase). They defined infection as testing positive for COVID. Sophisticated methods were used to reduce the influence of confounders and to characterize intra-individual eGFR trajectory. They also looked at outcomes based on whether patients were non-hospitalized, hospitalized, and admitted to intensive care. They excluded patients who had a prior history of ESKD or developed ESKD in the acute phase of COVID-19 (30 days immediately following the positive test for COVID-19). They report a markedly increased risk of AKI, eGFR decline, ESKD, and the composite endpoint of eGFR decline ≥50%, ESKD, or all-cause mortality.

The data were especially concerning for the increased risk of AKI (adjusted hazard ratio [aHR], 1.94, 95% confidence interval [CI], 1.86-2.04), and of ESKD (aHR, 2.96, 95% CI, 2.49-3.51). The rate of eGFR loss correlated with the severity of COVID infection, and whether patients were hospitalized (worse among those who hospitalized and developed AKI as part of their acute COVID infection (–8.41 [95% CI, –9.72 to–7.10] ml/min/1.73 m^2 per year in those hospitalized with an AKI).

The Bowie study has several limitations, including generalizability—only men in the VA system and in the United States were evaluated, and no individual data, such as urine data, were examined in evaluating AKI. Additionally, while the authors used established and valid statistical methods to reduce the potential effect of confounding, they could not exclude it completely. All that said, the study was a remarkably well-conducted analysis and that has three implications.

First, if the study result is generalized, then the sheer number of individuals who might have some form of kidney involvement is staggering. This will need to be factored into the developing of future healthcare infrastructure for taking care of patients with

kidney disease. The authors suggest integrated multidisciplinary post-COVID clinics. This has already been implemented in many parts of the world: Ireland[5], Egypt[6], and in the United States in the form of post-COVID care centers (PCCC).[7,8] This conventional approach is time-consuming and potentially expensive. Novel alternatives have been proposed, including using artificial intelligence deep learning algorithms (DLA) to screen patients for CKD. Data to support this approach with retinal photographs were published by **Sabanayagam** and colleagues in *Lancet Digital Health*.[9] Data mining electronic medical records could be the future.

Second, research into understanding the mechanistic factors associated with this increased risk of kidney involvement needs to be pursued with great urgency. So far, the cause(s) for long COVID have proven elusive. Important questions need answers: Is persistent subclinical SARS-CoV-2 infection the cause of kidney involvement in long COVID? What risk factors increase the likelihood of kidney disease? What is the role of social determinants in increasing this risk?

Third, if the number of patients requiring dialysis dramatically increases because of the long-term effects of COVID-19, the cost of taking care of additional patients will need to be planned. Stage 4 and 5 CKD costs more than USD 45,000 each year and the cost increases as patients transition onto dialysis (in the United States more than USD 90,000 per year).[10]

In summary, the Bowie study was well done and should ring alarm bells, because of its potential impact on patient care and planning for healthcare resources and funding. ■

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Combination of Changes in UACR and eGFR

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in eGFR as a surrogate for progression to kidney failure. **Brendon L. Neuen, MBBS (Hons.), MSc,** and colleagues conducted a study to test the hypothesis that combined changes in urinary albumin-creatinine ratio (UACR) and eGFR would predict advanced kidney disease more accurately than either measurement alone. Results of the study were reported in the *American Journal of Kidney Diseases* [2021;78(3):350-360].

The primary outcome of the observational cohort study was advanced CKD, defined as sustained eGFR <30 mL/min/1.73 m^2. Secondary outcomes were kidney failure, cardiovascular disease, and all-cause mortality. Study participants were primary care patients gathered from the Clinical Practice Research Datalink in the United Kingdom between 2000 and 2015. Exposures were changes in UACR and eGFR (categorized as ≥30% increase, stable, or ≥30% decrease), alone and in combination, over a 3-year period.

A total of 91,319 individuals had paired UACR and eGFR assessments over an approximate 3-year esposure window. Mean interval times between UACR and eGFR assessments were 8 days at the beginning of the exposure ascertainment period and 3 days at the end of the exposure ascertainment period. Mean age of the cohort was 65.0 years, 43.4% (n=39,613) were women, and 77.7% (n=70,957) had diabetes.

Mean eGFR at baseline was 72.6 mL/min/1.73 m^2, and median UACR was 9.7 mg/g. Median follow-up was 2.9 years. During follow-up, 2541 participants progressed to advanced CKD and kidney failure occurred in 379 participants. A total of 7185 developed cardiovascular disease and 9853 died.

Over the 3-year exposure window, 20.0% of participants (n=18,238) experienced a ≥30% decrease in UACR, 52.6% (n=48,008) had a stable UACR, and 27.5% (n=25,073) experienced a ≥30% increase in UACR. Four point six percent of participants (n=4246) experienced a 30% increase in eGFR, 90.3% (n=82,477) had stable eGFR, and 5.0% (n=4596) experienced a ≥30% decrease in eGFR.

Those in the group with greater increases in UACR were more likely to be older and to have a lower baseline eGFR and UACR, a history of cardiovascular disease, and more use of renin-angiotensin system (RAS) blockade and other antihypertensive medication (all $P<.001$). Those with greater decreases in eGFR were older, had higher baseline UACR and blood pressure, and were more likely to have a history of cardiovascular disease and greater use of RAS blockade and other antihypertensive medications (all $P<.001$).

There was an association between increases in UACR and greater risks of advanced CKD and kidney failure. Compared with those with stable UACR, the hazard ratios (HRs) for a ≥30% increase in UACR were 1.78 (95% confidence interval [CI], 1.59-1.98) for advanced CKD and 4.16 (95% CI, 2.74-6.32) for kidney failure. There were also associations between reductions in UACR and a decreased risk of kidney outcomes: the HRs for a ≥30% decrease in UACR were 0.77 (95% CI, 0.68-0.87) for advanced CKD and 0.46 (95% CI, 0.26-0.84) for kidney failure. There were associations between increases and decreases in UACR and greater and lesser risk of cardiovascular disease and all-cause mortality, respectively; the magnitude of those associations was smaller than those for kidney outcomes.

There were strong associations between decreases in eGFR and the risk of advanced CKD and kidney failure. The HRs for a ≥30% decrease in eGFR for advanced CKD and kidney failure were 7.53 (95% CI, 6.70-8.445) and 5.09 (95% CI, 3.27-7.92), respectively. Increases in eGFR were associated with substantially lower risk of advanced CKD and kidney failure. Decreases in eGFR were associated with a risk for cardiovascular disease and all-cause mortality that was lower than the risk for kidney outcomes. There were no associations between increases in eGFR and lower risk of cardiovascular disease. Both increases and decreases in eGFR were associated with greater risk of all-cause mortality.

Compared with participants with stable UACR and eGFR, there was an association between a combined increase in UACR and eGFR and increased risk of kidney, cardiovascular, and mortality outcomes. The magnitude of the association was greatest for kidney outcomes. Compared with participants with stable values, the HR for a combined increase in UACR and a decrease in eGFR for advanced CKD was 15.15 (95% CI, 12.43-18.46). The corresponding HR for kidney failure was 16.68 (95% CI, 7.80-35.69).

Combined changes in UACR and eGFR improved the discrimination of advanced CKD better than either alone; the magnitude of the improvement was greater when change in eGFR was added. Combined exposure changes also improved discrimination for kidney failure better than either alone. Combined changes in UACR and eGFR also provided statistically significant improvements in discrimination for cardiovascular disease and all-cause mortality; the changes were of smaller magnitude than those for kidney outcomes.

Limitations to the study cited by the authors included possible selection bias, the relatively small proportion of participants without diabetes, and very few kidney failure events.

In summary, the researchers said, "In a large-scale general population, the combination of increased UACR and decreased eGFR was strongly associated with risk of advanced CKD. Further assessment of combined changes in UACR and eGFR as an alternative outcome for kidney failure in trials of CKD progression is warranted." ■

TAKEAWAY POINTS

- Results of an observational cohort study to test the hypothesis that combined changes in urinary albumin-creatinine ratio (UACR) and estimated glomerular filtration rate (eGFR) predict advanced kidney disease better than either alone.
- There was a strong association between an increase in UACR and a decrease in eGFR with the risk of advanced chronic kidney disease.
- The combination of changes in UACR and eGFR predicted kidney outcomes better than either alone.

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exclusively related to glomerular disease, including proteinuria, dyslipidemia, and exposure to immunosuppressants. Study results were reported in the *American Journal of Kidney Diseases* [2021;78(1):66-74].

The outcomes of interest were ambulatory hypertension, left ventricular mass index (LVMI), triglycerides, and high-density lipoprotein (HDL) cholesterol. Eligible participants were children with mild-to-moderate CKD with at least one cardiovascular parameter measurement (ambulatory blood pressure, LVMI, or lipid profile).

The analysis was stratified by cause of CKD. Socioeconomic status (health insurance, household income, maternal education, food insecurity, abnormal birth history) was adjusted using inverse probability weighting. The association between race and cardiovascular markers was assessed using linear and logistic regression.

Of the 1032 participants in the CKiD study, 174 were excluded for self-report of a race other than White or African American, and another 230 were excluded for missing outcomes of interest, or not meeting age or estimated glomerular filtration rate (eGFR) inclusion criteria. The final cohort for the present analysis included 3103 visits from 628 children. At baseline, median age was 10.7 years and median eGFR was 43.2 mL/min/1.73 m^2. Of the 628 children, 20.8% were African American and 26.3% had glomerular CKD.

Regardless of the cause of CKD, African American children had shorter lengths of study follow-up than White children (median, 4.4 years vs 5.2 years for nonglomerular CKD and 2.6 vs 3.7 years for glomerular CKD). Among the 463 children with nonglomerular CKD, 383 were White and 80 were African American. Of the 165 children with glomerular CKD, 114 were White and 51 were African American.

The proportion of adverse socioeconomic characteristics was greater among African American children than among White children regardless of CKD cause. African American children were more likely to have public health insurance, food insecurity, and abnormal birth history, in addition to lower maternal education and household income. There were no differences between the two groups in household smoking. Among African Americans, maternal age <18 years was more prevalent in the glomerular cohort; there was no significant difference by race in the cohort with nonglomerular CKD.

Use of angiotensin-converting enzyme inhibitor/angiotensin II receptor blocker (ACEi/ARB) was higher among White children in the nonglomerular group than among African American children (45% vs 33%, respectively; *P*=.04). The same pattern was

nominally present in the group with glomerular CKD (85% vs 78%, respectively) but did not reach statistical significance. Regardless of the CKD cause, obesity was more prevalent among African American children.

Rates of immunosuppressive medication, nephrotic-range proteinuria, and higher urinary protein-to-creatinine ratio were higher among participants with glomerular CKD; the nonglomerular group was more likely to be diagnosed with CKD at birth.

In the nonglomerular CKD cohort, prior to and after adjusting for socioeconomic status, age, and sex, there was a significant association between African American race and a more favorable lipid profile (lower triglycerides and higher HDL cholesterol); the magnitude of the differences was attenuated in the adjusted models for triglycerides and HDL cholesterol. African American race was associated with significantly higher odds of ambulatory hypertension prior to and after adjusting for socioeconomic status, age, and sex; the magnitude of the difference was attenuated in the model adjusted for socioeconomic status, age, and sex, but the difference remained statistically significant. LVMI was significantly higher among African Americans than among White participants.

In the glomerular CKD group, there was a significant association between African American race and higher LVMI in both the unadjusted (20.6%) and adjusted (32.1%) models (*P*<.001). There were no statistically significant differences in ambulatory hypertension, triglycerides, or HDL cholesterol between African American and White participants in the unadjusted or adjusted models in the glomerular CKD group.

The researchers conducted an additional ad hoc model in a subset of 828 visits of 366 children who had both LVMI and ambulatory blood pressure monitoring performed at the first follow-up visit to determine if racial differences in LVMI persisted following additional adjustments for ambulatory hypertension.

In the nonglomerular CKD group, African American children had 12.1% (unadjusted; *P*=.001) higher LVMI than White children; in the subset with LVMI and ambulatory blood pressure monitoring, African American children had 13.1% higher LVMI than White children (unadjusted; *P*=.009). In the ad hoc analysis, there was a nominal association between African American race and higher LVMI following adjustment for socioeconomic status, age, sex, and ambulatory hypertension; the association was not statistically significant.

In the glomerular CKD group, LVMI was 20.6% higher in African American children compared with Whites (unadjusted; *P*<.001); in the subset, the percentage in African American children was 16.4% (unadjusted; *P*=.009). Following adjustments, the association between African American race and higher LVMI remained statistically significant (23.0%; *P*=.004).

In citing limitations to the findings, the researchers noted that the study design limited causal inference.

In conclusion, the authors said, "African American children are disproportionately affected by socioeconomic disadvantages compared with White children. The degree to which cardiovascular markers differ by race is influenced by etiology of CKD. African Americans with nonglomerular CKD have increased LVMI, more ambulatory hypertension, and more favorable lipid profile, but the magnitude of these differences appears slightly attenuated after adjustment for socioeconomic status. African American children with glomerular CKD have increased LVMI but exhibit similar lipid profiles and ambulatory hypertension compared with White children before and after adjustment for the socioeconomic status factors included in this analysis. Further research should use more sensitive measurements of subclinical cardiovascular dysfunction and focus on investigating elements of racism as determinants of cardiovascular health in children with CKD." ■

TAKEAWAY POINTS

- Researchers reported results of an analysis to identify differences in socioeconomic factors and subclinical cardiovascular disease markers by race among participants in the Chronic Kidney Disease in Children study.
- The analysis was stratified by CKD cause: glomerular CKD and nonglomerular CKD.
- African American children were disproportionately affected by adverse socioeconomic factors compared with White children. The degree to which cardiovascular markers differ by race was influenced by disease etiology.

CV Outcomes in CKD

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models were used to examine the association between sex and each outcome, stratified by clinical site and adjusted for key sociodemographic and clinical variables.

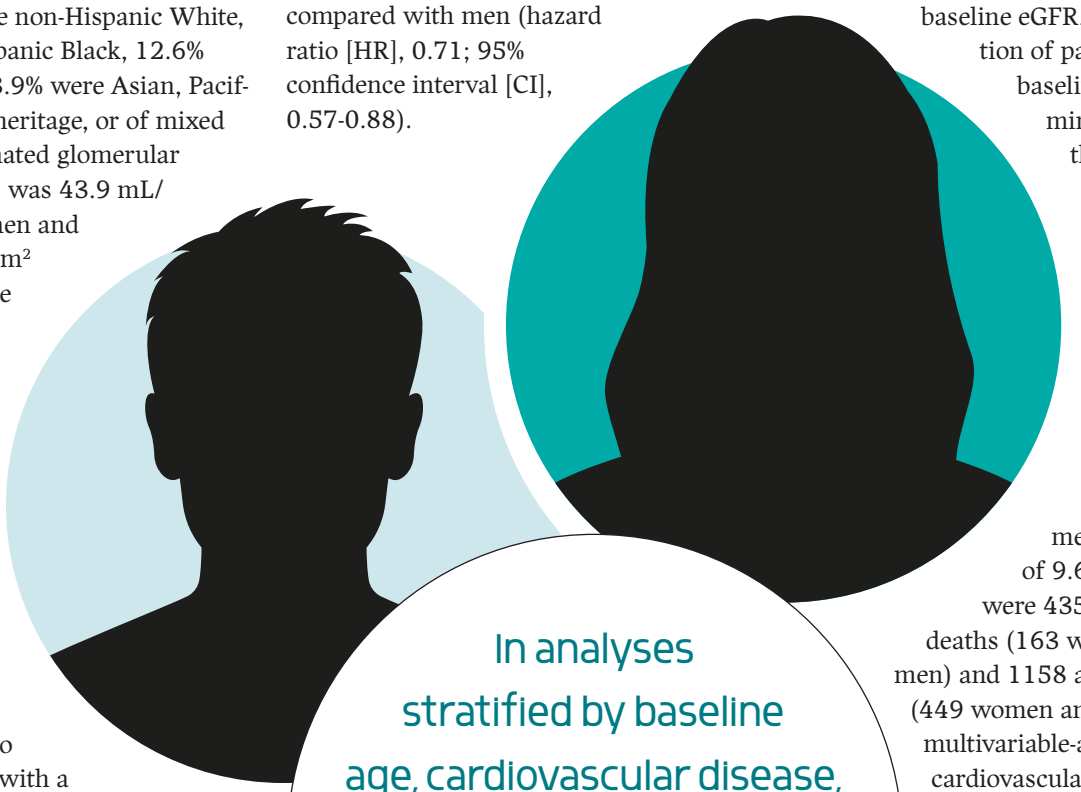
The study cohort included 3939 eligible participants in the CRIC study. Of those, 45% (n=1778) were women and 55% (n=2161) were men, with a mean age of 58 years at study entry. Of the 3939 participants, 41.5% were non-Hispanic White, 41.8% were non-Hispanic Black, 12.6% were Hispanic, and 3.9% were Asian, Pacific Islander, of other heritage, or of mixed heritage. Mean estimated glomerular filtration rate (eGFR) was 43.9 mL/min/1.73 m^2 in women and 45.87 mL/min/1.73 m^2 in men. Median urine protein excretion was 113 mg/d in women and 268 mg/d in men.

The women were more likely than the men to be of a racial/ethnic minority subgroup and to have less than a high school education, and less likely to be married or living with a partner, to have seen a nephrologist in the past, to have a family history of coronary heart disease, or to report a prior history of cardiovascular disease. Women were also less likely to report regular physical activity and more likely to have never smoked. Women were more likely than the men to have higher levels of high-sensitivity C-reactive protein (hs-CRP) and N-terminal pro ß-natriuretic peptide (NT-proBNP) and lower levels of high-sensitivity troponin T (hs-TnT). Women were also less likely to report the use of angiotensin-converting enzyme inhibitor/angiotensin receptor blocker, ß-blocker, aspirin, and statin.

A total of 460 participants (252 men and 208 women) were excluded from multivariable regression analyses due to missing covariate data. Compared with those included in the final regression model, excluded participants were less likely to be non-Hispanic White and have a high school education or greater. The two groups were similar in baseline eGFR, median proteinuria, and all other clinical characteristics.

Median follow-up was 8.9 years. During follow-up, there were 698 atherosclerotic events (264 in women and 434 in men). The majority of those events were myocardial infarction events (163 in women, 247 in men). The rates of the atherosclerotic composite outcome events were lower in women than in men (1.9/100 person-years vs 2.7/100 person-years, respectively). The rates of myocardial infarction, stroke, and peripheral artery disease were lower in women than in men.

Following adjustment for sociodemographic characteristics, baseline kidney function, and clinical and laboratory characteristics, results of regression models demonstrated that women experienced 29% lower risk of atherosclerotic events compared with men (hazard ratio [HR], 0.71; 95% confidence interval [CI], 0.57-0.88).



In analyses stratified by baseline age, cardiovascular disease, and eGFR, the risk of the atherosclerotic composite outcome was lower in women than in men.

The risk of atherosclerotic composite events remained lower among women following adjustment for hs-CRP (HR, 0.70; 95% CI, 0.56-0.86), NT-proBNP (HR, 0.70; 95% CI, 0.56-0.86), hs-TnT (HR, 0.76; 95% CI, 0.62-0.95), or time-updated eGFR (HR, 0.69; 95% CI, 0.55-0.86). The association of sex with myocardial infarction and stroke was in the same direction but not statistically significant.

In analyses stratified by baseline age, cardiovascular disease, and eGFR, the risk of the atherosclerotic composite outcome was lower in women than in men. There was no evidence of interaction between sex and race/ethnicity or diabetes status.

There were 762 heart failure events during a median follow-up of 8.8 years (331 women and 431 men). The rates of heart failure were lower in women than in men (2.4/100 person-years vs 2.7/100 person-years, respectively). In multivariable analysis, the risk of heart failure was 26% lower in women than in men (HR, 0.74; 95% CI, 0.60-0.92). Following adjustment for hs-CRP, NT-proBNP, or time-updated eGFR, the association remained statistically significant. When hs-TnT was added to the model, the association was in the same direction, but not statistically significant.

Results were similar in analyses stratified by age, cardiovascular disease, and baseline eGFR, with the exception of participants with baseline eGFR <30 mL/min/1.73 m^2, where the risk of heart failure in men and women was similar. There was no evidence of interaction between sex and race/ethnicity or diabetes status.

During a median follow-up of 9.6 years, there were 435 cardiovascular deaths (163 women and 274 men) and 1158 all-cause deaths (449 women and 709 men). The multivariable-adjusted risk of cardiovascular death and death from any cause was lower in women than in men (HR, 0.55; 95% CI, 0.42-0.72 and HR, 0.58; 95% CI, 0.49-0.69, respectively). After adding hs-CRP, NT-proBNP, hs-TnT, or time-updated eGFR, the associations remained statistically significant. The association of sex with cardiovascular or all-cause death was similar across strata of age and baseline eGFR.

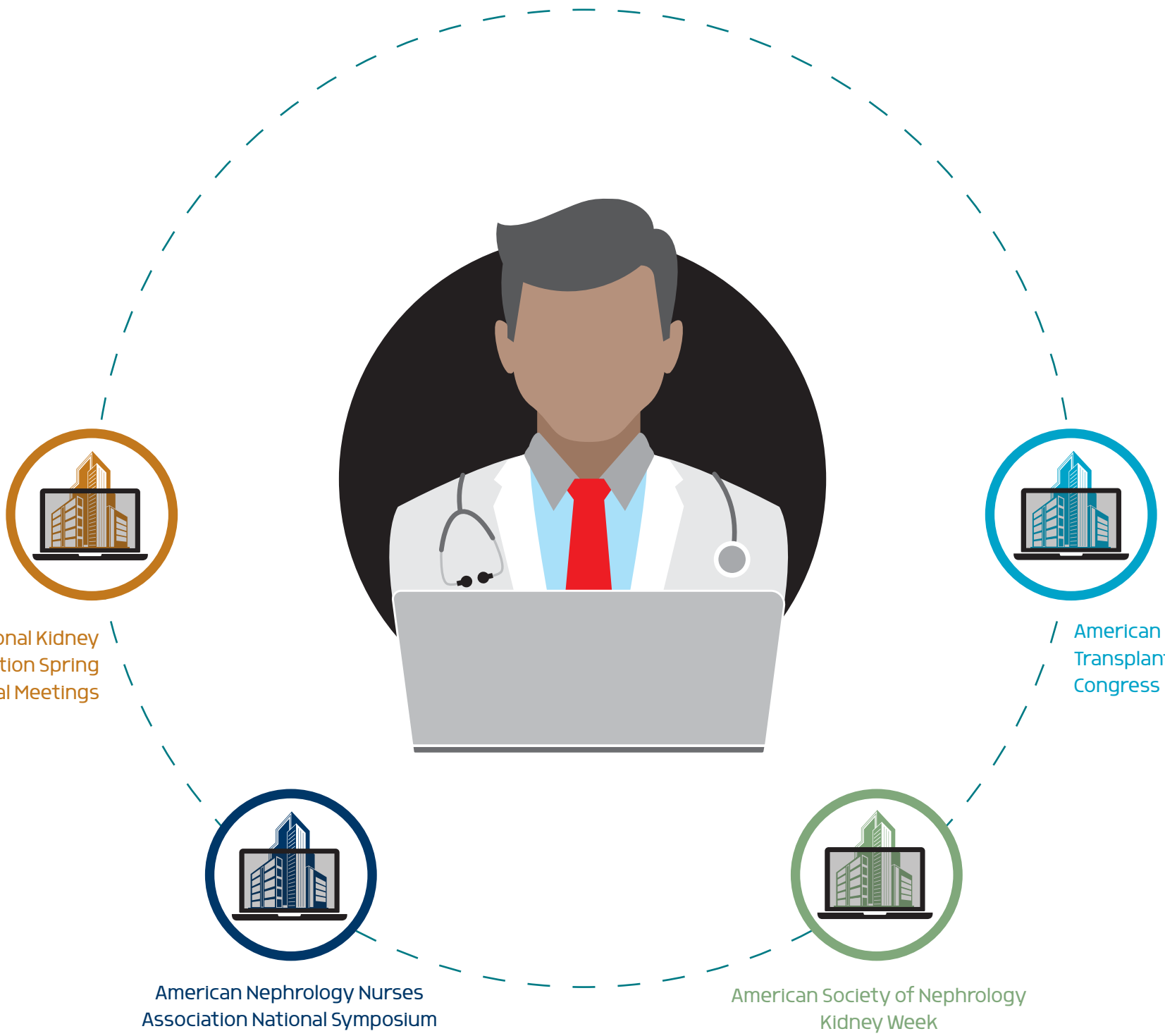
Limitations to the study findings cited by the authors were not including assessment of sex hormones that may play a role in cardiovascular risk and the inability to assess cardiovascular health-seeking behaviors in women versus men.

In conclusion, the researchers said, "Women with CKD had a lower risk of cardiovascular events and mortality compared with men, and this difference was not explained by cardiac biomarkers of myocardial distention, injury, or inflammation. From the clinician's perspective, it is concerning that most baseline risk factor control and cardioprotective medication use were suboptimal in both women and men. Importantly, women with CKD should still be considered to be at very high cardiovascular risk. Future work is needed to evaluate the differential impact of risk factor management to improve outcomes in women and men with CKD." ■

TAKEAWAY POINTS

- Researchers conducted a prospective cohort study among participants with chronic kidney disease in the Chronic Renal Insufficiency Cohort study to examine sex-related differences in different types of cardiovascular events and death.
- Compared with men, women had lower risks of cardiovascular events, cardiovascular mortality, and death from any cause.
- The differences were not explained by measured cardiovascular risk factors.

Whether in person or virtual, we have you covered.



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AMERICAN TRANSPLANT CONGRESS

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.

The American Transplant Congress 2021 was held virtually, providing a showcase for the latest research and advances made by the transplant community in the past year. This is part two of our meeting coverage.

Pre-Transplant C-Peptide Level and Post-Transplant Outcomes

Pancreatic beta-cells produce insulin by cleavage of a prohormone precursor into equal parts insulin and C-peptide. When administered to patients with type 1 diabetes, C-peptide is known to have renoprotective properties, including decreasing microalbuminuria, reduced hyperfiltration injury, and regression of diabetic histologic changes on kidney biopsy. There are few data available on the relationship between pretransplant C-peptide levels and outcomes following kidney transplantation.

A. J. Vinson and **K. Tennankore** of the Nova Scotia Health Authority division of nephrology, Halifax, Nova Scotia, Canada, conducted a retrospective cohort study to identify the association of pretransplant C-peptide levels dichotomized around the median and (1) delayed graft function; (2) proteinuria; and (3) median estimated glomerular filtration rate (eGFR) at 1 year post-transplant. Results of the study were reported during a virtual session at the American Transplant Congress 2021 in a presentation titled *The Association of Pre-Kidney Transplant C-Peptide Level with Post-Transplant Outcomes*.

The study also examined C-peptide level as a continuous variable categorized into quartiles. The association between pre-transplant C-peptide level and eGFR at 1-year post-transplant was determined using multivariable linear regression.

Pre-transplant mean and median C-peptide levels were 3458 and 3118 pmol/L. respectively; in an initial analysis, pre-transplant C-peptide level was dichotomized at 3000 pmol/L. Among patients with low C-peptide levels, the incidence of delayed graft function was higher than in patients with C-peptide levels ≥3000 pmol/L (8/31 [25.8%] vs 6/33 [18.2%], respectively). At 1-year, eGFR was lower in the group with C-peptide levels <3000 than in those in the ≥3000 pmol/L group (49.8 mL/min/1.73 m^2 vs 60.0 mL/min/1.73 m^2; P=.0877).

When C-peptide level was categorized based on quartile, there was also a steady increase in eGFR from the lowest to the highest quartile (46.5 mL/min/1.73 m^2 [C-peptide level ≤1940 pmol/L] to 57.3 mL/min/1.73 m^2 [C=peptide level >4616 pmol/L]).

In analyses treating C-peptide as a continuous variable, the association between pre-transplant C-peptide and eGFR at 1-year post-transplant reached statistical significance (coefficient=0.0043; 95% confidence interval 0.00038-0.0081; P=.032).

"A higher pre-transplant C-peptide level is associated with a lower risk of delayed graft function, and a higher eGFR and lower proportion with proteinuria at 1 year after kidney transplant," the authors said.

Source: Vinson, A.J., Tennankore K. The association of pre-kidney transplant C-peptide level with post-transplant outcomes. Abstract of a presentation at the virtual American Transplant Congress 2021 (Abstract #912), June 5, 2021.

Delayed Graft Function in Pediatric Kidney Transplant Recipients

Rates of delayed graft function are low in pediatric recipients of living donor kidneys. **M. MacConmara** and colleagues at UT Southwestern Medical Center, Dallas, Texas, conducted a study designed to assess the incidence, risk factors, and outcomes of delayed graft function in pediatric kidney transplant recipients who received a living donor allograft. Results of the study were reported in a virtual presentation at the American Transplant Congress 2021. The presentation was titled *Delayed Graft Function in Pediatric Living Donor Kidney Transplantation*.

The researchers queried the United Network for Organ Sharing database to identify all pediatric patients who received a living donor transplant between 2000 and 2020. The study defined pediatric recipient as one who received the transplant prior to reaching age 18. The analysis included donor and recipient demographic data, as well as data on survival and outcomes. Delayed graft function was defined as the need for dialysis within the first week after transplant.

During the study period, 6480 pediatric patients received a living donor kidney transplant. Of those 4.2% (n=269) developed delayed graft function post-transplant. Donors of patients in the two groups (delayed graft function and control) were similar in age (37.2 years vs 37.0 years, respectively), had similar preoperative creatinine (0.86 mg/dL in both groups), sex, and ethnicity. Donor body mass index (BMI) was higher in the delayed graft function group (27.6 vs 26.8 kg/m^2, respectively, P=.004). Cold ischemia time was similar in both groups (2.4 vs 2.3 hours).

Among recipients, both groups were similar in age (9.8 vs 10.1 years). Recipients in the delayed graft function group had higher BMI than those in the control group (20.3 vs 19.4 kg/m2; P=.002). Initial and final calculated panel-reactive antibodies were similar in the two groups (2.2% vs 2.4% initial; 10.5% vs 8.9% final). Human leukocyte antigen mismatch was also similar (3.0 vs 2.8). The most common diagnosis (23%) in recipients with delayed graft function was focal segmental glomerulosclerosis (FSGS). FSGS was significantly more frequent in the delayed graft function group than in the control group (23% vs 10%, respectively; P=.001).

Recipients with body weight <15 kg had a significantly higher rate of delayed graft function (24.9% vs 19.8%; P=.04). Length of stay for recipients with delayed graft function was twice that of the control group (23.4 vs 10.1 days, respectively, P<.0001).

At 6 and 12 months post-transplant, rates of rejection were higher among patients in the delayed graft function group than in the control group (24.8% vs 8.0% at 6 months, respectively, P<.0001; 26.4% vs 11.6% at 12 months, respectively, P<.0001). Those in the delayed graft function group had significantly worse allograft survival compared with the control group; 1-year graft survival was more than 30% lower in the delayed graft function group than in the control group (67% vs 98%). Graft thrombosis (25.3%), rejection (17.5%), and recurrent disease (15.6%) were the most common causes of allograft loss.

In conclusion, the researchers said, "Pediatric living donor kidney transplant recipients who experience delayed graft function have significantly poorer allograft survival. Immunologic events, recurrent disease, and technical complications appear to underlie these poor outcomes and should be considered especially in younger recipients with FSGS. Optimizing the donor recipient combination to avoid compounding risks should allow for better outcomes."

Source: MacConmara M, Shah J, De Gregorio L, Desai D, Vagefi P, Hwang C S. Delayed graft function in pediatric living donor kidney transplantation. Abstract of a presentation at the virtual American Transplant Congress 2021 (Abstract #82), June 5, 2021.

CMV Discordance in Elderly Kidney Transplant Recipients

Previous studies have linked high-risk CMV (cytolmegavirus) discordance (R-/D+) with adverse outcomes following kidney transplantation. Due to severe immunosenescence, elderly transplant recipients are at increased risk for CMV infections. **A. Dinesh** and colleagues conducted a retrospective analysis to examine survival outcomes in kidney transplant recipients ≥60 years of age by CMV concordance status.

Results of the analysis were reported during a virtual session at the American Transplant Congress 2021. The presentation was titled *Does High-Risk CMV Discordance Affect Elderly Kidney Transplant Recipient Survival? A Multivariable Analysis*.

The review included all primary kidney transplant recipients ≥60 years of age at the University of Minnesota, Minneapolis, from 2008 to 2019. The center uses thymoglobulin (r-ATG) as induction with early steroid withdrawal followed by calcineurin inhibitor (CNI) plus mycophenolate mofetil (MMF) maintenance. Typically, patients receive CMV prophylaxis with valganciclovir for 90 days for recipients with low-risk (CMV immunoglobulin G [IgG] R+/D+, R+/D-, or R-/D-) status and 180 days for recipients with high-risk (CMV IgG R-/D+) status.

The researchers stratified the study population into two groups: clinically high risk (CMV IgG R-/D+) status recipients (n=85) and low-risk (CMV IgG R+/D+. R+/D-, or R-/D-) status recipients (n=376). Recipient survival, death-censored graft survival, and CMV-infection-free survival with follow-up censored at 5 years were assessed using Kaplan-Meier curves. Multivariable Cox proportional hazards model adjusted for age, sex, race, body mass index, maintenance immunosuppression, donor type, and donor age were used to examine the effect of CMV high-risk status on the outcomes of interest. Due to severe proportional hazard violations, CMV-free survival was not modeled.

There was no difference observed in patient survival or death-censored graft survival between the two groups in univariate analysis (log-rank, P=.372 and log-rank. P=.844, respectively). CMV-survival was significantly lower in the high-risk group (log-rank, P<.001). At 2 years from engraftment, the cumulative incidence of CMV infection in the high-risk group was 42% compared with 21% in the low-risk group. In the multivariable model, CMV status was not a predictor of patient survival (hazard ratio [HR], 1.10; 95% confidence interval [CI], 0.54-2.23; P=.80) or graft survival (HR, 0.90; 95% CI, 0.28-2.86; P=.86).

In conclusion, the researchers said, "In primary kidney transplant recipients ≤60 of age, receiving r-ATG induction immunosuppression followed by CNI plus MMF maintenance with early steroid withdrawal, the incidence of post-transplant CMV viremia is significantly higher in the high-risk CMV discordant recipients. However, we did not detect an association between CMV discordance and patient or graft survival."

Source: Dinesh A, Jackson S, Riad S, Pruett T. L. Does high-risk CMV discordance affect elderly kidney transplant recipient survival? A multivariable analysis. Abstract of a presentation at the virtual American Transplant Congress 2021 (Abstract #784), June 5, 2021.

Outcomes in Living Kidney Donors with Prior COVID-19

R. Prashar and colleagues at the Henry Ford Transplant Institute, Detroit, Michigan, performed an analysis to examine short-term outcomes among living kidney donors who were previously infected with COVID-19 as well as outcomes in recipients of kidneys from those donors. Results of the analysis were reported during a virtual presentation at the American Transplant Congress 2021. The presentation was titled *Short-Term Outcomes in Previously COVID Positive Living Kidney Donors and Their Recipients.*

Following a brief COVID-19 related hiatus in transplants from March 2020 to May 2020, the institute performed 33 living donor transplants as of the date of the presentation. Of those, the researchers identified three consecutive living kidney donors who were diagnosed with COVID-19 prior to transplant. The analysis included retrospective data on clinical characteristics for donors and recipients.

The transplants were approved following meeting the institutional requirements of resolution of COVID. COVID-19 resolution requirements for both donors and recipients were negative nasopharyngeal testing by nucleic acid test for SARS-CoV-2 at 28 days after resolution of COVID-19 symptoms and a repeat negative test 48 hours prior to transplant.

TABLE

Patient	Age at donation (years)	Sex	Race	Severity of COVID	Days from COVID diagnosis to donation	Pre-donation eGFR (mL/min/1.73 m²)	Post-donation complications	Post-donation eGFR at 2 weeks (mL/min/1.73 m²)
Donor #1	22	Male	Middle Eastern	Mild	72	134	None	81
Donor #2	52	Female	Middle Eastern	Mild	50	105	Incidental finding of IgAN on post perfusion biopsy	58
Donor #3	22	Female	White	Mild	47	123	None	80

Mean time from COVID-19 diagnosis to donation was 56 days. All donors had mild disease that did not require hospitalization; none had hematuria or proteinuria prior to donation. With the exception of expected initial decline in estimated glomerular filtration rate, the post-donation course was uncomplicated in all three donors. Findings in post-perfusion biopsy in donor 2 showed an incidental finding of immunoglobin A nephropathy (Oxford classification 0). There were no viral particles on electron microscopy.

In recipient #2, there was patchy podocyte foot process effacement, believed to be due to recurrence of focal segmental glomerulosclerosis (FSGS). Recipient #1 had COVID-19 prior to transplantation. The post-transplant course was uneventful in two of the three recipients. Recipient #2 developed recurrence of FSGS immediately post-transplant; her course was further complicated by mild COVID-19 on day 7 following transplant. Her COVID-19 was managed by reduction in immunosuppression, bamlanivimab, steroids, and remdesivir. The exact COVID exposure for patient #2 is not known; she appears to have contracted it from the community.

In conclusion, the researchers said, "Living kidney donors with previously resolved COVID-19 appear to have an uncomplicated immediate post-donation course. Recipients of living kidney donors with resolved COVID tend to do well. Questions remain regarding optimal timing of donation and transplant after COVID resolution to minimize risk of SARS-CoV-2 transmission through tissue, even with negative nasopharyngeal PCR [polymerase chain reaction]."

Source: Prashar R, Khoury N J , Ramesh M, Patel A K. Short term outcomes in previously COVID positive living kidney donors and their recipients. Abstract of a presentation at the virtual American Transplant Congress 2021 (Abstract #LB 54), June 5, 2021.

Access to Transplantation for Hispanic Americans in Texas

Longstanding cultural and geographical disparities are key contributors to the disproportionately reduced access to kidney transplantation among Hispanic Americans. The cultural disparities are multifactorial; geographic disparities include long distances to transplant centers. Delayed referral to transplant also plays a role.

As reported by **A. Padilla** during a virtual session at the American Transplant Congress 2021, the University of Texas Medical Branch, Galveston, Texas, operates multiple clinics across Texas, including in the Rio Grande Valley (RGV), near the Texas-Mexico border. The session was titled *Gray on the Border: A Closer Look at the Gap in Access to Kidney Transplantation for Hispanic Americans.*

The study cohort included all patients evaluated at the center for kidney transplantation between January 2015 and August 2020. The researchers compiled sociodemographic characteristics, comorbidities, and time between declaration of end-stage kidney disease (ESKD) and evaluation. The data were compared by race/ethnicity and between two clinical sites run by the center. The sites were separated by more than 390 miles and had distinct population demographics: RGV (border) and MC (main campus, inland). The researchers also calculated the proportion of life spent with ESKD prior to evaluation.

A total of 2156 patients were evaluated for kidney transplantation during the study period: RGV, 441; MC, 1723. At both sites, 4% of patients had spent at least 20% of their lives with ESKD prior to transplant evaluation. At the RGV site, a greater proportion were Hispanic compared with the MC site (93% vs 38%, $P<.01$).

Across both sites, the Hispanic patients were significantly younger at the time of evaluation (51 years vs 56 years; $P<.01$). The time with ESKD at evaluation was significantly longer at RGV than at the MC site (3.3 years vs 2.7 years; $P<.01$). The proportion of life spent living with ESKD prior to evaluation was also significantly longer at RGV than at MC (6.9% vs 5.7%, $P<.01$).

In conclusion, the researchers said, "Previous analyses of access to transplantation have focused on waitlist and transplant characteristics. The study demonstrated significant differences between both clinics at the beginning of the transplant process, the evaluation. These data support the need for continued efforts to create and maintain access to transplantation in at-risk socio-cultural groups such as Hispanic Americans."

Source: Padilla A, Mujtaba M, Samper-Ternent R, et al. Gray on the border: A closer look at the gap in access to kidney transplantation for Hispanic Americans. Abstract of a presentation at the virtual American Transplant Congress 2021 (Abstract #1272), June 5, 2021.

Racial Disparities in Living Donor Kidney Transplantation

Kidney transplant recipients who receive a kidney from a living donor experience significant survival benefit over recipients who undergo deceased donor kidney transplantation. There are well recognized racial disparities in access to living donor kidney transplantation, disparities that have increased over the past two decades.

Contextual poverty and socioeconomic variability are the two factors commonly thought to contribute to inequities in access to living donor kidney transplantation. However, according to **A. C. Killian** and colleagues, the association between living donor kidney transplantation and comprehensive measures of social vulnerability is not well established. The researchers conducted a retrospective study to assess the relationship between social vulnerability and access to living donor kidney transplant. Results of the study were reported during a virtual session at the American Transplant Congress 2021 in a presentation titled *Living Donor Kidney Transplantation Racial Disparities Persist Independent of Social Vulnerability.*

Using data from the Scientific Registry of Transplant Recipients, the researchers identified adult, kidney-only transplant recipients between January 1, 2018, and December 31, 2018. Census tract-level data from the Centers for Disease Control and Prevention's 2018 Social Vulnerability Index (SVI) were linked to recipients by zip code. After controlling for patient- and community-level characteristics, the association between living donor kidney transplantation and SVI and race was assessed using logistic regression. Average adjusted predicted probabilities of living donor kidney transplantation across SVI were plotted by race.

The study included 20,380 kidney-only transplants; 30% of those were living donor transplants. There was a significant association between higher SVI (greater social vulnerability) and lower odds of living donor kidney transplant (adjusted odds ratio [aOR], 0.47; 95% confidence interval [CI], 0.40-0.57; $P<.0001$). Following controlling for SVI, African Americans had 57% lower odds of living donor transplant (aOR, 0.43; 95% CI, 0.39-0.48; $P<.001$); other races had 45% lower odds (aOR, 0.55; 95% CI, 0.48-0.63; $P<.0001$) of living donor kidney transplant compared with their White counterparts. At the lowest SVI, the average marginal effects for living donor kidney transplant were 13% for African Americans and 9% for other races, relative to White recipients.

In summary, the researchers said, "Greater social vulnerability is significantly associated with lower odds of living donor kidney transplant. Racial disparities in living donor kidney transplant persist independent of social vulnerability, suggesting that other factors, such as sociocultural barriers and unconscious biases require greater attention to mitigate inequities."

Source: Killian A C, McLeod M C, Shelton B, et al. Living donor kidney transplantation racial disparities persist independent of social vulnerability. Abstract of a presentation at the virtual American Transplant Congress 2021 (Abstract #369), June 8, 2021.

RACIAL DISPARITIES

Tacrolimus XR Dosing Strategies by Race

In May 2008, the Medical University of South Carolina, Charleston, dealt with the nationwide shortage of tacrolimus IR, requiring implementation of a de novo tacrolimus XR protocol. In a virtual presentation at the American Transplant Congress 2021, **N. Patel** and colleagues at the center, reported on two different strategies of dosing tacrolimus XR in African American and non-African American de novo kidney transplant recipients. The presentation was titled *Racial Differences in Tacrolimus XR Dosing in De Novo Kidney Transplant Recipients.*

The retrospective study included adult kidney transplant recipients between May 2020 and September 2020. The cohort was divided into two groups across two dosing strategies: non-African American and African American, and then further stratified based on initial dosing. The initial dosing strategy called for treating all patients between 0.12 mg/kg and 0.17 mg/kg tacrolimus XR, regardless of race. The second strategy called for treating non-African American patients with 0.12 mg/kg and African American patients with 0.15 mg/kg tacrolimus XR.

The primary end point was days to a therapeutic tacrolimus trough (>7 ng/mL). Other end points were dose at steady state, number of doses held, dose at post-operative day 30, time in therapeutic range in the first month, and adverse effects.

The study included 122 patients: 57 in the African American group and 27 in the non-African American group. In the African American cohort, there was a statistically higher number of deceased donor kidney transplants and donation-after-cardiac death transplants. Recipients in the African American cohort also had significantly higher estimated post-transplant survival score, higher human leukocyte antigen mismatches, longer duration of dialysis, and were more likely to receive induction with anti-thymocyte globulin.

In the initial analyses, there was a significant interaction between race and dosing strategy for the outcome of time to therapeutic level. During the initial dosing strategy, time to achieving a therapeutic trough was significantly longer among African Americans than among non-African Americans (6.2 days vs 4.4 days; $P=.03$). Also, during the initial dosing strategy, the incidence of neurotoxicity was significantly higher in the non-African American group than in the African American group.

After the dosing strategy was changed for African American recipients, the time to a therapeutic level decreased to 4 days, with no significant difference between the two groups. The higher level of neurotoxicity in the non-African American recipients remained higher than in the African American recipients.

"The results demonstrate that African Americans can achieve a similar time to therapeutic tacrolimus trough concentrations with tacrolimus XR, as compared to non-African Americans, using a race stratified dosing strategy. Future analyses are underway to assess the impact of CYP 3A5 genotype on dose requirements and time to achieve therapeutic levels," the researchers said.

Source: Patel N, Carcella T, Bartlett F, Rohan V, Taber D. Racial differences in tacrolimus XR dosing in de novo kidney transplant recipients. Abstract of a presentation at the virtual American Transplant Congress 2021 (Abstract #1273), June 5, 2021.

Differences in Access to Repeat Kidney Transplantation by Age and Race

Due perhaps to improvements in survival among kidney transplant recipients, the incidence of graft failure is increasing. The benefits of repeat kidney transplantation have been well documented. However, according to **S.S. Patole** and colleagues, there are disparities in access to repeat kidney transplantation.

The researchers conducted a study to examine the trends and disparities in access to repeat transplantation. Results were reported during a virtual session at the American Transplant Congress 2021 in a presentation titled *Age and Racial Disparities in Access to Re-kidney Transplantation.*

The study utilized data from the United States Renal Data System to identify 93,014 adults patients whose first kidney transplant graft failed between 1995 and 2017. Trends in graft failure over time and outcomes following graft failure were assessed by age, sex, and race. The Kaplan Meier method and adjusted Cox proportional hazards models were used to estimate the chance of listing for repeat kidney transplant, waitlist mortality, and repeat transplant among those who were listed for repeat transplant (n=46,613) by age, sex, and race.

During the study period, there was an increase in the number of graft failures from 2320 in 1995 to 4988 in 2017. The proportions of patients ≥65 years of age with graft failure increased from 5.7%to 27.5% during the study period. Among the population with graft failure, the proportion of Black patients remained stable: 33.5% in 1995 and 31.3% in 2017. The proportion of women was 41.1% in 1995 and 39.9% in 2017.

The chance of being listed for repeat kidney transplant was lower among older patients (adjusted hazard ratio [aHR], 0.37; 95% confidence interval [CI], 0.36-0.39) and Black patients (aHR, 0.79; 95% CI, 0.77-0.81). The risk of waitlist mortality was higher among older patients (aHR, 2.59; 95% CI, 2.40-2.79).

Older patients (aHR, 0.92; 95% CI, 0.85-0.99) and Black patients (aHR, 0.53; 95% CI, 0.50-0.55) were less likely to receive repeat kidney transplantation. There were no differences by sex in listing, waitlist mortality, or repeat kidney transplantation.

In conclusion, the researchers said, "There are age and racial disparities in access to repeat kidney transplantation. Efforts should be made to improve equitable access to repeat kidney transplantation for older and Black patients with graft failure."

Source: Patole S S, Ahn J, Sandal S, Segev D, McAdams Demarco M. Age and racial disparities in access to re-kidney transplantation. Abstract of a presentation at the virtual American Transplant Congress 2021 (Abstract #285), June 7, 2021.

Short-Term Outcomes in Transplant Recipients with Prior COVID-19

Researchers at Mount Sinai Hospital, New York, New York, conducted a study to examine short-term outcomes and peri- and post-transplant complications in patients with prior COVID-19 who subsequently underwent kidney transplantation. **A. Santeusanio** reported results of the single-center, retrospective cohort study during a virtual session at the American Transplant Congress 2021 in a presentation titled *Kidney Transplantation in Patients with Prior Coronavirus Disease 2019 (COVID-19)*.

The study included all recipients of isolated living- or deceased-donor kidney transplants at the center between April 1, 2020, and October 1, 2020. Patients with prior COVID-19 confirmed on polymerase chain reaction (PCR) were deemed candidates for kidney transplantation if they were a minimum of 4 weeks post-infection, had resolution of symptoms, and had one negative nasopharyngeal PCR swab specimen.

At the time of transplant, recipients received standard doses of induction and maintenance immunosuppression, including anti-thymocyte globulin, tacrolimus, mycophenolate, and tapering corticosteroids. Patients were followed from the date of the transplant until the conclusion of the study (November 1, 2020). The researchers compared short-term patient and allograft outcomes between recipients with prior COVID-19 and COVID-19 naïve controls who received a kidney transplant during the study period.

During the study period, 81 patients received isolated kidney transplants at the center. Of those, 13 (16.0%) had recovered from prior COVID-19 infection. Median time between diagnosis of COVID-19 and transplantation was 71 days. Ten patients who were tested had evidence of significant antibody titers to the SARS-CoV-2 spike protein. Among the group with prior COVID-19, 69.2% had mild disease; three patients required hospital admission and supplemental oxygen and one required mechanical ventilation. The two groups were similar in baseline characteristics, with the exception of a greater proportion of Hispanic/Latino patients in the group with prior COVID-19 than in the control group (53.8% vs 17.6%; $P<.01$).

At the conclusion of the study, following a median of 36 months of follow-up, patient and allograft survival were similar between the two groups (92.3%/92.3% vs 100%/98.5%), and mean baseline serum creatinine was 1.5 mg/dL in both groups. One patient in the prior COVID-19 group (mild) died due to a pulmonary embolism within 1 month of transplantation; there were no significant differences overall in the rate of thromboembolism between the groups (7.7% vs 4.4%; $P=.61$).

The two groups were similar in index hospital length of stay and 30-day readmission rate; patients in the prior COVID-19 group had a higher incidence of delayed extubation post-transplant (15.4% vs 1.5%; $P=.02$). There were no cases of COVID-19 reinfection or biopsy proven allograft rejection among patients in the prior COVID-19 group.

In conclusion, the authors said, "In our preliminary experience, patients with prior COVID-19 infection appeared to have similar short-term outcomes when compared with COVID-19 naïve patients. We did observe a potential signal for increased peri-operative respiratory complications in patients with prior CVOID-19, which may warrant additional monitoring and further study in multi-center cohorts."

Source: Santeusanio A, Bhansali A, Rana S, et al. Kidney transplantation in patients with prior coronavirus disease 2019 (COVID-19). Abstract of a presentation at the virtual American Transplant Congress 2021 (Abstract LB 44), June 5, 2021.

The two groups were similar in index hospital length of stay and 30-day readmission rate; patients in the prior COVID-19 group had a higher incidence of delayed extubation post-transplant (15.4% vs 1.5%; $P=.02$).

Simultaneous Pancreas/Kidney Transplant versus Kidney Transplantation Alone

Researchers at Tianjin First Central Hospital, Tianjin, China, led by **X. Y. Fu,** conducted a study to compare renal function, metabolic profiles, and survival outcomes among patients with end-stage kidney disease (ESKD) and diabetes mellitus undergoing simultaneous pancreas kidney transplantation (SPK) with those undergoing kidney transplantation alone. Results of the study were reported during a virtual session at the American Transplant Congress 2021. The presentation was titled *Superior Metabolic Function of Type 2 Diabetes Mellitus Patients after Simultaneous Kidney/Pancreas Transplantation compared with Kidney Transplantation Alone*.

The researchers retrospectively analyzed data on patients with ESKD and type 2 diabetes who underwent SPK (n=85) or kidney transplantation alone (n=71). Data on demographics, perioperative parameters, postoperative blood glucose and lipid profiles, complications, and survival outcomes in the two cohorts were analyzed. Mixed effects models were used to compare data between the cohorts.

In general, patients in the SPK group were younger than those in the kidney transplantation alone group (mean, 49.01 years vs 52.14 years; $P=.018$); donor age in the SPK group was also younger than in the kidney transplantation alone group (mean, 32.1 years vs 47.14 years; $P<.001$).

Renal function and metabolic outcomes were superior in the SPK group compared with the kidney transplantation alone group, including higher estimated glomerular filtration rate ($P=.393$), lower fasting serum glucose level ($P<.001$), lower triglyceride level ($P=.0439$), and lower cholesterol level ($P=.002$). The rate of infection was higher in the SPK cohort than in the kidney transplantation alone cohort (38% vs 22.4%, respectively; $P=.003$). There were no significant differences between the two cohorts in survival outcomes.

In conclusion, the researchers said, "SPK provides better renal function and metabolic outcomes, but has higher rate of infection than kidney transplantation alone for ESKD-type 2 diabetes mellitus patients. The 5-year survival outcomes of recipients and grafts were comparable between the two groups."

Source: Fu X Y, YU C, Wang H, et al. Superior metabolic function of type 2 diabetes mellitus patients after simultaneous kidney/pancreas transplantation compared with kidney transplantation alone. Abstract of a presentation at the virtual American Transplant Congress 2021 (Abstract #896), June 5, 2021.

Single versus Double Incision for Liver/Kidney Transplant

Patients with concomitant end-stage liver disease and severe chronic kidney disease or end-stage kidney disease (ESKD) are candidates for simultaneous liver and kidney transplantation (SLK). In recent years, the number of SLK performed in the United States has been consistently on the increase.

SLK is traditionally performed using a subcostal incision for the liver allograft and a lower abdominal incision for the kidney transplant (dual incision [DI]). During a virtual presentation at the American Transplant Congress 2021, researchers at Virginia Commonwealth University, Richmond, report that a single subcostal incision (SI) is performed for SLK at their center. Led by **D. Imai,** the researchers presented results of a study designed to assess outcomes using single and dual incisions for SLK. The presentation was titled *Single Incision Simultaneous Live Kidney Transplantation: Outcomes and Feasibility.*

The researchers conducted a retrospective analysis of all SLK performed at Virginia Commonwealth University from January 2015 to November 2020. The analysis included statistical comparisons of demographic characteristics, complications, and intraoperative findings and complications after SI and DI. Subgroup analyses were conducted based on early and late experience with single incision SLK.

During the study period, a total of 34 SLK were performed; of those, 18 were DI and 16 were SI. The two groups were similar in MELD (Model for End-Stage Liver Disease) score, age, and indications for transplant. Patients in the SI group had higher body mass index; the difference was not statistically significant.

Cold ischemia time of kidney transplantation was significantly shorted in the SI group (P=.002). In the early era analysis, complications were slightly higher in the SI group; the difference did not reach statistical significance. Both groups were similar in hospital length of stay and warm ischemia time. In the SI group, post-operative morphine requirements were lower, as was overall operative time, compared with the DI group.

In conclusion, the researchers said, "Single incision SLK is technically feasible and has comparable outcome to dual incision SLK. Single incision SLK was associated with shorter cold ischemia time for kidney transplant as well as lower overall operative time without any impact on outcome. Further study is required to delineate additional benefit of single incision SLK with particular focus on patient acceptance and recovery from the surgical wound."

Source: Imai D, Sambommatsu Y, Khan A, et al. Single incision simultaneous liver kidney transplantation: Outcomes and feasibility. Abstract of a presentation at the virtual American Transplant Congress 2021 (Abstract #983), June 5, 2021.

Risk Factors in Long-Term Graft Survival in Pediatric Transplant Recipients

Post-transplant outcomes are generally good among pediatric kidney transplant recipients. However, it is important to understand the multifactorial nature of long-term graft survival due to the younger age and longer lifespan following transplantation in that patient population.

A. Anand and colleagues at Baylor College of Medicine, Houston, Texas, conducted a retrospective analysis to examine factors associated with 10-year survival with an eye toward identification of areas for improvement in care for pediatric kidney transplant recipients. Results of the analysis were reported in a virtual presentation at the American Transplant Congress 2021. The presentation was titled *Risk Factors Predicting Outcomes in Long-Term Pediatric Kidney Transplant Graft Survival.*

Using data from the United Network for Organ Sharing, the researchers performed Kaplan-Meier analysis with log-rank tests as well as univariate and multivariate logistic regression methods to examine data on 7785 kidney transplant recipients from January 1, 1998, to March 9, 2008. Following exclusion of recipients whose graft failed within 1 year of transplant, the end point was death-censored 10-year graft survival.

Recipients 5 to 18 years of age had lower graft survival, which worsened as age increased: 5 to 9 years of age, odds ratio (OR), 0.66; 95% confidence interval (CI), 0.52-0.83; 10 to 14 years of age, OR, 0.43; 95% CI, 0.33-0.55); 15 to 18 years of age, OR, 0.34; 95% CI, 0.26-0.44. Outcomes were worse among recipients of African American ancestry (OR, 0.67; 95% CI, 0.58-0.78) and among those with Hispanic donor ethnicity (OR, 0.82, 95% CI, 0.72-0.94) compared with other recipient and donor ethnicities. Outcomes among patients on dialysis at the time of transplant were also worse than those among patients not dialysis-dependent at time of transplant (OR, 0.82; 95% CI, 0.73-0.91). Recipients with private insurance had improved 10-year graft survival compared with recipients with other insurance status (OR, 1.35; 95% CI, 1.22-1.50).

In summary, the researchers said, "By establishing the role of age, race, and insurance status on long-term graft survival, we hope to guide clinicians identifying patients at high risk for graft failure. This study highlights the need for increased allocation of resources and medical care to reduce the disparity in outcomes for certain patient populations."

Source: Anand A, Malik T H, Dunson J, et al. Risk factors for predicting outcomes in long-term pediatric kidney transplant graft survival. Abstract of a presentation at the virtual American Transplant Congress 2021 (abstract #81), June 5, 2021.

Financial Hardship and Risk of Incident Diabetic Kidney Disease

Approximately 30.3 million individuals in the United States are affected by diabetes; since the 1980s, there has been a rise in the prevalence of diabetes, accompanied by a rise in diabetic kidney disease (DKD). DKD affects ~40% of those with diabetes, putting them at increased risk of cardiovascular disease and progression to end-stage kidney disease. There are also associations between DKD and increased healthcare costs and risk of mortality.

Growing evidence suggests the role of social determinants in diabetes outcomes. Social determinants of health include the conditions in which individuals are born, grow, live, work, and age. Those conditions exacerbate health disparities at global, national, local, and individual levels, and impact individuals' socioeconomic status. The standard metrics of socioeconomic status, including education, occupation, and income, may be insufficient to capture the true burden some individuals are experiencing.

Financial hardship is a measure that accounts for material conditions, psychological response, and coping behaviors related to interaction with the healthcare system. Associations between financial hardship and poor health are well recognized. However, there are few data available on the association between financial hardship and incident diabetic kidney disease (DKD) in the United States.

Timothy R. Corwin and colleagues conducted a study designed to assess the longitudinal relationship between financial hardship and incident DKD among older adults with diabetes. The researchers sought to test the hypothesis that there is a positive longitudinal relationship between financial hardship and incident DKD among older adults in the United States with diabetes. The second hypothesis was that there is a positive association between positive, negative, and persistent financial hardship change and incident DKD in adults with diabetes in the United States. Results were reported online in *BMC Nephrology* [doi.org/10.1186/s12882-021-02373-3].

Using four waves of data (2006-2012) from the Health and Retirement study, a national longitudinal cohort, the analyses included 2735 adults ≥50 years of age with diabetes and no DKD. The primary outcome of interest was incident DKD based on the question: Has your diabetes caused you to have trouble with your kidneys or protein in your urine?

Based on validated surveys, financial hardship was defined as: (1) difficulty paying bills; (2) food insecurity; and (3) cost-related medication nonadherence. Using all three measures, the researchers constructed a dichotomous financial hardship variable (0 vs 1 or more). The variable was generated by coding all yes responses as 1 and no responses as 0. Financial hardship was defined as a score of ≥1. In addition, a 4-category change in financial hardship experience was created for those who answered the financial hardship question during the follow-up interview as: (1) those who reported no financial hardship in both interviews were categorized as no financial hardship; (2) those who reported financial hardship in both interviews were categorized as persistent financial hardship; (3) those who reported financial hardship in the first interview and no financial hardship in the second interview were categorized as positive financial hardship change; and (4) those who reported no financial hardship in the first interview and financial hardship in the second interview were categorized as negative financial hardship change.

After adjusting for demographics, socioeconomic status, and comorbidities, the association between financial hardship, change in financial hardship experience, and incident DKD was estimated using Cox regression models.

Median follow-up was 4.1 years (10,686 person-years of follow-up). A total of 347 adults developed incident DKD. Mean age in the overall cohort was 68.1 years; mean age of those without financial hardship (n=1648) was 69.8 years; in those with financial hardship (n=1087), mean age was 65.4 years. Compared with those without financial hardship, adults in the financial hardship group were more likely to be female, of ethnic minority, have less education, and have a low household income.

During follow-up, the rate of incident DKD was higher in those with versus those without financial hardship (4.12 per 1000 person-years vs 27 per 1000 person-years). Following adjustment, the likelihood of developing incident DKD was significantly increased in those with financial hardship compared with those without financial hardship (hazard ratio [HR], 1.32; 95% confidence interval [CI], 1.04-1.68). Persistent financial hardship and negative financial hardship were associated with incident DKD compared with no financial hardship experience (adjusted HRs, 1.52; 95% CI, 1.06-2.18 and 1.54; 95% CI, 1.02-2.33, respectively).

Positive financial hardship was not statistically significant in unadjusted and adjusted models (adjusted HR, 0.89; 95% CI, 0.55-1.46). Independent of other financial hardship measures, cost-related medication nonadherence was associated with incident DKD (adjusted HR, 1.43; 95% CI, 1.07-1.93).

The researchers cited some limitations to the findings, including substantial heterogeneity in the literature in measures of financial hardship, limiting the ability to compare the findings with other studies; using self-report as the basis of the presence of diabetes and DKD, perhaps underestimating the prevalence of DKD; the possibility of residual confounders; and restricting the study population to older adults, limiting the ability to generalize the findings to younger adults with diabetes.

In conclusion, the researchers said, "In a longitudinal cohort of older US adults we show that compared with individuals without financial hardship, individuals with financial hardship experience were significantly more likely to develop DKD. In particular, individuals reporting persistent financial hardship had a higher probability of patient reported incident DKD while individuals reporting negative financial hardship change may be at risk of incident DKD. Our study findings suggest cost-related medication nonadherence may be an important target for future intervention studies to mitigate adverse outcomes. Future studies are needed to explore factors not included in this study that may explain the relationship between financial hardship and incident DKD." ■

TAKEAWAY POINTS

- Researchers reported results of an analysis of data from a national longitudinal cohort of adults in the United States with diabetes to examine the longitudinal relationship between financial hardship and incident diabetic kidney disease (DKD) in that patient population.
- Incident DKD was higher among those with versus those without financial hardship: 41.2 per 1000 person-years versus 27 per 1000 person-years. In adjusted analysis, the likelihood of developing DKD was significantly increased in those with financial hardship compared with those without financial hardship.
- Persistent financial hardship and negative financial hardship change were associated with incident DKD compared with no financial hardship experience.

Development of a 4-Marker Panel to Estimate GFR without Inclusion of Race

Routine medical care for adults includes clinical assessment of kidney function. Estimates of glomerular filtration rate (GFR) incorporate clinical and demographic factors, including age, sex, and race, that explain some of the variation of markers unrelated to GFR; estimated GFR (eGFR) is more accurate and useful than serum concentrations of endogenous filtration markers alone in each demographic group.

Most laboratories report eGFR when serum creatinine is measured ($eGFR_{cr}$). Confirmatory tests for $eGFR_{cr}$ include eGFR based on cystatin C ($eGFR_{cys}$) or the combination of creatinine and cystatin C ($eGFR_{cr-cys}$). The inclusion of creatinine in $eGFR_{cr-cys}$ requires specification of the patient's race. There is mounting scrutiny of the use of race in estimation of GFR, including attention by the US Congress to algorithms that include race.

> The addition of age and sex improved the performance of the 3-marker and 4-marker panels compared with panels without age and sex. The addition of race did not improve performance further.

According to **Lesley A. Inker, MD, MS,** and colleagues, a panel of endogenous filtration markers could improve the accuracy of GFR estimation by reducing the impact of the non-GFR determinants of each marker and by obviating clinical and demographic factors, particularly race.

ß2-microglobulin (B2M) and B-trace protein (BTP) are low-molecular-weight proteins that are filtered by the glomeruli and degraded by tubules. Those markers are useful in estimating GFR and are less influenced by age, sex, and race than creatinine. Dr. Inker et al. conducted an analysis to determine whether the inclusion of B2M and BTP in a panel eGFR would enable performance comparable to or better than currently recommended equations without the need for creatinine or race. Results of the analysis were reported in the *American Journal of Kidney Diseases* [2021;77(5):673-683].

The analysis included seven studies with a total of 5017 participants in the development population. The data set was randomly divided into separate datasets for initial development (n=3363) and internal validation (n=1654). Seven additional studies with a total of 2245 participants were included in the external validation population.

The researchers developed new equations using both B2M and BTP rather than either alone, with creatinine (4-marker panels) and without creatinine (3-marker panels). Each was tested with and without a race coefficient. Reference equations used were the 2009 Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI), the 2012 CKD-EPI cystatin C equation, and the 2012 CKD-EPI creatinine-cystatin C equation.

In the development population, mean measured GFR (mGFR) was 58.1 mL/min/1.73 m^2, mean age was 55.7 years, 43.8% were female, and 38.6% were Black. In the validation population, mean mGFR was 83.2 mL/min/1.73 m^2, mean age was 52.8 years, 29% were female, and 24% were Black. Five of the seven development cohorts included Black participants (>5% in three of the seven cohorts and 39% overall) and in all validation cohorts (>5% in five of the seven cohorts and 24% overall). In the development cohort, 1296 participants had diabetes, and mean body mass index (BMI) was 29.0 kg/m^2. In the external validation cohort, 34.7% had diabetes and mean BMI was 27.5 kg/m^2.

All filtration markers were correlated negatively with mGFR and positively with each other in the development population. Following adjustment for mGFR, the correlations among filtration markers ranged from 0.508 (95% confidence interval [CI], 0.487-0.528) for creatinine and BTP to 0.774 (95% CI, 0.762-0.785) for cystatin C and B2M.

Regardless of inclusion or exclusion of age and sex or race, 4-marker panels were more accurate than corresponding 3-marker panels. The addition of age and sex improved the performance of the 3-marker and 4-marker panels compared with panels without age and sex. The addition of race did not improve performance further. In subgroups of participants from Black versus other communities, results were generally similar.

In the external validation cohort, the 4-marker panels were more accurate than the 3-marker panels ($P<.001$). The 3-marker panel without race was more accurate than $eGFR_{cys}$, and the 4-marker panel without race was as accurate as $eGFR_{cr-cys}$. Across subgroups, results were generally consistent.

Limitations to the findings cited by the authors included lack of representation of participants with severe comorbid illness and from geographic areas outside North America and Europe. In addition, the mean GFR in the development population was higher than in the CKD populations used to develop the 2015 equations and lower than in the development populations for the 2009 creatinine and 2021 cystatin C equations and the external validation population in the current study.

In conclusion, the researchers said, "We present 3-marker and 4-marker panel eGFRs that use B2M and BTP but do not include race as confirmatory or alternative rests for $eGFR_{cr}$. The 4-marker panel eGFR is less dependent on creatinine and is as accurate as the 2012 creatinine-cystatin C equation. An eGFR that does not require race and is less dependent on creatinine could provide more robust GFR estimates across a greater variety of populations. Further studies are required to understand how best to use these equations in clinical practice, especially in diverse clinical settings and geographic locations." ■

TAKEAWAY POINTS

- The inclusion of creatinine in assessment of glomerular filtration rate (GFR) requires specification of a patient's race. Alternate filtration markers that may be less influenced by race are ß2-microglobulin (B2M) and B-trace protein (BTP).
- Researchers utilized a pooled dataset of seven studies to develop new estimating equations based on combinations of the markers with and without age, sex, or race.
- Using a separate dataset of seven studies, an equation that used all four markers, including age and sex but not race, was as accurate as estimated GFR based on the combination of creatinine and cystatin C.

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Outcomes among Patients with VTE with and without CKD

The third most common factor associated with cardiovascular death is venous thromboembolism (VTE), including deep vein thrombosis (DVT) and pulmonary embolism (PE). Patients with chronic kidney disease (CKD) are at increased risk of developing VTE compared with those without CKD. Further, decreased kidney function following PE is both a short-term and long-term independent risk factor associated with mortality rates. Increasing age is associated with increased risk for CKD and VTE as well as the prevalence of other risk factors such as type 2 diabetes and hypertension. In addition, due to the clearance of direct oral anticoagulant (DOAC) medications by the kidneys, therapy choices may be more limited in patients with CKD.

There are limited data available on the efficacy and safety of DOAC therapy for the treatment of patients with advanced CKD; patients with severe kidney impairment (creatinine clearance level <25-30 mL/min) have been excluded from phase 3 randomized trials of DOAC therapy in patients with VTE. Some DOAC medications are approved for the treatment of VTE in patients with moderate to severe CKD and are licensed for use in patients with creatinine clearance levels as low as 15 mL/min.

The GARFIELD-VTE (Global Anticoagulant Registry in the Field-Venous Thromboembolism) study is an ongoing worldwide prospective noninterventional registry designed to observe initial and extended therapeutic strategies and clinical outcomes among patients with VTE who are being treated according to local standard practices. **Shinya Goto, MD, PhD,** and other GARFIELD-VTE investigators conducted an analysis comparing baseline characteristics, treatment patterns, and 12-month outcomes between patients with CKD stages 3-5 and those with CKD stages 1-2 enrolled in the study. Results of the analysis were reported in *JAMA Network Open* [doi:10.1001/jamanetworkopen.2020.22886].

The primary outcomes of interest were all-cause mortality, recurrent VTE, and major bleeding. All-cause mortality was considered a competing risk for other clinical outcomes in the estimation of cumulative incidences.

A total of 10,684 patients in the GARFIELD-VTE trial had objectively confirmed VTE; of those, 8979 (84.0%) had available data on serum creatinine. Of the 8979, 49.4% (n=4432) were female and 65.8% (n=5912) were White. Overall, 6924 eligible patients (77.1%) were classified as having mild to no CKD (2991 patients with CKD stage 1 and 3933 patients with CKD stage 2) and 2055 patients (22.9%) were classified as having moderate to severe CKD (1650 patients with CKD stage 3, 190 patients with stage 4 CKD, and 215 patients with stage 5 CKD). CKD stages were calculated using the Modification of Diet in Renal Disease equation.

Patients with moderate to severe CKD compared with those with mild to no CKD were more likely to be female (1173 [57.1%] vs 3259 [47.1%] and ≥65 years of age (1278 patients [62.2%] vs 2313 patients [33.4%]). The Spearman correlation coefficient for estimated glomerular filtration rate (eGFR) and creatinine clearance was 0.75.

The distribution of VTE events at baseline was comparable between the two groups. In the moderate to severe CKD group, 57.0% (n=1171) presented with DVT alone, 26.6% (n=547) presented with PE alone, and 16.4% (n=337) presented with both DVT and PE. In the mild to no CKD group, 58.9% (n=4079) presented with DVT alone, 24.9% (n=1723) presented with PE alone, and 16.2% (n=1122) presented with both DVT and PE.

At baseline, the receipt of parenteral therapy alone was comparable between the two groups: 17.3% (n=355) patients in the moderate to severe CKD group versus 18.1% (n=1253) patients in the mild to no CKD group. Patients in the moderate to severe CKD group were less likely to be receiving DOAC therapy, either alone (27.1% [n=557] vs 30.9% [n=2139]) or in combination with parenteral therapy (15.5% [n=319] vs 17.9% [n=1239]).

At 12 months, the unadjusted rate of all-cause mortality in patients with moderate to severe CKD was higher than that of patients with mild to no CKD: 12.8 deaths per 100 person-years (95% confidence interval [CI], 11.3-14.6 deaths per 100 person-years) versus 6.7 deaths per 100 person-years (95% CI, 6.1-7.3 deaths per 100 person-years). Patients in the moderate to severe CKD group were more likely than those in the mild to no CKD group to die of cardiac-associated conditions but less likely to die of cancer and VTE-associated conditions. In the group with moderate to severe CKD, the rate of recurrent VTE was higher than in the group with mild to no CKD. There was a greater proportion of PE recurrences (with or without VTE) in patients with moderate to severe CKD than in patients with mild to no CKD.

Major bleeding was also more common in the moderate to severe CKD group compared with the mild to no CKD group. The most frequent sites of bleeding in both groups were the upper gastrointestinal tract and the lower gastrointestinal tract.

Following adjustment for potential confounders, the incidence of all-cause mortality remained higher in patients with moderate to severe CKD than in those with mild to no CKD: adjusted hazard ratio (aHR), 1.44; 95% CI, 1.21-1.73. At 12 months, the incidence of recurrent VTE (aHR, 1.40; 95% CI, 1.10-1.77) and major bleeding (aHR, 1.40; 95% CI, 1.03-1.90) was also higher in patients with moderate to severe CKD than in patients with mild to no CKD. There was no difference between the two groups in incidence of cancer (aHR, 1.15; 95% CI, 0.83-1.60).

The researchers cited some limitations to the study findings, including the absence of creatinine clearance measurements in 16.0% of the patients with objectively confirmed VTE, and the heterogeneous distribution of patients' CKD stages, with only a small number of patients in the GARFIELD-VTE study with advanced CKD.

"In this study, the presence of concomitant moderate to severe CKD among patients with VTE was associated with increases in the risk of death, recurrent VTE, and major bleeding within 12 moths of VTE diagnosis compared with the presence of mild to no CKD, even after adjustment for baseline participant characteristics," the researchers said. "Improving the quality of care for patients with VTE and concomitant moderate to severe CKD remains an important challenge. Future work within the GARFIELD-VTE will assess the impact of both the dose and the duration of anticoagulant treatment for VTE recurrence and bleeding up to 3 years after VTE diagnosis." ■

TAKEAWAY POINTS

- Investigators in the Global Anticoagulant Registry in the Field-Venous Thromboembolism [VTE] study conducted an analysis to compare clinical characteristics, treatment patterns, and 12-month outcomes among patients with VTE and mild to no chronic kidney disease (CKD) with those in patients with VTE and moderate to severe CKD.
- Patients with moderate to severe CKD were less likely than those with mild to no CKD to be receiving direct oral anticoagulant therapy, either alone or in combination with parenteral therapy.
- At 12 months, patients with moderate to severe CKD had a higher risk of all-cause mortality, major bleeding, and recurrent VTE compared with those with mild to no CKD.

OPTIMIZE Trial: Prevention of Over-Immunosuppression in Elderly Transplant Recipients

Elderly patients are an increasing sector of both the dialysis and kidney transplant population. In the Netherlands, 30% of the newly kidney transplanted kidney transplant recipients in 2019 were >65 years of age, as were more than 60% of the dialysis population.

Compared with younger kidney transplant recipients, risk profiles among the elderly population are different; death-censored graft loss among elderly transplant recipients is relatively rare.

In a report online in *BMC Nephrology* [doi.org/10.1186/s12882-021-02409-8], **S. E. de Boer** and colleagues described the OPTIMIZE (Open label multicenter randomized trial comparing standard immunosuppression with tacrolimus and mycophenolate mofetil with a low exposure tacrolimus regimen in combination with everolimus in de novo renal transplantation in elderly patients) trial. The trial is designed to test the hypothesis that reduced calcineurin inhibitor (CNI) exposure in combination with everolimus will lead to improved kidney transplant function, a reduction in the incidence of complications, and improvements in health-related quality of life for kidney transplant recipients ≥65 years of age, compared with standard immunosuppression.

The trial will include two strata of kidney transplant recipients: (1) those who received kidneys from older deceased donors (≥65 years of age) (stratum 1)and (2) those who received kidneys from living donors of all ages and younger (<65 years of age) deceased donors (stratum 2). The comparator will be the standard CNI exposure in combination with mycophenolate mofetil.

The study will (1) examine the impact of transplantation and adapted immunosuppression on frailty and health-related quality of life in elderly Dutch and Belgian kidney transplant recipients; (2) monitor the function of the aging immune system following transplantation and the effect of low CNI exposure in combination with everolimus on parameters of immunosuppression compared with standard, tacrolimus-based immunosuppression; and (3) identify immunologic biomarkers that may serve as biomarkers of immunosenescence for future clinical application.

The study is an investigator-driven, randomized, multicenter, open-label, intervention trial that will include 374 patients. Six transplant centers in the Netherlands and one in Belgium will participate.

At the time of transplantation, patients will be randomized 1:1 to receive either standard quadruple immunosuppression regimen with tacrolimus and mycophenolate mofetil (the tacrolimus, mycophenolate mofetil, prednisolone group [TMP group], or a low exposure tacrolimus regimen in combination with everolimus (the tacrolimus, everolimus, prednisone group [TEP group]).

Patients in the TMP group will receive a starting dose of 7 mg Envarsus® once daily (or an equivalent dose of Advagraf®), with an initial target trough concentration of 8-12 ng/mL tapered to 6-10 from 3 months onward, and 5-8 mg/mL from 6 months after transplant. Patients in the TMP group will receive mycophenolate mofetil throughout the trial. Patients in the TEP group will receive a starting dose of 5 mg Envarsus once daily (or an equivalent dose of Advagraf) with an initial target trough concentration of 5-7 tapered to 3-4 ng/mL from 3 months onward, and 1.5-4 ng/mL from 6 months after transplant. Everolimus will be started at an initial dose of 1.5 mg twice a day with a target trough concentration of 3-6 ng/mL throughout the trial.

The trial's primary end point will be successful transplantation, defined as survival with a functioning allograft with an estimated glomerular filtration rate >30 mL/min/1.73 m^2 in stratum 1 and >45 mL/min/1.73 m^2 in stratum 2 at 2 years post-transplantation. Secondary end points include the primary end point analyzed separately per stratum and the incidence of biopsy-proven rejection, the presence of and changes in immunosenescence, frailty and comorbidities, and assessment of and changes in health-related quality of life as a patient-reported outcome.

Safety objectives include standard assessments of serious adverse events, including drug-related adverse events and drug-related discontinuation of the study medication, and specific objectives regarding clinically relevant infections, post-transplantation diabetes, malignancy, and cardiovascular events. Immunosenescence will be examined by assessment of the immunological phenotype pre-transplant and identification of T cell aging characteristics associated with the risk for acute rejection and infection following kidney transplant. The study will also assess immunological aging within a 2-year period following kidney transplantation in relation to the two immunosuppressive regimens.

There will be nine study visits: baseline, 7 days, 4 weeks, 3, 6, 9, 12, 18, and 24 months post-transplant. Frailty, cognitive and physical functioning, health-related quality of life, illness perceptions, symptom burden, and adherence to immunosuppressive medications will be monitored using several instruments, both objective and subjective. All study data will be entered into the secured OPTIMIZE project database.

Safety assessment will be based on the frequency of adverse events, including all serious adverse events. Adverse events will be summarized by presenting the number and percentage of patients experiencing any adverse event.

The study began in July 2019. As of the first quarter 2021, all centers had started and 116 patients were included (64 in stratum 1 and 52 in stratum 2). A total inclusion time of 4 years was initially projected; however, due to the COVID-19 pandemic, study inclusion will be delayed.

The researchers said, "The OPTIMIZE study is a unique clinical trial; it is the first randomized clinical trial to extensively examine the effect of a low exposure tacrolimus regimen in combination with everolimus specifically in de novo elderly kidney transplant recipients. The study also pays attention to the quality of life, cognitive and physical functioning of the participants. The unique character of the study in combination with the data it will yield will position the OPTIMIZE study to have profound impact on future kidney transplant practice in elderly recipients." ■

TAKEAWAY POINTS

- Researchers describe the OPTIMIZE trial that will compare standard immunosuppression with tacrolimus and mycophenolate mofetil with a low exposure tacrolimus regimen in combination with everolimus in de novo renal transplantation in elderly patients.
- The primary endpoint will be successful transplantation, defined as survival with a functioning allograft with an estimated glomerular filtration rate >30 mL/min/1.73 m^2 (stratum 1) or eGFR >45 mL/min/1.73 m^2 (stratum 2).
- Secondary end points are the primary end point analyzed separately per stratum and assessment at months 12 and 24 of death, graft loss, and eGFR below 30 or 45 mL/min/1.73 m^2.

Outcomes of Simultaneous Heart-Kidney Transplant versus Kidney Transplant Alone

In heart transplant recipients, end-stage renal insufficiency is associated with poor postoperative survival of approximately 50% after 12 months. To improve patient outcomes, simultaneous heart-kidney transplantation is increasingly being performed. According to data from the Organ Procurement and Transplantation Network, simultaneous heart-kidney transplantation has increased nearly 5-fold from 2004 to 2018 (44 vs 202). However, compared with kidney transplants alone, heart-kidney transplants are associated with severely increased in-hospital mortality of up to 22% and, thus, reduced 1-year survival rates that range from 62% to 84%.

There are limited data on renal graft outcomes in the setting of simultaneous heart-kidney transplantation; however, reports of reduced graft survival in simultaneous heart-kidney transplantation have led to concern regarding adequate organ utilization. **Oliver Beetz, MD,** and colleagues conducted a retrospective study designed to evaluate prognostic factors and outcomes of patients undergoing simultaneous heart-kidney transplant in comparison with patients undergoing solitary kidney transplantation at one of the largest transplant centers in Europe. Results of the study were reported online in *BMC Nephrology* [doi.org/10.1186/s12882-021-02430-x].

The study examined data from patients who underwent heart-kidney transplantation and from a matched cohort of patients who underwent solitary kidney transplantation at the Hannover Medical School, Hannover, Germany, between September 1987 and October 2019. Matching was based on date of transplant (±4 years), sex, age, body mass index, cold ischemic time, human leukocyte antigen-mismatches, current and highest pre-existent percent panel reactive antibodies, and donor time in the intensive care unit. Electronic medical records from participating departments were used to analyze peri- and postoperative course of each patient.

The total study cohort included 27 patients who underwent simultaneous heart-kidney transplant and 27 matched solitary kidney transplant recipients. Among the 27 heart-kidney transplant recipients, 17 were male, and median age was 54 years. There were no statistically significant differences in characteristics of the heart-kidney transplant recipients compared with those of the kidney transplant recipients, with the exception of the rate of prior dialysis (18 [66.7%] vs 27 [100%], respectively; $P<.001$) and time on dialysis prior to transplant (9 vs 86 months, respectively; $P<.001$).

Implantation times of renal grafts were shorter in the patients undergoing heart-kidney transplant (101 minutes vs 134 minutes; $P=.022$), as were cold ischemia times (900 minutes vs 1118 minutes; $P=.269$). The rates of transfusion of packed red blood cells and fresh frozen plasma and the number of units transfused were significantly higher in the heart-kidney transplantations than in the solitary kidney transplantations.

In patients who underwent solitary kidney transplantation, since 2002, induction therapy with basiliximab was performed. Two of the 27 patients received anti-thymocyte globulin and one patient received alemtuzumab. Long-term therapy was based on cyclosporine A until 2017. After 2017, tacrolimus was mainly used as calcineurin inhibitor. In 2005, triple therapy was established, including mycophenolate mofetil, everolimus, or mycophenolic acid in addition to steroids.

Median patient follow-up was 100.33 months. In patients in the heart-kidney transplantation group, time spent in the ICU (5.5 days vs 1 day; $P<.001$) and the length of hospital stay (27 days vs 20 days; $P=.022$) were significantly longer compared with patients in the kidney transplantation only group.

The frequency of postoperative complications was higher in the heart-kidney transplantation cohort. Complications related to the kidney transplant occurred in 10 of the 27 patients: postoperative hematoma (n=3), hemorrhage (n=2), wound infection (n=3), and abnormal duplex sonography (n=3). Eight of the 27 heart-kidney transplantation patients underwent 15 thoracotomies for early complications, including cardiac tamponage (n=10), pericardial empyema (n=1), postoperative hemorrhage (n=1), and deep sternal wound infection (n=3).

In the cohort of solitary kidney transplantation, there was no primary nonfunction observed. There was graft loss in four patients as a result of chronic graft failure/chronic vascular rejection (n=3) and amyloidosis (n=1). Nine grafts were lost due to death; none of the nine patients died during the primary hospital stay.

Five of the patients in the heart-kidney transplantation cohort experienced primary nonfunction of the renal grafts; only one patient was still alive at the time of follow-up. Four of the five patients were considered high risk with a history of prior cardiac surgery requiring sternotomy. The rate of subsequent dialysis in the postoperative course was significantly higher after simultaneous heart-kidney transplantation than after kidney transplantation alone (48.1% [n=13] vs 22.2% [n=6]; $P=.0444$).

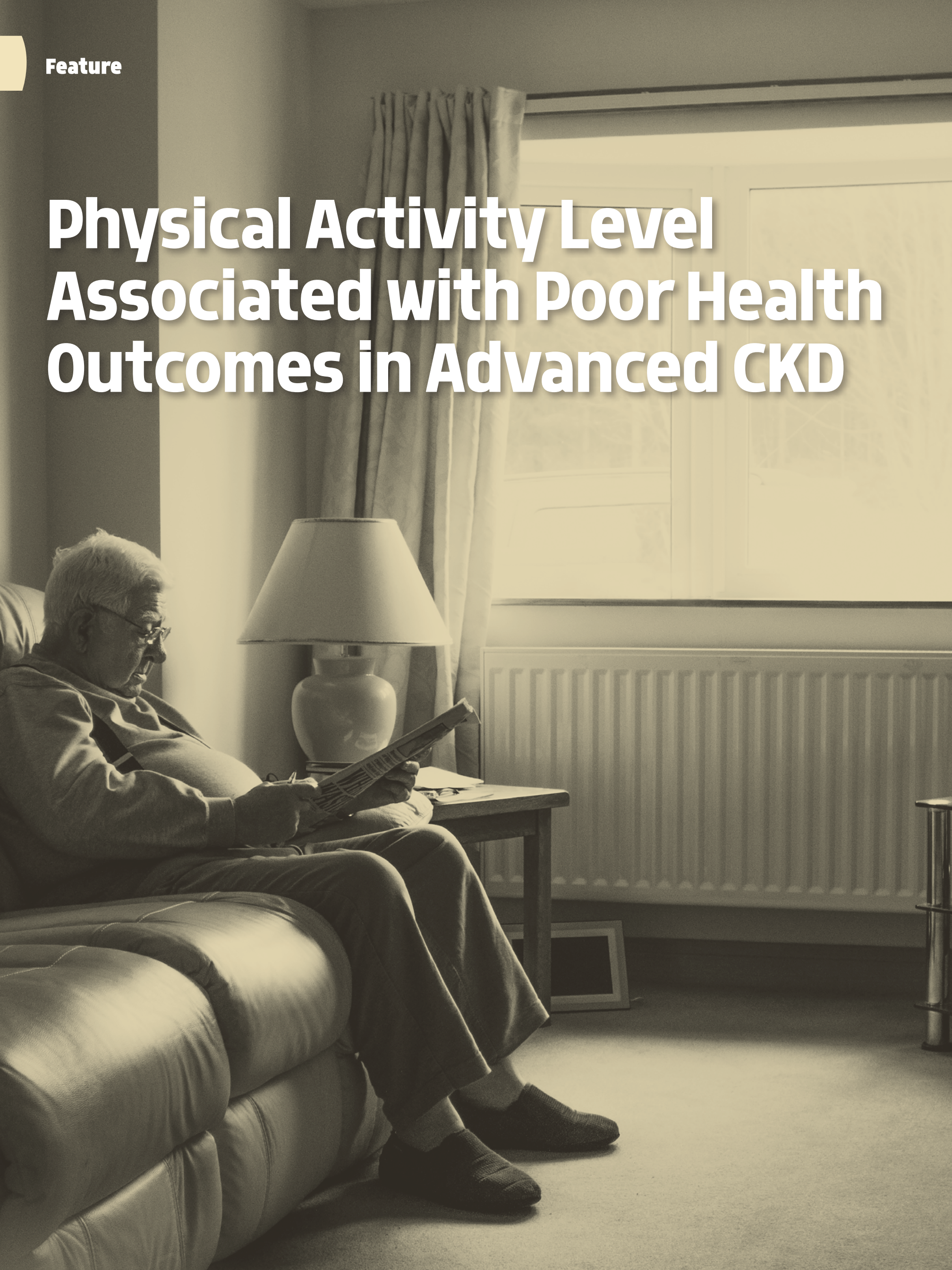
Despite lower 5-year kidney graft survival in the heart-kidney transplantation cohort compared with the solitary kidney transplantation cohort (62.6% vs 92.1%; 111.73 months vs 183.03 months), graft function monitored by estimated glomerular filtration rate over time and patients survival were not significantly inferior in the overall heart-kidney transplantation cohort. However, heart-kidney transplantation in patients with prior heart surgery resulted in poor graft and patient survival (57.00 months and 94.09 months, respectively) compared with patients undergoing kidney transplant alone (183.08 months and 192.71 months; $P<.001$) and with patients undergoing heart-kidney transplant without prior heart surgery (203.22 months [$P=.016$] and 203.22 months [$P=.019$], respectively).

"Our data demonstrate the increased rate of early kidney graft loss and thus significantly inferior graft survival in high-risk patients undergoing simultaneous heart-kidney transplantation. Thus, we advocate for a 'kidney-after-heart' program in such patients to ensure responsible and reasonable utilization of scarce resources in times of ongoing organ shortage crisis," the researchers said. ■

TAKEAWAY POINTS

- Researchers reported results of a retrospective study evaluating prognostic factors and outcomes among 27 patients undergoing simultaneous heart-kidney transplantation in comparison with 27 patients undergoing kidney transplantation alone between September 1987 and October 2019 at a transplant center in Germany.
- Despite lower 5-year kidney graft survival in the heart-kidney transplant cohort (111.73 vs 183.08 months), graft function and patient survival were not significantly inferior in the heart-kidney transplant cohort in general.
- Among patients in the heart-kidney transplant cohort with a history of prior heart surgery, early graft and patient survival were reduced compared with patients in the solitary kidney transplant cohort and with those in the heart-kidney transplant cohort without prior heart surgery.

Physical Activity Level Associated with Poor Health Outcomes in Advanced CKD



The prevalence of chronic kidney disease (CKD) is approximately one in eight individuals; CKD is disproportionately more common in older adults. Those with CKD tend to be more sedentary and have lower levels of physical activity compared with the general population. There are multifactorial explanations for this, most likely related to a combination of malnutrition, sarcopenia, anemia, vascular dysfunction, and neuropathy.

Low levels of physical activity are associated with poor health outcomes such as reduced quality of life and increased cardiovascular disease, hospitalizations, and all-cause mortality. There is also an association between poor physical activity level and worsening of CKD; an increase in physical activity level has been shown to result in modest increases in estimated glomerular filtration rate (eGFR). Level of physical activity is also a modifiable risk factor for adverse outcomes in individuals on hemodialysis and those with mild-to-moderate CKD.

According to **Christie Rampersad, MD,** and colleagues, there are few data available on the association of physical activity level with adverse outcomes in populations with advanced CKD who are not receiving kidney replacement therapy (KRT). As part of the Canadian Frailty Observation and Interventions Trial (CanFIT), patients in that population self-reported physical activity using the Physical Activity Scale for the Elderly (PASE), a questionnaire that includes activities commonly performed by older adults.

Dr. Rampersad et. al. reported results of the multicenter prospective cohort study in the *American Journal of Kidney Diseases* (2021;78(3):391-398). The primary objective of the study was to determine whether lower physical activity levels were associated with adverse health outcomes. The outcomes of interest were all-cause mortality, time to kidney failure, and falls. The patient population included patients with CKD glomerular rate categories 4 and 5 (G4-G5) not receiving KRT. Outcomes were analyzed using time-dependent proportional hazards models and logistic regression models.

Patients were recruited for CanFIT from four Canadian multidisciplinary renal health clinics from September 1, 2012, to July 1, 2018. The study population included 600 adult patients with CKD glomerular filtration rate categories 4 and 5. A total of 579 patients completed PASE assessments at baseline and then annually. Mean age was 72 years and 59% were male. Six patients received a kidney transplant. Mean follow-up time was 1194 days for the primary outcome of mortality and 903 days for the secondary outcome of progression to kidney failure.

The patients were stratified according to PASE score: 24.5% (n=142) had a PASE score of 0-40 (low physical activity); 34.2% (n=198) had a PASE score of 41-90 (light physical activity); and 41.3% (n=239) had a PASE score of >90 (moderate-to-high physical activity). Patients in the moderate-to-high physical activity tertile had a lower prevalence of nearly all comorbidities compared with the tertiles with low and light physical activity, with the exception of the patients with diabetes and neurological disease.

In assessments of the association of physical activity level with mortality, there were 118 deaths during the study period. There was an association of light physical activity and lower mortality risk in the unadjusted-time dependent Cox model only (hazard ratio [HR], 0.62; 95% confidence interval [CI], 0.41-0.92). There was an association between moderate to high physical activity level in both the unadjusted model (HR, 0.23; 95% CI, 0.14-0.39) and following adjustment for age and sex (aHR, 0.35; 95% CI, 0.21-0.60) or adjusted for age, sex, and comorbidities (aHR, 0.48; 95% CI, 0.27-0.85).

During the study period, 204 individuals progressed to kidney failure. There were no significant associations between low or moderate to high physical activity and progression to kidney failure in patients with advanced CKD in either unadjusted or adjusted time-dependent cause-specific hazards models. There were no associations between physical activity levels and progression to kidney failure when the Fine-Gray model was used. The Fine-Gray model did not violate the Cox proportional hazards assumption.

In analysis of all-cause mortality, baseline light physical activity and moderate physical activity were associated with a lower risk of mortality in unadjusted models (HR, 0.58; 95% CI, 0.39-0.88 and HR, 0.30; 95% CI, 0.19-0.48, respectively). Following adjustment for age, sex, and comorbid conditions, there was an association between moderate-to-high physical activity and a 41% reduction in the risk of all-cause mortality (aHR, 0.59; 95% CI, 0.36-0.98).

In the age- and sex-adjusted models, there was an association between moderate-to-high level of physical activity at baseline and a lower risk of progression to kidney failure (aHR, 0.61; 95% CI, 0.42-0.90). There was no association in the unadjusted model (HR, 0.94; 95% CI, 0.67-1.39) or following adjustment for laboratory variables and comorbid conditions (HR, 1.11; 95% CI, 0.74-1.68).

A total of 400 individuals had follow-up assessments. Of those, 129 had a future fall event. In unadjusted and adjusted models, there was no association between moderate to high physical activity level and future falls. Only a history of falls was associated with future falls.

Limitations to the study findings cited by the authors included inherent errors in using a tool that measures physical activity based on self-reporting, the makeup of the study population that was largely of European ancestry with some individuals of Asian ancestry, the inability to adjust for smoking, body mass index, and proteinuria, and the observational study design.

"In conclusion," the researchers said, "our study found that higher levels of physical activity are associated with reduced all-cause mortality in patients with advanced CKD. Interventional studies are now needed to investigate the effect of maintaining or increasing physical activity in the CKD population." ■

TAKEAWAY POINTS

- Researchers conducted a multicenter prospective cohort study to assess whether lower physical activity levels are associated with adverse health outcomes in patients with advanced chronic kidney disease (CKD).
- The outcomes of interest were all-cause mortality, progression to kidney failure, and future falls.
- There was an association between moderate-to-high physical activity and a 41% reduction in the risk of all-cause mortality and a lower risk of progression to kidney failure.

David Cook Named to NKF Board

David J. Cook, MD, MHA, FAHA, has been appointed to the national board of directors of the National Kidney Foundation (NKF). Dr. Cook is the senior vice president at OptumLabs at UnitedHealth Group, responsible for organizational efforts in diabetes and kidney disease.

In a press release from NKF, **Kevin Longino,** CEO of NKF, said, "We're excited for Dr. Cook to join the national board to share his extensive experience in health administration. Kidney disease is a public health crisis affecting 37 million adults in the US and continues to worsen each day due to COVID-19 contributing to an increase in kidney disease. Dr. Cook's insight regarding the future direction of healthcare delivery will be critical as we continue addressing inequities in healthcare and seeking innovative strategies that allow us to help as many people fighting this disease as possible."

Dr. Cook said, "For two decades of ICU practice, and having lost my father to kidney disease, I have seen firsthand the devastating impact kidney disease and end-stage renal failure have on patients and their families. I'm honored to join the National Kidney Foundation board of directors and look forward to helping support the organization's mission of preventing and treating kidney disease."

Conviva Care Centers and Strive Health Expand Collaboration

Conviva Care Centers, a network of 300 primary care physicians (PCPs) specializing in treating seniors, has expanded its relationship with Strive Health, a leader in value-based kidney care. The expanded relationship will deliver specialized kidney disease care management services for eligible patients in Daytona and Jacksonville, Florida, and the surrounding areas. Strive Heath's care teams work with Conviva's PCPs to provide specialized, technology-enabled care services for patients with chronic kidney disease and end-stage kidney disease (ESKD).

In 2020, Strive Health and Conviva Care Centers announced an arrangement that focused on eligible patients in South Florida.

Steve Lee, MD, president of Conviva Physicians Group, said, "Strive Health understands the complexities of kidney disease and works closely with our providers to deliver a seamless experience to our patients. Our locations in northern Florida face the challenges of both urban and rural environments, necessitating partners that will closely collaborate with our teams and tailor their approach to meet the needs of the individual. Working with Strive Health's clinicians helps us advance the preventive, personalized healthcare we offer our patients. We are excited to expand this program."

Chris Riopelle, CEO and cofounder of Strive Health, said, "Strive Health serves as a bridge between nephrology and primary care, delivering transformative and holistic kidney care. Our close collaboration with Conviva has helped elevate the patient experience with this complex chronic condition, and we look forward to expanding these services to more Florida residents and potentially to new Conviva markets in the future."

New President for FMCNA Renal Therapies Group

In a late summer press release, Fresenius Medical Care North American (FMCNA) announced that **Joe Turk** was named president of the company's Renal Therapies Group. Previously, Mr. Turk served as FMCNA's president of home and critical care therapies.

As president of the Renal Therapies Group, he will oversee renal products and pharmaceutical operations, including sales, clinical support, product marketing and management, customer and technical services, and regulatory affairs, with a focus on efficiently delivering new technologies to support living with kidney disease.

"Joe's decades of strategy and market development experience have been critical in expanding our footprint and technologies in home dialysis and critical care since he joined us as part of the NxStage merger in 2019," said **Bill Vale,** FMCNA CEO. "Joe's leadership will be instrumental as we focus on better leveraging best practices across divisions for the benefit of our customers, partners, field teams, and most importantly our patients."

Mr. Turk said, "I am thrilled to bring our exceptional teams together at this important time. We have an incredible opportunity as the market leader to work together to ensure we're providing the highest quality care and renal products to the patients we are privileged to serve."

AKF Names Two Clinical Scientists as Nephrology Fellows

The American Kidney Fund (AKF) has announced that **Christine Limonte, MD,** and **Elizabeth Kermgard, MD,** are the recipients of research funding from the Fund's Clinical Scientist in Nephrology Program. The program has been funding promising emerging clinical researchers in nephrology for more than 30 years. Dr. Limonte is a nephrology clinical research fellow at the University of Washington and Dr. Kermgard is a pediatric nephrology fellow at Children's Hospital Los Angeles.

LaVarne A. Burton, AKF president and CEO, said, "We are proud to award our newest AKF Clinical Scientist in Nephrology fellowships to two impressive women who are paving the way to advance clinical research and have a lasting impact on people with kidney disease. We are grateful for the support of our funders for their generosity in helping to fund this important research program, which has made invaluable contributions to our understanding of kidney disease and improvements in patient care for more than 30 years."

Dr. Limonte's research focuses on utilizing novel analytics techniques to determine whether blood vessel disease in the back of the eye can reveal information about kidney function and kidney disease. Dr. Kermgard is studying the relationship between gut microbiome and CKD, and how the interactions of bacteria in the body may impact normal bone growth and turnover.

Moving Patients from Dialysis to Transplant

The National Kidney Foundation (NKF) has released a position paper establishing a path for research and innovation to address barriers to access to kidney transplantation, availability of donor organs, and long-term allograft survival in the United States. The paper was developed by 16 nephrology experts from 13 institutions.

In a press release, lead author, **Krista L. Lentine, MD, PhD,** of the Saint Louis University Center for Abdominal Transplantation, said, "While kidney transplantation provides the best treatment option for kidney failure to thousands of patients each year, the goal of universal access to this treatment remains elusive. Addressing the priorities outlined in this research agenda had the potential to transform kidney patient care by expanding

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opportunities for safe living donation, improving waitlist access and transplant readiness, maximizing use of available deceased donor organs, and extending graft longevity."

Based on a roundtable discussion in December 2019 that included nephrologists, surgeons, NKF leadership, and patients, seven priorities for research innovations and 23 recommendations were developed. The seven priorities are: (1) expand living-donor kidney transplantation; (2) improve management and readiness of the kidney waitlist; (3) reduce the number of kidneys removed for transplant but not used; (4) increase organ acceptance using novel technology; (5) preserve, resuscitate, or evaluate kidney allografts before implementation; (6) sustain one transplant for life; and (7) optimize transplantation for pediatric recipients.

NKF CEO, **Kevin Longino,** said, "One of our top priorities at NKF is to make transplantation available to everyone who needs or wants a transplant. These recommendations will help frame our research and funding initiatives to accelerate innovation and create the solutions we need to make transplantation a reality for all."

Amgen Joins AKF as Corporate Member

In a recent press release, the American Kidney Fund (AKF) announced that Amgen has joined the 2021 class in the fund's Corporate Membership Program as a Champion-level member. The program helps support AKF's programs and services that fight kidney disease and help patients live healthier lives. Amgen's membership funds AKF's work to advance kidney disease awareness, prevention, early detection, treatment, and research.

LaVarne A. Burton, president and CEO of AKF, said, "We are thankful to Amgen for once again joining us as a Champion-level member in the AKF Corporate Membership Program. Amgen's generous support of our lifesaving initiatives helps AKF raise awareness of kidney disease, support clinical research that improves the quality of care for kidney patients, and directly assist one out of every six US dialysis patients with healthcare expenses."

Amgen and AKF have had a strong partnership for more than three decades with Amgen's support of the fund's patient-focused programming. Most recently, Amgen has supported AKF's educational initiative on secondary hyperparathyroidism, a condition commonly associated with kidney failure.

Ned Endler, executive director at Amgen, said, "Amgen is pleased to join the American Kidney Fund's Corporate Membership Program at the Champion level and help AKF enable all people with kidney disease to live their healthiest lives. We are proud to support AKF's meaningful programs and resources, including kidney disease management education, award-winning public and professional materials, accredited continuing education courses, and webinars."

NKF-ASN Task Force Report Finalized

The final report from the National Kidney Foundation (NKF)-American Society of Nephrology (ASN) Task Force on Reassessing the Inclusion of Race in Diagnosing Kidney Diseases has been submitted for publication. In a joint press release, the NKF and the ASN congratulated the task force for their work.

The press release states, "On behalf of the leadership of NKF and ASN, we are excited for the kidney community—as well as other stakeholders, particularly the medical students, residents, and fellows who have spearheaded the call to action on this important issue—to consider the task force's recommendations for how best to remove race modifiers from the assessment of kidney function. Additionally, we thank each member of the task force for their remarkable effort, thoughtfulness, and cooperation in completing their charge.

"By identifying an initial approach that does not incorporate specification of an individual's race, is not based on existing equations, and should be able to be rapidly implemented in all laboratories, the NKF-ASN Task Force has completed its charge to find a race-free approach for estimation of GFR [glomerular filtration rate]. The task force's final report is currently under review. Once the final report is published and publicly available, we look forward to laboratories, institutions, and other entities adopting this equation to provide a harmonized, race-free estimation of kidney function.

FDA Approves Korsuva™ for Pruritus

In late summer, the US FDA approved Korsuva™ (difelikefalin) for injection for the treatment of moderate-to-severe pruritus associated with chronic kidney disease in adults undergoing hemodialysis. In a press release from Cara Therapeutics and Vifor Pharma, the companies said the approval was based on the New Drug Application filing that was supported by positive data from two pivotal phase 3 trials—KALM-1, conducted in the United States, and the global KALM-2.

Derek Chalmers, PhD, DSc, president and CEO of Cara Therapeutics, said, "The FDA

CONFERENCE COVERAGE SPRING CLINICAL MEETINGS

Pooled Results of Roxadustat Phase 3 Studies

Daniel Coyne, MD, and colleagues reported pooled results from roxadustat phase 3 studies vis-à-vis the rates of red blood cell transfusion and volume-related adverse events post-transfusion among non-dialysis-dependent chronic kidney disease (NDD-CKD) patients enrolled in studies of roxadustat versus placebo.

The pooled results were reported during a virtual poster session at the NKF Spring Clinical Meetings 2021. The poster was titled *Risk of RBC Transfusion and Volume-Related Adverse Events in Patients with Non-Dialysis-Dependent Chronic Kidney Disease: Pooled Results from Roxadustat Phase 3 Studies.*

Roxadustat is an oral hypoxia-inducible factor prolyl hydroxylase inhibitor. The pooled results were from three double-blind, placebo-controlled, phase 3 studies. Patients in the roxadustat group received roxadustat in doses to maintain hemoglobin (Hb) at 11 gm/dL. To reduce regional variation, the transfusion rate was calculated in US patients, based on Hb <8, 8 to <10, and ≥10 gm/dL on treatment up to 28 days after last dose. The rates of volume-related adverse events were assessed during the 14 days post-transfusion period and during the follow-up period.

The risk of red blood cell transfusion over 52 weeks was reduced by 74% with roxadustat versus placebo in the global NDD-CKD patient pool (hazard ratio [HR], 0.26; 95% confidence interval [CI], 0.21-0.32; $P<.0001$) and by 81% in the subgroup of US patients (HR, 0.19; 95% CI, 0.12-0.32; $P<.0001$).

In the US patients, the transfusion rate was ~4-fold higher in patients who achieved Hb <10 vs ≥10 gm/dL, regardless of treatment arm (for roxadustat, 175.2 vs 6.4 events/100 patient exposure years; for epoetin alfa, 174.4 vs 7.2 events/100 patient exposure years).

The risk of volume-related adverse events globally was greater in the 14-day post-transfusion period for both arms: roxadustat, 147.1 events/100 patient exposure years versus 13.1 during follow-up; placebo, 121.1 versus 13.4, respectively.

In conclusion, the researchers said, "Roxadustat reduced the risk of red blood cell transfusion versus placebo in patients with NDD-CKD. In US patients, risk of transfusion was lowest at achieved Hb ≥10 gm/dL, and globally, volume-related adverse events were higher in the 2-week post-transfusion period."

Source: Coyne D, Provenzano R, Szczech L, et al. Risk of RBC transfusion and volume-related adverse events in patients with non-dialysis-dependent chronic kidney disease: Pooled results from roxadustat phase 3 studies. Abstract of a poster presented at the National Kidney Foundation virtual Spring Clinical Meetings 2021 (Abstract #165), April 9, 2021.

approval of Korsuva injection is a transformational milestone for Cara and a significant advancement for the substantial number of adult hemodialysis patients suffering from moderate-to-severe pruritus. We look forward to working closely with our commercial partner, Vifor Pharma, to launch Korsuva injection in the US in the coming months. We extend our deepest gratitude to the patients who participated in our KALM-1 and KALM-2 clinical trials, the study investigators, and especially our employees, as their commitment through over 10 years of collective effort made this important milestone possible."

Frank Maddux, MD, global chief medical officer of Fresenius Medical Care, said, "We are pleased to see that Korsuva injection has received FDA approval as the first treatment option approved for moderate-to-severe pruritus in adult CKD patients on hemodialysis. Participating in the robust clinical trial program we have learned that Korsuva injection represents an effective treatment option. We have seen substantial improvement in symptoms and meaningful relief for people suffering from severe and debilitating itch."

Vifor Pharma expects to begin promoting Korsuva injection in the first quarter of 2022, with reimbursement expected in the first half of 2022, subject to Centers for Medicare & Medicare Services guidelines.

Budget Impact Model for Kidney-IntelX™ Testing Shows Significant Savings

Renalytix AI, Inc., has released results from an external chronic kidney disease (CKD) budget impact analysis projecting 5-year savings of $1.1 billion for a population of 100,000 patients with type 2 diabetes and CKD tested with the Renalytix KidneyIntelX™ testing solution. According to a press release, the savings were driven by more effective pharmacy management and appropriate specialist referral compared with current standard of care for patients at high risk for disease progression and kidney failure.

The clinical and cost analysis concluded that health systems and insurance plans would realize the cost savings based on slowed disease progression (52% of savings), delayed or prevented dialysis and transplants (32% of savings), and reduced dialysis crashes (11% of savings).

CDPHP president and CEO, **John D. Bennett,** said, "These findings are significant and further demonstrate that predicting kidney disease risk at its earliest stages—when it matters most—is a major benefit to patients, providers, and payers."

The budget impact model was developed in collaboration with Boston Healthcare Associates, in accordance with the International Society for Pharmacoeconomics and Outcomes Research good practices. ■

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Abstract Roundup

COVID-19

AKI in Children with SARS-CoV-2 Infection with and without MIS-C

Frontiers in Pediatrics. doi:10.3389/fped.2021.692256

Researchers, led by **Manpreet K. Grewal, MD,** conducted a retrospective chart review to examine the prevalence and factors associated with the risk of acute kidney injury (AKI) in pediatric patients with SARS-CoV-2 infection and multisystem inflammatory syndrome in children (MIS-C).

The review included 113 patients with SARS-CoV-2 infection with and without MIS-C who were admitted at Children's Hospital of Michigan from March to August 2021. The final analysis included 92 patients. Of those, 24% (n=22) developed AKI, with eight of the 22 (36%) developing AKI stage 3. The prevalence of AKI was substantially higher in patients with MIS-C (54%; 15/28) than in those with acute SARS-CoV-2 infection (11%; 7/64), *P*<.001.

Overall, compared with patients without AKI, those with AKI were older (11 vs 6.5 years; *P*=.007), were Black (86% vs 58%; *P*=.0028), had a diagnosis of MIS-C (68% vs 19%; *P*<.001), required admission to the intensive care unit (91% vs 20%; *P*<.001), had cardiac dysfunction (63% vs 16%; *P*<.001), required inotropic support (59% vs 6%; *P*<.001) and had a greater elevation in inflammatory markers. In multivariable analysis, the most significant predictors for AKI were the requirement of inotropes (odds ratio [OR], 22.8; *P*<.001), Black race (OR, 8.8; *P*=.023), and MIS-C diagnosis (OR, 5.3; *P*=.013). All of the patients had recovery of kidney function, and none required kidney replacement therapy.

In conclusion, the authors said, "Children with acute SARS-CoV-2 infection and MIS-C are at risk for AKI, with the risk being significantly greater with MIS-C. The pathogenesis of AKI in acute SARS-CoV-2 infection appears to be a combination of both renal hypoperfusion and direct renal parenchymal damage whereas in MIS-C, the renal injury appears to be predominantly prerenal from cardiac dysfunction and capillary leak from a hyperinflammatory state. These factors should be considered by clinicians caring for these children with a special focus on renal protective strategies to aid in recovery and prevent additional injury to this high-risk subgroup."

COVID-19 Vaccine Efficacy in Kidney Transplant Recipients

American Journal of Transplantation. doi.org/10.1111/ajt.16814

Kidney transplant recipients treated with belatacept have reported suboptimal responses to mRNA COVID-19 vaccine after two vaccine injections. **Nathalie Chavarot, MD,** and colleagues performed the humoral response to kidney transplant recipients treated with belatacept without a history of SARS-CoV-2 infection who received three injections of BNT162b2-mRNA COVID-19 vaccine. The analysis also examined vaccine immunogenicity in belatacept-treated kidney transplant recipients with prior COVID-19 and characterized symptomatic COVID-19 infections after vaccine in belatacept-treated kidney transplant recipients.

Of the 62 kidney transplant recipients without a history of COVID-19, 58% were male, and median age was 63.5 years. Of those, only four patients (6.4%) developed anti-SARS-CoV-2 IgG with low antibody titers (median 209 AU/mL); 71% were treated with mycophenolic acid and 100% were treated with steroids in association with belatacept. Conversely, in all five kidney transplant recipients with history of prior COVID-19, mRNA vaccine induced strong antibody response with high antibody titers (median 10769 AU/mL) after two injections.

In 35 kidney transplant recipients not treated with belatacept, seroprevalence after three vaccine doses was 37.1%. Twelve kidney transplant recipients developed symptomatic COVID-19 following vaccination, including severe forms (50% or mortality). Five percent of fully vaccinated patients developed breakthrough COVID-19.

The researchers said, "Administration of a third dose of BNT162b2 mRNA COVID-19 vaccine did not improve immunogenicity in kidney transplant recipients with belatacept without prior COVID-19. Other strategies aiming to improve patient protection are needed."

CHRONIC KIDNEY DISEASE

External Validation of Kidney Failure Prediction Models

Journal of the American Society of Nephrology. 2021;32(5):1174-1186

There are various models designed to predict the risk of kidney failure among patients with chronic kidney disease (CKD). However, according to **Chava L. Ramspek, PhD,** and colleagues, there have been no head-to-head comparisons of guideline-recommended models, there are few data available regarding validation of the models in patients with advanced CKD, and most of the models do not account for competing risk.

The researchers utilized data on patients with advanced CKD from two large cohorts, the European Quality Study (EQUAL) and the Swedish Renal Registry (SRR), to externally validate 11 existing models of kidney failure, taking the competing risk of death into account. The outcome of the models was kidney failure, defined as end-stage kidney disease treated with renal replacement therapy.

The analysis included data on 1580 patients from EQUAL and 13,489 patients from SRR. The average c statistic over the 11 validated models was 0.74 in the EQUAL cohort and 0.80 in the SRR cohort. In most models with longer prediction horizons, the risk of kidney failure was considerably overestimated. The 5-year Kidney Failure Risk Equation (KFRE) overpredicted risk by 10% to 18%, The four- and eight-variable 2-year KFRE and the 4-year Grams model showed "excellent calibration and good discrimination in both cohorts."

In summary, the authors said, "Some existing models can accurately predict kidney failure in patients with advanced CKD. KFRE performed well for a shorter time frame (2 years), despite not accounting for competing events. Models predicting over a longer time (5 years) overestimated risk because of the competing risk of death. The Grams model, which accounts for the latter, is suitable for longer-term predictions (4 years)."

Muscle Mass Measured by CTMM-L3 as Predictor of Mortality in CKD

Journal of Renal Nutrition. 2021;31(4):342-350

Evaluation of nutritional disturbances in patients with chronic kidney disease (CKD) can be achieved using measurement of muscle mass. There are associations between low muscle mass and increased morbidity and mortality. According to **André V. Bichels, MS,** and colleagues, assessment of muscle mass by computed tomography at the third lumbar vertebra region (CTMM-L3) is an accurate method not subject to errors from fluctuation in the hydration status. The researchers conducted a prospective observational cohort study designed to determine whether CTMM-L3 would predict mortality in nondialyzed CKD stage 3-5 patients.

The study cohort included 223 nondialyzed patients with CKD; mean age was 60.3 years, 64% were male, 50% had diabetes, and mean glomerular filtration rate was 20.7 mL/min/1.73 m^2. The software Slice-O-Matic was used to measure muscle mass by CTMM-L3; measurements were analyzed according to percentile and adjusted for sex. Nutritional parameters, laboratory data, and comorbidities were evaluated. Follow-up for mortality was 4 years.

During the study period, 63 of the 223 patients died; the main cause of death was cardiovascular disease. Patients who died were older, had lower hemoglobin and albumin, and lower muscle markers. There was an association between CTMM-L3 below the 25th percentile and higher mortality, according to the Kaplan-Meier curve (*P*=.017) and in Cox regression analysis (crude hazard ratio [HR], 1.87; 95% confidence interval [CI], 1.11-3.16). The association remained after adjusting for potential confounders (HR, 1.83; 95% CI, 1.02-3.30).

"Low muscle mass measured by computed tomography at the third lumbar vertebra region is an independent predictor of increased mortality in nondialyzed CKD patients," the researchers said.

Review and Meta-Analysis: Platelet Function in CKD

Journal of the American Society of Nutrition. 2021;32(7):1583-1598

Patients with chronic kidney disease (CKD) are at high risk for thrombotic and hemorrhagic complications. Central to those complications are abnormalities in platelet function. According to **Constance C. F. M. J. Baaten, MS,** and colleagues, reports on platelet function in relation to CKD are conflicting, and vary from decreased platelet reactivity to normal or increased platelet responsiveness. Findings on the direct effects of uremic toxins on platelet function have also been variable.

The researchers conducted a systematic review and meta-analysis of platelet activity in CKD, with a focus on nondialysis-induced effects in order to clarify how CKD affects platelet function.

The review included 73 studies; of those, 11 described CKD's effect on ex vivo platelet aggregation and were included in the meta-analysis. Findings on platelet abnormalities in CKD were inconsistent; however, bleeding time was mostly prolonged and platelet adhesion mainly reduced. The meta-analysis also revealed significant reduction in maximal platelet aggregation in patients with CKD upon collagen stimulation. The researchers found that relatively few uremic toxins have been examined for direct effects ex vivo; ex vivo analyses had varying methods and results, revealing both platelet-stimulating and inhibitory effects. Eight of the 12 uremic toxins tests in animal models mostly induced prothrombotic effects.

"Overall, most studies report impaired function of platelets from patients with CKD," the researchers said. "Still, a substantial number of studies find platelet function to be unchanged or even enhanced. Further investigation of platelet reactivity in CKD, especially during different CKD stages, is warranted."

Determinants of Exercise Capacity in CKD

Journal of the American Society of Nephrology. 2021;32(7):1813-1822

Patients with chronic kidney disease (CKD) commonly experience impaired capacity for exercise, a complication that is associated with poor survival. There is growing interest in applying exercise as a diagnostic tool or as therapy in patients with CKD. However, according to **Shanmugakumar Chinnappa, MBBS, MRCP,** and colleagues, there are few data on the understanding of exercise physiology in CKD.

The researchers conducted a cross-sectional study to examine the role of cardiac (central) and noncardiac (peripheral) determinants of exercise capacity in CKD. The study cohort included 70 male patients with CKD stages 2 to 5 without diabetes or cardiac disease, 35 healthy controls, and 25 patients with heart failure. Peak O_2 consumption ($VO2_{peak}$) and peak cardiac output were measured simultaneously using an integrated car-

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diopulmonary exercise test using CO_2 rebreathing technique. The researchers also calculated peak peripheral O_2 extraction (C[a-v]O_2), the peripheral determinant (the ability of exercising skeletal muscles to extract oxygen). The individual contribution of central and peripheral factors was quantitatively assessed using multiple regression analysis and Bayesian information criteria (BIC) changes.

Compared with the healthy controls, in patients with CKD, the VO_{2peak} was impaired proportionate to its severity. In the healthy controls and the cohort with heart failure, the predominant determinant of VO_{2peak} was peak cardiac output. In patients with CKD, C(a-v)O_2 played a more significant role in determining VO_{2peak} (ß=0.68, P<.001), compared with cardiac output (ß =0.63, P<.001). Further, the magnitude of BIC reduction was greater for C(a-v)O_2 compared with cardiac output (BIC, 298.72 vs 287.68) in CKD.

In conclusion, the researchers said, "In CKD, both peak cardiac output and peak C(a-v)O_2 are independent predictors of VO_{2peak}, and the more significant role played by peak C(a-v)O_2 highlights the independence of noncardiac factors in determining exercise capacity in CKD."

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DIALYSIS

Restriction of Dietary Potassium in Hemodialysis Patients

Journal of Renal Nutrition. 2021;31(4):411-420

Clinical practice guidelines for hemodialysis patients call for restriction of dietary potassium intake due to concerns regarding potential hyperkalemia that could lead to malignant arrhythmias and mortality. However, according to **Yoko Narasaki, MD, PhD,** and colleagues, there are few data available informing recommendations for dietary potassium intake in patients on hemodialysis. The researchers conducted a study to examine the relationship between dietary potassium intake and risk of mortality in a prospective cohort of hemodialysis patients.

The prospective Malnutrition, Diet, and Racial Disparities in Chronic Kidney Disease study included 415 hemodialysis patients from 16 outpatient dialysis clinics. Food Frequency Questionnaires administered from October 2011 to March 2015 were used to obtain data on dietary potassium intake. Cox regression models were used to assess associations between baseline dietary potassium intake stratified into tertiles and risk of mortality. Logistic regression was used to identify clinical characteristics associated with low dietary potassium intake (i.e., the lowest tertile).

In expanded case-mix Cox analyses, patients in the lowest tertile of dietary potassium intake had higher mortality (ref: highest tertile) (adjusted hazard ratio [aHR], 1.74; 95% confidence interval [CI], 1.14-2.66). Following adjustment for laboratory and nutritional covariates, the associations had greater magnitude of risk (aHR, 2.65; 95% CI, 1.40-5.04).

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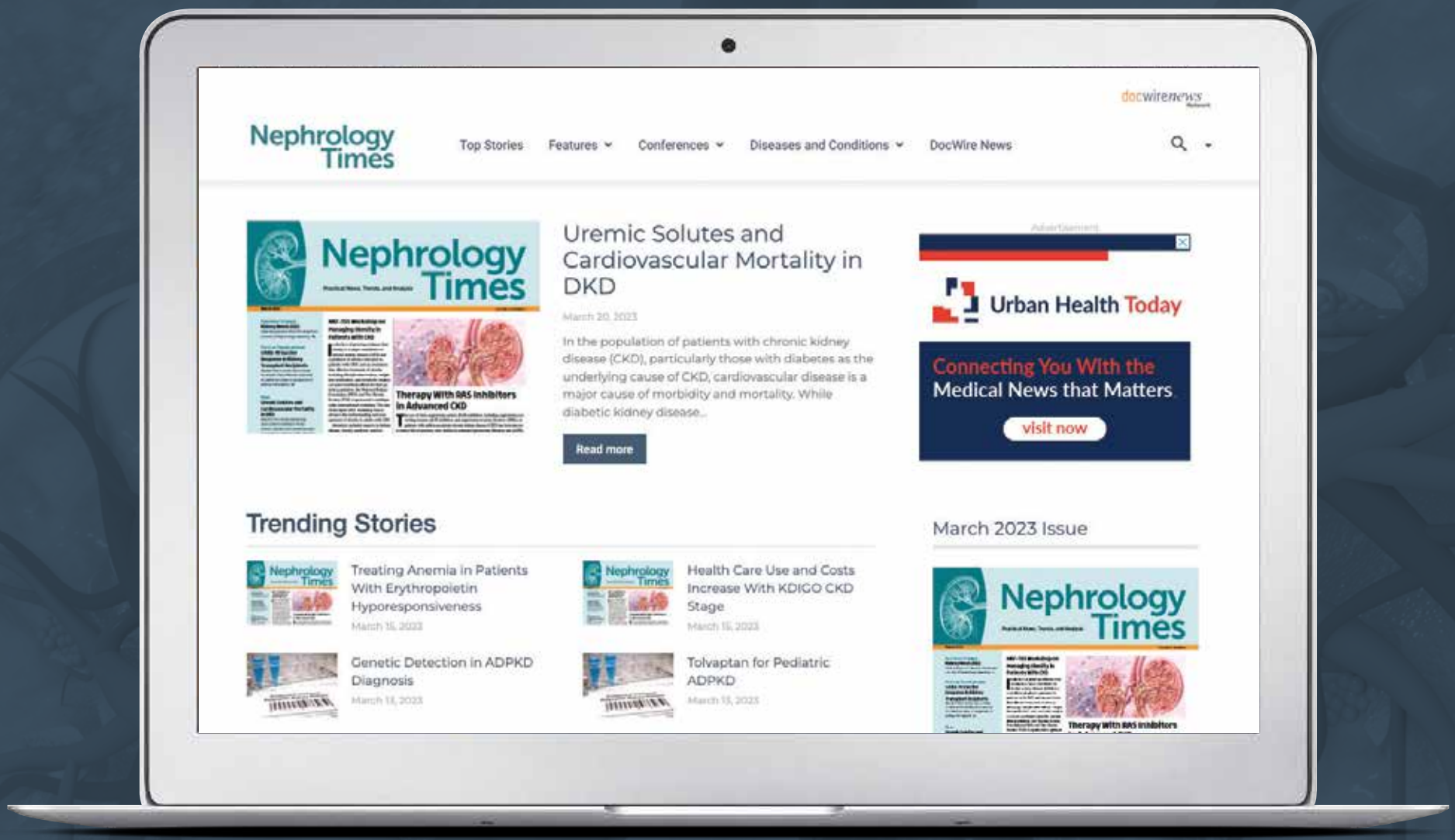

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In expanded case-mix restricted cubic spline analyses, there was a monotonic increase in risk of death with incrementally lower intake of dietary potassium. In expanded case-mix logistic regression models, low dietary potassium intake was associated with female sex, higher serum bicarbonate, and lower dietary energy, protein, and fiber intake.

In conclusion, the researchers said, "In a prospective cohort of hemodialysis patients, lower potassium intake was associated with higher mortality risk. These findings suggest that excessive dietary potassium restriction may be deleterious in hemodialysis patients, and further studies are needed to determine the optimal dietary potassium intake in this population."

Print-only Content

TRANSPLANTATION

Preemptively Waitlisting Patients with Top 20% EPTS Scores

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For most patients with end-stage kidney disease (ESKD), kidney transplantation is associated with the best outcomes. Patients with Estimated Post-Transplant Survival (EPTS) scores in the top 20% are prioritized by the national Kidney Allocation System for expedited access to optimal deceased donor kidneys. **Jesse D. Schold, PhD,** and colleagues conducted analysis of adults ≥18 years of age in the United States Renal System database with top 20% EPTS scores who had been previously waitlisted or who initiated dialysis between 2015 and 2017. Using unadjusted and adjusted multivariable survival models, the analysis included time to waitlist placement, transplantation, and mortality.

A total of 42,445 patients had top 20% EPTS scores; mean age was 38.0 years, 57% were male, 49% were White, and 31% were Black. Of the 42,445, 7922 were preemptively waitlisted. Among 34,523 patients who initiated dialysis, the 3-year cumulative waitlist placement incidence was 37%.

There were independent associations between waitlisting and race, income, and having noncommercial insurance. Waitlisting was less likely for Black versus White patients, and for patients in the lowest-income neighborhoods compared with those in the highest-income neighborhoods. Among the patients who initiated dialysis, 61% lost their top 20% EPTS status within 30 months compared with 18% of patients who were preemptively listed.

The 30-year incidence of deceased and living donor transplantation was 5% and 6%, respectively, for those who initiated dialysis. The corresponding percentages were 26% and 44%, respectively, for those who were preemptively listed.

"Many patients with ESKD qualifying with top 20% EPTS status are not placed on the transplant waitlist in a timely manner, with significant variation on the basis of demographic and social factors. Patients who are preemptively listed are more likely to receive benefits of top 20% EPTS status. Efforts to expedite care for qualifying candidates are needed, and automated transplant referral for patients with the best prognoses should be considered," the researchers said. ■

Sarah Tolson

An Overview of the No Surprises Act

If you are a regular reader of this column, you are probably familiar with the No Surprises Act. The act was passed in December 2020 with the intent of protecting patients from unexpected out-of-network (OON) medical bills. As someone who has received surprise OON bills from radiology and lab companies used by my in-network physician, I can appreciate this legislation. As someone who battles with insurance companies for the reimbursement owed to my clients for the services they've rendered, this act presents both challenges and advantages for providers that render surprise OON services.

KEY POINTS OF THE NO SURPRISES ACT

To effectively prepare your practice for the No Surprises Act, it is beneficial to understand the key points of the act. Reviewing these key points is the focus for this edition of From the Field; in the next edition we will discuss steps you can take to prepare your practice for the act.

The act considers surprise scenarios to be situations where the patient receives services from an OON provider at an in-network facility. An example of this that I have seen frequently with nephrologists is when the doctor is rounding at a hospital that is in-network for a patient, but the nephrologist is OON with the patient's insurance.

The next key point has to do with the type of insurance plan involved and the state where services are rendered. The No Surprises Act defers to state laws that cover surprise medical billing—but not every state has a law. Additionally, there are certain types of insurance plans that states have no jurisdiction to regulate, such as federal health care exchange plans and ERISA plans. To clarify, if a patient is covered by an insurance plan administered by the state and services were rendered in a state that has a no surprise billing law, the federal No Surprises Act would not apply. However, if a patient is covered by a federal insurance plan, the No Surprises Act would apply.

The act protects patients by limiting the amount they are required to pay to OON providers to that of their estimated in-network co-insurance and/or deductible amounts. The patient's cost-sharing amount is based on what is referred to in the act as a "qualifying payment amount," or QPA. The QPA is defined as the lesser of the billed charges or the patient's health plan's median contracted rate. Additionally, the act has provisions for determining the amount to be paid to the OON provider. These provisions are as follows:

- An amount determined by an applicable All-Payer Model Agreement under section 1115A of the Social Security Act;
- If there is not an applicable all payer model agreement, an amount determined by a specified state law;
- If there is not an applicable all payer model agreement or state law, an amount agreed upon by the insurance plan and the provider;
- If the three previous conditions do not apply, an amount determined by an independent dispute resolution (IDR) entity.

Providers must attempt to come to an agreement with an insurance company regarding the reimbursement rate for OON services for a minimum of 30 days, after which the insurance company must issue an initial payment or denial to the provider. In the event the provider does not agree with the initial payment, the provider may initiate the IDR process within 4 days of the receipt of the initial payment.

At the conclusion of the IDR process, the provider may not take the other party to IDR for the same item or service for 90 days. This means that once a provider concludes the IDR process with an insurance company—for example, for hospital E & M encounters—the provider may not bring the insurance company to IDR for 90 days (allowing for the possibility of denials or underpayments from the insurance company for OON services that would not be subject to IDR).

The act also requires providers to publish a notice on balance billing protections that may be available for patients. CMS has provided on the CMS.gov website a template disclosure that providers may use (form CMS-10780).

In the next edition of this column, we will cover some processes and protections for providers to consider in their practices to mitigate the impact of the No Surprises Act. Please stay tuned. ■

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