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Practical News, Trends, and Analysis

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Water Intake in Patients with Autosomal Dominant Polycystic Kidney Disease

Autosomal dominant polycystic kidney disease (ADPKD), the most common genetic kidney disease, is due to heterozygous germline variants in either *PKD1* or *PKD2*. In young adults, the phenotype of ADPKD is characterized by multiple small subcentimeter kidney cysts that expand, causing chronic kidney pain and kidney failure by mid-life. Results of studies conducted in the past 10 years suggest that arginine vasopressin is a critical growth factor for kidney cysts, making it a target for therapeutic intervention in patients with ADPKD.

Arginine vasopressin is reduced with increased water intake, which has been suggested as an approach to slow the growth of cysts in the kidney. However, findings in preclinical models of cystic kidney disease have been inconsistent, and previous trials in humans were uncontrolled and of short duration. **Gopala K. Rangan, PhD,** and colleagues conducted a randomized controlled trial designed to test the hypotheses that kidney cyst growth in patients with ADPKD would be reduced with prescription of increased water intake to a degree to lower urine osmolality to iso-osmolar levels over 3 years. Results of the study were reported online in *NEJM Evidence* [doi: 10.1056/EVIDoa2100021].

The researchers utilized the validated method by Wang et al. to

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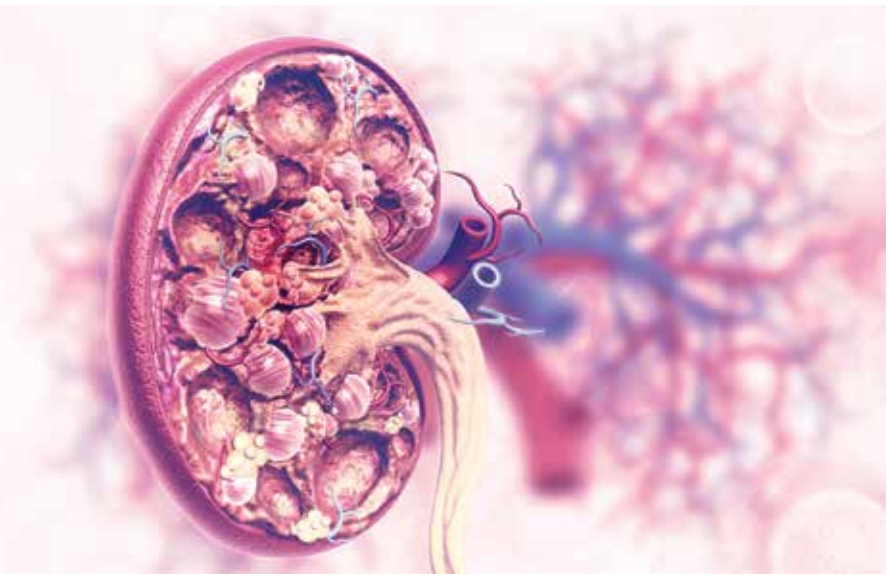

Mortality and Resource Use: CKD versus Nonmetastatic Cancer

Chronic kidney disease (CKD) is associated with poor outcomes and high burden of healthcare resources. It has been challenging to communicate the importance of preventing and managing CKD to decision-makers, in part because the clinical outcomes from advanced kidney disease are not well understood, according to **Marcello Tonelli, MD, SM, MSC,** and colleagues. Conversely, decision-makers and the general public are aware of the risks of mortality and disability associated with cancer, particularly the most common solid malignant tumors.

Dr. Tonelli et al. conducted a cohort study designed to compare clinical consequences of incident severe CKD and the first diagnosis with a solid malignant

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Kidney Failure Risk Equation and Patterns of Healthcare Resource Utilization

In patients with chronic kidney disease (CKD), as kidney function declines the costs of care increase rapidly due, in part, to higher rates of hospitalizations and visits to the emergency department. The approximately 10% to 15% of the population affected by CKD account for 20% of healthcare costs. Patients with CKD commonly experience comorbid conditions such as diabetes mellitus and congestive heart failure, contributing additional burden to the cost of care.

Costs of care for patients with kidney failure requiring dialysis are exponentially higher than for patients with CKD. In addition, patients on dialysis struggle to remain employed, creating additional burden on society.

The kidney failure risk equation (KFRE) was developed in 2011 and is an accurate predictor of the risk of kidney failure requiring dialysis in patients at risk of progression to kidney replacement therapy. The equation has been validated in several populations, however, according to **Bhanu Prasad, MD, FRCPC,** and colleagues, there are few data available on the ability of the KFRE to predict healthcare and resource utilization in patients with CKD and estimated glomerular filtration rate (eGFR) of 15 to 59 mL/min/1.73 m^2.

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Print-only Content

Imagine Halting Progression of Kidney Disease in Patients with Type 2 Diabetes

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Nearly one-half of all patients with kidney failure requiring dialysis have diabetes as the cause of the kidney disease. Patients with end-stage renal disease have a higher mortality, rate of hospitalization, and increased cost to the health system. Ninety percent of these patients with diabetes have type 2 diabetes mellitus (T2DM).

Over the past two decades, control of blood sugar, managing blood pressure, and renin-angiotensin system blockade (RAAS blockade), using ACE inhibitor or angiotensin receptor blocker (ARB) therapy, have been the mainstay of slowing kidney progression. However, it is estimated that renin-angiotensin blockade contributes only approximately 20% relative risk reduction in patients with T2DM and chronic kidney disease. Therefore, finding newer agents for reducing the progression of kidney disease, especially in patients with CKD from T2DM has been a holy grail of sorts.

On May and July of 2021, the FDA approved dapagliflozin (Farxiga®) based on results from the DAPA-CKD trial,[1] and finerenone (Kerendia®) based on the FIDELIO-DKD[2] trial, as agents for slowing progression of CKD. Another agent, atrasentan, an endothelin-A receptor antagonist, while not approved has generated excitement based on findings from the SONAR (Study of Diabetic Nephropathy with Atrasentan) trial.[3]

In a Perspective article in *CJASN,*[4] Moura-Neto and Ronco contend that "until more robust evidence is available, we must still be careful when deciding to prescribe finerenone to patients with advanced CKD." Their caution centers around three concerns: first that the finerenone in the FIDELIO-DKD trial used a composite outcome; second that the relative risk reduction with finererone was less than that for dapagliflozin or atrasentan and third that finererone was associated with significant hyperkalemia. They suggest that "recent data suggest that dapagliflozin, atrasentan, and canagliflozin may be better alternatives than finerenone for patients with CKD and diabetes mellitus."

The criticisms by Moura-Neto and Ronco can be rebutted: both the DAPA-CKD study and the FIDELIO-DKD used composite outcomes; while it is true that dapagliflozin in the DAPA-CKD study was associated with a greater risk reduction than finererone in FIDELIO-DKD, these studies were designed differently -only a head-to-head study will be able to ascertain their differential benefits to preventing CKD progression. The hyperkalemia associated with finererone is a legitimate concern: as noted in their paper,[2] patients treated with finererone had twice as many hyperkalemia-related adverse effects as compared with placebo (18.3% and 9.0%, respectively). In a more recent *post hoc* analysis Agarwal and colleagues[5] report that 4.5% and 1.4% of patients randomized to finererone and placebo experienced moderate hyperkalemia (defined as a K of >6.0 mmol/L). They suggest that because hyperkalemia is an uncommon phenomenon it can be medically managed.

Still, I suggest that Moura-Neto and Ronco are missing the point. The opportunity with these newer agents is to use them concurrently so that we can obtain more than the 20% contribution to slowing kidney progression with renin-angiotensin blockade. The goal is to largely *halt* the progression of kidney disease in patients with T2DM.

The currently approved agents target different pathways in preventing kidney progression. The primary effect of renin-angiotensin blockade is in improving glomerular hemodynamics, with perhaps a secondary effect on kidney fibrosis. Dapagliflozin, a sodium glucose co-transporter 2 (SGLT2) inhibitor, reduces hyperglycemia in T2DM and improves glomerular hypertension through a reduction in blood pressure and extracellular volume. Finererone, a selective third generation nonsteroidal mineralocorticoid receptor antagonist, confers kidney protection through its anti-inflammatory and anti-fibrotic effects. Could using a combination of agents have additive effects on kidney protection?

In Fidelio-DKD, the majority of patients received some form of RAAS blockade (~34% ACE inhibitor, and ~66% ARB), but only 4.6% were being treated with an SGLT-2 inhibitor. Thus, the FIDELIO-DKD trial demonstrates that patients *can be* concurrently treated with RAAS blockade and an MRA. While hyperkalemia was an issue in a small proportion of patients, in a real-world clinical setting, hyperkalemia could be managed using newer agents.[6] It is certainly possible that using all three agents concurrently (and possibly a fourth in the form of atrasenta) is where the future lies with slowing the progression of kidney disease. The next series of trials need to combine all of these therapies and evaluate their aggregate benefit for kidney protection. ■

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Mortality and Resource Use

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tumor, focusing on the 10 leading causes of cancer in men and women in Canada. Results were reported online in *JAMA Network Open* [doi:10.1001/jamanetworkopen.2021.44713].

The study cohort included individuals ≥19 years of age with severe CKD or certain types of cancer between 2004 and 2015 in Alberta, Canada. Data analysis was performed in November 2021. Participants were categorized as having severe CKD (defined as estimated glomerular filtration rate <30 mL/min/1.73 m^2 or nephrotic albuminuria without dialysis or kidney transplant) or nonmetastatic or metastatic cancer (defined by a diagnosis of lung, breast, colorectal, prostate, bladder, thyroid, kidney or renal pelvis, uterus, pancreas, or oral cancer).

The outcomes of interest were all-cause mortality, number of hospitalizations, total number of hospital days, and placement into long-term care, calculated after diagnosis.

The total cohort included 200,494 individuals; 52.2% (n=104,559) were women, and median age was 66.8 years. The cohort was divided into three groups: severe CKD (n=51,159), nonmetastatic cancer (n=115,504), and metastatic cancer (n=33,831). Median ages were 76.5 years in the CKD group, 63.7 years in the nonmetastatic cancer group, and 65.8 years in the metastatic group. In the CKD group, 56.5% were women; in the nonmetastatic cancer group, 49.6% were women, and in the metastatic group, 54.2% were women.

In the group with nonmetastatic cancer, the most common cancers were prostate (21%) and breast (20%), followed by colorectal, lung, and bladder cancer. In the group with metastatic cancer, lung cancer was the most common (30%).

Comorbidity burden was high in all disease groups; comorbidities were most common in the CKD group and least common in the nonmetastatic group. Of participants in the CKD group, 4.6% (n=2353) developed kidney failure, requiring dialysis or kidney transplant; only 0.1% of those in the cancer groups developed kidney failure. Of those in the CKD group, 7.9% developed a cancer of interest and of those in the cancer groups, 4.0% developed severe CKD.

For patients in the severe CKD group, the Kaplan-Meier 1-year survival was 83.3% (95% confidence interval [CI], 83.0%-83.6%); for patients in the nonmetastatic cancer group, 91.2% (95% CI, 91.0%-91.4%) and for those in the metastatic cancer group, it was 52.8% (95% CI, 52.2%-53.3%). Kaplan-Meier 5-year survival was 54.6% (95% CI, 54.2%-55.1%) for those with CKD, 76.6% (95% CI, 76.3%-76.8%) for those with nonmetastatic cancer, and 33.9% (95% CI, 33.3%-34.4%) for those with metastatic cancer. For participants who entered the study in later years, Kaplan-Meier estimates for 1- and 5-year survival were longer compared with those who entered in earlier years, suggesting small improvements over time for those with CKD or nonmetastatic cancer (*P* for trend <.001 for both), but not for metastatic cancer (*P* for trend=.22).

Compared with nonmetastatic cancer, following adjustment for age, sex, and comorbidities, the relative rate of death during the first year of follow-up was similar for CKD (adjusted relative rate, 1.00; 95% CI, 0.97-1.03). Between years 1 and 5 of follow-up, the adjusted rate of death was higher for CKD (adjusted relative rate, 1.23; 95% CI, 1.19-1.26) than for nonmetastatic cancer (2.95; 95% CI, 2.85-3.05). The most common cause of death among the CKD group was cardiovascular disease; most patients in the two cancer groups died of cancer.

In unadjusted analyses, in the first year of follow-up, the rate of placement into new long-term care was highest for those with metastatic cancer (0.25 per 1000 person-days; 95% CI, 0.23-0.26 per 1000 person-days) compared with those with CKD (0.14 per 1000 person-days; 95% CI, 0.14-0.15 per 1000 person-days) and those with nonmetastatic cancer (0.06 per 1000 person-days; 95% CI, 0.06-0.06 per 1000 person-days). During years 1 and 5, the unadjusted rate was highest for the CKD group.

Following adjustment for age, sex, and comorbidities, the rates of new placement in long-term care during the first year were 0.88 for patients with CKD and 4.02 for patients with metastatic cancer compared with those with nonmetastatic cancer. Between years 1 and 5, the adjusted rate was higher for patients with CKD compared with those with nonmetastatic cancer (adjusted relative rate, 1.36; 95% CI, 1.29-1.43).

During the first year of follow-up, the unadjusted rates of the number of hospitalizations were highest for metastatic cancer (7.97 per 1000 person-days; 95% CI, 7.89-8.05 per 1000 person-days), compared with CKD (2.73 per 1000 person-days; 95% CI, 2.69-2.77 per 1000 person-days) and nonmetastatic cancer (2.98 per 1000 person-days; 95% CI, 2.97-3.00 per 1000 person-days). During years 1 to 5, the rates of hospitalization were highest for CKD followed by metastatic cancer; the rates were lowest for nonmetastatic cancer.

Following adjustment for age, sex, and comorbidities, the rates of hospitalization during the first year were 0.65 for CKD and 2.65 for metastatic cancer, compared with nonmetastatic cancer. Between years 1 and 5, the adjusted rates were higher for CKD compared with nonmetastatic cancer. Findings for length of stay were generally similar to those for the number of hospitalizations.

Limitations to the study cited by the authors included the use of administrative data rather than a prospective cancer registry to identify individuals with cancer, and requiring only a single outpatient measurement of either eGFR or albuminuria to meet the threshold for severe CKD.

In conclusion, the researchers said, "In this cohort study, unadjusted mortality at 1 and 5 years was higher among patients with incident severe CKD than among patients with common forms of nonmetastatic cancer. In unadjusted analyses, the total number of hospital days and the likelihood of lost capacity for independent living were both higher among patients with CKD than those with nonmetastatic cancer. After adjustment for age and comorbidity, mortality, rates of placement in a long-term care facility, and rates of hospitalization remained higher for patients with CKD than those with nonmetastatic cancer at 1 to 5 years, although the magnitude of the excess was attenuated. These data highlight the importance of CKD as a public health problem." ■

TAKEAWAY POINTS

- Researchers reported results of a study to examine differences in clinical consequences associated with severe chronic kidney disease (CKD) compared with cancer.
- In the population-based cohort study in Canada, the unadjusted mortality among patients with CKD at 1 year and 5 years was higher than that among patients with nonmetastatic cancer.
- The findings highlight the importance of CKD as a public health problem.

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Water Intake

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prescribe and personalize the amount of water needed to suppress urine osmolality. Based on a systematic review of methods to increase water intake, the study intervention was implemented using a multipronged approach, including coaching and tools for self-monitoring.

The study, PREVENT-ADPKD (Randomized Controlled Trial to Determine the Efficacy and Safety of Prescribed Water Intake to Prevent Kidney Failure Due to Autosomal Dominant Polycystic Kidney Disease), was an investigator-initiated, 3-year trial conducted at 13 centers in Australia from December 2015 to June 2021. Inclusion criteria were age 18 to 67 years, diagnosis of ADPKD, estimated glomerular filtration rate (eGFR) of ≥30 mL/min/1.73 m^2, height-corrected total kidney volume in Mayo imaging subclass categories 1B to 1E, and provision of written consent.

Key exclusion criteria were presence of potential safety risk for increased water intake, a contraindication to undergoing magnetic resonance imaging (MRI), a subjective risk of noncompliance with study procedures, comorbid conditions with the potential to confound end point measures, and/or participation in other clinical trials. Due to the risk of hyponatremia, diuretics were completely withdrawn (in consultation with the treating nephrologist) in eligible patients who were willing to participate in the study.

The primary end point was the annualized rate of change (slope) in height-corrected total kidney volume from baseline to month 18 and to month 36 (normalized as a percentage). Secondary end points were surrogate markers of systemic arginine vasopressin activity, progression of kidney disease (slope of decline in eGFR from baseline and 3 months to 36 months, mean arterial pressure, and spot urine albumin-to-creatinine ratio), kidney pain, and a composite end point of kidney disease progression (≥25% reduction in eGFR from baseline or week 12, worsening hypertension, worsening albuminuria, and clinically significant kidney pain), a physiological measure of treatment adherence, and treatment acceptability.

During the period December 2015 until June 2017, 1571 patients were screened for eligibility. Of those, 276 gave permission for study participation and attended the first visit for screening. A total of 187 patients met the eligibility criteria; three did not attend the randomization visit. The remaining 184 were randomly assigned to the water ad libitum group (n=92) or prescribed water intake group (n=92). Of the total cohort, 85.9% (n=158/184) completed the 3-year follow-up: 88.0% in the ad libitum water intake group and 83.7% in the prescribed water intake group. All 184 patients were included in the analysis of the primary and secondary end points.

The two groups were similar in demographic, clinical, and laboratory characteristics. At baseline, mean 24-hour urine osmolality and median 24-hour urine volume of the total cohort were 432 mOsmol/kg and 2253 mL, respectively.

Over the 3 years of the study, median absolute changes in height-corrected total kidney volume per year were 55.0 mL/m in the ad libitum water intake group and 39.0 mL/m in the prescribed water intake group. There was no statistically significant difference between the groups in the annualized rate of change in height-corrected total kidney volume: 7.8 percentage points per year (95% confidence interval [CI], 6.6 to 9.0) in the ad libitum water intake group compared with 6.8 percentage points per year (95% CI, 5.8 to 7.7) in the prescribed water intake group (P=.18). The rate of growth was similar in the two groups.

There was no difference in the annual decline in eGFR from baseline through 3 years for either group: ad libitum group, –2.38 mL/min/1.73 m^2 per year (95% CI, –3.13 to –1.63); prescribed group, –2.31 mL/min/1.73 m^2 per year (95% CI, –3.07 to –1.55). Mean difference between the groups was 0.07 m:/min/1.73 m^2 per year (95% CI, –1.00 to 1.14). There was also no difference in the annual decline in eGFR from post-treatment (week 12) through 3 years.

In the prescribed water intake group, eight patients developed hyponatremia, versus two in the ad libitum water intake group (total of 10 episodes). Nine episodes were mild, one was moderate, and all resolved with the exception of one patient in the ad libitum water intake group who developed intermittent hyponatremia during the study period that persisted until the final study visit. The proportion of patients who experienced adverse events was similar in the two groups.

Study limitations cited by the authors included the open-label design, not excluding patients who were at target urine osmolality at baseline, possible confounding in changes in urine osmolality, and including patients with an intermediate predicted rate of kidney cyst growth as well as those with a rapid predicted rate of kidney cyst growth.

In conclusion, the researchers said, "Prescribed water intake compared with ad libitum water intake in people with ADPKD, although associated with about a 10% incidence of reversible hyponatremia, that led to a sustained increase in urine volume and achieved target urine osmolality in half of the patients did not change MRI-measured kidney volume growth over 3 years. The results of our study do not support the routine use of prescribed enhanced water intake for people with ADPKD." ■

TAKEAWAY POINTS

- Researchers reported results of a study to test the hypothesis that prescribing increased water intake to a degree to lower urine osmolality to iso-osmolar levels over a 3-year period would reduce growth of kidney cysts in patients with autosomal dominant polycystic kidney disease.
- There was no difference in the annualized rate of change over 3 years in height-corrected total kidney volume between the ad libitum water intake group and the prescribed water intake group.
- The two groups were similar in the incidence of adverse events.

Kidney Failure Risk Equation

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TAKEAWAY POINTS

- Researchers in Canada conducted a retrospective cohort study to determine patterns of healthcare utilization in patients with chronic kidney disease (CKD) on the basis of their risk of progression to kidney failure as determined by the kidney failure risk equation (KFRE).
- Patients with CKD with estimated glomerular filtration rate (eGFR) of 30-59 mL/min/1.73 m^2 at high risk for progression to kidney failure utilized 50% more hospital-based services than did those with low risk for progression.
- In the group of patients with eGFR of 15-29 mL/min/1.73 m^2 the costs of hospital admissions, physician visits, and drug dispensations over the study period were higher in the group at high risk of progression compared with those at low risk.

The researchers hypothesized that it could be useful if the KFRE can help identify patients with low-cost/nominal resource-intensive treatment from those with high-cost/resource-intensive treatment. Such identification could help outpatient multidisciplinary care-based kidney clinics determine patient management and resource allocation. The research team conducted a retrospective cohort study to examine the association between the risk of progression by KFRE and resource utilization (hospitalizations, physician visits, and drug usage) and associated costs in the setting of a universal healthcare system. Results were reported in the *Clinical Journal of the American Society of Nephrology* [2022; 17:17-26].

The cohort included adults with CKD and eGFR of 15 to 59 mL/min/1.73 m2 enrolled in multidisciplinary clinics in the province of Saskatchewan, Canada. Data were collected from January 1, 2004, to December 31, 2012; patients were followed for 5 years (until December 2017). Patients were stratified by eGFR and risk of progression; the groups were compared with regard to the number and cost of hospital admissions, physician visits, and prescription drugs.

A total of 1794 patients with eGFR ranges of 60 to 89, 30 to 59, 15 to 29, and <15 mL/min/1.73 m^2 were referred to CKD clinics in Saskatchewan during the study period. Following application of inclusion and exclusion criteria, the final CKD cohort included 1003 patients with eGFR of 30 to 59 mL/min/1.73 m^2 (n=529) or 15 to 29 mL/min/1.73 m^2 (n=474). Median follow-up was 5 years in both groups.

Mean age in the overall cohort was 71 years and 57% were men (n=570); 75% of patients were ≥65 years of age. In the 30 to 59 mL/min/1.73 m^2 eGFR group, 59% (n=311), 28% (n=150), and 13% (n=68) were in low-, medium-, and high-risk categories by KFRE, respectively. Among patients in the group with eGFR 15 to 29 mL/min/1.73 m^2, 58% (n=275), 18% (n=86), and 24% (n=113) were in low-, medium-, and high-risk KFRE categories, respectively.

At the end of 5 years of follow-up, of the patients in the eGFR 30 to 59 mL/min/1.73 m^2 group, 4% of the low-risk subgroup, 11% of the moderate-risk subgroup, and 26% of the high-risk group had progressed to kidney failure requiring dialysis (*P*<.001). During the 5-year follow-up period, 31% at low risk, 36% at medium risk, and 28% at high risk for progression to kidney failure died.

Of patients in the eGFR 15 to 29 mL/min/1.73 m^2 group, 7% at low risk, 17% at medium risk, and 48% at high risk of kidney failure progressed to dialysis over 2 years (*P*<.001). During the 2 years, 15% at low risk, 21% at moderate risk, and 16% at high risk of progression to kidney failure died.

> In the group with eGFR 30 to 59 mL/min/1.73 m^2, patients in the high-risk subgroup utilized 50% more hospital-based services (inpatient and day surgeries) than patients in the low-risk subgroup over the 5-year study period (*P*=.006).

After controlling for potential confounders, in the group with eGFR 30 to 59 mL/min/1.73 m^2, patients in the high-risk subgroup utilized 50% more hospital-based services (inpatient and day surgeries) than patients in the low-risk subgroup over the 5-year study period (*P*=.006). High-risk patients also had 52% more higher utilization of physician services compared with low-risk patients. There were no statistically significant differences across the risk groups in drug dispensations. Findings were similar in the group with eGFR 15 to 29 mL/min/1.73 m^2: high-risk patients consumed 72% more hospital services and 2.2 times more physician services than patients in the low-risk group (both *P*<.001). There were no differences in drug dispensations.

In the group with eGFR 15 to 29 mL/min/1.73 m^2, comparing patients at high risk for progression to kidney failure with those at low risk of progression, the costs of hospital admissions, physicians visits, and drug dispensations over the 5-year study period were (Canadian dollars): $89,265 versus $48,374 (*P*=.008); $23,423 versus $11,231 (*P*<.001), and $21,853 versus $16,757 (*P*=.01), respectively.

The costs for hospital admissions, physician services, and drug dispensations in the group with eGFR 30 to 59 mL/min/1.73 m^2 for high-risk versus low-risk patients were $55,944 versus $36,740 (*P*=.10), $13,414 versus $10,370 (*P*=.08), and $20,394 versus $14,902 (*P*=.02), respectively.

Limitations to the study findings cited by the authors included the possible lack of generalizability outside of the Canadian healthcare system and the lack of data on variables such as socioeconomic characteristics and health behaviors.

In conclusion, the researchers said, "In our study of patients with CKD referred to multidisciplinary CKD clinics, KFRE, designed to predict the risk of dialysis in patients with CKD, helps identify patients with higher health resource utilization and healthcare costs compared with those with lower health resource use. Integration of KFRE in risk-based treatment pathways that guide the intensity of CKD care may improve health system and patient outcomes." ■

CONFERENCE COVERAGE KIDNEY WEEK 2021

Excess Vitamin C and AKI in Hyperoxaluria

The causes of secondary hyperoxaluria, which can manifest as end-stage renal disease or hypothyroidism, include increased ingestion of oxalate or oxalate precursors, increased oxalate enteric absorption due to fat malabsorption, or changes in intestinal microflora.

During a virtual poster session at ASN Kidney Week 2021, **Katherine Julian, MD,** and colleagues at Penn State Health Milton S. Hershey Medical Center, Hershey, Pennsylvania, presented a case report of a female, 55 years of age, with a history of hyperparathyroidism and hypothyroidism who was not medication compliant; the patient presented with myxedema coma secondary to uncontrolled hypothyroidism. The poster was titled *Excess Vitamin C Leading to Hyperoxaluria and AKI.*

The initial workup revealed elevated potassium (7 mmol/L), blood urea nitrogen (194 mg/dL), serum creatinine (35 mg/dL), and thyroid-stimulating-hormone (TSH) (>100 µIU/mL). She was treated with intravenous (IV) levothyroxine, IV liothyronine, insulin, calcium gluconate, and hydrocortisone.

The patient had no known underlying chronic kidney disuse, nephrolithiasis, or nephrocalcinosis; hemodialysis was initiated in the setting of acute kidney injury (AKI). Autoimmune, gastrointestinal, and hepatobiliary AKI etiologies were ruled out. Renal oxalosis was revealed on renal biopsy. Investigation of possible secondary causes of renal oxalosis revealed consumption of large quantities of vitamin C in hopes of preserving her health during the COVID-19 pandemic.

With continuing dependency on hemodialysis, the patient was discharged on levothyroxine 150 mcg sublingual daily, followed by nephrology and endocrinology care. At the time of discharge, TSH remained >100 µIU/mL, but free T4 (thyroxine) was 0.86 ng/dL without any hypothyroid symptoms. Consumption of high doses of vitamin C was discontinued.

The researchers said, "The combination of severe hypothyroidism resulting in myxedema coma and the excessive intake of vitamin C, a precursor for oxalate stones in the kidney, resulted in AKI. However, we believe the severe hypothyroidism was a result of medication noncompliance versus manifestation of systemic oxalosis. We recommend considering secondary oxalosis in cases of dialysis-dependent AKI in the setting of high dose vitamin C consumption or increased exogenous oxalate ingestion and confirming this diagnosis with renal biopsy."

Source: Julian K, Abendroth C, Zebi AM, Karasinski AA, Jain, Rohit. Excess vitamin C leading to hyperoxaluria and AKI. Abstract of a poster presented at the American Society of Nephrology virtual Kidney Week 2021 (Abstract P00305), November 2021.

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Oral Ferric Maltol for Iron-Deficiency Anemia Related to CKD

Anemia associated with chronic kidney disease (CKD) becomes more prevalent and severe as kidney function decreases. Patients with CKD who do not require kidney replacement therapy who experience a decrease in serum ferritin, low concentrations of iron, and reduced transferrin saturation (TSAT) are in negative iron balance. Oral of intravenous (IV) iron-replacement therapies are used to replenish iron stores and correct anemia in patients with iron-deficiency anemia.

IV iron is used when oral agents are ineffective or not tolerated or when the level of iron deficiency exceeds what oral agents can deliver. Limits to IV administration of iron include venous access problems, reactions at the injection site, and, rarely, anaphylaxis. Oral ferrous compounds are readily available and widely used, but according to **Pablo E. Pergola, MD, PhD,** and **Nelson P. Kopyt, OD,** the iron in those preparations may be poorly and variably absorbed.

Ferric maltol is a complex of ferric iron and maltol (3-hydroxy-2-methyl-4-pyrone), a naturally occurring sugar derivative in many food products and stable at physiologic pH. Results of previous studies demonstrated a favorable benefit-risk ratio for ferric maltol during treatment for up to 1 year in patients with iron-deficiency anemia in the context of inflammatory bowel disease.

Drs. Pergola and Kopyt conducted a study designed to evaluate the effects of treatment with ferric maltol for up to 1 year in patients with stage 3 or 4 CKD and iron-deficiency anemia. Results of the phase 3, double-blind, randomized, placebo-controlled trial (AEGIS-CKD) and open-label extension were reported in the *American Journal of Kidney Diseases* [2021;78(6):846-857]. The study was funded by Shield Therapeutics (UK) Ltd.

Trial participants were adults with stage 3 or 4 CKD and iron-deficiency anemia at 30 centers in the United States. Participants were randomized 2:1 to receive oral ferric maltol at 30 mg or placebo twice daily for 16 weeks, followed by ferric maltol at 30 mg twice daily for up to 36 weeks for all participants. The primary outcome of interest was the change from baseline in hemoglobin level at week 16. Secondary outcomes included change from baseline in ferritin, TSAT, and serum iron, as well as safety.

A total of 167 patients underwent randomization between December 2016 and October 2018 (intent-to-treat population). Of those, 111 were randomized to the ferric maltol group and 56 were randomized to the placebo group. A baseline, the two groups were similar in demographic and clinical characteristics.

From baseline to week 16, the mean change in hemoglobin was 0.6 g/dL in the ferric maltol group and –0.1 g/dL in the placebo group, for a statistically significant difference between the two groups (least-squares mean, 0.5 g/dL; 95% confidence interval, 0.1-0.9; *P*=.01). Improvements in hemoglobin were seen consistently with ferric maltol versus placebo regardless of estimated glomerular filtration rate (eGFR). The difference was more pronounced in the subgroup with eGFR above 30 mL/min/1.73 m^2. In patients with baseline ferritin of ≤250 ng/mL, the difference between groups favored ferritin maltol, but was reversed in the subgroup with baseline ferritin >250 ng/mL (that subgroup included very few patients).

At week 16, 20% of patients (n=22) in the ferric maltol group and 9% of patients (n=5) in the placebo group had an increase in hemoglobin of at least 1 g/dL; seven of the 22 patients in the ferric maltol group had an increase of at least 2 g/dL compared with none in the placebo group. In the ferric maltol group, 27% of patients (n=30) had hemoglobin concentrations of at least 11 g/dL at week 16, compared with 13% (n=7) in the placebo group.

In the ferric maltol group, ferritin, TSAT, and serum iron values all increased from baseline to week 16; those values declined in the placebo group. The differences between groups were not

CONFERENCE COVERAGE KIDNEY WEEK 2021

Access to Living Donor Kidney Transplantation in High Minority Communities

Racial disparities in living donor kidney transplantation are increasing. There are associations between living in linguistically isolated communities or in areas with large minority populations and decreased access to transplant. Living donor kidney transplant recipient/donor pairs are 95% racially concordant. There are few data available on the contemporary relationship between access to living donor kidney transplantation in communities with high minority and in less English-proficient populations.

Alixandra C. Killian, MD, MPH, and colleagues conducted an analysis to examine access to living donor transplants in such communities. Results of the analysis were reported during an oral session at the virtual ASN Kidney Week 2021. The presentation was titled *Living in High Minority, Less English-Proficient Communities May Facilitate Living Donor Kidney Transplantation among Asian Americans and Pacific Islanders.*

The analysis utilized the Scientific Registry of Transplant Recipients to identify adult, kidney-0only transplant recipients from January 1, 2018, to December 31, 2018. Recipients' zip codes were matched to the Minority Status and Language Theme of the Centers for Disease Control and Prevention 2018 Social Vulnerability Index. The likelihood of living donor kidney transplantation was evaluated using modified Poisson regression.

The study included data on 18,950 kidney transplant recipients; of those 32% received a living donor transplant. Black (adjusted relative risk [aRR], 0.60; 95% confidence interval [CI], 0.49-0.74) and Asian American and Pacific Islander (AAPI) recipients (aRR, 0.52; 95% CI, 0.39-0.70) were less likely to receive a kidney from a living donor compared with White recipients.

Overall, there was no association between community minority status and language proficiency and living donor kidney transplantation (aRR, 1.01; 95% CI, 1.00-1.02); however, the effect of this vulnerability measure varied by race. Among AAPI recipients only, there was an association between living in higher minority, less English-proficient communities and increased likelihood of receiving a kidney from a living donor (ratio of aRR, 1.66; 95% CI, 1.12-2.47).

In summary, the authors said, "While all minority recipients had lower likelihood of living donor kidney transplantation, living in higher minority, less English-proficient communities may be paradoxically advantageous for AAPI patients. Given living donor kidney transplantation racial concordance, living in areas with shared culture or language may facilitate living donor kidney transplantation access among AAPI."

Source: Killian AC, Shelton BA, MacLennan PA, et al. Living in high minority, less English-proficient communities may facilitate living donor kidney transplantation among Asian Americans and Pacific Islanders. Abstract of an oral presentation at the American Society of Nephrology virtual Kidney Week 2021 (Abstract TH-OR58), November 4, 2021.

statistically significant, however. In the ferric maltol group, the increase in iron storage parameters was achieved regardless of the degree of underlying chronic inflammation, reflected by high-sensitivity C-reactive protein analysis.

The improvements in hemoglobin in patients in the ferric maltol group during the double-blind treatment period were maintained with continued open-label ferric maltol to week 52; the total increase in hemoglobin from baseline to week 52 was 0.7 g/dL. In the group moving from placebo in the double-blind period to ferric maltol in the open-label period, changes in hemoglobin mirrored those seen with ferric maltol in the double-blind treatment period, with a total increase of 0.5 g/dL by the end of the study.

During the double-blind treatment period, the proportions of patients in the two groups who experienced treatment-emergent adverse events and serious adverse events were similar. In each group, the most frequent adverse events were gastrointestinal disorders (randomized phase: 41% in the ferric maltol group vs 30% in the placebo group; open-label phase: 56% vs 46%, respectively). Adverse events deemed related to the study drug occurred in 19% of patients (n=21) in the ferric maltol group and 11% of patients (n=6) in the placebo group.

In seven patients in the ferric maltol group and five in the placebo group, adverse events led to treatment withdrawal during the double-blind treatment phase, and in 11 patients during the open-label extension.

Heterogeneity in ferritin levels at baseline in the two groups, the high proportion of female participants, and the single-arm open-label extension were cited by the authors as limitations to the study findings.

In conclusion, the researchers said, "The AEGIS-CKD trial shows that oral ferric maltol raises and sustains hemoglobin to provide iron for erythropoiesis in patients with eGFR as low as 30 mL/min/1.73 m^2; even in those with more severe CKD and a higher contribution of erythropoietin insufficiency, there may still be a benefit. Furthermore, ferric maltol provides significant and sustained increases in iron storage indices, providing long-term control of iron-deficiency anemia. In this population, ferric maltol was generally well tolerated, with a low rate of discontinuation due to adverse events. A drug such as ferric maltol that is able to replace and restore iron, that is orally administered, and that patients are able to tolerate will provide a clinically relevant treatment option for patients with moderate-to-severe CKD and anemia due to iron deficiency." ■

TAKEAWAY POINTS

- Patients with chronic kidney disease (CKD) not requiring kidney replacement therapy commonly experience iron-deficiency anemia; researchers conducted a study to assess the effects of oral iron replacement therapy with ferric maltol in that patient population.
- There was an association between ferric maltol and a statistically significant and sustained increase in hemoglobin and iron indices in patients with CKD and iron deficiency.
- Ferric maltol was well tolerated during treatment for up to 52 weeks.

Maturation and Patency Rates of Arteriovenous Fistula Hemodialysis Access

Among the population of patients with kidney failure, the creation and maintenance of a functional arteriovenous hemodialysis access remains a concern. The National Kidney Foundation's (NKF) Dialysis Outcome Quality Initiative originally recommended use of the autogenous arteriovenous fistula (AVF) over the prosthetic alternative arteriovenous graft and a tunneled dialysis catheter (TDC) due to benefits of an AVF, including improved patency, decreased morbidity, decreased mortality, and cost.

The NKF guidelines called for a target incidence of ≥50% and prevalence of >40% for AVFs in the United States. The Centers for Medicare & Medicaid Services implemented the National Access Vascular Initiative (2003-2006), the Fistula First Breakthrough Initiative for AVFs with an updated prevalence target of 66% by 2009. The increased emphasis on AVFs resulted in a higher rate of nonmaturation and TDC use in the United States.

The high maturation failure rate led the national Institutes of Health National Institute of Diabetes and Digestive and Kidney Diseases to create the Hemodialysis Fistula Maturation (HFM) Consortium, a group of seven clinical centers charged with examining the influences of vascular anatomy bioloigy, clinical attributes, and healthcare processes on AVF maturation.

The HFM data set included patients with dialysis-dependent kidney failure and those with predialysis chronic kidney disease (CKD). **Thomas S. Huber, MD, PhD,** and colleagues conducted a case series analysis to examine AVF maturation, longer-term patency, and remedial procedures to facilitate maturation, manage complications, or maintain patency in the HFM cohort. Results were reported in *JAMA Surgery* [2021;156(12):1111-1118].

A total of 602 participants with kidney failure or CKD were enrolled in the HFM study; of those, 535 were included in the case series analysis. The primary outcome of interest was unassisted maturation of the AVF. Kaplan-Meier analyses were used to summarize functional patency, freedom from intervention, and participant survival.

Of the 535 participants, 66.0% (n=353) had kidney failure and 34.0% (n=182) had CKD. The cohort included 372 men (69.5%) and 163 women 30.5%); mean age was 54.6 years, and 58.1% (n=311) had diabetes. Overall, the racial distribution was relatively equal; 45.4% (n=243) were Black, 45.6% (n=244) were White, and 9.0% (n=48) were other. There was racial variation in dialysis status: kidney failure, Black 50.4% (n=178), White 39.9% (n=141); CKD, Black 35.7% (n=65), White 56.6% (n=103).

Overall, mean body mass index was 30.3 kg/m^2; 25.2% (n=135) had coronary artery disease and 14.4% (n=77) had peripheral artery disease. Most of the participants with kidney failure were undergoing dialysis through a TDC at study enrollment, and nearly one-third (115 [32.6%]) had a prior permanent access. The target cannulation site for 64% (n=342) of study access procedures involved the upper arm; the brachial/ulnar/radial-cephalic configuration was the most common (kidney failure, 36.8%; CKD, 47.8%). The groups were similar in the frequency of the forearm radial/ulnar-cephalic access, but the incidence of brachial/radial/ulnar-basilic/brachial appeared to be higher among participants with kidney failure (90 [25.5%]) compared with the group with CKD (35 [19.2%]).

The maturation rates for participants with kidney failure versus participants with CKD were 29% versus 10% at 3 months, 67% versus 38% at 6 months, and 76% versus 58% at 12 months. Approximately one-third of participants in both groups underwent intervention to facilitate maturation or manage access complications before ascertainment (kidney failure group: 37.7%, n=133; CKD group, 34.6%, n=63). The most common intervention for both groups was for AVF stenosis (kidney failure, 26.3%; CKD, 22.5%). Other interventions to facilitate maturation or manage complications were substantially less common (access vein branch > central vein stenosis > thrombosis) and did not differ meaningfully between the two groups.

In the group with kidney failure, 49% successfully used their AVFs without intervention at 12 months, and 27% underwent an intervention before successful maturation. In the CKD group, maturation was expectedly delayed, with 39% achieving unassisted maturation and 19% achieving assisted maturation at 12 months.

Median time from access creation to maturation was 115 days overall, but differed by initial indication: CKD, 170 days; kidney failure, 105 days. Participants with kidney failure required a TDC for a mean of 2.9 months prior to access ascertainment. In the group with kidney failure, 37.7% (n=133) required at least one inpatient hospitalization for any cause before AVF ascertainment, as did 33.5% (n=61) of those in the group with CKD.

The functional patency for the AVFs that matured at 1 year was 87% (95% confidence interval [CI], 83.2%-90.2%) and 75% at 2 years (95% CI, 69.7%-79.7%). There was no significant difference in functional patency between those that received interventions before maturation and those that did not receive interventions. Nearly half (47.5%, n=188) of the AVFs that matured had further intervention to maintain patency or treat complications.

The researchers cited some limitations to the study, including the study being performed by clinicians with a dedicated interest in hemodialysis access, primarily at academic medical centers. Because the primary objective was to identify predictors of AVF maturation, participants were all considered reasonable candidates for creation of an AVF. Enrollment criteria may have been liberalized, resulting in enrollment of participants with a low likelihood of successful maturation. However, the rate of early thrombosis (5.3% within 18 days) and the rate of maturation were good and consistent with other reports. Also, the maturation end point was indeterminant in a small proportion of participants who were excluded from the analysis; their outcomes could have affected the results. Finally, the HFM study only included single-stage AVF procedures despite the increasing application of a 2-stage brachial basilic approach.

In conclusion, the authors said, "The findings of this study suggest that the AVF remains a reasonable option for patients who require access for hemodialysis access, although both their maturation and continued use require a moderate number of interventions to maintain patency and treat associated complications." ■

TAKEAWAY POINTS

- The use of autogenous arteriovenous fistulas (AVFs) for hemodialysis access is recommended by national guidelines; researchers conducted a case series analysis to examine AVF usability, longer-term functional patency, and rates of interventions to facilitate maturation and manage complications.
- Maturation rates for participants with kidney failure were 67% at 6 months and 76% at 12 months; nearly one-third required an intervention to facilitate maturation or manage a complication.
- The study findings suggest that maturation and patency rates are suboptimal, but reasonable considering the alternatives.

HBA Copy Number and CKD Incidence Among Black Americans

Even after accounting for socioeconomic factors and comorbid medical conditions, kidney disease develops at younger age among Black Americans than among other racial/ethnic groups and Black Americans are three times more likely to progress to end-stage kidney disease (ESKD). DNA sequence variants that are associated with an increase in the risk of kidney disease (including one in the hemoglobin b locus (HBB), sickle cell trait, and apolipoprotein L-1 (APOL1) are more common among Black Americans, but do not fully explain the racial diversity in kidney disease.

According to **A. Parker Ruhl, MD, MHS** and colleagues, Black Americans and other minority populations are underrepresented in many large-scale longitudinal US population studies, hindering investigations into kidney disease and other chronic diseases.

Previous studies have identified nitric oxide signaling as important as protection against and recovery from ischemic or oxidative injury to the kidney, yet there are few data available on associations between genetic variants in nitric oxide signaling pathways in the kidney and kidney function or kidney disease. Results of some studies have suggested α-globin as a regulator of nitric oxide signaling in the endothelial cells of small resistance arteries.

α-Globin is expressed by the *HBA1* and *HBA2* genes that are organized in tandem on chromosome 16. The gene (*HBA*) copy number is variable in people of African descent and other populations worldwide. The sequence similarity of the *HBA1* and *HBA2* genes makes them susceptible to deletions, which are common among people from Africa, Southeast Asia, the Pacific Islands, and the Mediterranean. This depletion spans part of the *HBA2* and *HBA1* genes and reduces the functional gene copy number by one, resulting in a decrease in total α-globin gene (*HBA*) expression in red cell precursors.

Dr. Ruhl et al. conducted a national longitudinal cohort study to test the hypothesis that, given the protective effect of nitric oxide in the kidney, there would be associations between α-globin gene deletions and protection against prevalent CKD, incident reduced estimated glomerular filtration rate (eGFR), and incident ESKD among Black Americans. Results were reported in the *Journal of the American Society of Nephrology* [2022;33:213-224].

The cohort included participants from the REGARDS (Reasons for Geographic and Racial Differences in Stroke) study that was designed to determine the reasons for racial disparities in stroke and cognitive decline in Black and White Americans ≥45 years of age. Of the 30,239 participants enrolled from 2003 to 2017, 41% (n=12,514) were Black and were from states considered to be in the stroke belt, where stroke incidence is highest in the United States.

HBA copy number was measured as a numeric variable with values of 2, 3, 4, 5, or 6 as determined by droplet digital PCR (ddPCR) analysis of genomic DNA. The ddPCR copy number assay targeted a unique sequence within the 3.7-kb insertion/deletion polymorphism. The copy number of the target relative to a reference gene was determined.

The prevalence of CKD was defined by an eGFR <60 mL/min/1.73 m^2 or a urine albumin-creatinine ratio ≥30 mg/g or at baseline. Modified Poisson multivariable regression was used to calculate the prevalence ratio of CKD and the relative risk of incident reduced eGFR. Cox proportional hazards multivariable regression was used to calculate the hazard ratio of incident ESKD. Analyses were adjusted for demographic, clinical, and genetic risk factors.

Following application of inclusion and exclusion criteria, the cohort for the current analysis included 9908 patients. Of those participants, 4% (n=393) had two *HBA* copies, 28% (n=2744) had three *HBA* copies, 67% (n=6668) had four *HBA* copies, 1% (n=101) had five *HBA* copies, and <1% (n=2) participants had six *HBA* copies.

In adjusted analysis, there was an association between a one-copy increase in *HBA* and 14% greater prevalence of CKD (prevalence ratio, 1.14; 95% confidence interval [CI], 1.07-1.21; *P*<.0001). The prevalence of CKD increased with *HBA* copy number. Among participants with two *HBA* copies, CKD prevalence was 20%; among those with three copies, 25%; among those with four copies, 25%; and among those with five or more copies, CKD prevalence was 35%. Red blood cell parameters varied according to HBA copy number (*P*<.0001): a hypochromic, microcytic anemia was seen in participants with two copies of *HBA*.

The association between *HBA* copy number and incident reduced eGFR was analyzed in 3733 participants who were evaluated at a second in-home visit. Following adjustment for relevant factors, there was no association between *HBA* copy number and incident reduced eGFR (relative risk, 1.06; 95% CI, 0.94-1.19; *P*=.38).

Of the 9905 participants included in the ESKD analysis, 342 developed ESKD over a median of 10.7 years of follow-up. In adjusted analysis, there was no significant association between *HBA* copy number and the hazard of incident ESKD (hazard ratio [HR], 1.07; 95% CI, 0.88-1.29; *P*=.50). In an analysis adjusted for 13 factors selected *a priori*, there was an association between each additional copy of *HBA* and a 32% increase in the hazard of incident ESKD (HR, 1.32; 95% CI, 1.06-1.61; *P*=.005).

The researchers cited the lack of an independent replication cohort as a limitation to the study findings.

In conclusion, the authors said, "We report that higher *HBA* copy number was independently associated with greater CKD prevalence and ESKD incidence after accounting for known clinical, demographic, and genetic risk factors in this national longitudinal study of Black Americans. The high frequency of *HBA* gene deletion found in Black Americans may act to reduce the overall burden of kidney disease in this population." ■

TAKEAWAY POINTS

- Researchers reported results of a study designed to test the hypothesis that α-globin gene (*HBA*) deletions would be associated with p rotection against prevalent chronic kidney disease (CKD), incidence reduced estimated glomerular filtration rate (eGFR), and incident end-stage kidney disease (ESKD) among Black Americans.
- Among 9908 participants, the prevalence of CKD increased with *HBA* copy number.
- In an adjusted subgroup analysis of 9905 participants, there was association between each additional copy of *HBA* and a 32% increase in the hazard of incident ESKD.

SARS-CoV-2 Vaccine Response in Kidney Transplant Recipients

Patients on hemodialysis and those who are recipients of kidney transplantation are at high risk for SARS-CoV-2 infection and more serious COVID-19 course. Patients in those populations are strongly advised to receive vaccination against COVID-19; however, the protective immune response is significantly lower in those patients, particularly when comparing kidney transplant recipients with healthy individuals.

Early data suggest that a third dose in kidney transplant recipients elicits a seroresponse among a significant number of previous nonresponders (40%-50%) and augments serotiters above those seen following a second vaccine dose in previous responders.

There is growing evidence of a correlation between neutralizing antibody levels measured by commercially available assays and protection against (re)infection. However, according to **Louise Benning, MD,** and colleagues, most studies were conducted with the SARS-CoV-2 wild-type and B.1.1.7 (a) strains were the predominant variants, and the situation may not translate to the situation with emerging variants of concern, including B.1.351 (ß) and B.1.617.2 (δ). In particular, B.1.617.2 has significantly higher transmissibility and may escape vaccine-induced immunity.

There are few data available regarding protection against the variants in immunocompromised patients. The researchers conducted a prospective two-center study to examine whether kidney transplant recipients with seroconversion following two-dose vaccination are protected against emerging variants of concern. Results of the study were reported in the *Clinical Journal of the American Society of Nephrology* [2022;17(1):98-106].

Antispike 1 IgG and surrogate neutralizing antibodies were measured in 173 kidney transplant recipients and 166 healthy controls with different vaccination schedules. Additionally, different SARS-CoV-2 epitope antibodies from 135 vaccinated kidney transplant recipients were compared with antibodies in 25 matched healthy controls after the second vaccination. In 36 kidney transplant recipients with seroconversion, neutralization against B.1.1.7 (a), B.1.351 (ß), and B.1.617.2 (δ) was determined on VeroE6 cells and compared with neutralization in 25 healthy controls.

Seropositivity was defined as a result above the respective threshold in at least two of the three commercially available assays: anti-S1 IgG (measured by chemiluminescent immunoassay; cutoff index greater than or equal to one), surrogate neutralizing antibodies (measured by the surrogate virus neutralization test; cutoff ≥30%), and antireceptor-binding domain (anti-RBD) antibodies (measured by the bead-based Luminex assay; cutoff mean fluorescence intensity [MFI] ≥3800).

Participants were prospectively enrolled from December 29, 2020, to June 21, 2021. Anti-S1 and surrogate neutralizing antibodies were measured in 73 and 135 kidney transplant recipients and in 115 and 134 healthy controls after the first and second vaccinations, respectively. Antibodies against various SARS-CoV-2 target epitopes were measured following the second vaccinations by multiplex analysis in 135 kidney transplant recipients and compared with results in 25 healthy controls matched for type of vaccine, age, and sex.

Median age in the kidney transplant recipient cohort was 55 at first vaccination and 55 at second vaccination; median age in the full healthy cohort median age at first vaccination was 39 and 43 at second vaccination 43). At both the first and second vaccination, the full healthy cohort was more likely to be female, compared with the kidney transplant cohort.

Immunosuppression medications used by the kidney transplant recipients included calcineurin inhibitor, mycophenolic acid, mammalian target of rapamycin inhibitor, azathioprine, belatacept, and steroids.

Kidney transplant recipients had significantly lower seroconversion rates compared with healthy controls. Following the first vaccination with an mRNA (BioNTech or Moderna) or AstraZeneca (AZ) vaccine, anti-S1 IgG antibodies were significantly lower in kidney transplant recipients with median indices of 0.1 and 0.1 compared with 9 and 2, respectively, in the full healthy control cohort. First vaccination with an mRNA vaccine resulted in a median surrogate neutralizing antibody activity that was significantly lower in kidney transplants with 0% compared with 69% in the full healthy control cohort ($P<.001$). In participants who received a first vaccination with the AZ vaccine, neutralizing antibody activity did not differ between the groups (median, 21% in kidney transplant recipients and 16% in healthy controls).

After the second vaccination, reactivity against different measured spike protein epitopes were significantly lower in 135 kidney transplant recipients compared with 25 healthy controls matched for vaccine type, sex, and age. Median MFI values of kidney transplant recipients were 914 for the full spike, O for the S1, 227 for the RBD, and 0 for the SC protein, compared with 23,166; 16,682; 19,650; and 8908 in matched healthy controls, respectively ($P<.001$ for all).

Neutralization activity against different variants of concern was analyzed after the second dose. The analysis utilized a neutralization assay on VeroE6 cells in 36 seropositive kidney transplant recipients and compared the results with those in 25 matched healthy controls. All seropositive kidney transplant recipients showed neutralizing activity against the B.1.1.7 (a) variant with a median ID_{50} of 80; only 23 of 36 (64%) and 24 of 36 (67%) seropositive kidney transplant recipients showed neutralization activity against the variants of concern, B.1.351 (ß) and B.1.617.2 (δ), respectively. Median ID_{50} values were 20 and 20, respectively. All matched healthy controls showed neutralizing activity against all tested variants.

Study limitations cited by the authors included the largely unknown correlate of protection against symptomatic infection or severe disease progression; there may be significant variation in the known correlates of protection between different strains of SARS-CoV-2. Another limitation is the lack of data on cellular immunity, that may be impaired in kidney transplant recipients.

In summary, the researchers said, "This study shows that a large proportion of kidney transplant recipients may not be adequately protected against the emerging variants of B.1.351 (ß) and B.1.617.2 (δ) with the standard vaccination regimens currently used in the healthy general population. Even if seroconversion is detectable by various commercially available assays, neutralization of these variants may not be sufficient to protect against infection. Additional vaccinations appear to be required in kidney transplant recipients to maintain high levels of neutralizing antibodies, especially when B.1.617.2 (δ) or other variants with partial escape from neutralizing antibodies become more prevalent." ■

TAKEAWAY POINTS

- In kidney transplant recipients, antibody response following vaccination against SARS-CoV-2 infection is impaired; emerging variants such as B.1.351 (ß), and B.1.617.2 (δ) are of particular concern due to their higher transmissibility.
- Results of a two-center prospective study measuring antispike 1 IgG and surrogate neutralizing antibodies in 173 kidney transplant recipients in comparison with 166 matched healthy controls were reported.
- Compared with the healthy controls, kidney transplants had significantly lower seroconversion rates following the standard two-dose vaccination regimen.

Risk of Post-Transplant Diabetes Mellitus in Older and Obese Patients

Patients receiving a solid organ transplant commonly develop post-transplant diabetes mellitus (DM), often within the first 2 to 3 years after transplant. Post-transplant DM occurs in 10% to 20% of nondiabetic kidney transplant recipients and is associated with premature cardiovascular disease, loss of graft, and mortality.

Risk factors for post-transplant DM include obesity, metabolic syndrome, cytomegalovirus infection, hepatitis C viremia, and calcineurin inhibitor (CNI) therapy. Older age has also been shown to be a strong and consistent risk factor for post-transplant DM among kidney transplant recipients and is associated with greater post-transplant morbidity. Median age at time of kidney transplant has been increasing worldwide, driven both by population aging and increasing acceptance of kidney transplant candidates >55 years of age for waitlisting and transplant. Previous studies have suggested that kidney transplant recipients have a 1.5-fold higher risk per decade of age of developing post-transplant DM.

One potentially modifiable risk factor for developing post-transplant DM is immunosuppression selection. Recommendations in 2014 suggested that immunosuppression regimens should fully optimize patient and allograft survival without concern for post-transplant DM. However, current guidelines recommend that tacrolimus and mycophenolate mofetil be used as first-line maintenance immunosuppression agents with appropriate induction medications.

Older kidney recipients often have a lower risk of acute rejection due to immunosenescence reducing the risk of rejection, and, potentially, the need for long-term triple therapy. Recent evidence suggests that lower-intensity immunosuppression regimens (e.g., steroid-sparing) may be beneficial in older kidney transplant recipients, reducing post-transplant death and graft loss. Further, obese patients have more than a 2-fold increase in the incidence of post-transplant DM compared with nonobese patients; however, they have an increased risk of rejection.

David A. Axelrod, MD, MBA, and colleagues conducted a retrospective database study designed to examine the impact of immunosuppression selection on the risk of post-transplant DM among both older and obese kidney transplant recipients. Results were reported in *Kidney Medicine* [2022;4(1):1-11].

The study participants were kidney-only transplant recipients ≥18 years of age from 2005 to 2016 in the United States, identified from the US Renal Data system records that integrate Organ Procurement and Transplantation Network/United Network for Organ Sharing records with Medicare billing claims. The study exposures were various immunosuppression regimens during the first 4 months following transplantation. The outcome of interest was development of DM >3 months to 1 years post-transplant.

Of the 193,984 kidney transplant recipients in the study period, 40,108 had Medicare coverage at the time of transplant and did not have pretransplant diabetes. There were differences between the study sample of Medicare beneficiaries without diabetes and the general transplant population in age, race, employment status, body mass index (BMI), and cause of end-stage kidney disease. Of the 40,108 individuals in the study sample, 38.0% were ≥55 years of age, 58.8% were men, 30.2% were African American, and 27.5% had a BMI of ≥30 kg/m^2.

The most common immunosuppression regimen was tacrolimus + mycophenolic acid/azathioprine + prednisone), after T-cell-depleting induction: antithymocyte globulin (TMG) or alemtuzumab (ALEM) + triple therapy (47.2%), followed by TMG/ALEM + no prednisone (20.0%), triple maintenance after IL-2 receptor antibody (IL2rAb): IL2rAb + triple therapy (16.0%), CsA-based regimens (6.5%), and mammalian target of rapamycin inhibitor (mTORi)-based regimens (5.7%). IL-2rAb + no prednisone (2.2%), and tacrolimus or tacrolimus + prednisone (2.2%%) with any induction (3.3%) were not commonly used.

Among older adults in the sample (≥55 years of age), the incidence of DM >3 months to 1 year after transplant was significantly higher than among those <55 years of age (16.7% vs 10.1%; P<.001). Among the older patients, the incidence of post-transplant DM within the first year varied more than 2.3-fold across regimens, from 11.6% among those on TMG/ALEM + no prednisone to 26.3% among those on mTORi-based regimens. Among younger patients, the incidence varied from 6.1% among those on IL2rAb + no prednisone to 20.2% among those on mTORi.

Following adjustment for potential confounding differences due to clinical characteristics, the risks of developing DM post-transplant remained significantly different across regimens. Among older recipients, the risk was decreased in recipients treated with TMG/ALEM + no prednisone (adjusted hazard ratio [aHR], 0.69; 95% CI, 0.60-0.79) or with IL2rAb + no prednisone (aHR, 0.76; 95% CI, 0.58-0.99); the risks were higher with mTORi-based therapy and CsA-based regimens than with TMG/ALEM + triple therapy. There was variation by age in the impact of mTORi immunosuppression on the risk of post-transplant DM.

Regardless of immunosuppression regimen, patients who were obese had significantly greater risk of post-transplant DM: BMI <30 kg/m2, 10.9%; BMI ≥30 kg/m^2, 17.1%; P<.0001). The incidence of DM was highest among obese patients treated with mTORi-based regimens >3 months to 1-year post-transplant (32.4%); nonobese patients on tacrolimus or tacrolimus + prednisone had the lowest (7.1%). In patients with a BMI ≥30 kg/m^2, the use of TMG/ALEM + no prednisone reduced the risk of post-transplant DM to 11.5%; 16% of patients on IL2rAb + no prednisone developed post-transplant DM.

Following adjustment for confounding, steroid avoidance with TMG/ALEM induction reduced the risk of post-transplant DM in obese patients (aHR, 0.67; 95% CI, 0.57-0.76). Steroid avoidances with IL2rAb induction resulted in a risk of post-transplant DM equivalent to that of obese patients managed with triple therapy (aHR, 0.99; 95% CI, 0.66-1.49).

Limitations to the study cited by the authors included the lack of data on levels of immunosuppression, including trough levels of CNIs and/or mTORi; other laboratory data were also not available. In addition, the choice of immunosuppression may have been affected by risk factors not captured in the database, and the possibility that post-transplant DM was underreported when gathered from Medicare claims.

In summary, the researchers said, "Among Medicare-insured kidney transplant recipients, steroid-free immunosuppression is associated with a lower risk of post-transplant DM. This benefit was confirmed for high-risk patients (older adults; BMI ≥30 kg/m^2); however, the importance of concomitant cell depleting differed. These data support the consideration of the risk of nonimmune complications along with the rejection risk when selecting immunosuppression regimens in kidney transplant recipients to minimize patient morbidity from immunosuppression-associated side effects." ■

TAKEAWAY POINTS

- In a retrospective database study, researchers examined the impact of immunosuppression selection on the development of post-transplant diabetes mellitus among older and obese kidney transplant recipients.
- Among patients ≥55 years of age, there were benefits of corticosteroid-sparing regimens with appropriate induction therapy on risk of DM post-transplant.
- There were also reductions in the risk of post-transplant DM with corticosteroid-sparing regimens with appropriate induction therapy among patients with body mass index of ≥30 kg/m^2.

Reducing the Risk of Incident Gout in Women

Gout is a metabolic condition that causes the most common form of inflammatory arthritis, associated with painful recurrent flares and joint damage. Historically, gout has been considered a disease of affluent, middle-aged men; however, over past decades the prevalence of gout has seen a substantial increase. Recent analyses of the Global Burden of Disease Study revealed a disproportionate increase in gout burden among women between 1990 and 2017. That study results highlighted the need for dietary management and other preventive strategies to mitigate the increases.

Female gout is associated with key comorbidities more frequently than male gout, including coronary artery disease, hypertension, type 2 diabetes, and chronic kidney disease. According to **Chio Yokose, MD,** and colleagues, despite perceived differences from males in gout risk factors and disproportionate worsening in disease and comorbidity burden globally, there are few female-specific gout data available.

The 2020 to 2025 Dietary Guidelines for Americans recommend multiple healthy eating patterns for the prevention of cardiovascular-metabolic outcomes; the guidelines may also be relevant to the prevention of female gout. Dr. Yokose et al. conducted a prospective cohort study to examine the associations of dietary scores for the latest guideline-based healthy eating patterns with the risk of incident female gout. Results were reported online in *JAMA Internal Medicine* [doi:10.1001/jamainternmed.2021.7419].

The study exposures were four healthy patterns that reflect the 2020 to 2025 Dietary Guidelines for Americans: (1) Dietary Approaches to Stop Hypertension (DASH); (2) Alternative Mediterranean Diet Score; (3) Alternative Healthy Eating Index (AHEI); and (4) Prudent. The researchers compared adherence to the four healthy patterns with the Western diet (unhealthy). Scores were derived from validated food frequency questionnaires. The primary outcome of interest was incident, physician-diagnosed female-specific gout.

The study included 80,039 women in the United States in the Nurses' Health Study who were followed via questionnaires every 2 years beginning in 1984. Eligible participants in the current study had no history of gout at baseline; questionnaire responses through 2018 were used for the analysis.

Statistical analyses were preformed from September 2020 to August 2021. The researchers used Cox proportional hazards modeling to estimate the risk for incident gout. Dietary pattern scores were divided into quintiles, with the highest quintile indicating greatest adherence to a given pattern.

During 34 years of follow-up, there were 3890 documented cases of incident gout among the 80,039 women. Mean age at baseline was 50.5, and mean body mass index was 25.0 m/kg^2. For each of the four healthy diets, women in the highest quintile tended to be older than those in the lowest quintile; for the Western diet, the reverse was seen. Women in the highest quintile of DASH and AHEI scores tended to have lower intakes of alcohol and coffee compared with the lowest quintile. Among the controls (Western diet), there was little difference in alcohol and coffee intake across quintiles.

Women in the highest quintile of the Western score has the highest total energy intake, followed by women in the highest quintiles of the Prudent and Mediterranean dietary scores. Spearman correlation coefficients between the four health diet scores ranged from 0.478 to 0.68 (all $P<.001$). With the exception of use of hormone replacement therapy (HRT), the nondietary variables were well-balanced between quintiles within each dietary pattern; HRT tended to be higher in quintile 5 of the healthy diets and quintile 1 of the Western diet.

There were consistent associations between lower risk of incident gout and the four healthy dietary patterns. The risk of reduction was greatest with the DASH dietary pattern, with a 32% reduced risk of incident gout in the most adherent quintile compared with the least adherent (multivariable hazard ratio [HR], 0.68; 95% confidence interval [CI], 0.61-0.76; *P* for trend <.001). For the three other healthy dietary patterns, the corresponding risk reduction for the highest versus the lowest quintile of adherence ranged from 12% to 25%.

There was an association between the highest quintile score of the Western diet (the most unhealthy) and 49% increased risk in incident gout compared with those with the lowest quintile (healthiest) (HR, 1.49; 95% CI, 1.3301.68; P for trend <.001).

SUBGROUP ANALYSES

At the time of gout diagnosis, 43% of the women in the cohort (n=1659) were using diuretics, 41% (n=1593) were obese, and 52% (n=2210) used alcohol. When the participants were stratified by those variables, the associations of each diet with the risk of incident gout persisted, with the exception of the Mediterranean diet among overweight or obese women, with seemed to have minimal or no effect on gout risk. Results were similar in additional subgroup analyses according to menopausal status and HRT use.

In the joint analysis, the women with normal body mass index who were most DASH adherent had a 68% lower risk of gout (HR, 0.32; 95% CI, 0.26-0.38) compared with the least adherent women who were obese or overweight. When DASH diet adherence was combined with no diuretic use, the corresponding risk reduction was 65% (HR, 0.35; 95% CI, 0.30-0.40); however, the joint effects between DASH diet and alcohol use were less notable. Trends were similar with the Mediterranean, AHEI, and Prudent dietary patterns. The joint associations of those factors and the Western diet were notable in the opposite direction, with a nearly 3.5-fold higher risk of gout among overweight or obese women most adherent to Western diet, and a 3-fold higher risk among the women using diuretics.

The researchers cited the observational design of the study as a possible limitation to the findings; the design created the possibility that the findings were subject to unmeasured or residual confounding. In addition, the absolute rates of gout and the distribution of dietary intake may not be representative of a random sample of American women.

In conclusion, the authors said, "These large-scale, long-term prospective cohort findings extend the pleotropic benefits of the 2020 to 2025 Dietary Guidelines for Americans to female gout prevention, offering multiple healthy eating patterns that can be adapted to individual food traditions and preferences to reduce women's underrecognized risk of developing gout while simultaneously addressing cardiovascular comorbidities." ■

TAKEAWAY POINTS

- Researchers conducted a prospective cohort study to examine associations of dietary scores for guidelines-based healthy eating patterns with the risk of incident female gout.
- Participants from the Nurses' Health Study with highest adherence to one of four healthy eating patterns had lower risk of incident gout compared with those who ate an unhealthy diet.
- The risk reduction reached 65% to 68% in women who ate a healthy diet and had normal weight and did not use diuretics.

ATC Resumes In-Person Meeting

The American Transplant Congress (ATC), the joint meeting of the American Society of Transplantation and the American Society of Transplant Surgeons, will return to an in-person Congress, June 4 to 8, 2022, at the John B. Hynes Convention Center in Boston, Massachusetts. The meeting will provide current information on transplant science.

The program will include in-depth symposia, two and a half hour sessions on a specific topic of interest; IMPACT session, where industry innovators discuss how the transplant industry is transforming daily work lives; meet the expert, providing access to experts in the field of transplants; controversies in transplantation, debates on topics on transplantation and public policy; plenary oral abstract sessions; a women's networking event; and more.

Somatus Raises $325 Million in Series E Financing

Somatus has announced an oversubscribed Series E financing of $325+ million, at a valuation of more than $2.5 billion. The funding will be used to further the reach and impact of the company's value-based kidney care model. The model, described in a press release, is based on caring for the whole person by actively partnering with locally based providers and providing personalized, in-home care and support directly to patients with kidney disease.

Ikenna Okezie, MD, CEO and cofounder of Somatus, said, "Since our inception, Somatus has always been committed to bringing superior evidence-based integrated care to patients with kidney disease which delays disease progression, improves quality of life, and lowers total cost of care. This investment puts us in a great position to fund the expansion of our proven care model and continue building a nationwide network of providers and connected patients, who alongside our care teams are working together to improve lives and transform the industry."

The funding round was led by Wellington Management and included new investments from RA Capital Management, GIC, Fidelity Management & Research Company, as well as other leading investment organizations. Existing investors Anthem, Blue Venture Fund, Deerfield Management Company, Flare Capital Partners, Inova Health System, Longitude Capital, and Optum Ventures were also contributors.

New Kidney Care Payment Models

In a recent press release, Fresenius Medical Care North American (FMCNA) announced partnerships with more than 1000 nephrology providers as part of the Kidney Care Choices (KCC) model announced by the Centers for Medicare & Medicaid Services (CMS) in 2019, and formally beginning in 2022. The majority of the physicians are members of InterWell Health. The partnerships comprise 20 of the 55 approved Kidney Contracting Entities announced by CMS.

David Pollack, president of FRCNA's Integrated Care Group, said, "We appreciate the more than one thousand nephrology providers who have chosen to partner with us in this important government value-based program to improve care for people living with late-stage kidney disease and kidney failure. We are committed to delivering better outcomes while reducing total costs to our healthcare system. Our innovative solutions have shown we can truly make a difference as we work to intervene earlier to treat kidney disease under new value-based models of care."

Within the Comprehensive Kidney Care Contracting options of the KCC, FMCNA will help manage care for more than 50,000 individuals, providing specialized education and support services designed to slow the progression of kidney disease, increase the prevalence of preemptive transplants, and increase the use of a planned start to life-sustaining treatment.

Terry Ketchersid, MD, MBA, chief medical officer of FMCNA's Integrated Care group, said, "We are excited to bring our many years of experience and learning from previous government initiatives to this new program. Under the direction of the nephrologist, care coordinators will ensure the patient's plan of care is carrier out, providing access to social workers and renal dietitians well before dialysis is needed. Too often patients with kidney disease crash into the hospital with critical health issues and require an urgent start to dialysis, so this program helps incentivize earlier interventions to create a better plan for treatment and management of this disease."

NKF Announces 2022 Award Recipients

David M. Hume Award

The National Kidney Foundation (NFK) has announced the winner of the 2022 David M. Hume Award, presented to a scientist-clinician in the field of kidney and urologic diseases: **Susan T. Crowley, MD, MBA, FASN, FNKF,** professor of medicine (nephrology) at Yale University School of Medicine and national program director for the Veterans Health Administration (VA) Kidney Disease and Dialysis Program.

Susan T. Crowley, MD, MBA, FASN, FNKF

In a press release from NKF, Dr. Crowley said, "I am deeply honored to accept the National Kidney Foundation's David M. Hume award and do so on behalf of the community of kidney health professionals in the Veterans Health Administration which I am privileged to lead. Created to immortalize the humanism and scholarship of Dr. Hume's life work as a kidney clinician-scientist, the award seems especially appropriate to share with my VA colleagues, who strive to optimize the kidney health of our nation's veterans via patient-centered care and scientific discovery in kidney and urologic disease."

Paul Palevsky, MD, president of NKF, said, "One of my duties I most enjoy as the president of NKF is to award the David M. Hume aware, especially to this year's winner, Dr. Crowley. I have worked closely with Dr. Crowley for many years and am thrilled that she is being recognized for all that she does for individuals with kidney disease, and particularly her advocacy for the care of veterans with kidney disease. Susan exemplifies the same dedication as Dr. Hume and I can think of no one better to be named as this year's winner."

Celeste Castillo Lee Patient Engagement Award

In a press release, the National Kidney Foundation announced the recipient of the 2022 Celeste Castillo Lee Patient Engagement Award. The award was presented to **Cari Maxwell** of Lancaster, Pennsylvania, a member of the NKF Advocacy Committee and champion for patient education, early detection, and patient-centered research. She was diagnosed with polycystic kidney disease in 1989.

Cari Maxwell

Paul Palevsky, NFK president, said, "Cari has followed in the footsteps of Celeste Castillo Lee in putting patients at the center of all aspects of healthcare through her involvement with NKF and so many community partners. We sometimes forget that advocates like Cari are doing so much to advance kidney care while also dealing with a serious illness—kidney disease. It makes her accomplishments all the more poignant."

Ms. Maxwell said, "Receiving this award is a tremendous honor. It's truly humbling to be recognized among the other fantastic advocates who have received this award. It validates our collective hard work and dedication to those living with kidney disease, their caregivers, and those we've lost to kidney disease. I'm grateful to the NKF for providing the platform and opportunity to get involved in the kidney disease community and to meet the wonderful advocates , physicians, scientists, and other stakeholders who lie me are working toward out common goal."

Veterans Health Administration Begins Using Race-Free Test of Kidney Health

In 2020, the National Kidney Medicine Program for the Veterans Health Administration (VA) issued a national strategic plan to prevent kidney failure in veterans by using a race-free kidney health screening test and best treatment practices. Past math formulas to calculate estimated glomerular filtration rate from blood tests required adjustment for race; however, a broadened understanding suggests benefits to using a race-free formula instead.

A plan for all VA laboratories to use the race-free eGFR formular was established in early 2021. The formula was developed by a panel of experts assembled by the American Society of Nephrology and the National Kidney Foundation. The panel published the plan in late 2021 that is required for all VA locations as of April 1, 2022, according to a blog on va.gov.

Enrollment Begins in Trial of AI-based Predictive Technology

In a recent press release, Cibiltech announced the enrollment of the first patient in CIBIL (Clinical Impact of the iBox as an Early Intervention tool) trial. The study is a randomized controlled trial assessing the use of a software predicting allograft survival in the follow-up of recipients of kidney transplant (NCT05112315).

Carmen Lefaucher, MD, PhD, transplant nephrologist at Saint-Louis Hospital in Paris, France, said, "We are excited to start recruitment int eh CIBIL study."

Alexandre Loupy, MD, PhD, head of the Paris Transplant Group, added, "Following promising preliminary results, we are now looking forward to seeing the clinical benefits of using the iBox as an early intervention monitoring tool for kidney transplanted patients.

Predigraft is a CE-marked class IIa medical device under MDR 2017/745, offering physicians and hospitals an easy-to-use platform that simplifies access to data and decision making. Predigraft embeds the iBox algorithm, an AI-based technology predicting individual long-term kidney allograft survival. The algorithm gives the probability that the graft will still be functional at 3, 5, and 7 years following evaluation by the healthcare professional.

AKF Appoints Five New Board Members

The American Kidney Fund (AKF) has added five new members to its national volunteer Board of Trustees. All of the new board members have devoted their careers to the advancement of health equity and advocation for improvements to healthcare quality and quality of life for those whose lives are affected by kidney disease.

The new members are: **Kenneth R. Bridges, MD,** principal medical director and vice president of medical affairs at Global Blood Therapeutics; **Oliver T. Brooks, MD,** chief medical officer at Watts Healthcare Corporation and medical director for L.A. Care Health

Plan; **Jamie A. Green, MD,** associate professor of medicine and clinical research, co-director of the Kidney Health Research Institute and medical director of quality and innovation for medicine specialties at Geisinger; **Malay B. Shah, MD,** associate professor of surgery and surgical director of liver transplantation at University of Kentucky; and **Priscilla VanderVeer,** vice president of public affairs at the Pharmaceutical Research and Manufacturers of America.

LaVarne A. Burton, AKF president and CEO, said, "We are so pleased to bring aboard these five talented individuals who will no doubt make an immediate impact on our national Board of Trustees—a passionate group with a steadfast commitment to fighting on behalf of 37 million Americans who have this life-altering disease."

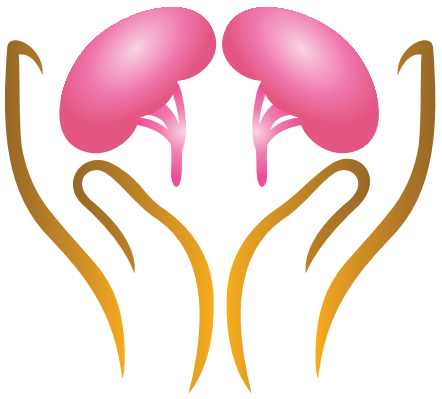
AOPO Supports Improvement of Organ Donation System

The Association of Organ Procurement Organizations (AOPO) released a press release in support of the efforts of the National Academy of Sciences, Engineering, and Medicine (NASEM) Committee on a Fairer and More Equitable, Cost-Effective, and Transparent System of Donor Organ Procurement, Allocation, and Distribution.

AOPO issued the press release in support of NASEM's recommendations to create standardized metrics and establish national performance goals to improve donation and transplantation rates among minority and disadvantaged populations, reduce the prevalence of organs recovered and not accepted for transplant, increase the number of organs procured from medically complex donors, including donation after circulatory determination of death, and increasing the number of transplants to at least 50,000 by 2026.

Jan Finn, RN, MSN, president of AOPO and president and CEO at Midwest Transplant Network, said, "AOPO and its OPO members are committed to advancing the work of NASEM and implementing strategies from the report. These findings share data-driven, peer-reviewed scientific research and expert perspectives to determine gaps in the organ donation and transplantation system and comprehensive solutions to foster improvement.

"The guidance aligns with AOPO's goal to achieve 50,000 annual organ transplants in 2026 through increasing collaboration, reducing health inequities, maximizing organ utilization, and driving innovation. We look forward to taking a deeper look at the details outlines in the report to ensure we are successfully doing our part to save more patient lives." ■



Print-only Content

Abstract Roundup

ACUTE KIDNEY INJURY

Trends in In-Hospital and Long-Term AKI Mortality

Clinical Journal of the American Society of Nephrology. doi.org/10.2215/CJN.01730221

Acute kidney injury (AKI) in hospitalized patients is associated with increased short- and long-term mortality. **Ryann Sohaney, DO,** and colleagues conducted a retrospective cohort study to examine trends in in-hospital and 1-year mortality associated with AKI. AKI was defined using Kidney Disease Improving Global Outcomes serum creatinine criteria.

The study utilized data from the national Veterans Health Administration on all patients hospitalized from October 1, 2008, to September 30, 2017. Cox regression with year as a continuous variable was used to analyze in-hospital and 1-year mortality trends in patients with and without AKI.

During the study period, there were 1,688,457 patients and 2,689,093 hospitalizations. Of the patients with AKI, 6% died during hospitalization and 28% died within 1 year of discharge. Conversely, in-hospital and 1-year mortality rates among non-AKI hospitalizations were 0.8% and 14%, respectively. There was a slight decrease in crude in-hospital AKI-associated mortality during the study period (hazard ratio [HR], 0.98 per year; 95% confidence interval [CI], 0.98-0.99); the decrease was attenuated following adjustment for patient demographics, comorbidities, and acute hospitalization characteristics (adjusted HR, 0.99 per year; 95% CI, 0.99-1.00). The stable temporal trend in mortality persisted at 1 year (adjusted HR, 1.00 per year; 95% CI, 0.99-1.00).

In conclusion, the researchers said, "AKI associated mortality remained high, as greater than one in four patients with AKI died within 1 year of hospitalization. Over the past decade, there seems to have been no significant progress toward improving in-hospital or long-term AKI survivorship."

CHRONIC KIDNEY DISEASE

Phosphate Intake and Bone and Mineral Biomarkers

Journal of Renal Nutrition. 2022;32(1):58-67

Adverse outcomes associated with higher serum phosphate include cardiovascular disease. In patients with chronic kidney disease (CKD), abnormalities of bone and mineral metabolism, including higher serum phosphate, are key risk factors for increased cardiovascular disease. However, according to **Marguerite Comley, MNutDiet, BSi (ExSportSci),** and colleagues, there are few data available on the associations between dietary phosphate intake and biochemical and cardiovascular parameters in non-dialysis CKD patients. The researchers conducted a study to examine associations between phosphate intake and biomarkers of bone and mineral metabolism and intermediate cardiovascular markers in adults with CKD stage 3-4.

Participants in the Impact of Phosphate Reduction on Vascular

End Points in Chronic Kidney Disease trial were asked to join the current sub-study. Dietary phosphate intake and source (animal, plant, or a mixture of both) were determined at baseline using a 7-day self-administered diet food record; measurements of serum and urinary phosphate, serum calcium, parathyroid hormone, fibroblast growth factor-23, and the intermediate cardiovascular markers pulse wave velocity (PWV) and abdominal aortic calcification were obtained. Pearson's correlation and linear regression were used to explore the relationships between dietary phosphate and those bone metabolism and cardiovascular markers. Compositional data analysis was used to analyze the effect of source of phosphate intake.

The analysis included 90 individuals; 68% were male, mean age was 64 years, estimated glomerular filtration rate was 26.6 mL/min/1.73 m^2, and dialysis phosphate intake was 1544 mg. Correlations among dietary phosphate and biochemical measures, PWV, and abdominal aortic calcification ranged from $r = -0.13$ to $r = +0.13$. Results of linear regression showed no association between dietary phosphate measurement and biochemical or cardiovascular parameters. There was an association between source of phosphate intake and PWV (P=.01); there was no association with other biomarkers of bone and mineral metabolism. Higher PWV values were associated with higher intake of plant-based relative to animal-based phosphate (1.058, P=.003).

In summary, the authors said, "Levels of total dietary phosphate intake measured by dietary food record show no statistically significant relationship with biochemical markers of bone and mineral metabolism or intermediate cardiovascular markers. Higher PWV level associated with higher intake of plant-based relative to animals-based phosphate intake were an unexpected finding and further research is needed in this area."

Weight Change Correlates with Adverse Outcomes in CKD

Journal of Renal Nutrition. 2021;31(6):569-578

Both obesity and being underweight put patients with chronic kidney disease (CKD) at risk for adverse outcomes. However, according to **Hyunjin Ryu, MD, MS,** and colleagues, there are few data available of the effect of longitudinal weight changes in patients with predialysis CKD. The researchers conducted an analysis to examine the effects of weight change over time on adverse outcomes in patients with non-dialysis CKD.

The analysis included longitudinal data from KNOW-CKD, a multicenter prospective cohort study. In a cohort of 2022 patients, the percent weight change per year was calculated using regression analysis. Study participants were classified into five categories: group 1, ≤–5% per year; group 2, –5 to ≤–2.5% per year; group 3, –2.5< to <2.5% per year; group 4, ≤2.5 to <5% per year; and group 5, ≥5% per year. Incidence of end-stage kidney disease (ESKD) and the composite outcome of cardiovascular disease and death were calculated in each group and compared to group 3 as reference.

Median follow-up was 4.4 years. During that time, there were 414 ESKD and 188 composite of cardiovascular disease and mortality events. Independent risk factors for adverse events included both weight gain and weight loss. There was a U-shaped correlation between the degree of longitudinal weight change and ESKD (hazard ratios for group 1, 2, 4, and 5 were 3.61, 2.15, 1.86, and 3.66, respectively) and for the composite of cardiovascular disease and death (hazard ratios, 2.92, 2.15, 1.73, and 2.54, respectively) when compared with the reference group 3. The U-shape correlation was most prominent in the subgroup of estimated glomerular filtration rate <45 mL/min/1.73 m^2.

"Both rapid weight gain and weight loss are associated with high risk of adverse outcomes, particularly in advanced CKD," the authors summarized.

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COVID-19

Gender and Race and Risk of COVID-19-related AKI

Frontiers in Cellular and Infection Microbiology. Doi.org/10.3389/fcimb.2021.778636

SARS-CoV-2 infection has a strong transmission capacity and can lead to severe and potentially fatal respiratory diseases. COVID-19 can also affect the heart, the kidneys, and the digestive tract. Clinical data reveal that kidney injury is a common complication of COVID-19, and severely ill patients often develop acute kidney injury (AKI).

Data from the United States and from China suggest associations between increased risk of COVID-19-related AKI and male sex, Black race, older age, chronic kidney disease, diabetes, hypertension, cardiovascular disease, and higher body mass index.

Researchers in China, led by **Weihang He,** conducted a literature search and review of COVID-19-related AKI. The review revealed sex and ethnic differences in the occurrence and development of AKI in patients with COVID-19.

The researchers noted, "By summarizing the mechanism of gender and ethnic differences in AKI among patients with COVID-19, we found that male and Black race have more progress to COVID-19-induced AKI than their counterparts."

Study on Vaccine Response in Severe CKD

BMC Nephrology. doi:10.1186/s12882-022-02680-3

In patients with chronic kidney disease (CKD) stages G4-G5,or receiving kidney replacement therapy (KRT: dialysis, or kidney transplantation), there are associations between COVID-19 and increased morbidity and mortality. Trials of SARS-CoV-2 vaccine do not commonly include that patient population. It is known that vaccination against other viruses is less effective in kidney patients. **P.Bouwmans, PhD,** and colleagues described a national prospective observational study examine the safety and efficacy of various types of SARS-CoV-2 vaccines in patients with CKD stages G4-G5 or on KRT.

The study cohort will include 12,000 patients with CKD stages G4-G5 or on KRT following SARS-CoV-2 vaccination according to the Dutch vaccination program. Blood will be drawn for measurement of antibody response at day 28 and month 6 following completion of vaccination. Registration data and questionnaires during 2 years of follow-up will be used to determine patient characteristics and outcomes. Results will be compared with a control group of non-vaccinated patients. To predict protection against COVID-19 breakthrough infection, the level of antibody response to vaccination will be assessed in subgroups.

The primary end point of interest is the efficacy of SARS-CoV-2 vaccination, determined as the incidence of COVID-19 after vaccination. Secondary end points are the antibody based immune response at 28 days after vaccination, the durability of the response at 6 months after vaccination, mortality, and (serious) adverse events.

The researchers said, "This study will fulfill the lack of knowledge on efficacy and safety of SARS-CoV-2 vaccination in patients with CKD stages G4-G5 or on KRT."

Abstract Roundup

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DIABETES

Biomarkers and Kidney Outcomes in Early Stage Diabetic Kidney Disease

Clinical Journal of the American Society of Nephrology. 2022;17(2):251-259

Clinical trials in nephrology are enriched for patients with micro- or macroalbuminuria to enroll patients at risk of kidney failure. Patients with normoalbuminuria can also progress to kidney failure. Previous studies have demonstrated associations between TNF receptor-1, TNF receptor-2, and kidney injury marker-1 (KIM-1) and progression of kidney disease in patients with micro- or macroalbuminuria.

Simke W. Waijer, MSc, and colleagues conducted a study to examine the value of TNF receptor-1, TNF receptor-2, and KIM-1 as prognostic biomarkers for progression of chronic kidney disease (CKD) in patients with type 2 diabetes and normoalbuminuria.

Patients with type 2 diabetes at high cardiovascular risk participating in the Canagliflozin Cardiovascular Assessment Study were included. TNF receptor-1, TNF receptor-2, and KIM-1 were measured using immunoassays in plasma samples. Multivariable adjusted Cox proportional hazards analyses were used to estimate hazard ratios per doubling of each biomarker for the kidney outcome. The study population was stratified by the fourth quartile of each biomarker distribution, and the number of events and event rates were assessed.

The markers of interest were measured using immunoassay in plasma samples from participants in the Canagliflozin Cardiovascular Assessment Study with type 2 diabetes at high risk for cardiovascular disease. Multivariable adjusted Cox proportional hazards analyses were used to estimate hazard ratios (HR) per doubling of each biomarker for the kidney outcome. The population was stratified by the fourth quartile of each biomarker distribution and the number of events and event rates were assessed.

The analysis cohort included 2553 patients with normoalbuminuria. During a median follow-up of 6.1 years, there were 51 kidney outcomes recorded (event rate, 3.5; 95% confidence interval [CI], 2.6 to 4.6 per 1000 patient-years). Each doubling of baseline TNF receptor-1 (HR, 4.2; 95% CI, 1.8-9.6) and TNF receptor-2 (HR, 2.3; 95% CI, 1.5-3.6) was associated with a higher risk for the kidney outcome. There were no associations between baseline KIM-1, urinary albumin-creatinine ratio, and eGFR and kidney outcomes. Event rates in the highest quartile of TNF reception-1 (≥2992 mg/mL) and TNF receptor-2 (≥11,394 mg/mL) were 5.6 and 7.0 events per 1000 patient-years, respectively, compared with 2.8 and 2.3 events per 1000 patient-years, respectively, in the lower three quartiles.

In summary, the researchers said, "TNF receptor-1 and TNF receptor-2 are associated with kidney outcomes in patients with type 2 diabetes and normoalbuminuria."

DIALYSIS

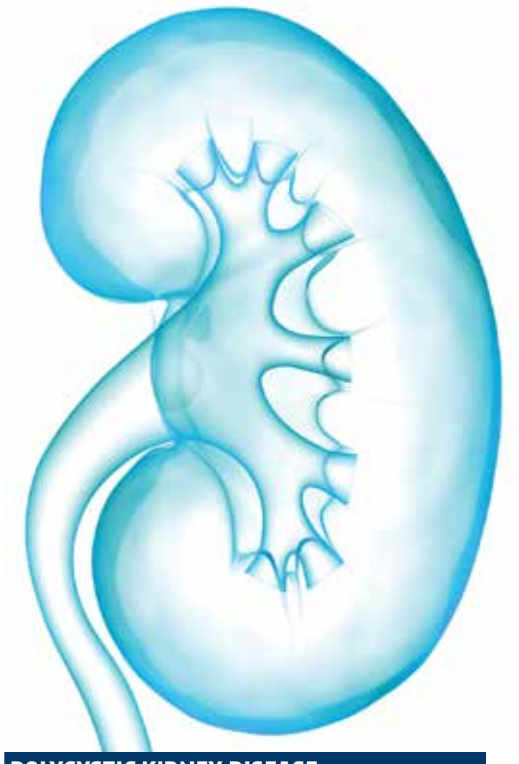
Peritoneal Dialysis to Treat Heart Failure

Reviews in Cardiovascular Medicine. 2021;22(3):649-657

Worldwide, heart failure remains a significant health problem despite available therapies; many patients reach advanced stages of heart failure, complicated by diuretic resistance, kidney dysfunction, and refractory congestion, all prevalent in advanced disease. Options for treatment of fluid overload include hemodialysis or peritoneal dialysis.

Over the past few decades, peritoneal dialysis has emerged as an attractive therapy, due to benefits demonstrated in numerous cohort studies including functional class improvement, reduction in hospital admissions, improved quality of life, and reduction in mortality. However, according to **Ronald O. Morales, MD,** and colleagues in Barcelona, Spain, most of the previous studies were observational and included a limited number of patients. Further, the optimal timing for peritoneal dialysis therapy and the subgroup of patients who would derive the most benefit is unknown.

The researchers reviewed the contemporary evidence of the use of peritoneal dialysis in patients with heart failure and diuretic resistance across the spectrum of ventricular dysfunction and degree of renal dysfunction.



POLYCYSTIC KIDNEY DISEASE

Risk for IAs in Patients with ADPKD

Nephrology Dialysis Transplantation. doi.org/10.1093/ndt/gfac027

Patients with autosomal dominant polycystic kidney disease (ADPKD) face increased risk for developing intracranial aneurysms (IAs). **Siriane LeFèvre, MD,** and colleagues conducted an analysis to examine the frequency of diagnosis of IAs to describe IAs associated with ADPKD and to analyze the risk factors associated with the occurrence of IAs in patients with ADPKD.

The analysis utilized data from the cross-sectional, population-based Genkyst cohort performed in 26 nephrology centers in western France. All participants underwent genetic testing for *PKD1/PKD2* and other cystogenes.

At baseline, of the 2449 participants in the Genkyst study, 4.6% (n=114) had a previous diagnosis of ruptured or unruptured IA, and approximately 47% of those had a positive familial history for IAs. Most aneurysms were small and saccular and were located in the anterior circulation; 26.3% of the patients had multiple IAs.

At ages 50, 60, and 70 years, the cumulative probabilities of a previous diagnosis of IAs were 3.9%, 6.2%, and 8.1%, respectively. In participants <50 years of age, the risk was similar in men and women; however, after age 50, the risk increased more markedly in women, reaching 10.8% versus 5.4% at age 70 years. In *PKD1* versus *PKD2,* the diagnosis rate of IAs was more than 2-fold higher with no influence of PKD1 mutation type or location.

Following adjustment for various factors, there were associations between female sex, hypertension <35 years, smoking status, and *PKD1* genotype and increased risk for diagnosis of IAs.

In conclusion, the authors said, "This study presents epidemiological data reflecting real-life clinical practice. The increased risk for IAs in postmenopausal women suggests a possible protective role of estrogen." ■

Print-only Content

Sarah Tolson

Taking a Closer Look at Medication Reimbursement

Since the last edition of From the Field, the Centers for Medicare & Medicaid Services (CMS) has released instructions regarding how to report difelikefalin, the new drug used to treat ESKD-related pruritus, on dialysis claims for the claim to process correctly. The instruction provided by CMS indicates claims containing charges for difelikefalin. Effective with dates of service starting April 1, 2022, CMS has indicated it will process claims containing charges for difelikefalin the same way Transitional Drug Add-on Payment Adjustment (TDAPA) claims were processed previously. Personally, I am really excited for the opportunity to bill for TDAPA medications because, as I learned when calcimimetics were reimbursed under TDAPA, it presents many interesting challenges when it comes to collecting reimbursement from insurance companies.

Dialysis programs considering providing medications covered under TDAPA to their patients may find it beneficial to understand which insurances are likely to reimburse for the medications and which are likely not to have an idea of the financial impact that utilization of the medication will have on the program. Some things to consider when determining if an insurance is likely to reimburse for a TDAPA medication are the dialysis program's contract status with the insurance company, insurance plan type, and current reimbursement type (fee for service, percentage of billed charges, bundled per treatment reimbursement, Medicare rates).

The contracting status of a dialysis facility plays a big role in determining whether the insurance will reimburse for a TDAPA medication. If there is a contract in place, regardless of insurance plan type, the terms of the contract may give you a clue. Contracts that pay an all-inclusive rate per dialysis treatment likely will not provide separate reimbursement for a TDAPA medication unless there is a provision that specifies how medications that are new to the market will be reimbursed under the contract. In the event your dialysis program will be providing significant amounts of TDAPA medications to patients covered by insurances that reimburse dialysis with an all-inclusive rate per treatment, it may be worthwhile to look at renegotiating your agreement.

In the event there is no contract in place, the type of insurance plan may help you determine if reimbursement is a possibility. During the time calcimimetics were covered under TDAPA, the company I work for had the opportunity to work with many commercial, Medicare Advantage, Medicaid, and Medicaid Managed Care plans across the country. Commercial insurance companies were generally slow to add medications to their formulary for coverage when there was no contract in place. Since medications are reimbursed under TDAPA for a relatively short period of time, it was incredibly inconvenient to have commercial insurances take anywhere from 12 to 18 months to add medications to their formulary.

We found traditional Medicaid to be even slower in adding medications to its formulary. Additionally, since Medicaid Managed Care plans frequently reimburse at the same rate and cover the same services as traditional Medicaid, these types of plans typically did not provide reimbursement for TDAPA medications when billed as a primary payer. In the event Medicaid or a Medicaid Managed care plan was billed as a secondary payer, however, we found it would stick to its reimbursement method for Medicare assigned coinsurances. This means that if it had previously paid 100% of the coinsurance assigned by Medicare, it would continue to do so even with the increased coinsurances from the TDAPA medication. However, if Medicaid had previously only issued payment when the amount Medicare paid for dialysis was less than the Medicaid fee schedule, it was highly unlikely secondary payments would be issued by Medicaid.

The last time I had the opportunity to bill for a TDAPA medication, my favorite type of insurance company to work with were Medicare Advantage Plans where the dialysis program did not have a contract. Claims covered by this type of insurance company should be reimbursed at the same rate as Medicare. We frequently found that regional Medicare Advantage Plans were not familiar with TDAPA, and their claims processing systems were not prepared to calculate the reimbursement for TDAPA medications. It was very rewarding for me to work with these insurance companies to help them identify the resources they needed to update their systems and process claims for our clients. Since difelikefalin is the second medication reimbursed under TDAPA I would imagine Medicare Advantage Plans will be better prepared to process TDAPA claims, but I am looking forward to the unique challenges that come with a change to reimbursement. ■

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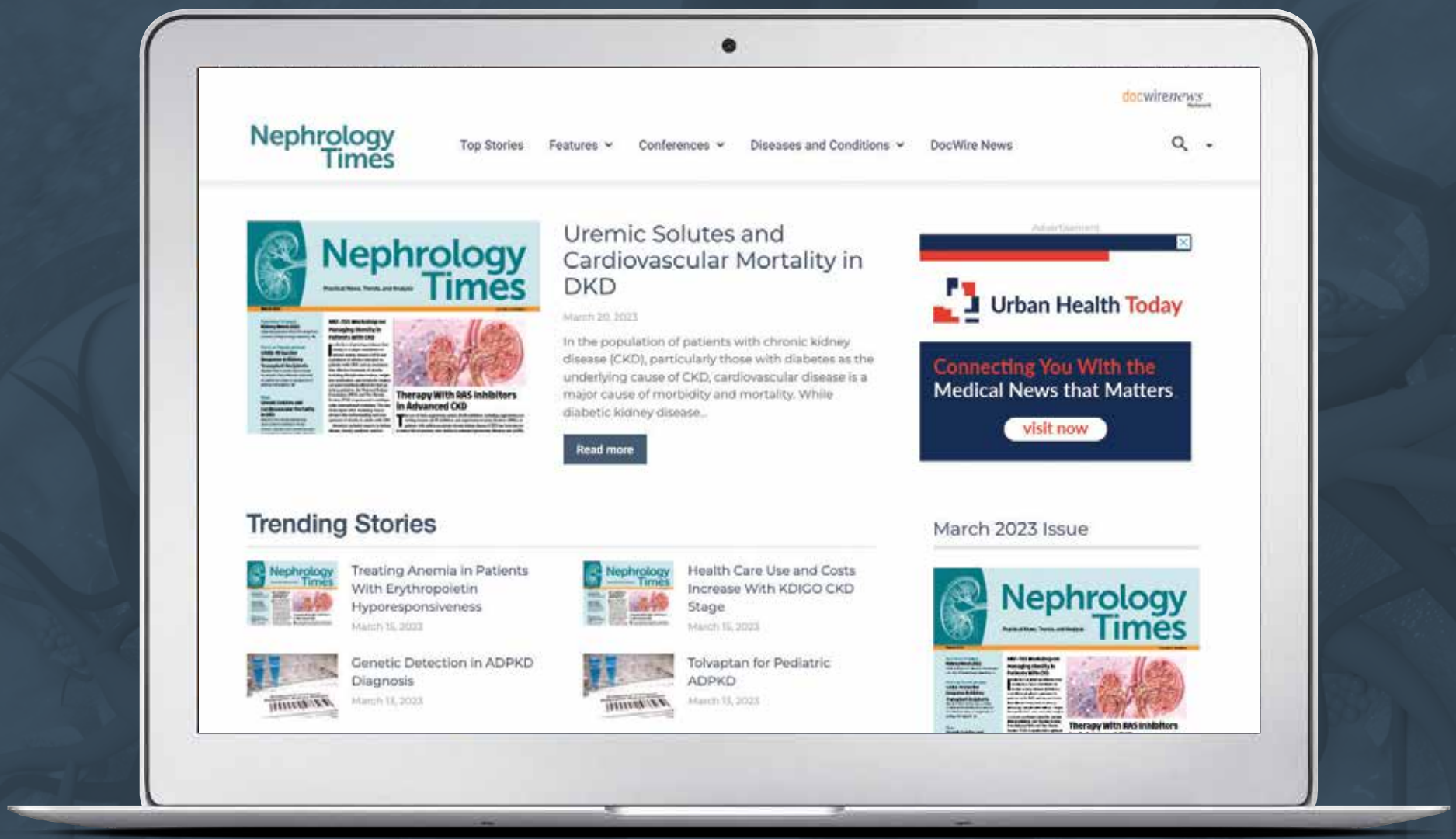

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