Nephrology Times

Practical News, Trends, and Analysis

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Testing for Coronary Heart Disease Before Kidney Transplantation

Patients being evaluated for kidney transplant routinely undergo screening for coronary heart disease (CHD). Testing, both noninvasive and invasive, in asymptomatic patients is prevalent in clinical practice, and 40% of Medicare beneficiaries who underwent kidney transplantation were screened for CHD in the year prior to transplantation.

Numerous studies published in the 2000s argued against CHD screening in asymptomatic patients. However, proponents of screening contend that the trials did not include patients with advanced kidney disease and/or did not examine perioperative risk specifically. In addition, regulatory agencies have used posttransplant survival as the primary metric to evaluate and accredit transplant programs, creating an incentive to avoid perioperative events that may be associated with early death.

According to **Xingxing S. Cheng, MD, MS,** and colleagues, there are few data demonstrating the positive association of CHD screening with kidney transplant outcomes. The researchers conducted a retrospective cohort study designed to estimate the association of pretransplant CHD testing with rates of death and myocardial infarction (MI). Results were reported online in *JAMA Internal Medicine* [doi:10.1001/jamainternmed.2022.6069].

The study included all adult, first-time kidney transplant recipients from

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Kidney Function Decline in Children With CKD

The incidence of pediatric chronic kidney disease (CKD) is low, and there are gaps in the quantity and quality of evidence informing clinical decision-making in pediatric CKD. Causes of CKD in children include congenital anomalies of the kidney and urinary tract (CAKUT) and acquired disease. Glomerular disease is the most common form of acquired pediatric CKD leading to kidney failure. Repeated episodes of acute kidney injury are also associated with increased risk for the development and progression of CKD in children.

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Disparities in Acute Care Utilization in Patients With Glomerular Disease

Patients with glomerular disease may experience acute medical complications such as anasarca, infections, acute kidney injury, thromboembolism, and cardiovascualr events that require utilization of acute care (emergency department [ED] visit or hospitalization). In addition, patients with glomerular disease being treated with immunosuppressive therapies commonly experience infections that can result in utilization of acute care.

According to **Jill R. Krissberg, MD, MS,** and colleagues, the risk of utilization of acute care may be affected by race, ethnicity, and socioeconomic status (SES). The researchers conducted a prospective cohort study designed to compare rates of acute care utilization across racial and ethnic groups in adults and children with glomerular disease in the CureGN (Cure Glomerulonephropathy) cohort. They sought to test the hypothesis that rates of acute care utilization would be increased among Black or Hispanic patients but that lower SES and more severe glomerular disease in those groups would explain any observed differences. Results of the study were reported in the *American Journal of Kidney Diseases* [2023;81(3):318-328].

The study cohort included 1456 adults and 768 children with biopsy-proven glomerular disease enrolled in the CureGN cohort. The study exposure was race and

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Limited Utilization of SGLT2 Inhibitors: Why the Inertia?

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Sodium-glucose transport protein 2 (SGLT2) inhibitors (SGLT2i), or gliflozins, block SGLT2 cotransporters in the proximal tubules and reduce renal glucose and sodium reabsorption.[1] Reduced reabsorption of sodium results in natriuresis, which, through tubuloglomerular feedback, causes a reduction of intraglomerular pressure. SGLT2i have been shown to not only slow kidney progression in patients with chronic kidney disease regardless of diabetes status, but also improve glucose control, reduce the risk of heart failure, and reduce blood pressure, and they do so in a cost-effective manner.[2]

The use of SGLT2i has been limited despite approval in the United States since 2013 (canagliflozin). One important factor, which research suggests might be a myth, is that underutilization of SGLT2i therapy is due to their high cost or high copayments.

Two recent studies have reported on utilization of SGLT2i where cost was not a factor, namely the US Department of Veterans Affairs (VA), where prescriptions are free. The first study by Mahtta et al looked at SGLT2i use in 537,980 patients with atherosclerotic cardiovascular disease (ASCVD) and type 2 diabetes mellitus (T2DM) in 130 VA facilities.[3] They reported that approximately 11% of patients were on SGLT2i therapy. Surprisingly, among individuals with an estimated glomerular filtration rate of >30 mL/min/1.73m^2, only 14% of individuals were being treated with an SGLT2i.

> I've also wondered whether there is confusion among providers about who owns the therapy–the diabetologist, the cardiologist, or the nephrologist?

The second study was presented by Hussain and colleagues on March 3, 2023, at the American College of Cardiology meeting in New Orleans.[4] The authors evaluated 105,799 patients with ASCVD, heart failure, and T2DM across 130 VA facilities; 14.6% of those patients received SGLT2i. There was significant facility-level variability in both analyses, suggesting that practice patterns may be an important factor.

Some argue that underutilization of SGLT2i is not surprising because adoption of novel therapies often takes several years. This "therapeutic inertia,"[5,6] defined as continuing an older clinical treatment despite less efficacy and failing to start a new medication that has proven more effective,[6] has been ascribed to both patient and provider factors.[7] For patients, old habits die hard, and they become comfortable with an older medication. Changing medications can sometimes be confusing and adds to pill burden. In the case of SGLT2i, a conversation about the risk of genital infections and the importance of genital hygiene could be viewed as awkward.

Providers, on the other hand, may have inertia because of the work involved in starting and up-titrating the SGLT2i. Another common refrain could be that "there isn't enough time in the day" to complete all the paperwork required to get the patient's insurance to approve initiation of SGLT2i. In addition to these factors, I've also wondered whether there is confusion among providers about who owns the therapy—the diabetologist, the cardiologist, or the nephrologist?

Things could change over the next 2 years as the main product patents on SGLT2 inhibitors expire between 2023 and 2025. With generics on the market, the price of SGLT2i is likely to fall dramatically. Still, reducing the price could have other inadvertent effects. With less revenue from SGLT2i, pharma may decide to spend money on the promotion, education, and research of other emerging products. Lack of financial incentives may also influence prescribing patterns.[8] The VA analyses point to considerable practice-level variability and suggest that some providers are reluctant, perhaps because of inertia, to use SGLT2i. Here, education and guideline-directed care are likely to be key. The American Diabetes Association and Kidney Disease: Improving Global Outcomes, among other organizations, have published guidelines, which should make a difference.

The bottom line is that we should be disappointed that 10 years after the first approval of SGLT2i therapy, less than 15% of patients are receiving treatment with them. These agents have been demonstrated to reduce progression of kidney disease and delay end-stage kidney disease. They have clear cardioprotective benefits. We all need to pull up our socks and start using them. ■

REFERENCES

1. Vallon V, Verma S. Effects of SGLT2 inhibitors on kidney and cardiovascular function. *Annu Rev Physiol*. 2021;83:503-528. doi:10.1146/annurev-physiol-031620-095920

2. McEwan P, Foos V, Martin B, Chen J, Evans M. Estimating the value of SGLT2 inhibitors within the context of contemporary guidelines and totality of evidence. *Diabetes Obes Metab*. 2023. doi:10.1111/dom.15040

3. Mahtta D, Ramsey DJ, Lee MT, et al. Utilization rates of SGLT2 inhibitors and GLP-1 receptor agonists and their facility-level variation among patients with atherosclerotic cardiovascular disease and type 2 diabetes: insights from the Department of Veterans Affairs. *Diabetes Care*. 2022;45(2):372-380. doi:10.2337/dc21-1815

4. Hussain A, Ramsey D, Mahtta D, et al. Utilization rates of SGLT2 inhibitors and their facility-level variation among patients with type 2 diabetes (T2DM), heart failure, (HF) and atherosclerotic cardiovascular disease (ASCVD): insights from the Department of Veteran Affairs (VA). *J Am Coll Cardiol*. 2023;81(8_Supplement):1645. doi:10.1016/S0735-1097(23)02089-2

5. Okemah J, Peng J, Quiñones M. Addressing clinical inertia in type 2 diabetes mellitus: a review. *Adv Ther*. 2018;35(11):1735-1745. doi:10.1007/s12325-018-0819-5

6. Steinman MA, Landefeld CS. Overcoming inertia to improve medication use and deprescribing. *JAMA*. 2018;320(18):1867-1869. doi:10.1001/jama.2018.16473

7. Bergethon KE, Wasfy JH. Increasing the adoption and diffusion of a novel pharmacological therapy that is both mortality reducing and cost-effective. *J Am Heart* Assoc. 2019;8(3):e011783. doi:10.1161/JAHA.118.011783

8. Bergethon KE, Blumenthal DM. The interplay between financial incentives, institutional culture, and physician behavior: an incompletely understood relationship worth elucidating. *J Hosp Med*. 2019;14(1):60-62. doi:10.12788/jhm.3098

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The most comprehensive data on the progression of CKD in children are from the Chronic Kidney Disease in Children (CKiD) study, an ongoing prospective cohort study that has enrolled more than 1000 children over three recruitment waves. According to **Caroline A. Gluck, MD,** and colleagues, CKiD data are limited by the relatively small sample size. The researchers conducted a study utilizing electronic heath record (EHR) data from a national multicenter pediatric network in the United States to identify a large cohort of children with CKD.

The retrospective cohort study was designed to evaluate progression of CKD in the pediatric population and examine clinical risk factors for decline in kidney function. Results of the study were reported online in the *Clinical Journal of the American Society of Nephrology* [doi.org/10/2215/CJN.000000000000051].

The cohort included children seen in six pediatric health systems in PEDSnet between January 1, 2009, and February 28, 2022. PEDSnet is a clinical research network that has aggregated EHR data from inpatient and outpatient settings in the United States for more than 7 million patients. Criteria used to identify children with CKD were two estimated glomerular filtration rate (eGFR) values <90 mL/min/1.73 m^2 and ≥15 mL/min/1.73 m^2 separated by at least 90 days, without an intervening value >90 mL/min/1.73 m^2.

CKD progression was defined as a composite outcome of eGFR <15 mL/min/1.73 m^2, ≥50% decline in eGFR, long-term dialysis, or kidney transplant. Subcohorts were identified based on CKD etiology (glomerular, nonglomerular, or malignancy). The association of hypertension (two or more visits with hypertension diagnosis code) and proteinuria (one or more urinalysis with one or more + protein) within 2 years of cohort entrance on the composite outcome was examined.

The study sample derivation yielded a cohort of 11,240 children. Overall, median age at entrance to the cohort was 11 years, and median follow-up time was 5.1 years. Children in the nonglomerular cohort included those with CAKUT, such as hydronephrosis renal dysplasia, renal agenesis, and obstructive and reflux nephropathy. Those with a history of malignancy were younger at cohort entrance and had longer follow-up time than those in the other subcohorts. There were no significant differences in sex across cohorts.

At cohort entrance, most children had eGFR 60 to 89 mL/min/1.73 m^2. Median eGFR was 75.3 mL/min/1.73 m^2. In the glomerular CKD subcohort, median eGFR was lower and a greater proportion had eGFR 15 to 59 mL/min/1.73 m^2 compared with the other subcohorts.

Within 2 years of cohort entrance, overall and across subcohorts, at least 31% had proteinuria and at least 32% had hypertension. The burden of proteinuria and hypertension was highest among those with glomerular CKD. Sixty-one percent of those with hypertension were treated with any antihypertensive within the first 2 years, and 59% of those with both hypertension and proteinuria were treated with renin-angiotensin-aldosterone system blockade. Across the subcohorts, the proportion of children with a cardiac diagnosis at cohort entrance was 16% to 26%.

Overall, 1874 children progressed to the composite kidney failure outcome. A ≥50% decline in eGFR occurred in 15% of the overall cohort (n=1633), and 10% of the cohort (n=1135) reached eGFR <15 mL/min/1.73 m^2. Long-term dialysis occurred in 4% of the cohort (n=448) and 4% (n=465) underwent kidney transplant. Those in the glomerular CKD subcohort were more likely to reach the composite outcome compared with those with nonglomerular CKD and those with a history of malignancy (40%, 13% and 23%, respectively).

The most rapid progression to kidney failure was seen in children in the glomerular CKD subcohort; children in the history of malignancy subcohort progressed to kidney failure more rapidly than children in the nonglomerular CKD subcohort. The effect of disease etiology was mitigated by worse eGFR category on cohort entrance.

There were associations between hypertension and proteinuria and more rapid decline in kidney function. Those with CKD and both hypertension and proteinuria had the fastest progression to kidney failure.

In the sensitivity analysis for the cohort with eGFR <60 mL/min/1.73 m^2, CKD associated with glomerular disease and CKD associated with malignancy were associated with higher risk for progression of kidney disease. When death was analyzed as a competing risk, there was no significant effect on cumulative incidence of the composite kidney failure outcomes in both the main analysis and the sensitivity analysis requiring eGFR <60 mL/mnin/1.73 m^2 for cohort entry.

Results of multivariable Cox analyses demonstrated the significant and independent effects of hypertension and proteinuria on CKD progression: adjusted hazard ratio (aHR) associated with hypertension, 1.49 (95% CI, 1.22-1.82) and proteinuria, 2.23 (95% CI, 1.89-2.62). Those with glomerular disease and a history of malignancy compared with those with nonglomerular CKD had higher risks of CKD progression (aHR, 2.01 [95% CI, 1.78-2.28] and aHR, 1.79 [95% CI, 1.52-2.11], respectively).

Children with both proteinuria and hypertension had higher risk of CKD progression compared with those without proteinuria or hypertension (aHR, 3.98; 95% CI, 3.40-4.68). The highest risk of reaching the composite outcome was among children with greater CKD severity (lower eGFR category) at cohort entrance; the highest risk was among children with eGFR 15 to 29 mL/min/1.73 m^2 (aHR, 5.75; 95% CI, 5.05-6.55).

> Children with both proteinuria and hypertension had higher risk of CKD progression compared with those without proteinuria or hypertension (aHR, 3.98; 95% CI, 3.40-4.68).

Study limitations cited by the authors included basing determinations of CKD etiology and comorbid conditions on diagnosis codes only, the inability to determine whether hypertension was controlled, and lack of information on the method of creatinine measurement in the study cohort.

In conclusion, the researchers said, "Overall, this study leveraged large-scale multi-institutional EHR data collected in real-world settings to study a rare disease, pediatric CKD, over an extended time period and includes a previously underrepresented population, children with a history of cancer. Our findings confirm several previously established risk factors for CKD progression from prior observational studies (glomerular disease, proteinuria, and hypertension) and provide face validity to our novel approach for studying pediatric CKD. This study may serve as the foundation for future pragmatic clinical trials in children with CKD and as a roadmap for use of EHR data networks to adequately power the study of rare disease." ■

TAKEAWAY POINTS

- Researchers reported results of a retrospective cohort study using electronic health record data to identify a large cohort of children with chronic kidney disease (CKD), examine progression of CKD, and identify clinical risk factors for decline in kidney function.
- Seventeen percent of the overall cohort progressed to the composite kidney failure outcome.
- Lower estimated glomerular filtration rate category, hypertension, and proteinuria were associated with increased risk for progression to kidney failure among children with CKD.

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ethnicity as a participant-reported social factor. Race and ethnicity were categorized as White, including non-Hispanic White; Black, including participants of Black race and any ethnicity; Asian, including participants of Asian race and any ethnicity; and Hispanic, including Hispanic White. The outcome of interest was acute care utilization defined as hospitalizations or visits to the ED.

The highest rates of acute care utilization were among Black adults, and the lowest were among Asian adults (45.6 events per 100 person-years vs 29.5 for Hispanic adults, 25.8 for White adults, and 19.2 for Asian adults; *P*<.001).

Associations between race and ethnicity and utilization of acute care were estimated using multivariable recurrent event proportional rate models. The analyses were serially adjusted for confounders using six sequential models: the first model examined unadjusted associations between race and ethnicity and utilization of acute care; the second model additionally adjusted for demographic characteristics; the third model additionally adjusted for socioeconomic factors; the fourth for chronic disease indicators; the fifth for disease severity and activity markers at enrollment; and in the sixth model, estimated glomerular filtration rate (eGFR) was incorporated as a time-varying covariate.

Of the 1456 adults in the study, 65% (n=950) were non-Hispanic White, 16% (n=233) were Black (of which 14 were Hispanic), 11% (n=154) were Asian (of which none were Hispanic), and 8% (n=119) were Hispanic White. Compared with the adults who were White or Asian, those who were Black or Hispanic were less likely to have a college education, more likely to have US public insurance, and more likely to be on medical leave, disabled, or unemployed.

Black adults had the highest frequency of focal segmental glomerulosclerosis (FSGS) (45%); Asian and Hispanic adults had the highest frequency of immunoglobulin A nephropathy/vasculitis (39%-40%). Hispanic adults had the lowest eGFR, and Black adults had the highest urinary protein-creatinine ratio (UPCR). Black adults were most likely to have obesity, and Asian adults were least likely to have obesity or hypertension. The racial and ethnic groups were similar in frequency of use of glucocorticoid or other immunosuppression at enrollment.

Of the 768 children in the study, 66% (n=507) were non-Hispanic White, 18% (n=141) were Black (of whom four were Hispanic), 6% (n=48) were Asian (one of whom was Hispanic), and 10% (n=72) were Hispanic White. Compared with White or Asian children, Black or Hispanic children were less likely to have US private insurance (59%, 50%, 34%, 34%, respectively). The parents of Black or Hispanic children were less likely to be college educated compared with the parents of White or Asian children.

The frequent diagnosis overall was minimal change disease, but Black children were most likely to have FSGS. Black children had the lowest eGFR and highest UPCR. Obesity, hypertension, or a family history of kidney disease were more likely in Black or Hispanic children than in the other racial/ethnic groups. Frequency of use of glucocorticoid or other immunosuppression at enrollment was similar across racial and ethnic groups.

The highest rates of acute care utilization were among Black adults, and the lowest were among Asian adults (45.6 events per 100 person-years vs 29.5 for Hispanic adults, 25.8 for White adults, and 19.2 for Asian adults; *P*<.001). The rates of acute care utilization were higher overall in children. The rates of acute care utilization in Black, Hispanic, White, and Asian children were 55.8, 42.5, 40.8, and 13.0 per 100 person-years, respectively; *P*<.001. The rates of intensive care utilization were higher in Black or Hispanic children compared with White or Asian children.

In unadjusted analysis, there was an association between Black race and a higher rate of acute care utilization compared with White race (rate ratio [RR], 1.76; 95% CI, 1.37-2.25) in adults. Following multivariable adjustment, the effect was attenuated but remained statistically significant (RR, 1.31; 95% CI, 1.03-1.68). There were no statistically significant differences between Hispanic and non-Hispanic White adults in rates of acute care utilization.

There was no significant association between Black race and acute care utilization in children; there was a significant association between Asian race and lower acute care utilization (RR, 0.32; 95% CI, 0.14-0.70). There were no significant associations between Hispanic ethnicity and acute care utilization observed.

The researchers cited some limitations to the study findings, including a lack of complete data for all participants, using indirect measures of SES, including only eGFR as a time-updated variable in the final model, and the use of ED for acute care that may reflect limited clinic hours of specialty care.

In conclusion, the authors said, "In this large, multinational cohort study of adults and children with glomerular disease, Black race was associated with higher rates of acute care utilization in adults and Asian race was associated with lower rates of acute utilization in children, even after adjusting for racial and ethnic differences in SES and disease characteristics. Addressing socioeconomic barriers to accessing and adhering to treatment and determining the influence of race and ethnicity on treatment effectiveness might help to minimize health care disparities." ■

TAKEAWAY POINTS

- Researchers reported results of a prospective cohort study examining the effects of race, ethnicity, socioeconomic status, and disease severity on utilization of acute care in patients with glomerular disease.
- In adults, there was a significant association between Black race and acute care utilization, a finding that was somewhat attenuated after multivariable adjustment but remained statistically significant.
- In children, there was a significant association between Asian race and lower rates of acute care utilization.

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Testing for Coronary Heart Disease

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January 2000 through December 2014 in the US Renal Data System. Eligible patients had at least 1 year of Medicare enrollment prior to and following the transplant. The study utilized an instrumental variable (IV) analysis; the IV was the program-level CHD testing rate in the year of the transplant. Because the rate of CHD testing varied over time, analyses were stratified by study period. Exposure, IV, covariates, and outcomes were determined using a combination of US Renal Data System variables and Medicare claims.

The study exposure was receipt of nonurgent invasive or noninvasive CHD testing during the 12 months preceding kidney transplant. The primary outcome of interest was a composite of death or acute MI within 30 days after kidney transplant, adjusted for age, sex, race, education, dialysis vintage, history of CHD, diabetes, and transplant type (living vs deceased donor).

The IV cohort included 121,101 waitlist candidates. To examine outcomes, the researchers created a study cohort of 79,334 adult, first-time kidney transplant recipients with 1 year of Medicare Parts A and B coverage before and after kidney transplantation from 2000 to 2014. Of the 79,334 patients, 38% (n=30,147) were women, 21% (n=25,387) were Black, and 61% (n=48,394) were White. Mean age was 56 years during 2012 to 2014.

The proportion of low-risk, waitlisted patients who underwent elective CHD (IV cohort: eligible patients on the waitlist on January 1 of each year) was 0.13 (range, 0 to 0.44 across programs).

Patients were stratified into quintiles of the IV by era. *Era 2000-2003*: quintile [range] of program-predicted CHD testing rate: 0-6.6; 6.6-8.4; 8.4-10.0; 10.0-13.7; and 13.7-44.4. *Era 2004-2007*: 0-7.8; 7.8-10.8; 10.8-13.1; 13.1-15.2; and 15.3-31.5. *Era 2008-2011*: 0-9.2; 9.2-12.2; 12.2-15.3; 15.3-17.8; and 17.8-33.3. *Era 2012-2014*: 0-10.7; 10.7-13.9; 13.9-16.9; 16.9-21.6; and 21.6-46.7. The proportion of study patients who underwent CHD testing during the 12 months before kidney transplant increased monotonically across increasing IV quintiles.

Of the 34,688 kidney transplant recipients who underwent CHD testing in the year prior to transplant, the median time between CHD testing and transplant was 188 days. A total of 8125 patients (23%) underwent testing on or prior to joining the waitlist; 77% (n=26,563) underwent testing after joining the waitlist.

The primary outcome of death or acute MI occurred in 5.3% (n=4604) of the study cohort within 30 days of kidney transplant. During the study period, there was a decrease in the 3-day event rate from 6.6% in the 2000 to 2003 era to 4.4% in the 2012 to 2014 era.

During the 2012 to 2014 era, the CHD testing rate was 56% in patients in the fifth IV quintile (the most test-intensive quintile) and 24% in patients in the first IV quintile (the least test-intensive quintile), $P<.001$. The pattern was similar across study periods.

Results of the main IV analysis demonstrated that, compared with a reference of no testing, there was no association between CHD testing and change in the rate of the primary outcome at 30 days post-transplant (rate difference, 1.9%; 95% CI, 0%-3.5%). The effect sizes were constant across the eras, with the exception of 2000 to 2003 when a slight increase in event rate (greater than the basal rate of 6.6%) associated with CHD testing was observed (6.8%; 95% CI, 1.8%-12.3%). In sensitivity analysis that excluded covariates from the model and used the alternative definition of IV (program-level CHD testing rate in high-risk candidates), results were generally similar.

Citing limitations to the study findings, the researchers included residual confounding that may not be fully resolved by the quasiexperimental IV study design; different kidney transplant programs may have different thresholds for risk acceptance overall; the study determined CHD testing based on Medicare A claims and did not include testing submitted to private insurers or financed via the Organ Acquisition Cost Center; and the inability to identify the actual indication for CHD testing.

During the study period, there was a decrease in the 3-day event rate from 6.6% in the 2000 to 2003 era to 4.4% in the 2012 to 2014 era.

In conclusion, the authors said, "This quasiexperimental cohort study using program-level CHD testing as an IV was unable to demonstrate that pretransplant CHD testing was associated with reduced early death and MI within 30 days of kidney transplant. There is even a potential signal that CHD testing was associated with harm during the earlier study eras. Ideally, a US-based, randomized controlled trial can verify or disprove these results. However, in places where such a study is not possible, pragmatic studies in countries with less perceived regulatory pressure and a more integrated health delivery system (eg, CARSK [Canadian-Australian Randomised Trial of Screening Kidney Transplant Candidates for Coronary Artery Disease]) offer the best hope. Studies such as ours, in a US population using quasiexperimental methods, potentially help to complement these interventional studies in other countries and may pave the way to deescalating CHD testing before kidney transplantation." ■

TAKEAWAY POINTS

- Researchers reported results of a retrospective cohort study designed to examine the association between pretransplant coronary heart disease (CHD) testing and rates of death and myocardial infarction following transplant.
- The primary outcome (death or myocardial infarction within 30 days after kidney transplantation) occurred in 5.3% of the 79,334 patients in the study cohort.
- The study results suggested that testing for CHD may not be associated with reduced adverse outcomes early after kidney transplant.

Vitamin D Therapies for Secondary Hyperparathyroidism

By 2040, chronic kidney disease (CKD) is projected to be one of the top four leading causes of potential years of life lost. CKD is associated with various comorbidities and complications, including secondary hyperparathyroidism (SHPT) and vitamin D insufficiency (VDI). As patients experience decline in kidney function, there are significant alterations in the metabolism of calcium, phosphorus, and vitamin D that cause increased production and secretion of parathyroid hormone (PTH).

The combination of decreased kidney function, mineral abnormalities, and high rates of comorbidities are associated with reduced quality of life for many patients. SHPT develops as a result of abnormalities in these parameters. Low levels of serum total 25-hydroxyvitamin D (25D) and 1,25-dihydroxyvitamin D play a major role in the progression of SHPT.

Concurrent diagnoses of CKD and SHPT have been linked to increased risk of progression of kidney disease, cardiovascular disease, and mortality. Patients with CKD and SHPT have significantly higher medical costs and use of health care resources compared with patients with CKD alone. Poor vitamin D status and elevated levels of PTH commonly occur in patients with stage 3 to 5 CKD, and can emerge as early as stage 2. Early and sustained control of SHPT is necessary to bring PTH, 25D, calcium, phosphorus, and other metabolic parameters into balance.

In adults with stage 3 to 4 CKD and vitamin D insufficiency, standard treatment includes extended-release calcifediol (ERC), active vitamin D hormones and analogs (AVD), and nutritional vitamin D (NVD). Clinical trials assessing the effectiveness of these therapies for increasing serum total 25D and reducing elevated PTH have shown varying results.

TAKEAWAY POINTS

- Researchers reported results of a retrospective chart review to assess real-world experience with extended-release calcifediol (ERC) and other vitamin D therapies in the management of secondary hyperparathyroidism (SHPT).
- Patients were separated into three groups: those receiving ERC; those receiving active vitamin D hormones and analogs; and those receiving nutritional vitamin D.
- Serum total 25-hydroxyvitamin D rose in all three cohorts; the highest increase was in the ERC cohort. Parathyroid hormone declined with ERC treatment but remained unchanged in the other two cohorts.

Michael J. Germain, MD, and colleagues conducted a retrospective chart review designed to examine real-world experience of ERC and other vitamin D therapies in increasing 25D and reducing PTH. Results of the review were reported in *BMC Nephrology* [doi.org/10.1186/s12882-022-02993-3].

The review included the medical records of 376 adult patients with stage 3 to 4 CKD and a history of SHPT and VDI from 15 nephrology clinics in the United States for up to 1 year prior to and following initiation of ERC, AVD, or NVD. Key study variables were patient demographics, concomitant use of medications, and laboratory data.

Mean age of the study cohort was 69.5 years, with sex and racial distributions representative of the US CKD population. A total of 376 patients were enrolled. Enrolled patients were grouped by treatment into three cohorts: ERC (n=174), AVD (n=55), and NVD (n=147). The cohorts were similar in mean baseline levels for serum 25D (18.8-23.5 ng/mL), calcium (9.1-9.3 mg/dL), phosphorous (3.7-3.8 mg/dL), and estimated glomerular filtration rate (eGFR) (30.3-35.7 mL/min/1.73 m^2). Mean PTH at baseline was 181.4 pg/mL for the ERC cohort versus 156.9 pg/mL for the AVD cohort and 134.8 pg/mL (P<.001) for the NVD cohort. Mean follow-up during treatment ranged from 20.0 to 28.8 weeks.

Of the overall cohort of 376 patients, 46.3% (n=174) initiated treatment with ERC (99.4% at a daily dose of 30 mcg); 14.6% (n=55) initiated treatment with AVD (80% received calcitriol at 0.25 mcg/day, 11% received calcitriol at 0.50 mcg/day, 7% received doxercalciferol at 2.5 mcg/day, and 2% received paricalcitol at 1.0 mcg/day); and 39.1% (n=147) initiated treatment with NVD (weekly oral ergocalciferol [n=97] or cholecalciferol [n=50] at doses of ≥50,000 IU [64.7%], 14,000 to <50,000 IU [23.1%], or 5000 to <14,000 IU [12.2%] for ≥7 months [55.8%], 4-6 months [19%], or 103 months [25.2%]).

In the overall cohort, mean body mass index (BMI) was 32.8 kg/m^2, 50.8% were female, 88.8% were non-Hispanic, and 64.6% were White. BMI was highest in the ERC cohort. The ERC and AVD cohorts had more patients with CVD stage 4 than patients with stage 3; the reverse was true in the NVD cohort.

Most prescriptions had durations of >6 months. The mean observed prescription length of ERC was 63.5 weeks versus 51.3 weeks for AVD and 41.5 weeks for NVD. A small percentage of patients in the ERC cohort (1.7%) up-titrated dose; patients in the AVD and NVD cohorts maintained a constant dose for the duration of the study.

In the ERC cohort, treatment with ERC raised 25D by 23.7 ng/mL (P<.001) and decreased PTH by 34.1 pg/mL (P<.001). There was no significant impact on serum calcium and phosphorus. There was a downward trend in serum total alkaline phosphatase. There was a decrease in eGFR of 3.1 mL/min/1.73 m^2. Mean follow-up for those parameters ranged from 23.4 to 28.8 weeks. Normalized for the duration of the follow-up (mean 28.1 weeks), the mean decrease in eGFR per patient-week was 0.11 mL/min/1.73 m^2.

In the AVD cohort, serum 25D rose by 5.5 ng/mL with no statistically significant impact on PTH and serum phosphorous levels. There was a downward trend in serum total alkaline phosphatase. There was a decrease in eGFR of 1.6 min/mL/1.73 m^2. Normalized for duration of the follow-up (mean 21.4 weeks), the mean eGFR decrease per patent-week was 0.08 mL/min/1.73 m^2.

In the NVD cohort, serum 25D rose by 9.7 ng/mL with no significant impact on PTH or serum calcium and phosphorous levels. There was a decrease in eGFR of 1.2 mL/min/1.73 m^2. Normalized for the duration of the follow-up (mean 20.0 weeks), the mean eGFR per patient-week decrease was 0.07 mL/min/1.73 m^2.

Limitations to the study cited by the authors included insufficient duration to assess end points related to cardiovascualr disease, fractures, hospitalization rates, and mortality, as well as the possibility of selection bias.

In summary, the authors said, "Results from the current study highlight ERC's strong potential to successfully address unmet treatment needs associated with AVD and NVD in patents with SHPT, stage 3-4 CKD, and VDI. These real-world data demonstrated ERC's ability to reliably increase serum 25D and reduce elevated PTH levels without significant negative clinical impact on serum calcium and phosphorous levels. Future research into factors influencing clinical patient follow-up and dose titration practices, as well as what patient-related characteristics are influential in treatment outcomes, can further contribute toward informing optimal SHPT management and treatment practices to improve clinical effectiveness and safety." ■

Impact of Itching on Health-Related Quality of Life in Patients on Dialysis

Patients with end-stage renal disease (ESRD) commonly experience multiple comorbidities, including fatigue, muscle cramps, itching, sleep problems, and depressive symptoms. The heavy symptom burden is associated with impaired health-related quality of life (HRQoL) in that patient population.

Chronic kidney disease-associated pruritus (itching) is a common and distressing symptom, and is experienced by both patients on hemodialysis and those on peritoneal dialysis; the prevalence is ~50% among patients with ESRD. Previous studies have demonstrated that itching is one of the 10 most burdensome symptoms associated with dialysis, and it is considered a research priority by patients, caregivers, and health care professionals.

The pathogenesis of itching in dialysis patients is not fully understood, but studies suggest that abnormal calcium, phosphate, and parathyroid hormone levels may influence the occurrence or burden of itching. In addition, opioid imbalance, peripheral neuropathy, dialysis efficiency, and dry skin may also be contributing factors. Itching is associated with adverse clinical outcomes such as hospitalization and mortality, as well as with poor patient-reported outcomes that include decreased HRQoL, depressive symptoms, and sleep problems.

According to **Esmee M. Van Der Willik, PhD,** and colleagues, there are few data available on the impact of itching on the course of HRQoL over time and the extent to which the combination of pruritus-associated symptoms affect patients' physical and mental HRQoL. The researchers conducted a study to examine the impact of itching in dialysis patients by examining the persistence of itching, the effect of itching on the course of HRQoL, and the combined effect of itching with sleep problems and with psychological symptoms on HRQoL. Results were reported in *Nephrology Dialysis Transplantation* [doi.org/10.1093/ndt/gfC022].

The study utilized data from RENINE, the nationwide Dutch renal registry of patients receiving renal replacement therapy. The registry collects data on demographics and clinical characteristics as well as patient-reported outcome measures (PROMs). PROMs include the 12-item Short Form Health Survey to assess HRQoL and the Dialysis Symptom Index to assess symptom burden. Data from 2018 to 2020 were included in the current analysis.

The primary analyses were conducted both cross-sectionally and longitudinally to ensure that all patients and all PROMs measurements would be included. Cross-sectional analysis was conducted at baseline and included all patients in the study population. The longitudinal analysis included all PROMs measurements (n=5042), with 40.9% of the total cohort having multiple measurements.

A total of 2978 patients completed PROMs at least once during the study period. Of those, approximately half experienced itching at baseline (the time of the patient's first PROM measurement). Itching was more common among patients receiving peritoneal dialysis (59.4%) compared with those receiving hemodialysis (48.7%).

> Of the patients who experienced itching at baseline, itching persisted over time in nearly 70%.

Compared with patients without itching, those with itching were more often male, had a higher socioeconomic status, and more often had diabetes as the primary kidney disease. There were no differences between the two groups in calcium, phosphate, and parathyroid hormone levels. Patients without itching reported lower total symptom burden compared with those with itching (average 8 symptoms with a median total burden score of 19 vs average 14 symptoms with a median total burden score of 35, respectively). Patients with itching more often had dry skin compared with those without itching (73% vs 43%, respectively). Sleep problems were experienced by 70% of patients with itching compared with 52% of patients without itching. Psychological symptoms occurred in 36% of patients with itching compared with 19% of patients without itching.

Multiple PROMs were available for 1218 patients, with an average 6.7 months between baseline and the second measurement. During the total study period, the prevalence of itching was 50% with a moderate burden. There were no clear differences in prevalence or burden of itching between the yearly quartiles (ie, no seasonal effects). Of the patients who experienced itching at baseline, itching persisted over time in nearly 70%. Among the patients who did not experience itching at baseline, 30% to 40% developed itching during follow-up. The majority of patients also experienced persistent sleep problems and psychological symptoms over time.

Mean physical and mental HRQoL scores in the total dialysis population were 35.8 and 48.1, respectively. Patients with itching experienced a lower physical (–3.35; 95% CI, –4.12 to –2.59; $P<.001$) and mental HRQoL (–3.79; 95% CI, –4.56 to –3.03; $P<.001$) compared with those without itching. There were additional negative effects on HRQoL with sleep problems and psychological symptoms. There was no interaction between itching and sleep problems or psychological symptoms in the association with HRQoL.

HRQoL remained stable during the 2-year study period and there were no differences in trajectories between patients with itching and those without itching. A post hoc subgroup analysis showed an increase in physical and mental HRQoL when itching disappeared (+0.56 [$P=.49$] and +1.78 [$P=.02$], respectively), and a decrease when itching newly occurred (–0.44 [$P=.61$] and –0.68 [$P=.38$], respectively) between the first and second PROMs measurements.

The researchers cited some limitations to the study findings, including only dialysis patients, the lack of available data on treatments that may have induced or reduced itching, and the lack of information regarding factors that may influence itching.

In conclusion, the authors said, "The high prevalence and persistence of itching, its impact on HRQoL over time, and the additional effect on HRQoL of the often co-occurring sleep problems and psychological symptoms emphasize the need for recognition and effective treatment of itching to reduce symptom burden and improve HRQoL in dialysis patients. No individual prognosis can be derived from our study, but the findings may be used in shared decision-making. We hope that this study provided insights into and awareness of the major impact that itching can have, to enable early recognition and treatment of itching." ■

TAKEAWAY POINTS

- Researchers reported results of a study in the Netherlands designed to examine the impact of itching on health-related quality of life (HRQoL) among patients on dialysis.
- Persistent itching was reported in approximately half of the study cohort and was more common in those receiving peritoneal dialysis than those receiving hemodialysis.
- Patients with itching had a lower physical and mental HRQoL, which remained stable during 2 years of follow-up.

Nutritional Status at Dialysis Initiation and Long-term Mortality Risk

There is an association between nutritional status and survival among patients on dialysis. However, according to **Sara Blumberg Benyamini, PhD,** and colleagues, available data focus on patients who have undergone hemodialysis treatment for a minimum of 8 weeks. There are only limited data on the association between clinical outcome and baseline nutritional status at initiation of dialysis and any changes following dialysis initiation.

The researchers conducted a retrospective observational study to examine how baseline nutritional status at the time of dialysis initiation, and the improvement or worsening of nutritional status during the first 3 months of dialysis treatments, affect survival for up to 5 years following the start of renal replacement therapy. Results were reported in the *Journal of Renal Nutrition* [2022;32(6):758-765].

During the study period of March 1, 2009, to March 1, 2019, 299 patients initiated hemodialysis at the Nephrology and Hypertension Department at the E. Wolfson Medical Center, Holon, Israel. Of those, 287 patients had data on initial nutritional score and first 3 months of nutritional score available.

Nutritional status was determined using the Integrative Clinical Nutrition Dialysis Score (ICNDS) that is based on biochemical assessment of albumin, creatinine, urea, cholesterol, dialysis adequacy, C-reactive protein (CRP), and post-dialysis weight change. Improvement or worsening in nutrition status was monitored by calculating the ICNDS slope for each patient enrolled in the study from three ICNDS values for the first 3 months in dialysis. The baseline ICNDS and the slope of three subsequent monthly ICNDS values were tested for correlation with the odds of all-cause mortality for each of the first 5 years on dialysis.

Of the overall cohort, median age was 67.6 years and 35.9% were female. A total of 203 of the 287 eligible patients had a baseline ICNDS of ≥75.

Of those with an initial ICNDS <75, diabetes mellitus, cardiovascualr disease, and history of malignancy were significantly more prevalent than among those with an initial ICNDS ≥75 (diabetes mellitus: 55.6% in patients with initial ICNDS ≥75 and 70.7% in those with initial ICNDS <75; *P*=.022; cardiovascular disease, 55.1% and 68.3%; *P*=.046; history of malignancy, 19% and 30.5%, respectively; *P*=.021). Those in the group with initial ICNDS <75 were significantly older than those with ICNDS ≥75 (70.6 years vs 66.5 years; *P*=.025). The two groups were similar in sex and history of stroke.

Among the patients with initial ICNDS ≥75, the results for albumin, creatinine, urea, and cholesterol were significantly higher than among those with initial ICNDS <75. The level of CRP was significantly higher in the group with initial score <75. The groups were similar in delivered dose of dialysis or percent weight change.

TAKEAWAY POINTS

- Researchers reported results of a study examining the association between nutritional status at initiation of dialysis and change in nutritional status over the first 3 months and survival after 5 years on dialysis.
- There was an association between nutritional status at the start of dialysis and long-term 5-year survival; a decline in nutritional status over the first 3 months significantly increased the risk of death during the first 3 years on dialysis.
- There was a significant difference in the mortality hazard ratio of patients who started dialysis with an Integrative Clinical Nutrition Dialysis Score (ICNDS) ≥75 and those who started with an ICNDS <75.

> There was an association between a negative slope for the monthly ICNDS values over the first 3 months of dialysis and increased mortality during the 1 to 3 years following dialysis initiation.

The study examined the association between ICNDS and mortality using the baseline ICNDS and the mortality hazard ratio (HR) for each of the first 5 years on dialysis. There was a significant association between an ICNDS value <75 at initiation of dialysis and increased mortality hazard compared with an ICNDS ≥75 (HR, 2.505; 95% CI, 1.235-5.079; *P*=.011 after 1 year; HR, 1.798; 95% CI, 1.053-3.069; *P*=.005 after 2 years; HR, 1.838; 95% CI, 1.200-2.813; *P*=.005 after 3 years; HR, 1.489; 95% CI, 1.027-2.159; *P*=.036 after 4 years; and HR, 1.543; 95% CI, 1.083-2.198; *P*=.016 after 5 years of dialysis).

There was an association between a negative slope for the monthly ICNDS values over the first 3 months of dialysis and increased mortality during the 1 to 3 years following dialysis initiation: HR, 2.792; 95% CI, 1.372-5.681; P=.005 after 1 year; HR, 2.194; 95% CI, 1.311-3.672; P=.003 after 2 years; and HR, 1.732; 95% CI, 1.151-2.607; P=.008 after 3 years. There was no association between a negative slope for the first 3 months and increased mortality after 4 or 5 years of dialysis.

There was a significant effect of age at baseline on survival from the second to the fifth year on dialysis: HR, 1.039; 95% CI, 1.014-1.065; P=.002 after 2 years; HR, 1.029; 95% CI, 1.010-1.049; P=.003 after 3 years; HR, 1.041; 95% CI, 1.023-1.059; P=.001 after 4 years; and HR, 1.041; 95% CI, 1.024-1.058; P=.001 after 5 years.

After the second year of dialysis, diabetes had a significant worsening effect on survival: HR, 1.716; 95% CI, 0.996-2.958; P=.052 after 2 years; HR, 1.660; 95% CI, 1.074-2.568; P=.023 after 3 years; HR, 1.901; 95% CI, 1.309-2.759 after 4 years; and HR, 1.925; 95% CI, 1.350-2.745: *P*=.001 after 5 years.

A history of stroke had a worsening effect on survival after 3 years on dialysis, and cardiovascular disease had a worsening effect on survival after 4 and 5 years on dialysis.

The researchers cited some limitations to the study findings, including the relatively small sample size and the single-center design, the observational approach, and the inclusion of patients who initiated dialysis following treatment for end-stage renal disease as well as those who started dialysis as an emergency treatment.

In summary, the authors said, "The results of our study confirm that the nutritional status at commencement of hemodialysis and the change in nutritional status over the first 3 months on dialysis are major prognostic long-term survival factors. Further research is needed to explore the possible survival implications of transition between nutritional scores and slopes while on dialysis." ■

Using Spot Urine Samples to Estimate 24-Hour Urinary Excretion

Kidney stone disease has an estimated prevalence of 8%-9%, and is associated with substantial rates of recurrence. While not completely understood, both genetic and environmental factors are known to be associated with the formation of kidney stones. Major international guidelines on the diagnostic workup and clinical management of patients with kidney stones emphasize the use of metabolic evaluation, including 24-hour urine collection to determine parameters that include volume, pH, calcium, oxalate, citrate, uric acid, potassium, and magnesium.

However, according to **Pietro Manuel Ferraro, MD, MSc, PhD,** and colleagues, there are conflicting data regarding actual implementation of 24-hour urine collections. In addition to imprecision and incompleteness, collecting urine throughout the day is perceived as being impractical and difficult to perform in clinical practice.

The researchers conducted an analysis to assess the performance of spot urine measurement to estimate 24-hour excretion in patients with kidney stones. Results of the analysis were reported in *Nephrology Dialysis Transplantation* [2022;37(11):2171-2179].

The study recruited 74 adult patients ≥18 years of age with urinary stone disease from two centers (BioHealth Italia, Torino, Italy [n=54], and Tufts University School of Medicine, Maine Medical Center, Portland, Maine [n=20]) from October 2013 to September 2014. At both centers, patients were instructed to perform a complete 24-hour urine collection, starting from the second micturition of a given day, and including the first of the subsequent day. A sample of the latter, collected in the fasting state, was taken for spot urine analysis.

In the Tufts study population, patients were also asked to collect two additional spot urine samples, one before dinner and the other after dinner. Demographic and clinical data (age, sex, weight, and height) were collected for all patients. All study participants were White.

Urinary concentrations of creatinine, calcium, oxalate, uric acid, citrate, and magnesium were measured on both 24-hour and spot samples. Daily urinary excretions were computed by multiplying the urinary concentration of each analyte by the urine volume over 24 hours. Urine samples from the Tufts cohort were analyzed by Litholink; samples from the Torino cohort were analyzed at the laboratory of Mauriziano Hospital (Torino, Italy).

The study utilized four approaches to estimate 24-hour urinary excretion, multiplying the ratio of the spot urinary analyte to creatinine concentration by (1) measured 24-hour urinary creatinine excretion (Prediction 1); (2) estimated 24-hour urinary creatinine excretion (Prediction 2); (3) assumed 1-g 24-hour urinary creatinine excretion (Prediction 3); or (4) assumed 1.5-g 24-hour urinary creatinine excretion (Prediction 4). For each parameter, the researchers computed Lin's concordance correlation coefficients (CCCs), Bland-Altman plots, and 95% limits of agreement.

The two cohorts were similar, with the exception of a larger proportion of females and higher body weight and body mass index in the cohort at Tufts. Urine chemistries were comparable across samples, with the exception of higher urinary creatinine in the Tufts sample.

Estimated urinary creatinine excretion exhibited a Lin's CCC of 0.62 (95% CI, 0.49-0.75), bias –132 mg (95% CI, –828 to 564 mg), and P30 79.7%. Conversely, assuming a daily excretion of 1-g was imprecise: the median difference between measured and assumed urinary excretion was 511 mg, with 49 patients (65.3%) showing values of measured creatinine excretion below (1 patient [1.4%]) or above (48 patients [64.9%]) the 30% assumed creatinine excretion.

Overall, the performance of estimates obtained with Prediction 1 and Prediction 2 was similar for all parameters, with the exception of citrate and uric acid. For those two parameters, Prediction 2 performed significantly worse. In general, both estimation approaches performed adequately well in predicting 24-hour urinary excretion.

The approaches performed particularly well for citrate (CCC 0.82 [95% CI, 0.75-0.90] for Prediction 1 and CCC 0.67 [95% CI, 0.54-0.79] for Prediction 2). Performances on other parameters were considered to be adequate: oxalate (CCC 0.66 [95% CI, 0.55-0.78] for Prediction 1 and CCC 0.63 [95% CI, 0.52-0.74] for Prediction 2); magnesium (CCC 0.66 [95% CI, 0.54-0.77] for Prediction 1 and CCC 0.66 [95% CI, 0.52-0.78] for Prediction 2); and calcium (CCC 0.63 [95% CI, 0.50-0.75] for Prediction 1 and CCC 0.63 [95% CI, 0.49-0.77] for Prediction 2).

The approaches did not perform well for uric acid (CCC 0.52 [95% CI, 0 .36-0.68] for Prediction 1 and CCC 0.30 [95% CI, 0.10-0.49] for Prediction 2).

Compared with the other approaches, the performance of Prediction 3 was consistently worse. Performances for Prediction 4 were similar to those of Predictions 1 and 2 for some parameters and worse for others.

Overall, the performance of estimates obtained with Prediction 1 and Prediction 2 was similar for all parameters, with the exception of citrate and uric acid.

Results of analysis of performance of spot urine samples taken at different times in the Tufts cohort suggested no major differences with the exception of postprandial oxalate and citrate, which performed worse. In general, postprandial samples tented to perform numerically worse compared with fasting morning and preprandial samples with the exception of uric acid. There were no noticeable differences in performance when using various combinations or averages of the three spot samples.

The authors cited some limitations to the study, including the relatively small sample size, the study population including only White patients, and the lack of repeated measurements for the same participant over time.

In conclusion, the researchers said, "Spot urine samples combined with specific indexing techniques may be useful in population-based studies or urinary stone disease. Our data do not suggest at present that spot urine samples can replace 24-hour collections for direct patient care. Future studies in this area will need to employ measured or estimated 24-hour urinary creatinine rather than assuming a given creatinine excretion." ■

TAKEAWAY POINTS

- Researchers reported results of a study designed to assess the performance of spot urine measurement to estimate 24-hour excretion in patients with kidney stone disease.
- The study compared four approaches to predicting 24-hour urine excretion based on spot urines.
- While the study data do not support using spot urine in the management of kidney stone disease, spot urine samples may be useful for clinical and population-based research.

Transplant Referral and Waitlisting After 2014 Allocation Policy Change

Currently in the United States there are more than 500,000 patients with kidney failure on dialysis. The preferred treatment for kidney failure is kidney transplantation. Compared with dialysis, transplantation is associated with longer survival, better quality of life, and fewer hospitalizations. There are national policy directives for dialysis facilities designed to maximize access to transplantation and incentivize waitlisting. However, according to **Rachel E. Patzer, PhD, MPH,** and colleagues, only approximately 18.5% of patients with kidney failure are on the transplant waitlist.

In December 2014, the United Network for Organ Sharing (UNOS) Organ Procurement and Transplantation Network (OPTN) implemented a policy that has had substantial impact on the way kidneys are allocated. Improvement in transplantation access equity was a major goal of the new kidney allocation system (KAS). The primary determinant of priority for organ allocation is allocation time. The new system changed the start of the allocation time from the date of waitlisting to the date of dialysis initiation (with the exception for pre-emptively waitlisted patients).

Since the implementation of KAS, waitlisting has declined. Dr. Patzer et al conducted a cohort study designed to examine the impact of the 2014 KAS policy change on referral and evaluation for transplantation in a population of both incident and prevalent patients. Results were reported in the *American Journal of Kidney Diseases* [2022;80(6):707-717].

The researchers utilized data from a unique dataset encompassing Georgia (GA), North Carolina (NC), and South Carolina (SC). All new patients who initiated maintenance dialysis between January 1, 2012, and December 31, 2016, in GA, NC, or SC dialysis facilities were included. Follow-up continued through December 2017.

Exclusion criteria were preemptive transplantation (n=4167), <18 or >80 years of age (n=3553), or preemptively waitlisted (n=1672). The final study cohort included 37,676 patients following exclusion of those referred prior to kidney failure.

The study compared demographic, clinical, and socioeconomic characteristics between incident patients before and after KAS. Overall, the two groups were similar.

During the study period, 43.4% of patients were referred to transplantation. Of those, 52.4% started the evaluation process and 35.2% were waitlisted. There were minimal differences in sociodemographic and clinical characteristics in the proportions of patients who had each outcome prior to versus following KAS. For example, among referred patients, a slightly higher proportion were >70 years of age in the post-KAS period versus the pre-KAS period (11.46% vs 10.25%), had a BMI of >35 kg/m^2 (27.04% vs 25.74%), and had comorbidities (eg, congestive heart failure, 23.00% vs 21.08%). After KAS, waitlisting declined or remained the same in these subgroups.

Pre-KAS, Black patients represented 55.87% of all kidney failure patients (vs 52.2% post-KAS). Compared with White patients, Black patients represented a larger proportion of those referred; differences before and after KAS were minimal (62.44% vs 61.99%, respectively). Among patients following completion of the evaluation process, Black patients represented 56.85% of waitlisted patients before KAS but 62.71% after KAS.

Following implementation of KAS, inactive listings of patients who had started evaluation (and had available active/inactive waitlist status data) declined (38.1% pre-KAS vs 26.4% post-KAS). In adjusted analyses, among incident patients there was a positive association between KAS implementation and referral (adjusted hazard ratio [aHR], 1.16; 95% CI, 1.12-1.20) and evaluation (aHR, 1.16; 95% CI, 1.10-1.21). There was a negative association between KAS implementation and overall waitlisting (aHR, 0.70; 95% CI, 0.65-0.76). Evaluated patients had lower active waitlisting (aHR, 0.81; 95% CI, 0.74-0.90) after versus before KAS.

In the prevalent population, there was an association between KAS implementation and a nonsignificant increase in referral (aHR, 1.18; 95% CI, 0.86-1.61), no impact on evaluation start (aHR, 0.99; 95% CI, 0.75-1.30), higher waitlisting (aHR, 1.74; 95% CI, 1.15-2.63), and higher active waitlisting (aHR, 2.01; 95% CI, 1.16-3.49).

The mean increase in referral after KAS among 790 dialysis facilities was 6.93% (median, 2.12%). A total of 422 facilities (53.4%) increased their referrals after KAS (median increase, 14.16%), and 314 facilities (39.7%) decreased their referrals after KAS (median, –10.10%). Fifty-four facilities (6.8%) did not have a change in referrals. From prior to and following AKS implementation, the median time from referral to waitlisting increased (4.6 months vs 6.0 months, respectively; $P<.001$). In addition, the proportion of patients who were preemptively waitlisted represented 9.87% of the waitlisted population (21.1% were actively waitlisted) prior to KAS and increased to 18.8% (43.2% actively waitlisted) after KAS ($P<.001$).

The researchers cited some limitations to the study, including the observational design, and the possibility that the results are not generalizable outside the southeast United States where obesity, diabetes, and hypertension are more prevalent and transplant rates are among the lowest in the country.

In conclusion, the authors said, "Overall, the effect of KAS implementation differed by transplant step and by incident versus prevalent dialysis patients; and overall declines in waitlisting observed in the post-KAS era are largely due to decreased transplant center waitlisting of referred patients. These findings suggest that the change in KAS policy likely influenced provider behavior both at dialysis facilities (with respect to transplant referrals) as well as transplant programs (eg, evaluations and waitlisting practices). This study offers context for why overall waitlisting rates have declined nationally since the implementation of the 2014 KAS change and underscores the need to collect surveillance data on these important prewaitlisting process measures nationally, particularly as new changes in kidney allocation and new quality measures in dialysis facilities and transplant programs are under development." ■

TAKEAWAY POINTS

- Researchers reported results of a cohort study designed to examine the impact of the 2014 kidney allocation system (KAS) policy change on referral and evaluation for transplantation.
- Among incident dialysis patients, there was an association between KAS and increased referrals and evaluation starts among those referred.
- In the prevalent dialysis cohort, KAS was associated with increases in overall waitlisting and active waitlisting among those evaluated for transplant.

TCMR After Kidney Transplantation and HLA T-Cell Epitope Targets

In kidney transplantation, the mismatch in the human leukocyte antigen (HLA) system between the donor and recipient transplant pair has a central role in both Banff-defined rejection phenotypes, T-cell-mediated rejection (TCMR) and antibody-mediated rejection (ABMR), primarily related to the presence of donor-specific antibodies to HLA (HLA-DSA). According to **Aleksander Senev, MD, PhD,** and colleagues, the relationship between HLA molecular mismatches and TCMR is unknown.

The researchers conducted a retrospective cohort study to examine the associations between the different donor HLA-derived T-cell epitope targets and the occurrence of TCMR as well as borderline histologic changes suggestive of TCMR following kidney transplantation and graft failure after kidney transplantation. Results of the study were reported in the *American Journal of Kidney Diseases* [2022;80(6):718-729].

The PIRCHE-II (Predicted Indirectly Recognizable HLA Epitopes by Recipient HLA Class II Molecules) algorithm evaluates and quantifies the T-cell epitope targets, linear peptides of the mismatched donor HLA molecules. The study exposure was scores calculated by the HLA matching algorithm PIRCHE-II and HLA eplet mismatches. The outcomes of interest were TCMR, borderline changes suggestive of TCMR, and allograft failure. The association between HLA epitope targets and study outcomes was calculated using multivariable cause-specific hazards models.

All models were adjusted for donor and recipient age, cold ischemia time, repeat transplantation, donor type (brain death, circulatory death, living), panel-reactive antibody (%), and induction therapy (no induction vs basiliximab vs other treatment). Sensitivity analyses in the HLA-DSA-negative patients were performed in the subpopulation of patients without pretransplant HAL-DSA.

Eligible patients underwent single kidney transplantation at the Leuven University Hospital, Leuven, Belgium, between March 1, 2004, and February 6, 2013. The transplantations were performed with compatible T- and B-cell complement-dependent cytotoxicity tests and compatible ABO blood groups. Clinical data were extracted using electronic files. The large majority of patients were prescribed tacrolimus, mycophenolic acid, and corticosteroids as a basic immunosuppressive regimen. No desensitization therapies for HLA antibodies were used.

Among the 893 patients who met inclusion criteria, retransplant HLA antibodies were present in 233 patients and 40.8% (n=95) had pretransplant HLA-DSA, which were mainly directed against HLA class II molecules. Forty-three patients developed de novo HLA-DSA, and they were also mainly against the donor HLA Class II molecules (33/43; 79%).

Median follow-up was 8 years. For 85.3% of the cohort, standard maintenance immunosuppression consisted of tacrolimus, mycophenolic acid, and corticosteroids. Of the total cohort, 41.3% (n=369) received induction therapy, primarily basiliximab (317/369; 85.9%).

Median total, HLA class I, and HLA class II PIRCHE-II scores were 310, 140, and 177, respectively. Of all the HLA molecules, HLA-DQA1/B1 had the highest median PIRCHE-II score at 75.

Following the baseline biopsy, histologic follow-up included 3515 posttransplant biopsies (2611 protocol and 904 indication biopsies). A total of 277 patients developed TCMR (not including borderline TCMR) in at least one posttransplant biopsy. According to the Banff classification, 43.0% (n=119) had grade I acute TCMR, 55.2% (n=153) had grade II acute TCMR, and 1.8% (n=5) had grade III acute TCMR.

Following adjustment for donor and recipient age, donor type, cold ischemia time, repeat transplantation, panel-reactive antibody, and induction therapy, results of multivariable cause-specific hazards analyses demosntrated there was an association between each 10-point greater total of PIRCHE-II score and an increased risk of developing TCMR (hazard ratio [HR], 1.01; 95% CI, 1.00-1.02; *P*=.009). Analyses on each HLA molecule separately demonstrated that the association was primarily related to the PIRCHE-II score for HLA class II molecules (HR, 1.01; 95% CI, 1.01-1.02; *P*=.002). There was no trend for association between the PIRCHE-II score for HLA class I and the occurrence of TCMR.

Beyond the 277 patients with Banff-grade TCMR, 134 others showed only borderline changes suggestive of TCMR in at least one posttransplant biopsy during histologic follow-up. The findings in this subgroup were similar to those in the group with acute TCMR: the adjusted cause-specific hazards model showed the PIRCHE-II score for HLA-DRB1 (HR, 1.07; 95% CI, 1.04-1.10; *P*<.001) and HLA-DQAI1/B1 (HR, 1.02; 95% CI, 1.01-1.03; *P*=.002) independently contributed to the combined outcome of acute TCMR and borderline TCMR. There was no association between the PRICHE-II score for class I molecules and the combined acute TCMR/borderline TCMR outcome.

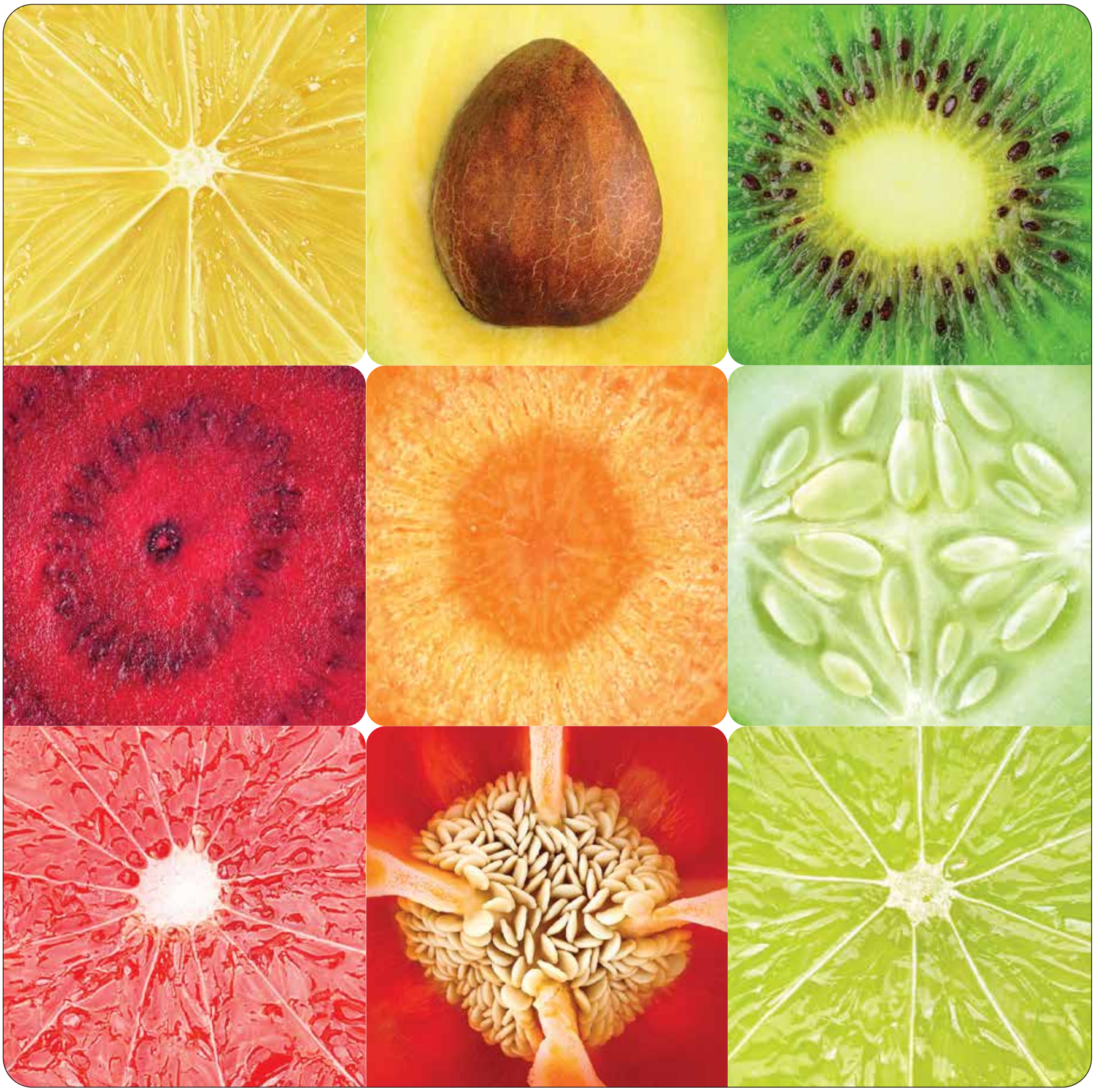
If restricted to rejection episodes during the first 3 months following transplantation, there was an association with early acute TCMR and only the T-cell epitope targets originating from the donor's HLA-DRB1 and HLA-DQB1; there was no association between class I molecules and early acute TCMR. Further, there was a statistical difference between the median PIRCHE-II score for HLA class II in patients with TCMR compared with those without TCMR (129 vs 201, respectively; *P*<.001). Those differences were not seen for class I PRICHE-II scores.

The researchers cited some limitations to the study findings, including the single-center design, the predominately White European population with general and continued access to immunosuppression, the lack of detailed data on histological findings other than acute TCMR, borderline TCMR or the type of treatment used to treat TCMR, and the possibility that the stringency used in the PIRCHE-II score is too low.

In conclusion, the authors said, "This study suggests that PIRCHE-II scores for HLA-DRB1 and DQB1 molecules are consistently independent predictors for the development of acute TCMR and kidney graft failure. This study provides clinical evidence of the importance of the HLA class II molecular mismatches on the development of cellular alloimmunity in the absence of overt humoral alloreactivity. Our clinical findings suggest that in the presence of standard immunosuppression, donor HLA class-II-directed immune responses play a crucial role in T-cell alloimmune activation from very early after kidney transplantation. Further validation of these findings and refinement of the exact allorecognition in early rejection episodes is warranted, taking into consideration the different immunogenicity of DRB1 and DQB1 molecular mismatches. These insights will help in better predicting the occurrence of TCMR after kidney transplantation and could be used for improved risk stratification." ■

TAKEAWAY POINTS

- Researchers reported results of a retrospective cohort study to examine the associations between the different donor HLA-derived T-cell targets and the occurrence of T-cell-mediated rejection (TCMR).
- In a cohort of 893 patients, 277 developed TCMR, and 134 developed only borderline changes suggestive of TCMR.
- HLA class II mismatches were associated with early episodes of acute TCMR and allograft failure. There was no association with class I mismatches.



Fruit and Vegetable Intake Among Patients With CKD

Chronic kidney disease (CKD) affects approximately 13% of the population of the United States. Many patients adhere to preventive dietary patterns; however, according to **Shirin Pourafshar, PhD, MSCR, RDN,** and colleagues, empiric evidence to guide use of such measures is limited. Current dietary guidelines for patients with CKD focus on recommended nutrient intakes (sodium, potassium, and phosphorous) rather than on whole foods such as fruits and vegetables.

Patients with CKD at risk for hyperkalemia limit intake of fruits and vegetables to avoid excess dietary potassium intake. Patients with mild-to-moderate CKD do not face a high risk of hyperkalemia, and restriction of dietary potassium may lower consumption of healthy foods such as fruits and vegetables. The 2000 update to the Clinical Practice Guideline for Nutrition in CKD from the National Kidney Foundation and the Academy of Nutrition and Dietetics includes the need for further evidence on food patterns and intake of fruits and vegetables in patients with CKD.

Dr. Pourafshar et al conducted a study to examine the relationship between CKD and intake of fruits and vegetables in US adults with and without CKD. Results were reported in the *Journal of Renal Nutrition* [2023;33(1):88-96].

The researchers characterized patterns of fruit and vegetable intake in participants in the National Health and Nutrition Examination Survey (NHANES) to assess similarities or differences between those with and those without CKD. The primary outcome of interest was patterns of fruit and vegetable intake based on participant self-reported dietary intake.

The study included three cohorts: NHANES III (1988-1994); Continuous NHANES cycle 2003-2010; and Continuous NHANES cycle 2011-20218. Patterns of fruit and vegetable intake were assessed using latent class analysis; weighted multinational logistic regression was used to compare intake patterns across the three temporal cohorts. Data from adults 18 years of age or older with complete, valid dietary recall data in each of the three NHANES cycles were analyzed.

The primary diet assessment method in NHANES was 24-hour dietary recall interview. In NHANES III one recall per participant was conducted; two recalls were performed in Continuous NHANES. Following general principles in the NOVA food classification system, foods were categorized into (1) unprocessed, (2) minimally processed, (3) and ultra-processed fruits and vegetables. Each fruit and vegetable was also classified by phytochemical content, resulting in four groupings: glucosinolate-rich; carotenoid-rich; polyphenol-rich; and starchy vegetable.

The percentage of the population with CKD across the years ranged from 13.6% (NHANES III) to 15.2% (Continuous NHANES 2011-2018). When CKD was defined by estimated glomerular filtration rate <60 mL/min/1.73 m^2 only (stage G3a or higher), 6.5% in NHANES III, 6.6% in Continuous NHANES 2003-2010, and 6.9% in Continuous NHANES 2011-2018 would have CKD, indicating a large proportion with albuminuria only, particularly in later cohorts.

Among the CKD population, average age was 58.5 years compared with 41.0 years among non-CKD participants in NHANES III; 60.3 years and 43.4 years in Continuous NHANES 2003-2010; and 60.0 years and 44.6 years in Continuous NHANES 2011-2018. In all three cohorts, participants with CKD were likely to be older, female, and Black, and to have higher body mass index, hypertension, and diabetes compared with participants without CKD.

In all three cohorts, total energy intake was significantly higher among participants without CKD compared with those with CKD. In NHANES III and Continuous NHANES 2003-2010, the percentage of calories from protein (P<.001 and P=.007, respectively) and carbohydrate (P=.005 and P<.001, respectively) was significantly higher in those with CKD. Unadjusted macronutrient densities of fiber, phosphorus, sodium, and potassium, but not dietary carotenoids, were higher in those with CKD in most cycles.

Within the three datasets, the researchers identified one pattern of overall low consumption of fruits and vegetables (overall low intake), one pattern with higher intake of unprocessed fruits and vegetables in all phytonutrient categories (high unprocessed), one pattern with high intake of ultra-processed fruits and vegetables (high ultra-processed), and one pattern with generally moderate intake of processed fruits and vegetables in all phytonutrient categories (moderate processed). There were subtle differences noted between NHANES III and Continuous NHANES cycles in those patterns with unprocessed fruits and vegetables and ultra-processed fruits and vegetables, with unprocessed fruits and vegetables and ultra-processed fruits and vegetables more common in some patterns.

> The overall association of CKD with fruit and vegetable intake patterns was significant in NHANES III (P=.05) and Continuous NHANES 2003-2010 (P=.005).

In all cohorts and among participants with CKD, the most prevalent pattern was the overall low intake pattern. In adjusted analyses, the pattern was less common in those with CKD. Following adjustment for demographic and selected clinical variables (age, sex, race, waist circumference, diabetes, and hypertension), those with CKD were more likely to be classified as overall low intake in each cohort compared with those without CKD.

The overall association of CKD with fruit and vegetable patterns was significant in NHANES III (P=.05) and Continuous NHANES 2003-2010 (P=.005). The difference was not significant in Continuous NHANES 2011-2018 (P=.4).

The authors cited some limitations to the study findings, including the relatively modest classification diagnostics observed; the use of expert consensus and available literature to decide which fruits and vegetables are rich in carotenoids, polyphenols, or glucosinolates; and the inability to classify fruits and vegetables that may have been consumed in mixed dishes that could lead to some misclassification.

In conclusion, the researchers said, "To our knowledge, this study is novel in its interest in patterns of fruit and vegetable intake in the US population and in patients with CKD, with a focus on their phytochemical content and processing. Most of the current research on dietary intake in CKD has focused on single nutrients (eg, sodium, potassium, phosphorus, and protein) or simple foods. Dietary pattern is a complex phenotype. It is important to consider the interaction of nutrients in foods rather than isolating nutrients or restricting them in the diet. Understanding patterns of fruit and vegetable intake among CKD patients may provide a perspective different than traditional restrictive dietary guidelines." ■

TAKEAWAY POINTS

- Researchers reported results of a study designed to characterize patterns of fruit and vegetable intake in a cohort of US adults with and without chronic kidney disease (CKD).
- Four similar patterns were identified: overall low intake, high unprocessed, high ultra-processed, and moderate processed fruits and vegetables.
- In adjusted analyses, patients with CKD compared with those without CKD were more likely to be classified as overall low intake in each cohort.

Providence Health Plan and Interwell Health Partnership Announced

In a press release, Providence Health Plan and Interwell Health announced a value-based care initiative designed to provide earlier identification, education, and support to plan members with late-stage chronic kidney disease and end-stage kidney disease. Members across the spectrum of insurance options offered by Providence Health Plan, including commercial and Medicare Advantage, are eligible for the program.

Robert Gluckman, MD, chief medical officer for Providence Health Plan, said, "Providence Health Plan has long been out front driving the shift to new models of care that include a more integrated approach with providers in Oregon. We are excited to partner with Interwell Health and leverage their comprehensive model to slow progression of chronic kidney disease, provide more access to transplant and home dialysis, and avoid unnecessary hospitalizations."

The partnership aims to improve coordination of care of members through Interwell Health's network of local nephrologists committed to driving results in the new value-based care model. Interwell Health works to enable members to undergo preemptive kidney transplant or planned transition to dialysis when required, with an emphasis on home therapies. Earlier identification of kidney disease and subsequent interventions will help reduce the number of patients needing urgent inpatient dialysis.

George Hart, MD, chief medical officer at Interwell Health, said, "We know that earlier education and support in tight alignment with physician practices can have a big impact on patient outcomes. We look forward to working closely with Providence Health Plan to help identify patients earlier in their disease progression and provide the support these patients need to live their best lives."

WellSky and Dialyze Direct Announce Collaboration in SNFs

WellSky, a health and community care technology company, has announced a partnership with Dialyze Direct, a provider of home hemodialysis services in skilled nursing facilities (SNFs). According to a press release from WellSky, hospitals and health systems using WellSky's CarePort Care Management or CarePort Discharge care transition solutions will be able to coordinate with Dialyze Direct for the appropriate next level of care for patients requiring on-site dialysis treatment.

The new partnership will close gaps in patient care and simplify the discharge process, resulting in improved patient outcomes. Complications in patients with chronic kidney disease and end-stage kidney disease are a key reason for hospital read-

missions from SNFs, leading to higher costs of care and longer recoveries.

Robert Aberman, senior vice president of Dialyze Direct, said, "In a significant enhancement of the current dialysis discharge process, Dialyze Direct's collaboration with WellSky and its suite of CarePort solutions will now allow discharge planners to identify Dialyze Direct's SNFs with on-site dialysis in a single search for purposes of ensuring an optimized and seamless discharge."

Lissy Hu, MD, president of WellSky, said, "We're thrilled to partner with a cutting-edge organization like Dialyze Direct to simplify care coordination and improve patient care. WellSky's CarePort solutions strengthen the ability of hospitals to connect with Dialyze Direct and offer patients critical services that allow for a safer, more comfortable transition to their next level of care."

XORTX Therapeutics Highlights 2022 Achievements

XORTX Therapeutics, Inc., a pharmaceutical company focusing on therapies to treat progressive kidney disease, released a report highlighting progress in 2022 and plans for 2023. **Allen Davidoff, PhD,** president and CEO, said, "2022 marked a year of

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Print-only Content

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substantial technological and clinical progress and established the foundation for the company's 2023 goals. The advancements and accomplishments made could not have happened without the efforts of our board of directors, employees, consultants, vendors, and shareholders. We believe the goals set for 2023 will advance our technology closer to marketing approval and transform XORTX into a high-value company."

In 2022, the company made progress in formulation development and nonclinical studies using XORLO™ to attenuate progression of kidney disease in animal models. In addition, the first clinical study (XRX-OXY-101) in support of the XRx-008 program for autosomal dominant polycystic kidney disease (ASPKS) was completed.

In 2023, the company plans to focus on advancing XORLO as part of the XRx-009 for ADPKD into a phase 3 registration clinical trial, submitting an Orphan Drug Designation, initiating special protocol assessment discussions with the FDA, and initiating commercialization activities for XORLO.

Sparsentan Receives FDA Accelerated Approval

The FDA has granted accelerated approval to FILSPARI™ (sparsentan), a drug to reduce proteinuria in adults with primary IgA nephropathy (IgAN) at risk for rapid disease progression (generally urine protein-to-creatinine ratio ≥1.5 g/g). According to a press release from Travere Therapeutics, Inc., the indication is granted under accelerated approval based on reduction in proteinuria.

Eric Dube, PhD, president and CEO of Travere Therapeutics, said, "The accelerated approval of FILSPARI is a significant milestone on our path to advancing a transformative treatment for the IgA nephropathy community. As a first-of-its-kind, nonimmunosuppressive therapy, we believe FILSPARI has the potential to ultimately become the new standard of care for IgA nephropathy and offer hope to those living with this condition who until now have had few treatment options. We are grateful to the patients, caregivers, clinical trial investigators, health care providers, and advocates who have worked alongside us to develop this innovative first-in-class therapy."

Bonnie Schneider, executive director and cofounder of the IgA Nephropathy Foundation, said, "For decades people living with IgA nephropathy have had limited treatment options while facing a progression toward kidney failure. Today is a day of celebration for the rare kidney disease community, for our patients and their families."

In the second half of 2023, Travere Therapeutics, together with its collaborator CSL Vifor, anticipates a review decision by the European Medicines Agency on the potential approval of the Conditional Marketing Authorization application for sparsentan for the treatment of IgAN in Europe. ■

ADPKD

Psychological Indicators in Early-Stage ADPKD

Nephron. doi.org/10.1159/000526840

Life expectancy and quality of life are predicted by the presence of psychological disorders. Diagnosis of autosomal dominant polycystic kidney disease (ADPKD) is often diagnosed prior to the onset of subjective symptoms, according to **Magdalena Jankowska, MD, PhD,** and colleagues. ADPKD is of genetic origin and may be a source of psychological disorder, particularly in the early stages.

The researchers conducted a study designed to identify data on the acceptance of illness, the emotional suppression of anger, anxiety, depression, and satisfaction of life among patients with asymptomatic ADPKD. The study cohort included young patients with early-stage ADPKD who were matched to healthy demographically similar individuals.

Fifty patients in the asymptomatic stage of ADPKD with an estimated glomerular filtration rate >60 mL/min/1.72 m^2 were matched to 50 healthy demographically matched individuals. Participants completed a set of three psychological questionnaires: (1) Acceptance of Illness Scale (AIS), (2) Courtauld Emotional Control Scale ; and (3) Satisfaction With Life Scale.

On the AIS, the asymptomatic patients with ADPKD had 80% scores indicative of disease acceptance. Compared with the healthy study participants, the group with ADPKD presented with significantly stronger suppression of both anxiety and depression, but no anger. Satisfaction with life was significantly lower among the ADPKD group than in the healthy group.

"Asymptomatic ADPKD patients had a high level of disease acceptance. Anger suppression in the group was comparable to healthy individuals, but anxiety and depression were controlled more intensively," the researchers said. "Despite the asymptomatic course of the disease, ADPKD patients revealed lower satisfaction with life in comparison to healthy persons."

CHRONIC KIDNEY DISEASE

Slope of Decline in GFR in Elderly Individuals

Clinical Journal of the American Society of Nephrology. 2022;17(8):1119-1128

There are few data available on the age-related course of glomerular filtration rate (GFR) in older adults. According to **Elke S. Schaeffner, MD, MS,** the scarcity of those data may be associated with misjudgment of the clinical relevance of reduced GFR in elderly patients.

The researchers utilized the longitudinal design of the Berlin Initiative Study (BIS) with repeated estimation of GFR over a median of 6.1 years of follow-up to describe the course of GFR in older adults and derive reference values in population-based individuals. The study cohort included 2069 community-dwelling older adults; mean age at study inclusion was 80 years (range, 70-99 years).

The BIS-2 equation was used to estimate GFR (eGFR) biennially, including standardized creatinine and cystatin C levels, sex, and age. A mixed-effects model was used to describe the crude and adjusted course of GFR; the influence of death on the GFR course was analyzed applying joint models. GFR equations based on creatinine and/or cystatin C were used to compare GFR slopes.

In the study cohort of elderly adults, there was a decreasing, thus nonlinear, decline in eGFR with increasing age. The estimated 1-year slope for ages 75 and 90 diminished for men from –1.67 to –0.99 and from –1.52 to –0.97 for women. The modeled mean eGFR for men ≥79 years of age and for women ≥78 years of age was <60 mL/min/1.73 m^2.

In multivariate adjustment analyses, the slopes were attenuated only minimally. There was no alteration in the nonlinear decline in eGFR after taking death into account by applying joint models. Using eGFR equations based on creatinine only showed linear slope patterns in contrast to nonlinear patterns for equations including cystatin C.

In conclusion, the researchers said, "The eGFR decline depended on sex and age and changed only marginally after multivariable adjustment but decelerated with increasing age. Equations including cystatin C demonstrated a nonlinear slope challenging the previously assumed linearity of the decline of eGFR in old age."

Dietary Protein and Carbohydrate Quality Index and Risk of CKD

Frontiers in Nutrition. doi.org/10.3389/fnut.2022.1003545

Farshad Teymoori, PhD, and colleagues conducted a population-based cohort study to examine associations between dietary protein score and carbohydrate quality index (CQI) and the risk of chronic kidney disease (CKD) in Iranian adults. The study was conducted within the Tehran Lipid and Glucose Study and included 6044 adults ≥18 years of age; mean follow-up was 7.7 years.

A food frequency questionnaire was used to determine dietary protein score and CQI. CKD was defined as estimated glomerular filtration rate <60 mL/min/1.73 m^2. The risk of CKD across tertiles of protein score and CQI was estimated using a multivariate Cox proportional hazard regression model.

Mean age of the study cohort was 37.9 years and mean body mass index was 26.8 kg/m^2. During follow-up, there were 1216 cases of CKD (20.1%). In the final adjusted model, those in the highest tertile of protein score had decreased risk of CKD (hazard ratio [HR], 0.85; 95% CI, 0.74-0.98; *P* for trend=.033). There was also a significant association between total carbohydrate score (HR, 0.85; 95% CI, 0.73-0.99; *P* for trend=0.16), the ratio of whole grain/total grains (HR, 0.81; 95% CI, 0.70-0.94; *P* for trend=.004), and glycemic index (HR, 1.30; 95% CI, 1.12-1.51; *P* for trend<.001) and risk of CKD. Total protein intakes, plant-to-animal ratio, and solid carbohydrate/total carbohydrate were not significantly associated with the risk of CKD.

In conclusion, the authors said, "Our results revealed a diet with a high protein score and high quality of carbohydrates, characterized by higher intakes of plant proteins, low glycemic index carbohydrates, whole grains, fibers, and lower intakes of animal proteins, can be related to reduced CKD risk."

DIABETES

Risk Prediction Models for Kidney Failure in Patients With Type 2 Diabetes

Clinical Journal of the American Society of Nephrology. 2022;17(12):1783-1791

There is an association between type 2 diabetes and a higher risk of developing kidney failure. **Helena Bleken Østergaard, MD,** and colleagues conducted a study designed to develop and validate a decision support tool to aid in estimating the 10-year and lifetime risks among individuals with type 2 diabetes of developing kidney failure. The researchers also sought to examine individual treatment effects of preventive medication in that patient population.

The researchers utilized data from the Swedish National Diabetes Register for 2002-2019 on 707,077 individuals with prevalent and incident type 2 diabetes to

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Abstract Roundup

COVID-19

COVID-19 Vaccine and Relapse of Glomerular Disease

Journal of the American Society of Nephrology. 2022;33(12):2247-2257

Relapses of glomerular disease following COVID-19 vaccination have been identified in case reports; however, there are few data showing evidence of a true association. **Mark Canney, MD, PhD,** and colleagues conducted a retrospective population-level analysis to examine the relative and absolute risks of relapse of glomerular disease after vaccination against COVID-19.

The researchers utilized a centralized clinical and pathology registry (2000-2020) to identify 1105 adult patients in British Columbia, Canada, with biopsy-proven glomerular disease that was stable on December 14, 2020, the day COVID-19 vaccines became available. The primary outcome of interest was disease relapse. Disease relapse was defined as changes in kidney function, proteinuria, or both. Extended Cox regression models, modified by disease type, were used to model vaccination as a 30-day time-varying exposure.

Follow-up extended for 281 days. During the follow-up period, 12.1% of patients (n=134) experienced a relapse. There was no association between the first vaccine dose and risk of relapse (hazard ratio [HR], 0.67; 95% CI, 0.33-1.36). There was a two-fold risk of relapse following exposure to a second or third dose (HR, 2.23; 95% CI, 1.06-4.71). The pattern of relative risk was similar across glomerular diseases.

The absolute increase in the 30-day relapse risk associated with a second or third vaccine dose varied from 1% to 2% in antineutrophil cytoplasmic antibody-related glomerulonephritis, minimal change disease, membranous nephropathy, or focal segmental glomerulosclerosis and from 3% to 5% in IgA nephropathy or lupus nephritis. Four of 24 patients who had a relapse related to the vaccine had a change in immunosuppression, and none required a biopsy.

In conclusion, the authors said, "In a population-level cohort of patients with glomerular disease, a second or third dose of COVID-19 vaccine was associated with higher relative risk but low absolute increased risk of relapse."

COVID-19 Outcomes in Kidney Transplant Recipients

Cureus. doi:10.7759.cureus.31375

Kidney transplant recipients are at increased risk of severe disease and death related to COVID-19.

Gina Defelice, MD, and colleagues conducted a study among adult kidney transplant recipients at a single transplant center who were diagnosed with COVID-19 and hospitalized between March 5, 2020, and January 15, 2021. The analysis included patient demographics, comorbid risk factors, and inpatient clinical courses for patients who recovered from the infection. Kidney function was measured preinfection, during the initial hospitalization, and up to 12 months postinfection.

During the study period, 48 kidney transplant recipients were diagnosed with COVID-19 infection. Of those, 18 required hospitalization for symptoms of fever and respiratory distress. Four of the 18 patients died from complications related to COVID-19.

Of the 14 remaining patients, 85.7% were Black, and median time from transplant was 4 years. Of the analysis cohort, 64.3% developed acute kidney injury (AKI), with an average peak serum creatinine of 2.6 mg/dL and an average glomerular filtration rate (GFR) of 35 mL/min/1.73 m^2. Prior to infection, the mean serum creatinine was 2 mg/dL and mean GFR was 44 mL/min1.73 m^2, representing an increase in serum creatinine of 34% and a decrease in GFR of 29%.

Mean follow-up postinfection was 14.5 months. At 3 to 6 months postinfection, mean serum creatinine was 1.87 mg/dL and mean GFR was 47 mL/min/1.73 m^2. At 9 to 12 months postinfection, the values were 1.89 mg/dL and 48 mL/min/1.73 m^2.

Five of the 14 patients developed new onset proteinuria (36%); all had complete resolution at 3 to 6 months of follow-up. Among the patients who developed AKI, 78% had complete recovery at 3 to 6 months of follow-up. One patient experienced graft loss.

"AKI is common among kidney transplant recipients who are hospitalized with COVID-19 infection," the researchers said. "Most of these recovered, although we noted that patients with baseline lower kidney function and existing proteinuria had a lower recovery rate."

DIALYSIS

Hyperphosphatemia in Dialysis Patients With Hypertension

BMC Nephrology. doi:10.1186/s12882-022-02918-0

Patients with end-stage renal disease on maintenance hemodialysis commonly develop hyperphosphatemia, a complication that is associated with increased mortality risk. While it is known that hyperphosphatemia contributes to vascular calcification, there are accumulating data that suggest an association with endothelial cell dysfunction.

Jinwoo Jung, MD, and colleagues conducted a cross-sectional study among patients on hemodialysis with hypertension. The researchers obtained prehemodialysis measurements of total peripheral resistance index (TPRI, noninvasive cardiac output monitor) and plasma levels of endothelin-1 (ET-1) and asymmetric dimethylarginine (ADMA). They then determined the routine peridialytic blood pressure measurements from that treatment and the most recent prehemodialysis serum phosphate levels.

Independent associations between serum phosphate and blood pressure, TPRI, ET-1, and ADMA were determined using generalized linear regression analysis, while controlling for demographic variables, parathyroid hormone (PTH), and interdialytic weight gain.

The analyses included data from 54 patients. Mean prehemodialysis supine and seated systolic and diastolic blood pressures were 146, 158, 91.5, and 86.1 mm Hg, respectively. Mean serum phosphate was 5.89 mg/dL.

Phosphate was significantly correlated with all prehemodialysis blood pressure measurements (r=.03, *P*=.04; r=0.4, *P*=.002; r=0.5, *P*<.001; and r=0.5, *P*=.003, respectively). The correlations with phosphate and TPRI, ET-1, and ADMA were 0.3 (*P*=.01), 0.4 (*P*=.007), and 0.3 (*P*=.05), respectively.

After controlling for baseline characteristics, PTH, and interdialytic weight gain, the independent associations between phosphate and prehemodialysis diastolic blood pressure, TPRI, and ET-1 were retained.

"Serum phosphate concentration is independently associated with higher prehemodialysis blood pressure, vasoconstriction, and markers of endothelial cell dysfunction," the researchers said. "These findings demonstrate an additional negative impact of hyperphosphatemia on cardiovascular health beyond vascular calcification." ■

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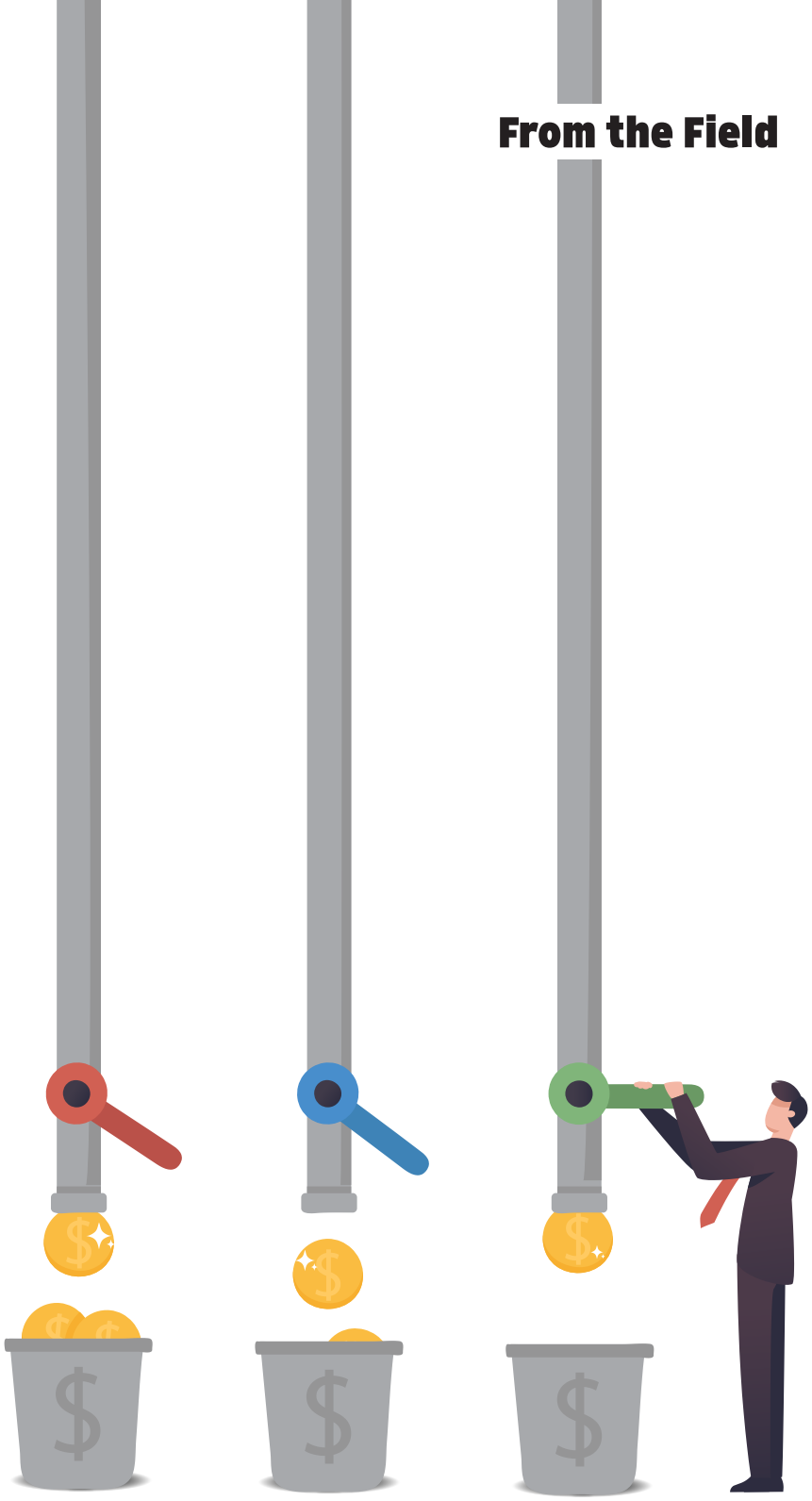
develop the prediction algorithm. Kidney failure was defined as the first occurrence of kidney transplantation, long-term dialysis, or persistent estimated glomerular filtration rate <15 mL/min/1.73 m^2. Using routinely available predictors, two Cox proportional regression functions for kidney failure and all-cause mortality as respective end points were developed. The functions were combined into life tables to calculate the predicted survival without kidney failure while using all-cause mortality as the competing outcome. A cohort of 256,265 individuals with incident type 2 diabetes from the Scottish Care Information Database between 2004 and 2019 was used to externally validate the model.

Median follow-up was 6.8 years. During follow-up, 8004 (1%) individuals with type 2 diabetes in the Swedish register developed kidney failure, and 202,078 (29%) died. The model performed well, with c statistics for kidney failure of 0.89 (95% CI, 0.88-0.90) for internal validation and 0.74 (95% CI, 0.73-0.76) for external validation. Results of calibration plots showed good agreement in observed versus predicted 10-year risk of kidney failure in both the internal and external validation models.

"This study derived and externally validated a prediction tool for estimating 10-year and lifetime risks of kidney failure as well as life years free of kidney failure gained with preventive treatment in individuals with type 2 diabetes using easily available clinical predictors," the researchers said.

Sarah Tolson

Exploring Dialysis Facility Cost Reports as a Revenue Stream



You read that right. The Medicare cost report that dialysis facilities submit each year can be an opportunity to capture revenue for certain bad debts. At a time when costs to run a dialysis facility are outpacing revenue, maximizing every available revenue source is more important than ever. With that in mind, I thought it would be helpful to provide some basic information about the dialysis facility cost report for those who are new to the renal industry or newly responsible for their facility's Medicare cost report.

The current form used to submit a cost report for freestanding dialysis facilities is the CMS-265-11. The Centers for Medicare & Medicaid Services (CMS) uses the cost report to gather data on treatment counts across all modalities, medication and supply utilization, costs to provide treatment and run the dialysis facility, as well as revenue and uncollected bad debt. If you are a dialysis facility administrator, you are likely familiar with collecting this information each year to pass on to whomever prepares your cost report. Filing a cost report could be likened to filing taxes; both are complex, can have serious financial and legal implications if done incorrectly, and are commonly outsourced to professionals who specialize in their preparation and submission.

Prior to the End-Stage Renal Disease Prospective Payment System (ESRD PPS) that was implemented in 2011, to receive any reimbursement from the cost report, a dialysis facility had to have uncollected bad debt that met CMS criteria and had to have lost money in the cost-reporting period. When dialysis reimbursement shifted from the composite rate to the ESRD PPS, CMS also modified who qualified to receive reimbursement for bad debt on a cost report as well as how the allowable amount is determined. Since the implementation of the ESRD PPS, all freestanding dialysis facilities whose cost reports include bad debt that meets CMS criteria qualify to receive reimbursement for the bad debt at a rate of 65% that pertains to the composite rate portion of the dialysis treatment.

So what exactly does CMS consider to be allowable bad debt? Medicare-assigned coinsurances and deductibles that were determined to be uncollectible during the cost-reporting period are generally considered to be allowable bad debts by CMS. There are also some requirements regarding how much time can pass between the coinsurance being assigned to the patient and when the coinsurance is deemed to be uncollectible. Familiarity with these requirements is key to ensuring the bad debts claimed on your cost report meet the CMS guidelines.

When claiming a bad debt amount on the cost report, CMS requires dialysis facilities to include an itemization of each bad debt whose totals comprise the total bad debt claimed on the cost report. It is helpful to keep in mind that the Medicare Administrative Contractor (MAC) that your cost report is submitted to will perform an audit of the bad debts at some point in the future. Compliance with CMS requirements, accuracy, and keeping complete records to substantiate any bad debts will benefit you immensely when it is time for the audit.

In order to get all available reimbursement for uncollectible Medicare-assigned coinsurances and deductibles, facilities should ensure that the individuals who handle bad debts are well educated on the criteria that must be met to qualify each balance as an allowable bad debt. Additionally, a standardized process for documenting and tracking potentially allowable bad debts should be implemented, followed, and periodically audited for compliance. As cost reports for dialysis facilities are incredibly complex and require a significant amount of expertise in dialysis facility reimbursement, I would recommend working with a cost report preparer who is familiar with and has experience filing dialysis facility cost reports. In addition to being well versed in the data needed to complete the cost report, they may also assist you in determining what kinds of things are generally reviewed in desk audits from your specific MAC. ■

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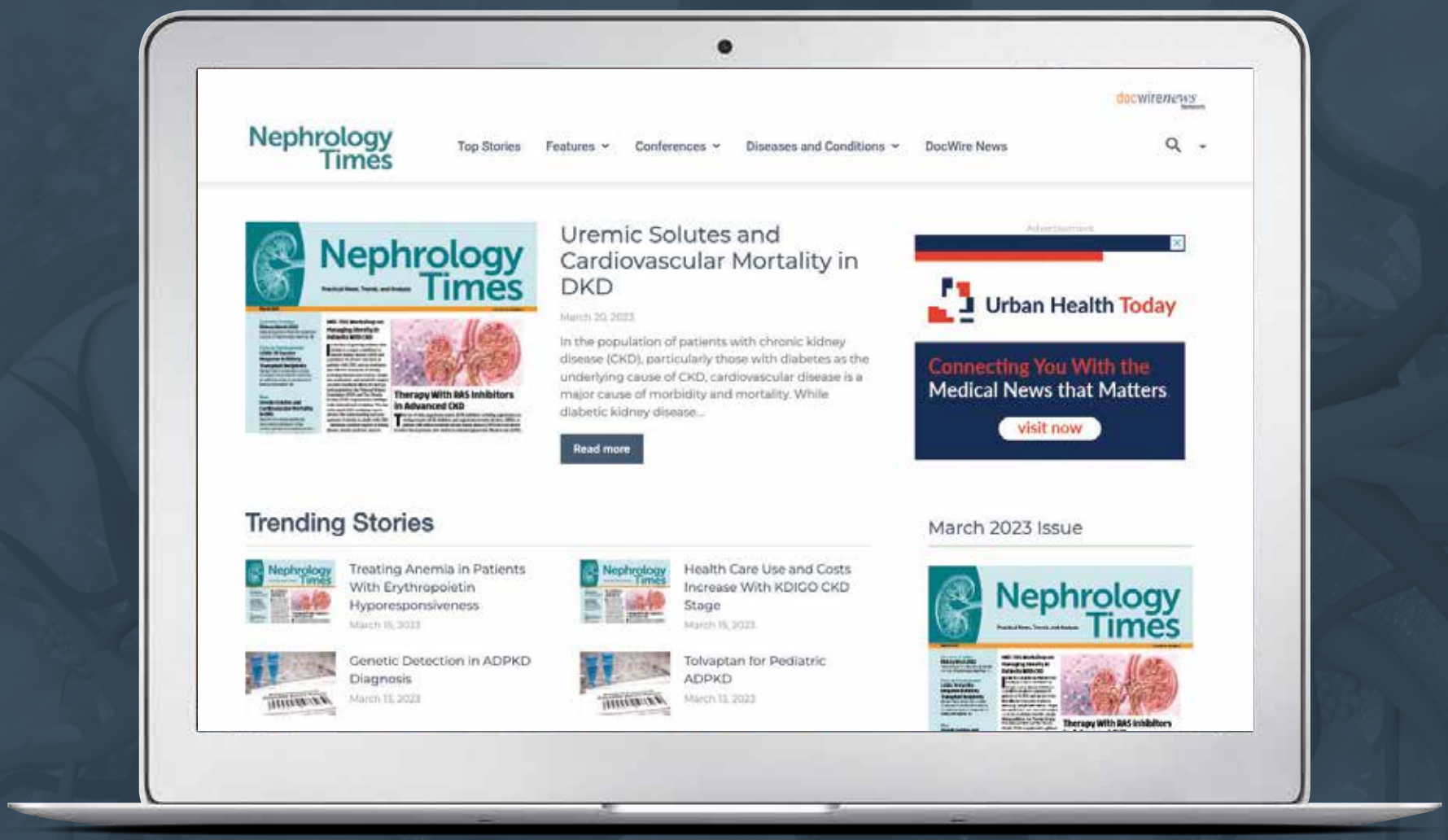

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