Nephrology Times

Practical News, Trends, and Analysis

July/August 2024

VOLUME 16, NUMBER 5

Risk Prediction Model for AKI After Cisplatin

The chemotherapy drug cisplatin is used to treat a variety of cancers, including advanced bladder cancer, non-small cell lung cancer, mesothelioma, head and neck cancer, gynecologic cancers, and testicular cancers. However, cisplatin-associated acute kidney injury (CP-AKI) is a common and serious toxicity.

Accurate assessment of the patient's susceptibility to CP-AKI could help clinicians determine the risks and benefits of cisplatin use, adjust dosing, and identify patients who need closer monitoring. That need prompted researchers, including **Shruti Gupta, MD,** to use data from six major US academic cancer centers to develop and externally validate a prediction model for moderate-to-severe CP-AKI. Their results were reported in *BMJ* [doi:10.1136/bmj-2023-077169].

The multicenter cohort study examined data of adult patients aged ≥18 years who received a first intravenous dose of cisplatin between 2006 and 2022. Patients with end-stage renal disease, whose baseline serum creatinine level was missing, or who were lacking at least one follow-up serum creatinine value within 14 days of first dose of cisplatin were excluded. In addition to baseline lab values, data collected included age, sex, race, ethnicity, body mass index, comorbidities, and smoking status.

The primary outcome was CP-AKI, defined as a twofold or greater increase in serum creatinine level

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Effects of a Lifestyle Intervention on Kidney Outcomes

Lifestyle interventions have proven effective at aiding weight loss and improving risk factors for chronic kidney disease (CKD), including obesity, diabetes, and hypertension. However, their impact on kidney function (measured as estimated glomerular filtration rate [eGFR]) over time has not been widely reported.

The Action for Health in Diabetes (Look AHEAD) trial randomized patients with diabetes and either obesity or overweight into two groups: one that received an intensive lifestyle intervention and another that received usual care (diabetes support and education). The trial ended early when it found no significant difference between the two groups in terms of cardiovascular morbidity and mortality.

Using creatinine-based eGFR, researchers led by **Linda-Marie U. Lavenburg, DO,** conducted a post hoc analysis of Look AHEAD data to determine whether the lifestyle intervention had any significant effect on kidney function over 10 years. Their results were published in *Kidney Medicine* [doi:10.1016/j.xkme.2024.100814].

Look AHEAD participants were 5145 adults aged 45-75 years who were supervised by a primary care provider and had type 2 diabetes, body mass index (BMI)

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How Clinician Preconceptions Affect Peritoneal Dialysis Utilization

Kidney replacement therapy (KRT) is essential to patients with kidney failure. Dialysis is the primary means of providing KRT, comprising 78% of KRT, but just 11% of KRT is performed using peritoneal dialysis (PD). Although PD is simple, effective, and fairly inexpensive, its utilization is limited in many countries. Despite strong support of home dialysis among clinicians and patients worldwide, hemodialysis remains the predominant method of KRT, including in the United States.

Nikhil Shah, MBBS, DNB, and fellow researchers posited that a major barrier to PD utilization is clinicians' perceptions of their patients' suitability and capability to safely perform the treatment. In a study published in *KI Reports* [doi:10.1016/j.ekir.2024.01.041], the researchers examined the prevalence of myths about PD use

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Go With the Flow

Ajay K. Singh, MBBS, FRCP, MBA
Brigham and Women's Hospital and Harvard Medical School
BOSTON, MASSACHUSETTS

The FLOW study published recently in the *New England Journal of Medicine* by **Vlado Perkovic, MBBS, PhD,** and colleagues[1] provides the definitive fourth pillar in slowing kidney progression in patients with type 2 diabetes mellitus and kidney disease (diabetic kidney disease, or DKD; see FIGURE). This landmark study comes on the back of meta-analyses that point to the benefit of glucagon-like peptide 1 receptor agonists (GLP1-ra) in slowing kidney progression.[2]

FLOW recruited 3533 patients with moderately advanced DKD who were randomized to receive either subcutaneous semaglutide (1.0 mg/week) or placebo and followed for a median of 3.4 years. The primary outcome was major kidney disease events, a composite of the onset of kidney failure (dialysis, transplantation, or an estimated glomerular filtration rate [eGFR] <15 ml/min/1.73 m^2), at least a 50% reduction in eGFR from baseline, or death from kidney-related or cardiovascular causes. Semaglutide treatment resulted in a 24% reduction in the primary outcome event of major kidney disease events (331 vs 410; hazard ratio, 0.76; 95% CI, 0.66-0.88; *P*=.0003). Likewise, the kidney-specific components and death from cardiovascular diseases also strongly favored semaglutide.

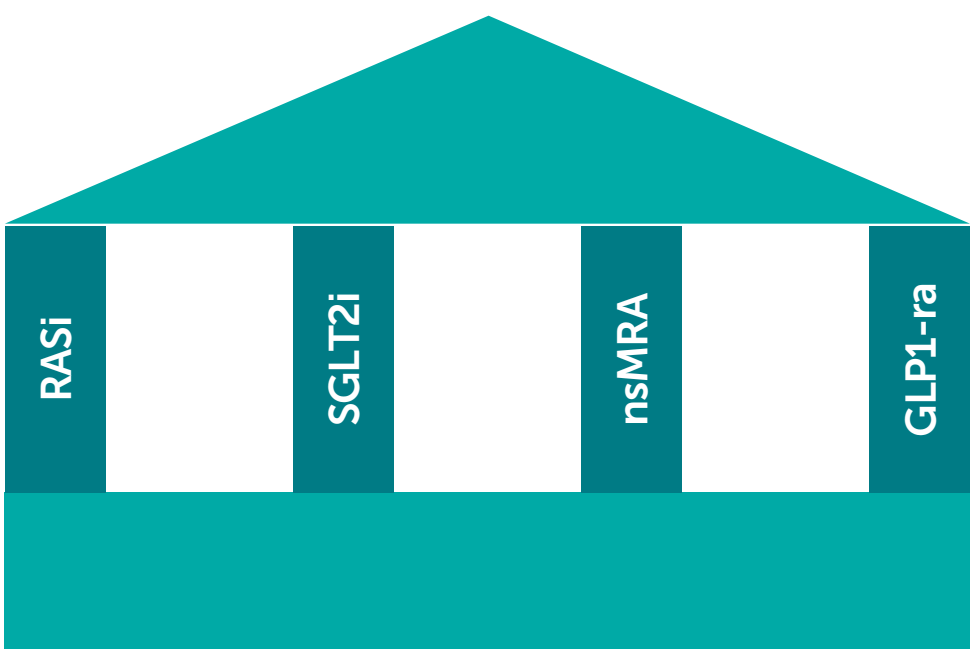
The mechanism for why GLP1-ra are renoprotective has not been fully elucidated, but reducing oxidative stress and endothelial dysfunction seem the most likely explanations. The beneficial effect on slowing kidney progression is likely to extend to the whole class of GLP1-ra, including lixisenatide, liraglutide, exenatide, dulaglutide, and albiglutide.

Semaglutide is available as both a subcutaneous (SC) and an oral medication. The data from SC administration were presented in FLOW. It is likely that the oral form of semaglutide will be similarly efficacious, but a trial may be needed to definitively prove this hypothesis. The benefits of oral versus SC administration include convenience, storage, and discomfort from injections with the SC route.

The pillar approach to treating DKD has been championed by **George Bakris, MD,** who recently passed away[3] and was a giant in the field.[4] This approach is now widely recommended. Indeed, Dr. Bakris and a colleague, **Sandra Naaman, MD, PhD,** wrote, "Practice guidelines articulate that clinicians should start first by titrating to maximally tolerated [renin-angiotensin system] blockade before introducing these medications ([sodium-glucose transport inhibitors, nonsteroidal mineralocorticoid receptor antagonists, and GLP1-ra]) ... endocrinologists, nephrologists, and cardiologists are strongly encouraged to use a pillared approach to DKD using the framework described, irrespective of the degree of kidney impairment, down to an eGFR of 25 mL/min/1.73 m^2."

The bottom line and rather tongue-in-cheek "go with the flow" in the title of this editorial really means that maximizing renoprotection is not now an uncertain exercise but rather one of using the pillar approach, and each of these pillars is based on high-quality, randomized, controlled trials. ■

FIGURE **Pillar Approach to Slowing the Progression of DKD**



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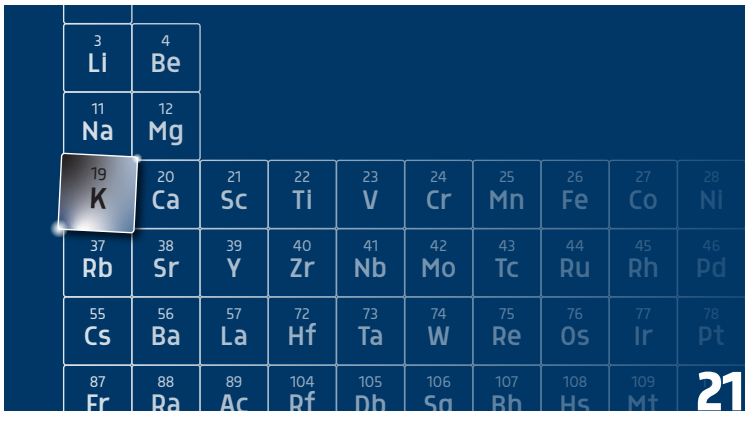

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Nephrology Times (ISSN 1940-5960) is published bi-monthly by AMC Media Group, at 630 Madison Avenue, Manalapan, NJ 07726. Printed in the U.S.A.

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Lifestyle Intervention

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of ≥25 kg/m^2, and the ability to complete a maximal exercise test. The kidney-focused post hoc analysis included 4901 of those participants whose data were archived in the National Institute of Diabetes and Digestive and Kidney Diseases data repository.

Median participant age was 58 (interquartile range, 55-64) years, and there was no significant difference in the number of lifestyle intervention versus usual care participants with normal urine albumin-creatinine ratio (UACR; 84% vs 82%), microalbuminuria (13% vs 14%), or macroalbuminuria (3% vs 3%). Both randomization arms were balanced regarding sex (59% female), race/ethnicity (66% non-Hispanic White, 16% non-Hispanic Black, and 14% Hispanic), mean BMI (36 kg/m^2), eGFR (89 mL/min/1.73 m^2), and serum creatinine level (0.8 mg/dL). The majority (75%) of participants had an eGFR of >80 mL/min/1.73 m^2.

All Look AHEAD participants were instructed to eat a low-fat, reduced calorie diet. Those in the lifestyle intervention group were to increase physical activity to 175 minutes/week, with the goal of decreasing their starting body weight by ≥7%. The intervention was individual or group sessions led by a trained interventionist to help the participants meet dietary and physical activity goals using behavior modification techniques.

The study authors chose slope of eGFR (mL/min/1.73 m^2 per year) as the primary study outcome, hypothesizing that the long-term cumulative effect of reduced glomerular pressure would decrease eGFR slope. Secondary outcomes were mean eGFR and slope and mean UACR (mg/mg), used to evaluate the kidneys' response to physiologic changes over the course of follow-up. Serum creatinine, urine albumin, and urine creatinine were measured at baseline, yearly for the first 5 years, and then every other year.

The researchers evaluated differences in baseline demographics, clinical characteristics, eGFR, and UACR between randomization arms using a two-sample *t* test or Wilcoxon-rank sum for continuous covariates and the χ^2 test of proportions for categorical covariates. They used linear mixed effects modeling with random slopes and intercepts for distinctive participant identifiers to evaluate the association of the randomization arm with within-individual repeated measures of eGFR and UACR over 10 years.

Kidney function in both groups decreased over the 10-year study period, although there appeared to be a smaller annual decline in the lifestyle intervention arm. There was no significant difference in the eGFR slope between randomization arms (adjusted difference: +0.070 mL/min/1.73 m^2 per year; 95% CI, −0.032 to 0.17; *P*=.18) in adjusted and unadjusted analyses.

Compared with the usual care arm, the lifestyle intervention group had a slightly higher mean eGFR over 10 years of follow-up by +0.73 (95% CI, −0.068 to 1.53; *P*=.07) relative to the usual care arm in the unadjusted linear mixed effects model. The adjusted mean difference in eGFR over 10 years was +0.40 mL/min/1.73 m^2 (95% CI, 0.060-0.740; *P*=.02). Further examination determined that age was a significant effect modifier on mean eGFR; participants aged ≥65 years in the lifestyle intervention group had a slightly higher mean eGFR (+0.99 mL/min/1.73 m^2; 95% CI, 0.16-1.82; *P*=.02) versus the usual care group. Baseline eGFR did not change the effect of the lifestyle intervention on eGFR slope or mean eGFR. There was no significant difference in UACR slope (adjusted: −0.00098 mg/mg per year; 95% CI, −0.0043 to 0.0023; *P*=.57) or adjusted mean UACR (−0.0054 mg/mg; 95% CI, −0.013 to 0.0026; *P*=.19) between randomization arms.

Limitations of the study include the limited generalizability of trials with lengthy follow-up, which often recruit highly motivated participants. Furthermore, there were no participants with kidney disease or significant albuminuria, which could lead to underestimation of the effects of intensive lifestyle interventions in patients with uncontrolled CKD risk factors.

In summary, the authors wrote, "In patients with type 2 diabetes and preserved kidney function, intensive lifestyle intervention did not change eGFR slope over 10 years. Among participants with baseline eGFR <80, lifestyle intervention had a slightly higher longitudinal mean eGFR than usual care. Further studies evaluating the effects of intensive lifestyle intervention in people with kidney disease are needed." ■

TAKEAWAY POINTS

- Lifestyle interventions can improve chronic kidney disease (CKD) risk factors such as diabetes, hypertension, and obesity. However, the effects on kidney function (measured as estimated glomerular filtration rate [eGFR]) over time were not well known.
- Researchers analyzed data from the Action for Health in Diabetes trial. All participants had diabetes and overweight or obesity and were randomized to either an intensive lifestyle intervention group or a diabetes support and education group.
- The change in eGFR over 10 years did not differ between groups, but the intervention group had slightly higher eGFR than the usual care group, especially if eGFR was low at baseline. This finding suggests that lifestyle interventions may preserve eGFR, but studies in patients with CKD are needed.

Clinician Preconceptions

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among kidney care physicians. They studied physician attitudes about PD initiation according to physical (eg, obesity), social (eg, pet ownership), and clinical (eg, previous surgery) characteristics.

The researchers gathered an international team of nephrologists to develop a survey that used a Likert scale, allowing respondents to select whether they would "always," "probably," "probably not," or "definitely" offer a patient PD in various situations. Elements of common misconceptions about PD eligibility were included, such as suitability of PD for patients with specific comorbidities (eg, obesity, cirrhosis, polycystic kidney disease, cognitive impairment, immunosuppression), previous abdominal surgeries, stomas, and those requiring urgent-start PD (PD within 2 weeks of catheter insertion). Questions also focused on the presence of pets, swimming, and planning for a future pregnancy.

Respondents were recruited via several large nephrology and dialysis organizations, an international network of contacts supplied by the authors, and social media channels. Clinician information compiled included professional experience, years in practice, profession, size of PD unit, experience in an ambulatory PD unit, participation in specific home dialysis training, and demographic data such as age, gender, and country of practice. Each country was categorized as a low-income country (LIC), lower middle-income country (LMIC), upper middle-income country (UMIC), or high-income country (HIC). Answers were collected from September 2021 to January 2022.

A total of 717 clinicians opened the survey, of whom 645 (522 nephrologists and 123 trainees; 56% male) from 54 countries (66% HICs, 22% UMICs, 12% LMICs, 1% LICs) answered at least one question; 574 respondents (89%) answered all the questions. Of those who responded to the survey, 84% worked in units that offered ambulatory or outpatient PD services and 22% had undergone specific home dialysis training.

In most scenarios, respondents recommended PD, including in situations with repeated exposure to heavy lifting (but only 49% recommended in the case of professional weightlifting) and swimming (especially in a private pool [72%] or sea/ocean [50%]), among patients with cirrhosis or cognitive impairment with support available, in patients with obesity (59% for patients with a body mass index greater than 40 kg/m^2), and in those living with a pet if the pet could be physically separated during PD. Some abdominal surgeries were deemed more acceptable with PD (hysterectomy, 90%) compared with others (hemicolectomy, 45%). Similarly, recommendations varied for different types of stomas (nephrostomies, 74%; suprapubic catheters, 53%; ileostomies, 27%). Across various scenarios, clinicians were more likely to recommend PD if they came from HICs or larger PD units, or if they had more clinical experience.

The authors acknowledge a few limitations of the study. For instance, most respondents come from countries where PD is more prevalent, making meaningful comparisons among countries difficult. Also, there is potential positive bias toward PD from respondents who were sourced through large nephrology organizations.

"In summary," the authors wrote, "we found that most nephrologists and nephrology trainees will consider commencing dialysis in the presence of historically reported barriers. We found some variations that may be driven by experience, unit-level characteristics, and region of practice. Globally, evidence-informed education is warranted to rectify misconceptions to enable greater PD uptake." ■

TAKEAWAY POINTS

- Peritoneal dialysis (PD) is underutilized worldwide as a means of kidney replacement therapy (KRT). One reason for this may be clinicians' preconceptions about its use under certain circumstances.
- Researchers studied clinicians' perceptions about PD according to different physical, social, and clinical characteristics of patients. Clinicians would recommend PD in most scenarios with which they were presented.
- However, there were disparities in recommending PD across various clinical scenarios driven by experience, unit-level characteristics, and region. Evidence-based education is needed to correct misconceptions and increase PD initiation.

CP-AKI Prediction Model

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compared with baseline or kidney replacement therapy within 14 days after the first dose of cisplatin, consistent with stage 2 or 3 AKI defined by Kidney Disease: Improving Global Outcomes guidelines.

The researchers used a multivariable logistic regression model to identify independent predictors of CP-AKI in a derivation cohort and tested them in a validation cohort. In the primary model, they assessed continuous variables using restricted cubic splines. They developed a simple risk model consisting of nine covariates by converting the odds ratios from the primary model into risk points. Then, they applied a multivariable Cox model to study the association between the severity of CP-AKI and 90-day survival.

There were 34,122 patients in the study: 15,752 comprising the derivation cohort and 18,370 comprising the validation cohort. After exclusion criteria were applied, the final dataset comprised 11,766 patients in the derivation cohort and 12,951 in the validation cohort; median age was 59 years (interquartile range [IQR] 50-67) and 60 years (IQR, 50-67), in each cohort, respectively. Baseline characteristics were mostly similar between the two groups. Patients in the derivation cohort received a higher median dose of cisplatin versus patients in the validation cohort. CP-AKI occurred in 5.2% (n=608) of patients in the derivation cohort and 3.3% (n=421) in the validation cohort. The incidence rates of CP-AKI were largely unchanged over time. In the investigation of primary outcomes, age, hypertension, diabetes mellitus, serum creatinine level, hemoglobin level, white blood cell count, platelet count, serum albumin level, serum magnesium level, and cisplatin dose were independently associated with a risk of CP-AKI.

The risk score predicted a higher risk of CP-AKI in a monotonic way in both the derivation and validation cohorts. Patients in the highest risk category had 24.00-fold (95% CI, 13.49-fold to 42.78-fold) higher odds of CP-AKI in the derivation cohort and 17.87-fold (10.56-fold to 29.60-fold) higher odds in the validation cohort compared with those in the lowest risk category. More severe CP-AKI was monotonically associated with shorter 90-day survival (adjusted hazard ratio, 4.63; 95% CI, 3.56-6.02 for stage 3 CP-AKI vs no CP-AKI). C statistics for previously published models ranged from 0.60 to 0.68. The primary model developed for this study had a C statistic of 0.75 and demonstrated better discrimination for CP-AKI than previously published models.

The authors acknowledge limitations of the study. Data on medications used at home were not available. Cancer type could not be differentiated based on *International Classification of Diseases* codes, so the association between severity of CP-AKI and survival should be interpreted with caution. The study was limited to US centers. Discrimination of the primary model was modest, with a C statistic of 0.75, although the researchers point out that their model outperformed all previous models, both for primary and secondary outcomes.

In sum, the simple risk score that the researchers developed was able to predict the risk of severe CP-AKI, which is strongly associated with death. The authors concluded, "We developed a simple, externally validated risk score for severe CP-AKI. This model should help providers weigh the risks and benefits of cisplatin and will allow for enrichment of prospective studies designed to prevent CP-AKI." ■

TAKEAWAY POINTS

- The chemotherapy drug cisplatin treats a wide range of cancers, but cisplatin-associated acute kidney injury (CP-AKI) is common and strongly associated with death.
- Researchers set out to develop and validate a model to predict severe CP-AKI using data from six major US academic cancer centers that included 24,717 adults.
- A simple risk score based on easily accessed variables from patients on cisplatin could help predict their risk of severe CP-AKI.

Midyear Highlights

A few of our editorial board members shared the nephrology research and news they have found most notable so far this year.

Mohamed G. Atta, MD, MPH

I would like to highlight this research paper from Taiwan that showed clinical benefits of sodium-glucose cotransporter-2 inhibitors in even chronic kidney disease (CKD) stage 5. Though not randomized, it would reduce providers' fears of using these agents in patients with very low glomerular filtration rate.
Yen F-S, Hwu C-M, Liu J-S, Wu Y-L, Chong K, Hsu C-C. Sodium-glucose cotransporter-2 inhibitors and the risk for dialysis and cardiovascular disease in patients with stage 5 chronic kidney disease. *Ann Intern Med*. 2024. doi:10.7326/M23-1874

Kenneth Liss, DO

For me, it is the potential impact of glucagon-like peptides on renal function.
Seksaria S, Dutta BJ, Kaur M, Gupta GD, Bodakhe SH, Singh A. Role of GLP-1 receptor agonist in diabetic cardio-renal disorder: recent updates of clinical and pre-clinical evidence. *Curr Diabetes Rev*. 2024. doi:10.2174/1573399820666230809152148

Joel M. Topf, MD, FACP

Complement factor B inhibitor looks like another effective therapy for IgAN.
Perkovic V, Kollins D, Renfurm R, et al. Efficacy and safety of iptacopan in patients with IgA nephropathy: interim results from the phase 3 APPLAUSE-IgAN study. *Kidney Int Rep*. 2024. doi:10.1016/j.ekir.2024.02.1414

The FLOW trial, of course.
Perkovic V, Tuttle KR, Rossing P, et al. Effects of semaglutide on chronic kidney disease in patients with type 2 diabetes. *N Engl J Med*. 2024. doi:10.1056/NEJMoa2403347

Minimal change is antibody-mediated. Rewrite the textbooks!
Hengel FE, Dehde S, Lassé M, et al. Autoantibodies targeting nephrin in podocytopathies. *N Engl J Med*. 2024. doi:10.1056/NEJMoa2314471

We figured out what the dense deposits are in dense deposit disease!
Madden B, Singh RD, Haas M, et al. Apolipoprotein E is enriched in dense deposits and is a marker for dense deposit disease in C3 glomerulopathy. *Kidney Int*. 2024. doi:10.1016/j.kint.2024.02.013

Finally, the KDIGO (Kidney Disease: Improving Global Outcomes) CKD guideline got updated for the first time since 2012!

61st ERA CONGRESS

The European Renal Association Congress (ERA) is the largest annual nephrology congress in Europe, welcoming thousands of attendees from all over the world. The program focuses on key learning features in the clinical field as well as the latest scientific innovations.

Renal Progenitor Cells as a Biomarker of Kidney Injury in Fabry Disease

Jessica Ugalde-Altamirano and fellow researchers conducted an open, observational, case-control, single-center study with the goal of demonstrating the presence of renal progenitor cells (RPCs) in urine as a noninvasive early marker for detecting renal damage in patients with Fabry disease (FD). They also hoped to show a correlation between RPC presence, deposition of the lipid globotriaosylceramide (GB3), and the potential association with the level of renal injury. The results were presented at the 61st ERA Congress.

FD is an inherited condition in which a mutation causes a defect in the metabolism of glycosphingolipids, leading to the deposition of GB3 in organs, including the kidneys. Podocytes are most often affected, leading to proteinuria, which can cause a rapid decrease in renal function if it exceeds 0.5 g.

Renal biopsy is the gold standard biomarker, but less invasive biomarkers are starting to gain prominence. RPCs contribute to cellular remodeling, and they express specific markers such as CD133/CD24 and CD106 in the parietal epithelium of Bowman's capsule; GB3 expresses CD77. If the proliferative response of RPCs becomes dysregulated, detachment and elimination in the urine occurs.

Ugalde-Altamirano's research group analyzed 75 urine samples from 59 patients, 16 with FD, 11 with Gittelman syndrome, 10 with CKD, and 22 healthy controls. They divided the samples for sediment and microalbuminuria analysis, and separately to isolate RPCs, then classified and quantified the isolated cell types. Positivity points were established using compensation panels with CD3 lymphocyte markers. Next, RPCs were identified through positivity for CD133+/CD24+, CD106+, and CD106- markers. After RPCs were identified, the researchers conducted GB3 marking using CD77+.

There was no or minimal presence of RPCs in the healthy control group, except in two patients who subsequently were found to have bilateral lithiasis and previously unknown hypertension. The Gittelman syndrome group had a higher prevalence of RPCs compared with the control group ($P>.05$). The FD and CKD groups showed clear RPC positivity as confirmed by biopsy ($P<.05$). When the level of renal disease was correlated with the presence of proteinuria, differences in the quantity of RPCs were noted (<0.5 g and >0.5 g; $P<.05$).

The authors wrote, "With these results, we can conclude that [RPCs] may serve as an early biomarker for silent renal injury of various etiologies. Furthermore, if we perform labeling with CD77, we can attribute it to the deposition of GB3 in [FD]."

Source: Ugalde-Altamirano J, Juarez JR, Tubita V, et al. Renal progenitor cells an early non-invasive biomarker of silent kidney injury in Fabry disease. Abstract #2908. Presented at the 61st European Renal Association Congress; May 23-26, 2024; Stockholm, Sweden.

Adverse Outcomes Across KDIGO Categories for Patients With T1DM

Kianoush Makvandi and others observed that the Kidney Disease: Improving Global Outcomes (KDIGO) classifications for evaluating the burden and impact of renal and cardiovascular (CV) adverse outcomes in patients with type 1 diabetes mellitus (T1DM) were underutilized. Therefore, they conducted a study to better understand: (1) the distribution of various KDIGO categories across the cohort, (2) the incidence of adverse renal and CV events for each category, and (3) the association of baseline KDIGO category and future excess risk for five major outcomes. Their results were presented at the 61st ERA Congress.

A total of 39,067 patients from the Swedish National Diabetes Register were included in the study, all of whom had T1DM. Based on their baseline albuminuria and creatinine, they were categorized into G1 to G5 estimated glomerular filtration rate (eGFR) and A1 to A3 albuminuria groups.

Outcomes of interest for the study included acute kidney injury (AKI), 40% eGFR decline from baseline, kidney failure (KF), renal death, and a composite outcome of either of the preceding renal outcomes (MAKE). CV outcomes were also tracked and included coronary heart disease, stroke and CV death, and a composite outcome comprising either of the preceding CV outcomes and heart failure (MACE). The researchers also analyzed all-cause mortality.

The researchers used Kaplan-Meier survival curves to assess cumulative incidence of outcomes, calculating the incidence rate per 1000 person-years. They used Cox proportional hazards regression risk models to study the association between baseline KDIGO category and the risk of five major outcomes: 40% eGFR decline, KF, MAKE, MACE, and all-cause mortality.

The mean follow-up was 9.1 years (350,000 person-years). Chronic kidney disease (CKD; eGFR <60 ml/min/1.73 m^2 and/or albuminuria) was present in 18.5% of participants; 8.1% were normoalbuminuric. In both the increasing eGFR and albuminuria categories, there was a progressive increase in the incidence and adjusted hazard ratio (HR) for all outcomes. This was true even in subjects with eGFR ≥60 ml/min/1.73 m^2.

Cox regression analyses were conducted referencing KDIGO categories combining G1A1 and G2A1 and then using only G1A1. Unexpectedly, repeat analysis using G1A1 alone found significantly elevated risk for all five major outcomes, even in G2A1, although this category normally would be considered low risk.

In sum, the study authors wrote, "A progressively increasing burden of adverse cardiorenal outcomes, including mortality, was observed with advancing KDIGO categories in [the] T1DM population. Even in subjects with preserved eGFR and normoalbuminuria, we identified an elevated risk for all major outcomes, indicating that early screening and implementation of preventive strategies may be beneficial in improving prognosis of this population."

Source: Makvandi K, Eliasson B, Carlsen HK, Bajd-Agrawal S. Burden and excess risk of adverse outcomes in patients with type 1 diabetes utilizing KDIGO classification: a national cohort study. Abstract #1750. Presented at the 61st European Renal Association Congress; May 23-26, 2024; Stockholm, Sweden.

FLOW Results Show Semaglutide Benefits Patients With T2D, CKD

Presenting their results at the 61st ERA Congress, **Vlado Perkovic, MBBS, PhD,** and other researchers found that semaglutide significantly decreases the risk of major kidney disease events, CV outcomes, and all-cause mortality in patients with type 2 diabetes (T2D) and CKD.

The findings came from the Evaluate Renal Function with Semaglutide Once Weekly (FLOW) study, a double-blind, randomized, placebo-controlled international trial to assess the safety and efficacy of semaglutide in preventing major kidney outcomes in people with T2D and CKD, namely kidney failure, significant loss of kidney function, and death from kidney or CV causes.

There were 3533 patients in the trial, receiving either placebo or semaglutide, a subcutaneous glucagon-like peptide 1 receptor agonist, 1 mg once weekly; median follow-up was 3.4 years. The patients receiving semaglutide had a 24% lower risk of the composite primary end point, including kidney outcomes and death due to CV and kidney causes, versus patients receiving placebo. This risk reduction was consistent across both kidney-specific and CV-related death outcomes.

Semaglutide also demonstrated benefits for the study's secondary end points. For patients receiving semaglutide, the total eGFR slope was 1.16 ml/min/1.73 m^2/year slower, the risk of major CV events decreased by 18%, and the risk of all-cause mortality shrank by 20%.

The FLOW results, which were also published in the *New England Journal of Medicine*, offer new hope for patients facing a dual diagnosis of T2D and CKD. Perkovic stated, "These findings offer great promise in reshaping treatment strategies for individuals at high risk of diabetes-related complications, offering a new avenue for kidney and cardiovascular protection."

Source: Perkovic V, Tuttle K, Rossing P, et al. Effects of semaglutide on chronic kidney disease in patients with type 2 diabetes. Presented at the 61st European Renal Association Congress; May 23-26, 2024; Stockholm, Sweden.

ORIGIN Study of Atacicept for IgA Nephropathy

The phase 2b ORIGIN study compared randomized groups of patients with IgA nephropathy (IgAN) receiving either atacicept or placebo. **Richard Lafayette** and others shared interim analysis results at the 61st ERA Congress.

Atacicept targets B-cell activating factor and a proliferation-inducing ligand (APRIL), both of which drive production of galactose-deficient IgA1 (Gd-IgA1) and its antibodies. Elevated Gd-IgA1 is the hallmark of IgAN.

ORIGIN included 116 participants with 24-hour urine protein >0.75 g/day or urine protein-to-creatine ratio (UPCR) >0.75 g/g and eGFR ≥30 mL/min/1.73 m^2 despite optimized treatment with renin-angiotensin system (RAS) blockade. The double-blind study randomized them to receive atacicept 150, 75, or 25 mg versus placebo (2:2:1:2) for up to 36 weeks. During a subsequent open-label extension period, participants could receive atacicept 150 mg for up to 60 additional weeks.

Of the 116 participants, 106 (91%) finished 72 weeks of treatment. At 72 weeks, atacicept achieved statistically significant eGFR stability and reduction in UPCR and Gd-IgA1 compared with placebo.

The eGFR change from baseline at 72 weeks was 0 mL/min/1.73 m^2 in all participants originally randomized to atacicept (all-atacicept group; n=82). After the placebo group switched to atacicept 150 mg, individuals in that group showed eGFR stabilization with -3.2 mL/min/1.73 m^2 change from baseline at 72 weeks compared with -4.9 mL/min/1.73 m^2 at 36 weeks. Atacicept 150 mg was also associated with quick Gd-IgA1 reduction in the group that switched from placebo at 48 weeks, and the reduction was sustained through 72 weeks.

At 72 weeks, UPCR change from baseline was -45% in the all-atacicept group, while the placebo switch group demonstrated a -47% UPCR change from baseline at 72 weeks versus +3% at 36 weeks. Hematuria resolution occurred in 81% (35/43) of participants in the all-atacicept group at 72 weeks and 59% (10/17) in the placebo switch group.

In addition to the clinical benefits observed, atacicept was well-tolerated and demonstrated safety comparable with the placebo.

Source: Lafayette R, Maes R, Israni R, et al. Phase 2b ORIGIN study open label extension with atacicept in patients with IgA nephropathy and persistent proteinuria: week 72 interim analysis. Abstract #812. Presented at the 61st European Renal Association Congress; May 23-26, 2024; Stockholm, Sweden.

Targeting Claudin-1 in Crescentic Glomerulonephritis

A study by Jean-Daniel Delbet and others examined the functional role of claudin-1 (CLDN1) in crescentic glomerulonephritis (CrGN) and the potential benefit of targeting CLDN1 in CrGN. Their results were presented at the 61st ERA Congress.

In CrGN, extensive glomerular parietal epithelial cells (PECs) multiply and form crescents that are progressively replaced by fibrosis. CLDN1 is a transmembrane protein involved in epithelial tight junctions that is highly expressed by glomerular PECs. CLDN1 can be exposed outside the tight junctions and mediate profibrotic pathways and extracellular matrix (ECM) remodeling. The monoclonal antibody lixudebart targets and blocks exposed CLDN1 in injured epithelial cells. The drug is the subject of a phase 2 clinical trial involving patients with antineutrophil cytoplasmic antibody-associated vasculitis (AAV) with rapidly progressive glomerulonephritis.

Delbet and fellow researchers used kidney multicolor immunofluorescence staining and spatial transcriptomics to analyze CLDN1 expression in the renal tissues of patients with CrGN. They then examined the association between CLDN1 expression and clinical end points (eGFR, proteinuria), disease biomarkers, and crescent progression. Finally, they developed a spatially resolved molecular roadmap from CLDN1-positive crescentic glomeruli and conducted proof-of-concept studies of an anti-CLDN1 monoclonal antibody in preclinical models of CrGN.

Immunofluorescence of 150 patients with AAV and IgAN showed upregulated CLDN1 expression by cellular and fibrocellular crescents. The extent of expression of both CLDN1 and CD44 at the surface of active PECs was associated with poor renal outcome (eGFR <30 ml/min) in AAV (median follow-up, 2.5 years) and IgAN patients (3.7 years). The researchers found an association between CLDN1-positive crescentic glomeruli and ECM genes.

In mice, treatment with anti-CLDN1 mAb reduced albuminuria, increased kidney function, and decreased fibrosis biomarkers in nephrotoxic serum-induced CrGN. In sum, the authors wrote, "Our results suggest a functional role of CLDN1 in the pathogenesis of CrGN, providing preclinical proof-of-concept for anti-CLDN1 antibodies as a novel therapeutic approach in patients with CrGN."

Source: Delbet J-D, Anquetil V, Saitoski K, et al. Novel therapeutic for crescentic glomerulonephritis through targeting CLDN1 in parietal epithelial cells. Abstract #2837. Presented at the 61st European Renal Association Congress; May 23-26, 2024; Stockholm, Sweden.

Machine Learning Classifier for Glomerulonephritis

In a proof-of-concept study presented at the 61st ERA Congress, **Anibal Pedraza** and others attempted to develop a machine learning classifier for 12 different classes of glomerulonephritis (GN) with convolutional neural networks and self-attention-based architectures.

Their dataset comprised 11,000 period acid-Schiff (PAS)-stained glomerular crops from 350 biopsies across four institutions. Each crop retained the diagnosis label from the 12 classes: (1) antibody-mediated GN; (2) anti-neutrophil cytoplasmic antibody; (3) C3-GN; (4) cryoglobulinemic GN (CryoGN); (5) dense deposit disease; (6) fibrillary; (7) infection-associated GN; (8) IgA GN; (9) membranoproliferative glomerulonephritis; (10) membranous; (11) proliferative GN with monoclonal immunoglobulin G deposits (PGNMID); and (12) systemic lupus erythematosus GN class IV. A 13th class, sclerotic, was created by stripping globally sclerotic glomerular crops from this diagnostic label.

Of the total dataset, 75% of samples were used for training, 15% for validation, and 10% for testing. A validation set comprising another 50 biopsies from an additional three centers yielded 2000 new crops. A classifier was trained and supervised for the 13 classes based on a collective of multiple transformer-based classification networks, including Swin-Transformer and ConvNext. Each network was trained under different circumstances, ensuring the system acquired a more global understanding versus relying on a sole method. To make the final decision, the system uses the prediction with the largest confidence threshold.

Metrics for classification performance were measured as precision, sensitivity, specificity, F1 score, and balanced accuracy. Balanced accuracy ranged from 0.4797 for CryoGN and 0.5949 for membranous. It was 0.6892 for the sclerotic class. Areas under the receiver operating characteristic curve were between 0.40 for PGNMID and 0.82 for membranous, and 0.81 for sclerotic.

Such complex classification generally requires immunostains, electron microscopy, and clinical data, but this study creates a baseline for classification. In sum, the authors wrote, "Our classification results even on single PAS glomerular crops appear promising. Combined with our automatic glomerular segmentation models, we could rapidly expand the training cohorts' sizes and even add more classes of GN."

Source: Pedraza A, Becker J, Altini N, et al. Machine learning glomerulonephritis diagnosis on single glomeruli. Abstract #3070. Presented at the 61st European Renal Association Congress; May 23-26, 2024; Stockholm, Sweden.

Nomogram to Predict Kidney Function Recovery After DI-AIN

Drug-induced acute interstitial nephritis (DI-AIN) is a common cause of AKI. The standard treatment is corticosteroid therapy (CS) and withdrawal of the problem-causing drug, but even with treatment, up to 50% of patients do not fully recover kidney function.

Fernando Caravaca-Fontán and other researchers conducted a retrospective, observational study to develop and validate a predictive nomogram to assess the probability of complete recovery (CR) of kidney function at 6 months after treatment for DI-AIN. Their findings were presented at the 61st ERA Congress.

The dataset was divided randomly into a training group (n=64) and a validation group (n=64). The team used least absolute shrinkage and selection operator (LASSO) regression to screen the main predictors of CR (serum creatinine value <25% of the last value before DI-AIN) and to build the nomogram. They assessed the nomogram's accuracy using discrimination and risk calibration in both sets.

The study included 224 patients with DI-AIN who were treated with CS between 1996 and 2023. Median age of participants was 70 years (interquartile range, 57-76 years); 115 patients (51%) were male. At 6 months after treatment with CS, 51 (31%) patients in the training group and 19 (32%) in the validation group achieved CR.

LASSO variables used to build the nomogram included age, gender, degree of interstitial fibrosis, and time to CS initiation. The area under the curve (AUC) of the nomogram was 0.809 (95% CI, 0.721-0.880), demonstrating good discrimination. The AUC after 1000 instances of bootstrap self-sampling for validation was 0.837 (95% CI, 0.705-0.931), indicating good predictive stability. Predicted outcomes aligned with observations, and decision curve and clinical impact curve analyses suggested clinical benefit.

Source: Caravaca-Fontán F, Praga M, Fernández-Juárez G. Development and validation of a nomogram for predicting complete kidney function recovery after drug-induced acute interstitial nephritis. Abstract #1347. Presented at the 61st European Renal Association Congress; May 23-26, 2024; Stockholm, Sweden.

Hemodialysis Frequency and Patient Survival

In a prospective, multicenter, nonrandomized trial, **Mabel Aoun** and other researchers studied patient survival with twice-weekly versus thrice-weekly hemodialysis. Their results were presented at the 61st ERA Congress.

The study included 203 patients from 10 dialysis units undergoing hemodialysis three times a week (n=133) or twice a week (n=70). Mean patient age was 67 ± 15 years; 54.2% were male; 55.5% had diabetes; 53.7% had coronary artery disease.

At the start of dialysis, median eGFR was 6 (4, 8) mL/min/1.73 m^2 for the thrice- and twice-weekly groups, and baseline median 24-hour diuresis was 500 (500, 1000) mL. The patients on twice-weekly hemodialysis had higher diuresis (P=.051). Mean hemoglobin at baseline was 9.6 ± 1.6 g/dL, and mean blood flow was 329 ± 76 mL/min. The median number of dialysis hours per week was 12 (10, 12) and 8 (8, 9) in the thrice- and twice-weekly groups, respectively. High-flux membranes with ultrapure dialysate were used in 55.0% of the thrice-weekly patients and 74.3% of the twice-weekly patients.

At 1 month, 3 months, and 6 months, residual diuresis was significantly higher in the twice-weekly arm versus the thrice-weekly arm. Serum potassium was significantly higher in the twice-weekly versus the thrice-weekly group at 3 months and 1 year. Interdialytic weight gain and blood pressure did not statistically differ between the groups at 1, 3, and 6 months and 1 year; 22.5% of patients in the thrice-weekly arm did not require antihypertensive medications at 6 months versus 12.1% in the twice-weekly arm. The cumulative dose of erythropoietin (EPO) given over 2 years was significantly higher in the twice-weekly group versus thrice-weekly (median 720,000 UI vs 500,000 UI; P=.001). There was no difference in hemoglobin, but ferritin was lower in the twice-weekly group (P=.005).

Although the twice-weekly timing was associated with higher EPO dose requirements, higher serum potassium levels, and more antihypertensive therapy, there was no difference in hospitalization rates between the two groups, nor did a Cox regression model show any survival difference between the two groups.

Source: Aoun M, Finianos S, Beaini C, et al. Twice against thrice-weekly hemodialysis: the TATH trial. Abstract #1809. Presented at the 61st European Renal Association Congress; May 23-26, 2024; Stockholm, Sweden.

Personalized Treatment Protocol for Membranous Nephropathy

Vesna Brglez and others reported on the efficacy of a personalized treatment protocol for membranous nephropathy (MN) versus the rituximab protocol established by the GEMRITUX study. They presented results at the 61st ERA Congress.

MN is a rare but serious autoimmune disease that affects kidney glomeruli. In 50% to 70% of cases, the major autoantigen is phospholipase A2 receptor 1 (PLA2R1) protein. In some cases, patients present antibodies against a single immunodominant cystine-rich domain, but in other instances they develop additional antibodies against C-type lectin domains (CTLDs) CTLD1, CTLD7, and/or CTLD8 of PLA2R1, defining a cascade immunization or epitope spreading. This epitope spreading can strengthen immune response to destroy a pathogen or may be associated with spurring autoantibody-mediated autoimmune pathologies.

An initial study by Brglez et al found that single domain recognition (nonspreader patients) is associated with higher odds for spontaneous remission of MN (45.00% vs 0.05% in GEMRITUX cohort) and a more positive response to treatment (100% of remission regardless of rituximab dose). Alternately, patients with multidomain recognition (spreader patients) of CTLD1 and/or CTLD7 domains have poorer prognoses, are less likely to achieve remission, and require a high dose of rituximab. Thus, the researchers proposed a more individualized protocol based on a patient's PLA2R1 epitope spreading status. The current study evaluated the efficacy of this treatment protocol versus the GEMRITUX protocol.

The researchers assigned 64 patients with PLA2R1-related MN from 12 French hospitals to either a control group that followed the GEMRITUX protocol (symptomatic treatment for 6 months, two infusions of rituximab 375 mg/m^2 at month 6 in case of persistent nephrotic syndrome [NS]) or a personalized treatment protocol group (PMMN). Patients without epitope spreading at 0 months were treated with the GEMRITUX protocol; those with epitope spreading at 0 or 6 months with ongoing NS received immediate treatment with infusions of rituximab 1 g. Age, gender, albumin, UPCR, anti-PLA2R1 titer, and the rate of PLA2R1 epitope spreading at baseline did not vary between the two groups. Three patients were omitted from the final analyses.

The primary outcome was rate of clinical remission at 12 months; secondary outcomes included complete and partial remission, immunological remission, serum creatinine, proteinuria, albuminuria, and PLA2R1 antibody titer. At 12 months, 34% of the GEMRITUX group and 69% of the PMMN group achieved partial remission (P=.0105; UPCR <3.5 g/g with a decrease greater than 50% from baseline), improved or normalized serum albumin, and increase of serum creatinine lower than 20%.

There was no difference in the remission rate of the GEMRITUX versus the PMMN group for nonspreader patients (38% vs 50%; P=.7107), but spreader patients were more likely to reach remission with the personalized protocol (36% vs 87%; P=.0078). The total clinical remission rate (UPCR <0.3 g/g and normal albumin) was nearly statistically significant for both the GEMRITUX and PMMN groups (0% vs 16%; P=.0538).

In conclusion, the study authors found that a personalized treatment protocol based on epitope spreading status was better at achieving remission at 12 months for patients with PLA2R1-related MN than standard GEMRITUX therapy. They recommend that patients with multiple domain recognition be treated immediately with high doses of rituximab to boost their odds of remission.

Source: Brglez V, Teisseyre M, Moranne O, et al. Protocol based on PLA2R1 epitope recognition is superior to standard protocol in achieving remission in PLA2R1-associated membranous nephropathy. Abstract #992. Presented at the 61st European Renal Association Congress; May 23-26, 2024; Stockholm, Sweden.

Risk Relapse Score for ANCA-Associated Vasculitis Treated With CYC

Although cyclophosphamide (CYC) is a cornerstone of induction therapy in antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV), the risk factors for relapse in patients undergoing CYC therapy are not well understood. **Gianmarco Lugli** and a team of researchers set out to develop a clinically useful tool to score robust predictors of relapse in these patients. Their results were presented at the 61st ERA Congress.

Study participants came from Ireland, Italy, and Spain; were aged >18 years; had a diagnosis of granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA), or eosinophilic granulomatosis with polyangiitis (EGPA); underwent induction treatment with intravenous (IV) or oral CYC; and had at least 12 months of follow-up.

The research team used a multivariate Cox analysis to develop the Relapse Evaluation and Cyclophosphamide Treatment (REACT) score, assigning each predictor a certain number of weighted points in proportion to its β regression coefficient.

The baseline assessment included clinical data, lab testing, and measurement of signs of GPA, MPA, and EGPA in each organ system. Relapse was defined as the presence of one or more new vasculitis manifestation after a remission of at least 3 months. Remission was defined as no disease activity regardless of glucocorticoid use. The Kaplan-Meier method was used to estimate time-to-remission and relapse-free survival probabilities.

There were 505 patients in the cohort; 223 (44.2%) had MPA, 217 (43.0%) had GPA, and 65 (12.9%) had EGPA. Of the total cohort, 183 (36.2%) patients experienced an AAV relapse. Multivariate Cox analysis found that independent risk factors for relapse included proteinase 3-ANCA HR, 1.30; 95% CI, 1.01-1.87), IV CYC (HR, 1.78; 95% CI, 1.31-2.41), CV involvement (HR, 1.82; 95% CI, 1.01-3.25), arthralgias/arthritis (HR, 1.46; 95% CI, 1.08-1.98), and the absence of rapidly progressive glomerulonephritis (HR, 1.37; 95% CI, 1.02-1.85).

For the creation of the REACT score, CV involvement and IV CYC each received two points, but otherwise each variable was assigned one point. Researchers identified three risk categories according to each patient's score: low risk of relapse (score zero or one), which comprised 138 (27%) patients; intermediate risk (score two or three), with 252 (49%) patients; and high risk (score four to seven), which included 115 (22%) patients. Kaplan-Meier analysis with paired comparisons between the risk groups found statistically significant differences in relapse probabilities among them.

The study authors concluded, "The REACT score can be employed at diagnosis to predict the risk of relapse in patients with AAV treated with [CYC] induction. Its value needs to be confirmed in external cohorts."

Source: Lugli G, Buscemi P, Calatroni M, et al. Development of a relapse risk score in patients with ANCA-associated vasculitis treated with cyclophosphamide induction. Abstract #1484. Presented at the 61st European Renal Association Congress; May 23-26, 2024; Stockholm, Sweden.

Interim Analysis Finds Atrasentan Reduces Proteinuria in IgA Nephropathy

Results of a prespecified interim analysis of the phase 3 ALIGN study of atrasentan led by **Hiddo Heerspink, PhD, PharmD,** and presented at the 61st ERA Congress found that the drug demonstrated a statistically significant 36.1% ($P<.0001$) proteinuria reduction compared with placebo and supportive care with a RAS inhibitor at 36 weeks in patients with IgAN.

The ALIGN study includes 340 patients with biopsy-proven IgAN with baseline total proteinuria ≥1 g/day despite optimized RAS inhibitor treatment. Participants were randomized to receive oral atrasentan (0.75 mg) once daily or placebo for approximately 2.5 years (132 weeks). Participants continue to receive a maximally tolerated and stable dose of a RAS inhibitor as supportive care (unless they cannot tolerate RAS inhibitor therapy). An additional group of 64 enrolled patients receiving a stable dose of sodium-glucose cotransporter 2 (SGLT2) inhibitor as background care for at least 12 weeks have also been enrolled. The primary end point is change in proteinuria as measured by 24-hour UPCR from baseline to 36 weeks.

ALIGN will continue in a blinded manner, and final results are expected in 2026. These results will include the secondary end point, which is change from baseline in eGFR at 136 weeks, and the exploratory SGLT2 cohort.

Atrasentan is an investigational oral endothelin A (ETA) receptor antagonist. Activation of the ETA receptor contributes to elevated proteinuria, which is associated with kidney damage, fibrosis, and loss of kidney function in IgAN. Atrasentan is currently in phase 3 development for IgAN and in early-stage development for other rare kidney diseases. Drug maker Novartis plans to submit atrasentan for US Food and Drug Administration approval during 2024.

Source: Heerspink HJL, Jardine M, Kohan D, et al. ALIGN phase 3 primary endpoint analysis: atrasentan shows significant reduction in proteinuria in patients with IgA nephropathy. Presented at the 61st European Renal Association Congress; May 23-26, 2024; Stockholm, Sweden.

Iptacopan Shows Significant Proteinuria Reduction in C3G

In research presented at the 61st ERA Congress, a team led by **David Kavanagh, MB ChB, PhD,** revealed that iptacopan with supportive care realized a 35.1% ($P=.0014$) reduction in proteinuria compared with placebo plus supportive care at 6 months. Iptacopan is an oral factor B inhibitor of the alternative complement pathway being investigated for use in adult patients with C3 glomerulopathy (C3G).

Results came from a 6-month double-blind period of the phase 3 APPEAR-C3G study, intended to evaluate the efficacy and safety of twice-daily oral iptacopan 200 mg in patients with C3G. During the double-blind period, adult patients were randomized 1:1 to receive iptacopan or placebo plus supportive care. The end point for the double-blind period was proteinuria reduction (as measured by 24-hour UPCR) from baseline at 6 months for iptacopan versus placebo.

There were other promising results from the double-blind period. The secondary end point of eGFR showed a numerical improvement of +2.2 mL/min/1.73 m^2 ($P=.1945$) over 6 months with iptacopan versus placebo. The study also found that the drug has a favorable safety profile.

"This is an exciting milestone for patients and the potential future management of C3G," Dr. Kavanagh stated.

The APPEAR-C3G study continues with a 6-month open-label period during which all patients receive iptacopan. APPEAR-C3G also includes a separate cohort of adolescent patients with C3G. The drug will be submitted to the US Food and Drug Administration for the adult C3G indication during the second half of 2024.

Source: Kavanagh D, Bomback A, Vivarelli M, et al. Efficacy and safety of iptacopan in patients with C3 glomerulopathy: results from the phase 3 APPEAR-C3G trial. Presented at the 61st European Renal Association Congress; May 23-26, 2024; Stockholm, Sweden.

Eligibility of Patients With CKD for Cardiovascular RCTs

Patients with CKD are ineligible for participation in many randomized, controlled trials (RCTs). In a pilot study presented at the 61st ERA Congress, **Julia Colombijn** and fellow researchers examined the eligibility of patients with CKD for five major cardiovascular RCTs and the reasons for ineligibility. The CREDENCE, DAPA-CKD, CIBIS II, CIBIS III, and AUGUSTUS studies were included.

The research team included patients from the Utrecht Patient Oriented Database (UPOD) with CKD, defined as eGFR 3 mg/mmol for >3 months. Eligibility criteria were extracted from the five RCTs and modeled on the patients from UPOD. A total of 9005 UPOD patients were included in the pilot study. Mean age was 65 ± 14 years, and 42% were female. Mean eGFR was 49 ± 17 mg/mmol; 1741 (19%) participants had a history of atherosclerotic cardiovascular disease, while 765 (8%) had a history of heart failure.

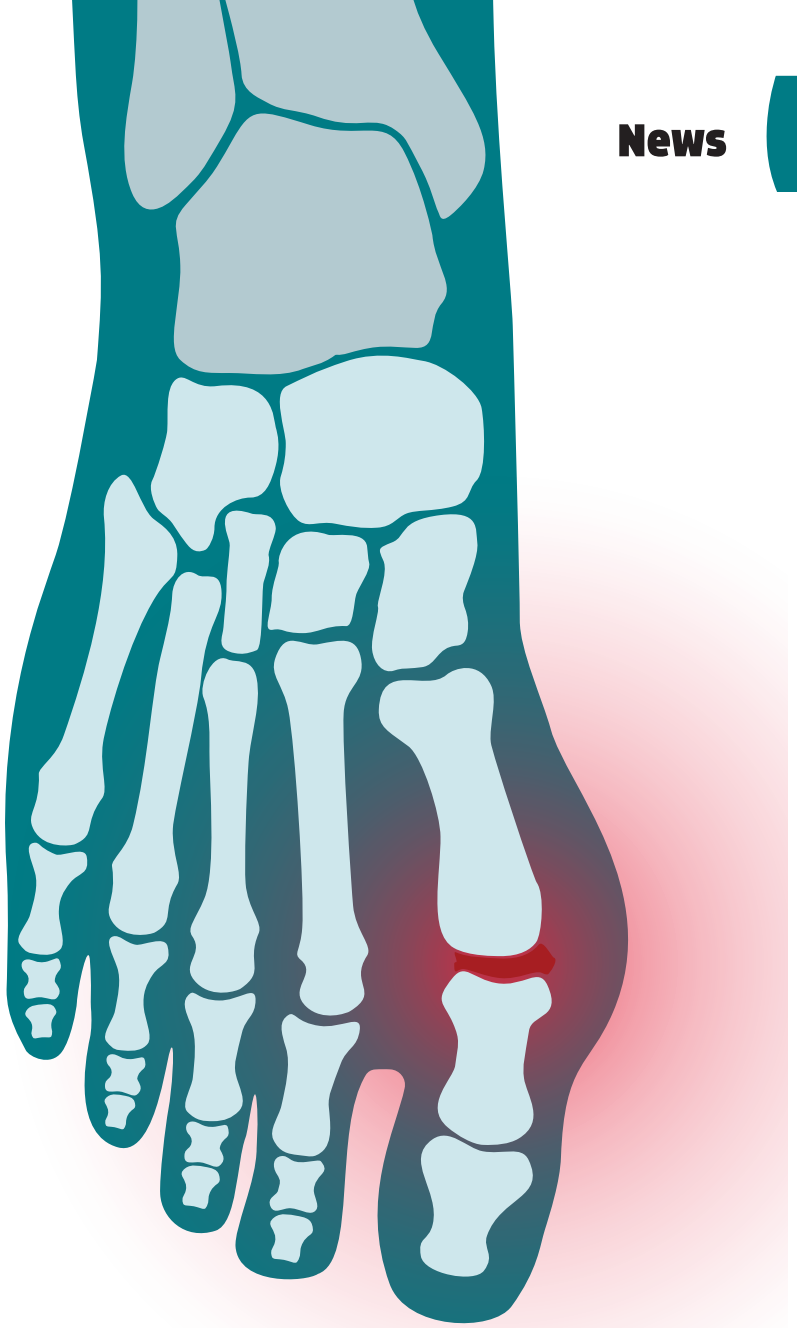
The researchers found that less than 3% of patients with CKD in routine clinical practice would be eligible to participate in cardiovascular RCTs. Just 0.05% of patients would be eligible for the DAPA-CKD trial and 0% for the CREDENCE trial. Of pilot study subjects with heart failure, 2% would have been eligible for CIBIS II and 3% for CIBIS III. Of those participants with coronary artery disease, 2% would have been eligible for AUGUSTUS.

Prevalent reasons for ineligibility included not meeting inclusion criteria for urine albumin-creatinine ratio, eGFR, or prescription of renin-angiotensin-aldosterone system inhibitors. For CIBIS II, other reasons for ineligibility included not fulfilling the inclusion criteria for left ventricular ejection fraction (LVEF; 50%) or prescription of an angiotensin-converting enzyme inhibitor (42%) or diuretic (33%). CIBIS III ineligibility was often due to not meeting the inclusion criteria for age (46%), LVEF (46%), or prescription of diuretics (31%). For AUGUSTUS, the primary reasons for ineligibility were not fulfilling the inclusion criteria of atrial fibrillation (79%) or percutaneous coronary interventions (91%). Not fulfilling certain exclusion criteria was also a major cause of ineligibility for each study.

The widespread exclusion of people with CKD from cardiovascular RCTs could limit such studies' generalizability for patients with CKD treated in a clinical setting. The pilot study authors wrote that, "to improve generalizability, RCTs in patients with CKD should aim to include more patients who reflect the patients with CKD treated in practice."

Source: Colombijn J, Huis in 't Veld L, Kusters M, et al. Generalisability of cardiovascular RCTs to patients with chronic kidney disease in clinical practice: a comparison between RCTs and real-world data. Abstract #615. Presented at the 61st European Renal Association Congress; May 23-26, 2024; Stockholm, Sweden.

ULT for CKD Patients With Asymptomatic Hyperuricemia



The worldwide prevalence of hyperuricemia and gout has grown. A cross-sectional survey of 3547 patients with chronic kidney disease (CKD) found the prevalence of hyperuricemia in patients with CKD stages 3, 4, and 5 in China to be 42.6%, 59.1%, and 61.2%, respectively. Hyperuricemia is associated with faster progression of CKD and an increased risk of poor renal prognosis and cardiovascular events in patients with CKD. It is also linked with a high risk of gout flare, which brings its own complications.

Results of studies on the effect of uric acid-lowering therapy (ULT) on renal and cardiovascular outcomes are controversial, and recommendations for ULT in CKD patients with asymptomatic hyperuricemia vary among different countries. Whether ULT should be used in CKD patients with asymptomatic hyperuricemia to prevent the progression of CKD remains uncertain. To provide clarity, **Yuxin Luo, MD,** and others embarked on a systematic review to examine the effects of ULT on renal outcomes in this patient population. Their results were published in *BMC Nephrology* [doi:10.1186/s12882-024-03491-4].

The research team conducted searches of PubMed, EMBASE, China National Knowledge Internet, and the Cochrane Library through January 2024 to find randomized, controlled trials (RCTs) assessing the effects of ULT, including febuxostat or allopurinol or other uric acid-lowering drugs versus a control group in patients with CKD. They included studies with: (1) adult CKD patients with hyperuricemia (serum uric acid [SUA] ≥7 mg/dl [420 µmol/L] in men or ≥6 mg/dl [360 µmol/L] in women) or at least mean baseline SUA ≥6 mg/dl (360 µmol/L) and no prior gout flares; (2) well-documented inclusion and exclusion criteria; (3) adequately documented dosage and duration of the intervention and control groups; (4) RCTs; and (5) changes in SUA, changes in serum creatinine (Scr), changes in estimated glomerular filtration rate (eGFR), acute kidney injury (AKI), or events of doubling of Scr without the requirement of dialysis used as outcome measures to assess the efficacy of agents for hyperuricemia in patients with CKD.

The initial searches generated 3400 studies; in total, 17 eligible studies with 2032 participants were included in the meta-analysis. Given the considerable heterogeneity in SUA level, only trials with SUA ≥7 mg/dl (420 µmol/L) in men or SUA ≥6 mg/dl (360 µmol/L) in women—or at least mean baseline SUA ≥6 mg/dl (360 µmol/L) with no prior gout flares—were included in the analysis.

Primary outcomes included the change in eGFR and Scr from baseline until the study's end. Compared with placebo or no treatment, the researchers found that use of ULT preserved the loss of eGFR (weighted mean difference [WMD] and 95% CI, 2.07 [0.15-3.98] mL/min/1.73 m^2) in the long-term subgroup. Meanwhile, the short-term subgroup also demonstrated that ULT preserved the loss of eGFR (WMD, 5.74 [2.09-9.39] mL/min/1.73 m^2). When compared with placebo or no treatment, ULT also reduced the increase in Scr in the short-term (WMD, −44.48 [−84.03 to −4.92] µmol/L) subgroup and long-term (WMD −46.13 [−65.64 to −26.62] µmol/L) subgroup.

> Researchers found that use of ULT preserved the loss of eGFR (weighted mean difference and 95% CI, 2.07 [0.15-3.98] mL/min/1.73 m^2) in the long-term subgroup.

Secondary outcomes included AKI and doubling of Scr without the requirement of dialysis (a deterioration of renal function, indicating an increase in Scr values exceeding 100% from baseline, without requiring dialysis). ULT was associated with a lower incidence of the events of doubling of Scr without dialysis (relative risk, 0.32 [0.21-0.49]; P<.001). However, there was no difference for lower incidence of AKI (P=.943).

The researchers acknowledged a few limitations of the study. They lacked some raw data on the standard deviation of GFR and Scr changes before and after ULT. In addition, the study is based on the analysis of existing clinical research data, and there is considerable heterogeneity between the various RCTs. The lack of a clear, unified definition for the starting level of uric acid reduction and target control may have affected study results. Finally, the team used Egger's regression test to assess the relationship between ULT and change in uric acid, which could have introduced publication bias from the included literature.

In summary, the authors wrote, "Our study suggests that [ULT] is beneficial in slowing CKD progression in patients with asymptomatic hyperuricemia, both in short-term and long-term follow-ups, and this is consistent across different races and different levels of baseline eGFR. Meanwhile, among patients aged less than 60 years, the protective impact of ULT on renal outcomes is notably enhanced. Nevertheless, it does not show a significant difference in the incidence of AKI. These findings underscore the importance of considering ULT in clinical strategies for CKD patients with asymptomatic hyperuricemia." ■

TAKEAWAY POINTS

- Asymptomatic hyperuricemia and gout play a key role in chronic kidney disease (CKD), but the effect of uric acid–lowering therapy (ULT) on outcomes of CKD patients with asymptomatic hyperuricemia is debated.
- Researchers sought to examine the influence of ULT on renal outcomes in patients with CKD. In a meta-analysis of 17 studies, they found ULT to be beneficial for slowing CKD progression, but it did not make a meaningful difference in the incidence of acute kidney injury.
- The study findings suggest that ULT should be considered in clinical strategies for CKD patients with asymptomatic hyperuricemia.

Can a CDS System Improve Hypertension Management With CKD?

Hypertension affects 60% to 90% of people with chronic kidney disease (CKD) and is a risk factor for adverse outcomes, such as kidney failure, cardiovascular events, and death. Therefore, lowering blood pressure (BP) is a key goal of published CKD treatment guidelines.

Primary care providers (PCPs) play an important role in identifying patients with CKD and addressing CKD risk factors, including hypertension. Unfortunately, research shows that PCPs are sometimes unaware of CKD management guidelines and have trouble implementing them. Computerized clinical decision support (CDS) systems are designed to assist by providing patient-specific information and evidence-based recommendations. However, CDS systems have demonstrated mixed results for CKD management.

CDS systems have shown decreased annualized loss of estimated glomerular filtration rate (eGFR), increased rates of diagnosis, increased urine albumin testing, and increased referral to nephrologists. However, they have not demonstrated a significant benefit for mitigating cardiovascular risk factors, including BP control. Incorporating principles of behavioral economics could help increase the effectiveness of CDS systems by addressing psychological factors that impact decision-making.

Lipika Samal, MD, MPH, and fellow researchers examined whether PCP use of an intervention, including a computerized CDS system based on behavioral economic principles and human-centered design, would result in a decrease in patients' systolic BP (SBP) compared with usual care. Their findings were published in *JAMA Internal Medicine* [doi:10.1001/jamainternmed.2023.8315].

This study took place within the Brigham and Women's Primary Care Practice-Based Research Network, and PCPs were the intervention's target. Using a matched-pair randomized design, researchers randomized one PCP in each pair to the intervention group and the other to the usual care group. The CDS system provided tailored, evidence-based recommendations to PCPs, including initiation or titration of renin-angiotensin-aldosterone system inhibitors. Patients in the control group received usual care from PCPs, with the CDS system functioning in silent mode.

All patients aged ≥18 years who visited a PCP at any of the intervention practices during the 2 years preceding the first visit during the study intervention period were eligible for the study. After the study started, each patient who had an office visit with a PCP and met criteria for CKD stage 3 or 4 (two prior eGFR measures of 16 to 59 mL/min/1.73 m^2 within the previous 2 years separated by 90 days or two prior urine albumin-to-creatinine ratio measures greater than 30 mg/g within the previous 2 years separated by 90 days) and uncontrolled hypertension (at least one ambulatory SBP measure greater than 140 mmHg within the 2 years preceding the visit at which the patient was assessed for study inclusion, plus an elevated SBP measure at the baseline visit) were included in the study.

A total of 174 PCPs and 2026 patients (mean [SD] age, 75.3 [0.3] years; 1223 [60.4%] female; mean [SD] SBP at baseline, 154.0 [14.3] mmHg) were selected for the study. Of those, 87 PCPs and 1029 patients were randomized to the intervention; 87 PCPs and 997 patients were randomized to usual care. In total, 1714 (84.6%) patients were treated for hypertension at baseline. There were 1623 (80.1%) patients with an SBP measurement at 180 days.

The primary outcome was change in mean SBP from baseline to 180 days in the CDS versus usual care group. Primary analysis was a repeated measures linear mixed model using SBP at baseline, 90 days, and 180 days in an intention-to-treat repeated measures model to account for missing data. Secondary outcomes included BP control and patient outcomes, including the percentage of patients who received an action supported by the CDS recommendations.

A statistically significant difference in mean SBP change was observed in the intervention group versus the usual care group (change, −14.6 [95% CI, −13.1 to −16.0] mmHg vs −11.7 [95% CI, −10.2 to −13.1] mmHg; P=.005). There was no difference in the proportion of patients who achieved BP control in the intervention group versus the control group (50.4% [95% CI, 46.5%-54.3%] vs 47.1% [95% CI, 43.3%-51.0%]). More patients in the intervention group received an action aligned with the CDS recommendations than those in the usual care group (49.9% [95% CI, 45.1%-54.8%] vs 34.6% [95% CI, 29.8%-39.4%]; P<.001).

> A statistically significant difference in mean systolic blood pressure change was observed in the intervention group versus the usual care group.

The authors acknowledged limitations of their study, including a small absolute effect size, unequal sex distribution and diastolic BP in study groups, possible falsely elevated BP measurements due to using first measurement, and possible imbalance among groups after four PCPs left their practices postrandomization. In addition, much of the decrease in SBP from baseline to 180 days could be related to regression to the mean. Finally, the effect in the intervention group could be attributed to the automated diagnosis of CKD and uncontrolled hypertension by the CDS system, rather than other features of the CDS.

In conclusion, the researchers wrote, "This randomized, clinical trial found that patients whose PCPs were randomized to a CDS intervention based on behavioral economics principles and human-centered design methods experienced a statistically significant decrease in SBP at 180 days compared with the decrease in SBP of patients whose PCPs were randomized to the usual care group. The CDS intervention group had a modest improvement in SBP, but no difference in the proportion achieving adequate control." The results suggest a CDS system could lead to better management of uncontrolled hypertension. ■

TAKEAWAY POINTS

- Researchers examined whether use of a computerized clinical decision support (CDS) intervention was associated with decreasing systolic blood pressure (SBP) for patients with chronic kidney disease (CKD) and uncontrolled hypertension.
- The randomized clinical trial included 184 randomized primary care practitioners and 2026 patients. Patients of clinicians who used the CDS system had significantly greater SBP change at 180 days compared with the usual care group.
- The results suggest that implementing such a computerized CDS system could help improve management of uncontrolled hypertension and possibly improve outcomes for patients with CKD at the population level.

Outcomes of Kidney Transplant When Deceased Donor Received Dialysis

Kidneys from deceased donors with acute kidney injury (AKI) are often discarded. Up to 44% of kidneys from deceased donors with stage 3 AKI are not transplanted. However, recent evidence suggests that transplanting kidneys from certain donors with AKI has a risk of graft failure comparable with kidneys from deceased donors without AKI. Research is lacking, as previous studies have not included deceased donors with the most severe AKI and those who received dialysis.

Researchers, including **Yumeng Wen, MD, PhD,** studied whether kidneys transplanted from deceased donors who received dialysis prior to donation were associated with worse outcomes in kidney recipients versus kidneys from deceased donors who did not have dialysis. Their findings were published in *JAMA* [doi:10.1001/jama.2024.8469].

Using data from the Organ Procurement and Transplantation Network, the researchers analyzed 1944 kidney transplant recipients. They identified 805 deceased donors aged 16 years or older from 2010 to 2018 who received dialysis prior to kidney donation. These were matched 1:1 with donors who did not undergo dialysis using a rank-based distance matrix algorithm. Of the 1944 transplant recipients studied, 954 received kidneys from deceased donors who had dialysis.

The short-term study outcome was delayed graft function (DGF; defined as receipt of dialysis by the kidney recipient within 1 week after kidney transplant). Longer-term outcomes were all-cause graft failure (a composite of death and graft failure), death-censored graft failure, death, estimated glomerular filtration rate (eGFR) at 6 months and 12 months post-transplant, and longitudinal decline in eGFR.

> Up to 44% of kidneys from deceased donors with stage 3 AKI are not transplanted.

Kidney transplants from donors who received dialysis prior to donation (n=954 kidney recipients) were associated with a higher risk of delayed graft function versus kidney transplants from donors who did not receive dialysis (n=990 kidney recipients; 59.2% vs 24.6%, respectively; adjusted odds ratio, 4.17 [95% CI, 3.28-5.29]).

However, at a longer-term follow-up (34.1 months), incidence rates did not significantly differ for all-cause graft failure (43.1 kidney transplants per 1000 person-years from donors who received dialysis prior to donation vs 46.9 kidney transplants per 1000 person-years from donors who did not receive dialysis; adjusted hazard ratio [HR], 0.90 [95% CI, 0.70-1.15]). Incidence rates at 34.1 months also did not differ significantly for death-censored graft failure (22.5 vs 20.6 per 1000 person-years, respectively; adjusted HR, 1.18 [95% CI, 0.83-1.69]) or death (24.6 vs 30.8 per 1000 person-years; adjusted HR, 0.76 [95% CI, 0.55-1.04]).

The authors acknowledged the limitations of their study. Because its design was retrospective, the study was subject to confounding and selection bias. The number of deceased donors who had dialysis was small, particularly among Black individuals. Demographic information on donors such as race, recipient comorbidities, and changes in immunosuppression over time was lacking.

In sum, the authors wrote, "Compared with receiving a kidney from a deceased donor who did not undergo dialysis, receiving a kidney from a deceased donor who underwent dialysis prior to kidney donation was associated with a significantly higher incidence of DGF, but no significant difference in graft failure or death at follow-up." ■

TAKEAWAY POINTS

- It was unknown whether kidneys from deceased donors who had dialysis were associated with adverse graft outcomes compared with kidneys from deceased donors who did not have dialysis.
- Researchers analyzed 1944 kidney transplant recipients, 954 of whom received kidneys from deceased donors who had dialysis. The incidence of delayed graft function was significantly higher when kidneys came from donors who had dialysis.
- At longer-term follow-up, however, graft failure and mortality did not differ significantly between transplant recipients whose donors had dialysis versus those who did not.

Safety of Nephrectomy in Older Living Kidney Donors

TAKEAWAY POINTS

- Living kidney donors (LKDs) aged ≥70 years have become more common, but the safety of nephrectomy in these older donors was unknown. Researchers studied outcomes of LKDs of this age after donor nephrectomy.
- The cohort of 1226 donors was grouped by age and compared by surgical outcomes, postoperative estimated glomerular filtration rate (eGFR) changes, end-stage renal disease (ESRD) rates, and mortality rates. None of the age groups had ESRD, and mortality was highest in the group aged 70 to 89 years.
- The results regarding surgical outcomes, eGFR changes, and ESRD rates support the safety of nephrectomy in LKDs aged ≥70 years. Although mortality rates are higher among those donors, this may be considered acceptable given their advanced age.

Due to a shortage of organs for transplantation, it has become more common for transplanted kidneys to come from donors aged ≥70 years. However, the safety of nephrectomy in these older donors has not been well studied. Often, studies of extended criteria donors focus on living kidney donors (LKDs) 55 to 65 years of age because fewer living donors aged 70 years or older exist. One study that focused on LKDs ≥70 years found that postdonor nephrectomy survival was better for this group than heavily matched controls, but it did not demonstrate the safety of nephrectomy.

To address this knowledge gap, **Takahisa Hiramitsu, MD, PhD,** et al examined outcomes of living kidney donors aged ≥70 years after donor nephrectomy. Their findings were published in *KI Reports* [doi:10.1016/j.ekir.2024.01.043].

Dr. Hiramitsu and colleagues enrolled 1226 LKDs and stratified them into age groups of 30 to 49 years (n=244), 50 to 69 years (n=803), and 70 to 89 years (n=179). For each group, respectively, 34.0% (83), 35.5% (285), and 44.7% (80) of participants were male. Researchers completed postoperative assessments at 1, 3, 6, and 12 months after transplantation, and annually thereafter. Follow-up was more frequent (every 1 to 3 months) if comorbidities were present.

The research team used the Kruskal-Wallis test for continuous variables and the chi-square test for categorical variables and confirmed normal distribution of estimated glomerular filtration rate (eGFR) data using histograms. They conducted a linear mixed model analysis to determine whether the LKD age groups affected eGFRs over time. Estimated marginal means and their standard errors and 95% CI were calculated and compared among the LKD groups at each time point. Researchers used the Benjamini-Hochberg method (a false discovery rate method) to adjust for multiple comparisons.

The reference standard for time was postoperative day (POD) 6, and the estimated mean and 95% CI of the difference (amount of change) relative to the eGFR on POD 6 were calculated and compared among age groups. Further analysis was performed using the same linear mixed model. For multivariate analysis, the research team developed a model with all variables (time, sex, and LKD age groups) using the forced entry method. They performed a survival analysis to determine whether LKD age groups influenced overall donor survival and determined the cumulative survival rate using the Kaplan-Meier method. $P<.05$ was considered significant in all analyses.

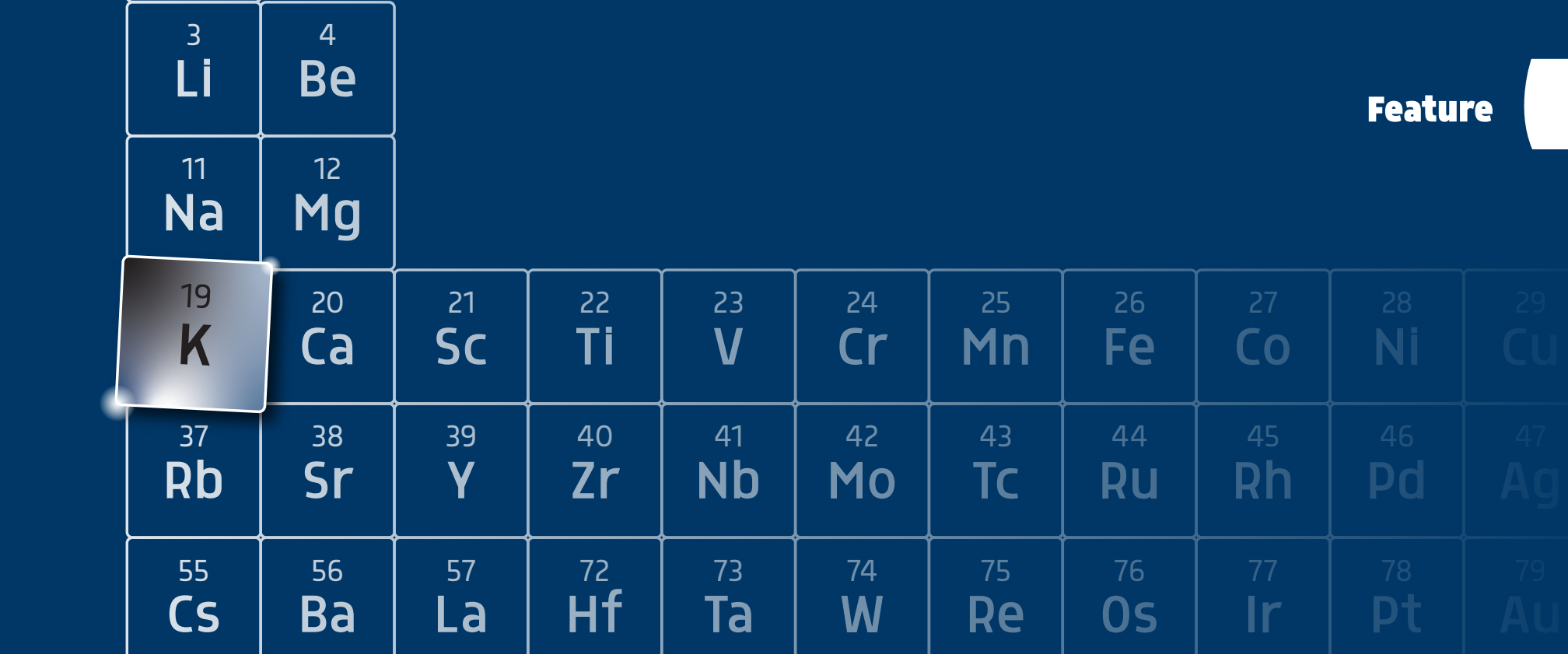
The research team compared surgical outcomes, postoperative eGFRs, end-stage renal disease (ESRD) incidences, and mortality rates among the different participant groups. Follow-up occurred from January 2008 through August 2022, with a median observation period of 73 months (interquartile range, 41-19 months).

Surgical outcomes, including graft quality and adverse events, were comparable among the three age groups. Among all three groups, eGFR changes were similar. The eGFRs of LKDs aged 30 to 49 and 70 to 89 years were the highest and lowest, respectively, among the three LKD age groups. The eGFR improved slightly for all groups after POD 6, but improvements were significantly lower in the group aged 70 to 89 years as indicated by the unadjusted (P=.009; estimate: −0.928; 95% CI, −1.624 to −0.231) and adjusted (P=.002; estimate: −1.074; 95% CI, −1.763 to −0.385) analyses. This group also had the highest mortality rate, although the authors noted that this may be considered acceptable given their advanced age. A total of 19 LKDs died of different causes. There was no ESRD observed in any group.

Limitations of the study include its retrospective nature, lack of comparison with a healthy population, and low incidence of events. These limitations warrant studies of a larger population with longer observation periods, according to the researchers.

Surgical outcomes, including graft quality and adverse events, were comparable among the three age groups. Among all three groups, eGFR changes were similar.

The study authors concluded that donor nephrectomy is safe for LKDs aged ≥70 years. "Despite the low eGFR changes and improvement after donor nephrectomy, LKDs aged 70 years or older can maintain their kidney function without ESRD," they wrote. "Regarding life expectancy, [living kidney donor transplants] involving LKDs aged 70 years or older are associated with favorable outcomes. The results of this study may aid in the discovery of optimal indications for preoperative eGFRs of LKDs and increase the number of eligible LKDs." ■



Association Between Hyperkalemia, Dietary Potassium With NDD-CKD

Hyperkalemia is a serious complication of chronic kidney disease (CKD) that is associated with an increased risk of cardiovascular events and all-cause mortality. Dietary restriction of potassium, including from fruits and vegetables, is a longstanding aspect of hyperkalemia management supported by clinical guidelines. However, recent research has begun to question such dietary recommendations, and evidence on the association between hyperkalemia and dietary potassium is inconsistent.

Nobuhisa Morimoto, PhD, and others decided to study the association between potassium intake from different food sources and hyperkalemia in patients with non–dialysis-dependent CKD (NDD-CKD). Their findings were published in the *Journal of Renal Nutrition* [doi:10.1053/j.jrn.2024.03.008].

Morimoto et al recruited 285 patients (median age, 72 years; 33% female) with NDD-CKD from three hospitals in Tokyo who were admitted between April 1, 2022, and March 31, 2023. CKD was defined as having an estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2, a history of nephrotic syndrome or glomerulonephritis that had been treated, or persistent proteinuria or hematuria for at least 3 months.

The researchers estimated patients' dietary potassium intake based on responses to a validated diet history questionnaire. Patients also answered questions about their lifestyle, including smoking, alcohol consumption, and bowel movements. Blood and urine samples were collected from most (>80%) patients within 1 month before or after they completed the questionnaire. Data on comorbidities, medical history, and medication use came from the three hospitals' electronic medical records.

The primary outcomes were serum potassium level (a continuous variable) and hyperkalemia, defined as serum potassium level ≥5.0 mEq/L. Patients with CKD stages 3b and 4 comprised approximately 60% of the study population. The median patient eGFR was 31.2 mL/min/1.73 m^2. The mean serum potassium level was 4.4 ± 0.5 mEq/L. Prevalence of hyperkalemia was 13.3%, and 14.0% of participants used potassium binders.

The research team used multivariable linear regression to examine associations of potassium intake from all foods and individual food groups with serum potassium among potassium binder nonusers. They used multivariable logistic regression to study the association between tertile groups of potassium intake and hyperkalemia.

Among the 245 potassium binder nonusers in the study, total potassium intake was only weakly associated with serum potassium (β=0.147; 95% CI, 0.018-0.277; *P*=.026). No association with hyperkalemia was observed (first vs third tertile: adjusted odds ratio [aOR], 0.98; 95% CI, 0.29-3.26). Looking at different food groups, potassium from pulses, potatoes, and green/yellow vegetables had a positive association with serum potassium (β=0.847; 95% CI, 0.159-1.535; *P*=.016; β=0.574; 95% CI, 0.102-1.046; *P*=.017; and β=0.358; 95% CI, 0.012-0.704; *P*=.042, respectively).

Total potassium intake was not associated with hyperkalemia (first vs third tertile: aOR, 0.98; 95% CI, 0.29-3.26; *P*=.975). Only potassium from potatoes was associated with hyperkalemia; patients in the highest tertile of potassium intake from potatoes had higher odds of hyperkalemia versus those in the lowest tertile (aOR, 4.12; 95% CI, 1.19-14.34; *P*=.026). Furthermore, only potassium intake from potatoes remained associated with serum potassium levels among patients with more advanced CKD (eGFR <30 mL/min/1.73 m^2).

The authors acknowledged some limitations of their study. Its observational nature did not allow for examination of a causal relationship between dietary potassium intake and serum potassium level or the effects of unmeasured or residual confounders. There was a risk of misreporting, recall bias, and selection bias. Results may not be directly extrapolated to the overall CKD population in Japan and may not be generalizable to patients with CKD in non-Japanese populations.

In conclusion, the researchers observed associations between higher potassium intake from potatoes, pulses, and green/yellow vegetables and greater serum potassium levels. However, only the potassium intake from potatoes remained associated with serum potassium levels among patients with more advanced CKD, and only potassium intake from potatoes had an association with hyperkalemia.

"These findings suggest the possibility that replacing potatoes, which have high potassium bioavailability, with other types of vegetables with lower potassium bioavailability may decrease serum potassium levels while maintaining dietary fiber intake that may confer cardiovascular benefits," they wrote. ■

TAKEAWAY POINTS

- Recent research has started to question clinical guidelines favoring dietary restriction of potassium for hyperkalemia management with chronic kidney disease (CKD).
- Researchers found that, in patients with non-dialysis-dependent CKD, potassium intake was weakly associated with serum potassium and not associated with hyperkalemia. Potassium intake from potatoes was associated with hyperkalemia.
- It is important to consider the food source of potassium when managing hyperkalemia in CKD.

Conference Coverage

Philadelphia, Pennsylvania | June 1-5, 2024

AMERICAN TRANSPLANT CONGRESS

The American Transplant Congress (ATC) is the joint annual meeting of the American Society of Transplant Surgeons and the American Society of Transplantation. The Congress provides a forum for the exchange of new scientific and clinical information related to solid organ and tissue transplantation. Presentations and posters provide information on advances in research and care to transplant physicians, scientists, nurses, organ procurement professionals, pharmacists, and other transplant professionals. The American Transplant Congress was held June 1-5 in Philadelphia, Pennsylvania, providing a showcase for the latest research and advances made by the transplant community in the past year.

Xenothymokidney Maintained for 2 Months in Brain-Dead Decedent

Jeffrey Stern, MD, discussed the case of a brain-dead decedent in whom an alpha-gal knockout porcine kidney with thymus autograft (alpha Gal-KO xenothymokidney) was maintained for 2 months. The presentation won the People's Choice Award for most impactful plenary abstract at ATC 2024.

The brain-dead decedent had bilateral native nephrectomies and transplantation of a Gal-KO xenothymokidney utilizing a clinically approved immunosuppression regimen. Researchers measured the decedent's urine output (UOP), serum creatinine (sCr), 6-hour urine creatinine clearance (6CrCl), and 24-hour urine creatinine clearance throughout the 2-month period. They performed protocol and for-cause biopsies on days 10, 14, 21, 28, 33, 45, 49, 56, and 61.

UOP was healthy upon xenothymokidney implantation, at 4.76 L/day (range 1.1-19.8 L/day). The decedent's sCr reached its lowest point of 0.32 mg/dL on day 13, corresponding with a 6CrCl of 156 mL/min. The day 10, 14, 21, and 28 biopsies found no evidence of rejection. However, sCr rose to a peak of 0.7 mg/dL (6CrCl of 65.6 mL/min) between days 29 and 33, and the day 33 biopsy identified antibody-mediated rejection (AMR).

The decedent subsequently received plasmapheresis, high-dose corticosteroids, rabbit antithymocyte globulin, and pegcetacoplan. After this treatment regimen, sCr and CrCl improved to 0.18 mg/dL and 111.9 mL/min, respectively. Biopsy showed that microvascular injuries were resolved, and renal scintigraphy measured the final glomerular filtration rate as 150 mL/min.

In sum, the Gal-KO xenothymokidney functioned in the brain-dead decedent for 2 months and AMR was treated successfully.

Source: Stern JM, Kim J, Tatapudi V, et al. Normal function and successful treatment of rejection in a xenothymokidney maintained for 2 months in a brain-dead decedent. Abstract #245. Presented at the American Transplant Congress 2024; June 1-5, 2024; Philadelphia, Pennsylvania.

Changes in SARS-CoV2-Specific T-Cell Responses After Kidney Transplant

A small study of 13 patients evaluated SARS-CoV2-specific T-cell immune responses in kidney transplant recipients pre- and post-transplantation. The aim was to understand the dynamic association between donor characteristics, induction immunosuppression, and recipient features in the post-transplant period. Results of the study by **Ambreen Azhar, MD, MS,** and others were presented during ATC 2024.

Three patients were SARS-CoV2 positive and 10 were SARS-CoV2 negative; all were deceased donor kidney transplant recipients. No participants received vaccines during the study period. All participants demonstrated SARS-CoV-2 T-cell immunity during the pretransplantation period.

Post-transplant, three (24%) patients had a loss of immunity. Of these, one received increased immunosuppression due to antibody-mediated rejection; one with pretransplant oncologic chemotherapy exposure had post-transplant failure to thrive; and one with pretransplant biologic exposure from ulcerative colitis had a protracted hospital stay with other infections. One asymptomatic patient who was transplanted in the presence of a positive SARS-CoV-2 nasopharyngeal swab had positive CD8 status at 4 weeks post-transplant. One unvaccinated patient maintained a CD4 immune response despite receiving post-transplant desensitization with plasmapheresis and intravenous immunoglobulins.

In sum, the authors concluded that SARS-CoV2 T-cell responses are largely preserved despite T-cell depletion induction. "Augmented immunosuppression due to rejection and other medical histories may compromise responses and should be considered as factors to target patients for future available prophylactic therapies or augmented vaccination," they wrote.

Source: Azhar A, Kleiboeker S, Saeed M, et al. Dynamic changes in SARS-CoV2-specific T cell immune response post kidney transplant. Abstract #B054. Presented at the American Transplant Congress 2024; June 1-5, 2024; Philadelphia, Pennsylvania.

Decision Tree to Determine Impact of Pathology on Kidney Discard Determinations

Kathryn Sarullo, PhD, and others developed a decision tree to determine the impact of histopathology in kidney discard determinations. They presented results at ATC 2024.

The researchers posited that healthy donor kidneys are being discarded due to inaccurate biopsy interpretation. Machine learning can aid in improving the accuracy of histopathologic examination, potentially lowering the rate of discarded kidneys.

The team trained a decision tree on histopathologic data, evaluating 2681 kidney biopsy referrals between 2015 and 2020 (n=5168 slides). At the start, the classes were unbalanced (keep, n=4339; discard, n=829); discard data were duplicated until the classes were balanced (keep, n=4339; discard, n=4145).

Pathology findings informing decisions to discard included global glomerulosclerosis above 20%, interstitial fibrosis, arteriosclerosis, necrosis, and fibrin thrombi. The decision tree found that the number of additional criteria met was more important than global glomerulosclerosis. If one or more criteria were met, the kidney was categorized as discarded. If no criteria were met, any biopsy with global glomerulosclerosis above 5.1% was categorized as discarded. Of the kidney biopsies labeled for discard, 55% (n=455) did not demonstrate significant histopathologic findings.

Large decision trees have higher accuracy and a higher F1 score (harmonic mean of precision and recall) than histopathology alone. Including histopathologic criteria in addition to global glomerulosclerosis increases the F1 score significantly.

The researchers concluded that, "Although all histologic data is used in the discard decision, there are other unknown factors leading to organ discard. Future studies are warranted to determine the nature of other discard factors and their rationale, especially in cases where kidneys appear transplantable by histology."

Source: Sarullo K, Gaut JP, Swamidass J. Does pathology impact decisions to discard or keep donor kidneys? Abstract #C150. Presented at the American Transplant Congress 2024; June 1-5, 2024; Philadelphia, Pennsylvania.

Gut Permeability, Transplant Recipient Immunity, and Acute Rejection

Fernando Yuen Chang, MB ChB, BSc, and others examined the relationship between gut microbiota and recipient immunity in kidney transplantation. Their findings were presented at ATC 2024.

The researchers hypothesized that increased gut permeability and reduced availability of bacterial-derived metabolites associated with immunoregulation promotes a less tolerogenic environment and increases the risk of acute rejection (AR) of the kidney. Their longitudinal study included 92 transplant recipients and 23 live donors. Blood, urine, and stool samples were collected at baseline and up to 12 months post-transplant.

They assessed regulatory B cells by using flow cytometry and gut permeability by measuring plasma intestinal fatty acid binding protein (I-FABP). They used 16S rRNA sequencing of fecal metagenome isolated from stool samples to assess the diversity, composition, and abundance of gut bacteria. Finally, they used mass spectroscopy to identify fecal short-chain fatty acids and indole derivatives.

Transplant recipients with biopsy-proven AR showed increased I-FABP before transplantation and decreased indole derivatives despite an increase in tryptophan availability post-transplantation. In AR, there was a decrease in IL-10:tumor necrosis factor ratio in CD19+ B cells, especially within the transitional B-cell compartment (CD45+CD19+CD24hiCD38hiIL10+), at 3 months (0.140 ± 0.107 vs 0.080 ± 0.040; $P<.05$) and 6 months (0.11 ± 0.05 vs 0.07 ± 0.05; $P<.05$) versus those who did not experience AR. There was an increased frequency of regulatory B cells in nonrejectors after transplantation compared with baseline (2.66% ± 1.86% vs 4.62% ± 1.99%; $P=.01$) and at 6 months compared with rejectors (2.96% ± 1.69% vs 1.75% ± 1.25%; $P<.05$).

In conclusion, the researchers found that increased gut permeability and reduced immunoregulatory metabolites are associated with a reduction in IL-10+ regulatory B cells, making AR more likely to occur.

Source: Yuen Chang F, Vaitkute A, Attrill M, et al. Altered intestinal barrier and immunoregulatory gut-derived metabolites contribute to acute rejection in renal transplantation. Abstract #547. Presented at the American Transplant Congress 2024; June 1-5, 2024; Philadelphia, Pennsylvania.

Eplet-Based Matching and Disparities in Kidney Transplant Access

Prevention of eplet mismatches (EpMM) is associated with better long-term kidney transplant outcomes. Researchers led by **Ross Doyle, MB BCh, BAO, PhD,** investigated whether eplet-based matching could lead to disparities in deceased donor (DD) kidney transplantation access. Their results were presented at ATC 2024.

The researchers conducted a retrospective analysis of consecutive DD allocation sequence runs over 3 months. The patients studied were waitlisted transplant candidates from different ethnic groups in British Columbia. Only those who were blood-group-compatible and had a negative virtual crossmatch could appear on the allocation sequence and be considered for a kidney offer.

The team used high-resolution human leukocyte antigen (HLA) genotypes of donors and recipients to perform eplet mismatch analysis. EpMM was calculated based on the single molecule eplet mismatch load at HLA-DR (DR) and HLA-DQ (DQ), with DR <7 and DQ <9 being low risk. The researchers calculated the proportion of organ offers with low EpMM among ABO- and HLA-compatible active waitlisted candidates.

There were 51 DD and 260 active waitlisted candidates during the study period. A low EpMM donor offer for both donor kidneys could be accomplished for 57% of DDs. Within each allocation run, a median of 14% (interquartile range, 8%-21%) of candidates had a low EpMM kidney offer, while 56% of waitlisted candidates never matched with a low EpMM kidney after 51 allocation runs over the study period. Among White candidates, 52% had no low EpMM offers, 27% had one low EpMM offer, and 21% had several low EpMM kidney offers. These percentages were similar among other ethnic groups ($X^2=6.5$; $P=.77$).

"Analysis of actual allocation sequence runs in a single multiethnic transplant center showed that kidney allocation based on eplet matching appeared to be possible for the majority of deceased donors without exacerbating disparities in access to transplantation," the authors concluded.

Source: Doyle R, Tran J, Hendren E, et al. The impact of eplet based kidney allocation on access to transplant among candidates of different ethnicity: a real world assessment. Abstract #346. Presented at the American Transplant Congress 2024; June 1-5, 2024; Philadelphia, Pennsylvania.

Post-Acute Sequelae of SARS-CoV-2 Infection in Transplant Recipients

A group of researchers, including **Leela Morená, MD,** investigated the prevalence of post-acute sequelae of SARS-CoV-2 infection (PASC) in solid organ transplant recipients (SOTRs) infected during the Omicron phase and the associations between clinical characteristics and the development of PASC symptoms. They presented their findings at ATC 2024.

The cross-sectional study followed patients who had a COVID-19 infection during the Omicron period (December 28, 2021, to November 4, 2022) and surveyed them from September 29, 2023, to December 1, 2023. The survey used a PASC score that included 13 symptoms experienced for ≥30 days. Patients were categorized as having PASC if they scored ≥12.

Of 299 SOTRs invited to take the survey, 93 completed it. Their mean age was 58 years (±13) and 43% were female. The most common type of transplantation was kidney (44%), and median time since transplantation was 4.1 years (interquartile range, 2.1-7.7). There were 46 SOTRs (49%) who reported having ≥1 PASC symptom for ≥30 days. Those who experienced symptoms had an average of 3 symptoms at 2 months postinfection. This number decreased to 1.6 symptoms at 12 months postinfection.

According to the scoring method used, 13 (14%) SOTRs met the definition of PASC. Multivariable analysis found that female sex (adjusted odds ratio [aOR], 0.32; 95% CI, 0.12-0.83), years since transplantation (aOR, 0.90 per additional year; 95% CI, 0.81-0.99), and tixagevimab-cilgavimab preexposure prophylaxis (aOR, 0.33; 95% CI, 0.12-0.84) were associated with significantly lower odds for developing ≥1 PASC symptom.

The authors concluded that PASC symptoms were common in SOTRs during the Omicron period, but patients with female sex, longer time since transplantation, and use of tixagevimab-cilgavimab had lower chances of developing PASC symptoms. "New prevention and treatment strategies for SARS-CoV-2 infection should also evaluate PASC symptoms as outcomes," they wrote.

Source: Morená L, Al Jurdi A, El Mouhayyar C, et al. Post-COVID sequelae among solid organ transplant recipients: insights from the Omicron period. Abstract #A017. Presented at the American Transplant Congress 2024; June 1-5, 2024; Philadelphia, Pennsylvania.

Utility of an AI Model in Predicting Risk of Kidney Allograft Rejection

The discrimination performance of AlloView, an artificial intelligence (AI) model to predict kidney transplant rejection (KTR) risk, has been validated in a large cohort. However, there are few data describing a reference range or threshold to guide clinicians in using AlloView data when deciding whether to perform biopsy.

A group of researchers, including **S.V. Shah, MD,** compared AlloView results by histological diagnosis. They presented results at ATC 2024. In their primary analysis, the researchers compared median AlloView results stratified by histological diagnosis: acute cellular rejection (ACR), acute antibody-mediated rejection (AMR), borderline rejection, and no rejection or acute tubular injury/necrosis (no rejection). They used nonparametric tests to analyze categorical and numerical variables. Their analysis included KTR occurring between January 1, 2017, and December 31, 2020, with initial donor-derived cell-free DNA (dd-cfDNA) result within 90 days of transplant, at least one biopsy, and a dd-cfDNA result ≤30 days before biopsy.

In sum, 41 AlloView results from 41 KTRs met the criteria for analysis. There were three biopsies with ACR, eight AMR events, seven borderline rejections, and 23 no rejection or acute tubular necrosis episodes. There were no significant differences in most baseline characteristics among different groups.

The median AlloView score was significantly higher in the ACR (62.9%; interquartile range [IQR], 51.1%-65.7%) and AMR (62.6%; IQR, 50.6%-76.4%) groups versus the no rejection group (15.5%; IQR, 9.3%-24.6%; P=.0273 and P=.0006, respectively). Borderline rejection had a median AlloView score of 28.9% (IQR, 20.4%-54.7%), statistically similar to the no rejection group (P=.0418).

The study authors concluded, "The significant differences seen highlight the utility of AlloView in discriminating patients' individual risk of rejection. With further validation, these references may support interpretation of the model."

Source: Shah SV, Voora S, Hanson, PJ, et al. Utilization of artificial intelligence (AI) in predicting the risk of kidney allograft rejection. Abstract #D148. Presented at the American Transplant Congress 2024; June 1-5, 2024; Philadelphia, Pennsylvania.

Immune Tolerance With MDR-101 in Transplant Recipients

D.B. Kaufman, MD, PhD, FACS, and others studied recipients of HLA-matched living donor (LD) kidney transplants who received an investigational cellular product (MDR-101) to produce immune tolerance, allowing stoppage of immunosuppression (IS) for 2 years compared with standard of care. They reported results at ATC 2024.

Participants comprised adult recipients of a first kidney from an HLA-matched related LD who were randomized 2:1 to a treatment arm (TA, n=20) or control arm (CA, n=10). Patients in the CA arm received IS per standard of care. Patients in the TA arm were transplanted at day (D) 0 and received (rabbit) antithymocyte globulin D0-4 and low-dose total lymphoid irradiation to induce chimerism after MDR-101 infusion on D11. IS was given throughout 1 year and then discontinued. Steroids were withdrawn by D10, and mycophenolate mofetil was given D11-D39. Tacrolimus began on D11, and monotherapy continued from D40 until D180 and then gradually was withdrawn 1 year after transplant if mixed chimerism was ≥5% and there was no biopsy-proven acute rejection, graft-versus-host disease (GVHD), or kidney loss.

Nineteen (95%) TA patients discontinued all IS 1 year post-transplant; 16 (84%) were IS-free after 2 years; three resumed IS after temporary withdrawal. There was no graft loss, death, GVHD, post-transplant lymphoproliferative disorder, or other cancers. There was no significant difference in estimated glomerular filtration rate between groups.

In conclusion, the authors wrote, "MDR-101 safely achieved donor mixed chimerism and functional immune tolerance with complete elimination of all IS with no death, graft loss, or GVHD in HLA-matched LD kidney transplant recipients with improved quality of life."

Source: Kaufman DB, Stegall M, Akkina S, et al. MDR-101-MLK-operational immune tolerance achieved in living related HLA-matched kidney transplant recipients. Abstract #627. Presented at the American Transplant Congress 2024; June 1-5, 2024; Philadelphia, Pennsylvania.

ATC 2024 Award Recipients

The ATC announced its award winners in transplantation research and achievements on behalf of the American Society of Transplantation (AST), American Society of Transplant Surgeons (ASTS), and *American Journal of Transplantation* (*AJT*). In each of the respective achievement awards, grant programs, and article awards, ATC 2024 recognized transplantation experts, students, and scholars for their impact on the field, as well as their influential and promising research to continue advancing innovation in transplantation.

AST Lifetime Achievement Award

Allan Kirk, MD, PhD, FACS

AST Achievement Awards

Transplant Advocacy Award: **Valen Keefer**

Advancing Advocacy in Organ Transplantation Award: **Belinda Paganafanador, BSN, MBA, MS, MS, BS**

Mentoring Award: **Peter Heeger, MD**

Physician of Distinction Award: **Lara Danziger-Isakov, MD, MPH**

Senior Achievement in Clinical Transplantation Award: **Michael Ison, MD, MS**

Basic Science Established Investigator Award: **Daniel Kreisel, MD, PhD**

Basic Science Investigator Award: **Jamil Azzi, MD, PhD,** and **Leonardo Riella, MD, PhD**

Basic Career Science Development Award: **Thiago Borges, PhD**

Clinical Science Established Investigator Award: **Jennifer Lai, MD, MBA**

Distinguished Senior Career Award: **Lisa Potter, PharmD, BCTXP, BCPS, FCCP, FAST,** and **Joelle Nelson, PharmD, BCPS, BCTXP, FAST**

Distinguished Early Career Award: **Kayla Joyal, PharmD**

ASTS Pioneer Award

Igal Kam, MD

AST Grant Recipients

Advanced Transplant Provider Research Grant (ASTS Foundation): **Maya Clark-Cutaia, PhD, ACNP-BC,** and **Lisa Coscia, RN, BSN, CCTC, FAST**

Collaborative Scientist Grant (ASTS Foundation): **Joel Adler, MD, MPH**

Faculty Development Grant (ASTS Foundation): **Steven Kim, MD**

Jon Fryer Resident Scientist Scholarship (ASTS Foundation): **Imad Aljabban, MD**

Presidential Student Mentor Grant (ASTS Foundation): **Chris Seung**

Presidential Student Mentor Grant (Member Funded): **Tran Ngo, Julia Bruner, Pranay Singh, Brendan Lohmar, Alexander Nguyen, Joshua Kettelkamp,** and **Zachary Kaplan**

Ronald and JoAnn Busuttil Surgeon Scientist Scholarship (ASTS Foundation): **Jonathan Merola, MD, PhD**

Gift of Life Socio Economic and Racial Disparity Grant: **Pedro Rodrigo Sandoval, MD**

Takeda Socio Economic and Racial Disparity Grant: **Nassir Thalji, PhD**

TransMedics Faculty Perfusion Grant: **Blayne Sayed, MD, PhD**

Veloxis Advanced Transplant Provider Research Grant: **Elaina Weldon, MSN, ACNP-BC**

Veloxis Fellowship in Transplantation Grant: **Davide Cina, MD, PhD**

AJT Outstanding Article Awards

Basic Science: **Maria-Luisa Alegre, MD, PhD,** "Microbiota-dependent and -independent effects of obesity on transplant rejection and hyperglycemia"

Translational Science: **David A. Hildeman** and **E. Steve Woodle, MD,** "Effects of in vivo CXCR4 blockade and proteasome inhibition on bone marrow plasma cells in HLA sensitized kidney transplant candidates"

Clinical Research: **Joel T. Adler, MD, MPH,** "Increased volume of organ offers and decreased efficiency of kidney placement under circle-based kidney allocation"

ACHC Announces Long-Term Care Dialysis Certification

Accreditation Commission for Health Care, Inc. (ACHC) will offer a new Long-Term Care Dialysis Certification that will be available to all providers, regardless of accreditor. The certification focuses on understanding individual residents' unique needs for dialysis treatment; infection control before, during, and after treatment; and education and training for both dialysis and long-term care staff members relating to the delivery of quality care.

In 2017, the Centers for Medicare & Medicaid Services (CMS) acknowledged the benefits of dialysis performed in a long-term care or other skilled nursing facility when that is the patient's place of residence. Guidance from CMS introduced in 2018 and revised in 2023 permits hemodialysis in nursing homes, allowing facilities that are contracted with an end-stage renal dialysis provider to offer dialysis services to residents.

"ACHC's Long-Term Care Dialysis Certification incorporates the existing requirements for home dialysis care with additional standards that recognize the higher acuity level of dialysis patients living in long-term care or skilled nursing facilities," said **Teresa Hoosier,** associate clinical director for renal dialysis accreditation at ACHC. "Our dual focus on continuous improvement in clinical outcomes and efficient operational practices supports the need for effective treatment plans for these patients through collaboration between the dialysis provider and the facility staff."

Susan Quaggin Wins ASN's John P. Peters Award

The American Society of Nephrology (ASN) has selected **Susan Quaggin, MD,** as this year's recipient of the John P. Peters Award. Named for a founder of the field of nephrology, the award recognizes individuals who have made substantial research contributions to nephrology and have sustained achievements in one or more areas of academic medicine, including clinical care, education, and leadership.

Dr. Quaggin is the Irving S. Cutter Professor of Medicine, Department of Medicine chair, and director of the Feinberg Cardiovascular and Renal Research Institute at Northwestern Medicine in Chicago, Illinois. She is the immediate past president of ASN, a councilor of the American Society for Clinical Investigation and the Association of American Physicians, an American Heart Association distinguished scientist, and a member of the National Academy of Medicine, National Academy of Inventors, and American Academy of Arts and Sciences. In addition, she serves as the deputy editor of *The Journal of Clinical Investigation,* co-editor of *Seldin and Geibisch's: The Kidney,* and co-editor of the pathophysiology section of *Current Opinion in Nephrology and Hypertension Renal Physiology.*

Dr. Quaggin's extensive body of research focuses on kidney and vascular health. Her work has led to connections between growth factor inhibition and thrombotic microangiopathy and kidney failure; inspired new protocols for renal assessments and led to new insight into preeclampsia; and improved treatments for patients at high risk of cardiovascular mortality due to kidney disease.

Congressional Kidney Caucus, Kidney Groups Want Kidney Disease Screening Recommendations

The Congressional Kidney Caucus and four kidney patient and professional organizations called on the Agency for Healthcare Research and Quality and the US Preventive Services Task Force (USPSTF) to develop federal screening recommendations for chronic kidney disease (CKD). They submitted the request in a letter cosigned by 44 members of Congress.

The four organizations signing on to the letter are the ASN, American Association of Kidney Patients, American Kidney Fund (AKF), and National Kidney Foundation (NKF). In December, those groups participated in a bipartisan briefing in collaboration with the Congressional Kidney Caucus on creating equitable kidney care and removing barriers to screening, diagnosis, and treatment.

There are currently no federal screening guidelines in place even though kidney disease affects 37 million Americans. As many as 90% of people who have CKD are unaware of it, according to AKF president **LaVarne Burton.**

"Early identification of kidney disease could slow the progression to kidney failure and the need for dialysis,"

Print-only Content

said **Sylvia Rosas, MD, MSCE,** president of NKF.

The letter pointed to a crucial need to ensure that the methodical approach adopted by USPSTF does not inadvertently restrict access to essential screening for vulnerable populations and worsen disparities in timely kidney care. USPSTF's framework should recognize diseases like diabetes and hypertension as independent risk factors of CKD, allowing for a more inclusive and effective screening strategy, the letter stated.

House Energy and Commerce Committee Passes Honor Our Living Donors Act

The US House of Representatives Energy and Commerce Committee unanimously passed the Honor Our Living Donors Act (HR 6020). If enacted, the legislation will ensure that only the income of a living donor can be considered when determining eligibility for federal financial assistance provided to living donors.

The ASN praised the advancement of the act and reiterated its support of policies to make living donations financially neutral.

The federal government provides limited financial assistance to living donors, but under current law, the incomes of both the living donor and the transplant recipient are required to determine eligibility, although the assistance is provided only to the donor.

"While a transplant recipient's insurance covers the cost of donation surgery, donors face thousands of dollars of direct out-of-pocket costs in order to donate an organ, such as dependent care, travel for donor evaluation, and lost wages," noted **Roslyn B. Mannon, MD, FASN,** chair of the ASN's Policy and Advocacy Committee.

The bipartisan legislation now awaits action on the House floor and in the Senate. ■

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ADPKD

Mortality Risk in ADPKD

BMC Nephrology. doi:10.1186/s12882-024-03484-3

The leading hereditary cause of end-stage renal disease (ESRD) is autosomal dominant polycystic kidney disease (ADPKD). However, data regarding mortality specific to patients with ADPKD are limited. So, **Deirdre Mladsi, BA,** and others conducted a study of mortality in this population using data from the United States Renal Data System.

The researchers analyzed data of 1936 patients with ADPKD and non-ESRD chronic kidney disease (CKD) and 37,461 patients with ADPKD and ESRD. They measured overall mortality rates with 95% CI and calculated mortality rates by age, sex, and race for the total dataset, then again for a subset of patients aged ≥65 years.

Age-adjusted mortality was 18.4 deaths per 1000 patient-years in the non-ESRD CKD group and 37.4 deaths per 1000 patient-years in the ESRD group. In the non-ESRD CKD cohort, patients with CKD stages 4 and 5 had a greater risk of death than patients in stage 3 (hazard ratio [HR], 1.59 for stage 4 and HR, 2.71 for stage 5). Among the ESRD cohort, patients on dialysis were more likely to die than patients who received a transplant (HR, 2.36).

Mortality rates specific to patients aged ≥65 years imply that there are racial differences in mortality among these patients in both the non-ESRD CKD and ESRD cohorts. In the non-ESRD CKD group, age-adjusted mortality for patients aged ≥65 years was highest for Black patients (82.7 deaths per 1000 patient-years), but it was highest for White patients of the same age in the ESRD group (136.1 deaths per 1000 patient-years).

CHRONIC KIDNEY DISEASE

Age, Competing Risk of Death, and Racial Disparities in Kidney Failure

Journal of the American Society of Nephrology. doi:10.1681/ASN.0000000000000300

Black adults have a much higher incidence of kidney failure than White adults, but the reason for this is uncertain. Using the race-free 2021 CKD Epidemiology Collaboration equation, researchers, including **Guofen Yan, PhD,** examined racial differences in kidney failure and death from the onset of CKD and the extent to which those differences could be attributed to factors present at the time of CKD onset.

The study cohort included 547,188 US veterans (103,821 non-Hispanic Black and 443,367 non-Hispanic White) aged 18 to 85 years. All participants had new-onset CKD between 2005 and 2016 and were tracked for incident kidney failure with replacement therapy (KFRT) and pre-KFRT death through 10 years or until May 2018.

Black veterans were on average 7.8 years younger than their White counterparts at the onset of CKD. The cumulative incidence of KFRT was 2.5 times higher for Black individuals than White individuals at any point in time from CKD onset. Black veterans also had hazards of KFRT that were more than twice as high during follow-up (HR [95% CI], 2.38 [2.31-2.45]); they had 17% to 48% decreased hazards of pre-KFRT death. Differences decreased after adjusting for the racial difference in age at CKD onset.

In conclusion, the higher cumulative incidence of kidney failure in Black veterans was attributable to a combination of higher hazards of progression to kidney failure and lower hazards of competing risk of death. Both factors are likely due largely to Black veterans' younger age at CKD onset compared with White veterans.

Daprodustat and Heart Failure in CKD

Journal of the American Society of Nephrology. doi:10.1681/ASN.0000000000000321

The traditional treatment for anemia in patients with CKD is injectable erythropoietin-stimulating agents (ESA). Daprodustat is an oral hypoxia-inducible factor prolyl hydroxylase inhibitor that provides an alternative. Patients who have CKD are at a greater risk of heart failure, but it is unknown whether daprodustat affects the risk of heart failure hospitalization.

Jonathan W. Cunningham, MD, MPH, and other researchers compared daprodustat to ESA in patients with CKD-related anemia who did or did not require dialysis in the ASCEND-D (n=2964) and ASCEND-ND (n=3872) trials, respectively. They identified risk factors for heart failure hospitalization then assessed the effect of daprodustat versus traditional ESA on heart failure hospitalizations. A history of heart failure, diabetes, and higher systolic blood pressure were independently associated with heart failure hospitalization in both trials.

A greater proportion of first heart failure hospitalizations occurred in patients treated with daprodustat compared with ESA. This was true in both the group not receiving dialysis (HR, 1.22 [0.95-1.56]; *P*=.12] and in those receiving dialysis (HR, 1.10 [0.84-1.45]; *P*=.47). However, the differences were not statistically significant. HRs in patients with and without a history of heart failure were 1.37 (0.89-2.11) compared with 1.08 (0.79-1.46; *P*-interaction=.36) in ASCEND-ND and 1.52 (0.97-2.38) versus 0.93 (0.66-1.30; *P*-interaction=.09) in ASCEND-D, respectively.

In post hoc analyses, daprodustat increased the total number of heart failure hospitalizations in participants not receiving dialysis (rate ratio, 1.46 [1.11-1.92]; *P*=.007) but not in participants receiving dialysis (rate ratio ,1.01 [0.74–1.39], *P*=.93). Daprodustat did not significantly influence the risk of a composite outcome of first heart failure hospitalization or death.

COVID-19

Oxidative Stress, Immune Response Against SARS-CoV-2

Free Radical Biology and Medicine. 2024;215:14-24

COVID-19 increases the risk of severe illness and poor vaccination response among patients with kidney disease. Oxidative stress may play a role, and it can be measured by assessing serum free thiols (R-SH, sulfhydryl groups). In a post hoc analysis of the RECOVAC IR observational study, **Larissa E. van Eijk** and colleagues studied the association between serum free thiols and kidney patients' ability to mount a humoral immune response to SARS-CoV-2 vaccination.

The team measured serum free thiol concentrations in patients with CKD stages 4 and 5 (G4/5; *n*=46), on dialysis (*n*=43), kidney transplant recipients (KTR; *n*=73), and controls (*n*=50). They analyzed baseline serum free thiol and interferon-γ-induced protein-10 (a biomarker of the interferon response) for associations with seroconversion rates and SARS-CoV-2 spike-specific immunoglobulin G concentrations after two doses of the mRNA-1273 vaccine.

The researchers found that albumin-adjusted serum free thiol concentrations were much lower in patients with CKD G4/5 (*P*<.001), on dialysis (*P*<.001), and KTR (*P*<.001) compared with controls. After full vaccination, seroconversion rates were greatly lessened in KTR (52.1%) and were significantly associated with albumin-adjusted free thiols (OR, 1.76; *P*=.033). However, the significance did not remain after adjustment for mycophenolate mofetil use, hemoglobin, and estimated glomerular filtration rate (eGFR; odds ratio [OR], 1.49; *P*=.241).

In sum, transplant recipients had suboptimal serological responses to SARS-CoV-2 vaccination, which is inversely associated with serum R–SH. This indicates systemic oxidative stress. The association could be at least partially involved in transplant recipients' poor serological response to SARS-CoV-2 vaccination.

DIABETES

Variability of UACR in Patients With T2D

American Journal of Kidney Diseases. doi:10.1053/j.ajkd.2023.12.018

Albuminuria is known as a leading diagnostic and prognostic marker of diabetic CKD. However, its day-to-day variability has not been sufficiently considered, so **Natasha Rasaratnam, MD,** and other researchers conducted a cross-sectional analysis to quantify the within-individual variability of albuminuria in patients with type 2 diabetes (T2D) to help guide clinical albuminuria monitoring.

The study included individuals who took part in the Progression of Diabetic Complications cohort study and had T2D. There were 826 study participants, 64.9%

of whom were male; median age was 67.1 years (IQR, 60.3-72.4). To examine the variability of urinary albumin-creatinine ratio (UACR), four spot urine samples were collected within 4 weeks for measurement.

There was a high variability of UACR within individuals (coefficient of variation, 48.8%; 95% limits of random variation found a repeated UACR to be as high/low as 3.78/0.26 times the first). When a single-collection UACR increased from 2 to 5 mg/mmol, the probability that UACR increased by at least 30% was only 50%; this rose to 97% when two samples were taken at each time point. The ranges of diagnostic uncertainty were 2.0-4.0 mg/mmol after an initial UACR test, which narrowed to 2.4-3.2 and 2.7-2.9 mg/mmol for the mean of two and three collections, respectively.

Female sex and moderately increased albuminuria corresponded with higher within-individual UACR variability. Reduced eGFR and treatment with sodium-glucose cotransporter 2 inhibitor, angiotensin-converting enzyme inhibitor, or angiotensin receptor blocker correlated with lower within-individual UACR variability.

Taking multiple urine samples to measure UACR may help with monitoring changes over time in clinical and research settings. However, this approach may not be necessary for diagnosing albuminuria.

DIALYSIS

Infection Prevention Barriers and Facilitators in Dialysis Centers

American Journal of Kidney Diseases. doi:10.1053/j.ajkd.2023.12.024

Although infection prevention efforts in dialysis centers can help prevent patient morbidity and mortality, such measures can be difficult to implement. Therefore, **Sarah Henrickson Parker, PhD,** and others studied how work system design might contribute to infection prevention efforts in outpatient dialysis centers.

Their observational study included six US dialysis centers. Over 8 months, a multidisciplinary team visited each facility and made structured macroergonomic observations using the SEIPS 1.0 model. They collected ethnographic observations around staff encounters with patients, used selective and axial coding to conduct qualitative analysis, and used descriptive statistics to report quantitative data.

The researchers identified both barriers to and facilitators of infection prevention that were organizational and sociotechnical in nature. These included elements of human performance, such as interruptions, alarms, and task stacking; work system design features, such as physical space, leadership, culture, and scheduling; and extrinsic factors, such as patient-related characteristics. They found that several features were common across facilities, indicating that further research should be undertaken.

Clinical Prediction Models for Life Expectancy of Patients on Hemodialysis

American Journal of Kidney Diseases. doi:10.1053/j.ajkd.2023.12.013

The life expectancy of patients being treated with maintenance hemodialysis (MHD) is varied. However, current tools for measuring life expectancy focus primarily on near-term mortality, which can affect care decisions.

Researchers, including **Benjamin A. Goldstein, PhD,** developed predictive models for near-term mortality and long-term survival on MHD. Their data came from the electronic health record systems of midsize, nonprofit dialysis providers and included 42,351 patients over 11 years. The data included demographics, laboratory results, vital signs, and service utilization information.

For each patient month, the researchers determined near-term mortality (death within the next 6 months) and long-term survival (survival over >5 years while receiving MHD or after a kidney transplant). They used least absolute shrinkage and selection operator logistic regression and gradient-boosting machines to predict each outcome, compared the results to time-to-event models spanning both time horizons, and examined the performance of decision rules at different cut points.

All models achieved area under the receiver operating characteristic curve ≥0.80 and optimal calibration metrics in the test set. The long-term survival models performed significantly better than near-term mortality models. Time-to-event models performed comparably to binary models. By applying different cut points from the first to 90th percentile of the predictions, the models could achieve a positive predictive value (PPV) of 54% for near-term mortality; however, sensitivity was only 6%. They could achieve a PPV of 71% for long-term survival with 67% sensitivity.

While predictive modeling built on readily available clinical data holds promise as a clinical decision support tool, the researchers' retrospective models would need to be prospectively validated before use.

END-STAGE RENAL DISEASE

KRT for ESRD Due to Primary Glomerular Disease

Nephrology Dialysis Transplantation. doi:10.1093/ndt/gfae034

Primary glomerular disease (PGD) is a leading cause of ESRD resulting in kidney replacement therapy (KRT). Using data from the European Renal Association (ERA) Registry, **Samar Abd ElHafeez, MD,** and others identified incidence of patients starting KRT for ESRD due to PGD. They also investigated these individuals' survival and causes of mortality.

A total of 69,854 patients who began KRT for ESRD due to PGD between 2000 and 2019 were included in the study. The researchers further identified six PGD subgroups based on ERA primary renal disease codes and studied age and sex standardized incidence, trend of incidence, and survival.

The standardized incidence of KRT for ESRD due to PGD was 16.6 per million population (pmp). The PGDs with the highest incidence were IgA nephropathy (IgAN) and focal segmental glomerulosclerosis (FSGS), at 4.6 pmp and 2.6 pmp, respectively. Histologically nonexamined PGDs comprised more than 50% of cases in Serbia, Bosnia and Herzegovina, and Romania; these were also common in Greece, Estonia, Belgium, and Sweden. The incidence declined from 18.6 pmp in 2000 to 14.5 pmp in 2013, then stabilized. The likelihood of survival was more than 50% for all PGD subgroups. Crescentic glomerulonephritis demonstrated the highest risk of death (adjusted HR, 1.8 [95% CI, 1.6-1.9]) versus IgAN. The most common cause of death was cardiovascular disease (33.9%).

While the lack of kidney biopsy facilities in some countries may have affected the accuracy of results, the study demonstrates that there are substantial differences among countries in the incidence of KRT for ESRD due to PGD. The incidence and outcomes of KRT among different PGD subgroups should be considered when determining an individualized approach to care.

PEDIATRIC NEPHROLOGY

Mild Dehydration and Risk of Childhood CKD Progression

Pediatric Nephrology. doi:10.1007/s00467-024-06332-6

Although children with CKD may be especially susceptible to dehydration, little research has been published regarding the frequency of dehydration and the risk of its complications in this population. Researchers, including **Amelia K. Le Page, MBBS, FRACP,** reviewed the risk factors and effects of mild dehydration and underhydration in CKD, focusing on its potential role in the risk of CKD progression.

The study authors acknowledge that analyzing dehydration in the CKD population is more challenging than in the healthy population, which complicates the definition of sufficient hydration and clinical research in this area. However, they reviewed pathophysiologic studies, which suggest that mild dehydration and underhydration can cause hyperfiltration injury and affect renal function. Arginine vasopressin is a key mediator of these risks.

Randomized, controlled trials in adults have not demonstrated that improved hydration affects CKD outcomes. However, more vulnerable populations with baseline low fluid intake or poor kidney concentrating capacity should be studied.

The authors suggest that routine pediatric CKD management should include an assessment of individual dehydration risk along with a treatment plan. However, they acknowledge a need for continued research. ■

Sarah Tolson

Navigating New Waters: The Challenges of Integrating Oral-Only Medications Into Dialysis Programs

Running a dialysis program is inherently challenging, requiring a balance between clinical efficacy, regulatory compliance, and operational efficiency. Dialysis program administrators are facing a potential new challenge: the inclusion of payment for oral-only medications such as phosphate binders in the End-Stage Renal Disease Prospective Payment System (ESRD PPS). Currently, the American Taxpayer Relief Act states that the ESRD PPS will include oral-only ESRD medications effective January 2025. This change presents logistical, patient insurance coverage, and cost-related challenges that administrators must navigate to ensure the continued delivery of high-quality care.

LOGISTICAL CHALLENGES

One primary logistical challenge posed by the inclusion of oral-only medications in the ESRD PPS is integrating these medications into the existing management and distribution systems. Unlike injectable medications provided during dialysis treatment or during the monthly clinic visit, oral phosphate binders must be taken several times daily. The dialysis program would need to contract with a retail pharmacy to ensure patients receive medications for home use, adding to the complexity of medication management and necessitating a more integrated tracking system. It is crucial for dialysis programs to update their internal systems to ensure seamless coordination between prescription, procurement, delivery, and billing processes.

PATIENT INSURANCE COVERAGE CHALLENGES

In addition to logistical challenges, dialysis programs should closely monitor each patient's insurance coverage, which will likely determine which patients will continue to receive phosphate binders from their local pharmacy and which patients will receive the medication through their dialysis program. During the first years of the Transitional Drug Add-On Payment Adjustment, dialysis programs struggled to obtain reimbursement for calcimimetics from payers other than traditional Medicare. This reduced the availability of calcimimetics to patients without traditional Medicare. Many Medicare Advantage plans took over a year to update their claims processing systems to accurately reimburse for calcimimetics, and some never did due to contract issues. There is a concern in the renal community that insurance coverage and reimbursement issues may cause unnecessary barriers to reimbursement that could make it challenging for patients to obtain necessary medications.

COST CHALLENGES

The inclusion of oral-only medications in the ESRD PPS also brings substantial financial implications. It is not breaking news that dialysis programs operate under tight budget constraints. The ESRD PPS aims to cover all necessary services, but there are many challenges that prevent dialysis programs from recouping the costs associated with every patient's treatment. The addition of oral medications to this bundle without a commensurate increase in reimbursement rates from all payer sources, not just Medicare, strains the financial viability of many facilities.

Studies have examined the potential impact of the costs of oral phosphate binders on dialysis programs. Many of these studies indicate that it is unlikely the reimbursement afforded in the ESRD PPS will be sufficient to cover the costs associated with phosphate binders and could jeopardize dialysis programs' ability to continue to provide care.

Over the last decade, the renal community has successfully demonstrated to the US Congress that the inclusion of oral-only medications, such as phosphate binders, in the ESRD PPS should be postponed. Clear processes that ensure adequate reimbursement and help dialysis programs navigate the many challenges associated with providing phosphate binders to dialysis patients should be in place before oral-only ESRD drugs are included in the ESRD PPS.

At the time of this writing, HR 5074, a bill to delay the inclusion of oral-only ESRD drugs in the ESRD PPS until January 1, 2033, or until an approved intravenous drug is available, is making its way to be passed by the US House of Representatives. Dialysis programs will be ahead of the game if they plan for oral-only drugs to be included in the ESRD PPS in January 2025, even though many in the renal community are hopeful HR 5074 is signed into law and the inclusion of oral-only drugs is delayed. ■

Sarah Tolson is the director of operations for Sceptre Management Solutions, Inc., a company specializing in billing for outpatient ESRD dialysis programs, nephrology practices, interventional nephrology, and Medicare cost reports for dialysis programs. Your questions are welcome, and she can be reached at stolson@sceptremanagement.com, 801.775.8010, or via Sceptre's website, www.sceptremanagement.com.

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