Nephrology Times

Practical News, Trends, and Analysis

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Effect of APOL1 Risk Variants on Kidney Function of Healthy, Middle-Aged Patients

Black Americans have a greater incidence of chronic kidney disease than White individuals. This difference is likely due, in part, to variants in the apolipoprotein L1 (APOL1) gene. Approximately 12% to 15% of Black Americans carry two APOL1 risk variants; they are virtually absent in people of European ancestry.

Previous research has determined that patients with CKD who have two APOL1 kidney risk variants (high-risk genotype) experience a more rapid decline in kidney function compared with those who have one or zero variants (low-risk genotype). Therefore, physicians may test Black patients with CKD and proteinuria for APOL1 kidney risk variants. APOL1 genetic testing is also used to evaluate Black living kidney donor (LKD) candidates to help determine their level of risk for future kidney disease. However, most patients carrying the high-risk APOL1 genotype will not develop kidney disease; a second hit is required. It is unclear from current research whether kidney donation is the instigating event for some LKDs carrying the high-risk APOL1 genotype to progress to CKD or end-stage renal disease.

There is a knowledge gap regarding the baseline risk of kidney disease in healthy patients with two APOL1 variants. This information could help clinicians better understand the effect

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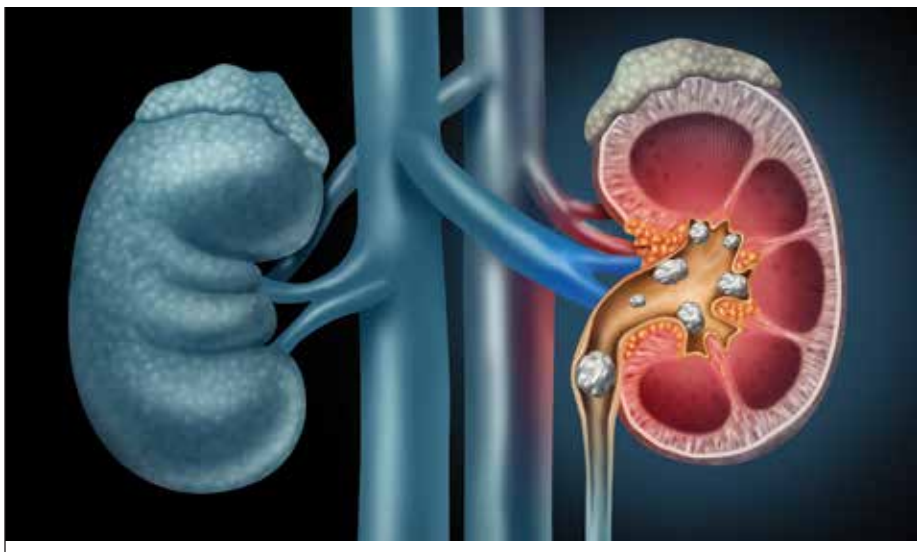

Incidence, Outcomes of Kidney Failure Due to Stones

Kidney stones are a common condition, and their prevalence is increasing. They currently affect up to 10% of adults, and the risk of stone recurrence can be as high as 20% to 50%. People who experience kidney stones are an increased risk of developing chronic kidney disease and have double the risk of developing kidney failure (KF). The risk of both CKD and KF increases with the number of stone episodes.

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Sex, Cardiovascular Outcomes With Kidney Failure

The exclusion of women and people with kidney disease from cardiovascular disease clinical trials has resulted in a knowledge gap regarding how cardiovascular health status may differ between men and women with kidney failure (KF). This is of particular importance because cardiovascular disease is the leading cause of morbidity and mortality among individuals with KF.

To help address this gap, a group of researchers, including **Silvi Shah, MD,** examined sex differences in cardiovascular events, cardiovascular death, and all-cause mortality using data from the United States Renal Data System (USRDS). Their findings were published in the *Journal of the American Heart Association* [doi:10.1161/JAHA.123.029691].

The study cohort comprised 508,822 patients from USRDS with linked claims for Medicare Part A and B or Medicare Primary Other as the primary payer, who had incident end-stage renal disease and started dialysis between January 1, 2005, and December 31, 2014. All patients were ≥18 years of age, and the mean age at the start of the study was 69.9±12.4 years; 44.7% were women; 61.6% were White, 23.5% were Black, 10.6% were Hispanic, 3.4% were Asian, and 0.9% were Native American. The mean age was higher for women than men (70.3±12.3 years vs 69.7±12.5 years), and women were more likely to be Black (27.2% vs 20.5%) and less likely to be White (57.7% vs 64.8%) than men.

Most (91.4%) study subjects had a history of cardiovascular disease. Women were more likely than men to have comorbidities of diabetes (56.0% vs 52.3%)

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You Will Be Greatly Missed, Nick Madias

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In the ABBA song "I Have a Dream," there is a line, "I believe in angels / Something good in everything I see." I, too, believe in angels who do good for everyone. **Nicolaos Madias, MD,** was a nephrology angel who died recently. I knew Nick and admired him as a wonderful human being—looking up to him in awe because of the massive difference he made to nephrology, especially in our understanding of acid base and electrolyte physiology, and because he was a gentleman to the core.

I first met Nick in 1987. Nick was chief of the Division of Nephrology at Tufts Medical Center (Tufts MC). He supported me through my early career until I was recruited to Brigham and Women's Hospital. He nurtured colleagues in the renal division at Tufts MC like no one I have worked with either prior or since. Special memories include the Christmas parties that he and his beloved wife, Ourania, had each year. We kept in touch over the years, and he would be there whenever I visited St. Elizabeth's Medical Center, where he was chair of medicine.

Nick published extensively on acid base. In the early years, these studies, focusing on the effect of hypocapnia and hypercapnia on serum bicarbonate in dogs, were with **William Schwartz, MD,** and **Jordan Cohen, MD.** In later years, Nick worked on the molecular characteristics of the sodium-hydrogen exchanger (NHE-1) gene. He published studies on renovascular hypertension and even gave time to publishing a case report with me on predominant tubulointerstitial nephritis.

In more recent years, Nick published highly impactful and practical review articles with **Horacio Adrogue, MD,** and **Jeff Kraut, MD,** in the *New England Journal of Medicine* and many leading nephrology journals, deepening our understanding of how to manage disorders of sodium and water metabolism and of acid base dysregulation.

Many have said great things about Nick; here are a few notable tributes.

From **Mark Sarnak, MD,** current chief of nephrology at Tufts MC: "Nick was an outstanding teacher who had the unique ability to explain extremely complex subjects in easily understandable terms. He nurtured a culture of respect for everyone, hard work, and devotion to every patient. He was a friend and colleague who had a profound positive influence on many of our lives."

From **Andrew Levey, MD,** Nick's immediate successor as chief of nephrology at Tufts MC: "I worked with him during my entire career, and never did I hear him raise his voice or criticize a colleague or employee. Instead, he was endlessly patient and supportive. As his successor as chief of the Division of Nephrology at Tufts Medical Center, I learned from him that a leader respects each person for his or her contributions and does not expect anyone to do more than they are able to."

From **Ron Perrone, MD,** scientific director of the Clinical and Translational Research Center and director of the Polycystic Kidney Disease Center at Tufts MC: "Nick taught me ethics and a kind and supportive leadership style by setting a remarkable example, which, to this day, has set the tone for how the division operates."

From Dr. Horacio Adrogue, emeritus professor of medicine at Baylor University: "I had the enormous privilege of working with Nicolaos E. Madias for almost half a century, starting in Boston in 1975, when both of us were research fellows, performing experimental acid base studies in conscious dogs in the large environmental chamber of the renal division at Tufts MC. We became close colleagues, research collaborators, and best friends, co-authoring multiple studies published in high-impact medical journals. Such interaction allowed me to discover his multiple virtues, immense passion for medical research, unbeatable moral values, remarkable humbleness, tenacity, hard work to the extreme, devotion to excellence, superb writing skills, warm heart, loyalty, dedication to his duties, and commitment to always keep his promises. The Academy of Athens recognized his immense talent and contributions to medical research and elected Nick as a contributing member in 2019. I will miss him profoundly, and science has lost a giant and luminary."

Nicolaos Madias, MD

Bertrand Jaber, MD, who succeeded Nick Madias as chair of medicine at St. Elizabeth's Medical Center in Boston: "The St. Elizabeth's Medical Center community has lost a gentle giant. Dr. Madias was a tireless leader of academic and clinical excellence. He was an enabler of the faculty of his department, a perpetual optimist, and a champion of civil and respectful engagement. For those who knew him well, he will be remembered as a great physician and colleague, a demanding mentor, and a selfless friend and confidant."

I always thought of Nick first as a clinician, then as a scientist who used his enormous acumen to explain complex clinical concepts using basic physiological principles.

Rest in peace, Nick! ■

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Feature

Health Care Costs at Different DKD Stages

Having an estimation of the costs incurred by diabetic kidney disease patients is a step toward containing such costs.

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From the Field

Incidence, Outcomes of Kidney Failure

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TAKEAWAY POINTS

- Research on kidney stones' incidence and outcomes in patients who progress to kidney failure (KF) with KRT is limited.
- Utilizing data from the Australia and New Zealand Dialysis and Transplant Registry (ANZDATA), researchers studied the incidence of KF due to kidney stones and compared outcomes with patients receiving KRT due to other causes.
- KF due to kidney stones was unchanged throughout the study period. Survival of KRT patients with kidney stones was better than for those requiring KRT due to other causes. Survival and risk of graft failure were similar in transplant patients with stones versus those without.

Most studies have only examined outcomes to the point of developing CKD or KF, but few have focused on complications and outcomes after developing KF and starting kidney replacement therapy. A group of researchers, including **Hicham Cheikh Hassan, MB BCh, BAO, FRACP,** used data from the Australia and New Zealand Dialysis and Transplant Registry (ANZDATA) to study the incidence of KF due to kidney stones over the last four decades, the all-cause mortality risk for dialysis patients who had stones versus dialysis patients without stones, and the all-cause mortality and graft survival risk for stone formers versus nonstone formers who received a kidney transplant. Their results appeared in *Nephrology Dialysis Transplantation* [doi:10.1093/ndt/gfae137].

A total of 78,705 patients ≥18 years of age began KRT (dialysis or transplant) between 1981 and 2020. Total follow-up time was 285,250.4 patient-years. Of these patients, 834 (1.1%) initiated KRT due to a primary diagnosis of kidney stones as a cause of KF. For the full cohort, the crude incidence of starting KRT because of kidney stones was 1.17 per million population (95% CI, 1.09-1.25); males had a crude incidence of 1.27 (95% CI, 1.16-1.39), while females had 1.07 (95% CI, 0.97-1.18) per million population. The annual incidence of KRT due to kidney stones was stable across Australia and New Zealand for the full study period (annual percentage change, –0.3% [95% CI, –1.5% to 0.9%]).

However, the prevalence of KF caused by kidney stones declined significantly over time. The study did not examine the reasons for this, but the authors posit that better management incorporating lifestyle advice or medications, patient awareness, and follow-up of patients with kidney stones may have contributed to a lower risk of progression to KF.

Survival was higher in patients with kidney stones receiving dialysis compared to those without (HR, 0.89; 95% CI, 0.82-0.96), with similar estimates in a matched cohort. In patients who received kidney transplants, the time to transplant was longer for those with kidney stones compared to nonstone patients (2.5 vs 1.7 years; *P*=.001). There was no difference in mortality (HR, 1.02; 95% CI, 0.82-1.28) or graft loss (HR, 1.07; 95% CI, 0.79-1.45) between patients with and without stones.

Limitations of the study include possible selection bias, residual confounding, and misidentification. Stone type and severity of disease are unknown, the risk of post-KRT stone recurrence was not examined, and no information was included on patients who progressed to KF and were not dialyzed or who were conservatively managed, possibly leading to underestimation of overall and annual incidence rates.

"In conclusion," the authors wrote, "data from the ANZDATA Registry show a significant decline in the incidence of KF undergoing KRT due to kidney stones over the last 10 to 15 years. Our findings also suggest that the prognosis of KF due to kidney stone patients is better than those with other causes of KF on dialysis. Finally, we showed that patients with kidney stones as a cause of KF fare similar to those with nonstone causes in terms of survival and graft survival in the kidney transplant population. Our results can be used to inform and reassure care providers in the management of patients with kidney stones, particularly those approaching KF and who are being considered for dialysis or transplantation." ■

Effect of APOL1 Risk Variants on Kidney Function

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TAKEAWAY POINTS

- Black people with kidney disease who have two variants of the APOL1 gene (high-risk genotype) have a faster decline in kidney function than those with zero or one risk variant. However, the effect of the high-risk genotype on the kidney function of healthy middle-aged people was unclear.
- Researchers studied the effect of the APOL1 genotype on kidney function in patients with a mean age of 53 years who had normal kidney function and blood pressure at baseline.
- At 25 years of follow-up, the high-risk APOL1 genotype did not seem to be a major factor in future kidney disease risk.

of the high-risk APOL1 genotype on post-donation outcomes and guide unaffected family members of patients with APOL1-mediated kidney disease. Therefore, a team of researchers led by **Mona D. Doshi, MBBS,** used data from the Atherosclerosis Risk in Communities (ARIC) study to evaluate the effect of self-reported race and APOL1 genotype on long-term kidney function in a cohort of healthy patients aged 45-64 years. The researchers hypothesized that having the APOL1 high-risk genotype does not adversely affect the long-term kidney function of those who survive to middle-age with good health and normal kidney function. Their results were published in *Kidney Medicine* [doi:10.1016/j.xkme.2024.100828].

ARIC launched in 1987 and enrolled 15,792 participants aged 45-64 years, of whom 15,026 (95%) consented to public use of their data. The researchers used ARIC to identify healthy middle-aged individuals who met criteria for LKD selection (blood pressure <140/90 mm Hg, fasting blood sugars <126 mg/dL, nonuse of antihypertensive and diabetic medications, eGFR ≥80 mL/min/1.73 m^2, and body mass index <35 kg/m^2). A total of 5,886 (39%) participants met the eligibility criteria at the time of enrollment.

Race was self-reported; participants who reported Black race were genotyped for APOL1 kidney risk variants. Selected participants were divided into three groups: 5,075 White participants (86%), 54% of whom were women; 110 Black participants with the APOL1 high-risk genotype (2%), 60% women; and 70 Black participants with the APOL1 low-risk genotype (12%), 58% women. Individuals with race other than Black or White were excluded. The mean age at baseline was 53±6 years.

The primary outcome was eGFR at 10 and 25 years, percentage of patients with CKD stage 3a or higher (creatinine- and cystatin C-based eGFR [eGFRcr-cys] ≤60 mL/min/1.73 m^2), and microalbuminuria (urinary albumin-creatinine ratio [UACR] >30 mg/g) in each group. The secondary outcome was the percentage of patients among healthy participants from the main ARIC cohort, including those who declined public use of their data (n=6980) to reach ESRD, death, or both.

At 10 years, White subjects had lower eGFRcr-cys than the low- and high-risk Black groups (89±16 vs 91±16 and 92±15) mL/min/1.73 m^2, respectively; *P*<.001). White participants again had lower eGFRcr-cys than the low-risk Black group at 25 years (70±18 vs 72±19) mL/min/1.73 m^2; *P*<.001). However, this was not true in comparison with the high-risk Black group (67±23 mL/min/1.73 m^2). There was no difference in UACR among the groups at 10 years (*P*=.87) or 25 years (*P*=.91).

At 10 years, the percentage of participants with CKD stage 3a or higher was highest in the White and low-risk Black groups compared to the high-risk Black group (3.4% and 3.9% vs 1.4%, respectively; *P*=.02). At 25 years, the three groups were comparable (30% in White, 25% in low-risk Black, and 33% in high-risk Black participants, respectively; *P*=.22). The chances of developing CKD stage 3a or worse did not differ in White participants or the low-risk participants compared to the high-risk participants in either the unadjusted or adjusted model (*P*=.61 and *P*=.91, respectively).

Regarding the secondary outcome, ESRD and death rates were the same among all three groups. At 30 years, <5% of the full cohort had ESRD; the composite ESRD and death rate for the full cohort was 45%.

The authors acknowledged a few major limitations of the study. These include large and variable intervals between study visits, resulting in greater loss to follow-up, and a lack of information on family history of ESRD in first-degree relatives, which is a significant risk factor for advanced kidney disease.

"In conclusion," the authors wrote, "we report a lack of association of the APOL1 genotype with long-term kidney function among middle-aged Black individuals screened for good health and absence of kidney disease at baseline." They determined that, "[g]iven the data we have to date, despite the study limitations, we recommend that Black middle-aged and older individuals considering kidney donation or unaffected family members of patients with CKD attributed to APOL1 should be educated about APOL1 kidney risk variants and the availability of APOL1 testing. In addition, these individuals should be counseled that APOL1 kidney risk variants are not major drivers of their future risk of kidney disease." ■

Sex, Cardiovascular Outcomes With Kidney Failure
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and poor functional status (19.9% vs 15.6%) but less likely to have the comorbidity of smoking (4.3% vs 6.1%). Women were more likely than men to experience kidney failure due to malignancy (3.0% vs 2.1%) or glomerulonephritis (4.8% vs 3.9%). Women were also more likely to have unfavorable laboratory measurements of albumin <3.5 mg/dL and hemoglobin <11 g/dL than men.

The analysis found that women on dialysis, compared to men, had a 14% higher risk of cardiovascular events (HR, 1.14; 95% CI, 1.13-1.16), a 16% higher risk of heart failure (HR, 1.16; 95% CI, 1.15-1.18), and a 31% higher risk of stroke (HR, 1.31; 95% CI, 1.28-1.34). The risk of ACS was comparable between women and men (HR, 1.01; 95% CI, 0.99-1.03).

The event rates for cardiovascular death and all-cause death were lower for women than men. Cardiovascular death rates were

> [W]omen with kidney failure have higher risks of cardiovascular events, including those of heart failure and stroke, but lower risks of cardiovascular mortality than men.

The primary outcomes of the study included the occurrence of a composite cardiovascular event, defined as hospitalization with a primary diagnosis of acute coronary syndrome (ACS; myocardial infarction or unstable angina), heart failure, or stroke; separate occurrence of ACS, heart failure, or stroke; cardiovascular death; and all-cause death. The researchers studied the association of sex with these outcomes using adjusted time-to-event models.

104 per thousand person-years (PTPY; 95% CI, 103-105) for women and 116 PTPY (95% CI, 115-117) for men; all-cause death rates were 275 PTPY (95% CI, 273-276) for women compared to 285 PTPY (95% CI, 284-286) for men. In the time-to-event model, women's risk of cardiovascular death (HR, 0.89; 95% CI, 0.88-0.90) was lower than men's. In the model predicting all-cause death, women had a lower risk (HR, 0.96; 95% CI, 0.95-0.97) than men.

The authors acknowledge several limitations of the study. They could not determine causality due to the study's observational design. Only patients with Medicare as their primary payer were included in the follow-up period. Comorbidity reporting on the Medical Evidence Report form was not validated, possibly leading to some nondifferential misclassification. Quality and completeness of data on form 2728 of the USRDS data varied. Researchers were unable to assess cardiovascular health-seeking behavior in women compared to men and could not account for endogenous hormone levels, which may play a role in the sex differences observed. Men and women may have been coded differently in terms of cardiovascular events, including fluid overload with heart failure. The authors lacked information on laboratory parameters and medications used to treat cardiovascular disease.

"In conclusion," the authors wrote, "women with kidney failure have higher risks of cardiovascular events, including those of heart failure and stroke, but lower risks of cardiovascular mortality than men. These differences were not explained by age, race or ethnicity, or history of prior cardiovascular disease. Women with kidney failure should be considered at high cardiovascular risk, and sex-specific interventions should focus on early diagnosis and prevention and optimal management of cardiovascular disease in patients with kidney failure." ■

TAKEAWAY POINTS

- Patients with kidney failure are at higher risk of cardiovascular events. However, it is unclear how cardiovascular health status differs between men and women with kidney failure.
- Researchers examined the association of sex with outcomes of cardiovascular events, cardiovascular death, and all-cause mortality in dialysis patients using adjusted time-to-event models.
- Women on dialysis have higher rates of heart failure and stroke but a lower adjusted risk of cardiovascular mortality and all-cause mortality compared to men. Efforts to prevent cardiovascular disease in this population should consider sex differences.

Amino Acid Infusion Reduces Risk of AKI in Cardiac Surgery Patients

Patients undergoing cardiac surgery commonly experience acute kidney injury, leading to an increased risk of morbidity and mortality, including chronic kidney disease, even in patients with mild or moderate AKI. Treatment for patients with severe AKI may include kidney replacement therapy. There is an association between severe AKI and doubling of hospitalization costs, decreased quality of life, and higher long-term mortality.

According to **Giovanni Landoni, MD,** and colleagues, with the exception of implementation of supportive measures, there is no single protective intervention for AKI resulting from complications in patients undergoing cardiac surgery. The researchers reported results of the PROTECTION (Intravenous Amino Acid Therapy for Kidney Protection in Cardiac Surgery) trial in the *New England Journal of Medicine* [doi:10.1056/NEJMoa2403769].

Infusion of intravenous acids in the context of renal hypoperfusion has been shown to provide renoprotective effects by recruiting renal functional reserve. PROTECTION, a multinational, double-blind, randomized, placebo-controlled trial, included adult patients scheduled to undergo cardiac surgery with cardiopulmonary bypass. Researchers sought to test the hypothesis that intravenous amino acid therapy would result in a lower occurrence of postoperative AKI compared with placebo.

The primary outcome of interest was the occurrence of AKI defined according to the Kidney Disease: Improving Global Outcomes creatinine criteria. Secondary outcomes included AKI severity, the use and duration of KRT, and all-cause 30-day mortality. Patients scheduled to undergo cardiac surgery were randomly assigned to receive an intravenous infusion of either a balanced mixture of amino acids (2 g per kilogram of ideal body weight per day) or placebo for up to 3 days.

A total of 4,415 patients were screened for eligibility from October 2019 through January 2024 at 22 centers in three countries. Of those, 3,512 were enrolled in the trial. Prior to initiation of the trial regimen, one patient in the placebo group withdrew consent, resulting in a study population of 1,759 patients in the amino acid group and 1,752 patients in the placebo group. The two groups were similar in baseline demographic and clinical characteristics, surgical interventions, and management.

The median dose of amino acids was 1,260 ml, corresponding to 126 g of amino acids. Median duration of infusion was 30 hours in the amino acid group and 31 hours in the placebo group. In both groups, median infusion rate was 40 ml per hour.

Researchers sought to test the hypothesis that intravenous amino acid therapy would result in a lower occurrence of postoperative AKI compared to placebo.

Overall, at discharge from the intensive care unit (ICU), 72.1% of the study population stopped receiving the amino acids or placebo (2,530/3,511); 22.6% (n=795) of patients completed the maximum 72-hour infusion. A total of 20 patients discontinued the regimen at initiation of KRT. In 1.6% (n=56) of patients, the regimen was discontinued in error. Fourteen patients died prior to the end of the 3-day infusion period, and one patient withdrew consent. Crossover occurred in four patients.

As of time of hospital discharge, AKI had developed in 474 (26.9%) patients in the amino acid group and 555 (31.7%) in the placebo group (relative risk [RR], 0.85; 95% CI, 0.77-0.94; *P*=.002). Stage 1 AKI was the most common stage (430/474 in the amino acid group and 492/555 in the placebo group). Twenty-nine patients in the amino acid group and 52 in the placebo group developed stage 3 AKI. Results were similar in the per-protocol analysis, the as-treated analysis, and in all sensitivity analyses.

KRT was used in 24 (1.4%) patients in the amino acid group and 33 (1.9%) in the placebo group (RR, 0.73; 95% CI, 0.43-1.22). Mean duration of KRT was 64 hours in both groups. Mean duration of stay in the ICU was 30 hours in the amino acid group and 34 hours in the placebo group. Mean duration of hospital stay was 7 days in both groups.

In the amino acid group, mortality prior to discharge from the ICU occurred in 34 (1.9%) patients, compared to 38 (2.2%) in the placebo group. Thirty-day mortality occurred in 50 (2.8%) patients in the amino acid group and 49 (2.8%) in the placebo group.

The two groups were similar in the numbers of patients with prespecified adverse events. Seventy patients in the amino acid group and 62 in the placebo group underwent surgical revision for bleeding. There were no adverse drug reactions reported in either group.

The researchers cited some limitations to the study, including limiting diagnosis of AKI to serum creatinine level alone, lack of measurement of newly identified biomarkers of kidney injury, and lack of a strict protocol for management or prevention of AKI. Furthermore, there were substantial differences between the trial population and patients in low- and middle-income countries and from patients in geographic regions with ethnic distributions that differed from the trial group. The lack of data on tubular injury and obtaining of serum creatinine measurements a few days prior to surgery were also cited as potential study limitations.

In summary, the authors said, "In this trial involving adult patients scheduled to undergo elective cardiac surgery with cardiopulmonary bypass, the infusion of amino acids significantly decreased the overall occurrence of AKI." ■

TAKEAWAY POINTS

- Patients having cardiac surgery often experience AKI, but aside from supportive measures, there is no single protective intervention for AKI resulting from cardiac surgery complications.
- In the PROTECTION trial, patients scheduled for cardiac surgery received either an intravenous infusion of a balanced mixture of amino acids (2 g per kilogram of ideal body weight per day) or placebo for up to 3 days.
- Among the patients in the study, infusion of amino acids decreased the occurrence of postoperative AKI compared to placebo.

Dropout After Switch From Hemodialysis to Peritoneal Dialysis

Patients with end-stage renal disease need lifelong kidney replacement therapy—hemodialysis (HD), peritoneal dialysis (PD), or transplantation. Nearly half (49%) of patients change modalities within the first year of starting dialysis. PD offers more flexibility than HD and is associated with lower risk of infection, better preservation of kidney function, and lower health care costs. Still, more than 35% of patients on dialysis drop out of PD in favor of HD.

A study by **Xingge Sun** and colleagues examined what occurs when patients switch from HD to PD, including the rate and reasons for PD dropout and the difference in mortality following time on HD prior to switching to PD. Their results appeared in *BMC Nephrology* [doi:10.1186/s12882-024-03542-w].

The researchers conducted a systematic review and meta-analysis of information from four databases: Cochrane, Embase, Medline, and PubMed. Studies that were included: (1) involved adults aged >18 years on dialysis; (2) compared two groups, including patients on HD for any length of time who then changed to PD (HD to PD group) and patients started on PD as initial therapy (PD first group); (3) demonstrated outcomes associated with the incidence or reasons for PD dropout and mortality; (4) were written in English; and (5) were randomized controlled trials, nonrandomized controlled trials, or observational studies. Exclusion criteria were also applied.

The research team identified 4,966 articles from databases and five from references. After duplicate removal and screening, 20 studies were selected for full-text review. Of those, 13 were ultimately included in the systematic review; 12 were cohort studies and one was a case control study. The total number of patients and events (PD dropout and mortality) in the PD first groups and HD to PD groups were extracted from the included studies. The Mantel-Haenszel odds ratio (OR) with 95% CI was used to summarize categorical data on PD dropout and mortality in a random effects model. The I^2 statistic was used to determine statistical heterogeneity.

Duration of HD varied from less than 1 month to 286 months; follow-up time ranged from 1 month to 132 months. The sample sizes of the PD first groups and HD to PD groups ranged from 37 to 9,404 and 28 to 3,757 patients, respectively. Patients came from America, Argentina, Australia, Canada, China, France, Iran, New Zealand, Poland, and Turkey. Patient characteristics noted in the studies included sample size, mean age, body mass index, time on HD, diabetes as a cause of ESRD, creatinine clearance, urine output, hemoglobin, albumin, and time of follow-up.

> [T]here was a statistically significant decrease in the rate of mortality in the PD first group (OR, 0.48; 95% CI, 0.25-0.92; I^2=73%; *P*=.03) compared to the HD to PD group.

Study outcomes included factors leading to the change from HD to PD, the rate and reasons for PD dropout, and differences in mortality in the PD first group compared to the HD to PD group. Meta-analysis uncovered no statistically significant difference in PD dropout in the PD first group (OR, 0.81; 95% CI, 0.61-1.09; I^2=83%; *P*=.16). However, there was a statistically significant decrease in the rate of mortality in the PD first group (OR, 0.48; 95% CI, 0.25-0.92; I^2=73%; *P*=.03) versus the HD to PD group.

The main reasons for switching from HD to PD included cardiovascular disease, vascular access failure, social issues, and patient preference. Reasons for PD dropout varied between the two groups, but inadequate dialysis and peritonitis were the primary reasons cited by both groups.

Limitations of the study include potential bias due to varied definitions of PD dropout across different studies and low-quality meta-analysis.

"This study confirmed that HD history may not impact PD dropout rates but could impact mortality. There were no significant differences in reasons of PD dropout in [the] PD first and HD to PD groups," the authors concluded.

However, they emphasized the need for additional research examining the psychosocial differences between the HD to PD group and the PD first group. "In the future, multidisciplinary training and dialysis education programs could be developed to emphasize the importance of [residual renal function] assessments and evaluate the impact of providing more psychosocial support to HD patients transferring to PD," they wrote. "There is also a need for a consensus on the definition of PD dropout to establish a standard for future research." ■

TAKEAWAY POINTS

- More than 35% of patients on dialysis drop out of peritoneal dialysis in favor of hemodialysis, although PD provides better outcomes, more flexibility, and lower costs.
- Researchers conducted a systematic review of 13 studies to examine the switch from HD to PD, including the rate and reasons for PD dropout and the difference in mortality following time on HD prior to switching to PD.
- The analysis found that a previous HD history may not impact PD dropout rates but could impact mortality in patients who switch from HD to PD. Inadequate dialysis and peritonitis were the primary reasons for PD dropout.

Initial eGFR Changes After Tolvaptan Administration Predict Longer-Term Response

Tolvaptan, a vasopressin V2 receptor antagonist, is the only pharmaceutical treatment for ADPKD. The phase 3 Tolvaptan Efficacy and Safety in Management of Autosomal Dominant Polycystic Kidney Disease and Its Outcomes (TEMPO) 3:4 study showed that tolvaptan could reduce the rates of total kidney volume (TKV) increase (49% reduction in rate of change of TKV at the end of 3 years; *P*=.001) and kidney function decline (26% reduction in rate of kidney function decline; *P*=.001) in patients with ADPKD.

Toshio Mochizuki and colleagues conducted a post hoc analysis of data from the TEMPO 3:4 study to examine whether the initial changes in eGFR between baseline and week 3 after tolvaptan administration were predictive of the longer-term effects of tolvaptan on TKV and eGFR in patients with ADPKD. Their results were published in *Kidney360* [2024;5(4):522-528].

TEMPO 3:4 was a phase 3, multicenter, double-blind, placebo-controlled study of the safety and efficacy of tolvaptan in patients aged 18-50 years with ADPKD. All participants had a TKV of ≥750 mL and creatinine clearance of ≥60 mL/min. The subjects were randomized 2:1 to tolvaptan or placebo. Those in the tolvaptan group (n=961; 51.51% male; mean age, 38.56 years) received the drug twice daily for 36 months at the maximum tolerated dose after a 3-week titration period. During the first week of the titration period, patients in the tolvaptan group received 45 mg in the morning and 15 mg in the afternoon, with the dose increasing to 60/30 mg and 90/30 mg each week as tolerated.

In the post hoc assessment, Mochizuki et al assessed the effects of tolvaptan on kidney function and kidney volume using the eGFR mean rate of change calculated from week 3 of tolvaptan administration up to 36 months and the TKV rate of percentage growth calculated from baseline up to 36 months. They estimated GFR using the creatinine-based Chronic Kidney Disease Epidemiology Collaboration equation at baseline, week 3, weekly during tolvaptan dose escalation, and every 4 months during treatment up to month 36 after tolvaptan initiation.

Reciprocal serum creatinine provided a more accurate assessment of change in kidney function. This was calculated using the formula 1/Pcr, where Pcr equals serum creatinine concentration (mg/dL). The researchers evaluated TKV using standardized kidney magnetic resonance imaging at baseline and at months 12, 24, and 36 after tolvaptan initiation. They assessed blood urea nitrogen (BUN) and fasting urine osmolality (uOsm) at baseline.

At baseline, mean eGFR was 81.35 mL/min/1.73 m^2 and mean TKV was 1,704.82 mL. At 3 weeks after starting tolvaptan, mean ± SD eGFR was (76.58±21.13) mL/min/1.73 m^2, with a mean decrease from baseline of (4.42±8.81) mL/min/1.73 m^2. The change in eGFR from baseline to 3 weeks was significantly associated with the mean rate of change per year in eGFR, and the larger the initial change in eGFR, the smaller the mean rate of change per year.

Univariate regression analysis identified the baseline characteristics of eGFR, age, body mass index (BMI), TKV, BUN, and fasting uOsm as significant factors for predicting eGFR at 3 weeks. Multivariate regression analysis identified eGFR, age, TKV, and BUN as significant factors. However, no association was found between initial change in eGFR and the rate of percent growth in TKV per year. Univariate regression analysis found that male sex, lower age, higher baseline BMI, and higher baseline TKV had a significant association with greater percent growth in TKV per year; these factors were significantly associated with TKV rate of change on multivariate analysis.

The authors acknowledged certain limitations. The TEMPO 3:4 study only included a few patients with more advanced kidney dysfunction, so their findings may not apply to such patients. The race-free eGFR equation was not used, so the interpretation of results may be limited. The authors recommended using the race-free calculation for future research.

"In conclusion," they wrote, "this post hoc analysis of the TEMPO 3:4 study demonstrated that initial changes in eGFR 3 weeks after initiation of tolvaptan treatment, which can be easily measured in clinical practice, are predictive of the long-term effects of tolvaptan." ■

TAKEAWAY POINTS

- Researchers conducted a post hoc analysis of data from the phase 3 TEMPO 3:4 study to examine the longer-term effects of tolvaptan on total kidney volume (TKV) and eGFR in patients with autosomal dominant polycystic kidney disease.
- TKV was estimated for 961 patients using magnetic resonance imaging at baseline and after 12, 24, and 36 months of treatment with tolvaptan. The drug's effect on kidney function and kidney volume was assessed by measuring changes in eGFR from week 3 and TKV from baseline up to 36 months.
- The initial change in eGFR from baseline to week 3 was a strong predictor of the mean rate of change in eGFR per year, indicating that the change was related to tolvaptan treatment. However, the initial change in eGFR was not associated with the rate of growth in TKV per year.

Health Care Costs at Different DKD Stages

Type 2 diabetes (T2D) is a major contributing factor to kidney disease and the need for dialysis and kidney replacement therapy. Between 20% and 40% of patients with T2D develop diabetic kidney disease (DKD). The prevalence of DKD results in a significant economic burden. On average, T2D patients with commercial health insurance incur $24,209 in total costs annually after the onset of kidney disease. One recent analysis of commercial health care claims estimated the annual cost to payers in the United States was $7,725 per 4 months for patients with stage 1 or 2 DKD and $11,879 for stage 5.

The cost of DKD care also poses a burden to the Veterans Health Administration (VHA), the largest integrated health care system in the United States. Having a precise estimation of the costs incurred by DKD patients is an important step in finding ways to contain such costs. To fill this knowledge gap, **Kibum Kim, BPharm, PhD,** and fellow researchers conducted a retrospective cost-of-care study using data from the VHA. Their findings appeared in *Kidney Medicine* [doi:10.1016/j.xkme.2024.100873].

The study focused on US veterans diagnosed with DKD between January 2016 and March 2022. Participants had T2D confirmed by either two or more health care encounters with T2D diagnosis within 365 days or records of noninsulin antidiabetic agent use along with one or more T2D diagnosis within 365 days.

The study cohort comprised 685,288 patients with DKD, of whom 96.51% were male, 74.42% were White, and 93.54% were non-Hispanic. Study participants had at least one T2D encounter prior to the record of eGFR or microalbuminuria for DKD. The analytic cohort included patients with DKD, with either eGFR lower than 60 mL/min/1.73 m^2 or microalbuminuria (UACR ≥30 mg/g), indicating kidney function decline and kidney damage. Stage G3a DKD comprised 50.16% of the cohort, while stage G3b comprised 25.03%.

The researchers utilized a generalized linear model to calculate the cost of DKD care based on the stage, dialysis phase, and KRT needs of participants. The study outcome of interest was all-cause health care costs covered by VHA. Mean and median per-patient-per-month (PPPM) expenditures were estimated, and descriptive statistics were used to present the number of patients at different DKD stages after the analytic cohort entry and subsequent stage transition. Continuous variables, such as age, body mass index, and lab test values were summarized using means and standard deviations.

Mean and median PPPM costs increased along with disease progression. The mean (SD) PPPM costs were $1,597 ($3,178) for stage 1; $1,772 ($4,269) for stage 2; $2,857 ($13,072) for stage 3a; $3,722 ($12,134) for stage 3b; $5,505 ($14,639) for stage 4; and $6,999 ($16,901) for stage 5. The average monthly cost for patients receiving regular dialysis was $12,299. Costs peaked at $38,359 during the first month of KRT but decreased to $6,636 after a year.

Limitations of the study include lack of a control group; a focus strictly on US veterans, which may have limited generalizability and led to underestimation of the total costs associated with DKD; and general limitations of any retrospective data analysis, such as selection bias and misclassification.

In conclusion, the authors summarized, "Over a million patients across varying DKD stages were studied, revealing that the majority were in stage 3a. It was evident that certain health complications, including anemia, gout, and hypertension, became more prevalent in more advanced DKD stages. Furthermore, there was a significant racial disparity, with [Black patients] being more present in advanced DKD stages. Health care costs, correspondingly, increased monotonically with higher DKD stages. The findings of this study could provide valuable insights for health care providers, policymakers, and stakeholders in optimizing care and resource allocation for DKD patients." ■

TAKEAWAY POINTS

- Diabetic kidney disease affects about one-third of people in the United States who have type 2 diabetes, and it carries a high economic burden.
- Researchers used data from the Veterans Affairs database to calculate the cost of DKD patient care based on stage, dialysis phase, and kidney replacement therapy.
- Health care costs increased monotonically with higher DKD stages. Preventing progression to advanced stages of DKD will minimize its economic impact.

Felzartamab Safe, Effective in Antibody-Mediated Rejection

Kidney allograft failure is most commonly associated with antibody-mediated rejection (AMR). Banff classification describes diagnosis of AMR based on serologic, morphologic, and molecular criteria. To date, there are no approved therapies to treat AMR.

Targeting CD38, a transmembrane glycoprotein expressed by immune and hematopoietic cells to inhibit graft injury caused by alloantibodies and natural killer (NK) cells, may offer a therapeutic option. Felzartamab, an investigational fully human IgG1 monoclonal CD38 antibody, depletes target cells through antibody-dependent cellular cytotoxicity and phagocytosis.

The results of this trial suggest that felzartamab may have the potential to effectively and safely reverse ongoing [AMRs].

TAKEAWAY POINTS

- There are currently no approved therapies for the treatment of antibody-mediated rejection, but targeting CD38 may offer a therapeutic option.
- In a phase 2 trial, researchers studied the safety and side effect profile of felzartamab, a fully human IgG1 monoclonal CD38 antibody, compared to placebo.
- The felzartamab group had a lower molecular score reflecting the probability of AMR and the level of donor-derived cell-free DNA. Felzartamab was found to be safe and may be able to reverse ongoing AMRs effectively and safely.

Katharina A. Mayer, MD, and colleagues conducted a phase 2, randomized, double-blind, placebo-controlled trial designed to evaluate the safety, side effect profile, and preliminary efficacy of felzartamab in the treatment of AMR occurring at least 180 days following kidney transplantation. Results were reported in the *New England Journal of Medicine* [2024;391(2);122-132].

The primary outcome of interest was the safety and side effect profile of felzartamab. Secondary outcomes included renal biopsy results at 23 and 52 weeks, donor-specific antibody levels, peripheral NK cell counts, and donor-derived cell-free DNA (cfDNA) levels.

The study was conducted from October 2021 to March 2023. The study population included 22 patients with AMR occurring at least 180 days after transplantation. Of those 22 patients, 11 were randomly assigned to receive felzartamab and 11 were assigned to receive placebo. One patient in the placebo group had graft loss caused by rejection at week 14 of the trial; 21 patients completed the trial treatment. Following completion of the last scheduled patient visit, the database was locked and unblinded on March 7, 2024.

Median time until trial inclusion was 9 years following transplantation. The two groups were generally well balanced in baseline characteristics, with the exception of median age (patients in the placebo group were older: 33 years of age in the felzartamab group vs 46 years of age in the placebo group). In addition, median eGFR was higher in the felzartamab group than in the placebo group (60 mL/min/1.73 m^2 vs 36 mL/min/1.73 m^2, respectively).

In the total study population, 32% (n=7/22) of patients had active AMR, and 68% (n=15/22) had chronic active AMR. In 59% (n=13/22), the presence of human leukocyte antigen class II donor-specific antibody was observed. In 36% (n=8/22), a mean fluorescence intensity of donor-specific antibody of more than 10,000 was observed. Median eGFR was 37 mL/min/1.73 m^2. The median ratio of spot urine protein-to-creatinine was 993, with urinary protein measured in milligrams and creatinine measured in grams. Most patients had fully developed AMR as revealed on molecular analysis. In 18 of the 22 patients, triple immunosuppression was being administered.

In safety analyses, all patients experienced adverse events (AEs), all of which were reported as predominantly mildly or moderately severe. Patients in the felzartamab group reported a greater incidence of AEs compared to those in the placebo group (119 vs 81 events). The incidence of AEs the trial investigators deemed to be related to felzartamab was also greater in the felzartamab group than in the placebo group (27 vs 11 events). There were no fatal AEs, and no patients discontinued treatment due to AEs. The frequency of serious AEs (primarily infection-related events) was lower in the felzartamab group than in the placebo group (one patient vs four patients, respectively).

Infections were the most frequent AEs (n=17/22 patients; 77%) and were more frequent in the felzartamab group than in the placebo group (10 patients [91%] vs seven patients [64%]). Eight patients in the felzartamab group reported infusion-related reactions, compared with zero in the placebo group, during the first infusion. The frequency of nasopharyngitis was greater in the felzartamab group than in the placebo group (nine patients vs three patients, respectively), as was the frequency of COVID-19 (seven patients vs three patients, respectively).

Biopsy procedures were performed at 24 weeks and 52 weeks in 11 patients in the felzartamab group and 10 in the placebo group. Resolution of morphologic AMR (including either chronic [inactive] rejection or no rejection) at week 24 was more frequent in the felzartamab group (82%; n=9/11 patients) compared to the placebo group (20%; n=2/10 patients). The between-group difference was 62 percentage points (95% CI, 19-100) and a risk ratio of 0.23 (95% CI, 0.06-0.83).

The median microvascular inflammation score was lower in the felzartamab group than in the placebo group at 24 weeks (0.0 vs 2.5; mean difference, –1.95; 95% CI, –2.97 to –0.92). The molecular score reflecting the probability of AMR was also lower in the felzartamab group than in the placebo group (0.17 vs 0.77; mean difference, –0.39; 95% CI, –0.64 to –0.14), as was the level of donor-derived cfDNA (0.31% vs 0.82%).

At 52 weeks, survival in both groups was 100%. One patient in the placebo group experienced graft loss due to persistent chronic active AMRs. The one-year eGFR slope in the felzartamab group was –0.39 mL/min/1.73 m^2 compared to –4.53 mL/min/1.73 m^2 in the placebo group. In both groups, there was no change in spot urinary protein-to-creatinine ratio over time.

The small sample size and short duration were cited by the authors as limitations to the study findings, as was the possibility that the results in this predominantly White European transplant population may not be generalizable to transplant populations in other regions, including North America.

In conclusion, the researchers said, "The results of this trial suggest that felzartamab may have the potential to effectively and safely reverse ongoing [AMRs], which underscores the potential of felzartamab as a therapeutic option warranting further investigation in the context of late or even early rejection after organ transplantation. "The present pilot trial showed that felzartamab met its primary outcome of apparent safety and an acceptable side effect profile." ■

Does Living Kidney Donation Affect Hypertension and Albuminuria Risk?

Although there are risks associated with living kidney donation, it is generally considered safe. Some evidence suggests that hypertension and albuminuria may be more common among living kidney donors, but the quality of that evidence is questionable. It is possible that the higher risk is due to nephrectomy, hereditary factors, or a higher number of follow-up assessments, which create more opportunity for determining outcomes among donors than nondonors.

A group of researchers led by **Amit X. Garg, MD, PhD,** investigated whether donors have a higher risk of hypertension than nondonors in the first 7 years after kidney donation. They also compared rates of eGFR decline and risk of albuminuria. The results of their prospective cohort study were published in *JAMA* [doi:10.1001/jama.2024.8523].

The study included 924 living kidney donors from 17 transplant centers in Australia and Canada and 396 nondonors; the non-donor number increased to 928 after statistical weighting. All participants were aged 18 to 70 years, had a body mass index less than 35, blood pressure (BP) less than 140/90 mm Hg, serum creatinine level less than 115 µmol/L in men or less than 90 µmol/L in women, and no comorbidities that would contraindicate kidney donation. Within the donor cohort, 66% of participants were female, mean age was 47 years, and mean eGFR was 100 mL/min/1.73 m^2. Donors were more likely than nondonors to have a family history of kidney failure (464/922 [50%] vs 89/394 [23%], respectively).

Participant recruitment took place from 2004 to 2014 and included a pilot phase from 2004 to 2008. Follow-up occurred until November 2021. Baseline assessment included a standardized health questionnaire; measurement of BP, height, and weight; and laboratory testing for proteinuria and serum creatinine. Baseline characteristics were similar between the two groups.

Twelve months after baseline, all participants were asked to complete 12 to 18 at-home BP measurements plus lab testing of blood and urine samples; they repeated the measurements annually through 2019. In addition, participants completed health questionnaires at 3 and 12 months after baseline and then annually.

Over a median follow-up of 7.3 years (IQR, 6.0-9.0), in weighted analysis, the rate of hypertension was 17% in both donors (161/924) and nondonors (158/928; weighted HR, 1.11; 95% CI, 0.75-1.66). There were no meaningful differences between the groups for longitudinal changes in systolic BP, diastolic BP, or mean arterial pressure.

After an initial drop in eGFR after nephrectomy (mean, 32 mL/min/1.73 m^2), donors had a 1.4-mL/min/1.73 m^2 (95% CI, 1.2-1.5) annual lesser decline in eGFR than nondonors. More donors did, however, have an eGFR between 30 and 60 mL/min/1.73 m^2 at least once during follow-up (438/924 [47%]) vs nondonors (49/928 [5%]). The final median eGFR in donors versus nondonors was 67 (IQR, 59-77) and 91 mL/min/1.73 m^2 (IQR, 81-101), respectively.

New albuminuria occurred in 15% (132/905) of donors and 11% (95/904) of nondonors (incidence, 2.4 vs 1.7 events per 100 person-years; weighted HR, 1.46; 95% CI, 0.97-2.21). The weighted difference between groups in the albumin-to-creatinine ratio was not meaningful, at 1.02 (95% CI, 0.88-1.19).

Hypertension, albuminuria, and/or eGFR less than 60 mL/min/1.73 m^2 occurred in 543 (59%) donors compared with 273 (29%) nondonors (13.2 vs 4.5 events per 100 person-years; weighted HR, 2.87; 95% CI, 2.23-3.68). All three outcomes occurred in 24 (3%) donors versus 0 nondonors.

The authors acknowledged the limitations of their study. They cannot rule out that a true donation-attributable risk of hypertension and other outcomes may initially manifest decades following donation, and that some risks increase over time. Confidence intervals for some binary outcomes were not precise, and the nondonor convenience sample was much smaller than the donor sample. Results may not be generalizable to donors with certain medical complexities before donation or to donors in places lacking universal health care.

In conclusion, the authors wrote, "...where living kidney donors and nondonors had the same follow-up schedule over a median follow-up of 7 years, the risk of hypertension and albuminuria was not significantly greater in donors than nondonors after accounting for differences in baseline risk." ■

TAKEAWAY POINTS

- Researchers sought to determine whether normotensive living kidney donors have a higher risk of hypertension in the first 7 years after donation compared with nondonors.
- The study found no significant differences in the risk of hypertension, mean blood pressure (BP), or change in BP between living kidney donors and nondonors.
- The findings of comparable outcomes in living kidney donors versus nondonors support the safety of kidney donation.

AKF Issues Patient Guidelines for Managing Hyperkalemia

The American Kidney Fund (AKF), with support from AstraZeneca, has introduced patient-facing guidelines to help individuals with chronic kidney disease manage and treat hyperkalemia. Kidney disease is the most common cause of this potentially life-threatening elevation of potassium levels.

The guidelines, which are available in both English and Spanish, include information on checking potassium levels, hyperkalemia symptoms, medicines, and dietary advice. They also feature tips to help patients adhere to the plan created by their provider.

"Managing hyperkalemia can be overwhelming and stressful," said AKF President and Chief Executive Officer **LaVarne A. Burton.** "These guidelines will help people with hyperkalemia understand the importance of keeping potassium at a healthy level and will give them the knowledge they need to take an active role in managing their health care."

To develop the guidelines, AKF gathered input from both patients and professionals in focus groups and collaborated with medical experts to create evidence-based, health-literate content. Clinicians may refer patients to www.kidneyfund.org to view, download, and print the guidelines.

NKF Working Group Provides Guidance on Use of Genetic Testing for Kidney Diseases

A new report from a National Kidney Foundation (NKF) working group provides recommendations regarding the use of genetic testing for kidney diseases. Chronic kidney disease often has genetic causes, yet genetic testing in nephrology has lagged behind other medical fields.

The working group's final report, which was published in the *American Journal of Kidney Diseases,* includes 56 recommendations and charts to help clinicians identify patients who would benefit from testing, explain the rationale to the patient and their family, and provide follow-up for interpretation of results.

The group included experts in genetics, nephrology, kidney pathology, genetic counseling, and ethics and considered patient perspectives. It was co-chaired by **Nora Franceschini, MD, MPH,** professor of epidemiology at the University of North Carolina Gillings School of Global Public Health, and **Ali Gharavi, MD,** of the Columbia University Vagelos College of Physicians and Surgeons.

Genetic testing can provide a more precise CKD diagnosis to better identify the appropriate level of care for the patient and help determine the likely progression of the disease. It is also less invasive than advanced diagnostic techniques like kidney biopsies and can provide information on whether family members of the patient may develop the same condition.

FDA Approves Fabhalta for Treatment of Proteinuria in IgAN

The US Food and Drug Administration (FDA) has granted accelerated approval of Novartis' drug Fabhalta (iptacopan) for the reduction of proteinuria in adults with primary immunoglobulin A nephropathy (IgAN) at risk of rapid disease progression.

IgAN occurs when clumps of antibodies build up in the kidneys, resulting in inflammation that damages the glomeruli, making it more difficult for the kidneys to filter out waste. Fabhalta is an inhibitor of the alternative complement pathway, the activation of which is thought to contribute to the pathogenesis of IgAN.

The accelerated approval was based on prespecified interim analysis of the phase 3 APPLAUSE-IgAN trial, which found that Fabhalta reduced proteinuria by 43.8% compared to a placebo. Continued approval may be contingent on verification and description of clinical benefit from the ongoing study, evaluating whether Fabhalta slows disease progression as measured by eGFR decline over 24 months. The eGFR data should be available upon completion of the study next year.

The approval allows Fabhalta to compete with drug maker Calliditas' Tarpeyo and Travere Therapeutics' Filspari. Meanwhile, Novartis is developing two other drugs, atrasentan and zigakibart, to treat IgAN. Other drug makers, including Otsuka and Vera Therapeutics, are also working on IgAN treatments.

End Kidney Deaths Act Introduced in Congress

On August 12, 2024, US Representatives **Nicole Malliotakis** (R-NY), **Don Bacon** (R-NE), **Josh Harder** (D-CA), and **Joe Neguse** (D-CO) introduced the End Kidney Deaths Act in Congress. The bipartisan legislation would provide a refundable tax credit to living kidney donors who donate kidneys to nonfamily members, specifically patients who have been on the kidney waiting list the longest.

The act would provide living kidney donors with a $10,000 refundable tax credit each year for 5 years, for a total of $50,000. According to a press release from Rep. Malliotakis, if enacted, the legislation is expected to save the lives of up to 100,000 Americans and save taxpayers an estimated $10 to $37 billion.

The Organ Procurement and Transplantation Network reports that there are nearly 97,000 individuals on the kidney transplant waiting list. Meanwhile, the number of living kidney donors has remained steady, at around 6,000 annually. Supporters of the End Kidney Deaths Act hope that offering an incentive for living donation will increase the number of donors.

Trial of Gene Therapy for Cardiomyopathy in Patients With Fabry Disease Can Resume

In a second-quarter earnings report, 4D Molecular Therapeutics announced that the US Food and Drug Administration has lifted a clinical hold on the phase 1/2 INGLAXA clinical trial of the experimental gene therapy 4D-310 for Fabry disease cardiomyopathy.

INGLAXA was halted in early 2023 after cases of atypical hemolytic uremic syndrome among participants were observed. Now that the hold has been lifted, enrollment for INGLAXA is expected to resume this year.

Cardiomyopathy is the leading cause of death among patients with Fabry disease. The 4D-310 therapy uses the cardiac-targeted and evolved C102 vector to deliver a copy of the galactosidase alpha gene, which encodes for the alpha-galactosidase A (AGA) enzyme, to the heart after a single, low-dose, intravenous administration. The therapy is designed to generate high local levels of AGA directly within heart tissue and other affected organs, with the goal of reversing cardiomyopathy in patients with Fabry disease. ■

CHRONIC KIDNEY DISEASE

Association Between Adding Salt to Food, CKD Risk

JAMA Network Open. doi:10.1001/jamanetworkopen.2023.49930

It is unknown whether a higher salt intake is associated with CKD, so researchers led by **Rui Tang, MS, MPH,** investigated the association of self-reported frequency of adding salt to foods with incident CKD risk in a general adult population. Participants self-reported their frequency of adding salt to foods as never or rarely, sometimes, usually, or always.

The population-based study included UK Biobank participants aged 37 to 73 years who did not have CKD at baseline. There were 465,288 individuals in the cohort; 255,102 (54.83%) were female and 210,186 (45.17%) were male. Mean age was 56.32 (SD 8.08) years.

A higher self-reported frequency of adding salt to foods was significantly associated with a higher CKD risk after adjusting for covariates. There were 2,231 incident events of CKD reported during a median (IQR) follow-up of 11.8 (1.4) years. Compared to those who reported never or rarely adding salt to foods, participants who reported sometimes adding salt to foods (adjusted HR [aHR], 1.04; 95% CI, 1.00-1.07), those who reported usually adding salt to foods (aHR, 1.07; 95% CI, 1.02-1.11), and those who reported always adding salt to foods (aHR, 1.11; 95% CI, 1.05-1.18) had an increased risk of CKD (P<.001). Participants who self-reported a higher frequency of adding salt to foods were also more likely to smoke, have diabetes or cardiovascular disease (CVD) at baseline, have a higher body mass index (BMI), have a higher Townsend Deprivation Index score, and have a weakened baseline eGFR compared to those who reported less frequently adding salt to foods.

The results indicate that reducing the frequency of adding salt to foods could provide a strategy for lowering CKD risk in the general population.

Gestational Exposure to Glucocorticoids, CKD Risk

American Journal of Kidney Diseases. doi:10.1053/j.ajkd.2024.01.523

The impact of antenatal glucocorticoid exposure on children's health is unclear. Researchers led by **You-Lin Tain, MD, PhD,** examined the association between gestational exposure to maternal systemic glucocorticoids (SG) and risk of developing CKD in childhood. Their retrospective cohort study focused on newborns receiving care at Taiwan's largest health care system between 2004 and 2018. Maternal prescriptions for SG between the last menstrual period and childbirth served as a proxy for gestational exposure.

The primary study outcome was incidence of childhood CKD, including congenital anomalies of the kidney and urinary tract (CAKUT) and other kidney diseases (non-CAKUT) over 10 years. The researchers used Cox proportional hazards models with stabilized inverse probability of treatment weighting and a robust sandwich estimator to measure the average association between SG and incident CKD after adjusting for offspring characteristics (aHR).

A total of 23,363 singleton children were included in the study. Their gestational SG exposure was significantly associated with a higher risk of childhood CKD (aHR, 1.69 [95% CI, 1.01-2.84]). Stratified analyses found stronger associations between SG and childhood CKD within the strata of total dose of hydrocortisone equivalent >24 mg (aHR, 1.91 [95% CI, 1.05-3.47), birth <37 weeks gestational age (aHR, 2.38 [95% CI, 1.19-4.78]), male sex (aHR, 1.89 [95% CI, 1.00-3.55]), and gestational exposure in the second trimester (aHR, 6.70 [95% CI, 2.17-20.64]).

These findings suggest that gestational exposure to SG is associated with CKD in childhood. If further studies confirm these results, they may help enlighten clinicians who are considering prescribing SG during pregnancy.

Is CKD Associated With Age-Related Macular Degeneration?

Ophthalmology. doi:10.1016/j.ophtha.2023.12.030

CKD shares risk factors, pathogenic mechanisms, and genetic polymorphisms with age-related macular degeneration (AMD). It is also possible that CKD can increase susceptibility to AMD. However, previous research exploring an association between CKD and AMD has been inconclusive.

Can Can Xue, PhD, and colleagues further investigated the matter in a cross-sectional study using datasets from the Asian Eye Epidemiology Consortium. They conducted a pooled analysis using individual-level participant data to study associations between CKD and eGFR with early and late AMD adjusted for sex, age, BMI, smoking status, hypertension, diabetes, total cholesterol, and study groups.

The primary study outcome was odds ratio of early AMD and late AMD. The researchers defined AMD using the Wisconsin Age-Related Maculopathy Grading System, the International Age-Related Maculopathy Epidemiological Study Group classification, or the Beckman clinical classification. They defined CKD as eGFR <60 mL/min/1.73 m².

Of the 51,253 study participants (mean age, 54.1±14.5 years), 9.90% (5,079) had CKD, 9.00% had early AMD, and 0.71% had late AMD. Patients with CKD had higher odds of late AMD (OR, 1.46; 95% CI, 1.11-1.93; P=.008) after adjusting for confounders. Worse kidney function (per 10-unit eGFR decrease) was associated with late AMD (OR, 1.12; 95% CI, 1.05-1.19; P=.001), but CKD and eGFR did not demonstrate a significant association with early AMD (all P≥.149).

The findings show that CKD and compromised kidney function are significantly associated with late AMD, emphasizing the importance of eye exams for patients with CKD.

Effects of Restarting RASi Therapy After Discontinuation

Journal of the American Society of Nephrology. doi:10.1681/ASN.0000000000000425

Renin-angiotensin system inhibitors (RASi) are a common treatment for CKD but are often discontinued due to hyperkalemia and AKI. To determine whether restarting RASi after discontinuation would improve clinical outcomes, **Koki Hattori** and colleagues performed a target trial emulation study using the Osaka Consortium for Kidney Disease Research database.

The study cohort comprised 6,065 patients with an eGFR of 10-60 mL/min/1.73 m² who discontinued RASi between 2005 and 2021. The researchers used a clone-censor-weight approach to compare a treatment strategy for restarting RASi within a year after discontinuation with not restarting RASi. The study's primary outcome was a composite kidney outcome (initiation of kidney replacement therapy, a ≥50% decline in eGFR, or kidney failure [eGFR <5 mL/min/1.73 m²]). Secondary outcomes included all-cause death and incidence of hyperkalemia (serum potassium levels ≥5.5 mEq/L). Patient follow-up was 5 years maximum after RASi discontinuation.

Mean age was 66 (SD 15) years, 62% of subjects were male, and mean eGFR was 40 (SD 26) mL/min/1.73 m². In total, 2,262 patients (37%) restarted RASi within a year. Restarting RASi was associated with a lower risk of the composite kidney outcome (HR, 0.85; 95% CI, 0.78-0.93) and all-cause death (HR, 0.70; 95% CI, 0.61-0.80) compared to not restarting RASi. There was no significant difference in hyperkalemia incidence between the two strategies (HR, 1.11; 95% CI, 0.96-1.27).

The findings support a proactive approach to restarting RASi among patients with CKD.

COVID-19

Predictors of AKI in VA Patients With COVID-19

Vaccines. 2024;12(2):146

Information about AKI among patients with COVID-19 is lacking. To fill the knowledge gap, **Lilia R. Lukowsky** and colleagues used logistic regression models to examine predictors of AKI among a population of US veterans and also performed a survival analysis to study mortality in patients with COVID-19. The study involved 742,799 patients, of whom 95,573 were hospitalized within 60 days of a COVID-19 diagnosis.

The following factors were associated with AKI: use of vasopressors (OR, 14.73; 95% confidence limit [CL], 13.96-15.53), history of AKI (OR, 2.22; 95% CL, 2.15-2.29), male

gender (OR, 1.90; 95% CL, 1.75-2.05), Black race (OR, 1.62; 95% CL, 1.57-1.65), and age ≥65 years (OR, 1.57; 95% CL, 1.50-1.63).

Patients who were vaccinated against COVID-19 twice and had received boosters were the least likely to develop AKI (OR, 0.51; 95% CL, 0.49-0.53) compared to unvaccinated COVID-19 patients. Those who had two doses (OR, 0.77; 95% CL, 0.72-0.81) or a single dose (OR, 0.88; 95% CL, 0.81-0.95) were also less likely to develop AKI compared to unvaccinated patients.

Patients with AKI had four times higher mortality compared to those without AKI (HR, 4.35; 95% CL, 4.23-4.50). Vaccinated and boosted patients had the lowest mortality risk compared to unvaccinated patients (HR, 0.30; 95% CL, 0.28-0.31).

Vasopressor use, unvaccinated status, older age, male gender, and Black race were associated with AKI post–COVID-19. However, it is unclear whether COVID-19 vaccination, including boosters, lessens the risk of developing AKI.

DIABETES

Concordance With CKD Screening, Treatment Guidelines in T2D

JAMA Network Open. doi:10.1001/jamanetworkopen.2024.18808

CKD is a complication of type 2 diabetes (T2D) that requires annual screening for diagnosis. **Daniel Edmonston, MD, MHS,** and colleagues identified risk factors for nonconcordance with CKD screening and treatment guidelines in patients with T2D in a retrospective study at 20 health care systems.

The study included adults with an outpatient clinician visit associated with T2D diagnosis and without known CKD. Researchers conducted a separate review of prescription of angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) and sodium-glucose cotransporter 2 (SGLT2) inhibitors in adult patients with CKD (eGFR 30-90 mL/min/1.73 m^2 and UACR 200-5,000 mg/g) who had an outpatient clinician visit for T2D.

The study assessed concordance with CKD screening guidelines in 316,234 adults (median age, 59 [IQR, 50-67] years). A total of 51.5% were women, and 67.6% were White, 21.7% were Black, and 10.3% were Hispanic. Screening required measurement of creatinine levels and UACR within 15 months of the index visit. Treatment reflected prescription of ACEIs or ARBs and SGLT2 inhibitors within 12 months before or 6 months following the index visit.

Only 24.9% of patients had creatinine and UACR screening, 56.5% had one of the recommended screenings, and 18.6% had neither. Hispanic ethnicity was associated with not receiving screening (relative risk, 1.16; 95% CI, 1.14-1.18). Heart failure, hypertension, and peripheral arterial disease were associated with a lower risk of nonconcordance.

Of 4,215 patients who had CKD and albuminuria, 3,288 (78.0%) received an ACEI or ARB, 194 (4.6%) received an SGLT2 inhibitor, and 885 (21.0%) received none of those therapies. Peripheral arterial disease and lower eGFR were associated with CKD nontreatment. Hypertension or prescription of a diuretic or statin were associated with CKD treatment.

Patient-level factors could play a role in future strategies to improve CKD screening and treatment in patients with T2D.

Print-only Content

HYPERKALEMIA

Fiber and Hyperkalemia in Maintenance Hemodialysis Patients

Journal of Renal Nutrition. doi:10.1053/ j.jrn.2024.07.016

A group of researchers, including **Hui Li, MD,** studied the relationship between dietary fiber intake and hyperkalemia in 110 maintenance hemodialysis patients. The cohort of 67 males and 43 females was divided into two groups according to their predialysis serum potassium levels: those with normal serum potassium and a hyperkalemia group (serum potassium >5.5 mmol/L; n=38). There was no difference between the two groups in sex, residual kidney function, history of receiving potassium-lowering drugs, BMI, or intake of energy, fat, protein, calcium, sodium, or phosphorus (*P*>.05).

Diets were recorded using the 3-day dietary recording method, and daily dietary nutrient intake was analyzed. Researchers used logistic regression to analyze the relationship between fiber intake and hyperkalemia. Those in the normal group had higher carbohydrate intake (315±76 g/d vs 279±66 g/d, *P*=.016), dietary fiber intake (19±5 g/d vs 12±8 g/d, *P*<.0001), and potassium intake (1,698±392 mg/d vs 1,533±413 mg/d, *P*=.041) than patients in the hyperkalemia group. More patients in the normal group used RASi (52.78% vs 23.68%, *P*=.003).

Logistic regression analysis found that fiber

intake was an independent protective factor for hyperkalemia (OR, 0.766; 95% CI, 0.675-0.870; *P*<.0001), and receiver operating characteristic analysis showed that daily intake of fiber greater than 15.33 g may be helpful to prevent hyperkalemia.

The authors found that insufficient dietary nutrient intake is widespread in maintenance hemodialysis patients. This insufficiency may be associated with hyperkalemia and thus dietary balance should be of clinical concern.

TRANSPLANTATION

Cognitive Function Post-Transplantation

American Journal of Kidney Diseases. doi:10.1053/j.ajkd.2023.12.022

Kidney disease is known to negatively affect cognition. **Aditi Gupta, MD, MS,** and other researchers questioned the effect of kidney transplantation (KT) on cognitive abilities. They examined the effect of KT on different areas of cognition in a prospective cohort study of patients waitlisted for KT at an academic center.

The team measured cognitive function before KT (n=101), 3 months after KT (n=78), and 1 year after KT (n=83). The primary outcome was the change in cognitive function before versus after KT. They used tests for global cognition (Mini-Mental State Exam [MMSE]), episodic/declarative memory (Logical Memory), psychomotor speed/visuospatial function (Digit Symbol Substitution Test [DSST], Trail Making Test [TMT] A), working memory/attention (Digit Span), executive function (TMT B), and semantic memory/verbal fluency/language (Category Fluency). Using linear mixed model analysis, the researchers evaluated the changes in neuropsychological test scores adjusted for age, sex, race, education, and number of assessments.

Episodic and verbal declarative memory were found to normalize after KT, while semantic memory, verbal fluency, language, psychomotor speed, and visuospatial function showed partial improvement.

Prior to KT, Logical Memory I and II, DSST, MMSE, Category Fluency (animal naming), and Digit Span backward scores were low compared to normative values from the National Alzheimer's Coordinating Center data. Logical Memory I and II scores improved after KT (pre- vs post-KT: estimated group difference [d], 3.3; *P*<.001 for Logical Memory I; d, 4.27; *P*<.001 for Logical Memory II); post-KT scores were comparable with normative values (post-KT vs normative values: d, −0.37; *P*=.06 for Logical Memory I; d, −0.89; *P*=.08 for Logical Memory II). Category Fluency (d, 2.40; *P*<.001) and DSST (d, 3.12; *P*=.01) scores improved with KT, although post-KT DSST scores remained lower than normative values (post-KT vs normative values: d, −5.17; *P*<.001). MMSE, Digit Span, and TMT A and B scores did not change post-KT.

In sum, cognitive impairment in kidney disease is at least partially reversible with KT. ■

Print-only Content

Sarah Tolson

Critical Financial Shifts Ahead: How CY 2025 ESRD PPS Changes Could Impact Small Dialysis Facilities

As they do every year, the Centers for Medicare & Medicaid Services (CMS) released the proposed rule for the End-Stage Renal Disease Prospective Payment System (PPS) for calendar year (CY) 2025, which outlines several significant changes that will directly affect the financial health of dialysis facilities. For administrators of small and medium dialysis organizations, understanding these proposed updates is crucial to navigating the financial landscape ahead. This article highlights the key financial implications of the proposed rule and how they may affect your facility's bottom line.

While we have yet to see the CMS ESRD PPS Final Rule, one thing is clear: there will be significant reimbursement changes for CY 2025. Several of the notable changes being proposed for next year are the base rate of $273.20, a potential ESRD PPS-specific wage index, changes to items that would contribute to an outlier adjustment, a revamp of the Low-Volume Payment Adjustment (LVPA) structure, and inclusion of oral-only drugs in the ESRD PPS, just to name a few. Let's dive into the details.

CY 2025 ESRD PPS BASE RATE

The proposed base rate for CY 2025 is $273.20—an increase of $2.18 (0.8%) from the CY 2024 base rate of $271.02. One thing to keep in mind is that, due to adjustments for wage index, your program's base rate could be more or less than the amount above. CMS does intend to keep a wage index floor of 0.6000 and a 5% cap on wage index decreases year after year.

WAGE INDEX

CMS proposed using an ESRD PPS-specific wage index to adjust ESRD PPS payments for geographic differences in area wages. This proposed wage index would combine data from the Bureau of Labor Statistics Occupation Employment Wage and Statistics program and freestanding ESRD facility cost reports to calculate an ESRD PPS-specific wage index instead of the hospital data currently being used to determine wage index values for each geographic area.

OUTLIER POLICY

CMS has proposed expanding the list of ESRD outlier services to comprise drugs and biologicals that were included in the composite rate prior to the ESRD PPS. CMS has indicated that the intent behind this change is to increase the outlier payment per qualifying claim. The target for outlier payments would continue to be 1% of all payments, so while the outlier payment per claim may increase, the number of qualifying claims would decrease.

LOW-VOLUME PAYMENT ADJUSTMENT TIERED APPROACH

Small dialysis programs that provide fewer than 4,000 treatments per year for the three most recent cost-reporting periods have been eligible for a 23.9% payment adjustment under the LVPA. CMS is proposing that facilities with less than 3,000 treatments receive a 28.4% payment adjustment, and facilities rendering between 3,000 and 3,999 treatments receive an 18.1% payment adjustment. While this may ease the burden of being a dialysis program with approximately 19 patients, it may present challenges for programs in the 20 to 24 patient range.

ESRD PPS INCLUSION OF ORAL-ONLY DRUGS

At the time of this writing, it appears that dialysis programs should be preparing for the inclusion of oral-only drugs in the ESRD PPS. CMS has estimated that including oral-only drugs in the ESRD PPS will increase Medicare spending by $180 million in CY 2025. In addition, CMS intends for this change to expand access to these medications for patients who do not have Medicare Part D coverage.

Each year, when CMS publishes the ESRD PPS proposed and final rules, they also publish facility-level impact files that allow dialysis programs to estimate the monetary impact of the changes on their program. If you have not yet estimated your program's potential monetary impact for 2025, taking the time to do so may take the element of surprise out of next year's Medicare reimbursement. Just remember, we have yet to see the CY 2025 ESRD PPS Final Rule. ■

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