Nephrology Times

Practical News, Trends, and Analysis

January/February 2025

VOLUME 17, NUMBER 1

CKD RISK & APOL1 VARIANTS

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Barry Brenner: A Life Well Lived

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

Barry M. Brenner, MD, passed away August 6, 2024. Following is an excerpt of my remarks regarding Barry at the American Society of Nephrology (ASN) Brigham and Women's Hospital alumni reception.

"I knew Barry Brenner from summer 1998 until his demise—over 25 years—in my role as clinical chief at Brigham. I also connected socially, where I saw a human side of him—a gentleness with his beloved grandchildren and a love of fine things.

"To say that Barry was gifted is an understatement. He was without question the iconic nephrologist of our generation, but there were other aspects that stood out: his fierce loyalty to his family (Jane, Rob, Jenny, and his grandchildren) and to his friends (Dick Glassock, Beppe Remuzzi, John Dirks, Mark Zeidel, Julia Troy, Michelle Deraney, and Lee Riley, among many others); his stubborn determination to get answers to questions in nephrology through deep study, a clarity of purpose, and a dogged pursuit of the scientific method; his humanness, at times imperfect; his remarkable and unheralded generosity; and his commitment to the larger mission (the clinical applications of his research, leading various societies and journals, editing books, talking around the world for COMGAN [the International Society of Nephrology's Commission for the Global Advancement of Nephrology], or offering advice and career counseling to his many trainees)."

Julia Troy, MD, who spent virtually her whole career working with Barry, wrote, "Barry was my best friend, and I miss him terribly. He and Jane would always include me in their family events, and I have had the joy of being close to their children, Rob and Jenny (and their spouses), as well as their beautiful grandchildren.

"Working for Barry was a wonderful experience. He was extraordinarily inquisitive. He would think of something and would give it to me to figure out, expecting a yes or no answer, and he didn't take no for an answer. I was at a complete loss when the lab closed. It was a fun job, and I enjoyed going to work every day.

"We started working together at the National Institutes of Health. We went to San Francisco, then came together to Boston (Brigham/Harvard) in 1975—a time I will never forget, as Boston was celebrating the bicentennial, and the city was so beautiful and welcoming.

"Glomerular studies in rats were a new field. Nothing was in the literature about how the glomerulus functioned. Utilizing the limited instrumentation available to us at that time, and with Barry's unique ability to conceptualize how to measure pressure in rats properly, the original techniques of micropuncture and measuring glomerular pressure were developed.

"Barry invited fellows from all around the world to train with him, and his greatest gift was educating them to become leaders of their own research laboratories and clinical studies. In all of Barry's publications, he took great pleasure in giving credit to each one that worked in his laboratory."

Dick Glassock, MD, one of Barry's closest friends, former president of the ASN and himself a major figure in nephrology, shared, "His contributions to our noble profession are legion, impactful, and lasting. The magisterial hypotheses he and his valued colleagues originated, now morphed into accepted theories, on physical forces controlling tubular fluid reabsorption and glomerular filtration maladaptive glomerular hyperfiltration injury, glomerular capillary hypertension, and the adverse consequences of low nephron endowment, can be equated with other landmark achievements in the broad domain of science, including those of Isaac Newton in physics. Collectively, they have exerted a profound impact on clinical practice and led to improved and prolonged lives for millions of those who suffer from the ill effects of kidney disease."

Lee Riley and **Michelle Deraney,** who began working for Barry in their 20s, marking over 40 years with him, shared a playful, easygoing side of him that many of us did not know.

Michelle Deraney said, "Lee and I loved playing pranks on Dr. Brenner. One time after a holiday party, we literally stuffed 50-plus helium-filled balloons in his office bathroom. He came in the next morning (he always arrived around 4:30 or 5 am), and without turning a light on, opened the bathroom door. The balloons all came rushing out at him, and he claimed he had to put up his fists to fight the intruders off. He got over the incident and had a good laugh with us.

"Another time, we planted a rubber chicken in his briefcase right before he left for the day. At home, in the middle of night (when he often reached for an index card and pen to write his thoughts), he woke Jane up to say he thought there was a rat in his briefcase. He and she both got a broom ready to defend themselves. The next morning, he actually took the time to hang the rubber chicken up under the desk."

Dr. Brenner, not only did you have a life well lived, but you made a massive difference to the world. ●

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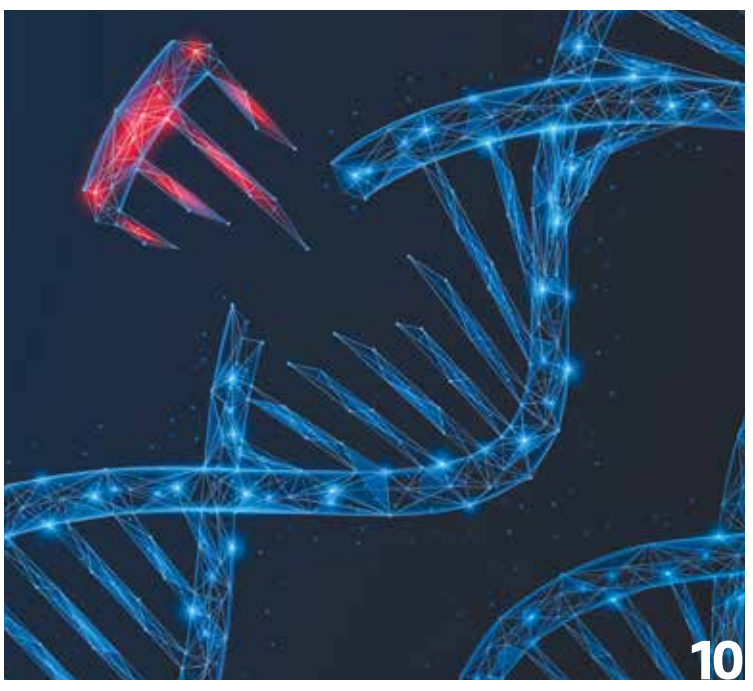
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Registered Dietitian Nutritionists Can Help Prevent Kidney Stones

Melanie Betz, MS, RD, CSR, FNKF, FAND

An estimated 10% of US adults will have a kidney stone; 75% will have a stone recurrence within 20 years.[1,2] The economic impact of lost work due to stones is massive, with an estimated $5 billion lost annually in the United States.[3]

Kidney stones are associated with common chronic diseases such as hypertension, chronic kidney disease (CKD), diabetes, metabolic syndrome, and bone disease.[2] Between the high recurrence rate and increased risk of developing other chronic diseases, health care professionals should not take kidney stones lightly. Nutrition is key for the treatment of metabolic conditions such as diabetes and heart disease, as well as the prevention of kidney stones. In fact, research suggests that diet is a significant driver for the increasing prevalence of kidney stones.[4]

Environmental factors that increase stone risk include living in a warm environment, lack of access to a bathroom, and stress.[5-7] A diet that is high in sodium, nondairy animal protein, and added sugar and lacking in fruits, vegetables, and calcium can also increase stone risk.[8] Many health conditions predispose a patient to kidney stones, including inflammatory bowel disease, hyperparathyroidism, and eating disorders. Gastric bypass surgery is also associated with stones.[2]

It is imperative that people with kidney stones get metabolic testing to identify the most probable cause of kidney stone disease. A 24-hour urine collection is the gold standard to assess kidney stone risk and is recommended by the American Urological Association (AUA) to be completed annually for all high-risk, recurrent, or interested stone formers.[9] Yet only 7% of people with kidney stones will get a 24-hour urine collection, indicating that a small percentage of people with kidney stones get the testing required for targeted, effective kidney stone prevention.[10]

Seven of the recommendations in the AUA's *Medical Management of Kidney Stones* include dietary changes, such as reducing sodium or nondairy animal protein and increasing dietary calcium or fruits and vegetables depending on 24-hour urine chemistries and stone composition.[9] A 2014 study found that 82% of urologists believe patients with kidney stones should be given dietary advice.[11] However, less than 50% of urologists report assessing a patient's diet before providing nutrition recommendations, and 36% feel they do not have enough time to provide nutrition education.[11]

Registered dietitian nutritionists (RDNs) are uniquely trained to provide both nutrition education and counseling to patients for the prevention and treatment of chronic diseases, including kidney stones. Medical nutrition therapy provided by an RDN has been shown to improve outcomes in a variety of health conditions, including CKD.[12] Counseling strategies such as motivational interviewing can induce behavior change and improve health outcomes, including by reducing hemoglobin A1c, cholesterol, and blood pressure.[13] A 2016 study found that shared medical appointments that included an RDN resulted in improved 24-hour urine chemistries.[14]

Despite these benefits, only 23% of urology clinics partner with a registered dietitian in any capacity.[11] The presence of RDNs in nephrology clinics is also limited.[15] This problem is exacerbated by inaccurate and generic kidney stone handouts provided in the emergency room and misinformation found online.[16,17]

It is imperative that an RDN trained in kidney stone prevention assess patients with kidney stones to make tailored dietary recommendations based on 24-hour urine chemistries, past medical history, lab values, current eating habits, and food preferences. Registered dietitians can also use behavior change strategies to help patients make difficult lifestyle changes to improve outcomes and reduce the risk of stone recurrence.

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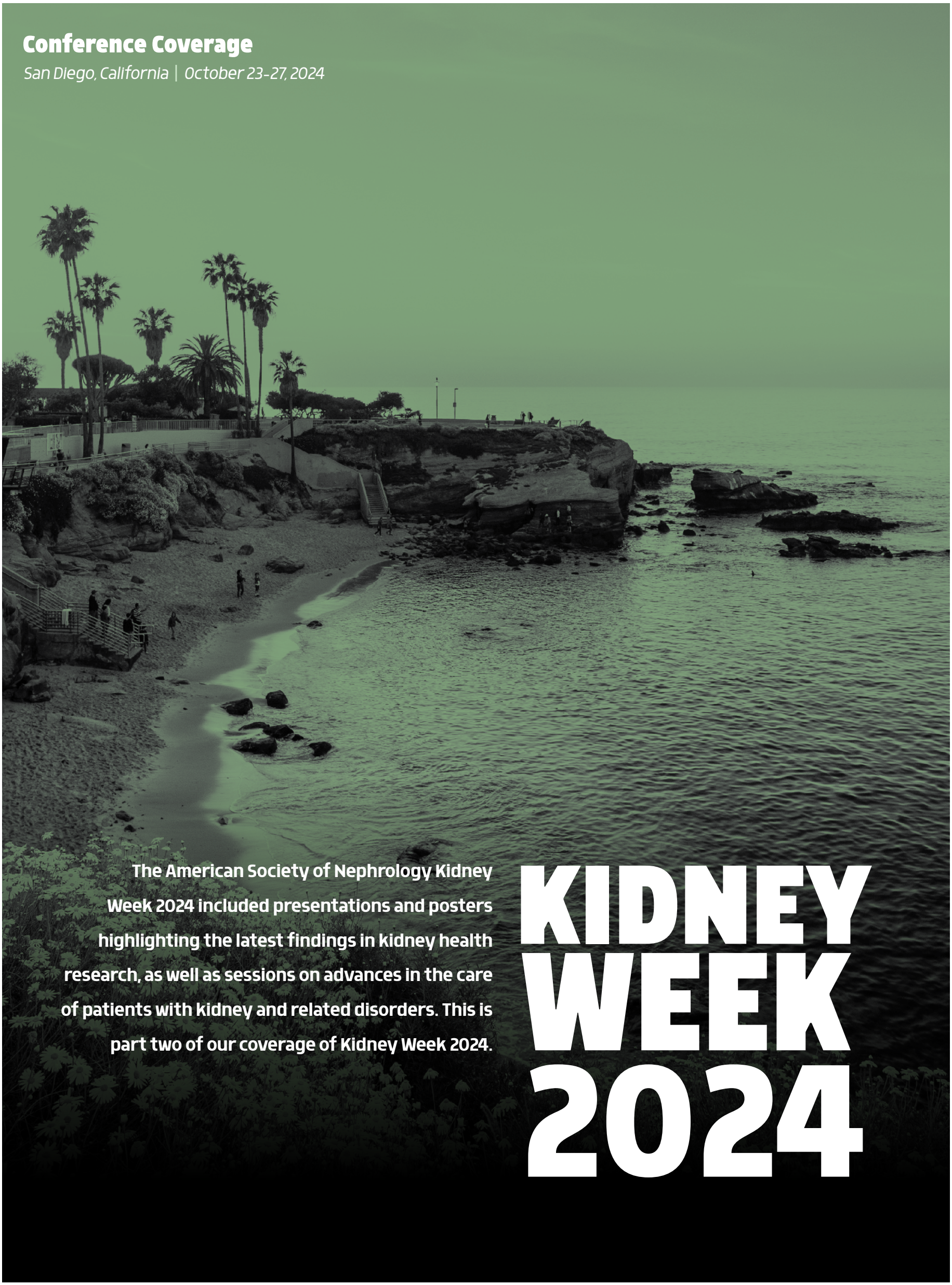
Conference Coverage

San Diego, California | October 23-27, 2024



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KIDNEY WEEK 2024

EMPA-KIDNEY Post-Trial Findings

The EMPA-KIDNEY trial assessed the effects of treatment with empagliflozin on patients with chronic kidney disease (CKD) at risk for disease progression. During an oral presentation at ASN Kidney Week 2024, **William G. Herrington, MBBS, MD,** and colleagues described findings from an additional two years of post-trial follow-up (PTFU). The session was titled *Long-Term Effects of Empagliflozin in CKD.*

The study included patients with estimated glomerular filtration rate (eGFR) of 20-44 mL/min/1.73m^2 or eGFR 45-89 mL/min/1.73m^2 and urine albumin-to-creatinine ratio (UACR) of ≥200 mg/g. Participants were randomized to empagliflozin or placebo and received treatment for a median of two years. After the study period, participants were studied off treatment, and local physicians could initiate an open-label sodium-glucose cotransporter-2 (SGLT2) inhibitor (maintaining blinding to the original allocation).

The primary composite outcome was progression of kidney disease or cardiovascular death for the full follow-up period (combination of the within-trial and PTFU periods). Of 6,609 randomized participants, 4,895 were included in PTFU and followed for a median of two years. SGLT2 inhibitor use was similar between the empagliflozin (43%) and placebo (40%) groups during the PTFU period.

In the empagliflozin group, a primary outcome occurred in 865 of 3,304 (26.2%) patients, and in the placebo group, a primary outcome occurred in 1,001 of 3,305 (30.3%) patients over the entire follow-up period (hazard ratio [HR], 0.79; 95% CI, 0.72-0.87). Relative effects on the primary outcome did not significantly differ across key subgroups, such as diabetes, eGFR, and UACR. Post-trial, there was a 13% (HR, 0.87; 95% CI, 0.76-0.99) reduction in risk of the primary outcome, meaning the absolute differences in the primary outcome were 57 (standard error [SE] 14) per 1,000 at the end of the within-trial period and 45 (SE 14) at the end of PTFU.

Assignment to the empagliflozin treatment decreased the risk of kidney disease progression (23.5% vs 27.1%), the composite of death or end-stage renal disease (16.9% vs 19.6%), and cardiovascular death (3.8% vs 4.9%).

In conclusion, the post-trial follow-up of EMPA-KIDNEY provides a more complete measurement of the total effects of two years of empagliflozin. Although the drug provided benefits for cardiorenal outcomes for a period after discontinuation, the post-trial benefit was smaller than during treatment and seemed to be temporary. "To maximize the cardiorenal clinical benefits of SGLT2 inhibitors therefore requires long-term treatment of patients with CKD," the researchers concluded.

Source: Herrington WG, Staplin N, Agrawal N, Haynes R. Long-term effects of empagliflozin in CKD. FR-OR103. Abstract of an oral presentation at the American Society of Nephrology Kidney Week 2024; October 25, 2024; San Diego, California. Commercial support was provided by Boehringer Ingelheim.

Effects of Hyponatremia Correction on Mortality and Rehospitalization

Hyponatremia is associated with higher mortality and rehospitalization, but it was unknown whether this is a causal relationship, making the problem difficult to correct. Therefore, **Julie Refardt** and colleagues evaluated the direct effects on mortality and rehospitalization rates of targeted hyponatremia correction versus routine care. They presented results at ASN Kidney Week 2024 in the oral session, *Impact of Targeted Hyponatremia Correction on 30-Day Mortality and Rehospitalization Rate.*

The researchers conducted a randomized, controlled, superiority, parallel-group, international, multicenter trial with blinded outcome assessment. The study included 2,174 patients hospitalized with hyponatremia <130 mmol/L from nine tertiary centers throughout Europe. Of the full cohort, 1,079 (49.6%) patients were randomized to undergo targeted correction of plasma sodium levels according to guidelines (intervention group), while 1,095 (50.4%) were assigned routine care for hyponatremia (control group). The primary outcome was the combined risk of death or rehospitalization within 30 days of inclusion in the study.

Of the intervention group, 641 (60.4%) patients achieved normonatremia compared to 493 (46.2%) patients in the control group. Within 30 days, death occurred in 93 (8.6%) patients in the intervention group, compared to 93 (8.5%) patients in the control group. Rehospitalization occurred among 138 (13.0%) patients in the intervention group and among 151 (14.0%) patients in the control group. This resulted in a combined event rate of 21.0% (224/1,079 patients) in the intervention group and 22.2% (239/1,095 patients) in the control group (estimated absolute difference in proportions 95% CI, -1.2% [-4.7, 2.3]; P=.50).

The results remained strong in the per protocol analysis and in subgroup analyses accounting for hyponatremia etiology, severity, or correction rate. In conclusion, targeted plasma sodium correction did not reduce 30-day mortality or rehospitalization rates. "This suggests that in hospitalized patients, chronic hyponatremia is a marker of disease severity rather than a cause of worse outcome," the researchers concluded.

Source: Refardt J, Potasso L, Pelouto A, et al. Impact of targeted hyponatremia correction on 30-day mortality and rehospitalization rate. SA-OR91. Abstract of an oral presentation at the American Society of Nephrology Kidney Week 2024; October 26, 2024; San Diego, California.

Effect of Hypotension and Hypertension Avoidance Strategies on Postoperative AKI Risk

Acute kidney injury (AKI) is a common complication of noncardiac surgeries. To understand more about AKI prevention, **Amit X. Garg, MD, PhD,** and other researchers conducted a prespecified substudy of the POISE-3 trial (NCT03505723).

The goal of the study was to find out whether a perioperative hypotension-avoidance strategy changes the risk of postoperative AKI compared to a hypertension-avoidance strategy (substudy protocol publication: PMID 35024154). The results were presented at ASN Kidney Week 2024 during the oral session, *Effect of a Perioperative Hypotension Avoidance Strategy vs. a Hypertension Avoidance Strategy on the Risk of AKI.*

The study was an open-label, randomized trial involving 7,307 high-risk patients from 110 hospitals in 22 countries having noncardiac surgery. Participants were ≥45 years and were on at least one antihypertensive medication. The primary study outcome was postoperative AKI (an increase in serum creatinine concentration of either ≥26.5 µmol/L [≥0.3 mg/dL] within 48 hours of randomization or ≥50% within seven days of randomization).

There were two patient groups, one participating in a hypotension-avoidance strategy (n=3,654) and one participating in a hypertension-avoidance strategy (n=3653). Hypotension avoidance included target intraoperative mean arterial pressure (MAP) of ≥80 mmHg; aiming to hold renin-angiotensin-aldosterone system inhibitors on the day of surgery and for two days afterward; and stepwise use of other long-term antihypertensive medications if systolic blood pressure was ≥130 mmHg. The hypertension-avoidance strategy comprised target intraoperative MAP ≥60 mmHg and continuance of all antihypertensive medications pre- and post-surgery.

The hypotension-avoidance group used fewer angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers than the hypertension-avoidance group (6% vs 38% of patients on the day of surgery, 6% vs 47% one day post-surgery, and 7% vs 50% two days post-surgery). The hypotension-avoidance group also spent less intraoperative time with a MAP <80 mmHg than the hypertension-avoidance group (average 28% vs 45% of the time).

Meanwhile, there was no difference in mean systolic or diastolic blood pressure or MAP outside the surgery, meaning on the day of surgery and for two days after surgery. There also was no difference in the risk of AKI between the two groups.

The study results remained consistent with multiple alternate continuous and categorical definitions of AKI, as well as in a subgroup with baseline chronic kidney disease. In summary, the risk of postoperative AKI was similar whether patients received a hypotension-avoidance strategy or a hypertension-avoidance strategy.

Source: Garg AX, Marcucci M, Cuerden MS, Sontrop JM, Devereaux PJ. Effect of a perioperative hypotension avoidance strategy vs. a hypertension avoidance strategy on the risk of AKI. FR-OR107. Abstract of an oral presentation at the American Society of Nephrology Kidney Week 2024; October 25, 2024; San Diego, California.

Dapagliflozin Safety and Efficacy in Advanced CKD

Dapagliflozin is known to improve kidney outcomes in patients with CKD, but it is unclear what effect late initiation of the drug has when eGFR is <25 mL/min/1.73 m^2.

To improve understanding, **Chi-Chih Hung, Yi-Wen Chiu,** and **Shang-Jyh Hwang** studied the efficacy and safety of dapagliflozin in patients with CKD stages 4 and 5. They shared findings during the oral presentation, *Efficacy and Safety of Dapagliflozin in Patients with CKD Stages 4-5 at ASN Kidney Week 2024*.

The DAPA advKD trial (NCT05196347) was a randomized, open-label trial that recruited 180 patients with eGFR 10-30 mL/min/1.73 m^2 and eGFR decline ≥2.5 mL/min/1.73 m^2/year. These patients were randomized 2:1 to dapagliflozin (5-10 mg/d) plus integrated CKD care, or integrated CKD care only.

The primary study outcome was maintenance of eGFR decline ≥0.75 mL/min/1.73 m^2/year. The first secondary outcome was renal endpoint (a composite of renal replacement therapy, eGFR <5 mL/min/1.73 m^2, renal or cardiovascular [CV] death, or a >50% eGFR decline). The second secondary outcome was renal and CV endpoint (a composite of renal outcome as defined above, AKI, and heart failure). Predefined safety outcomes were measured.

During a median period of 1.62 years, total eGFR slopes were -2.24 mL/min/1.73 m^2/year (-4.70 to -0.62 mL/min/1.73 m^2/year) for the dapagliflozin group and -3.67 mL/min/1.73 m^2/year (-7.16 to -1.25 mL/min/1.73 m^2/year) for the control group. The primary outcome of eGFR slope decline was 1.06 mL/min/1.73 m^2/year (0.10 to 0.32 mL/min/1.73 year; P=.019, linear mixed model).

The secondary renal outcome occurred in 24/120 (20%) patients in the dapagliflozin group, and in 21/60 (35%) in the control group (HR, 0.50 [0.28 to 0.89], P=.019). The secondary renal and CV outcome occurred in 25/120 (21%) patients in the dapagliflozin group and 21/60 (35.0%) in the control group (HR, 0.52 [0.29 to 0.93], P=.028). The control group experienced higher rates of heart failure and AKI but had a higher incidence of eGFR decline.

The researchers concluded, "Among patients with eGFR 10-30 mL/min/1.73 m^2, the risks of eGFR decline and composite renal outcomes were lower with dapagliflozin than with control group."

Source: Hung C-C, Chiu Y-W, Hwang S-J. Efficacy and safety of dapagliflozin in patients with CKD stages 4-5. SA-OR96. Abstract of an oral presentation at the American Society of Nephrology Kidney Week 2024; October 26, 2024; San Diego, California. Funding was provided by AstraZeneca.

Effect of Sparsentan Versus Irbesartan With Genetic FSGS

The DUPLEX trial examined the efficacy and safety of two potential treatments for focal segmental glomerulosclerosis (FSGS): sparsentan and irbesartan. Sparsentan demonstrated a greater reduction in proteinuria, but it is unclear whether its efficacy depends on the underlying pathogenesis of FSGS.

Genetic FSGS (gFSGS) is caused by mutations in podocyte genes and tends to be hard to treat. In a post hoc analysis of DUPLEX data, **Jennifer Lai Yee, MD, PhD,** and colleagues evaluated the efficacy of sparsentan in a subset of patients with gFSGS. Their results were shared in a poster at ASN Kidney Week 2024 titled *Outcomes of the DUPLEX Trial in Patients With Genetic Focal Segmental Glomerulosclerosis (gFSGS)*.

Three hundred and fifty-five DUPLEX patients were genotyped by the FSGS panel of PreventionGenetics. Those who had pathogenic or likely pathogenic variants in podocyte genes were classified as having gFSGS with Mendelian inheritance. In total, 8.7% (n=31) of patients were identified as having gFSGS. These patients were younger and had higher eGFR compared to the overall DUPLEX population at baseline, and most of them had proteinuria within nephrotic range.

The post hoc analysis studied changes in proteinuria, namely percentage reduction or achievement of complete remission (urine protein-to-creatinine ratio <0.3 g/g at any time) and percentage of patients reaching end-stage kidney disease (eGFR <15 mL/min/1.73 m^2, dialysis, or transplant) with sparsentan compared to irbesartan.

Sparsentan demonstrated a faster and more pronounced reduction in proteinuria than irbesartan. The effect was sustained and was also observed in a subset of patients with *NPHS2* mutations.

The only patients with gFSGS to achieve complete remission were those treated with sparsentan (n=1 [8%] vs n=0). Patients with gFSGS taking irbesartan more often reached end-stage kidney disease (n=3 [17%] vs n=1 [8%]). A pronounced early antiproteinuric response that was sustained over the treatment period was more common with sparsentan than with irbesartan.

The researchers concluded, "The findings support a recommendation for [sparsentan] administration to reduce proteinuria and achieve long-term kidney health benefits in this high-risk group of patients with gFSGS."

Source: Lai Yee J, Gong W, Inrig JK, Rheault MN, Komers R, Trachtman H. Outcomes of the DUPLEX trial in patients with genetic focal segmental glomerulosclerosis (gFSGS). TH-P01199. Abstract of a poster presented at the American Society of Nephrology Kidney Week 2024; October 24, 2024; San Diego, California. Commercial support for the study was provided by Travere Therapeutics, Inc.

Effect of Bardoxolone Methyl on eGFR in ADPKD

Interstitial fibrosis is found in nephrectomy samples of patients with autosomal dominant polycystic kidney disease (ADPKD). Bardoxolone methyl (BARD) is a potential treatment known to activate the nuclear-factor-related factor 2 pathway, which is believed to reduce inflammation and fibrosis.

Shuchi Anand, MD, and colleagues designed the FALCON trial (NCT03918447) to determine the safety and efficacy of BARD in patients with ADPKD. They presented their findings at ASN Kidney Week 2024 during the oral presentation, *Safety and Efficacy of Bardoxolone Methyl in Patients with Autosomal Dominant Polycystic Kidney Disease*.

FALCON was a phase 3, randomized 1:1, placebo-controlled clinical trial. Study participants had ADPKD, reduced eGFR (30-90 mL/min/1.73 m^2 for patients 12-55 years or 30-44 mL/min/1.73 m^2 for patients 56-70 years), and evidence of rapid eGFR decline (≥2.0 mL/min/year for two years). The primary endpoint was the change from baseline eGFR at week 108 (off treatment). The secondary endpoint was the change from baseline at week 100 (end of treatment). The trial's sponsor terminated the study early, before meeting target enrollment. There were 667 participants.

At baseline, the eGFR (mean [SD]) of the BARD (51.6 [15.5] mL/min/1.73 m^2) and placebo (51.2 [16.8] mL/min/1.73 m^2) groups were similar. Week 108 eGFR was available from 70 patients in the BARD group and 79 in the placebo group. There was no difference in the week 108 (off treatment) change from baseline between groups (0.97 [95% CI, -1.25 to 3.19] mL/min/1.73 m^2). At week 100 (end of treatment), eGFR was higher among BARD group participants (7.9 [95% CI, 6.41 to 9.47] mL/min/1.73).

Most patients in both groups (94% BARD, 89% placebo) experienced treatment-emergent adverse events. The most common adverse events in the BARD group were muscle spasms, aminotransferase elevations, and nausea. There were no serious cardiac events.

In conclusion, the authors said, "Among the subset of patients with available data on the primary endpoint in the FALCON trial, there was no evidence for preservation of eGFR among patients randomized to BARD at the end of 100 weeks of treatment and an eight-week washout period."

Source: Anand S, Chimalapati S, Montez-Rath ME, et al. Safety and efficacy of bardoxolone methyl in patients with autosomal dominant polycystic kidney disease. SA-OR97. Abstract of an oral presentation at the American Society of Nephrology Kidney Week 2024; October 26, 2024; San Diego, California. Commercial support provided by Reata.

Efficacy of SZC for Optimizing RAASi Treatment in DKD

Renin-angiotensin-aldosterone system inhibitors (RAASi) are the leading treatment for diabetic kidney disease (DKD), but their use can lead to hyperkalemia. However, reducing or discontinuing RAASi therapy impacts cardiorenal benefits.

Weiming Wang, MD, and colleagues examined the efficacy of adding sodium zirconium cyclosilicate (SZC) to allow patients with stage 3-4 DKD to maintain RAASi use. They presented the results of their research in a poster titled *Sodium Zirconium Cyclosilicate (SZC) to Enable Renin Angiotensin-Aldosterone System Inhibitor (RAASi) Use for Diabetic Kidney Disease: The CRYSTAL Study* at ASN Kidney Week 2024.

The study was a multicenter, open-label, randomized controlled phase 4 trial. Participants had stages 3-4 DKD with hyperkalemia, defined as serum potassium >5.0 mmol/L, within 90 days prior to enrollment. Patients were randomized 1:1 to SZC treatment (SZC + RAASi) or control (RAASi-only) groups. They were followed for 24 weeks, which included 12 weeks of RAASi titration and 12 weeks of maintenance. The primary endpoint was the percentage of participants with an increased RAASi dose by week 12.

There were 86 patients in the intention-to-treat (ITT) set and 56 who adhered to study protocol (per-protocol, PP) by June 28, 2024. The mean age among the ITT set was 58.7 years, and 59.3% were male.

Analyses of both the ITT and PP sets found that a higher percentage of patients in the SZC group achieved the endpoint of increased RAASi dose (angiotensin-converting enzyme inhibitor/angiotensin II receptor blocker) by week 12 compared to the control group. In the ITT set, 55.8% of the SZC group and 27.9% of the control group achieved a higher RAASi dose (P<.05). In the PP set, 71.4% of SZC group and 28.6% of control group patients achieved a higher dose (P<.05).

A higher percentage of SZC group patients in the PP set received ≥50% of the labeled maximum dose compared to control at weeks 12 (60.7% vs 42.9%) and 24 (53.6% vs 35.7%). Between baseline and week 24, UACR decreased in the SZC group (-63.5 mg/g) but increased in the control group (+316.9 mg/g). Adverse events occurred in 62.8% of SZC group participants and 72.1% of the control group.

In summary, the study found that using SZC to manage hyperkalemia may help improve RAASi treatment for Chinese stage 3-4 CKD patients with diabetes and hyperkalemia. "This can facilitate the use of RAASi at higher, guideline-recommended doses to achieve its cardiorenal benefits for DKD patients experiencing hyperkalemia," the authors said.

Source: Wang W, Gu L, Zang X, et al. Sodium zirconium cyclosilicate (SZC) to enable renin angiotensin-aldosterone system inhibitor (RAASi) use for diabetic kidney disease: the CRYSTAL study. TH-P01170. Abstract of a poster presented at the American Society of Nephrology Kidney Week 2024; October 24, 2024; San Diego, California. Commercial support for the study was provided by AstraZeneca China.

Effect of RGLS8429 on PC1/PC2 and htTKV in ADPKD

ADPKD is caused by mutations in the genes *PKD1* or *PKD2*. These mutations cause reduced expression or function of PKD-encoded proteins PC1 and PC2, resulting in dysregulated gene expression, overgrowth of renal tubular epithelia, formation of cysts, progressive enlargement of the kidneys, and decreasing renal function.

The microRNA miR-17 inhibits *PKD1* and *PKD2* and may play a role in the dysregulated gene expression that occurs in ADPKD. In several mouse models, treatment with the anti-miR-17 oligonucleotide RGLS8429 led to increased PC1 and PC2 and improvement of polycystic kidney disease.

Alan S.L. Yu, MB, BChir, and colleagues conducted a phase 2a multiple ascending dose trial of RGLS8429 in 42 human subjects with ADPKD. Their results were presented in a poster at ASN Kidney Week 2024 titled *RGLS8429 Increases Urinary PC1 and PC2 and May Reduce Height-Adjusted Total Kidney Volume (htTKV) in Patients With ADPKD.*

The randomized, double-blind, placebo-controlled study evaluated RGLS8429 in three weight-based cohorts (1, 2, and 3 mg/kg). Criteria for inclusion included Mayo imaging classification 1C, 1D, or 1E and an eGFR 30-90 mL/min/1.73 m^2. The duration of treatment was 12 weeks, with an end-of-study visit four weeks after the last dose.

Ten patients received subcutaneous injections of placebo once every two weeks (seven doses), while 32 patients received RGLS8429. Baseline characteristics were balanced between the placebo and RGLS8429 groups. Researchers measured urinary PC1 and PC2 levels before randomization and at multiple points afterward. An exploratory analysis was conducted to assess the change in htTKV from baseline to the end of the study.

The study found that RGLS8429 increased urinary PC1 and PC2 levels in a dose-dependent manner and was well tolerated. The change in PC1 and PC2 levels from baseline to study completion was statistically significant in the 3 mg/kg cohort (n=11) compared to the placebo cohort (n=9). Furthermore, 70% of participants who received 3 mg/kg RGLS8429 experienced a reduction in htTKV. The geometric least squares mean percentage change in htTKV over 16 weeks was 2.5, 1.4, -0.6, and -0.6 for the placebo, 1 mg/kg, 2 mg/kg, and 3 mg/kg groups, respectively.

In conclusion, RGLS8429 showed dose-responsive mechanistic activity on PC1 and PC2. The exploratory analysis indicates a reduction of htTKV at 2 mg/kg and 3 mg/kg doses over a short period. The researchers stated that the findings "validate miR-17 as a potential therapeutic target for ADPKD. A phase 2/3 registrational trial is being planned."

Source: Yu ASL, Garg R, Bellovich KA, et al. RGLS8429 increases urinary PC1 and PC2 and may reduce height-adjusted total kidney volume (htTKV) in patients with ADPKD. TH-P01200. Abstract of a poster presented at the American Society of Nephrology Kidney Week 2024; October 24, 2024; San Diego, California. Commercial support for the study was provided by Regulus Therapeutics.

Obinutuzumab Efficacy, Safety for FSGS Treatment

Ladan Zand, MD, and others examined the efficacy and safety of obinutuzumab, a type II anti-CD20 antibody, to treat patients with FSGS who were treatment resistant or dependent on immunosuppressive therapy. They reported findings in a poster presented at ASN Kidney Week 2024, titled *Single-Center, Phase 2, Open-Label Trial Evaluating the Efficacy and Safety of Obinutuzumab in Treatment of Immunosuppression-Resistant Primary FSGS, or Contraindication to High-Dose Corticosteroids.*

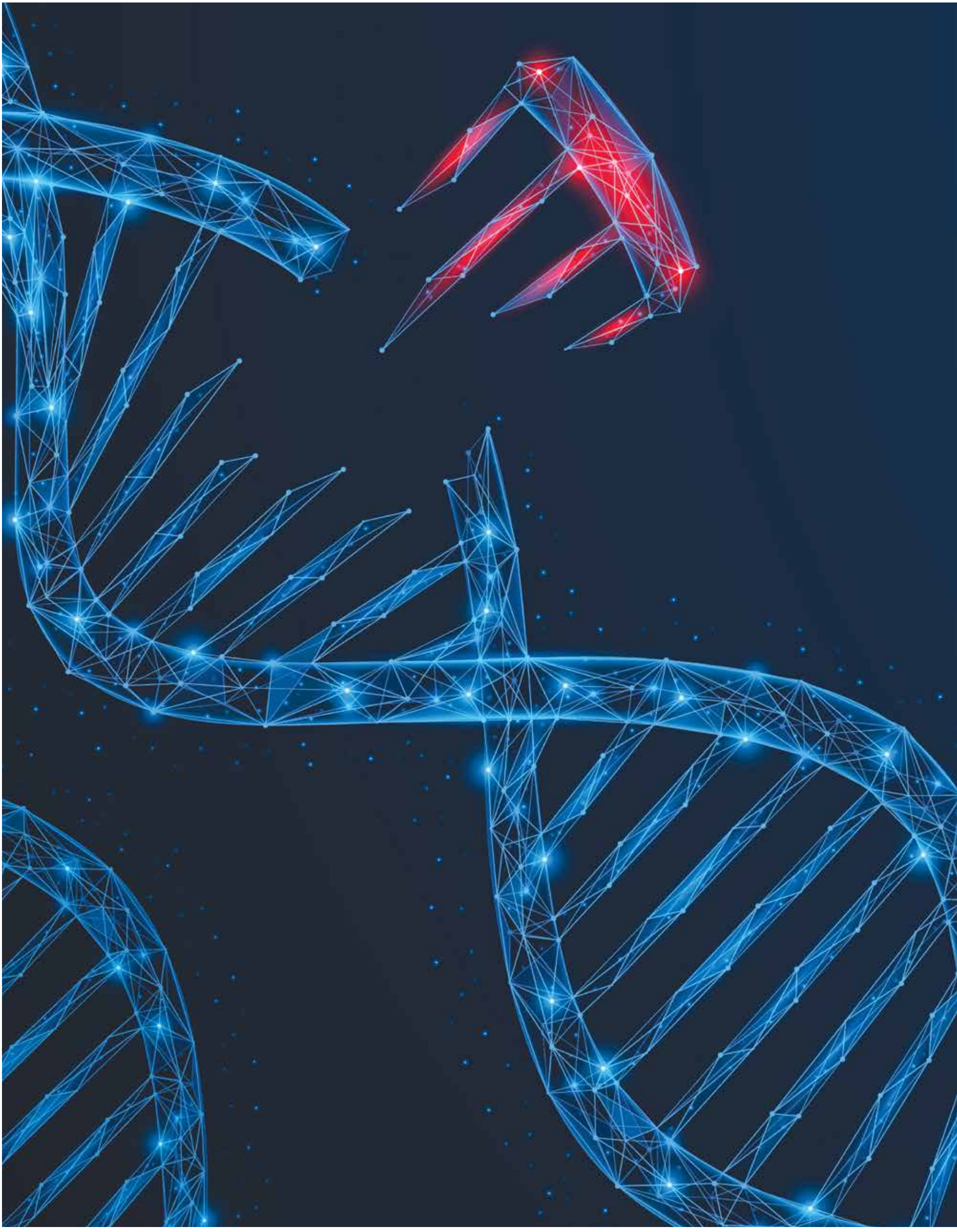
Study participants received two doses of 1 g obinutuzumab two weeks apart at baseline and six months. The primary outcome was the change in proteinuria from baseline to six and 12 months. Secondary endpoints included complete remission (proteinuria <0.3g/d) or partial remission (50% reduction in proteinuria and proteinuria <3.5 g/d) and rates of serious adverse events.

There were 20 patients in the study, and all had failed two to three prior therapies. The average age was 45.3±17.5 years and 55% were male. Systolic blood pressure was 132±17.5 mmHg and diastolic blood pressure was 77.1±9.5 mmHg.

Patients demonstrated a significant improvement in proteinuria, from 10.7 g/d (7.5-13.7) at baseline to 3.8 g/d (1.5-8.6)] at 12 months (P=.001). There were also significant improvements in serum albumin, cholesterol, and eGFR. At 12 months, eight patients (40%) achieved complete or partial remission, and none had a relapse. There were three serious adverse events, all of which were unrelated to obinutuzumab. Seven infusion-related adverse reactions and seven infections occurred, none of which resulted in hospitalization.

Overall, obinutuzumab significantly reduced proteinuria in patients with primary FSGS for whom two to three previous therapies had failed. "Reduction in proteinuria was associated with an improvement in eGFR and serum albumin with an acceptable side effect profile," the authors said.

Source: Zand L, Greene EL, Cheungpasitporn W, Vargas-Brochero MJ, Machado M, Sethi S, Ronco PM, Fervenza FC. Single-center, phase 2, open-label trial evaluating the efficacy and safety of obinutuzumab in treatment of immunosuppression-resistant primary FSGS, or contraindication to high-dose corticosteroids. TH-P01206. Abstract of a poster presented at the American Society of Nephrology Kidney Week 2024; October 24, 2024; San Diego, California. Commercial support for the study was provided by Genentech.



CKD RISK WITH APOL1 VARIANTS IN WEST AFRICAN INDIVIDUALS

Both biallelic and monoallelic risk variants increased CKD risk

The risk of chronic kidney disease (CKD) is four times greater for Black Americans compared to Americans of European ancestry. Variants in the apolipoprotein L1 gene (*APOL1*), found exclusively in Africans and people of African descent, are associated with higher risk of CKD and focal segmental glomerulosclerosis (FSGS) in Black people. The G1 and G2 variants have been identified as risk factors, and individuals who are homozygous or compound heterozygous for the G1 and G2 risk variants are at an increased risk for CKD from hypertension, kidney diseases such as FSGS, and human immunodeficiency virus-associated nephropathy.

However, few data exist regarding the genetic epidemiology of CKD and the clinical association of *APOL1* variants with CKD in West Africans. To address this gap, **R. A. Gbadegesin, MD, MBBS,** and colleagues conducted a case-control study of participants from Ghana and Nigeria to determine the association of *APOL1* risk variants and genotypes with CKD, including the type and severity of disease and the effect modification by clinical factors. The findings were published in *The New England Journal of Medicine* [doi:10.1056/NEJMoa2404211].

The study included 8,355 participants ages 1-74 years with CKD stages 2-5 (n=4,712), biopsy-proven glomerular disease (n=866), or no kidney disease (n=2,777). Participants with CKD had an estimated glomerular filtration rate (eGFR) of less than 90 mL/min/1.73 m^2 of body surface area according to the Chronic Kidney Disease Epidemiology Collaboration equation, a urinary albumin-to-creatinine ratio (UACR) of at least 30.0 (with albumin measured in milligrams and creatinine measured in grams), or both. Participants without kidney disease had an eGFR of at least 90 mL/min/1.73 m^2 and a UACR of less than 30.0.

The researchers used custom TaqMan assays (Applied Biosystems) to genotype *APOL1* kidney risk variants G1 and G2. Nonrisk *APOL1* alleles were designated as G0. Participants could have G1/G1, G2/G2, G1/G2, G0/G1, G0/G2, or G0/G0 genotypes. Kidney biopsies were conducted when eGFR was 15 mL/min/1.73 m^2 or less and UACR was greater than 50.0.

The authors analyzed the association of CKD with *APOL1* variants among participants with high-risk genotypes (two *APOL1* risk alleles) and those with low-risk genotypes (fewer than two *APOL1* risk alleles) by fitting logistic-regression models that controlled for covariates, including clinical site, age, and sex.

Among all participants, 43.0% carried monoallelic *APOL1* variants and 29.7% carried biallelic variants. The G1 variant was more predominant (40.7%) than the G2 variant (13.9%). The proportion of participants with two *APOL1* risk alleles was higher among those with CKD than those who did not have CKD (31.6% vs 25.7%).

The odds ratio for CKD among *APOL1* high-risk carriers compared to low-risk carriers was 1.25 (95% CI, 1.11-1.40) after adjusting for age, sex, HIV status, diabetes status, mean arterial pressure, clinical site, tobacco use, and ethnic group. Compared to the G0/G0 genotype, the odds of having CKD were 1.37 times as high (95% CI, 1.16-1.61) with the G1/G1 genotype, 2.05 times as high (95% CI, 1.35-3.13) with the G2/G2 genotype, and 1.34 times as high (95% CI, 1.12-1.61) with the G1/G2 genotype. The adjusted odds ratio (aOR) for CKD increased with CKD stage among biallelic *APOL1* carriers, from 1.20 (95% CI, 1.04-1.38) for stage 2, to 1.32 (95% CI, 1.12-1.56) for stage 3, and 1.37 (95% CI, 1.18-1.59) for stage 4-5.

The researchers assessed the effect on disease risk of having one *APOL1* risk allele. To do this, they compared the odds of CKD among participants with a single risk allele (genotype G0/G1 or G0/G2) with the odds among those with no risk alleles (genotype G0/G0). They found that the odds of having CKD were higher in participants with G0/G1 or G0/G2 than in those with the G0/G0 genotype (aOR, 1.18; 95% CI, 1.04-1.33).

Among the 866 participants who had kidney biopsies (with glomerulopathy), four major histologic patterns were found: minimal change disease (34.6%; n=300), FSGS (24.7%; n=214), lupus nephritis (11.7%; n=101), and membranous nephropathy (10.2%; n=88). Other conditions were identified in 161 (18.6%) participants.

Participants with the high-risk *APOL1* genotypes had 84% greater odds of FSGS than low-risk carriers (aOR, 1.84; 95% CI, 1.30-2.61), but their odds for minimal change disease, lupus nephritis, and membranous nephropathy did not increase. The odds of FSGS increased when one risk allele was present compared to no risk alleles (aOR, 1.61; 95% CI, 1.04-2.48).

The authors acknowledge several limitations to their study. The moderate association between *APOL1* high-risk genotypes and CKD could be due to the heterogeneity of CKD. The researchers were unable to perform genotyping for the recently reported *APOL1* N264K (rs73885316) G2 disease-associated modifier and did not screen for monogenic kidney diseases by whole-genome sequencing. Participants came from two West African countries, so the results may not be generalizable to other regions of Africa.

The authors summarized, "In this large study of the prevalence and association of high-risk *APOL1* genotypes with CKD in persons in West Africa, a region that contributed substantially to the ancestry of Black Americans, almost one third of those tested carried a high-risk *APOL1* genotype. Both monoallelic (G0/G1 and G0/G2) and biallelic (G1/G1, G2/G2, and G1/G2) risk variants increased the odds of CKD."

SZC With Dialysate Potassium Can Reduce Arrhythmias in Hemodialysis Patients With Hyperkalemia

The leading cause of death among patients receiving maintenance hemodialysis is sudden cardiac death. These patients also experience a high burden of atrial fibrillation (AF), which contributes to higher rates of stroke, cardiomyopathy, and other vascular events.

An important goal of hemodialysis is to remove potassium buildup between treatments while keeping serum potassium (sK^+) concentration within a functional range. Most kidney care providers prioritize removal of potassium and use low dialysate (≤2.5 mEq/L) potassium concentrations to help prevent hyperkalemia in patients on hemodialysis.

However, managing blood potassium concentrations in these patients is confounding because both low and high sK^+ concentrations may increase the risk of sudden death and heart arrhythmias. In addition, the increased degree and speed of potassium removal with lower dialysate potassium concentrations may increase the risk of peridialytic hypokalemia and associated arrhythmias.

Oral potassium binders may help. When administered regularly, they can limit the accumulation of total body potassium between hemodialysis sessions. This reduces the need for rapid dialytic removal and allows for the use of higher dialysate potassium concentrations, potentially lowering the risk of peridialytic hypokalemia and hypokalemia-induced AF and other arrhythmias.

A study led by **David M. Charytan, MD,** tested this theory. In the ADAPT trial, the researchers examined whether the use of the potassium binder sodium zirconium cyclosilicate (SZC) in combination with dialysate potassium could reduce the incidence of postdialysis AF and clinically significant cardiac arrhythmias (CSCAs). Their results were published in *Kidney International* [doi:10.1016/j.kint.2024.10.010].

ADAPT was a prospective, randomized, open-label, crossover study with a two-week screening period, two eight-week periods of treatment, and a visit at the end of the study. Participants received an implanted cardiac loop recorder and were assigned 1:1 to receive either 2.0 K^+/2.5 Ca^{2+} mEq/L dialysate bath without SZC (2.0K^+/noSZC) or 3.0 K^+/2.5 Ca^{2+} mEq/L dialysate bath with oral SZC on nonhemodialysis days (3.0K^+/SZC) for eight weeks. This was followed by a second treatment phase during which they switched to the other treatment. During a two-week run-in period before each treatment phase, participants were allowed to equilibrate to both the dialysate and SZC use. The SZC starting dose on nondialysis days (four days per week) was 5 g, which was uptitrated weekly in increments of 5 g up to 15 g to maintain the sK^+ concentration within 4.0 to 5.5 mEq/L.

In total, 148 patients from 13 sites including 19 dialysis units were screened for eligibility. Selected participants included 88 adults aged 18 or older with kidney failure and hyperkalemia confirmed by two predialysis sK^+ measurements of 5.1 to 6.5 mEq/L. All participants received in-center hemodialysis three days per week for a minimum of three months. Mean age was 57.1 years, 51% were male, 46% were White, and mean predialysis sK^+ was 5.5 mmol/L.

The primary outcome was the rate of adjudicated AF episodes lasting two minutes or longer. Secondary outcomes included clinically significant arrhythmias (bradycardia, ventricular tachycardia, and/or asystole) and the percentage of sK^+ measurements within an optimal window of 4.0–5.5 mEq/L.

The mean starting dose for SZC during the 3.0 mEq/L K^+ dialysate period was 8.1±3.6 g, while the ending dose was 10.2±4.0 g. Twenty-four (28%) participants received the 5 g dose, 30 (35%) received 10 g, and 32 (37%) received 15 g during 3.0K^+/SZC treatment. Mean time to titration to first 10 g SZC was 18.1±14.1 days.

Ninety-five percent of expected SZC doses were given during the eight-week treatment periods, totaling 1,114 administrations for sequence A and 1,260 for sequence B. The mean number of administrations per participant was 27.2±9.2 for sequence A and 30.0±5.0 for sequence B. Total treatment days were 1,975 for sequence A and 2,205 for sequence B. The mean number of days of exposure (including the run-in period) was 48.2±15.5 days for sequence A, with a maximum of 83 days, and 52.5±8.4 for sequence B, with a maximum of 56 days.

The follow-up period was 25.5 person-years, during which 296 AF episodes occurred in nine participants. Of these, 123 events occurred in six participants for 3.0K^+/SZC and 173 occurred in seven participants for 2.0K^+/noSZC. The unadjusted mean incidence rate per year for AF was 9.8 (95% CI, 8.0–11.5) with 3.0K^+/SZC and 13.4 (95% CI, 11.4–15.5) with 2.0K^+/noSZC. The modeled rate ratio using the quasi-Poisson model was 0.52 (95% CI, 0.41–0.65; $P<.001$).

The pattern was similar for CSCAs. Eighty-six events were observed in 11 participants with 3.0K+/SZC and 131 events were detected in 13 participants with 2.0K^+/noSZC. The unadjusted mean incidence rate per year for CSCA was 6.8 (95% CI, 5.4–8.3) for 3.0K^+/SZC and 10.2 (95% CI, 8.4–11.9) for 2.0K^+/noSZC. The modeled rate ratio was 0.47 (95% CI, 0.38–0.58; $P<.001$).

The mean duration of AF events was 1,191 (95% CI, 0–2,828) min/yr for 3.0K^+/SZC and 2,804 (95% CI, 0–6,450) min/yr for 2.0K^+/noSZC (mean difference, –1,613 min/yr; 95% CI, –5,594 to 2,367). The mean proportion of follow-up time spent in AF was 0.22% for 3.0K^+/SZC and 0.53% for 2.0K^+/noSZC (absolute risk difference, –0.30%; 95% CI, –1.11 to 0.45). For CSCA events, the mean duration was 3 (95% CI, 0–5) min/yr for 3.0K^+/SZC compared to 285 (95% CI, 0–610) min/yr for 2.0K^+/noSZC (mean difference, –282 min/yr; 95% CI, –607 to 43).

The chances of the sK^+ concentration falling outside the optimal window dropped by >70% with 3.0K^+/SZC (modeled odds ratio, 0.27; 95% CI, 0.21–0.35). This was mostly due to a reduction in postdialysis hypokalemia. Hyperkalemia (sK^+ concentration, >5.5 mEq/L) occurred infrequently with 3.0K^+/SZC, appearing in just three patients. The rates of postdialysis hypomagnesemia and hypophosphatemia differed little between the treatment groups.

A higher rate of adverse events (AEs) was observed in participants receiving 3.0K^+/SZC (43%) than in those receiving 2.0K^+/noSZC (33%). None of the AEs were related to treatment or led to dose interruption.

The study limitations include the small cohort size and short treatment duration. The study population was somewhat young, so generalizations should be made with caution. In addition, the design of the ADAPT trial does not allow for definitive determination of the proportion of the arrhythmia benefits attributable to the change from a dialysate K^+ concentration of 2.0 to 3.0 mEq/L and the subsequent reduction in postdialysis hypokalemia versus that attributable to the supplementary use of SZC on nondialysis days to limit the risks of predialysis hyperkalemia.

"In conclusion, in patients with hyperkalemia on maintenance hemodialysis, a combination of 3.0 mEq/L K^+ dialysate and SZC on nonhemodialysis days reduced the rates of AF, CSCA, and hypokalemia compared with 2.0K^+/noSZC," the authors wrote. The findings question current dialysis treatment paradigms, they noted, and warrant future prospective trials to determine whether 3.0K^+/SZC results in fewer episodes of symptomatic arrhythmia or other major cardiovascular events.

Hemodiafiltration Reduces Mortality Risk in Patients With ESRD

The new review examined the most current, reliable data

The rates of morbidity and mortality among patients with end-stage renal disease (ESRD) undergoing hemodialysis remain high. The leading cause of death in this patient population is cardiovascular disease, accounting for more than half of deaths with a known etiology (52.2%). One approach to improving the prognosis of patients receiving hemodialysis is the use of alternative hemodialysis modalities.

One such alternative is hemodiafiltration (HDF), a hybrid renal replacement therapy combining the principles of hemodialysis with hemofiltration. HDF provides the benefits of solute removal via blood diffusion and convection, resulting in more efficient clearance of medium and small molecular substances, compared to hemodialysis or hemofiltration alone.

Results of previous trials and meta-analyses comparing HDF to hemodialysis have resulted in contrasting findings. **Yifan Zhu, MM, Juan Li, MM,** and colleagues conducted a systematic review and meta-analysis to examine the most current and reliable data on the impact of HDF in patients with ESRD. Results were reported in *BMC Nephrology* [doi:10.1186/s12882-024-03810-9].

The researchers performed a systematic review of studies published in PubMed, EMBASE, and the Cochrane Library. Inclusion criteria were randomized controlled trial; study population ≥18 years of age; eligible patients receiving maintenance hemodialysis for at least three months, three times per week for a minimum of four hours each session; and patients receiving either hemodialysis or HDF. The search was conducted through January 14, 2024. Relevant data and evaluation of the quality of evidence were analyzed using Review Manager 5.3 software.

The analysis included data from 10 randomized controlled trials, representing a total of 4,654 patients. One study was conducted in South Korea and one in Turkey, and the remainder were conducted in Europe. The intervention group received HDF mode dialysis; seven used postdilution, two had an unknown dilution method, and one used predilution. Patients in the control group received hemodialysis; five used high-flux, three used low-flux, and the remaining two did not specify flux type.

The outcomes of interest included all-cause mortality (10 trials; 4,654 participants), cardiovascular mortality (six trials; 4,215 participants), sudden death (four trials; 2,783 participants), and infection-related mortality (three trials; 3,048 participants). Baseline data were generally evenly distributed across all trials.

Among the 10 studies that reported on all-cause mortality, 4,613 patients were followed for an average of 24 months. Of them, 21% (n=981) died from any cause. There was a significant reduction in mortality among patients in the intervention group compared to the control group (relative risk [RR], 0.84; 95% CI, 0.72-0.99; *P*=.04).

In the six trials reporting cardiovascular mortality, 9.2% of patients (n=383/4,141) died from cardiovascular causes during the follow-up period. In the four trials that reported sudden deaths, 3.9% (n=108/2,783) experienced sudden death. In the three trials that reported infection-related death, 5.0% (n=151/3,048) had an infection-related death.

There was a 26% reduction in cardiovascular mortality in the HDF group compared to the control group (95% CI, 0.61-0.90; *P*=.002). There were no statistically significant differences between the two groups in the incidence of sudden death (RR, 0.92; 95% CI, 0.64-1.34; *P*=.68) or infection-related mortality (RR, 0.70; 95% CI, 0.47-1.03; *P*=.07).

The researchers also performed subgroup analyses based on hemodialysis flux. Results revealed an association between HDF and a reduction in all-cause mortality and cardiovascular mortality when compared to high-flux hemodialysis (RR, 0.81; 95% CI, 0.69-0.96; *P*=.01 and RR, 0.76; 95% CI, 0.59-0.98; *P*=.04, respectively). There was no statistically significant difference in all-cause mortality between HDF and low-flux hemodialysis (RR, 0.93; 95% CI, 0.77-1.12; *P*=.44).

In results of subgroup analyses of all-cause mortality and cardiovascular mortality based on convection volume, there was an association between HDF with a convection volume of 22 L or greater and a reduction in both all-cause mortality and cardiovascular mortality (RR, 0.76; 95% CI, 0.65-0.88; *P*=.0002 and RR, 0.73; 95% CI, 0.57-0.94; *P*=.01, respectively). There was no statistically significant reduction in all-cause mortality (RR, 0.98; 95% CI, 0.66-1.47; *P*=.93) or cardiovascular mortality (RR, 0.76; 95% CI, 0.57-1.03; *P*=.08) with HDF with a convection volume less than 22 L.

The researchers cited some limitations to the findings, such as the study population including primarily individuals of European descent, possibly limiting the generalizability of the findings to other populations. In addition, the accuracy of the study conclusions may have been limited due to the inability to access individual-level data. Finally, the limited number of studies on sudden death and infection-related death may have had an impact on the precision of the conclusions drawn.

In summary, the authors said, "This meta-analysis suggests that hemodiafiltration leads to better outcomes for patients with end-stage renal disease, particularly a reduction in overall mortality and cardiovascular mortality. Notably, this benefit seems to be more pronounced for patients receiving HDF with a high convection volume."

Iptacopan Results in Significant Proteinuria Reduction in IgAN

Interim analysis assessed effects of iptacopan at nine months

IgA nephropathy (IgAN) is the most common glomerulonephritis worldwide and a frequent cause of kidney failure. With IgAN, immune complexes containing galactose-deficient IgA1 accumulate in the glomerular mesangium, which triggers local inflammation, scarring, and kidney damage. Complement proteins in the glomeruli of patients with IgAN have been noted, and research suggests the involvement of the alternative complement pathway in IgAN pathogenesis.

Iptacopan is an oral complement inhibitor that specifically binds to factor B and inhibits the alternative pathway. APPLAUSE-IgAN is an ongoing, international, double-blind, randomized, placebo-controlled phase 3 trial evaluating the effects of iptacopan on proteinuria and kidney function in patients with IgAN at risk of progression.

In *The New England Journal of Medicine* [doi:10.1056/NEJMoa2410316], **Vlado Perkovic, MBBS, PhD,** and colleagues reported the results of a prespecified interim analysis of APPLAUSE-IgAN data, which assessed the effects of iptacopan on proteinuria at nine months.

Selected participants had primary IgAN confirmed by biopsy within the last five years (for patients with an estimated glomerular filtration rate [eGFR] of ≥45 mL/min/1.73 m^2) or within two years if the biopsy found less than 50% tubulointerstitial fibrosis (for patients with an eGFR of 30 to <45 mL/min/1.73 m^2), and if they had a baseline 24-hour urinary protein-to-creatinine ratio (UPCR) of ≥1 despite optimized supportive therapy.

The primary trial population was randomized 1:1 to receive iptacopan (n=222) or placebo (n=221). Randomization was stratified according to geographic region (Asia vs all other regions), baseline proteinuria (24-hour UPCR [with protein and creatinine both measured in grams] of <2 vs ≥2), and eGFR (30 to <45 mL/min/1.73 m^2 of body surface area vs ≥45 mL/min/1.73 m^2).

The interim efficacy analysis included the first 250 participants who underwent randomization in the main trial population (125 patients in each group) and who stayed in the trial until month nine or discontinued the trial by month nine. The researchers assessed safety in all 443 patients in the main trial population. Baseline characteristics were balanced between the two trial groups. The average age was 39 years, 47.6% were women, and 51.2% were from Asia.

In the iptacopan group, the mean (±SD) eGFR was 62.7±26.0 mL/min/1.73 m^2, while it was 65.5±26.7 mL/min/1.73 m^2 in the placebo group. The 24-hour UPCR was 1.81 (interquartile range [IQR], 1.36-2.66) in the iptacopan group and 1.87 (IQR, 1.48-2.83) in the placebo group.

The percentage of participants in both groups using SGLT2 inhibitors was similar. At baseline, 12.8% of patients were taking SGLT2 inhibitors at a stable dose. Nearly all (99%) participants were taking angiotensin-converting–enzyme inhibitors or angiotensin-receptor blockers at baseline. The median time from confirmatory biopsy to baseline was 1.3 years in the iptacopan group and 0.8 years in the placebo group. The trial population broadly represented patients with IgAN at risk of progression.

The primary endpoint was the change in 24-hour UPCR from baseline to month nine, which was analyzed using a repeated-measures model. A secondary endpoint was the percentage of participants with a 24-hour UPCR of less than one at month nine without receiving rescue or alternative medication or having kidney replacement therapy.

The percentage of patients with a 24-hour UPCR less than one or less than 0.5 without receiving rescue or alternative medication or having kidney replacement therapy at month nine was evaluated separately using a logistic-regression model. Exploratory endpoints included reduction in 24-hour urinary albumin-to-creatinine ratio (UACR), total 24-hour urinary protein level, and total 24-hour urinary albumin level at month nine. The researchers also evaluated safety endpoints. Safety data were summarized descriptively.

The primary analysis found that iptacopan was superior to placebo at reducing 24-hour UPCR. The adjusted geometric mean 24-hour UPCR at month nine was 38.3% (95% CI, 26.0-48.6; two-sided $P<.001$) lower with iptacopan compared to placebo. Consistent with the primary analysis findings, the adjusted geometric mean 24-hour UPCR at nine months based on first morning urine sample was 35.8% (95% CI, 22.6-46.7) lower in the iptacopan group than in the placebo group.

The proportion of patients with UPCR less than one at month nine without receiving rescue or alternative medication or undergoing kidney replacement therapy was higher in the iptacopan (42.5%; 95% CI, 34.5-50.5) group compared to the placebo (21.9%; 95% CI, 14.8-29.0) group (odds ratio, 3.12; 95% CI, 1.68-5.79).

The analysis of patients with a 24-hour UPCR less than 0.5 without receiving rescue or alternative medication or having kidney replacement therapy at month nine showed a similar trend. Analyses of reductions in 24-hour UACR, total 24-hour urinary protein excretion, and 24-hour albumin excretion had findings consistent with those of the primary analysis.

There were no unexpected safety findings with iptacopan and no increased risk of infection. The incidence of adverse events was similar in both the iptacopan and placebo groups, and most were mild to moderate and reversible.

The authors acknowledge certain study limitations. The interim analysis was not designed to confirm the effects of iptacopan on measures of kidney function, such as eGFR. Those results have not been shared on the advice of regulatory agencies to avoid influencing the conduct of the ongoing trial, which should provide additional evidence of the drug's effects on kidney function and determine its role in IgAN management.

In summary, the authors wrote, "In this interim analysis, treatment with iptacopan resulted in a significant reduction in proteinuria as compared with placebo."

Survey Data Reveal Changes in Global Progress in Kidney Disease Care

An increase in the global burden of kidney disease persists, as does a continuation of inequities in access and availability of care for patients with the disease. The prevalence of chronic kidney disease (CKD) worldwide is an estimated one in 10 individuals. In low-income and lower-middle-income countries, the prevalence is more than 50%. Approximately 35.5 million adults in the United States are living with CKD. One third of those with diabetes mellitus and one fifth with hypertension may also have CKD.

Results of a large systematic review revealed significant gaps in access to kidney replacement therapies, particularly in sub-Saharan Africa and Asia, where as many as 91% and 83% of individuals who required kidney replacement treatment, respectively, were unable to access that care.

The 10-point International Society of Nephrology Global Kidney Health Atlas was developed in 2017 to examine gaps in care, research, and policies. The survey was conducted in 2017, 2019, and 2023 in 148 countries. Using data reported from 2019 and 2023 from countries that participated in both those years, **Ikechi G. Okpechi, MD, PhD,** and colleagues examined changes in key measures of kidney care and published their findings in the *BMJ.* [doi:10.1136/bmj-2024-079937].

The outcome measures of interest were kidney replacement treatment services, access, health financing, workforce, registries, and policies for kidney care. Country data were aggregated by International Society of Nephrology regions and World Bank income levels. Participating regions included Africa, Eastern and Central Europe, Latin America, the Middle East, Newly Independent States and Russia, North America and the Caribbean, North and East Asia, Oceania and Southeast Asia, South Asia, and Western Europe.

Of the 148 countries, 141 had available data regarding changes in funding for kidney replacement therapy. Overall, there was an increase in the proportion of countries with publicly funded hemodialysis, from 27% in 2019 to 28% in 2023. In high-income countries, the proportion increased from 40% to 55%, compared to a reduction from 21% to 18% in upper-middle-income countries and from 19% to 0% in low-income countries (P=.046). There was no change globally in the proportion of countries where hemodialysis was reimbursed through private funds and solely out-of-pocket. However, there was a change in Africa from 11% to 17% and from 13% to 19% in low-income countries.

Globally, there was an increase in the proportion of countries that covered peritoneal dialysis through public funding and provided it free at the point of delivery, from 23% to 28%. That proportion decreased in Africa (11% to 9%), the Middle East (36% to 27%), Newly Independent States and Russia (43% to 29%), and Oceania and Southeast Asia (20% to 7%). Across all country income groups, the proportions of countries where solely an out-of-pocket payment method was used for peritoneal dialysis remained stable, but there was a decrease from 13% to 6% in Eastern and Central Europe.

There was an increase globally from 31% to 36% in the proportion of countries where reimbursement for the costs of kidney transplantation and medications were provided through public funds and were free at the point of delivery. In Africa, the Middle East, and the Oceania and Southeast Asia regions, there was no change in that proportion. The proportion of countries where payments for kidney transplantation and medications were through out-of-pocket methods decreased from 8% to 6%. That decrease was 6% to 0% in Latin America and 36% to 0% in the Middle East region (P=.046).

Worldwide, there was an increase in the prevalence of hemodialysis centers, from 4.4 per million population (pmp) to 4.8 pmp (P<.001). There was a decrease from 3.8 pmp to 3.3 pmp in the Middle East, as well as a decrease in high-income countries (8.7 pmp to 8.6 pmp). Overall, the prevalence of peritoneal dialysis centers increased from 1.4 pmp to 1.6 pmp. There was a decrease in Eastern and Central Europe (2.3 pmp to 2.0 pmp), the Middle East (0.8 pmp to 0.7 pmp), North and East Asia (1.9 pmp to 1.3 pmp), and Oceania and Southeast Asia (2.2 pmp to 1.5 pmp).

There was an increase globally in the proportion of countries where hemodialysis was offered three times weekly (three to four hours per session), from 77% to 83%. The increase was seen in Africa, Latin America, Newly Independent States and Russia, North America and the Caribbean, and South Asia. The proportion of countries where adequate peritoneal dialysis was offered also increased (60% to 61%). There was no change overall in the countries with capacity for provision of adequate kidney transplantation. That proportion only increased in Latin America, North America and the Caribbean, and the North and East Asia region.

For hemodialysis and peritoneal dialysis, changes in the proportions of countries where more than 50% of the national populations were able to access treatment were 72% to 74% and 4% to 6%, respectively. There was a decrease from 30% to 29% in ability to access kidney transplantation. There were increases in Africa (3% to 6%), Latin America (17% to 22%), and Western Europe (60% to 85%). Increases in the proportion of countries with access to kidney transplantation were reported only in high-income countries. The proportion was reduced in lower-middle-income countries and remained stable in low-income countries and upper-middle-income countries.

The prevalence of nephrologists increased overall, from 9.5 pmp to 12.4 pmp (P<.001). Their prevalence decreased in Eastern and Central Europe and in North America and the Caribbean region. The prevalence of nephrologists increased across all income levels. There were variations in changes in the availability of kidney registries and in national policies and strategies for kidney care.

Listing possible limitations to the study findings, the researchers cited the use of survey questionnaires that are limited by subjectivity in responses and different respondents participating in both surveys in some countries.

In conclusion, the authors said, "Important changes in key areas of kidney care delivery were noted across both periods globally. These changes effected [sic] the availability of, and access to, kidney transplantation services. Countries and regions need to enact enabling strategies for preserving access to kidney care services, particularly kidney transplantation." ●

Clinical Relevance of Allograft Microvascular Inflammation

Challenges associated with the management of patients with end-stage kidney disease include high morbidity, mortality, and costs. Kidney transplantation is the gold standard of treatment for end-stage kidney disease. Allograft rejection leading to long-term allograft loss is a major contributor to those challenges.

The failure of kidney allografts is attributed to antibody-mediated alloimmune responses. Allograft microvascular inflammation is the hallmark histologic lesion of antibody-mediated graft injury. The heterogeneous clinical presentation of graft microvascular inflammation may result in adverse outcomes in recipients of kidney transplantation. The mechanisms underlying graft microvascular inflammation are unclear, as is the effect of microvascular inflammation on allograft outcomes.

Two new diagnostic categories were added to the 2022 Banff Classification of Renal Allograft Pathology: (1) probable antibody-mediated rejection (microvascular inflammation or injury [MVI], donor-specific antibody-negative [DSA-negative], and C4d-negative) and (2) microvascular inflammation without evidence of an antibody-mediated response (probable antibody-mediated rejection).

A team of researchers led by **Marta Sablik, MD,** and **Aurélie Sannier, MD, PhD,** conducted a large, population-based, multicenter cohort study to examine the clinical relevance of allograft microvascular inflammation. The researchers also assessed the implications of the newly recognized phenotypes as related to precision diagnostics for kidney allografts, risk stratification, allograft outcomes, and potential therapeutic strategies. Results of their study were reported online in the *New England Journal of Medicine* [doi:10.1056/NEJMoa2408835].

The study population included recipients of kidney transplants from more than 30 transplantation centers in Europe and North America. Eligible participants had undergone allograft biopsy between 2004 and 2023.

The primary outcome of interest was the association between the newly recognized microvascular inflammation phenotypes and allograft survival, defined as return to dialysis or preemptive kidney retransplantation. Secondary outcomes included new or recurrent antibody-mediated rejection and transplant glomerulopathy—a chronic and progressive form of allograft injury—in patients with a first microvascular inflammation-related diagnosis.

The primary analysis comprised 6,798 patients who had undergone at least one kidney-allograft biopsy following transplantation. Mean age was 44.6 years, 38.6% (n=2,590/6,708) were female, and 78.6% (n=5,270/6,705) had received a deceased-donor transplant. Of these patients, 12.7% (n=851/6,691) had undergone retransplantation, 1.6% (n=108/6,736) had an ABO-incompatible kidney transplant, and 25.1% (n=1,305/5,204) had circulating donor-specific antibodies.

The analysis included 16,293 kidney-transplant biopsy specimens. The median time from transplantation to biopsy was 8.1 months. The newly recognized microvascular inflammation phenotypes were identified in 4.8% of the specimens (n=788). Of them, 3.1% (n=503) had a phenotype of MVI, DSA-negative, and C4d-negative, and 1.7% (n=285) had a phenotype of probable antibody-mediated rejection.

> Graft survival was worse among patients with a nonrejection-related diagnosis according to the 2019 Banff classification who were subsequently reclassified.

Of the 788 specimens with the newly recognized inflammation phenotypes, 63.3% (n=641) were from patients with a nonrejection-related 2019 Banff classification (391 reclassified as MVI, DSA-negative, and C4d-negative and 250 reclassified as probable antibody-mediated rejection according to the 2022 Banff classification). According to the 2019 Banff classification, 781 specimens had a diagnosis of T-cell-mediated rejection. Of them, 9.7% (n=76) were reclassified according to the 2022 Banff classification as MVI, DSA-negative, and C4d-negative (n=48) or probable antibody-mediated rejection (n=28).

Graft survival was worse among patients with a nonrejection-related diagnosis according to the 2019 Banff classification who were subsequently reclassified as MVI, DSA-negative, and C4d-negative according to the 2022 Banff classification compared to those with a nonrejection-related diagnosis according to both Banff classifications (hazard ratio [HR] for graft loss, 2.1; 95% CI, 1.5-3.1).

Beyond year five following biopsy, patients with a nonrejection-related diagnosis with the 2019 Banff classification and a 2022 Banff diagnosis of probable antibody-mediated rejection had worse graft survival compared to patients with a nonrejection-related diagnosis according to both classifications (HR for graft loss, 1.7; 95% CI, 0.8-3.5). The difference was not seen through year five after biopsy (HR for graft loss, 1.3; 95% CI, 0.8-2.1).

Graft survival was worse among patients with a diagnosis of antibody-mediated rejection according to both Banff classifications compared to patients with a nonrejection-related diagnosis according to both classifications (HR for graft loss, 2.7; 95% CI 2.2-3.3). Results were similar in a sensitivity analysis of the cumulative incidence of allograft loss according to the reclassified diagnosis where death was treated as a competing risk.

The researchers also assessed the risk of new or recurrent antibody-mediated rejection during follow-up among 5,235 patients with a first microvascular inflammation-related diagnosis and no previous episodes of kidney-allograft rejection. Of them, 8.1% (n=423) had new or recurrent antibody-mediated rejection. Those with a diagnosis of MVI, DSA-negative, and C4d-negative or probable antibody-mediated rejection had an intermediate cumulative incidence of antibody-mediated rejection during follow-up compared to patients without a diagnosis of microvascular inflammation and those with active antibody-mediated rejection. Patients with MVI, DSA-negative, and C4d-negative and those with probable antibody-mediated rejection had similar risk of antibody-mediated rejection during follow-up.

The risk of progression of transplant glomerulopathy during follow-up was higher among the patients with a diagnosis of either of the newly recognized microvascular inflammation phenotypes compared to patients without microvascular inflammation. Patients in the MVI, DSA-negative, and C4d-negative group and those in the probable antibody-mediated rejection group had similar risks of progression.

The researchers cited some limitations to the study findings, including an inability to assess the association between graft outcomes and treatment, as well as an inability to fully assess the natural evolution of the microvascular inflammation phenotypes.

In summary, the authors said, "Our study, which included a highly characterized multicenter cohort of more than 6,000 kidney transplant recipients, provides a detailed analysis of the clinical characteristics and prognostic importance of specific microvascular inflammation phenotypes that were introduced in the 2022 Banff classification for pathological assessment of renal allografts." ●

Outcomes in Pediatric Kidney Transplant Recipients Vary by Age

Data highlight a need for personalized care based on age-specific risk

The optimal treatment for kidney failure is kidney transplantation. However, transplantation is associated with challenges to patient and graft survival, including allograft rejection, infection, and graft dysfunction. There have been few large multicenter outcomes studies conducted among pediatric kidney transplant recipients. According to **Maral Baghai Arassi, PhD,** and colleagues, there is a need for studies analyzing age-related differences in outcomes in the pediatric patient population.

Several benchmark studies among pediatric cohorts in North America and China have occurred. Data from the CERTAIN registry include 95 pediatric kidney transplant centers in 26 European countries and 3,930 pediatric patients. For the current retrospective, multicenter, longitudinal cohort study, the researchers utilized CERTAIN registry data to bridge the gap in age-related outcome data for pediatric kidney transplant recipients in Europe treated with a tacrolimus-based immunosuppressive regimen. Results were reported in *Kidney International Reports* [2024;9(11);3265-3277].

The analysis included 20-year data on 802 pediatric patients at 40 centers in 14 countries. To assess age-related differences in outcome, the cohort was divided into three age groups: (1) infants and children <6 years of age; (2) school-aged children 6 to 12 years of age; and (3) adolescents >12 years of age.

Outcomes of interest were infection, rejection, graft dysfunction, diabetes mellitus, death, and cumulative hospital days. The outcome measure was a death-censored composite endpoint, allograft dysfunction, defined as graft loss, or estimated glomerular filtration rate (eGFR) ≤30 mL/min/1.73 m^2, or a ≤50% decline from baseline eGFR at month three post-transplant.

Whole blood trough levels were used to quantify tacrolimus exposure. Trough level data were categorized into early (months one to three), mid (months 6-12), and late (months 18-24) post-transplant periods.

The study cohort included patients who underwent kidney transplantation at one of 40 study centers between 1999 and 2019. Of the 802 patients, 40.3% (n=323) were girls and 59.7% (n=479) were boys. Median age at transplantation was 11.1 years, 91.4% were of Caucasian descent, 3.1% were of African descent, and 5.4% were of Asian descent. The primary cause of kidney disease was congenital anomalies of the kidney and urinary tract (39.4%), followed by hereditary cystic or congenital diseases (25.3%) and primary glomerular diseases (17.6%).

Sixty-nine percent of patients received a kidney from a deceased donor. The initial immunosuppressive regimen for all 802 participants was tacrolimus, mycophenolate mofetil, and glucocorticoids. Forty-one percent of patients received additional induction therapy with basiliximab (34.2%), antithymocyte globulin (5.4%), rituximab (2.0%), or daclizumab (0.7%). The median follow-up time was 48 months post-transplant.

There were 206 patients in the infants and young children group, 278 in the school-aged children group, and 318 in the adolescent group. There were significant differences among the age groups in sex, follow-up times, preemptive transplantation, primary kidney disease, induction therapy, previous kidney transplants, immunosuppressive therapy at year one, and tacrolimus formulation.

Within the first two years following transplant, biopsy-proven rejection episodes occurred in 23.8% of patients. There were no statistically significant differences between recipients of living-donor transplants and deceased-donor transplants in the number of rejection episodes (26.0% and 22.8%, respectively). There were significant differences in the prevalence of rejection by age. The highest rate of rejection was in adolescents (28.9% vs 18.9% in infants and young children; P=.018).

Most rejections occurred in the first year after transplant when stratified by year. Adolescents experienced significantly more rejections than infants and young children and school-aged children. The rate of rejection in adolescents was 10.4%, compared to 4.7% in school-aged children and 4.9% in infants and young children (P=.042). Results of Kaplan-Meier analysis revealed significantly higher rejection-free survival in infants and young children than in adolescents throughout the entire 48 months of follow-up.

The most common outcome event in the first two years following transplantation was infection, with 65.2% of patients experiencing at least one infectious episode. The highest incidence of infections occurred in infants and young children (80.6%), followed by school-aged children (65.5%) and adolescents (55.0%; P<.0010). The incidence of recurrent infections was also highest among infants and young children (66.5% vs 33.6% in adolescents, P<.001), a pattern that was consistent in both years one and two post-transplant (both P<.001).

The most common type of infection was gastroenteritis, followed by lower respiratory tract infections and pyelonephritis (all P<.001 for infants and young children vs adolescents). More severe infections such as sepsis and other relevant infections were more common in infants and young children. The risk of infection was significantly higher in infants and young children than in adolescents and school-aged children.

During the first two years following transplant, the overall incidence of graft dysfunction, diabetes mellitus, and death was low (2.8%, 1.7%, and 0.1%, respectively). Diabetes mellitus was significantly more common in adolescents compared to school-aged children and infants and young children (3.8% vs 0.7% and 0%; P=.002).

There were no significant age differences over the follow-up period for graft dysfunction or death. At three, 12, and 24 months post-transplant, infants and young children and school-aged children had a higher eGFR compared to adolescents (P<.001).

Of the overall cohort, 91% experienced at least one hospitalization during the first two years after transplant. There was no significant difference between age groups. Infection was the most common reason for hospitalization. The total number of hospital days was significantly higher in infants and young children compared to adolescents and school-aged children. The risk of hospitalization was significantly higher among infants and young children than in adolescents and school-aged children.

Tacrolimus trough levels were significantly lower in infants and young children. Infants and young children also had lower tacrolimus concentration-to-dose ratios and higher tacrolimus interpatient variability (all P<.01) compared to adolescents.

The study findings were limited by the retrospective design, as well as by the inability to detail infections such as Epstein-Barr virus, BK polyomavirus, and CMV.

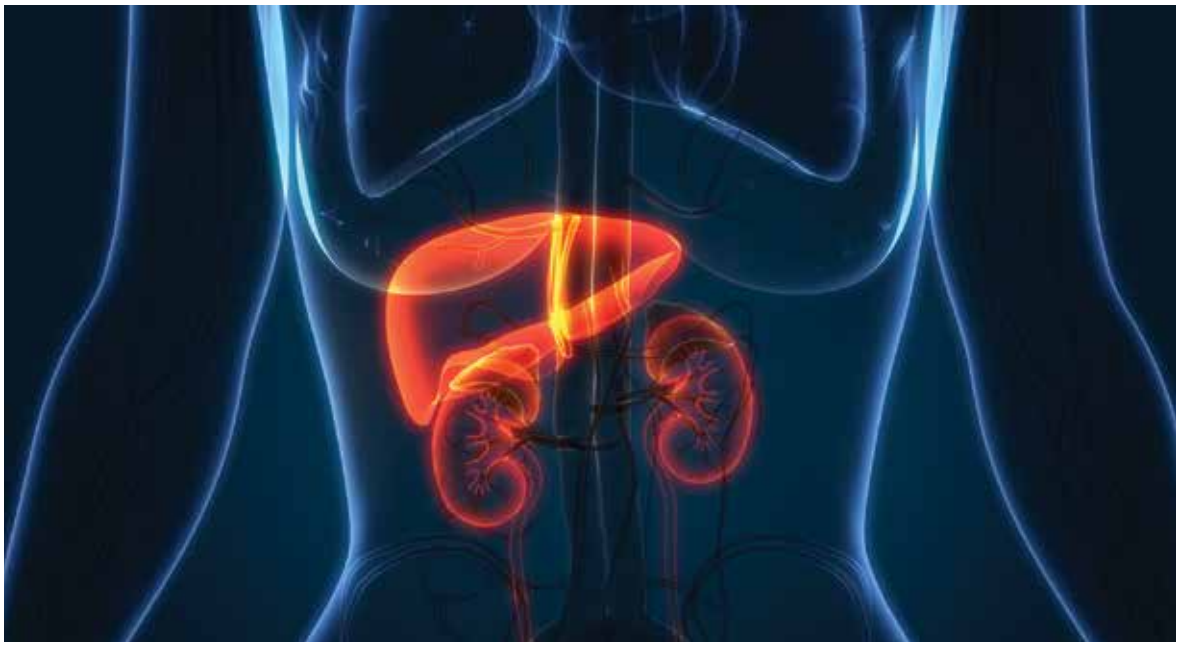
In conclusion, the authors said, "This is the largest study to date in European pediatric kidney transplant recipients on a tacrolimus-based immunosuppressive regimen, and it shows important age-related differences in rejection rates, infection episodes, as well as tacrolimus exposure and clearance. [These] data suggest that immunosuppressive therapy in pediatric kidney transplant recipients should be tailored and personalized according to the age-specific risk profiles of this heterogeneous patient population. The data may serve as a benchmark for future studies with novel immunosuppressive drugs."

European Ozempic Label Will Include Kidney Disease Indication

On December 12, Danish drug maker Novo Nordisk announced that the European Medicines Agency approved an addition to the label of its blockbuster drug Ozempic (once-weekly subcutaneous semaglutide). The label will be updated to add risk reduction for events related to kidney disease.

The decision stems from positive results of the FLOW trial, which examined risk reduction from Ozempic therapy in chronic kidney disease (CKD)-related events. The trial found that semaglutide 1.0 mg demonstrated a statistically significant and superior 24% risk reduction in kidney disease progression as well as cardiovascular and kidney death compared to placebo. In addition, semaglutide reduced the risk of major cardiovascular events by 18% and the risk of all-cause mortality by 20%.

Novo Nordisk has filed for a label expansion in the United States and expects a decision in the first half of 2025.



HHS Expands Access to Liver and Kidney Transplants for People With HIV

On November 27, the US Department of Health and Human Services (HHS) issued a final rule to expand access to kidney and liver transplants for people living with HIV.

As allowed by the HIV Organ Policy Equity (HOPE) Act, the HHS determined that clinical research will no longer be a requirement for transplantation from donors with HIV to recipients with HIV. The change is supported by research showing the safety and effectiveness of kidney and liver transplants between HIV-positive donors and HIV-positive recipients.

In tandem with the final rule, the National Institutes of Health sought public comments through December 12 on a proposed revision to its research criteria for HOPE Act transplants of other organs, such as heart, lung, and pancreas.

IOTA Final Rule Issued, Incentivizing Transplant Rates

The Centers for Medicare and Medicaid Innovation issued a final rule for the Increasing Organ Transplant Access Model (IOTA) on November 26.

IOTA incentivizes increased transplant rates and places greater emphasis on achieving long-term post-transplant outcomes and boosting transparency about the process for transplant candidates.

The 600-page rule adopted suggestions from stakeholders, including the American Society of Nephrology and the American Hospital Association. This included increasing the maximum upside payment participants may receive for success on a per-transplant basis from a proposed $8,000 to $15,000 and pushing back the start date to July 1, 2025. The mandatory payment model will be in effect for six years.

ISN Announces 2025 Award Winners

The International Society of Nephrology (ISN) has announced the 2025 recipients of the ISN Awards and ISN Pioneer Awards.

The ISN Award winners are **Marie Trudel** (Lillian Jean Kaplan International Prize), **Shilpanjali Jesudason** (Roscoe R. Robinson Award), and **Ariela Benigni** (Alfred Newton Richards Award).

The ISN Pioneer Awards are restricted to individuals from non–high-income countries and honor physicians who have made extraordinary efforts to advance nephrology in a specific country or region. The 2025 winners are **Boucar Diouf** (Senegal), **Liliana Garneata** (Romania), **Ana María Cusumano** (Argentina), **Shahrzad Ossareh** (Iran), **Lidia Lysenko** (Russia), **Everard N. Barton** (Jamaica), **Fan Fan Hou** (China), **Kriang Tungsanga** (Thailand), and **Amit Gupta** (India).

The ISN Award winners will receive their awards at the ISN World Congress of Nephrology 2025 (WCN'25) in New Delhi, India, taking place February 6–9. The ISN Pioneer Award winners will be recognized at WCN'25 and presented with their awards at regional events throughout 2025.

ACR Issues Summary of New Lupus Nephritis Guidance

The American College of Rheumatology (ACR) has issued a summary of the 2024 ACR Guideline for the Screening, Treatment, and Management of Lupus Nephritis. This is the ACR's first lupus nephritis guideline since 2012.

The new guideline will provide evidence-based, expert guidance for screening, treating, and managing lupus nephritis in adults and, for the first time, in children. Guideline recommendations are based on systematic evidence reviews, values and preferences from a lupus nephritis patient panel, and input from adult and pediatric rheumatologists and nephrologists and a rheumatology physician assistant.

The guideline summary provides 41 recommendations and good practice statements. The ACR expects that the full guideline manuscript will be published in its journals *Arthritis Care & Research and Arthritis & Rheumatology* in 2025. ●

ACUTE KIDNEY INJURY

Extracorporeal Blood Purification to Reduce AKI in Cardiac Surgery

JAMA. doi:10.1001/jama.2024.20630

Cardiac surgery-associated acute kidney injury (CSA-AKI) after cardiopulmonary bypass (CPB) is a serious problem. **Xosé Pérez-Fernández, PhD, MD,** and colleagues conducted a double-blind, randomized clinical trial to determine the efficacy of extracorporeal blood purification (EBP) in reducing CSA-AKI.

Participants comprised adult patients of two Spanish tertiary hospitals undergoing nonemergent cardiac surgery and at high risk for CSA-AKI. They were enrolled from June 15, 2016, through November 5, 2021, with follow-up data through February 5, 2022. Of an initial 1,156 patients, 343 were randomized to either EBP (n=169) or standard care (n=174). The mean (SD) patient age was 69 (9) years, and 119 patients were female. The primary study outcome was the rate of CSA-AKI in the seven days after randomization.

The prevalence of CSA-AKI was 28.4% (95% CI, 21.7-35.8) in the EBP group and 39.7% (95% CI, 32.3-47.3) in the standard care group (*P*=.03). The adjusted difference was 10.4% (95% CI, 2.3-18.5) using a log-binomial model (*P*=.01). No significant differences were observed in most of the predefined clinical secondary endpoints or post hoc exploratory endpoints.

A sensitivity analysis found EBP to be more effective at reducing CSA-AKI in patients with chronic kidney disease (CKD), diabetes, hypertension, low left ventricular ejection fraction (<40%), and lower body mass index (BMI; <30). No differences were seen between the EBP and standard of care groups regarding adverse event tracking.

In summary, there was a significant reduction in CSA-AKI within the first seven days after cardiac surgery when a nonselective EBP device connected to the CPB circuit was used.

Proton Pump Inhibitors, Immune Checkpoint Inhibitors, and AKI

Kidney360. 2024 Sep 1;5(9):1262-1269.

The use of proton pump inhibitors (PPIs) is associated with a higher risk of AKI. **Chinami Yamawaki** and colleagues conducted a nested case–control study to assess AKI risk with PPI use in patients with cancer who received immune checkpoint inhibitors (ICIs), a class of drugs used in cancer treatment, versus those who did not receive ICIs.

Demographic data, diagnoses, prescriptions, and laboratory results came from a database provided by the Health, Clinic, and Education Information Evaluation Institute. The study subjects comprised 38,930 patients with cancer who were new PPI or ICI users with no history of AKI prior to joining the cohort. Researchers estimated the odds ratio for AKI using conditional logistic regression models.

The mean follow-up was 8.3 months, during which 5,870 cases of AKI were observed (incidence rate, 21.9/100 person-years). The adjusted odds ratios of AKI were 2.20 (95% CI, 2.01-2.40) for current PPI use without ICI use, 1.72 (95% CI, 1.37-2.17) for past or never PPI use with prior ICI use, and 2.62 (95% CI, 1.75-3.93) for current PPI use with prior ICI use compared to never or past PPI use without ICI use. The risk of AKI was no higher in patients treated with both PPIs and ICIs than the additional or multiplication of the risks in those who were treated with PPIs or ICIs alone.

In conclusion, the results confirmed the association between PPI and ICI use and AKI risk, although the interaction between the two drugs was not identified. The findings emphasize the need to carefully monitor and evaluate kidney function in patients treated with PPIs and ICIs.

ADPKD

Proinflammatory Biomarkers in Patients With ADPKD

Kidney360. 2024 Sep 1;5(9):1289-1298.

Inflammation and fibrosis play an important role in the pathogenesis of autosomal polycystic kidney disease (ADPKD). Inflammatory markers associated with the development and progression of ADPKD have been identified, including monocyte chemoattractant protein-1 (MCP-1) and tumor necrosis factor-α (TNF-α). **Sita Arjune, PhD,** and colleagues conducted an exploratory pilot study to identify and evaluate potential proinflammatory biomarkers in patients with ADPKD from the German AD(H)PKD registry.

The researchers used multiplex immunoassay to measure serum concentrations of IL-1β, IL-2, IL-6, IL-8, IL-10, IL-13, IFN-γ, MCP-1, and TNF-α in adults with ADPKD from the registry (n=233). These patients were compared to an age- and sex-matched healthy control group (n=30).

The study found that IL-6, IL-8, MCP-1, TNF-α, and IFN-γ concentrations were significantly higher in patients with ADPKD compared to the healthy controls. Patient sex affected the concentrations of MCP-1 and TNF-α in both the ADPKD and control groups (MCP-1 male=134.8 pg/L, female=75.11 pg/L; *P*=.0055; TNF-α male=26.22 pg/L, female=21.08 pg/L; *P*=.0038).

The findings indicate that inflammation may have a critical role in the pathogenesis of ADPKD and could potentially serve as a target for biomarkers and therapeutic interventions.

Hyperphosphatemia and Kidney Outcomes in ADPKD

Clinical and Experimental Nephrology. doi:10.1007/s10157-024-02568-6

Serum phosphate levels tend to be lower in ADPKD than in other kidney diseases. This can obscure the clinical significance of hyperphosphatemia. **Kosaku Nitta, MD, PhD,** and colleagues wanted to determine whether serum phosphate levels could predict kidney outcomes in patients with ADPKD.

Their study included 235 patients with ADPKD who were not taking drugs to treat hyperphosphatemia. The researchers performed survival analysis for the renal outcome of a 50% reduction in estimated glomerular filtration rate (eGFR) or initiation of renal replacement therapy.

Multivariable Cox regression analyses found that serum phosphate (1 mg/dL increase; hazard ratio [HR]=2.03; *P*<.0001) was a significant risk factor for kidney disease progression. Meanwhile, hyperphosphatemia (phosphate >3.5 mg/dL, HR=2.05; >4.0 mg/dL, HR = 1.90; >4.5 mg/dL, HR = 2.78; >5.0 mg/dL, HR = 27.22) was significantly associated with kidney prognosis. Kaplan–Meier analysis found significantly lower kidney survival rates in patients with phosphate >3.5 mg/dL than in those without hyperphosphatemia (log-rank test, *P*<.0001). Similar Kaplan–Meier analysis results occurred for >4.0 mg/dL, >4.5 mg/dL, and >5.0 mg/dL.

The two-year kidney survival rate for patients with ADPKD with phosphate >3.5 mg/dL was 66.7% overall and 41.4% in patients with stage 4–5 CKD. Patients with phosphate >4.0 mg/dL had a survival rate of 46.8% overall and 28.2% in stages 4–5 CKD.

In summary, hyperphosphatemia was associated with kidney prognosis in patients with ADPKD. Even mildly elevated serum phosphate levels of >3.5 or >4.0 mg/dL should receive attention.

CHRONIC KIDNEY DISEASE

Obesity Severity, Duration Association With CKD

BMC Nephrology. 2024 Sep 27;25(1):320.

Although it is well known that obesity is a risk factor for CKD, the impact of the severity and duration of obesity on CKD incidence is uncertain. **Faranak Ghazy** and colleagues studied the association of obesity severity and duration with CKD incidence to fill this gap.

There were 8,697 participants in the study. Their mean age was 40±14 and 4,865 (56%) were women. The researchers calculated Cumulative Excess Weight (CEW) and Cumulative Excess Waist Circumference (CEWC) scores, which represent the accumulation of deviations from expected BMI and waist circumference values over time until the development of CKD or the end of the 15-year follow-up period. The research team used time-dependent Cox models, controlling for confounding variables, to examine the sex-stratified association of CEW and CEWC with CKD incidence.

During the follow-up period, 3,629 (41.7%) participants developed CKD. Among the patients with CKD, 829 (65.4%) men and 1,839 (77.9%) women had a BMI above 25. High waist circumference was observed in 934 (73.7%) men and 1,306 (55.3%) women. There was a significant association between one standard deviation change of CEW and the development of CKD in both men (adjusted HR [aHR], 1.155; 95% CI, 1.081-1.232) and women (aHR, 1.105; 95% CI, 1.047-1.167), but the association between CEWC and CKD development was only significant among men (HR, 1.074; 95% CI, 1.006-1.147).

In summary, accumulating general and central obesity was associated with an increased incidence of CKD development over the 15-year follow-up period.

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Kidney-Protection Benefits of Metabolic Surgery Versus GLP1-RA in Patients With CKD

Annals of Surgery. 2024 Sep 1;280(3):414-423.

The effects of metabolic surgery versus the use of glucagon-like peptide-1 receptor agonists (GLP-1RA) in patients with CKD have not been well described. Therefore, **Ali Aminian, MD,** and colleagues studied the renoprotective advantages of metabolic surgery in patients with obesity and CKD compared to patients who did not have surgery but continuously received GLP-1RA.

Participants had type 2 diabetes, obesity (defined as BMI ≥30 kg/m^2), and baseline eGFR 20-60 mL/min/1.73 m^2. Patients who had metabolic bariatric surgery at a large US health system between 2010 and 2017 were compared to nonsurgical patients who continuously received GLP-1RA.

The primary endpoint of the study was CKD progression, defined as an eGFR decline of ≥50% or decline to <15 mL/min/1.73 m^2, initiation of dialysis, or kidney transplant. The secondary endpoint was concurrent kidney failure (eGFR <15 mL/min/1.73 m^2, dialysis, or kidney transplant) or all-cause mortality. A total of 425 patients were studied, including 183 in the metabolic surgery group and 242 in the GLP-1RA group. The median follow-up period was 5.8 years (IQR, 4.4-7.6).

At eight years, the cumulative incidence of the primary endpoint was 21.7% (95% CI, 12.2-30.6) in the surgical group and 45.1% (95% CI, 27.7-58.4) in the nonsurgical group (aHR, 0.40; 95% CI, 0.21-0.76; *P*=.006). The cumulative incidence of the secondary composite endpoint at eight years was 24.0% (95% CI, 14.1-33.2) in the surgical group and 43.8% (95% CI, 28.1-56.1) in the nonsurgical group (aHR, 0.56; 95% CI, 0.31-0.99; *P*=.048).

In conclusion, metabolic surgery was significantly associated with a 60% lower risk of progression of kidney damage and a 44% lower risk of kidney failure or death compared to GLP-1RA in patients with type 2 diabetes, obesity, and CKD. "Metabolic surgery should be considered as a therapeutic option for patients with CKD and obesity," the authors wrote.

Association Between Preoperative CKD and Postoperative Outcomes

BMC Nephrology. 2024 Sep 13;25(1):305.

Although CKD is associated with a greater incidence of major surgery, previous studies have not examined the association between preoperative kidney function and postoperative outcomes across a wide range of procedures. To address this gap, **Carlos Riveros, MD,** and colleagues evaluated the association between CKD and 30-day postoperative outcomes across eight surgical specialties.

A total of 1,912,682 adult patients were included in the study. The primary endpoint was major complications, death, unplanned reoperation, cardiac complication, or stroke within 30 days following surgery. Secondary endpoints included Clavien-Dindo high-grade complications and cardiac, pulmonary, infectious, and thromboembolic complications.

The researchers used multivariable regression to evaluate the association between CKD and 30-day postoperative complications, adjusting for baseline characteristics, surgical specialty, and operative time. Patients with CKD stage 5 had higher odds of major complications (adjusted odds ratio [aOR], 2.14; 95% CI, 2.07-2.21), death (aOR, 3.03; 95% CI, 2.88-3.19), unplanned reoperation (aOR, 1.57; 95% CI, 1.51-1.64), cardiac complication (aOR, 3.51; 95% CI, 3.25-3.80), and stroke (aOR, 1.89; 95% CI, 1.64-2.17) than those with stage 1. The pattern was similar for the secondary endpoints.

In summary, the authors wrote, "This population-based study demonstrates the negative impact of CKD on operative outcomes across a diverse range of procedures and patients."

DIABETES

Renal Effects of Acetazolamide Therapy in Type 1 Diabetes

Journal of the American Society of Nephrology. doi:10.1681/ASN.0000000515

Sodium-glucose cotransporter-2 inhibitors (SGLT2i) lower kidney failure risk in patients with type 2 diabetes but are not approved for patients with type 1 diabetes because they heighten the risk of diabetic ketoacidosis.

The proximal tubule diuretic acetazolamide may provide an alternative. Acetazolamide delivers more sodium to the distal nephron and may activate tubuloglomerular feedback (which lowers GFR and intraglomerular pressure) like SGLT2i but without the added diabetic ketoacidosis risk.

The renal effects and safety of acetazolamide in patients with type 1 diabetes have not been well studied. **Charles Ginsberg, MD,** and colleagues addressed this gap with a dose-escalation trial in 12 patients with type 1 diabetes. They studied the effects of 62.5 mg, 125 mg, and 250 mg dosages of oral acetazolamide, all administered twice daily. The study participants were treated for two weeks, followed by a two-week washout before beginning the next dosage level. The mean patient age was 46±17 years. All participants were White, and 75% were female. The mean measured GFR at baseline was 89±18 mL/min/1.73 m^2.

The researchers assessed blood and urine chemistries, as well as iohexol measured GFR, before and after each treatment interval. They sought to identify a dose that maximized measured GFR reductions while minimizing adverse effects. After two weeks of acetazolamide, measured GFR was reduced by 15% (95% CI, 9-21), 14% (95% CI, 7-21), and 15% (95% CI, 10-21) at the 62.5 mg, 125 mg, and 250 mg twice-daily dosages, respectively. However, the GFR reduction reversed fully after each two-week washout period. Serum bicarbonate decreased by 2.3 mEq/L, 4.2 mEq/L, and 4.4 mEq/L at 62.5 mg, 125 mg, and 250 mg twice-daily dosages, respectively. No hypokalemia (<3.5 mEq/L) was observed.

In conclusion, the authors wrote, "Among persons with type 1 diabetes and preserved kidney function, acetazolamide caused an acute, reversible reduction in measured GFR without effects on glucose metabolism."

DIALYSIS

Identification of Modifiable Factors Associated With Fatigue and Dialysis Recovery Time

Kidney360. 2024 Sep 1;5(9):1311-1321.

Fatigue and dialysis recovery time (DRT) are important patient-reported outcomes that can affect the well-being and survival of patients receiving hemodialysis. **Mabel Aoun, MD,** and colleagues conducted a study to identify modifiable dialysis-related factors associated with fatigue and DRT so that they might be addressed in future trials.

The researchers conducted a multicenter, observational study of adults receiving chronic hemodialysis for more than three months in December 2023. Hospitalized patients and those with active

cancer or cognitive problems were not included. In sum, 536 patients and 2,967 sessions were studied. The mean patient age was 68.1±14.3 years and 60.9% were male. In addition, 33.2% had diabetes and 63.3% were receiving hemodiafiltration.

Fatigue was assessed by utilizing the French-validated Standardized Outcomes in Nephrology-Hemodialysis fatigue scale. DRT was identified by asking patients, "How long did it take you to recover from your last dialysis session?" over six sessions. The researchers used logistic regression analysis to evaluate the association between DRT >12 hours and a fatigue score of four or higher with all dialysis-related factors. They also conducted a subanalysis of DRT-related factors for patients aged 85 years and older.

Median dialysate sodium was 138 (136–140). Fatigue score was 3.1±2.3, 37.7% of patients had a score of four or higher, and 18% experienced no fatigue. Median DRT was 140 (45–440) minutes, but 14.9% of patients had a DRT >12 hours.

DRT was significantly associated with fatigue scores. Multivariable regression analysis found that intradialytic reduction in serum sodium and frequency of dialysis were significantly associated with DRT. Female sex and lower hemoglobin were associated with fatigue. Among the patients aged 85 years and older, hemodiafiltration was associated with sustained DRT.

In summary, modifiable factors associated with prolonged DRT are not strictly the same as those associated with fatigue, but "modifiable factors can be addressed in future interventional trials to improve patients' outcomes," the authors wrote.

GOUT

Effects of Empagliflozin on Uric Acid and Gout in CKD

Nephrology Dialysis Transplantation. doi:10.1093/ndt/gfae203

Kaitlin J. Mayne and colleagues conducted exploratory analyses of data from the EMPA-KIDNEY trial to determine the effects of SGLT2 inhibition on uric acid and gout in patients with CKD. EMPA-KIDNEY comprised 6,609 patients with CKD (eGFR ≥20 and <90 mL/min/1.73 m^2) who were randomized to receive empagliflozin 10 mg daily or placebo over a median of two years of follow-up.

The researchers measured serum uric acid at randomization, at two months, and at 18 months. They used a prespecified mixed model repeated measures approach to evaluate the effects of empagliflozin and analyzed patient-reported gout events in Cox regression models (first events) with the Andersen-Gill extension (total events). EMPA-KIDNEY primary and kidney disease progression outcomes were assessed in subgroups of baseline serum uric acid, and a post-hoc composite outcome included new initiation of uric acid-lowering therapy or colchicine.

Mean serum uric acid concentration was 431±114 µmol/L at baseline. Randomization to the empagliflozin group resulted in a serum uric acid between-group difference of -25.6 (95% CI, -30.3 to -21.0) µmol/L. Larger effects were observed in participants with higher eGFR (trend $P<.001$) and without diabetes (heterogeneity $P<.001$).

Empagliflozin did not significantly reduce first or total gout events compared to placebo (HR, 0.87; 95% CI, 0.74-1.02 for the 595 first events, and 0.86, 0.72-1.03 for the 869 total events). Hazard ratios were similar for the post-hoc composite and across subgroups, including diabetes and eGFR. The effects of empagliflozin on the primary outcome and kidney disease progression outcomes were similar regardless of baseline uric acid level.

In conclusion, the authors said, "SGLT2 inhibition reduces serum uric acid in patients with CKD with larger effects at higher eGFR and in the absence of diabetes. However, the effect on uric acid is modest and did not translate into reduced risk of gout in EMPA-KIDNEY."

METABOLIC ACIDOSIS

Review of Dietary Interventions to Treat Metabolic Acidosis With CKD

Nephrology Dialysis Transplantation. doi:10.1093/ndt/gfae200

Alkali therapy has long been used to treat metabolic acidosis, a common complication of CKD that can lead to disease progression. However, there are concerns about its safety and long-term tolerability.

Sepideh Mahboobi, PhD, and colleagues conducted a systematic review and meta-analysis summarizing research findings comparing dietary interventions to placebo, usual care, or no treatment in the management of metabolic acidosis in adult outpatients with CKD. Any dietary intervention with the goal of affecting dietary acid load was considered an intervention.

Data were gathered from Medline, Embase, Cochrane Central, CINAHL, and Web of Science Core Collection from inception through June 2022. Two independent reviewers performed data screening and extraction. Random effects meta-analysis was conducted to pool data. The primary outcome was the change in serum bicarbonate.

Compared to controls, dietary interventions led to clinically significant improvement in serum bicarbonate (mean difference [MD], 2.98; 95% CI, 0.77-5.19; I2, 91%) and higher eGFR (MD, 3.16; 95% CI, 0.24-6.08; I2, 67%). However, serum potassium, albumin, and BMI were unchanged. Dietary interventions were found to be safe.

In subgroup analyses, plant-based interventions were found to be preferable to non-plant-based interventions for the improvement of acid–base balance and eGFR. However, the subgroup findings came from low-quality and heterogeneous studies.

In summary, the findings demonstrated the beneficial effects of dietary interventions to reduce acid or add a base to manage metabolic acidosis and kidney function in adults with CKD. Moreover, there were no observed adverse effects on serum potassium and nutritional status. "Well-designed clinical trials looking at the treatment of metabolic acidosis with dietary interventions with a focus on adding base through fruit and vegetables are required," the researchers concluded.

PEDIATRICS

CKRT Survival Among Children and Young Adults

American Journal of Kidney Diseases. doi:10.1053/j.ajkd.2023.12.017

Studies describing the epidemiology and outcomes in children and young adults receiving continuous kidney replacement therapy (CKRT) are limited. Therefore, **Michelle C. Starr, MD,** and colleagues sought to describe the associations among patient characteristics, CKRT prescription, and survival.

The researchers conducted a retrospective, multicenter cohort study comprising 980 patients aged from birth to 25 years. All participants received CKRT between 2015 and 2021 at one of 32 centers in seven countries participating in the Worldwide Exploration of Renal Replacement Outcomes Collaborative in Kidney Diseases (WE-ROCK). Median participant age was 8.8 (IQR, 1.6-15.0) years, and median weight was 26.8 (IQR, 11.6-55.0) kg. The study outcome was death before intensive care unit (ICU) discharge.

The most common modality for CKRT was continuous venovenous hemodiafiltration. Citrate anticoagulation was used in 62% of patients, and the internal jugular vein was the catheter placement location for 66% of patients. CKRT began a median of two days (IQR, 1-6) after admission to an intensive care unit (ICU) and lasted a median of six days (IQR, 3-14).

A total of 629 participants (64.1%) survived until discharge from an ICU. The CKRT dose, filter type, and anticoagulation were similar among patients who survived until ICU discharge and those who did not. Practices did not seem to vary by institutional ICU size.

Approximately two-thirds of the study participants survived at least until discharge from an ICU. There were variations in modes of dialysis, dose, catheter size and location, and anticoagulation, yet those factors did not appear to be associated with survival. ●

Sarah Tolson

Navigating the 2025 ESRD PPS Final Rule:

Key Updates for Billing Departments

The Centers for Medicare and Medicaid Services (CMS) has released the final rule for the end-stage renal disease (ESRD) prospective payment system (PPS) for calendar year (CY) 2025. These updates contain several significant changes that billing departments of dialysis programs need to understand to ensure seamless compliance and optimal reimbursement. We will highlight the most critical updates in the 2025 ESRD PPS final rule and their potential impact on billing operations.

Updated Base Rate and Revised Wage Index Calculations

The ESRD PPS base rate for CY 2025 has been set at $273.82, reflecting an increase of $2.80 from the CY 2024 rate. The ESRD PPS wage index will be derived from Bureau of Labor Statistics data and ESRD facility cost reports. To determine the effect these changes will have on your dialysis program's bottom line, you can check your program's CMS certification number in the CMS facility level impact files. Visit www.cms.gov and search for "CMS-1805-F" and you will find the files in the downloads section.

Expanded List of Outlier Services

CMS has expanded the list of outlier services to include additional medications that were part of the composite rate before the ESRD PPS. This change had a significant effect on the amounts used to calculate outlier eligibility for pediatric claims. Below are the updated fixed dollar loss (FDL) and Medicare allowable payment (MAP) amounts.

- Pediatric FDL: Increased significantly to $234.26 (up from $11.32 in CY 2024), driven primarily by the inclusion of alteplase
- Pediatric MAP: Increased to $59.60 (up from $23.36 in CY 2024)
- Adult FDL: Decreased to $45.41 (from $71.76)
- Adult MAP: Decreased to $31.02 (from $36.28)

These adjustments highlight the importance of understanding the criteria for outlier payments. Billing teams should verify that medications and services qualifying as outliers are properly documented and billed to capture outlier adjustment amounts where applicable.

Low-Volume Payment Adjustment

The low-volume payment adjustment has transitioned to a two-tiered model: programs performing fewer than 3,000 treatments annually will receive a 28.9% adjustment to the base rate, and facilities with 3,000 to 3,999 treatments annually will receive an 18.3% adjustment. CMS will determine which tier a program is eligible for based on the median treatment count over the past three cost reporting periods. Billing departments should review historical data to verify their facility's tier and ensure proper reimbursement is received.

Inclusion of Oral-Only Drugs in the ESRD PPS

Effective January 1, 2025, oral-only drugs are included in the ESRD PPS. CMS will use the traditional drug add-on payment adjustment (TDAPA) to reimburse phosphate binders based on 100% of the average sales price, wholesale acquisition cost, or invoice cost depending on availability of pricing information. In addition, facilities will receive a fixed, per claim reimbursement of $36.41 for the costs associated with dispensing and storing these drugs.

Clinical and billing teams will need to collaborate when outlining processes around identifying the patients who need to continue to get their phosphate binders from a retail pharmacy and those who should receive their phosphate binders from the dialysis program. Thorough documentation around the patient's insurance plan, prescribed dose, and the quantities of phosphate binders distributed is critical to ensuring accurate billing and reimbursement. Billing departments must update their systems to incorporate oral-only drugs into claims and familiarize themselves with TDAPA processes to ensure full reimbursement.

Reimbursement for Home Dialysis and Training for AKI Beneficiaries

CMS will now allow reimbursement for home dialysis and home dialysis training for acute kidney injury (AKI) beneficiaries. Billing teams should confirm that training sessions and related services are documented and coded accurately and educate staff about the additional reimbursement opportunities for home dialysis services for patients with AKI.

Reporting 'Time on Machine'

Starting January 1, 2025, facilities must report the "time on machine" on each claim using value code D6. Billing departments should ensure electronic health records (EHRs) are configured to capture and transmit these data for inclusion on claims per CMS specifications.

Preparing for Implementation

With the CY 2025 ESRD PPS updates introducing several significant changes to requirements and reimbursement, dialysis programs must proactively educate their teams on changes that relate to their daily tasks and responsibilities. Confirming that billing software and EHR systems are updated to reflect new reporting requirements is a crucial step in preparedness. To achieve maximum reimbursement, all teams must work together to ensure clinical documentation supports billing data. ●

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