Nephrology Times

Practical News, Trends, and Analysis

December 2025

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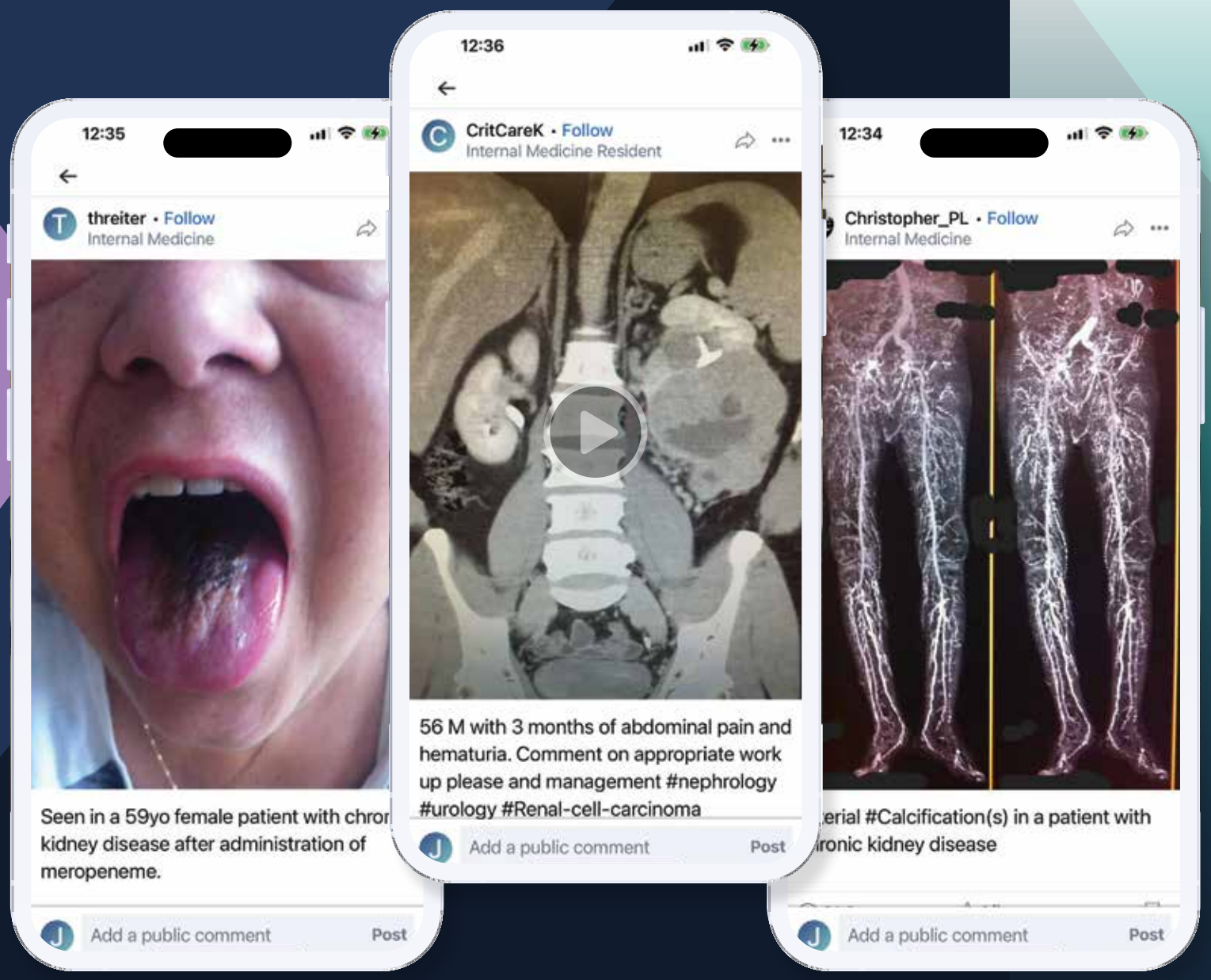

AI and Electron Microscopy: The Future Is Here

Ajay K. Singh, MBBS, FRCP, MBA

*By **Ajay K. Singh, MBBS, FRCP, MBA***

Electron microscopy (EM) is an invaluable tool in the diagnosis of glomerular disease and a key part of a morphologic triad alongside light microscopy and immunofluorescence.[1]

A key challenge with EM is the lack of a sufficient number of skilled nephropathologists to interpret findings from images. If EM interpretation could be more available, wider use might result. Artificial intelligence (AI) could come to the rescue by ultimately replacing human interpretation. Artificial intelligence could also increase efficiency by automating some labor-intensive and time-consuming tasks that slow down interpretation. Of course, AI applications of this type have the potential to revolutionize kidney pathology diagnosis everywhere, including the US.

The overarching value of EM in clinical care is illustrated by the following example. Thin basement membrane disease (TBMD) is part of the differential diagnosis of glomerular causes of microscopic hematuria. Identifying a thin glomerular basement membrane (GBM) relies on morphometric analysis and careful interpretation because the thickness varies based on the age and sex of the patient. Electron microscopy is essential in differentiating TBMD from Alport syndrome (AS). Electron microscopic findings in AS are very distinct: thickening and characteristic lamellation or "basket weave" patterns of the GBM. In TBMD, the most important feature is a uniform thinning of the GBM along its entire length. Also, in TBMD, the GBM retains its normal trilaminar structure: an inner lamina rara, a central lamina densa, and an outer lamina rara. Artificial intelligence could be trained and could automate measurement of GBM thickness across multiple GBM segments—a task that takes a pathologist time and a tremendous amount of attention to detail.

A recent paper published in *JAMA Network Open,* validating AI in augmenting EM kidney biopsy interpretation, demonstrates how far the field has already advanced. The future seems to be here.

Ma and colleagues[2] from China present a novel multimodular AI system, a "transmission electron microscopy image–based artificial intelligence–assisted device" (TEM-AID), which they propose represents a valid alternative to a pathologist's interpretation of EM data for the diagnosis of a broad variety of glomerular diseases.

Their study used 160,727 images from 31,670 patients from six health centers in China. The study was rigorous because the authors used both model training and internal validation on data from a single center and then further validated their TEM-AID using data from five additional institutions. The device consisted of four integrated modules: detection, segmentation, measurement, and classification. The authors also included an uncertainty estimation module and attention maps to improve model transparency.

> AI applications of this type have the potential to revolutionize kidney pathology diagnosis everywhere, including the US.

The article expresses results that are very technical unless one is familiar with the terminology. (Suffice it to say that as a nonexpert, I had to dig into the outcome measurements to understand them.) Ma and colleagues report a high degree of model validation and accuracy. Still more remarkable is the accuracy of their device, which exceeded clinician unaided performance and improved accuracy of their diagnosis when used in an assistive role.

An accompanying editorial by Cheungpasitporn and Farris[3] in the same issue of *JAMA Network Open* points to some important limitations of the study. The limitations include the following:

(1) **Limited types of glomerular diseases in the dataset:** They point to an overrepresentation of minimal change disease and membranous nephropathy, whereas rarer diseases were underrepresented (eg, TBMD and membranoproliferative glomerulonephritis).

(2) **Limited prospective validation:** Additional studies will be needed for this.

(3) **The model's limited generalizability:** Because the data were derived exclusively from Chinese institutions, testing in more diverse datasets will be needed.

As a side note, an article earlier in 2025 by Alton Farris[4] reviews the potential applicability of using AI augmentation to automate the Banff classification in the diagnosis of transplant rejection. Farris reviews the potential future impact of AI-based computer algorithms to automate objective assessment of cell and tissue features—another thread, no doubt, in the use of AI in kidney pathology.

To summarize, the paper by Ma and colleagues represents a new and important advance in showing where the field of AI augmentation is going. It also emphasizes that AI can play two roles: (1) it may ultimately replace human interpretation, and perhaps more relevant and even more likely, (2) it can supplement and make EM interpretation more accurate in kidney pathology diagnosis. ●

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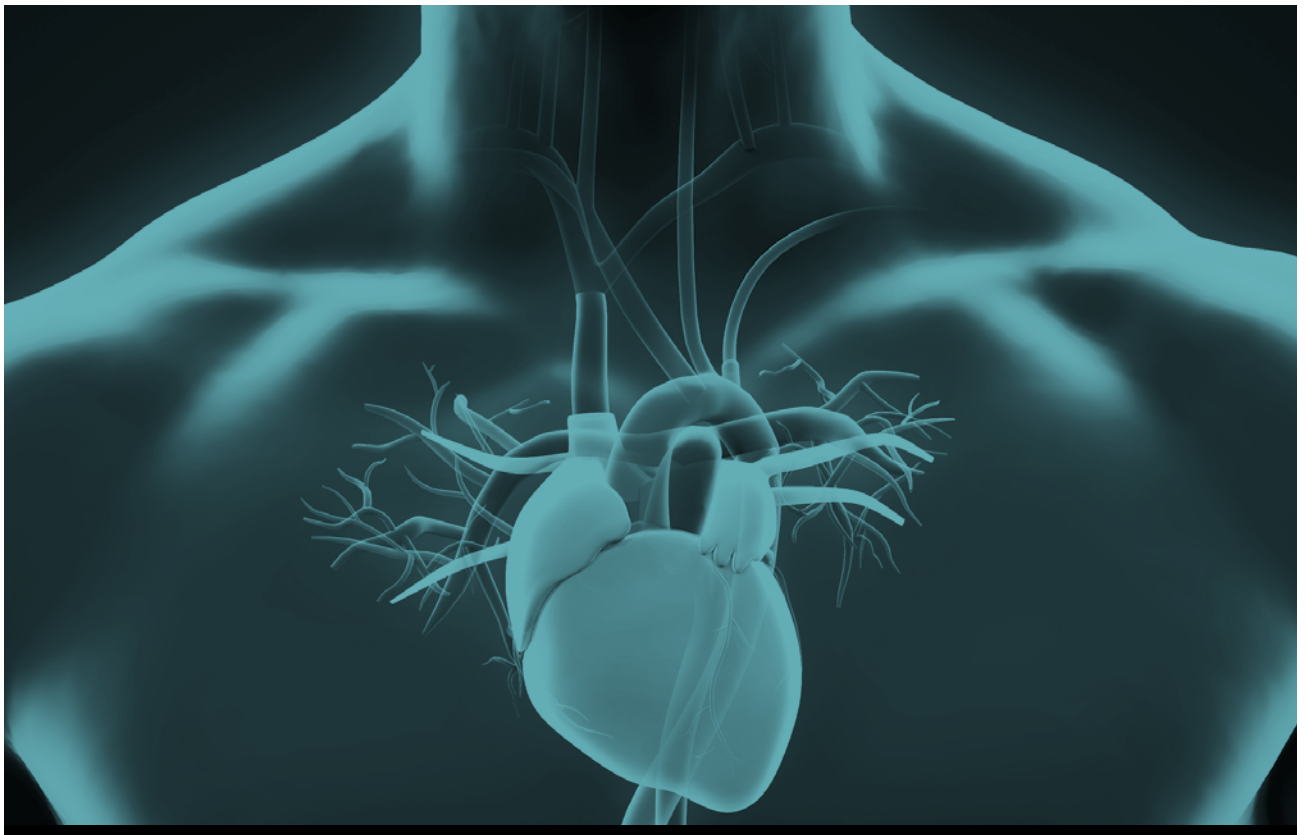

Stemming the Rising Tide of CKM Syndrome

Ben Talbot, MBBS, PhD

Claudio Hegenberger, MD, MBA, MSc

*By **Ben Talbot, MBBS, PhD,** and **Claudio Hegenberger, MD, MBA, MSc***

As the connections among heart disease, kidney disease, diabetes, and obesity have become increasingly well recognized, so has the need for a comprehensive definition and approach to diagnosis, risk stratification, and management.

Cardiovascular-kidney-metabolic (CKM) syndrome is a leading cause of death globally. With substantial increases in future incidence of cardiovascular disease (CVD) and stroke predicted,[1] the American Heart Association (AHA) issued a presidential advisory in 2023,[2] offering a framework to improve CKM health and related outcomes. Focusing on the need for early detection and multidisciplinary care, it highlights the potential role for nephrologists, along with cardiologists, endocrinologists, and primary care physicians, in delivering holistic, patient-centered care.

Overview

The AHA presidential advisory defines CKM syndrome as a systemic disorder characterized by pathophysiological interactions among metabolic risk factors, chronic kidney disease (CKD), and the cardiovascular system, leading to multiorgan dysfunction and a high rate of adverse cardiovascular outcomes,[2] providing clarity on the constituents and consequences of CKM syndrome and highlighting the multisystem impacts seen in clinical practice. It is this multidirectional pathophysiology that leads to the increased morbidity and mortality seen in CKM syndrome, which goes beyond the sum of its shared risk factors. Importantly, this definition includes individuals with metabolic risk factors or CKD who are at risk for, and with existing, CVD.

Mechanism

Excessive and dysfunctional adipose tissue, particularly visceral adipose tissue, secretes proinflammatory and prooxidative products that cause hemodynamic, metabolic, inflammatory, and fibrotic damage to arterial, cardiac, and kidney tissues and reduce sensitivity to insulin, leading to impaired glucose tolerance.[3] A constellation of abdominal obesity,

continued on next page

TABLE | **The Stages of CKM Syndrome[a]**

Stage	Definition
0 - No CKM risk factors	Individuals with normal BMI and waist circumference; no evidence of metabolic syndrome, CKD, or CVD
1 - Excess or dysfunctional adiposity "Early warning signs"	Individuals with overweight/obesity or dysfunctional adipose tissue without the presence of other metabolic risk factors or evidence of CKD
2 - Metabolic risk factors and CKD "Health risks start to show"	Individuals with metabolic risk factors (hypertriglyceridemia, hypertension, metabolic syndrome, diabetes) or CKD
3 - Subclinical CVD in CKM "Heart and blood vessel problems begin"	One of the following: · Subclinical ASCVD[b] or heart failure among individuals with excess/dysfunctional adiposity, other metabolic risk factors, or CKD · Very high-risk CKD (stage G4 or G5 CKD or as per KDIGO[c] classification) · High predicted 10-year CVD risk
4 - Clinical CVD in CKM "Signs and symptoms of heart problems"[d]	Clinical CVD (coronary heart disease, heart failure, stroke, peripheral artery disease, atrial fibrillation) among individuals with excess/dysfunctional adiposity, other CKM risk factors, or CKD

a. Adapted from Cardiovascular-Kidney-Metabolic Health: A Presidential Advisory From the American Heart Association[2] and the American Kidney Fund: Cardiovascular-Kidney-Metabolic (CKM) Syndrome[4]

b. ASCVD: atherosclerotic cardiovascular disease

c. KDIGO: Kidney Disease: Improving Global Outcomes

d. Stage 4 CKM syndrome is further defined by the presence of kidney failure into stage 4a (without kidney failure) and stage 4b (with kidney failure).

dysglycemia, dyslipidemia, and hypertension contributes to metabolic syndrome, which commonly progresses to type 2 diabetes, resulting from chronic insulin resistance, promoting further kidney and vascular damage through inflammation and fibrosis.[3] Metabolic syndrome and diabetes are risk factors for kidney disease, and CKD is itself a major amplifier of cardiovascular risk.

The AHA stages of CKM syndrome recognize the progressive course and stepwise increase in associated risk for the condition (Table 1).[2] The importance of risk-enhancing factors (high burden of adverse social determinants of health, high-risk demographic groups [including lower socioeconomic status and South Asian ancestry]), chronic inflammatory conditions, mental health or sleep disorders, sex-specific risk enhancers (including adverse pregnancy outcomes and premature menopause [age <40 years]), and family history of diabetes or CKD, which increase the likelihood of progression along the CKM stages, are also highlighted.

Screening and Risk Detection

The framework outlines an emphasis on active screening to detect patients early within the disease course when appropriate intervention could delay or prevent the onset of clinical CVD and kidney failure. Screening should include social determinants of health and biological factors, and raising awareness could translate each patient-healthcare interaction into an opportunity to achieve appropriate screening.

The AHA-commissioned PREVENT online CVD risk calculator, developed and validated to improve precision and equity, offers several advantages over previous equations, including estimating 10- and 30-year risk for total and atherosclerotic CVD and heart failure, an extended age range (30-79 years), and inclusion of estimated glomerular filtration rate as a predictor, which has often been excluded from risk equations historically. Additional components include options to identify high-risk individuals through the inclusion of Social Deprivation Index estimates and the incorporation of albuminuria. More precise risk estimates can aid meaningful patient-centered discussions and support tailored therapeutic strategies, including intensification of risk factor modification in appropriate individuals.

Models of Care

Traditionally, the components of CKM syndrome have been evaluated and treated separately, but a key step toward better CKM management is raising awareness of the interrelated nature of these conditions, with interdisciplinary care and incorporation of social determinants of health as overarching considerations. Value- and volume-based approaches are proposed.

Support and protocolized guidance from a multidisciplinary team, including primary care, cardiology, nephrology, endocrinology, pharmacy, nursing, and social/community health workers, all organized by a CKM coordinator, could facilitate patient care within the primary care setting for lower-risk patients (value-based), with targeted referrals to subspecialties for higher-risk patients (volume-based). The potential role of nephrologists in these care models was recently highlighted by Rangaswami and colleagues.[5] An integrated care team of social workers, case managers, community health workers, and patient navigators, supporting patients to access available resources to address the social determinants of health, is a critical component.

Despite entering a new era of kidney medicine, with dedicated trials among patients with CKM syndrome showing benefit for both kidney and cardiovascular outcomes with treatments such as sodium-glucose cotransporter-2 (SGLT2) inhibitors, glucagon-like peptide-1 (GLP-1) receptor agonists, and nonsteroidal mineralocorticoid antagonists, uptake of these treatments remains poor. Although potential barriers to the implementation of evidence-based CKM management are numerous,[6] a multifaceted approach, including education (of patients and healthcare professionals) to improve awareness, early screening (with the inclusion of risk-enhancing factors and knowledge of evidence-based treatments), coordinated multidisciplinary care (contextualized, holistic, nonjudgmental, and patient-centered), and government and pharmaceutical support (to ensure treatments are affordable and accessible, particularly in underserved populations), offers possible solutions.

Future research must involve cross-specialty collaboration, investigate the benefits of multiple and combination therapies, and evolve to include the full spectrum of patients with CKM syndrome, focusing on patients traditionally underrepresented in cardiovascular trials, including low- and middle-income regions, and ensuring equity in terms of ethnicity and gender and social determinants of health. ●

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Nephrologists' Role in Reproductive Health

By ***Charlotte Robinson***

Reproductive health is a critical but often overlooked aspect of care for patients with chronic kidney disease (CKD). Up to 6% of women in their childbearing years have CKD, which may affect their fertility, contraception, pregnancy planning, breastfeeding, and sexual health.

However, as highlighted in a qualitative study by **Silvi Shah, MD, Rachael Nolan, PhD,** and **Nedas Semaska,** of the University of Cincinnati, nephrologists frequently report uncertainty about when and how to address these topics. The researchers interviewed nephrologists across the United States to identify gaps in practice, training, and systemic support, highlighting opportunities to better integrate reproductive health into kidney care.

Silvi Shah, MD

Defining the Nephrologist's Role

Because nephrologists provide long-term care to patients with kidney disease, they are in a unique position to address concerns about reproductive health. Although it may seem to fall outside the scope of nephrology, reproductive health is affected by kidney function. In addition, some nephrologists' patients may not see an obstetrician or primary care clinician regularly.

However, reproductive health counseling by nephrologists is inconsistent—and often nonexistent. The survey found that many nephrologists are unsure who should initiate these discussions, and the absence of formal guidance contributes to hesitation.

"That was actually an eye-opener for us because we have guidelines for everything," Dr. Shah said. "Paucity of guidelines is one major barrier, which is preventing them from talking about reproductive healthcare with their patients." Without structured recommendations, physicians may avoid conversations about contraception, pregnancy, or sexual function, even when these issues are directly relevant to outcomes.

Gaps in Training

Mirroring the lack of guidelines, training regarding reproductive issues is deficient, the survey revealed. "Right now, there is no curriculum for reproductive healthcare which is mandated to be a part of nephrology fellowship training," Dr. Shah explained. Some programs offer lectures on reproductive topics, but this is inconsistent and depends on available faculty expertise.

Highlighting the downstream impact, Dr. Shah commented, "If we don't have a curriculum, fellows are not consistently being taught or educated about reproductive healthcare, which is contributing to their lack of knowledge, which ultimately is contributing to hesitancy and reproductive health being not addressed with the patients." Most nephrologists included in the survey were within 9 years of completing training, she noted, showing that even recent graduates often lack structured preparation. Dr. Shah emphasized that improving fellows' education through dedicated curricula could enhance reproductive health counseling across the profession.

Practical Tools

Dr. Shah noted that several tools could support integration of reproductive counseling into routine visits. One is using artificial intelligence to identify patients of childbearing age. "This could be just these patients getting flagged at the time of the visit ... like, this is a patient who is of childbearing age, and then we make sure we counsel these patients," she said.

Checklists can provide guidance for clinicians, helping them address contraception, pregnancy intentions, and referrals to obstetric care. Educational pamphlets for patients and clinicians can reinforce these discussions, covering topics such as contraception, pregnancy safety, sexual dysfunction, and breastfeeding. If they are provided with relevant tools, nephrologists can address reproductive health consistently, even within the constraints of busy clinical practice.

Addressing Fragmented Care

Another commonly cited issue was fragmented care across specialties. Nephrologists may assume patients receive guidance from primary care physicians or obstetricians, but many do not. In addition, clinicians often rely on patients to communicate information among specialties, which can create gaps.

Better integration of electronic health records could help, Dr. Shah said. Even without fully integrated records, nephrologists can ask patients directly about reproductive health needs and reinforce counseling at follow-up visits to help ensure that reproductive health is not overlooked.

Multidisciplinary Clinics

Specialized pregnancy and kidney disease clinics, although still rare, provide a model for improving care. By uniting nephrologists and obstetricians, these clinics offer coordinated counseling and reduce reliance on patients as intermediaries.

"If we have one unified clinic or a specialized clinic where they are seeing their obstetricians and they're seeing nephrologists as well, I think that integration of care would lead to very positive results," Dr. Shah said. Dr. Shah suggested that broader implementation of such clinics could significantly reduce the current barriers nephrologists face in addressing reproductive health.

Priorities Moving Forward

Dr. Shah emphasized two priorities. First, nephrologists must address reproductive health directly. "It's very important for us to address family planning and contraception for our patients," she said, "Pregnancy is associated with higher risk of adverse outcomes for patients with kidney disease, and the risk increases with the severity of kidney disease."

Second, systemic barriers, particularly limited clinic time, must be addressed. Many nephrologists cited time constraints as a reason reproductive health discussions are skipped. "Eventually, having policy changes which address these time constraints for physicians would be the next step," Dr. Shah said.

> Although it may seem to fall outside the scope of nephrology, reproductive health is affected by kidney function.

Addressing gaps in guidelines and fellowship training, implementing practical tools, and fostering integrated care models will help nephrologists provide more complete, patient-centered care. Reproductive health is central to CKD management, and structured approaches can improve outcomes for women with kidney disease. ●

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Scan the code to watch the interview.

From a Standard to Platform Approach: The Next Wave of Glomerular Disease Clinical Trials

*By **Katie Kosko***

Clinical trials are the backbone of medical research, and in glomerular diseases, they have driven drug approvals while also inspiring researchers to move beyond traditional designs toward innovative structures that deepen disease understanding and improve patient outcomes.

The standard trial design with a 9-month primary end point and 2-year outcomes related to estimated glomerular filtration rate (eGFR) has worked well for many years. However, challenges arise, such as how to define and redefine trials to continue to make progress around the world, according to **Vlado Perkovic, MBBS, PhD,** a physician and researcher at the University of New South Wales, Sydney, Australia.

Vlado Perkovic, MBBS, PhD

Dr. Perkovic discussed current trials, barriers, and ways to push clinical trials forward during a session at GlomCon Hawaii 2025 in September titled "Trial Designs: Basket Trials, Umbrella Trials, Platform Trials, Pragmatic Trials."

Breaking Trial Barriers

Through novel approaches, researchers can perhaps better understand different types of glomerular diseases. However, obstacles, such as adequate patient recruitment and handling multidrug therapies, pose a challenge in terms of being able to move on to the next wave of clinical trials.

"It's a challenge keeping a person on a randomized treatment for 2 years and asking them not to change those treatments or to use other treatments," Dr. Perkovic told *Nephrology Times.* "As we increasingly get new drugs approved, there is going to be pressure from people—perhaps those who were randomized to placebo—to switch to open-label therapy, which can compromise our ability to get robust information about newer agents coming through."

Dr. Perkovic continued, pointing out that questions also emerge regarding treatment sequencing. For instance, should patients with IgA nephropathy receive a more targeted treatment with B-cell therapies, or is it best to start with nonspecific therapies like renin-angiotensin system blockade?

Beyond the Standard

Current clinical trials are investigating single agents, but to increase options for high-risk groups, multidrug options are crucial. Such options are being explored through subgroup analyses examining the use of iptacopan in combination with sodium-glucose cotransporter-2 inhibitors, which has shown promising results, according to Dr. Perkovic.

In addition, an ongoing platform clinical trial could bring different agents in and out as evidence emerges. "This approach has been long used in cancer, and we saw it change the world during the COVID-19 pandemic," Dr. Perkovic said.

A platform trial is helpful because it combines a basket-type approach in which people with different

types of conditions could be included, or it could allow subgroups of one disease type who have been excluded from previous trials to be eligible, such as those with IgA vasculitis.

Furthermore, an umbrella trial approach would allow for the study of multiple treatments at the same time. The rolling infrastructure would use multiple arms—with new arms constantly being added—and ongoing recruitment. A common control arm would receive standard-of-care therapy.

"We can use sophisticated statistical techniques that look at the probability of success over time and incorporate both albuminuria and eGFR effects into a single outcome," Dr. Perkovic said.

Another advantage of an umbrella trial is that one individual may be able to be randomized to multiple arms, he explained.

It takes time and resources to set up these types of trials, but it is already being tried in Australia with the CAPTIVATE trial, the first platform trial for chronic kidney disease, which is actively recruiting.

Pragmatic trials will need to be used to guide nephrologists on where to start first, Dr. Perkovic said. He also highlighted the importance of more head-to-head comparisons, as well as larger and longer trials.

"Moving to this platform-type approach is a leap for us in the nephrology community. It's something we haven't done before. It will require bravery and a lot of collaboration and engagement with regulatory agencies."

Defining Future Directions

Several trials over the years have changed clinical practice and helped shed light on different approaches.

Dr. Perkovic emphasized the RECOVERY trial in the United Kingdom, which used the platform design to rapidly test potential treatments for patients with COVID-19, many of whom had acute kidney injury or underlying kidney disease.

Moreover, the I-SPY trial network used a similar approach to quickly identify effective, biomarker-targeted treatments for breast cancer. Several agents used during these trials moved on to later-phase studies and ultimately received approval from the FDA.

"Moving to this platform-type approach is a leap for us in the nephrology community. It's something we haven't done before," Dr. Perkovic said. "It will require bravery and a lot of collaboration and engagement with regulatory agencies."

Although platform trials are not a solution to the problems that still exist in glomerular disease, they can move treatment to the next stage, he explained.

A critical starting point is to ensure that all patients with a disease are considered for enrollment in clinical trials. Because recruitment is driven by nephrologists, Dr. Perkovic highlighted GlomCon's potential to strengthen participation through its broad reach across the kidney disease community.

"We don't have good treatments for these conditions. We are currently offering patients random care, and I would much rather see that we offer them randomized care. That way we can learn from it and develop new treatments that change outcomes for future patients," he said. ●

Review Gives Insight Into ADTKD

By ***Victoria Socha***

The emergence of genetic testing has enabled the increasing recognition of autosomal dominant tubulointerstitial kidney disease (ADTKD). ADTKD is the third most common monogenic cause of kidney failure, which is defined as the need for kidney replacement therapy or kidney transplantation. The disease is defined by three key features: (1) autosomal dominant inheritance, (2) bland urinary sediment without hematuria or proteinuria, and (3) chronic kidney disease (CKD) progressing to kidney failure between ages 20 and 80 years.

To provide an understanding of the clinical characteristics and subtypes of ADTKD, **Anthony J. Bleyer, MD,** and colleagues published a review of the disease in the *American Journal of Kidney Diseases.* The authors also sought to help clinicians understand, diagnose, and treat patients with ADTKD.

Before 2000, ADTKD largely went undiagnosed. In 2002, research identified pathogenic variants in the *UMOD* gene as a cause of ADTKD. This was followed by the identification of pathogenic *MUC1* variants as the cause of ADTKD. The Wake Forest ADTKD registry has identified 554 patients with ADTKD-*UMOD* and 317 with ADTKD-*MUC1* in the United States.

Because of limited recognition and access to genetic testing, it is difficult to determine the prevalence of ADTKD. Routine genetic panels do not screen for *MUC1* pathogenic variants, making the detection of the disease difficult. Estimates of the prevalence of ADTKD range from 3 to 16 cases per million. The authors said, "Based on our experience with the referral of over 1,000 families for genetic testing for ADTKD, we believe each clinical nephrology practice has at least 1 family with ADTKD."

ADTKD-*UMOD*

In a cohort of 447 patients with ADTKD-*UMOD*, 55% developed gout. The median age at onset was 28 years, and 25% developed gout before age 20 years.

Patients have an average loss of estimated glomerular filtration rate (eGFR) of approximately 3 mL/min/1.73 m^2. The average age at kidney failure is 45 years. The age at kidney failure varies within families, from 20 to more than 70 years; the reasons for the variations are not known. The condition progresses more rapidly in men than in women.

Genetic testing is definitive for diagnosis of ADTKD-*UMOD*. Nearly all inherited kidney disease gene panels include the *UMOD* gene. Whole-exome sequencing can also be used in the evaluation. Genetic testing should include variants of uncertain significance (VUS). Each VUS should be further evaluated for causality.

Allopurinol is used to prevent gout in patients with ADTKD-*UMOD*. After a discussion of the risks and benefits of allopurinol therapy, including the rare risk of allergic reaction, adolescent patients with elevated serum urate levels and a family history of early-onset gout may start allopurinol during their teenage years.

Clinicians should advise patients to maintain overall good health and avoid smoking and obesity. When their eGFR has declined below 20 mL/min/1.73 m^2, patients with ADTKD-*UMOD* should be referred for kidney transplantation. Potential related donors should be tested for the familial *UMOD* pathogenic variant.

The authors noted that professional genetic societies advise against testing of minors (<18 years old) if they are asymptomatic and there are no potential therapies. However, because allopurinol is a potential therapy for gout with ADTKD-*UMOD*, clinicians should take a patient- and family-specific approach to the testing of children. In families with mild disease, late onset of kidney failure, and absence of gout in the teenage years in other family members, testing of children is not recommended. For patients in families with more severe pathogenic variants, children should be referred to a genetic counselor to discuss potential testing.

ADTKD-*MUC1*

Chronic kidney disease is the only renal manifestation of ADTKD-*MUC1*. The age at kidney failure is variable between and within families. The median age at kidney failure is 46 years, and the average rate of loss of eGFR is 2 to 3 mL/min/1.73 m^2 per year.

In an observational study of 726 individuals, gout was less prevalent in ADTKD-*MUC1* compared with ADTKD-UMOD (26% vs 79%; $P<0.001$) and usually occurred in combination with CKD. The age at onset of gout in patients with ADTKD-*MUC1* was 45 years.

Genetic testing is the only way to diagnose ADTKD-*MUC1*. For families with ADTKD, genetic testing is available through the Broad Institute of Harvard University and the Massachusetts Institute of Technology and is coordinated by the Wake Forest Rare Inherited Kidney Disease Team. There is no cost for families with a history of ADTKD. Testing centers are also located in Europe.

Patients with ADTKD-*MUC1* are excellent candidates for kidney transplantation. There are no specific treatments, but a promising compound that removes MUC1fs protein from the endoplasmic reticulum–Golgi intermediate compartment has recently been identified in murine studies.

Because children are nearly always asymptomatic and there are no specific therapies available, testing of children for ADTKD-*MUC1* is not generally recommended. The authors noted that "testing is a patient-specific decision and should be made between the child, parent, genetic counselor, and nephrologist."

Regarding future research focusing on ADTKD, the authors concluded, "The current research goals include (1) identification [of] other genetic causes of ADTKD, (2) determination of whether variants of uncertain significance are pathogenic, (3) identification of factors associated with rates of progression, (4) identification of better forms of genetic testing to determine *MUC1* pathogenic variants, and (5) identification of potential therapies." ●

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Steroidal MRAs Raise Hyperkalemia Risk Without Improving Kidney Transplant Outcomes

By ***Victoria Socha***

Millions of people worldwide are affected by chronic kidney disease (CKD), putting them at an increased risk for kidney failure and the need for dialysis or kidney transplantation. Kidney transplantation offers significant advantages over dialysis, including improved survival rates, lower healthcare costs, enhanced quality of life, and the ability to return to a productive life.

Mineralocorticoid receptor antagonists (MRAs) protect kidney function among patients with CKD by lowering blood pressure, limiting cardiac remodeling, and reducing inflammation and fibrosis. However, few data are available regarding the role of MRAs in the treatment of kidney transplant recipients. The need for robust clinical trial data is associated with the lack of definitive guidelines, specifically endorsing the use of MRAs in the kidney transplant population.

Paula Dibo, MD, and colleagues recently conducted a meta-analysis designed to determine the efficacy of MRAs among kidney transplant recipients. The researchers aimed to provide an up-to-date literature review incorporating novel studies conducted since the last review in 2020.

The literature search included PubMed, Embase, and Cochrane Central Register of Controlled Trials from inception to June 2024. The search terms used were *kidney transplant, renal transplant, kidney allograft, post-transplant, mineralocorticoid receptor blockers, aldosterone antagonists, spironolactone, finerenone, eplerenone, canrenone,* and *mexrenone.*

The primary outcomes of interest were serum creatinine (sCR), glomerular filtration rate (GFR), hyperkalemia, systolic BP, diastolic BP, albuminuria, proteinuria, and interstitial fibrosis and tubular atrophy (IFTA) scores.

The initial search produced 1,501 results. After duplicate records and ineligible studies had been removed, 25 studies were fully reviewed based on inclusion criteria. Of those, five were included in the qualitative and quantitative review. The five studies represented 293 kidney transplant recipients; of those, 48.5% (n=142) received treatment with MRAs. Three of the five studies included spironolactone as part of the MRA regimen; the remaining two studies used eplerenone.

The mean age of participants in the MRA group was 42.5 years, and the mean age of those in the placebo group was 41.1 years. Overall, approximately two-thirds of the participants were male and had received dialysis before kidney transplant.

No statistically significant differences were observed between the placebo and MRA groups in GFR (mean difference [MD], 9.04 mL/min/1.73 m^2; 95% CI, –2.76 to 20.85; *P*=0.13). The two groups were also similar in sCR (MD, –0.21 mg/dL; 95% CI, –0.62 to 0.20; *P*=0.32).

No statistically significant differences were observed between those treated with MRAs and those without MRA treatment in systolic BP (MD, 0.69 mm Hg; 95% CI, –0.69 to 2.08; *P*=0.33) or diastolic BP (MD, 0.45 mm Hg; 95% CI, –0.69 to 1.59; *P*=0.44).

Patients treated with MRAs had a significantly higher risk for hyperkalemia compared with patients without MRA treatment (risk ratio [RR], 4.06; 95 % CI, 1.46-11.28; *P*=0.007). The groups were similar in IFTA scores (mild IFTA: RR, 1.21; 95% CI, 0.83-1.74; *P*=0.32; moderate IFTA: RR, 0.82; 95% CI, 0.45-1.50; *P*=0.51; severe IFTA: RR, 0.64; 95% CI, 0.24-1.76; *P*=0.39).

No differences were noted between the group treated with MRAs and the group without MRA treatment in the severity of albuminuria (MD, –0.06 mg/g; 95% CI, –0.37 to 0.25; *P*=0.71) or in severity of proteinuria (MD, –0.13 g/d; 95% CI, –0.67 to 0.41; *P*=0.18).

Researchers performed a series of sensitivity analyses to determine the elevated heterogeneity seen in the outcomes of GFR, systolic BP, and diastolic BP. Glomerular filtration rate had the highest heterogeneity (I^2=97.3%), followed by systolic BP (I^2=90.3%) and diastolic BP (I^2=86.7%). In the leave-one-out analysis for GFR, the exclusion of the SPIREN study reduced heterogeneity from I^2=97.3% to 89.2%; however, the pooled effect size remained stable.

Results of study quality assessment using the Cochrane RoB 2 quality assessment tool revealed that most of the studies were rated as having a low risk of bias or some concerns. In four of the five studies, patients and investigators were blinded. The fifth study was not blinded to the clinical researchers and was rated as having a high risk of bias in the measurement of outcome domain. Two studies had a rating of some concerns in the randomization domain.

Using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) tool, the certainty of evidence for the outcome of hyperkalemia was rated as high. Because of concerns about risk of bias from one study with unblinded outcome assessment, the outcomes of sCR and IFTA scores were rated as moderate certainty. Because of serious concerns related to the risk of bias, inconsistency, and imprecision, the certainty of evidence for GFR and systolic BP was rated as very low.

> The need for robust clinical trial data is associated with the lack of definitive guidelines, specifically endorsing the use of MRAs in the kidney transplant population.

The authors included the variability of study design, the substantial heterogeneity among the included studies, the variation in follow-up periods among the studies, and the possibility that some outcomes may be underpowered for a definitive conclusion on the absence of an effect as limitations of their study.

In conclusion, the researchers wrote, "In this meta-analysis of patients who underwent KT [kidney transplantation], we found no adverse effect of steroidal MRA use on sCR levels and no beneficial impact on IFTA scores, albuminuria, or proteinuria compared to placebo. However, steroidal MRAs led to a significantly higher risk of hyperkalemia." ●

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IVIG Linked to Stabilized Graft Function in Chronic Active AMR

By ***Victoria Socha***

Chronic active antibody-mediated rejection (AMR) is the leading cause of allograft loss beyond 5 years following kidney transplantation and occurs 3 to 6 months after transplantation. Although AMR usually occurs with donor-specific antibodies (DSAs) against human leukocyte antigen, the presence of DSAs is not required to make the diagnosis.

Compared with early AMR, chronic active AMR is less responsive to treatment, and no evidence-based, effective long-term treatment options for patients with chronic active AMR exist. Guidelines from the Transplantation Society's 2020 Consensus Treatment Recommendations define standard of care for chronic active AMR as optimization of baseline immunosuppression, including reintroduction of steroids and maintenance of trough tacrolimus levels at greater than 5 ng/mL.

Intravenous immunoglobulin (IVIG) has been administered to some patients with chronic active AMR. However, according to **William R. Mulley, PhD,** and colleagues, few data on the efficacy of IVIG in that patient population are available. The researchers conducted a prospective, multicenter, open-label, randomized controlled trial in Australia designed to determine whether IVIG therapy for patients with biopsy-proven chronic active AMR could improve clinical and histologic outcomes.

Thirty eligible participants were randomly assigned 1:1 to the IVIG group (n=15) or the no-IVIG group (n=15). Individuals in the IVIG group received Octagam 10% (Octapharma) or Privigen 10% (CSL Behring), 1 g/kg per month, for 3 months. Treatment was repeated for an additional 3 months if ongoing microvascular inflammation was observed on repeat biopsy.

The primary end point of interest was the difference in slopes of the Chronic Allograft Damage Index (CADI) scores between the two groups across four allograft biopsies (at baseline and 3, 6, and 12 months). Secondary outcomes included changes in estimated glomerular filtration rate (eGFR), change in DSA, allograft and patient survival, and change in intragraft mRNA expression (assessed at baseline and 3, 6, and 12 months).

The median age of the overall cohort was 54.3 years, 22 participants were male, and mean eGFR at baseline was 43.4 mL/min/1.73 m^2. One participant in the no-IVIG group withdrew from the study after 3 months but remained in the intention-to-treat analysis until 12 months. Eighty percent of the transplants were primary allografts. At baseline, immunosuppression included a calcineurin inhibitor for 97%, mycophenolate for 93%, and prednisolone for 80% of participants. After study enrollment, all participants continued to receive that combination. Exposure between the two groups was similar.

No change in the predicted CADI score was observed in the IVIG group (–0.004/month; 95% CI, –0.13 to 0.12; *P*=0.96). In the no-IVIG group, CADI scores increased (0.28/month; 95% CI, 0.14-0.41; *P*<0.001). For the treatment by time interaction, *P*=0.003. Results of assessments of components of CADI suggested that the differences were driven by the change in glomerular sclerosis, interstitial fibrosis, and tubular atrophy components. Greater increases were seen in the Banff scores for those components in the no-IVIG group than in the IVIG group.

Mean eGFR at baseline was 43.5 mL/min/1.73 m^2 in the IVIG group and 43.0 mL/min/1.73 m^2 in the no-IVIG group. Over the first 12 months of the trial, the slope of eGFR decline was significantly greater in the no-IVIG group than in the IVIG group (–1.1 mL/min/1.73 m^2 vs –0.4 mL/min/1.73 m^2, respectively; *P* for interaction = 0.024). The differences persisted for up to 24 months.

No difference was seen between the two groups in the trajectory of urine protein to creatinine ratios. The decline in the mean fluorescence index of the immunodominant DSAs was greater in the no-IVIG group than in the IVIG group (–352/month vs –76/month, respectively; *P* for interaction = 0.013).

At 12 months after study enrollment, one episode of allograft loss occurred in each group. At 5 years after study enrollment or at the study's end, five participants in the IVIG group and nine in the no-IVIG group had experienced allograft loss. There was no difference in the risk of allograft loss in the IVIG group relative to the no-IVIG group (hazard ratio, 0.38; 95% CI, 0.12-1.16; *P*=0.09). Chronic active AMR was associated with all allograft losses. After 5 years of enrollment or at the study's end, there were no deaths in the IVIG group and five in the no-IVIG group. The causes of the deaths in the no-IVIG group were considered to be infection (n=2), stroke (n=2), and withdrawal from dialysis (n=1).

Ninety IVIG infusions were administered, and five adverse events were reported by four participants. Hospitalization was required for one patient because of headache and for one patient because of bradycardia and nausea. The three remaining events related to nausea were headache, muscle spasm, and chest tightness. No long-term adverse events or events remote to the infusions were reported.

The authors cited some limitations to the study findings, including the lack of a placebo control group and missing vascular elements from some biopsies. In addition, the trial did not reach recruitment targets, resulting in a small sample size. The slow recruitment led to a long study period, raising the possibility of changes in clinical practice over time.

In conclusion, the researchers wrote, "IVIG therapy in patients with chronic active AMR was associated with stabilization of allograft histology and function. It should be considered for all patients with this condition who are represented by this study population and should be considered standard of care in any clinical trials of new therapies for chronic active AMR." ●

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ASN Issues Guidance on Potassium and Phosphorus Additives

The American Society of Nephrology (ASN) released its latest Kidney Health Guidance (KHG) addressing how potassium and phosphorus additives affect health risks, such as hyperkalemia and chronic kidney disease (CKD)-related mineral and bone disorder, for patients with kidney disease.

Published in the *Journal of the American Society of Nephrology,* the KHG recommends against the consumption of any phosphorous additives, finding that they have no health benefits for patients with CKD.

The KHG highlights differences between hyperkalemia, which tends to occur intermittently, and hyperphosphatemia, which develops slowly and continuously. Excess phosphorus intake may carry risks even without overt hyperphosphatemia. Unlike universally harmful phosphorus additives, potassium additives can be beneficial for many patients, underscoring the need to individualize dietary restrictions based on hyperkalemia risk.

Citing inadequate food labeling and nutrient databases, the KHG emphasizes that effective dietary strategies depend on awareness, access to healthy foods, and social support. It also calls for further research on the safety, bioavailability, and clinical impact of potassium and phosphorus additives and the effectiveness of dietary interventions in CKD.

Source: American Society of Nephrology.

FDA Grants Fast Track Designation to Investigational Anti-PAPP-A Antibody for ADPKD

The FDA granted Fast Track Designation to ABBV-CLS-628, an investigational therapy for autosomal dominant polycystic kidney disease (ADPKD).

Developed by Calico Life Sciences in collaboration with AbbVie, ABBV-CLS-628 is a human monoclonal antibody targeting pregnancy-associated plasma protein-A (PAPP-A). The agent is currently under investigation in a phase 2 trial evaluating its safety, tolerability, and potential efficacy in slowing ADPKD progression. Participants receive intravenous ABBV-CLS-628 or placebo every 4 weeks for 92 weeks, with safety follow-up for up to 15 weeks.

ADPKD, the most common inherited kidney disease, causes progressive cyst growth in both kidneys and leads to kidney failure in more than half of affected individuals by age 60.

Fast Track Designation facilitates development and accelerates FDA review of therapies for serious conditions with unmet medical needs, enabling closer communication with the agency and the potential for earlier patient access. ABBV-CLS-628 previously completed a phase 1 study in healthy volunteers, in which it was well tolerated with no significant adverse events.

Source: Calico Life Sciences.

Imlifidase Meets End Point in Trial for Highly Sensitized Kidney Transplant Recipients

Hansa Biopharma announced positive topline results from the phase 3 ConfIdeS trial of imlifidase in highly sensitized adult kidney transplant recipients (calculated panel reactive antibody score ≥99.9%) with a positive crossmatch against a deceased donor.

The trial met its primary end point of kidney function at 12 months, measured by mean eGFR, with a statistically significant and clinically meaningful difference: 51.5 mL/min/1.73m² in the imlifidase arm versus 19.3 mL/min/1.73m² in the control arm ($P<0.001$). Patients receiving imlifidase also achieved superior dialysis independence at 12 months, a key secondary outcome.

Transplant surgeon **Robert Montgomery, MD, PhD,** of New York University Langone Health, said in a statement, "The results from the US ConfIdeS trial are highly encouraging and demonstrate the significant potential for imlifidase to transform standard of care for highly sensitized kidney transplant patients."

Hansa plans to submit a Biologic License Application under the FDA's accelerated approval pathway by the end of 2025, with full results scheduled for presentation at a medical congress in 2026.

Source: Hansa Biopharma.

Nephrology Nursing Journal Inducted into INANE Nursing Journal Hall of Fame

The *Nephrology Nursing Journal,* the official publication of the American Nephrology Nurses Association, was inducted into the International Academy of Nursing Editors (INANE) Nursing Journal Hall of Fame. The honor recognizes journals that have published continuously for 50 years or more and demonstrated sustained contributions to nursing scholarship and practice.

Founded in 1974, the *Nephrology Nursing Journal* has long served as a peer-reviewed resource for clinical practice, professional development, research, and innovation in nephrology nursing. Under the leadership of Editor-in-Chief **Beth Ulrich, EdD, RN,** the journal has become a trusted platform for advancing nursing science, policy, and education, while supporting kidney health through knowledge dissemination.

The INANE Hall of Fame, established in 2018, celebrates nursing journals with exceptional longevity and influence. Dr. Ulrich received the induction at INANE's annual conference in Portland, Maine.

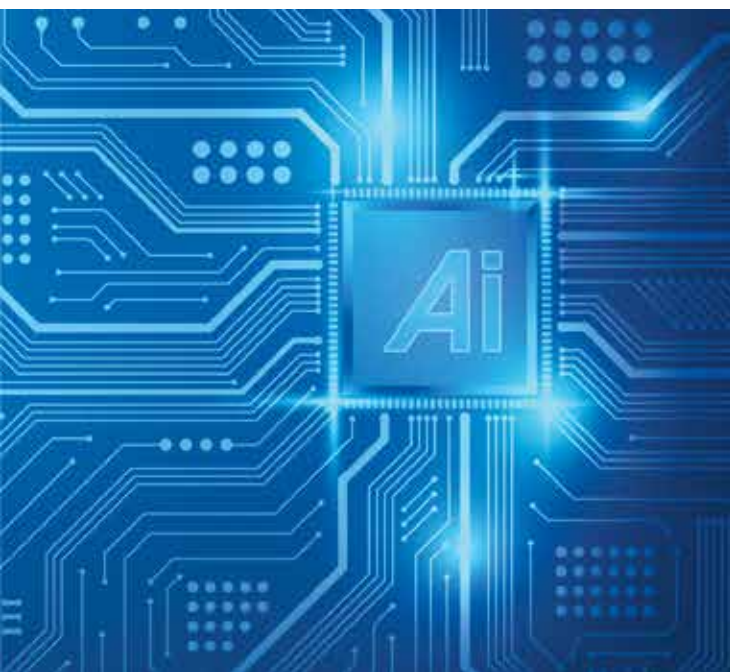
Source: American Nephrology Nurses Association.

Renalytix Teams With Tempus to Broaden Access to CKD Risk Test in Diabetes

Renalytix announced a collaboration with Tempus AI to make its FDA-approved, Medicare-reimbursed kidneyintelX.dkd prognostic blood test more widely available to eligible US patients with type 2 diabetes and CKD.

KidneyintelX.dkd, the first test in Tempus' CKD portfolio, is indicated as an aid in predicting risk for progressive kidney function decline—high, moderate, or low—in patients with CKD stages 1–3b. Under the agreement, Renalytix and Tempus will work with US health systems to facilitate test ordering within existing clinical workflows. A Renalytix laboratory will process the tests, with customized results reported electronically to clinicians and, where applicable, patient portals.

Source: Renalytix.



Partnership Will Harness AI for CKD Research and Care

Century Health and Balboa Nephrology announced a partnership to apply artificial intelligence (AI) to real-world clinical data, aiming to accelerate research and improve care in CKD.

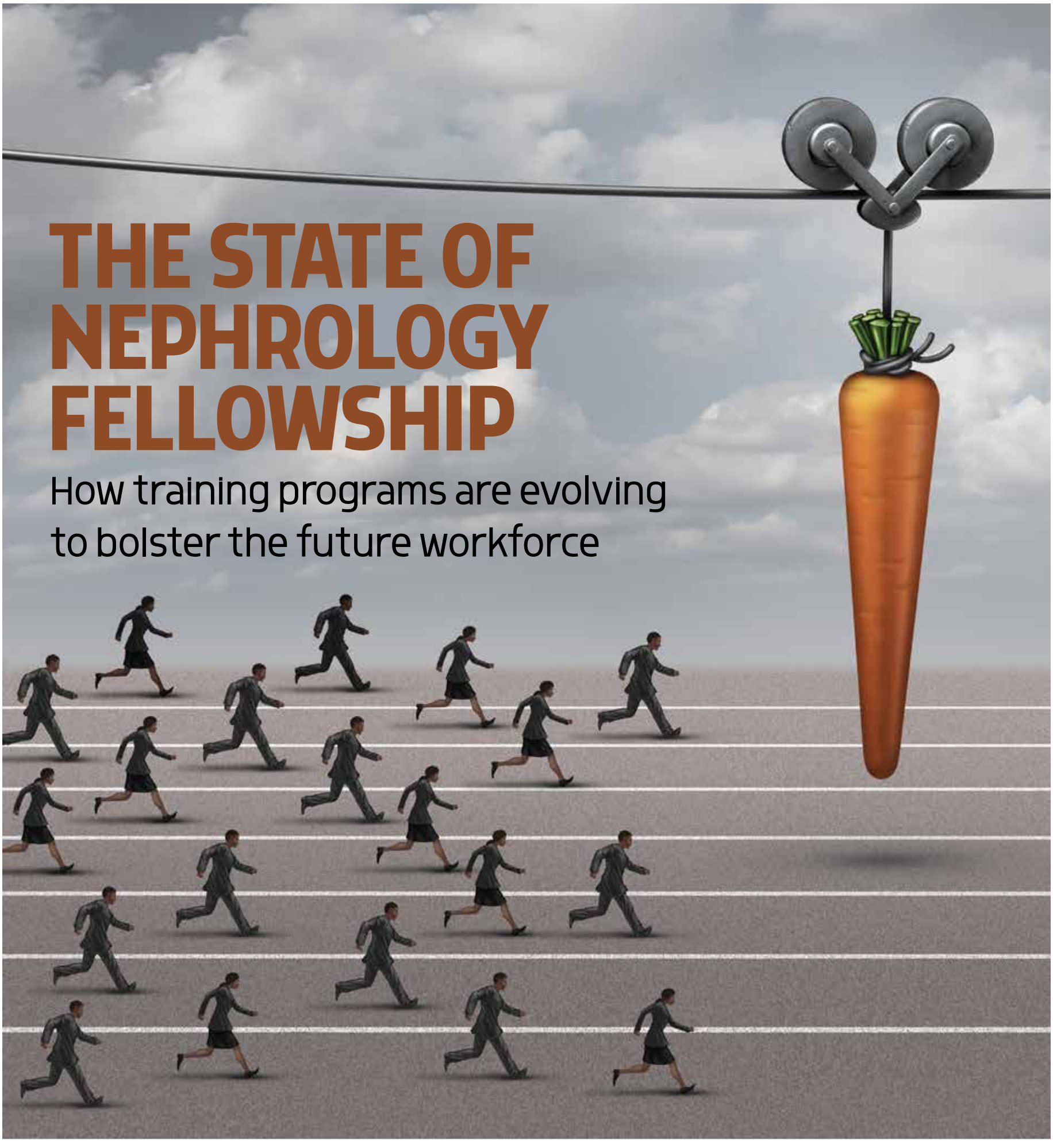
Balboa Nephrology will use Century Health's AI models to analyze electronic health records and surface complex, previously hard-to-capture variables that can inform care decisions, treatment effectiveness, and patient outcomes. The partners hope to combine clinical expertise with AI to improve care and accelerate treatments in conditions such as IgA nephropathy, lupus nephritis, and C3 glomerulonephritis.

The Century Health Abstraction and Retrieval Model aggregates estimated glomerular filtration rate (eGFR) data longitudinally and contextualizes it with complementary variables such as proteinuria and biopsy findings. This capability addresses challenges in monitoring kidney function, such as fluctuating eGFR values due to patient-specific factors, and highlights how AI can support research and care in CKD.

Source: PR Newswire.

THE STATE OF NEPHROLOGY FELLOWSHIP

How training programs are evolving to bolster the future workforce



*By **Keightley Amen, BA, ELS***

One way to see into the future of a medical specialty is to look at its fellowship. Some experts are concerned that the state of the nephrology fellowship paints a dim picture of the future of the field, as fellowship programs struggle to recruit, retain, and train enough specialists to meet the nation's ever-increasing need for kidney care.

The imperative to grow the nephrology workforce is clear. The demand for kidney care continues to grow among an aging population, but the number of specialists who can care for them continues to shrink due to the number of retiring physicians and fewer physicians choosing to specialize in nephrology.

Nephrology fellowship training programs and nephrologist recruiters are working to change perceptions and attract more physicians. They believe that when trainees better understand nephrology's benefits and opportunities, they will seriously consider the specialty.

Programs Struggle to Fill Positions Through the Match

Recent statistical trends from the National Resident Matching Program show stagnant or declining interest in nephrology as a specialty. The percentage of positions filled declined from more than 94% in 2010 to 66% in 2024. However, the most recent data show that perhaps the situation is improving. A total of 362 candidates matched into nephrology in the 2025 match—up 13% from the previous year.[1-3]

When fellowship programs are unable to fill all their positions through the main match, they must "scramble" to find enough trainees, said **Pietro Canetta, MD,** training program director of fellowship at New York-Presbyterian. Options include participating in the Supplemental Offer and Acceptance Program (SOAP), accepting allopathic candidates, or taking international medical graduates (IMGs) who have skipped residency. The latter is a particularly concerning trend because IMGs sometimes choose nephrology only as an entry point to the US medical education system but ultimately don't pursue the specialty, according to some sources.

"Other bits of data are also a bit concerning. We've seen a decrease in US-trained physicians who want to go into nephrology, so we have more foreign-trained [physicians] and more DOs [Doctors of Osteopathic Medicine]. Board passage rates have gone down over the years. As best we can tell, it seems trainees are doing worse as a population," Dr. Canetta said.

"We, as a nephrology community, feel that pressure, and we have to react to it to ensure that our field continues to be strong," said **Matthew Sparks, MD,** program director of the nephrology fellowship at Duke University School of Medicine in North Carolina. The goal is to fill all the openings through the match. Although many programs cannot achieve that yet, there is momentum. Dr. Sparks encourages people to look beyond the numbers. "We want to grow the next generation of leaders in nephrology, not just fill the slots," he said.

Potential Reasons for Declining Interest in the Specialty

Residents may not choose nephrology for many reasons.

Nephrologist recruiter **Tammy Elzy** tracks training statistics and has many one-on-one conversations with physicians. She says the biggest barrier they cite is compensation versus workload. Nephrologists make an average starting salary of $240,000 per year. That is higher than the average $217,000 for primary care physicians (PCPs); slightly below the average of all specialties; and well below specialties such as plastic surgery, orthopedic surgery, and cardiology.[4,5]

"The starting salary is similar to a PCP, but nephrologists require more training, have a heavier call schedule, and practice in multiple locations," Elzy said.

"There is a significant crisis in the workforce coming," according to **Anna Zisman, MD,** director of the Nephrology Fellowship Training Program at the University of Chicago in Illinois. "Local, individual experiences are making a huge impact as far as showing people that nephrology is interesting, stimulating, and rewarding, but the reality is that trainees have loans to pay back."

Ultimately, the solution lies in advocacy at the federal level regarding reimbursement, Dr. Zisman said. "It's largely a policy issue. What is currently valued are procedural specialties. We have to band together to make changes happen at the government and payer levels ... and ensure appropriate attention is being paid to nephrology."

Trainees may also have a misperception that nephrologists must work harder than many other specialists, said Elzy, founder of NephMD Recruitment. They may believe that nephrology requires emergency care, a complex blend of both inpatient and outpatient care, and night shifts or being on call. "Today's people want work-life balance. They work to live, not live to work," Elzy said.

A recent report from the American Society of Nephrology (ASN) confirms the increasing importance of lifestyle factors to trainees and early-career nephrologists. A recent ASN survey cited the top factors in career decisions: compensation, call frequency, desired practice location, and vacation.[5]

Brett Osinski, vice president at recruiting firm Nephrology USA, said the specialty is starting to respond to the need for work-life balance with nontraditional practice models, use of advanced practice providers, telehealth, more flexible call models, and less "windshield time" traveling from hospital to hospital.

"Trainees are exposed to in-hospital medicine, but in-hospital nephrology is just a small part of what nephrologists do—and often the hardest part of what we do," Dr. Canetta explains. "But nephrology encompasses so much more. We don't do a good enough job of demonstrating the breadth of nephrology, the patients who are doing really well managing chronic conditions, and the relationships that treating physicians and patients develop over time."

Innovations and Improvements in Fellowship Training

Training programs are responding to the challenges. "We're working hard to ensure that a great learning environment exists," Dr. Sparks said. "Adversity is needed for growth. We see that in our daily lives. It's an opportunity to learn and grow and change."

As part of their efforts to attract and prepare candidates, programs are:

- ***Teaching the business of nephrology:*** Programs have begun focusing on being more mindful about the transition from training to practice. This includes exposing trainees to opportunities in private practice, as well as training them to understand contracts and business principles.

- ***Reducing workload:*** Many training programs are taking steps to reduce workloads and prevent 24-hour shifts. Examples include adopting creative night-float structures and having attendings round without fellows, Dr. Sparks said. Dr. Zisman said her program has adopted a "4+2" (or "X+Y") residency schedule, which separates inpatient and outpatient training into distinct blocks. For example, residents may spend 4 weeks on inpatient services or electives and then have a 2-week block of ambulatory care, including continuity clinics, subspecialty clinics, and outpatient didactics.

- ***Highlighting a diversity of patients and settings:*** In traditional training models, fellows often focus on hospital nephrology, which is one of the most demanding settings. Some programs are now focusing on exposing trainees to other models, including pediatrics, academia, private practice, research, industry, and administration. This approach helps trainees become well-versed in the many kidney conditions and shows them that there are other opportunities to practice without the more intensive demands of a hospital setting.

- ***Implementing team-based care:*** Advanced practice providers are becoming more essential in all areas of medicine. Nephrology training programs are starting to integrate them into the learning environment, which has the dual benefit of giving trainees experience in the team-based care typical of real-world practice and reducing workloads.

- ***Establishing subspecialty practice:*** There has been a recent shift toward subspecialty tracks, Osinski said, such as transplantation, critical care, onco-nephrology, and cardionephrology.

- ***Pipeline programs:*** Programs have been established at local and national levels to introduce future physicians to the specialty. Examples include the ASN Kidney STARS (Students and Residents) Program and NephSim Nephrons.[6,7] Program directors also said they target their own residencies as a valuable pipeline.

Elzy and Osinski emphasized that recruiters can partner with training programs to help formally educate trainees about the future earning potential in the field, leadership tracks, opportunities available through practice partnerships, and access to ancillary income streams.

'Showing the Worth of Nephrology'

In addition to the changes that training programs are making, all the experts interviewed said there is still much work to be done.

Dr. Sparks encouraged everyone in the field to work on "showing the worth of nephrology" to all stakeholders, including the community, institutions, government, and patients. This support should include advocating for higher pay and ensuring that patients can access the newest treatments.

"The state of the art is still exciting. The field is successfully fighting disease, and there's a lot of innovation. We've made a lot of progress with glomerular disease, chronic kidney disease, and xenotransplantation," Dr. Canetta said. "We are very good at pushing forward the science. But we have not been as successful at spreading the word." ●

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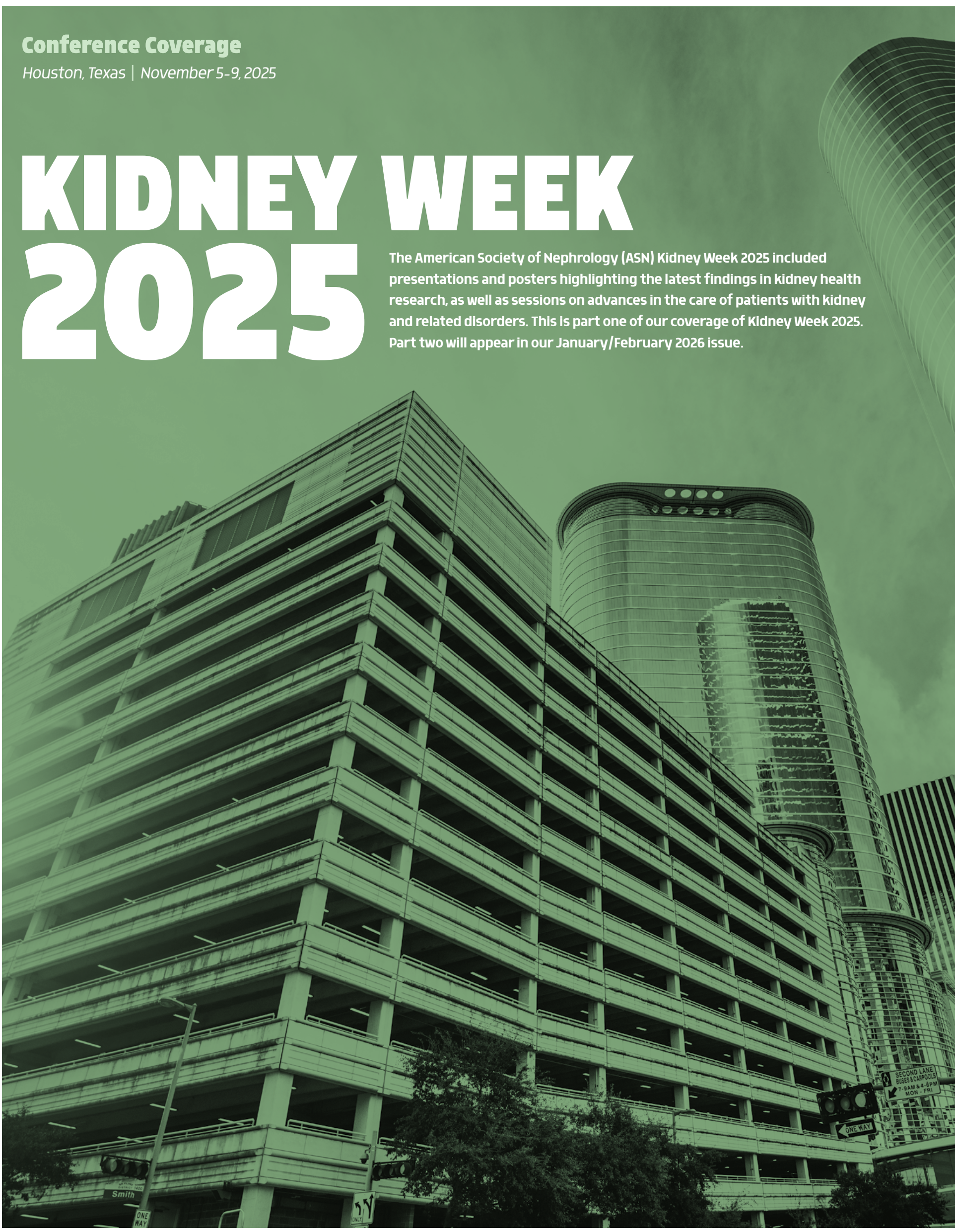
Conference Coverage

Houston, Texas | November 5-9, 2025

KIDNEY WEEK 2025

The American Society of Nephrology (ASN) Kidney Week 2025 included presentations and posters highlighting the latest findings in kidney health research, as well as sessions on advances in the care of patients with kidney and related disorders. This is part one of our coverage of Kidney Week 2025. Part two will appear in our January/February 2026 issue.



Pegcetacoplan Sustains Proteinuria Reduction Through 52 Weeks in C3G and IC-MPGN

Results of natural history studies have shown improved outcomes for patients with C3 glomerulopathy (C3G) and primary immune complex-membranoproliferative glomerulonephritis (IC-MPGN) with proteinuria less than 0.88 or 1 g/g or proteinuria reduction of 50% or greater.

The phase 3 VALIANT trial (NCT05067127) examined the efficacy of the C3/C3b inhibitor pegcetacoplan, which was approved to treat C3G/IC-MPGN in July 2025, for proteinuria reduction. The trial included a 26-week randomized controlled period (RCP), during which pegcetacoplan use led to a significant reduction in proteinuria compared with placebo among patients with C3G/IC-MPGN. All study participants received pegcetacoplan in the 26-week open-label period (OLP) that followed.

During an oral session at the American Society of Nephrology Kidney Week 2025 in Houston, Texas, **Carla M. Nester, MD,** and colleagues reported 52-week efficacy results among patients who completed all 52 weeks of treatment. The session was titled *Pegcetacoplan for 52 Weeks Results in Sustained Proteinuria Reduction to Remission (≤0.5 g/g) and Normalization (≤0.2 g/g): Phase 3 VALIANT Trial.*

A total of 59 of 63 patients in the pegcetacoplan-to-pegcetacoplan group and 55 of 61 in the placebo-to-pegcetacoplan group completed 52 weeks of treatment. The efficacy end points included change in proteinuria from baseline.

At week 26, 31.8% of patients (n=20) in the pegcetacoplan-to-pegcetacoplan group achieved complete remission and 17.5% (n=11) achieved normalization. At week 52, the results were maintained. In the placebo-to-pegcetacoplan group, 54.0% of patients (n=34) achieved 50% or greater proteinuria reduction at week 52. The percentage of patients in the placebo-to-pegcetacoplan group achieving remission and normalization was comparable to that of the pegcetacoplan group, with 41% (n=25) achieving a 50% or greater reduction in proteinuria.

In summary, the authors said, "Proteinuria reductions to normalization/remission achieved in the RCP were maintained by patients who received pegcetacoplan for 52 weeks, confirming pegcetacoplan's sustained efficacy. Consistent results were achieved in pegcetacoplan-to-placebo patients in the OLP."

Reference: 2025 American Society of Nephrology Kidney Week. Abstract No. SA-OR048.

2-Year Data Support Humacyte's Engineered Vessel as Viable Hemodialysis Access

The standard initial vascular access modality for patients requiring hemodialysis is autologous arteriovenous fistula (AVF). However, maturation of AVFs presents a significant clinical challenge. Humacyte Global's bioengineered human tissue conduit, the Acellular Tissue Engineered Vessel (ATEV), may provide durable access and reduce complications.

During an oral session at the American Society of Nephrology Kidney Week 2025, **Mohamad Anas Hussain, MD, PhD,** and colleagues presented results of an analysis of extended 2-year longitudinal outcomes of the phase 3, prospective, multicenter, randomized controlled CLN-PRO-V007 (NCT03183245) trial comparing ATEV with AVF for patients receiving hemodialysis. The session was titled *Two-Year Outcomes From a Prospective Randomized Trial of Humacyte's Acellular Tissue Engineered Vessel vs Autologous Arteriovenous Fistula for Hemodialysis Access.*

The CLN-PRO-V007 trial randomly assigned 242 patients requiring surgical vascular access for hemodialysis to receive either ATEV or autologous AVF. The researchers reported results from the 24-month analysis evaluating Kaplan-Meier estimates of time to secondary patency loss, duration of access use, infection-related access rates, clinically significant aneurysms or pseudoaneurysms, and the overall frequency and severity of adverse events.

Among the 242 participants, mean age was 58.6 years, and 29% were female. Participants in the ATEV group had a numerically longer duration of study access use compared with those in the AVF group (13.6 vs 12.5 months). In the ATEV group, 68.3% of patients maintained 12-month secondary patency, compared with 62.2% of those in the AVF group (as of December 2024). In a subgroup of those at high risk of AVF maturation failure (females and obese males with diabetes), 76.8% of the ATEV group and 46.3% of the AVF group maintained 12-month secondary patency.

Clinically significant pseudoaneurysms were seen with less frequency in the AVF group than in the ATEV group (3.3% vs 14.9%). The aneurysm rates between the two groups were equivalent (1.7% in both groups). Both groups experienced low rates of infections related to the study access model (7.4% in the ATEV group and 5.8% in the AVF group). Two patients in the AVF group reported access rupture; none in the ATEV group did so.

After adjusting for duration of access use, the two groups were similar regarding the overall frequency of serious adverse events, with no unexpected safety signals.

In summary, the researchers said, "ATEV demonstrated numerically longer duration of access use at 24 months, and a greater proportion maintained secondary patency at 12 months, with overall comparable safety relative to AVFs. These results support ATEV as a durable and clinically viable alternative for long-term hemodialysis access, particularly in patients at risk for AVF maturation failure."

This study was supported by Humacyte Global, Inc.

Reference: 2025 American Society of Nephrology Kidney Week. Abstract No. SA-OR026. doi:10.1681/ASN.2025s5e9mg2y

SGLT-2 Inhibition Lowers Risk of AKI Following Cardiac Surgery

Up to 50% of patients undergoing cardiac surgery may experience acute kidney injury (AKI). However, measures to prevent AKI are "largely lacking," according to **Maartina Oosterom-Eijmael, MD,** and colleagues at Amsterdam UMC Locatie AMC, the Netherlands. Results of previous trials, in which kidney and cardiovascular outcomes were evaluated, have suggested an association between sodium-glucose cotransporter-2 (SGLT2) inhibitors and lower incidence of AKI (hazard ratio, 0.66; 95% CI, 0.55-0.80).

During an oral session at the American Society of Nephrology Kidney Week 2025, the researchers reported results of a multicenter, triple-blinded, placebo-controlled randomized trial to test the hypothesis that perioperative treatment with dapagliflozin could reduce the incidence of postoperative AKI in patients undergoing cardiac surgery. The session was titled *proMoting Effective Renoprotection in Cardiac Surgery Patients by Inhibition of SGLT2 (MERCURI-2): A Randomized Controlled Trial in People Undergoing Cardiac Surgery.*

The study cohort included adult patients undergoing elective cardiac surgery. Participants were randomized to receive oral dapagliflozin (10 mg) or matching placebo once daily from the day before the surgery until the second day after the surgery. The primary outcome of interest was the difference between the two groups in the incidence of AKI as defined by Kidney Disease: Improving Global Outcomes criteria. Secondary outcomes included differences in individual stages of AKI.

A total of 784 patients were included in the intention-to-treat analysis between June 2023 and May 2025. Of those, 76% were male, mean age was 67 years, mean BMI was 27.2 kg/m^2, and 12% had type 2 diabetes. There was a significant reduction in the incidence of AKI in the dapagliflozin group compared with the placebo group (28% vs 53%; absolute difference, 25%; $P<0.001$).

In the dapagliflozin group, 23% (n=89), 4% (n=16), and 0.8% (n=3) of patients were diagnosed with AKI stage 1, 2, and 3, respectively. In the placebo group, 40% (n=156), 13% (n=49), and 0.3% (n=1) of patients were diagnosed with AKI stage 1, 2, and 3, respectively ($P<0.001$, $P<0.001$, and $P=0.317$, respectively).

In conclusion, the authors said, "This large multicenter trial confirmed that perioperative SGLT2 inhibition can prevent cardiac surgery-associated AKI."

Reference: 2025 American Society of Nephrology Kidney Week. Abstract No. SA-OR002. doi:10.1681/ASN.2025y8v7b58n

Rapid and Slow Fluid Replacement for Severe Hypernatremia Show Similar Efficacy

A randomized trial from Korea showed that two different fluid replacement strategies, rapid intermittent bolus (RIB) and slow continuous infusion (SCI), were similarly effective and safe for treating severe hypernatremia, although the bolus method achieved faster early correction with less total fluid.

Sejoong Kim, MD, PhD, and colleagues presented their findings in an oral session at the 2025 American Society of Nephrology Kidney Week meeting. Their session was titled *Efficacy and Safety of Rapid Intermittent Bolus Compared with Slow Continuous Correction in Patients with Severe Hypernatremia (SALSA II Trial).*

The prospective, multicenter study enrolled 178 patients with serum sodium levels of 155 mmol/L or higher between June 2021 and January 2025. Participants were randomly assigned to receive either intermittent boluses or continuous infusion of electrolyte-free water. The primary outcome was rapid sodium correction, defined as a reduction in serum sodium of at least 6 mmol/L within 24 hours or reaching a level of 150 mmol/L or lower.

Rapid correction occurred in 91.0% of patients treated with RIB and 88.8% treated with SCI ($P=0.62$). Sodium levels fell more quickly within the first 6 hours in the RIB group (−4.7 ± 2.6 vs −3.6 ± 2.6 mmol/L; $P=0.004$), and those patients received less total fluid over 48 hours (1,976 ± 1,285 vs 2,506 ± 1,705 mL; $P=0.04$). Target correction rates were similar between groups (95.2% vs 95.3%), as were rates of overcorrection (16.5% vs 14.1%) and 28-day survival (9.1% vs 12.4%).

The investigators concluded that both methods safely and effectively lowered serum sodium without significant differences in primary or safety outcomes. The intermittent bolus approach achieved faster initial sodium reduction with lower fluid volumes, suggesting it may help limit fluid overload. The findings support the feasibility of a simplified correction protocol that does not rely on complex electrolyte-free water clearance calculations.

Reference: 2025 American Society of Nephrology Kidney Week. Abstract No. TH-OR024.

Pegloticase Plus Low-Dose MMF Boosts Gout Control While Protecting Kidney Function

New research demonstrated that a low daily dose of mycophenolate mofetil (MMF) in combination with pegloticase may offer meaningful clinical benefits for patients with chronic kidney disease (CKD) and uncontrolled gout.

The findings were presented by **Luana Pillon, MD,** and colleagues at the 2025 American Society of Nephrology Kidney Week and showed that the treatment was tolerable, reduced serum uric acid (sUA) levels, and kept kidney function stable.

Although pegloticase plus MMF may be effective, the combination has the potential for gastrointestinal intolerance and infection, the researchers said. Previous research showed achievement of a greater percentage of targeted sUA levels and fewer infusion reactions when pegloticase 8 mg biweekly was combined with MMF 1,000 mg twice a day versus placebo.

In this small, retrospective study, the researchers evaluated a lower daily dose of MMF (500 mg or less twice a day). They collected patient information using deidentified data from community nephrology clinics.

Fifteen patients with CKD were included, with 14 receiving MMF 500 mg twice a day and one patient receiving MMF 500 mg once a day. Stage 2-3a CKD was present in six patients, and nine patients had stage 3b-5 CKD.

Tophi were visible at baseline in about two-thirds (66%) of patients with milder CKD and in 89% of patients with more advanced disease.

Patients with stage 2-3a CKD received a median of 19 pegloticase infusions over 188 days, and those with stage 3b-5 CKD received a median of 12 infusions over 287 days.

Results showed that using the lower dose of MMF with pegloticase helped to quickly lower sUA levels to less than 0.2 mg/dL, and those levels were maintained throughout treatment. One patient with stage 2 CKD had to discontinue pegloticase.

Kidney function remained stable for most patients, even for those with more advanced CKD. Estimated glomerular filtration rate in 50% of patients with stage 2-3a and 78% of those with stage 3b-5 demonstrated stable or improved kidney function.

The researchers also observed reduced gout symptoms and lower rates of adverse events in patients with less severe and those with more severe stages of CKD.

Amgen provided commercial support for the study.

Reference: 2025 American Society of Nephrology Kidney Week. Abstract No. TH-P01095.

ASN Awards Honored Leaders in Nephrology at Kidney Week

The ASN celebrated the achievements of leading figures in nephrology through its annual awards, which were presented at ASN Kidney Week 2025, in Houston, Texas, November 5-9.

LIFETIME ACHIEVEMENT AWARDS

The ASN Lifetime Achievement Awards recognize individuals who make a lasting impact on kidney care, research, and education.

Michelle A. Josephson, MD

BARBARA T. MURPHY AWARD

Michelle A. Josephson, MD, received the Barbara T. Murphy Award in recognition of her leadership in transplant nephrology and her commitment to education, research, and policy. A professor of medicine and surgery at the University of Chicago Pritzker School of Medicine, Dr. Josephson founded Illinois's first kidney transplant fellowship and directed the university's kidney and pancreas transplant program for more than 30 years. Her work has advanced care for transplant recipients and deepened understanding of post-transplant bone disease, pregnancy, and BK virus nephropathy. A past ASN president, she has also held leadership roles with the American Society of Transplantation, Kidney Disease: Improving Global Outcomes, and Women in Nephrology.

Biff F. Palmer, MD

ROBERT G. NARINS AWARD

Biff F. Palmer, MD, received the Robert G. Narins Award in recognition of his dedication to nephrology education and mentorship. A professor of education and internal medicine at Texas Tech University Health Sciences Center in El Paso, Dr. Palmer spent 35 years at the University of Texas (UT) Southwestern Medical Center, where he continues to lead renal education for medical students. An accomplished educator and researcher with more than 300 publications, he has shaped countless trainees through his leadership in nephrology programs and curriculum development. His many honors include the Piper Professor Award from the Minnie Stevens Piper Foundation and the Distinguished Biomedical Science Educator Award from The UT Southwestern Academy of Teachers.

Michael Allon, MD

BELDING H. SCRIBNER AWARD

Michael Allon, MD, received the Belding H. Scribner Award in recognition of his impact on dialysis care and vascular access research. A professor of medicine and associate director for clinical affairs in the Division of Nephrology at the University of Alabama at Birmingham Heersink School of Medicine, Dr. Allon has led numerous NIH-funded clinical trials that have reshaped vascular access practice. His pioneering studies introduced preoperative ultrasound mapping and patient-centered decisions for access type. An influential leader in national guideline development, he also serves as the inaugural editor-in-chief of *Kidney360*.

Harold I. Feldman, MD, MS, MSc

JOHN P. PETERS AWARD

Harold I. Feldman, MD, MS, MSc, received the John P. Peters Award in recognition of his contributions to kidney research and patient care. He is deputy executive director for patient-centered research programs at the Patient-Centered Outcomes Research Institute and editor-in-chief of the *American Journal of Kidney Diseases*. Dr. Feldman has led landmark studies, including the Chronic Renal Insufficiency Cohort, producing insights into CKD progression, comorbidities, and quality of life. A professor emeritus at the University of Pennsylvania, he has mentored generations of investigators, established global CKD networks, published more than 350 papers, and held leadership roles in epidemiology and nephrology organizations worldwide.

Katalin Susztak, MD, PhD

HOMER W. SMITH AWARD

Katalin Susztak, MD, PhD, received the Homer W. Smith Award for her pioneering work in deciphering kidney function and disease mechanisms. A professor of medicine and nephrology at the University of Pennsylvania, she directs the diabetic nephropathy program and co-directs the Penn-Children's Hospital of Philadelphia Kidney Innovation Center. Dr. Susztak's laboratory has identified novel CKD risk genes, mapped epigenetic changes, and created the first single-cell RNA-sequencing atlas of the kidney. She has published more than 250 papers, led the Transformative Research in Diabetic Nephropathy consortium, and holds multiple honors, including the Alfred Newton Richards Award from the International Society of Nephrology and ASN's Barry M. Brenner Lectureship.

Rafael Kramann, MD, PhD

DONALD W. SELDIN YOUNG INVESTIGATOR AWARD

Rafael Kramann, MD, PhD, received the ASN-American Heart Association Donald W. Seldin Young Investigator Award for his innovative research on kidney and heart fibrosis. A professor and chair of nephrology, rheumatology, immunology, and hypertension at Rheinisch-Westfälische Technische Hochschule Aachen University in Aachen, Germany, he directs the Center of Phase Transition in Chronic Disease. Dr. Kramann 's work integrates single-cell analysis, multiomics, gene editing, and ex vivo modeling to uncover mechanisms of chronic kidney and cardiovascular disease. He has published more than 200 papers, cofounded two biotech companies targeting fibrosis, and holds several scientific leadership roles.

Robert M. Califf, MD

ASN PRESIDENT'S MEDAL

Robert M. Califf, MD, a cardiologist and former commissioner of the FDA, received the ASN President's Medal in recognition of his national leadership in clinical research and evidence-based health policy. Dr. Califf led the FDA from 2016 to 2017 and 2022 to 2025, championing efficient and inclusive clinical trials, tobacco regulation, and drug oversight. A longtime Duke University faculty member and founding director of the Duke Clinical Research Institute, he has authored more than 1,300 publications advancing cardiovascular and population health. He cofounded the FDA-Duke Clinical Trials Transformation Initiative and is a member of the National Academy of Medicine.

MIDCAREER AWARDS

ASN's Midcareer Awards recognize midcareer clinicians, educators, health professionals, and researchers.

This year's Distinguished Educator Award went to **Benjamin S. Ko, MD,** associate professor of medicine and associate program director of the nephrology fellowship program at the University of Chicago Pritzker School of Medicine, and **Hitesh H. Shah, MD,** professor of medicine at the Donald and Barbara Zucker School of Medicine at Hofstra/Northwell in Hempstead, New York, and senior director of nephrology education in the Division of Kidney Diseases and Hypertension at Northwell Health.

This year's Distinguished Leader Award recipients were **Laura H. Mariani, MD, MS,** associate professor of internal medicine in the Division of Nephrology and assistant program director for the nephrology fellowship training program at the University of Michigan Medical School, and **Reem A. Mustafa, MD, PhD, MPH,** professor of medicine in the Division of Nephrology and Hypertension and director of the Agency for Healthcare Research and Quality-Designated Evidence-Based Practice and Impact Center at the University of Kansas Medical Center, Kansas City.

Aminu K. Bello, MD, PhD, professor of medicine at the University of Alberta in Edmonton, Canada; **Elaine Ku, MD,** associate professor in residence in the Departments of Medicine, Pediatrics, and Epidemiology and Biostatistics at the University of California, San Francisco School of Medicine; and **Simone Sanna-Cherchi, MD,** associate professor of medicine in the Division of Nephrology at Vagelos College of Physicians and Surgeons at Columbia University Irving Medical Center in New York City, received the Distinguished Researcher Award.

The Distinguished Clinical Service Award recipients were **Daniel Y. Lam, MD,** clinical professor of medicine in the Division of Nephrology at the University of Washington in Seattle, and **Shina Menon, MD,** associate professor of pediatrics and director for research in pediatric nephrology in the Division of Nephrology at Stanford Medicine.

Julia J. Scialla, MD, MHS, was honored with the Distinguished Mentor Award. She is an associate professor of medicine and public health sciences at the University of Virginia School of Medicine, Charlottesville, and serves as director of the Nephrology Clinical Research Center and director of outcomes research in the Departments of Medicine and Public Health Sciences.

Reference: American Society of Nephrology. *Kidney News Online*. Accessed October 22, 2025. https://www.kidneynews.org/view/journals/kidney-news/17/10/11/kidney-news.17.issue-10/11.xml

Combination of Zibotentan and Dapagliflozin Shows Promise for Albuminuria

The use of endothelin receptor antagonists (ERAs) is effective in reducing albuminuria. However, the broader use of ERAs for the treatment of patients with CKD is limited due to the possibility of fluid retention in that patient population. Albuminuria can be reduced with the use of sodium-glucose cotransporter-2 (SGLT2) inhibitors, which also have diuretic effects and provide cardio-kidney protection.

Victor Wasehuus, MD, and colleagues conducted a study designed to determine whether combination therapy with the ERA zibotentan and the SGLT2 inhibitor dapagliflozin would result in greater reduction in albuminuria compared with either drug alone, while also mitigating zibotentan-induced fluid retention among patients with CKD.

The researchers reported results during an oral presentation at the American Society of Nephrology Kidney Week 2025 in a session titled *Effects of Zibotentan and Dapagliflozin Combination Therapy on Albuminuria and Fluid Parameters in CKD: Results From the ZODIAC Trial.*

The randomized, double-blind, placebo-controlled, crossover trial included adults with CKD (estimated glomerular filtration rate [eGFR] ≥30 mL/min/1.72 m^2, urine albumin to creatinine ratio [UACR] 100-3,500 mg/g). In one of two randomized sequences across three 4-week treatment periods, each separated by a 4-week washout period, participants received placebo, zibotentan 1.5 mg/day (zibo), dapagliflozin 10 mg/day (dapa), and their combination (zibo/dapa).

The primary end point of interest was the percentage change from baseline in UACR at the end of each treatment period. Secondary outcomes of interest were changes in N-terminal pro-B-type natriuretic peptide, body weight, and fluid volume by bioimpedance and adverse events.

The study included 27 participants, of whom 11% were female. Their mean age was 63 years, median UACR was 304 mg/g, and mean eGFR was 71 mL/min/1.73 m^2. At the end of the study period, combination treatment was associated with a greater reduction in UACR compared with placebo (−48.9%; 95% CI, -73.5% to −1.8%; P=0.04), zibo (20.6%; 95% CI, 53.4%-35.3%; P=0.39), and dapa (37.7%; 95% CI, −65.4% to 12.2%; P=0.11).

Fluid retention increased with zibo alone but was mitigated with combination therapy of zibo/dapa. Six adverse events related to fluid retention occurred with zibo compared with one with placebo and none with dapa or zibo/dapa.

In conclusion, the authors said, "Zibo/dapa combination therapy reduced albuminuria in an additive manner, mitigated fluid retention, and was well tolerated. These findings support zibo/dapa combination as a promising strategy for kidney protection."

This study was funded by Astra Zeneca.

Reference: 2025 American Society of Nephrology Kidney Week. Abstract No. FR-OR020. doi:10.1681/ASN.2025n7x3kgpw

Self-Monitoring Program Among US Veterans Lowered BP

Some studies outside the US have tested the concept of self-monitoring and self-titration of antihypertensive medications, demonstrating safety and effectiveness of the approach. However, the method has not been tested in settings within the United States. **Dena E. Rifkin, MD,** and colleagues conducted a study to test a standardized self-management plan (SM) for antihypertensive medication titration compared with usual care (UC) among patients with hypertension.

The researchers presented results of the study during an oral presentation at the American Society of Nephrology Kidney Week 2025 titled *Self-Monitoring and Self-Management of Hypertension in US Veterans: A Randomized Controlled Trial.*

The unblinded, randomized controlled trial included participants at two Veterans Administration medical centers with baseline systolic BP (SBP) of greater than 130 mm Hg who were taking no more than two medications. The study intervention was SM with a protocol that included high/low alert values in addition to standardized changes in BP medication with target home BP lower than 120/80 mm Hg over 12 months. Participants in the UC arm were given a home BP cuff and were urged to share readings with their primary care physician. The primary outcome of interest was the 12-month BP difference between groups. Secondary outcomes included safety and acceptability.

Baseline mean SBP and diastolic BP (DBP) were 136.0/80.5 mm Hg in the SM arm and 140.3/78.7 mm Hg in the UC arm. At the end of the 12-month study period, mean BP in the SM arm decreased to 129.9/76.3 mm Hg (reduction, 6.1 mm Hg in SBP; P<0.01). In the UC arm, mean BP decreased to 137.0/77.6 mm Hg (reduction, 3.3 mm Hg; P=0.17).

The between-group change in SBP was lower in the SM group (1.9 mm Hg; P=0.55 between SM and UC); however, the difference was nonsignificant. Results of subgroup analyses were similar.

No serious adverse events occurred in the SM arm, but one possible related hospitalization in each arm and one death in the SM group took place before the initiation of SM. If such a program were offered, 80% of participants indicated they were likely to continue with the intervention.

In summary, the researchers said, "An SM BP protocol resulted in similar blood pressure reduction as UC. SM was safe and well accepted by participants and should be considered in US clinical practice."

Reference: 2025 American Society of Nephrology Kidney Week. Abstract No. FR-OR037. doi:10.1681/ASN.2025ztagnf21

ACUTE KIDNEY INJURY

Kidney Injury Related to Treatment Among Pediatric Patients With Cancer

Nephrol Dial Transplant. doi:10.1093/ndt/gfaf169

Pediatric patients with cancer treated with nephrotoxic medication face an increased risk for serious complications, including acute kidney injury (AKI). The risk for AKI may require modifications to standard treatment and may also contribute to an increase in the risk for chronic kidney disease (CKD) for those patients.

Paulien A. M. A. Raymakers-Janssen and colleagues in the Netherlands conducted a retrospective national cohort study designed to examine the incidence of AKI, the impact of treatment with nephrotoxic medications, and the association between AKI and development of CKD among pediatric patients with cancer. Acute kidney injury was classified using Kidney Disease: Improving Global Outcomes (KDIGO) criteria based on serum creatinine levels.

The study cohort included 1,525 patients treated at the Princess Máxima Center in Utrecht, the Netherlands, between 2015 and 2021. A cause-specific hazard regression model was used to assess the effect of nephrotoxic medications and other risk factors on the incidence and progression of AKI. A competing risk model with death as a competing event was used to estimate the cumulative incidence of AKI. CKD, defined as an estimated glomerular filtration rate (eGFR) of less than 90 mL/min/1.73 m^2 1 year after cancer treatment, was examined using logistic regression.

Of the 1,525 patients, 37% experienced AKI. Receipt of ifosfamide, amphotericin B, acyclovir, and busulfan was identified as a strong, independent risk factor for a first episode of AKI. Researchers also observed an association between older age and an increased risk of AKI.

One-year follow-up data were available for 1,159 patients; 13.6% had CKD (eGFR <90 mL/min/1.73 m^2) and 2.8% had an eGFR of less than 60 mL/min/1.73 m^2. The strongest predictor of CKD was development of AKI during treatment. The risk increased 2.6-fold after a single episode of AKI and nearly 16-fold after multiple episodes of AKI. The study analysis also identified nephrectomy as an independent risk factor for CKD.

The authors concluded that AKI is common among children with cancer and is strongly associated with an increased risk for CKD. "Comprehensive monitoring strategies should be implemented at diagnosis, during therapy, and during the post-treatment period to enable early detection and timely intervention, ultimately reducing the risk of AKI and its progression to CKD," they wrote.

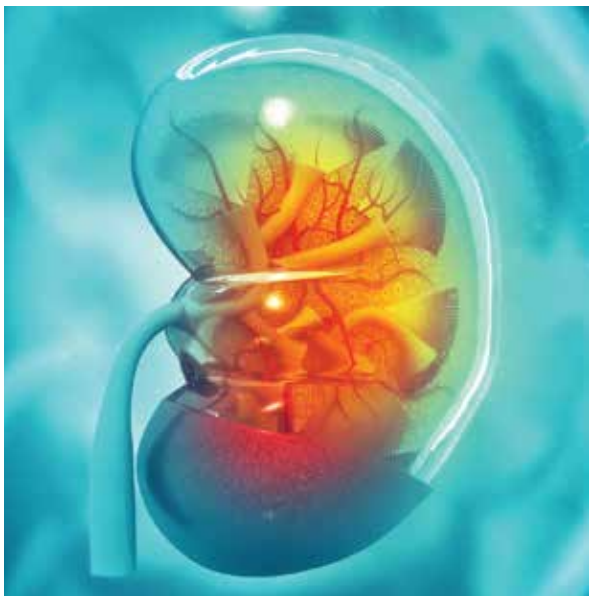
C3 GLOMERULOPATHY

Iptacopan Is Safe and Effective for Patients With C3G

Lancet. 2025;406(10512):1587-1598. doi:10.1016/S0140-6736(25)01148-1

The APPEAR-C3G study by **David Kavanagh, PhD,** and colleagues was designed to examine the efficacy and safety of iptacopan for the management of patients with C3 glomerulopathy (C3G), a rare, severe form of glomerulonephritis associated with the overactivation of the alternative complement pathway. Iptacopan is an oral, proximal complement inhibitor that targets factor B to selectively inhibit the alternative pathway of the complement cascade.

APPEAR-C3G was a multicenter, randomized, double-blind, placebo-controlled phase 3 study of iptacopan versus placebo. Both study arms also received supportive care, specifically renin-angiotensin-aldosterone system (RAAS) inhibitors and immunosuppression. Inclusion criteria were reduced serum C3 concentration (<77 mg/dL), urine protein-creatinine ratio (UPCR) of 1.0 g/d or higher at 75 and 15 days before randomization, eGFR of 30 mL/min/1.73 m^2 or greater at screening and 15 days before randomization, and vaccination against *Neisseria meningitidis* and *Streptococcus pneumoniae.* The



primary end point of interest was the relative reduction in proteinuria at 6 months.

The study enrolled eligible participants with biopsy-proven C3G from 35 hospitals or medical centers in 18 countries. Seventy-four participants were assigned randomly 1:1 to receive either iptacopan 200 mg twice daily (n=38) or placebo (n=36), stratified by treatment with corticosteroids, mycophenolic acid, or both (yes or no). The study included a 6-month double-blind period followed by a 6-month open-label period during which all participants received iptacopan 200 mg twice daily. One participant in the placebo group discontinued treatment during the open-label period.

At 6 months, the 24-hour percentage change in UPCR was –30.2% in the iptacopan group and 7.6% in the placebo group. The primary end point was met, with a relative reduction in 24-hour UPCR for iptacopan versus placebo of 35.1% (P=0.014).

Of the 38 participants in the iptacopan group, 79% (n=30) reported treatment-emergent adverse events (TEAEs), compared with 67% (n=24) of the 36 participants in the placebo group. Most adverse events were of mild or moderate severity. There were no deaths or meningococcal infections, and no one discontinued treatment due to TEAEs. Three participants in the iptacopan group and one in the placebo group reported serious adverse events.

In summary, the authors wrote, "Iptacopan showed a statistically significant, clinically meaningful proteinuria reduction in addition to RAAS inhibitors and immunosuppression at 6 months. Iptacopan was well tolerated with an acceptable safety profile in patients with C3 glomerulopathy."

CHRONIC KIDNEY DISEASE

Avacopan Effective for GPA and MPA With Kidney Involvement

Kidney Int Rep. 2025;10(8):2751-2765. doi:10.1016/j.ekir.2025.05.041

Long-term outcomes among patients with granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA) are impacted when kidney disease is present. **Duvuru Geetha, MBBS, MD,** and colleagues conducted a post hoc analysis of data from the ADVOCATE trial to examine the effect of avacopan (compared with a prednisone taper regimen) in a subgroup of trial participants with GPA or MPA and kidney involvement at baseline.

The analysis included data from 268 patients who met inclusion criteria. The primary efficacy outcomes of interest were remission at week 26, sustained remission at week 52, and relapse after remission through week 52. Researchers identified and stratified changes in eGFR according to baseline eGFR categories (≥90, 60-89, 45-59, 30-44, and 15-29 mL/min/1.73 m^2). Secondary outcomes of interest included changes in albuminuria and hematuria, glucocorticoid (GC) use, glucocorticoid toxicity index (GTI), and safety.

A total of 134 patients were included in the avacopan group, and 134 were included in the prednisone taper group. The primary outcome of remission at week 26 was achieved by 73.9% of patients in the avacopan group and 70.9% in the prednisone taper group. Sustained remission at week 52 was achieved by 67.9% in the avacopan group and 56.7% in the prednisone taper group.

In the avacopan group, the relapse rate after remission was lower than that in the prednisone taper group (9.4% vs 20.9%; hazard ratio [HR], 0.43; 95% CI, 0.22-0.85). The remaining outcomes (recovery of kidney function, speed of reduction in albuminuria and hematuria, and changes in GTI) favored the avacopan group. No new safety issues were reported in the subgroup of patients in the current analysis.

In summary, the researchers said, "In patients with GPA or MPA with kidney involvement, treatment with an avacopan regimen compared with a prednisone taper regimen achieved similar rates of remission, improved recovery of kidney function, led to faster reduction in albuminuria and hematuria, and lowered GC-related toxicity, with an acceptable safety profile."

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Physical Activity Shows Renal Protective Effects for Those With CKD

Clin J Am Soc Nephrol. doi:10.2215/CJN.0000000832

An increase in the aging population worldwide has led to a rising prevalence of CKD. However, data are lacking regarding the role of physical activity in slowing age-related kidney function decline among the general population.

Inger T. T. Enoksen, PhD, and colleagues reported results of the longitudinal RENIS (Renal Iohexol Clearance Survey) cohort that shed light on this question. The cohort included 1,837 individuals without self-reported diabetes, cardiovascular disease, or kidney disease at baseline. Using iohexol clearance, over a study period of 11 years, participants had repeated measurements of glomerular filtration rate (GFR). At baseline, researchers examined physical activity using a physical activity frequency, intensity, and duration questionnaire. They assessed the relationship between physical activity and change in GFR and accelerated GFR decline (the steepest 10% of GFR slopes) using linear mixed models and multiple logistic regression.

The median decline in measured GFR (mGFR) was –1.06 mL/min/1.73 m^2 per year. After adjustment, an association was seen between a higher frequency of physical activity and 71% lower odds of accelerated decline in GFR (odds ratio, 0.29; 95% CI, 0.11-0.78) compared with not engaging in physical activity. Before adjusting for smoking and alcohol consumption, frequency of physical activity and meeting the WHO's physical activity recommendations were associated with a slower annual decline in mGFR. Increasing physical activity demonstrated a dose-response trend (P=0.001). The mean decline in mGFR was slower among those who participated in near-daily physical activity by 0.47 mL/min/1.73 m^2 per year (95% CI, 0.13-0.80; P=0.006).

"Increasing PA [physical activity] was associated with a slower mean mGFR decline and a lower risk of accelerated mGFR decline," the researchers concluded. "Promoting regular PA should be prioritized as a low-cost, high-impact strategy to reduce the global CKD burden."

DIALYSIS

Apixaban Safe and Effective for Provoked VTE

N Engl J Med. 2025;393(12):1166-1176. doi:10.1056/NEJMoa2509426

Few data are available on the appropriate duration of anticoagulation for venous thromboembolism (VTE) among patients with a transient provoking factor such as surgery, trauma, or immobility and associated enduring risk factors. Venous thromboembolism is common among patients receiving dialysis.

Gregory Piazza, MD, MS, and colleagues conducted a single-center, double-blind, randomized trial among adults with VTE who experienced a transient provoking factor with at least one enduring risk factor.

Eligible participants who had completed a minimum of 3 months of anticoagulation were randomly assigned 1:1 to receive either oral apixaban 2.5 mg twice daily or placebo for 12 months. The primary outcomes of interest were the first symptomatic recurrent VTE and the first episode of major bleeding, as defined by the International Society on Thrombosis and Hemostasis.

The overall study cohort included 600 patients who underwent randomization. Their mean age was 59.5 years, 57.0% were female, and 19.2% were of non-White race. Of the 300 patients in the apixaban arm, four (1.3%) experienced symptomatic recurrent VTE compared with 30 patients (10.0%) in the placebo arm (HR, 0.13; 95% CI, 0.04-0.36; P<0.001).

One patient in the apixaban group experienced a major bleeding event; no major bleeding events occurred in the placebo group. Fourteen of 294 patients (4.8%) in the apixaban group experienced clinically relevant nonmajor bleeding compared with five of 294 patients (1.7%) in the placebo group (HR, 2.68; 95% CI, 0.96-7.43; P=0.06). One death occurred in the apixaban group and three deaths occurred in the placebo group; none of the deaths were attributed to cardiovascular or hemorrhagic causes. Six patients in each group experienced nonhemorrhagic, nonfatal adverse events.

In conclusion, the researchers wrote, "Among patients with provoked VTE and enduring risk factors, low-intensity therapy with apixaban for 12 months resulted in a lower risk of symptomatic recurrent VTE than placebo, with a low risk of major bleeding."

Pilot Trial Shows Feasibility of Large Study on AF Management With Dialysis

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Patients receiving dialysis commonly experience atrial fibrillation (AF). However, previous clinical trials examining the role of oral anticoagulation in the treatment of AF have excluded individuals receiving dialysis. **Ziv Harel, MD,** and colleagues conducted a study to determine the feasibility of performing a large, randomized trial designed to determine the optimal anticoagulation strategy for patients with AF receiving dialysis.

The SAFE-D (Strategies for the Management of Atrial Fibrillation in Patients Receiving Dialysis; NCT03987711) trial, a parallel-group, open-label, allocation-concealed, pilot randomized controlled trial, was conducted at 28 centers in Canada and Australia. The study cohort included adults aged 18 years and older receiving dialysis with a history of nonvalvular AF meeting the CHADS-65 criteria (Canadian Society of Cardiology Guideline).

Eligible participants were randomly assigned 1:1:1 to receive dose-adjusted warfarin, apixaban 5 mg twice daily, or no oral anticoagulation. Follow-up continued for 26 weeks. The primary outcomes of interest were two measures of feasibility: (1) recruitment of the target population within 2 years from the start of the trial and (2) adherence to the assigned treatment strategy at the end of the follow-up period by more than 80% of patients who were randomized. Secondary outcomes were stroke and bleeding.

A total of 151 patients met inclusion criteria and were randomized to receive apixaban (n=51), warfarin (n=52), or no oral anticoagulation (n=48). Allowing for pauses related to the COVID-19 pandemic, recruitment was completed in 30 months (December 2019 to June 2022). Eighty-three percent of participants completed the required follow-up in their treatment arm.

One patient experienced an adjudicated stroke event. Major bleeding events occurred in eight participants: four in the warfarin group, two in the apixaban group, and two in the no oral anticoagulation group. Fifteen patients died: nine in the warfarin group, two in the apixaban group, and four in the no oral anticoagulation group. In the warfarin group, time in the therapeutic range was 58%.

The researchers said, "We have demonstrated the feasibility of recruitment and adherence in a trial that compared different anticoagulation strategies in patients with atrial fibrillation receiving dialysis."

Study Does Not Support Spironolactone Use in Kidney Failure and Hemodialysis

Lancet. 2025;406(10504):705-718. doi:10.1016/S0140-6736(25)01194-8

To date, no pharmacologic therapies have been proven to improve the cardiovascular prognosis of individuals with kidney failure requiring chronic hemodialysis. To address this gap, **Patrick Rossignol, MD, PhD,** and colleagues examined the effects of spironolactone, a steroidal mineralocorticoid receptor antagonist, on cardiovascular outcomes among patients receiving chronic hemodialysis at high risk for cardiovascular events.

The study (ALCHEMIST) was an investigator-initiated, multicenter, double-blind, randomized, placebo-controlled, event-driven trial. ALCHEMIST was conducted at 64 academic hospitals, general hospitals, and nonprofit or private practice dialysis centers in France, Belgium, and Monaco. Patients were eligible to enroll if they were 18 years of age or older and had kidney failure requiring chronic hemodialysis and at least one cardiovascular comorbidity or risk factor.

The study began with a 4-week run-in period, with participants receiving open-label oral spironolactone 25 mg every other day. Participants were then randomly assigned 1:1 to receive oral spironolactone, titrated to 25 mg per day, or placebo. The primary end point of interest was time to first major adverse cardiovascular event, defined as cardiovascular death,

nonfatal myocardial infarction, acute coronary syndrome, stroke, or hospitalization for heart failure.

The researchers analyzed the end point among the intention-to-treat population. In addition, they incorporated data from ALCHEMIST into a meta-analysis of double-blind, randomized controlled trials of mineralocorticoid receptor antagonists among patients receiving chronic hemodialysis.

A total of 794 patients entered the run-in period. Of those, 320 patients were randomly assigned to spironolactone, and 324, to placebo. Due to a lack of funding from the sponsor, the trial was stopped prematurely. Median follow-up was 32.6 months.

In the spironolactone group, the primary end point occurred in 24% (n=78) of the patients, compared with 24% (n=79) of patients in the placebo group (HR, 1.00; 95% CI, 0.73-1.36; *P*=0.98). In the spironolactone group, hyperkalemia (potassium concentration >6 mmol/L) was reported in 42% (n=135) of patients, compared with 41% (n=134) in the placebo group (HR, 1.12; 95% CI, 0.88-1.43).

Results of the meta-analysis suggest that there was no reduction in all-cause or cardiovascular mortality of nonfatal cardiovascular events associated with mineralocorticoid receptor antagonists and no increase in the odds of hyperkalemia events (serum potassium concentration >6 mmol/L) associated with mineralocorticoid receptor antagonists.

In summary, the authors said, "In patients with kidney failure on hemodialysis and with high risk of adverse cardiovascular outcomes, spironolactone did not reduce the incidence of major cardiovascular events. The updated meta-analysis shows that mineralocorticoid receptor antagonists did not reduce all-cause or cardiovascular mortality. Therefore, off-label use of spironolactone in the setting is not supported by available evidence."

PEDIATRIC NEPHROLOGY

APD Shows No Quality-of-Life Advantage Over CAPD for Youth With Stage 5 CKD

Pediatr Nephrol. 2025;40(6):2029-2041. doi:10.1007/s00467-024-06632-x

A major goal in the management of stage 5 CKD is improving health-related quality of life (HRQOL). There are few data available comparing HRQOL between continuous ambulatory peritoneal dialysis (CAPD) and automated peritoneal dialysis (APD) among pediatric patients. **Montarat Thavorncharoensap, PhD,** and colleagues in Thailand conducted an open-label, randomized controlled trial designed to compare HRQOL among children with stage 5 CKD receiving CAPD versus APD.

The study randomly assigned children with stage 5 CKD 1:1 to receive either APD or CAPD. The primary outcome of interest was HRQOL, measured at baseline using EuroQOL 5-Dimension (EQ-5D) 5-Level and EQ-5D 3-Level questionnaires and the Pediatric Quality of Life Inventory (PedsQL). The measurements were repeated at weeks 16 and 48. Researchers used linear mixed models to analyze outcomes.

The study cohort included 60 patients, 30 receiving CAPD and 30 receiving APD. At baseline, the two groups were similar in general characteristics, utility scores measured by EQ-5D, and HRQOL score measured by PedsQL. No significant differences in utility

and HRQOL scores were seen at weeks 16 and 48.

Among children in the APD group, changes in the school and social domains of PedsQL seemed to be more favorable than those for children in the CAPD group. However, there was no significant difference in the improvement from baseline between the two groups.

In conclusion, the authors said, "No significant benefit of APD was found over CAPD in terms of HRQoL improvement. However, larger studies are warranted along with qualitative studies to examine the complete impacts of APD on HRQoL among pediatric patients with stage 5 CKD and their families."

TRANSPLANTATION

MDR-101 Produces Immune Tolerance Among Kidney Transplant Recipients

Am J Transplant. 2025;25(7):1461-1470. doi:10.1016/j.ajt.2025.01.044

Dixon B. Kaufman, MD, PhD, and colleagues examined MDR-101, an investigational cellular therapy to induce immune tolerance in kidney transplant recipients, in a phase 3 multicenter randomized trial comparing it with standard of care. The primary outcome of interest was being immunosuppression free for more than 2 years after transplant.

Eligible study participants comprised adult recipients of kidneys from 2-haplotype human leukocyte antigen–matched living siblings. Participants were randomly assigned 2:1 to the treatment group (n=20) or the control group (n=10). The MDR-101 product was from the same kidney donor. Those in the treatment group received a nonmyeloablative conditioning protocol with rabbit-antithymocyte globulin and low-dose total lymphoid irradiation (10 fractions).

The researchers withdrew steroids by day 10 and mycophenolate by day 39. They continued administration of tacrolimus until day 180, then tapered it to discontinuation 1 year after transplant for patients with donor hematopoietic mixed chimerism of 5% or greater. Patients in the control group received immunosuppression in line with institutional standard of care.

Of the 20 patients who received the MDR-101 infusion, none developed graft-vs-host disease, and 19 discontinued all immunosuppression approximately 1 year after transplant. Fifteen reached the primary outcome of being immunosuppression free more than 2 years after transplant. Four of the 20 resumed immunosuppression: one with recurrent IgA nephropathy (IgAN), one with recurrent IgAN and rejection, one with rejection, and one with borderline biopsy changes.

The researchers concluded, "Kidney transplant recipients receiving MDR-101 achieved donor mixed chimerism and functional immune tolerance for greater than 2 years with no death, graft loss, DSA [donor-specific antibodies], or graft versus host disease and demonstrated improved quality of life compared to standard treatment."

Tacrolimus Demonstrates Efficacy and Safety for Kidney Transplant Recipients

Kidney Int Rep. 2025;10(9):3102-3112. doi:10.1016/j.ekir.2025.06.016

Initial results of the SAILOR trial demonstrated the feasibility, safety, and efficacy of steroid avoidance (SA) at 2 years after kidney transplant. SAILOR was a multicenter, open-label, randomized controlled trial involving immunologically low-risk kidney transplant recipients. The trial enrolled 222 participants who were randomly assigned to one of two groups, receiving either antithymocyte globulin induction, low-dose tacrolimus, and mycophenolate mofetil (MMF) or basiliximab induction, low-dose tacrolimus, MMF, and prednisolone.

Jana Ekberg, MD, and colleagues reported results from the SAILOR follow-up observational study to confirm the extended safety and efficacy of the SA protocol beyond the short- to medium-term follow-up in current reports using low-dose tacrolimus. The follow-up study included clinical data from 215 participants in the original SAILOR trial at 1, 2, and 5 years and at the last follow-up.

The mean follow-up time after transplant was 7.3 years. Both study arms were similar regarding death-censored graft survival (91.8% vs 93.1%; *P*=0.88), patient survival (88% vs 93%; *P*=0.32), cumulative incidence of biopsy-proven rejection (19.8% vs 16.3%; *P*=0.6), and kidney function (eGFR, 50.8 mL/min/1.73 m^2 vs 54 mL/min/1.73 m^2; *P*=0.27).

Among the per-protocol population, participants in the SA arm had a significantly lower cumulative incidence of diabetes after transplant than those who received steroids. No significant differences between the two arms were seen regarding serious infections requiring hospitalization or malignancies. At the end of follow-up, two-thirds of participants in the SA arm remained on the steroid-free protocol.

"SA proved to be safe and effective in patients with low immunological risk for up to 7 years following kidney transplantation," the researchers wrote. "Our findings provide robust evidence supporting SA strategy with low-dose tacrolimus without compromising outcomes even at the extended 7-years follow-up."

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