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A 1-2 PUNCH

Effects of GLP-1 Receptor Agonists on Kidney and Cardiovascular Outcomes

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Rare Kidney Disease: Where Are We Now?

Developing therapies to tackle rare kidney disease is now a hot area in nephrology

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In a recent paper, Garrisi and colleagues[1] searched metadata on ClinicalTrials.gov and reported major increases in research focused on rare kidney disease (RKD). Comparing 2 periods, 2003-2012 and 2013-2022, they observed a 283% increase in observational studies and a 93% increase in interventional studies. The most frequent indications were lupus nephritis, autosomal dominant polycystic kidney disease (ADPKD), and IgA nephropathy (IgAN); all increased 77% to 166%, with proteinuria as the most frequent primary end point.

Three important factors have had an impact on the proliferation of RKD research: (1) the elucidation of the pathophysiology of several RKDs over the past decade or so, including IgAN, membranous nephropathy, antineutrophil cytoplasmic antibody–associated vasculitis, and genetic kidney diseases such as ADPKD; (2) the 2012 founding of the American Society of Nephrology's Kidney Health Initiative, a public-private partnership among the FDA, industry, and patient advocacy groups that enabled the FDA to accept proteinuria as a predictor of hard kidney disease outcomes; (3) increased funding from venture capital and private equity sources to fuel small biotech startups focused on RKD.

What defines a disease as rare? In Europe, a disease is considered rare when the prevalence is less than 1 in 2,000 individuals. In the US, the designation of a rare disorder is used when fewer than 200,000 Americans are affected. The guideline group Kidney Disease: Improving Global Outcomes (KDIGO) has identified about 150 conditions under the umbrella of rare kidney disease.[2] Some of the common and less common rare diseases are shown in TABLE 1.

TABLE 1

Common rare kidney diseases
Autosomal dominant polycystic kidney disease
IgA nephropathy
Alport syndrome
Other rare kidney diseases
Fabry disease
Atypical hemolytic uremic syndrome
Focal segmental glomerulosclerosis
Primary hyperoxaluria (type 1 or 2)
Cystinosis
Dent disease
Membranous glomerulopathy
C3 glomerulopathy

The prevalence of RKD is estimated to be 60 to 80 cases per 100,000 people in the United States and Europe.[2] More than 25% of patients receiving renal replacement therapy and approximately 5% to 10% of people with chronic kidney disease (CKD) have an underlying RKD as the cause.[3]

In an important contribution published in *The Lancet* in 2024, Wong and colleagues[4] reported data from the UK National Registry of Rare Kidney Diseases (RaDaR) comprising 27,285 individuals with a median follow-up of nearly 10 years. This registry was launched in 2010 by the UK Kidney Association. In their study, Wong et al[4] observed that patients with RKD differed from individuals with CKD in that they had a higher 5-year rate of kidney failure but also higher survival than other patients with stage 3-5 CKD.

Rare kidney disease networks are emerging, such as the European Rare Kidney Disease Reference Network (ERKNet).[5] The ERKNet encompasses nearly 100 pediatric and adult units across Europe that provide care for patients, online consultations, training opportunities, and a forum for guideline development. Such an elaborate network does not exist so far in the US.

So far, trial designs have been quite traditional parallel-group randomized controlled trials (RCTs). However, rare diseases may require a different approach, and other trial designs need to be considered (see TABLE 2).

Borrowing conceptually from oncology, 3 interesting trial designs are also likely to emerge for RKD studies: basket trials, umbrella trials, and platform trials.[6] In a basket trial, a targeted therapy is evaluated for multiple diseases that share molecular alternations. Umbrella trials evaluate multiple targeted therapies for a single disease that is stratified into subgroups by molecular alternation. Platform trials (multiarm, multistage design trials) evaluate several interventions against a common control group.

TABLE 2

Parallel group RCT: Gold standard
Crossover: Patients receive a random sequence of different prescriptions followed by a washout period and act as their own controls
Delayed start: Initial randomized placebo control phase followed by second phase during which all participants receive active treatment
Randomized withdrawal: All participants receive an open-label prescription to identify responders, then only responders are randomized to active prescription or placebo
Group sequential: Number of participants is not set in advance; trial data are monitored through interim analyses (IA) and potentially terminated early per IA rules
Adaptive: Probability of randomization shifts toward more promising results

In addition to trial design, the other major issue for RKD research is the lack of biomarkers to provide an early signal for efficacy. Biomarkers allow early assessment of success or allow for programs to "fail fast" if a favorable effect is not demonstrated. Although the diagnosis of acute kidney injury (AKI) has benefitted from the development of kidney injury molecule 1 and neutrophil gelatinase-associated lipocalin to predict AKI early, biomarkers for glomerular injury have proven elusive. Essentially, a reduction in proteinuria and a change in estimated glomerular filtration rate remain the biomarkers of choice.

The next decade is likely to see many new therapies with innovative approaches. Biomarker panels evaluating efficacy are also likely to emerge. A bright future lies ahead. Quoting Thomas Jefferson, "I like the dreams of the future better than the history of the past."

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The World Congress of Nephrology (WCN) is the annual scientific, educational, and networking meeting of the International Society of Nephrology. The WCN features regionally relevant symposia, presentations, training programs, and courses, offering the latest science and state-of-the-art education in nephrology.


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ON THE COVER

Effects of GLP-1 Receptor Agonists on Kidney and Cardiovascular Disease


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Unlocking the Power of Renal Nutrition

Lauren Budd Levy, MS, RDN, CSR

Renal dietitians are considered integral staff members in dialysis centers, but where are they in other aspects of chronic kidney disease (CKD) management?

This year's nutrition program at the National Kidney Foundation Spring Clinical Meetings (SCM25) in Boston covers various topics that focus on nutrition for patients receiving dialysis, with CKD, or with kidney stones; cultural competence in dietary patterns; and more. SCM25 presents an excellent opportunity for nephrology professionals to delve deeper into their specialty while also broadening their focus on other nephrology-related topics and interdisciplinary collaboration.

WHAT DOES A RENAL DIETITIAN DO?

The Spring Clinical Meetings offer renal dietitians an opportunity to stay updated on the latest research in kidney health while broadening their skills in other aspects of healthcare. At all stages of kidney disease, a renal dietitian assesses the patient's eating patterns to identify risks for electrolyte imbalances; proteinuria; and high blood pressure, cholesterol, and blood glucose levels. However, renal dietitians work with patients on more than just kidney health.

Renal dietitians look beyond kidney-specific risk factors and address overall health. They frequently assist with gastrointestinal issues, disordered eating, or weight loss to help patients live healthier lives and protect their kidneys.

Renal dietitians teach patients how to create kidney-friendly eating patterns that complement their medications to manage kidney risk factors while fitting the patient's lifestyle. All nephrology professionals can benefit from dietary-focused SCM25 sessions such as *Are Plant-Based Diets Feasible (or Even Possible) for Dialysis Patients?* and *Beyond Oxalate: Holistic Nutrition for Stone Prevention*.

IMPACT ON PATIENT CARE AND QUALITY OUTCOMES

The clinical benefit of nutrition interventions has been demonstrated repeatedly; for example, medical nutrition therapy (MNT) has been shown to delay the progression of CKD. An abstract presented at SCM24 demonstrated that MNT in late-stage CKD (glomerular filtration rate ≤15 mL/min/1.73 m^2) delayed the onset of dialysis by an average of 14 months and saved Medicare approximately $47,000 per patient.[1] The Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines also recommend MNT as a way to educate patients on modulating their eating patterns to follow low-sodium, reduced-protein—and when appropriate—low-potassium and low-phosphorus diets.[2]

Recently, new medications that impact eating behaviors have been approved for CKD. These medications have side effects that can be mitigated or completely avoided when patients follow a higher-fiber eating pattern.[3] Renal dietitians work with patients receiving such medications to help them achieve and maintain a healthy weight, minimize side effects, and meet kidney health goals. This topic will be reviewed during the interdisciplinary session *Enhancing Obesity Management Through Collaborative Care* at SCM25.

HOW TO ENGAGE WITH RENAL DIETITIANS

Cost should not be a barrier for patients seeking renal dietitian services. Medicare fully covers MNT for CKD, meaning patients have no copays or out-of-pocket costs for services. Commercial insurance coverage varies, but MNT is typically covered either through preventive services or medical coverage under most plans. Medicare requires a referral from a physician for services.

Location is also not a barrier to receiving services. Telehealth remains a viable option, with dietitians often licensed in multiple states. This important topic will be highlighted at SCM25 during the presentation *Maximizing Patient Outcomes and the Crucial Role of Registered Dietitian Nutritionists With Other Nephrology Professionals.*

WHERE TO FIND RENAL DIETITIANS

Finding a dietitian specializing in nephrology has historically been a barrier to care.[4] One option is to hire a renal dietitian to provide MNT services within a nephrology office. Referring patients to outside providers who bill insurance directly is another option.

The National Kidney Foundation maintains a list of renal dietitians who offer both in-person and telehealth services.[5] Patients can also contact their insurance company to find a dietitian who accepts their plan.

Large healthcare systems also employ outpatient dietitians who can see patients with CKD. If a renal dietitian is not on staff, nephrologists should advocate for their hire.

NUTRITION AT SCM25 AND BEYOND

The nephrology space is evolving, and SCM25 is a key opportunity to stay up to date. With new medications available to patients and an ongoing focus on improving outcomes, utilizing all nephrology practitioners, including dietitians, is essential now more than ever.

If you are attending SCM25 sessions in person or virtually on demand, consider checking out the nutrition program to broaden your knowledge and engage with a renal dietitian. Our services are invaluable to patients, who often tell me, "I wish I had understood how to protect my kidneys sooner." ●

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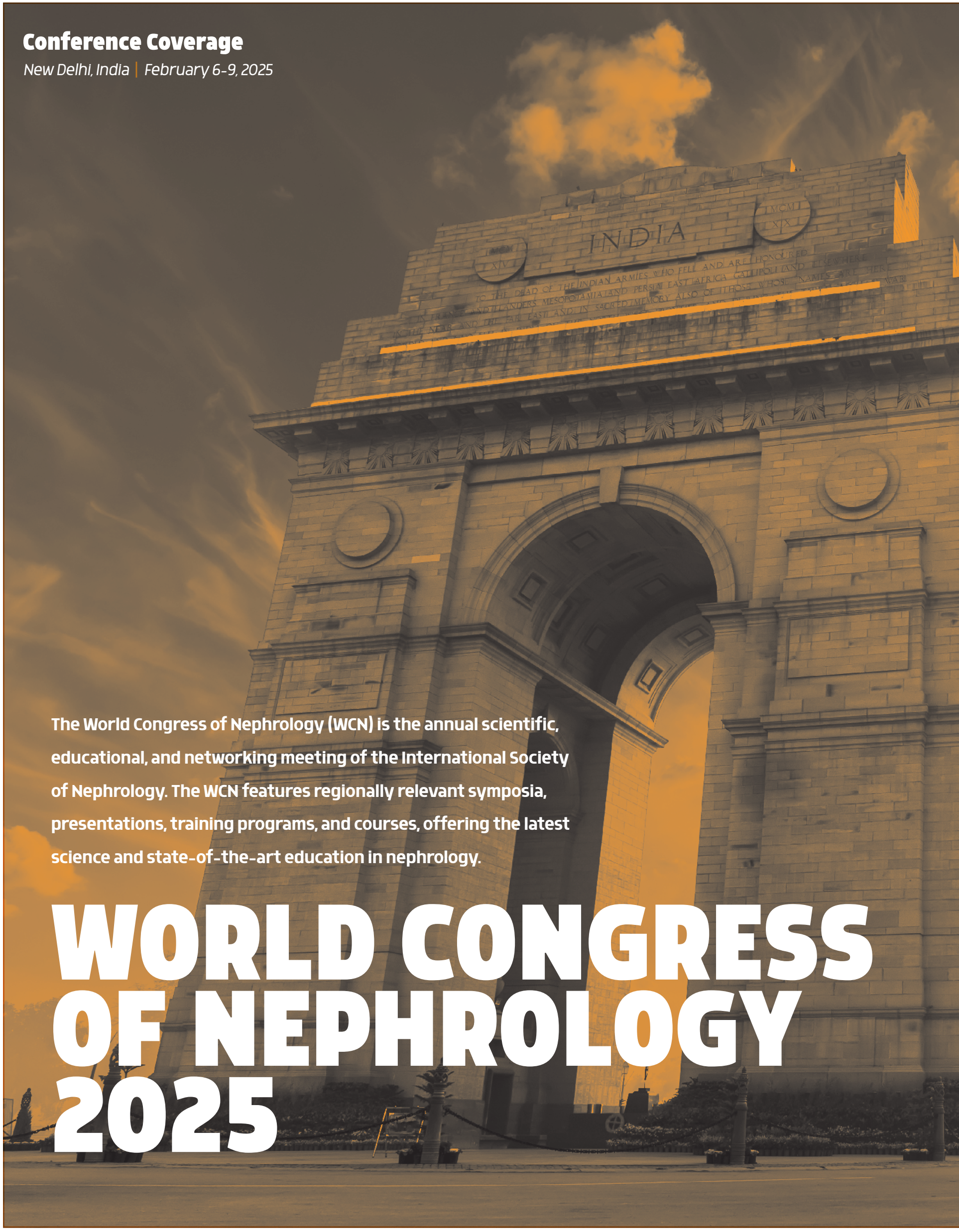


The World Congress of Nephrology (WCN) is the annual scientific, educational, and networking meeting of the International Society of Nephrology. The WCN features regionally relevant symposia, presentations, training programs, and courses, offering the latest science and state-of-the-art education in nephrology.

WORLD CONGRESS OF NEPHROLOGY 2025

BMD in Children Receiving Steroids for Kidney Diseases

Many childhood kidney diseases are treated with corticosteroids, including childhood nephrotic syndrome. However, steroids can have ill effects on bone mineral content and bone mineral density (BMD) and can lead to osteoporosis. **Sowrabha Rajanna** and colleagues conducted a clinical trial from February to October 2024 to assess the relationship between steroid exposure and BMD changes in a pediatric population.

The study included 25 children aged 5 to 18 years receiving steroids for renal indications for more than 12 weeks with an estimated glomerular filtration rate (eGFR) of greater than 90 mL/min/1.73 m^2 (steroid arm) and 25 children without a history of steroid use (control arm). All participants had a dual-energy x-ray absorptiometry (DEXA) scan and metabolic screening for bone health.

The dose and duration of steroids, calcium intake, outdoor activity, and other history were recorded. Clinical examination focused on growth, vital signs, edema, and ascites. Serum creatinine, serum albumin, serum calcium and phosphorus, alkaline phosphatase levels, serum vitamin D3 levels, and intact parathyroid hormone were measured.

All participants met their daily recommended calcium intake. Serum vitamin D was low (<30 international units) in 14 participants. Twenty-five children were receiving steroids: 18 for nephrotic syndrome, 4 for lupus nephritis, 1 for Takayasu arteritis, 1 for atypical hemolytic uremic syndrome, and 1 for complement 3 glomerulopathy. Only 9 of the children receiving steroids were of a height below the third centile.

DEXA scans were performed using the GE Healthcare Prodigy system. Z scores of total body less head (TBLH) and anteroposterior (AP) spine were recorded and compared with reference ranges of National Health and Nutrition Examination Survey data for the pediatric population. TBLH values were computed only for children younger than 7 years due to lack of reference data.

AP spine scores were low in 21 of 25 (84%) children in the steroid arm compared with 3 of 25 (12%) children in the control arm. TBLH scores were low in 15 of 19 children in the steroid arm and 1 of 21 children in the control arm, with the lowest TBLH Z score being -2.6.

The authors concluded that evaluating pediatric BMD periodically could help detect bone changes early. This could allow for minimizing steroids when possible and addressing vitamin D insufficiency and any other correctable issues. BMD DEXA could provide a tool to help minimize negative effects of long-term steroid use on bone growth.

Source: Rajanna S, Shetty M, Nagendra L, Prashanth SN, Ahmed S. Bone mineral density profile in children receiving corticosteroids for renal indications for more than twelve weeks. Abstract #WCN25-2795. Presented at the World Congress of Nephrology; February 6-9, 2025; New Delhi, India.

Economic Impact of SARS-CoV-2 Infection Among Recipients of Kidney Transplants

Recipients of kidney transplants are subject to comorbidities, chronic immunosuppression, and frequent contact with the healthcare system, which can put them at high risk for severe illness from COVID-19. To determine the economic costs of treating SARS-CoV-2 infection among kidney transplant recipients in Paraguay, about which little was known, **Juan Daniel Acosta González** and colleagues conducted an analysis of medical record data.

The medical records, spanning January to December 2021, included complete data regarding auxiliary methods of diagnosis, diagnosis, and treatment received; patients' identities remained anonymous. The researchers adopted a quantitative, descriptive, nonexperimental, transversal approach to their analysis.

Sixty-one patients were included in the study, of whom 61% were male. The average (SD) participant age was 50 (13.8) years, and the average wait time for a kidney transplant was 137.7 (99.6) months. The primary immunosuppressive therapy participants received was a combination of tacrolimus, mycophenolic acid, and prednisone.

Participants who were vaccinated against SARS-CoV-2 demonstrated better creatinine, creatinine clearance, and proteinuria parameters than participants who developed an infection and were unvaccinated at the time. The vaccinated population also had lower ferritin and D-dimer levels compared with unvaccinated participants ($P<0.05$). Rates of hospitalization, suspected organ rejection, and mortality were higher among unvaccinated patients compared with their vaccinated counterparts (57% vs 35%, 6% vs 4%, and 39% vs 8%, respectively).

Due to longer hospitalizations, a need for hemodialysis, and admission to intensive care units, the costs of SARS-CoV-2 infection were higher for unvaccinated patients (US$616,148) than for the vaccinated patients (US$15,007.67). The average hospital stay was 6.94±8.93 days for unvaccinated participants and 2.84±4.5 days for the vaccinated population.

Unvaccinated patients required greater use of antibiotics (81%), corticosteroids (56%), and anticoagulation with enoxaparin (47%) to limit the development of moderate to severe illness. Vaccinated participants, meanwhile, required less use of antibiotics (40%), anti-flu therapy (44%), and remdesivir (16%).

Source: González JDA, Orue MG, Martínez A, et al. Economic impact due to SARS-COV2 infection in vaccinated and unvaccinated kidney transplant patients during 2021. Abstract #WCN25-1258. Presented at the World Congress of Nephrology; February 6-9, 2025; New Delhi, India.

Zigakibart Shows Promise for IgAN in Phase 1/2 Trial

Researchers led by Jonathan Barratt presented 76-week results of ADU-CL-19, an ongoing phase 1/2 trial (NCT03945318) of zigakibart, an investigational treatment for IgA nephropathy (IgAN). IgAN has limited treatment options and is the leading cause of primary glomerulonephritis.

Zigakibart is a novel humanized monoclonal antibody that blocks A PRoliferation-Inducing Ligand (APRIL). APRIL is a cytokine that is elevated in patients with IgAN and promotes pathogenic galactose-deficient IgA1 production, which leads to inflammation and kidney injury.

Part 3 of the trial included patients aged 18 years and older with biopsy-proven IgAN, total urine protein ≥0.5 g/24 h or urine protein-to-creatinine ratio (UPCR) ≥0.5 g/g, and eGFR ≥30 mL/min/1.73 m^2 who were receiving a stable, optimized dose of renin-angiotensin-aldosterone inhibitors (RAASi) for 3 months or longer prior to screening or who were RAASi intolerant.

The objectives included evaluating the safety, tolerability, immunogenicity, pharmacodynamic effects, and preliminary effects of zigakibart on proteinuria and eGFR. Participants were given zigakibart, 450 mg intravenously once every 2 weeks, then transitioned to 600 mg subcutaneously every 2 weeks at 24 weeks or later (cohort 1; n=10) or 600 mg subcutaneously every 2 weeks (cohort 2; n=30) for up to 124 weeks.

Among the 40 enrolled participants, 70% were male, 60% were White, and 33% were Asian; the median age was 38.5 years. Zigakibart was well tolerated by participants, and no adverse events (AEs) that led to discontinuation or death occurred. However, AEs that were primarily infections (78%) of grade 1 or 2 severity occurred in 34 (85%) of participants. One participant experienced grade 3 infections, and 1 participant experienced infections that were thought to be treatment related.

Reduction in IgG from baseline was mild to modest, at 35%; IgA levels were reduced by 71% and IgM levels were reduced by 79%. Proteinuria (UPCR from a 24-hour collection) was reduced by 57% from baseline at week 76. Lymphocyte counts and eGFR were stable throughout the study period.

In summary, in the ADU-CL-19 study, zigakibart was well tolerated, and its use resulted in persistent, clinically significant reductions in proteinuria as well as eGFR stabilization. The authors noted that the phase 3 BEYOND study (NCT05852938) is also evaluating the efficacy and safety of zigakibart in adults with IgAN.

Source: Barratt J, Workeneh B, Kim SG, et al. A phase 1/2 trial of zigakibart in IgA nephropathy (IgAN). Abstract #WCN25-1585. Presented at the World Congress of Nephrology; February 6-9, 2025; New Delhi, India. Funding was provided by Chinook Therapeutics, a Novartis company. This abstract was also presented at the American Society of Nephrology Kidney Week 2024 (#FR-P0856).

APPLAUSE-IgAN Interim Analysis Finds Iptacopan Safe, Effective

Although evidence suggests that the alternative complement pathway is involved in the pathogenesis of IgAN, there are currently no approved therapies that target it. The phase 3 APPLAUSE-IgAN study (NCT04578834) examined the use of iptacopan plus optimized supportive care in IgAN. **Dmitrij Kollins** and colleagues reported results of 9-month prespecified analyses of APPLAUSE-IgAN data.

The randomized, double-blind, placebo-controlled study included patients with biopsy-confirmed IgAN and proteinuria ≥1 g/g by UPCR from 24-hour urine collection (UPCR-24h) despite receiving maximally tolerated RAASi for 3 months or longer. Patients were randomized 1:1 to receive iptacopan, 200 mg, twice daily or placebo.

The interim efficacy analyses included 125 participants in each study group. The interim safety analyses included 222 patients in the iptacopan group and 221 in the placebo group. Baseline characteristics were balanced between the 2 treatment groups.

Iptacopan reduced UPCR-24h by 38.3% from baseline to month 9 relative to placebo (95% CI, 26%-48.6%; 1-sided $P<0.0001$). It also decreased UPCR from first morning void as early as week 2, and the effect continued through month 9, with a reduction of 35.8% (95% CI, 22.6%-46.7%) relative to placebo at month 9. Nearly twice as many patients in the iptacopan group (marginal proportion, 42.5%; 95% CI, 34.5%-50%) achieved UPCR-24h less than 1 g/g at month 9 as those in the placebo group (21.9%; 95% CI, 14.8%-29.0%).

In addition, iptacopan was well tolerated. Treatment was discontinued due to adverse events among 2.7% of participants in each group, and the infection rate in the iptacopan group did not exceed that of the placebo group.

In conclusion, the interim APPLAUSE-IgAN data showed that iptacopan was superior to placebo at reducing proteinuria at 9 months. The positive effect was seen early and remained consistent. In addition, the drug was well tolerated and demonstrated a favorable safety profile.

Source: Kollins D, Papachristofi O, Hach T, et al. Efficacy and safety of iptacopan in patients with IgA nephropathy (IgAN): interim analysis (IA) of the phase 3 APPLAUSE-IgAN study. #WCN25-799. Presented at the World Congress of Nephrology; February 6-9, 2025; New Delhi, India. This abstract was also presented at the National Kidney Foundation Spring Clinical Meetings 2024 (#448).

MAMS Platform Trial to Examine IgAN Drug Strategies for South Asian Patients

After diabetes and hypertension, glomerular diseases are the most common cause of chronic kidney disease (CKD). The GRACE-IgANI study revealed that South Asian ethnicity is associated with a more severe phenotype and rapid progression of IgAN, the most common primary glomerular disease among adults.

However, few academic trials have focused on long-term drug strategies to provide better IgAN outcomes in South Asia. In addition, Kidney Disease: Improving Global Outcomes guidelines do not specifically address patients with IgAN who are receiving standard-of-care (SOC) and maximally tolerated RAASi therapy but are at high risk because they have proteinuria or renal function impairment.

Suceena Alexander and colleagues hypothesized that readily available and approved drugs–including oral steroids, gut-directed budesonide hydroxychloroquine, mycophenolate mofetil, and nonsteroidal mineralocorticoid receptor antagonists–paired with maximally tolerated RAASi and SGLT2i (SOC) could significantly improve renal outcomes among South Asian patients with IgAN.

The researchers are performing a phase 4 randomized, embedded, adaptive, multi-arm, multistage (MAMS) platform trial with a concurrent comparator arm and 4 interventional arms in 2 stages. Male and female South Asian adults aged 18 to 75 years are being recruited for the study. Participants must meet the following criteria for inclusion: biopsy-proven primary IgAN, receipt of the maximally tolerated dose of RAASi and SGLT2i for at least 3 months with a goal blood pressure of lower than 140/90 mm Hg, high risk for disease progression, baseline eGFR ≥25 mL/min/1.73 m^2, and UPCR ≥1 g/g.

Patients with secondary IgAN; those who have had immunosuppressive therapy in the preceding 6 months; women planning a pregnancy; those showing evidence of rapidly progressive glomerulonephritis; and those who have uncontrolled diabetes, certain concomitant comorbidities (eg, systemic autoimmune disorders, chronic infections, chronic liver disease), or concomitant CKD as shown in kidney biopsy will be excluded from participation.

The researchers plan to include 585 participants, allocated 1:1 in the control arm, with approximately 117 participants in each interventional arm. The study period will span about 2 years. Sample size calculations were based on the change in eGFR slope at 2 years in the intervention arm compared with the control group, with 90% power and a 1-sided type 1 error of 2.5% for each pairwise comparison.

The researchers have achieved several milestones since September 2023 and have begun recruiting participants. Ultimately, they hope to produce primary evidence of the clinical efficacy and toxicity of antiproteinuric and immunomodulatory therapies in primary glomerular diseases in a South Asian population. In conclusion, they said, "Platform MAMS trial design is being used for the first time in proteinuric kidney diseases, and it will help establish 'GRACE-Clinical Trial Network' for similar studies in glomerular diseases."

Source: Alexander S, Raj SS, Varughese S, et al. Design of randomized embedded adaptive platform clinical trial in South Asian kidney biopsy-proven primary glomerular diseases: multi-center, multi-arm and multi-stage. Abstract #WCN25-3803. Presented at the World Congress of Nephrology; February 6-9, 2025; New Delhi, India. Funding was provided by DBT/Wellcome UK/India Alliance.

SZC for RAASi Maximization Among Patients With CKD, HFrEF

Maximal dosing of RAASi for patients with heart failure and reduced ejection fraction (HFrEF) can reduce hospitalization and mortality. However, when CKD is also present, the risk of hyperkalemia introduces challenges to optimal RAASi dosing.

Debasish Banerjee and colleagues studied the role the potassium binder sodium zirconium cyclosilicate (SZC) might play in maximizing RAASi without resultant hyperkalemia in patients with HFrEF and moderate to severe CKD (eGFR <60 mL/min/1.73 m^2).

Their double-blind, placebo-controlled trial included 112 participants, randomized to SZC (n=53) or placebo (n=59) with 2 weekly interventions. Study outcomes included the percentage of patients in each arm reaching the target dose of RAASi without experiencing hyperkalemia (serum potassium >5.5 mmol/L) or severe hyperkalemia (serum potassium >6.0 mmol/L) and the number of patients developing hyperkalemia or severe hyperkalemia.

The mean (± SD) participant age was 74±11 years, 73% were male, and 67% were White. In addition, 54% had diabetes, 11% were current smokers, 62% had a history of ischemic heart disease, and 35% had CKD stages 4-5. Baseline eGFR was 35±12 mL/min/1.73 m^2. Baseline characteristics were well matched between the 2 groups. Sacubitril/valsartan and eplerenone were the most common types of RAASi used.

On average, serum potassium levels increased in both the SZC and placebo groups by 0.03 mmol/L (95% CI, 0.005-0.05; P=0.015) biweekly during the follow-up period. However, average serum potassium throughout the study period was 0.32 mmol/L (95% CI, 0.23-0.40; P<0.001) lower in the SZC group than in the placebo group, accounting for the follow-up period.

Forty-three (39%) participants achieved the maximal RAASi dose without hyperkalemia: 21 (40%) in the SZC group and 22 (38%) in the placebo group. There was no statistical difference between the 2 groups (P=0.792). Nineteen of 32 (59%) participants in the SZC group reached half the maximum dose of RAASi from less than half the dose compared with 10 of 23 (43%) patients in the placebo group, without hyperkalemia. There was no statistical difference between the 2 groups (P=0.283).

Forty-one patients developed hyperkalemia (serum potassium >5.5 mmol/L) over the study period: 27 (47%) in the placebo group and 14 (27%) in the SZC group (P=0.040). Four patients in the SZC group and 12 patients in the placebo group developed severe hyperkalemia (serum potassium >6.0 mmol/L; P=0.059).

The authors concluded that, "In this study of rapid RAASi maximization, hyperkalemia (>5.5 mmol/L) was more common in patients on placebo compared with SZC; however, there was no statistically significant difference in proportion of patients who reached target dose of RAASi in CKD patients with HFrEF."

Source: Banerjee D, Ster IC, Ali M, et al. Maximisation of renin-angiotensin-aldosterone inhibitors in heart failure patients with CKD using potassium binder; preliminary analysis of a randomised double-blind placebo-controlled trial. Abstract #WCN25-4625. Presented at the World Congress of Nephrology; February 6-9, 2025; New Delhi, India. Funding was provided by an externally sponsored research program of AstraZeneca.

Efficacy, Safety of WRAPSODY Stent for Venous Outflow Stenosis

Venous outflow circuit stenosis or occlusion often occurs within the arteriovenous graft (AVG) or arteriovenous fistula (AVF) for hemodialysis. Limited treatment options exist to address this potentially life-threatening complication. One option to restore access circuit patency could be WRAPSODY, a covered stent with flexible ends and a cell-impermeable layer that reduces cell migration and neointimal hyperplasia.

Prabir Roy-Chaudhury and colleagues presented 6-month clinical outcomes from the WAVE study (NCT04540302) examining the use of WRAPSODY in the treatment of access circuit stenosis in patients undergoing hemodialysis. The prospective, multicenter, international trial included 43 centers in the United States, the United Kingdom, and South America.

The study enrolled patients with venous outflow stenosis or occlusion, assigning them to either an AVG or AVF cohort depending on their hemodialysis mode of access. The AVG arm was a single cohort (n=113). Participants in the AVF cohort (n=245) were randomized 1:1 to treatment with WRAPSODY (n=122) or percutaneous transluminal angioplasty (PTA; n=123).

The study's primary efficacy end point was the percentage of participants with 6-month target lesion primary patency (TLPP), defined as being free from clinically driven target lesion revascularization or target lesion thrombosis. The primary safety end point was the percentage of participants experiencing no localized or systemic safety events affecting venous outflow circuit access and resulting in reintervention, hospitalization, or death throughout 30 days.

The safety and efficacy outcomes of the AVG cohort were compared with performance goals (TLPP benchmark: 60%; safety benchmark: 89%). The 6-month TLPP was significantly higher than the effectiveness performance goal (81.4% vs 60%; P<0.001). The percentage of patients in the AVG cohort who did not experience a safety event was significantly higher than the safety performance goal (95.4% vs 89%; P=0.0162).

Participants in the AVF WRAPSODY and PTA groups were well matched regarding demographics, medical history, and target lesion characteristics. The 6-month TLPP was significantly higher in the WRAPSODY group than in the PTA group (89.6% vs 62.3%; P<0.001). Safety events did not differ significantly between the 2 groups at 30 days after the procedure (WRAPSODY: 3.4%; PTA: 5.0%; P=0.54).

The authors summarized that "The results suggest WRAPSODY may be a promising alternative for treating venous stenosis/occlusion in the venous outflow circuit."

Source: Roy-Chaudhury P, Razavi M, Balamuthusamy S, et al. Six month clinical outcomes from the WAVE study of a novel endovascular stent for vascular access stenosis. #WCN25-4483. Presented at the World Congress of Nephrology; February 6-9, 2025; New Delhi, India. Funding was provided by Merit Medical. Some data were also presented at the American Society of Nephrology Kidney Week 2024.

Prescreening Performance of AI Versus Nephrologists

With its significant ability to analyze patient data, artificial intelligence (AI) has the potential to improve diagnostics and support more precise treatment decisions in nephrology and other areas of medicine.

Clinical prescreening can be time consuming and prone to human errors, especially when it involves a large patient cohort. Nephrologists usually review patient data and study inclusion and exclusion criteria before initiating formal screening, but this prescreening process may not be particularly efficient.

Niloufar Ebrahimi and colleagues conducted a study to determine how accurately and efficiently AI performs prescreening compared with nephrologists. The researchers used Google Forms to distribute a survey regarding 4 simulated clinical cases. The survey was shared between derived connections from investigators and social media platforms, including X and LinkedIn.

Using inclusion and exclusion criteria from the published NefigArd clinical trial, participating nephrologists were tasked with determining the prescreening eligibility of each case, using "yes" or "no" responses. Survey respondents were also asked to record and input how long it took to complete their assessments of each case. ChatGPT version 3.5 was used to evaluate the same cases, and the accuracy and speed of the AI were compared with those of the nephrologists.

Thirty-three nephrologists, primarily from the academic setting (69.7%), took part in the study. Of them, 9.1% were professors, 18.2% were associate professors, and 39.4% were assistant professors. Their median years of experience was 8 (interquartile range [IQR], 3.5-15).

AI achieved 100% accuracy among all cases and significantly outperformed the nephrologists, whose accuracy ranged from 21.9% to 90.6%. The accuracy of AI was significantly higher than that of the nephrologists for each case and overall (P<0.001). The overall accuracy of the nephrologists was 55.9% compared with 99.9% for AI.

AI also produced results faster. AI took an average of 11 (SD, 1) seconds with a median of 11 seconds (IQR, 11-12). Nephrologists, meanwhile, took an average of 117 seconds (SD, 146) with a median of 60 seconds (IQR, 29-120). The nephrologists' mean rank was 67.93, compared with 4.75 for AI. The speed of AI's evaluation was statistically significantly faster than that of nephrologists (P=0.001).

In summary, the authors said, "Integrating AI in nephrology in certain tasks with clear instructions, such as clinical trial prescreenings, might provide more accuracy and efficiency." They recommend additional studies.

Source: Ebrahimi N, Glassock RJ, Ghozloujeh ZG, et al. Comparing clinical trial prescreening "AI vs nephrologist". #WCN25-606. Presented at the World Congress of Nephrology; February 6-9, 2025; New Delhi, India.

Considerations for Assessment of Simultaneous Heart and Kidney Transplant Eligibility

More than 1% of US kidney transplants comprise simultaneous heart and kidney transplantation (SHKT), an increase from 0.2% in 2003. In June 2023, the United Network for Organ Sharing (UNOS) published medical eligibility criteria for SHKT candidates based on measured glomerular filtration rate (mGFR) or eGFR.

According to those criteria, a heart transplant candidate is eligible for SHKT if they have CKD (GFR <60 mL/min/1.73 m^2) and are receiving regular dialysis or if they have GFR/creatine clearance (CrCl) of 30 mL/min/1.73 m^2 or lower. If the heart transplant candidate does not have CKD, they are eligible for SHKT if they have been receiving dialysis for 6 weeks or have GFR/CrCl 25 mL/min/1.73 m^2 or lower.

Krishna Agarwal and colleagues highlighted the wide variation among creatinine-based eGFR (eGFRcr), measured CrCl (mCrCl), and mGFR and errors in eGFRcr as demonstrated by 6 cases of patients ranging in age from 33 to 62 years.

As part of evaluation for SHKT eligibility, the patients' eGFRcr, cystatin C-based eGFR (eGFRcys; per CKD Epidemiology [CKD-EPI] 2012), eGFR using both creatinine and cystatin C (eGFRcr-cys; per CKD-EPI 2021), 24-hour mCrCl, and mGFR using plasma iohexol clearance were obtained. The researchers evaluated bias (systematic error) as the mean difference between mGFR and eGFR. Positive bias revealed underestimation of mGFR, whereas negative bias revealed overestimation of mGFR.

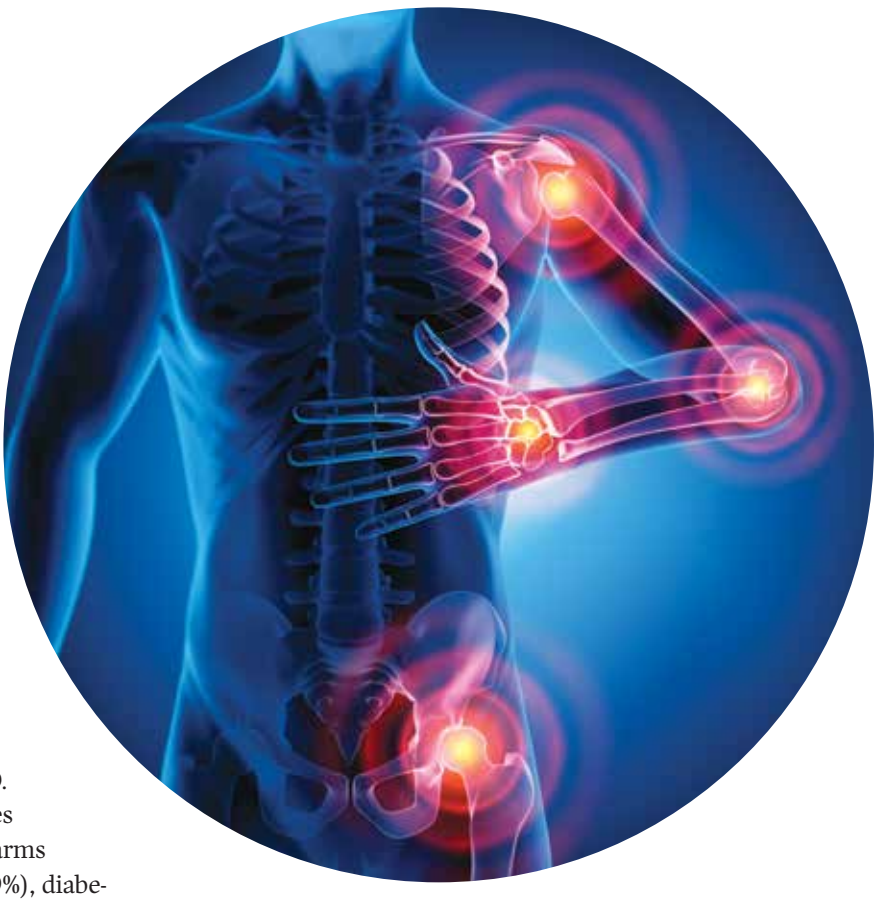
The researchers observed large discrepancies between eGFRcr, eGFRcys, mCrCl, and mGFR among the cases, with eGFRcr overestimating mGFR (mean overestimation, 7.5 mL/min/1.73 m^2). In addition, eGFRcr-cys was more like mGFR with the lowest bias (mean overestimation of mGFR, 1.3 mL/min/1.73 m^2). Just 50% of SHKT recipients received dialysis, compared with 87% receiving only kidney transplants, and more than 20% had a GFR greater than 45 mL/min/1.73 m^2 at the time of transplant.

Because multiorgan transplant recipients have lower patient and graft survival rates, it is critical that they be carefully vetted to ensure optimal equity and effectiveness of transplantation. The authors concluded that the current UNOS eligibility criteria for SHKT do not account for errors in eGFRcr, and centers should consider guidelines for eGFRcr-cys when making decisions about such eligibility.

Source: Agarwal K, Inker L, Levey A. Challenges and opportunities in assessing kidney function in simultaneous heart-kidney transplant candidates. #WCN25-989. Presented at the World Congress of Nephrology; February 6-9, 2025; New Delhi, India.

STOP Gout Trial

Noninferiority of Allopurinol and Febuxostat Among Subgroup With CKD



Patients with comorbid conditions such as cardiovascular disease, obesity, diabetes, and chronic kidney disease (CKD) commonly experience gout. Gout is associated with hyperuricemia and episodes of intense joint pain and swelling. There are several therapies designed to lower urate levels in patients with gout. The most common are the xanthine oxidase inhibitors febuxostat and allopurinol.

Estimates put the proportion of patients with gout and concomitant CKD stage 3 and above at 20% to 30%. Estimates with any degree of CKD stage (stage 1-5) reach 70%. Concerns regarding the risk of allopurinol hypersensitivity syndrome (AHS) limit the use and dosing of allopurinol in patients with CKD. Furthermore, the use of febuxostat has been associated with conflicting cardiovascular safety signals in that patient population.

The STOP Gout trial compared the efficacy and safety of allopurinol and febuxostat in the management of patients with gout using a treat-to-target approach. A team of researchers led by **Lindsay N. Helget, MD,** reported results of a preplanned secondary analysis of data from a subgroup of participants with stage 3 CKD in the STOP Gout trial in the *American Journal of Kidney Diseases* [doi:10.1053/j.ajkd.2024.04.017].

STOP Gout was a multicenter, randomized, double-blind, noninferiority comparative effectiveness trial. Enrollment occurred at 21 sites in the United States between 2017 and 2019. The final study visit was conducted in August 2019. As specified in the trial protocol, a minimum of one-third of the participants had CKD stage 3 (estimated glomerular filtration rate [eGFR] 30-59 mL/min/1.73 m^2). The primary outcome of interest was gout flare between weeks 49 and 72. Secondary outcomes included the achievement of the serum urate (sUA) goal and dosing of urate-lowering therapy, and serious adverse events.

Participants were randomized 1:1 to receive allopurinol or febuxostat. During weeks 0-24 (phase 1), urate-lowering therapy was titrated to achieve a goal of sUA concentrations of <6.0 mg/dL (<5.0 mg/dL with tophi). Dosing was maintained during weeks 24-48 (phase 2). Assessment of gout flares occurred between weeks 49 and 72 (phase 3).

Logistic regression models were used to compare binary outcomes between the 2 treatment groups and Poisson regression was used to compare flare rates. Multivariable models were used following adjustment for factors identified to be imbalanced.

Of the 940 participants in the study cohort, 37.3% (n=351) had CKD. Of them, 181 were randomized to the allopurinol treatment arm and 170 to the febuxostat arm. Mean age of the total CKD subgroup was 68.4 years, and 97.2% were male. Furthermore, 70.4% were White, 21.9% were Black, 2.0% were Asian, 0.6% were American Indian, 2.6 % were Native Hawaiian/Pacific Islander/Maori, and 2.6% were other race/ethnicity.

The mean eGFR was 47.7 mL/min/1.73 m^2 overall (47.4 mL/min/1.73 m^2 in the allopurinol arm and 48.1 mL/min/1.73 m^2 in the febuxostat arm), with mean sUA concentrations of 8.8 (1.5) mg/dL. Marked hyperuricemia (defined as a sUA exceeding 9 mg/dL) was observed in 41.9% of participants with CKD.

The most common comorbidities in the allopurinol and febuxostat arms were hypertension (86.2% vs 85.9%), diabetes (45.9% vs 51.2%), and cardiovascular disease (48.6% vs 34.1%), respectively. In the allopurinol arm, 54.1% of participants used a diuretic compared with 57.1% in the febuxostat arm. Serum creatinine concentration, diabetes, cardiovascular disease, BMI, and sUAs at baseline were defined as imbalanced factors between the 2 arms (standard difference >0.1).

The mean allopurinol dose in the subgroup with CKD was 394.6 mg (145.6) and the median dose was 400 mg (200 mg). In the febuxostat arm, mean dose was 63.7 mg (23.8 mg) and median dose was 80 mg (40 mg). At the discretion of the site investigator, 90.0% (n=316) of trial participants with CKD were administered colchicine alone, 6.6% (n=23) received glucocorticoids alone, 2.6% (n=9) received another therapy (combination therapy or not specified), and 0.9% (n=3) received nonsteroidal anti-inflammatory drugs.

During phase 3, fewer patients in the allopurinol treatment arm experienced 1 or more gout flares than those in the febuxostat treatment arm (32% vs 45%; *P*=0.02), despite similar attainment of sUA goal (79% vs 81%; *P*=0.06) by the end of phase 2. Participants in both treatment arms who did not reach target sUA at the end of phase 2 were significantly more likely to experience a flare in phase 3 compared with those who did achieve the sUA goal (flare rate 2.99 vs 1.59; *P*<0.001).

The occurrence of serious adverse events, defined as the proportion of participants with 1 or more serious adverse events reported, was similar in the 2 treatment arms. Rashes were more frequent in the allopurinol arm than in the febuxostat arm. Severe rashes resolved without evidence of AHS but led to study withdrawal.

Patients in the CKD subgroup in the allopurinol arm more commonly experienced acute kidney injury compared with those in the febuxostat arm (8% [n=15) vs 2% [n=4]; *P*=0.02). The most common etiology of AKI was volume depletion (7 events in the allopurinol arm vs 1 event in the febuxostat arm), followed by cardiorenal syndrome (5 in the allopurinol arm vs 0 for febuxostat).

The authors cited limitations to the findings, including limited power to assess infrequent safety events, the largely male makeup of the study population, and the percentage of older participants in the study.

The researchers concluded that the prespecified subanalysis focused on individuals with stage 3 CKD demonstrated allopurinol and febuxostat to be similarly effective in flare prevention and in reaching target sUA thresholds when used as part of a treat-to-target strategy. The analysis also revealed similarly favorable safety profiles with similar incidence of cardiovascular disease and low incidence of severe rashes.

"The higher AKI incidence in the allopurinol group needs to be interpreted with caution given higher baseline of cardiovascular disease in the allopurinol group and warrants further investigation," the researchers said. "Moreover, the clinical benefit gained from treat-to-target urate lowering therapy in gout management extends to those with CKD."

Vadadustat for Anemia in Patients With Dialysis-Dependent Chronic Kidney Disease

Patients with chronic kidney disease (CKD) commonly develop anemia, and the prevalence of anemia in this patient population increases with CKD stage. Patients with anemia of CKD face increased risks of adverse CKD-related outcomes, including cardiovascular morbidity and mortality, poor health-related quality of life, and increased utilization of healthcare resources.

Standard treatment for anemia of CKD includes regular iron supplementation (oral or IV) and erythropoiesis-stimulating agents (ESAs). Patients who do not respond to ESA therapy are also treated with red blood cell transfusions. However, studies have shown associations between targeting normal or near-normal hemoglobin concentrations with ESAs and increased risk of cardiovascular events.

One possible oral treatment option for anemia of CKD is hypoxia-inducible factor prolyl hydroxylase inhibitors (HIF-PHIs). These agents stabilize HIF, a transcription factor regulating hypoxic genes, resulting in increased endogenous production of erythropoietin and improved iron availability. Vadadustat, an oral HIF-PHI, is approved for treatment of anemia in Japan and for treatment of patients with dialysis-dependent CKD in the United States.

Hakan R. Toka, MD, and colleagues conducted FO_2CUS, a phase 3b, open-label, noninferiority trial to examine the efficacy and safety of conversion from treatment with the long-acting ESA methoxy polyethylene glycol-epoetin beta (MPG-EPO) to vadadustat 3 times per week compared with maintenance treatment with MPG-EPO. Results were reported in the *American Journal of Kidney Diseases* [doi:10.1053/j.ajkd.2024.09.006].

The study was conducted at various centers in the United States. Participants were randomized 1:1:1 to receive vadadustat starting dose, 600 mg 3 times per week; vadadustat starting dose, 900 mg 3 times per week; or MPG-EPG for up to 52 treatment weeks and 4 safety follow-up weeks after the end of treatment or early termination of treatment.

The primary efficacy outcome of interest was mean change in hemoglobin concentration from baseline during weeks 20 to 26. The secondary outcome was the mean change in hemoglobin concentration from baseline during weeks 46 to 52. Noninferiority was defined as a lower bound of the 95% CI above –0.75 g/dL for the difference in mean change in hemoglobin concentration from baseline. The primary safety end points were any treatment-emergent and serious adverse events.

The overall study cohort included 456 patients who were randomized to the following groups: vadadustat 600 mg (n=152), vadadustat 900 mg (n=152), or MPG-EPO (n=152). Five of the 456 patients did not meet screening criteria and were not treated. The treatment groups were generally balanced in terms of demographic and baseline characteristics. Ferritin values were substantially higher than the upper limit of the population reference range, and mean transferrin saturation values were at the high end of the reference range.

During the study period, the median monthly dose of MPG-EPO was 90.8 µg. During the trial period, the mean weekly dose of vadadustat in the 600 mg starting dose group increased; the mean weekly dose in the 900 mg starting dose group remained consistent.

After the 2 vadadustat groups were combined (n=304), vadadustat was noninferior to MPG-EPO for mean change in hemoglobin concentration from baseline to the primary evaluation period (least squares [LS] mean treatment difference, –0.33 g/dL; 95% CI, –0.53 to –0.13) and to the secondary evaluation period (LS mean treatment difference, –0.33 g/dL; 95% CI, –0.56 to –0.09). Vadadustat was also noninferior to MPG-EPO in the individual starting dose groups for both the primary and secondary evaluation periods.

Through week 6, there was an initial decline in the mean hemoglobin concentrations in the vadadustat 600 mg group. By week 12, the hemoglobin concentrations in that group returned to target range and remained stable throughout the remainder of the trial. In the MPG-EPO group, there was some variability in the mean hemoglobin concentrations on the upper side of the hemoglobin target range.

All treatments had overlapping error bars throughout the study period.

During the primary evaluation period, the proportion of patients with hemoglobin values within the target range (10.0–11.0 g/dL) was lower for those in the vadadustat total group than for those in the MPG-EPO group: 63.9% (154 of 241) versus 76.0% (98 of 129), respectively. The values during the secondary evaluation period were 60.5% (107 of 177) and 69.4% (77 of 111), respectively.

Throughout the trial period, the proportion of patients receiving ESA rescue therapy was higher in the MPG-EPO group than in the vadadustat groups: 14.2% versus 27.7%, respectively, during the primary evaluation period and 7.3% versus 16.2%, respectively, during the secondary evaluation period. The proportion of patients receiving red blood cell transfusions remained low throughout the study period in all groups; there were no statistically significant differences between the vadadustat and MPG-EPO groups. There were also no significant differences between the vadadustat and MPG-EPO groups in the proportion of patients receiving IV iron therapy.

By week 4, total iron-binding capacity increased in both vadadustat groups and remained consistently higher than in the MPG-EPO group throughout the study period. There was an initial slight decline in serum iron concentrations in the MPG-EPO group that persisted at subsequent time points; serum iron concentrations remained stable in the vadadustat groups. In all treatment groups, other iron-related laboratory parameters remained consistent.

The incidence of any treatment-emergent and serious treatment-emergent adverse events was similar across treatment groups.

The open-label design was cited by the authors as a possible limitation to the findings, as was the hemoglobin concentration target range of 10 to 11 g/dL, which is narrower than the range of 10 to 12 g/dL used in countries other than the United States. In addition, the relatively short trial duration and safety follow-up period did not allow for analysis of long-term effects. Finally, the high baseline oral iron doses may have been a confounding factor, limiting the generalizability of the study findings.

In summary, the researchers said, "Vadadustat 3 times weekly was noninferior to MPG-EPO in hemoglobin maintenance with a safety profile similar to MPG-EPO. Patients in the vadadustat 600 mg group often required dose adjustment after an initial decline in hemoglobin concentrations and were more likely to experience hemoglobin excursions to <9.0 g/dL than the vadadustat 900 mg group. Therefore, a 900 mg 3-times-weekly starting dose may be preferred for in-center hemodialysis patients switching from MPG-EPO." ●

Association of Sodium Correction Rates for Hyponatremia With Mortality

Severe hyponatremia can lead to hyponatremic encephalopathy, which requires emergency treatment with hypertonic saline. Otherwise, permanent neurological damage or death could occur.

Current guidelines recommend limiting correction of severe hyponatremia for the first 24 hours to prevent osmotic demyelination syndrome (ODS). US guidelines suggest limits of 10-12 mEq/L or less in any 24-hour period and 18 mEq/L or less in any 48-hour period. For patients at high risk for ODS, the suggested limit is 8 mEq/L per 24-hour period. However, the effect that limiting hyponatremia correction has on mortality is not well understood.

To address this knowledge gap, **Juan Carlos Ayus, MD,** and colleagues performed a meta-analysis of cohort studies to assess the associations of different rates of correction of severe hyponatremia with mortality, hospital length of stay (LOS), and ODS. Their findings were published in *JAMA Internal Medicine* [doi:10.1001/jamainternmed.2024.5981].

The researchers searched for randomized and nonrandomized clinical trials and observational comparative studies. There were no restrictions on language or publication status. Participants comprised adults hospitalized for severe hyponatremia (serum sodium <120 mEq/L) or with severe symptomatic hyponatremia (serum sodium <125 mEq/L plus severe symptoms, such as cardiorespiratory distress, seizures, Glasgow Coma Scale ≤8, or decreased level of consciousness).

Based on various rates of sodium correction reported in the included studies, the researchers named 4 categories of sodium correction rate: (1) very rapid (>12 mEq/L per 24 hours); (2) rapid (≥8-10 mEq/L per 24 hours); (3) slow (<8 or 6-10 mEq/L per 24 hours); and (4) very slow (<4-6 mEq/L per 24 hours).

The primary comparisons were made between the rapid versus slow rates and rapid versus very slow rates. However, each category was compared with every other category to examine dose-response gradients. The primary outcome of the study was mortality (both in-hospital and 30-day mortality). The secondary outcomes included hospital and intensive care unit (ICU) LOS and 90-day incidence of ODS.

The authors used Cochrane methods to perform meta-analyses for each comparison and used the random effects meta-analysis for the primary analysis. They calculated risk ratios (RRs) or odds ratios (ORs) with 95% CIs for dichotomous outcomes and mean difference for continuous outcomes.

The analysis included single-arm zero events studies and double-arm zero events studies; therefore, the Peto OR was not the optimal option. The authors used the Mantel-Haenszel risk difference, an empirical correction, and a continuity correction. Adjusted effect measures were used when available.

An I^2 greater than 60% was considered substantial statistical heterogeneity. Sources of heterogeneity were studied through prespecified subgroup analyses by admission sodium levels, sex, Charlson Comorbidity Index, alcohol use, desmopressin use, setting, and cause of hyponatremia. A funnel plot was used to find and correct publication and other reporting biases when there were 8 or more studies in the meta-analysis for a given comparison. Sensitivity analyses were performed by excluding high risk of bias studies or by using the fixed-effect model.

The researchers retrieved 5,010 records in their search for trials and evaluated the full text of 38 publications. Sixteen studies including a total of 11,811 patients met the inclusion criteria. In 14 of the studies included, the mean participant age was >60 years. The mean percentage of women was 56.7% in 15 of the included studies that reported sex. All but 1 study took place in high-income countries. Fifteen of the included studies reported in-hospital mortality, but only 6 reported adjusted in-hospital mortality of rapid correction compared with slow or very slow sodium correction. Eleven studies reported 30-day mortality, 14 reported ODS, 10 reported hospital LOS, and 6 reported ICU LOS.

Moderate-certainty evidence found that rapid sodium correction was associated with 32 (OR, 0.67; 95% CI, 0.55-0.82) and 221 (OR, 0.29; 95% CI, 0.11-0.79) fewer in-hospital deaths per 1,000 treated patients compared with slow and very slow correction, respectively. Low-certainty evidence implied that rapid correction was associated with 61 (RR, 0.55; 95% CI, 0.45-0.67) and 134 (RR, 0.35; 95% CI, 0.28-0.44) fewer deaths per 1,000 treated patients at 30 days.

A faster correction was consistently associated with shorter LOS, which suggests a potential dose-response effect. However, the difference in LOS was slight for very rapid compared with slow or very slow correction. ICU LOS was insignificantly shorter, and there was no estimated dose-response effect when comparing rapid sodium correction with slow or very slow sodium correction. Low-certainty evidence suggested that rapid correction was associated with a reduction in LOS of 1.20 (95% CI, 0.51-1.89) and 3.09 (95% CI, 1.21-4.94) days, compared with slow and very slow correction, respectively.

Due to sparse data, only the alcohol use disorder subgroup analysis could be completed. Rapid sodium correction was not associated with a statistically significant increased risk of ODS when compared with slow or very slow correction in patients with and without alcohol use disorder, with an I^2 of 0% in the test for subgroup differences.

Study limitations included the heterogeneity of inclusion and exclusion criteria, correction rate comparisons, cointerventions, and definitions of ODS among the included studies. In addition, ODS may have been underreported in the included studies because confirmatory imaging was required.

The authors concluded, "In this systematic review and meta-analysis, available evidence suggests that slow correction of sodium was associated with an increased risk of mortality and longer hospital LOS. These findings are further supported by dose-response effects with no statistically significant higher risk of ODS, suggesting a very favorable net benefit with rapid correction." ●

Moderate-certainty evidence found that rapid sodium correction was associated with 32 and 221 fewer in-hospital deaths per 1,000 treated patients compared with slow and very slow correction, respectively.

Treating Post-Transplant Renal Anemia in Routine Clinical Practice

Patients may develop anemia following kidney transplant, yet there are no specific post-transplant guidelines for management of the condition. Current international guidelines call for treatment recommendations and goals similar to those for patients with anemia of chronic kidney disease not dependent on dialysis (NDD-CKD). However, the incidence of post-transplant anemia is higher than the incidence of patients with CKD-NDD at the same estimated glomerular filtration rate (eGFR). The pathophysiology of post-transplant anemia is similar to that of CKD-associated anemia, but early post-transplant anemia is associated with additional factors related to surgery, induction therapy, and infections.

Researchers in the Spanish Society of Nephrology transplant working group (SENTRA) and the anemia working group (GAS) recommended a shared nationwide study in real-world clinical settings to address the need for guidelines specific to anemia in kidney transplant recipients. The TRANSNEMIA study is a joint initiative of the SENTRA and GAS. Results were reported by **José Portolés, MD,** and colleagues in the *Clinical Kidney Journal* [doi:10.1093/ckj/sfae269].

The retrospective, noninterventional, multicenter study included patients from 8 university kidney transplant hospitals in Spain. The study objective was to examine treatment patterns of anemia and objectives achieved in post-transplant patients, as well as the degree of compliance with current clinical guidelines in a clinical practice setting without intervention.

Data were obtained from electronic medical records, including demographics, cause of CKD, comorbidities (cancer, cardiovascular events, diabetes mellitus, and Charlson Comorbidity Index score), and kidney transplant characteristics (donor type, immunosuppressive therapy, actual serum creatinine, and eGFR). Data related to anemia management (laboratory values, previously prescribed treatments, and subsequent adjustments) were also included.

Anemia was defined as hemoglobin (Hb) <13 g/dL in men and Hb <12 g/dL in women, or any Hb treatment according to 2012 Kidney Disease: Improving Global Outcomes (KDIGO) guidelines. The European Renal Association position statement, European Renal Best Practice (EBPG) adapted the KDIGO recommendation for erythropoietic-stimulating agent (ESA) treatment for the European population, suggesting that Hb levels between 10 and 12 g/dL be achieved and maintained, while setting the target individually according to patient comorbidities. Hb values >13 g/dL should not be intentionally sought during ESA therapy according to the EBPG.

The study cohort included 297 kidney transplant recipients with anemia and a functioning graft. Mean age was 62.8 years, and 60% were male. The kidneys were primarily from cardiac death donors (31.1%) or brain death donors (61.6%). Median time since transplant was 2.5 years and eGFR was 37.3 mL/min/1.73 m^2. The patients were divided into 2 groups: (1) those with early post-transplant anemia (first 6 months following transplant), n=69 (23%); and (2) those with late post-transplant anemia (≥7 months following transplant), n=228 (77%).

In the 2 groups, the mean Hb was numerically lower in the early anemia group (1.3 vs 11.6 g/dL). The percentages of patients with Hb on target (10-12 g/dL) were similar in the 2 groups, and there were more patients with severe anemia (15.9% vs 8.8% Hb <10 g/dL) in the early anemia group. Patients in the early anemia group had received more blood transfusions in the previous 4 months (27.5% vs 4.8%) and presented with higher eGFR, ferritin, and transferrin saturation index (TSAT). The 2 groups were similar in distribution of absolute or relative iron deficiency.

Of the 297 transplant recipients, 53.2% (n=158) were receiving treatment with ESAs. The majority were being treated with darbepoetin (79.7%, median dose 1.0 µg/kg/month) or epoetin µ (19.6%, median dose 133.3 international units/kg/month). Of the patients not being treated with ESAs, 13 had Hb level <10 g/dL and 6 were prescribed ESAs following that lab result.

Functional iron deficiency was observed in 10.4% of the overall cohort, and 8.1% had absolute iron deficiency; distribution was similar for early and late anemia. The prevalence of iron deficiency and functional iron deficiency was higher among patients receiving treatment with ESAs. Those in the early anemia subgroup presented more iron deficiency compared with those in the late anemia subgroup (15.0% vs 8.5%, respectively).

A total of 110 patients on ESA treatment were not receiving iron supplementation. Of them, 44 had an indication to receive iron according to guidelines and 30 had absolute iron deficiency.

According to the EBPG recommendation, most patients receiving treatment with ESAs (n=71/158) had optimal Hb control within the range of 10-12 g/dL. Hb increased to the range of 12-12.9 g/dL in 42 patients, and it was above the limit of 13 g/dL in 27 of the 158 patients.

In the subgroup receiving treatment with ESAs, only 39 surpassed the limit for ESA resistance index, indicating poor response. ESA resistance was more frequent among patients with early anemia compared with patients with late anemia (26.1% vs 9.2%). Factors associated with the highest risk of resistance were iron profile, early post-transplant anemia, and eGFR.

The researchers cited, as limitations to the study findings, the lack of external validation and the inability to generalize the findings to other health systems or countries.

Summarizing the study's key findings, the authors wrote, "a majority of ESA prescriptions meet guidelines; Hb targets are personalized to fall between 12 and 13 g/dL; iron supplements remain underutilized; and iron deficiency emerges as the primary cause of hyporesponsiveness to ESAs."

The authors said the results highlight a need for improvement strategies, which may include organized dissemination of anemia guidelines, clinical pathways for IV iron administration in outpatient clinics, and assisted prescription tools and early identification of resistance to ESAs or inflammation. They also noted an urgent need for additional research on anemia in kidney transplant patients to help inform guidelines and care. ●

Increased Donor Time to Death and Kidney Transplant Outcomes

The optimal treatment for patients with end-stage renal disease who are undergoing dialysis is a kidney transplant. Kidney transplant provides significant benefits in survival and quality of life, as well as reductions in healthcare costs. However, concurrent with increases in the prevalence of chronic kidney disease worldwide are increases in transplant waiting times. Only 25% of patients listed for a transplant in the United States receive a deceased-donor transplant within 5 years, necessitating expanding the deceased donor pool or improving the use of organs from existing donors.

Time to death (TTD) in controlled donation after circulatory death (DCD) is a factor with the potential to expand the deceased donor pool. Currently, most international organ donation organizations (ODOs) wait no longer than 1 to 2 hours for potential donation following circulatory death; only 6.7% of US organ donation organizations routinely wait even 2 hours, resulting in a substantial number of viable kidneys being lost due to the strict wait times.

More than 10 years ago, the national standard in the United Kingdom for DCD wait time was set to a minimum of 3 hours. Utilizing data from the UK Transplant Registry from 2013 to 2022, **Samuel J. Tingle, MBBS,** and colleagues conducted a study to examine whether TTD from withdrawal of life-sustaining treatment is associated with kidney transplant outcomes. Results were reported in *JAMA Network Open* [doi:10.1001/jamanetworkopen.2024.43353].

The population-based cohort used data from all 23 kidney transplant centers in the United Kingdom from January 1, 2013, to December 21, 2021. Follow-up was the date of data extraction (October 2023).

The study exposure was the duration of TTD, defined as time from withdrawal of life-sustaining treatment to donor mechanical asystole. The primary outcome of interest was recipient 12-month estimated glomerular filtration rate (eGFR; Chronic Kidney Disease Epidemiology Collaboration 2021 formula). Recipients who lost their graft prior to 1 year after transplant were given a nominal eGFR value of 10 mL/min/1.73 m^2. Secondary outcomes included the incidence of delayed graft function (defined as the need for dialysis in the first week following transplant) and graft survival (censored at death or 5 years).

The cohort included 7,183 adult recipients of DCD kidney-alone transplants. Median recipient age was 56 years, 65.0% (n=4,666) were male, and 35.0% (n=2,515) were female. The participants received deceased-donor kidney transplants from 4,102 donors. The median donor age was 55 years. Median follow-up was 3.9 years.

Median TTD was 15 minutes (range, 0-407 minutes). An estimated 5,635 transplants were performed from donors with TTD of less than 30 minutes, 663 from donors with TTD of 30 to less than 60 minutes, 582 from donors with TTD of 1 to 2 hours, 261 from donors with TTD of 2 to 3 hours, and 42 from donors with TTD of more than 3 hours.

The association of TTD with recipient 12-month eGFR was assessed using a multiple linear regression model, adjusting for a wide range of factors. There was no association between donor TTD and recipient 12-month eGFR; the difference in 12-month eGFR per doubling of TTD was –0.25 (95% CI, –0.68 to 0.19; *P*=0.27). There were associations between increasing cold ischemic time (CIT) and worsening 12-month eGFR, as well as between increasing reperfusion time (also called second warm ischemic time) and worsening 12-month eGFR.

The association between donor TTD and delayed graft function was examined using a multivariable logistic regression model, adjusting for the same set of potential confounders. No association was observed between donor TTD and delayed graft function (adjusted odds ratio, 1.01; 95% CI, 0.97-1.06; *P*=0.65) each time TTD doubled.

Independent associations existed between increasing asystolic time, CIT, and second warm ischemic time and increased odds of delayed graft function. There was no association between nephrectomy time and increased odds of delayed graft function. Those findings were not changed in sensitivity analyses adjusting for year of transplant, recipient hospital, machine perfusion, and highly sensitized patients.

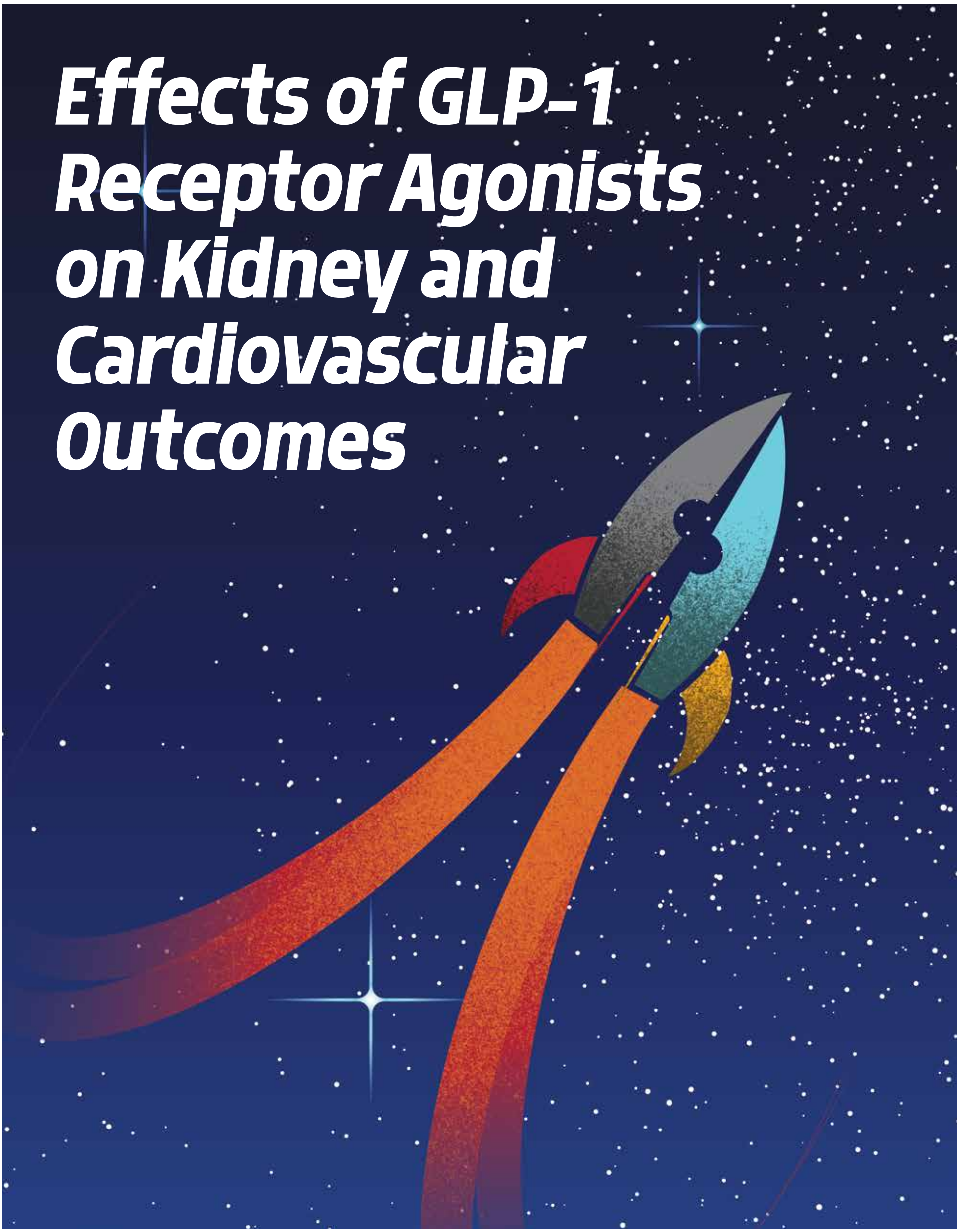
The association between donor TTD and graft survival was assessed using a multivariable Cox proportional hazards regression model (censored at 5 years; 799 events). There was no association between TTD and graft survival (adjusted hazard ratio for graft survival, 1.00; 95% CI, 0.95-1.07; *P*=0.92) each time TTD doubled. There were independent associations between CIT and second warm ischemic time and graft survival. There were no associations between graft survival and asystolic time and nephrectomy time. The findings were confirmed on restricted cubic spline modeling, revealing the association between donor age and graft survival to be nonlinear.

Compared with a theoretical wait time of 1 hour, the UK policy of a long DCD wait time of 3 hours has been associated with an estimated 885 extra transplants compared with 6,298 transplants between 2013 and 2021 (14.1% increase). Compared with a 2-hour wait time, the UK policy has been associated with 303 extra transplants compared with 6,880 transplants (4.4% increase).

The researchers cited some limitations to the study findings, including the registry cohort design and the inherent potential for selection bias.

In conclusion, the authors said, "In this cohort study of recipients of a DCD kidney, donor TTD was not associated with kidney transplant outcomes. This is by far the largest study to date on the topic, to our knowledge, and included a significant number of transplants from donors with TTD over 2 hours. Our results therefore challenge ODOs and transplant services internationally, most of which have maximum wait times of 1 to 2 hours. We show that meaningful increases to transplant numbers can be safely achieved by organizations that currently implement more conservative maximum wait times. We also suggest that 3 hours should not be used as a hard cutoff, and prolonging wait time beyond 3 hours should be a balance between ODO logistics and the likelihood of proceeding." ●

Effects of GLP-1 Receptor Agonists on Kidney and Cardiovascular Outcomes



Type 2 diabetes, chronic kidney disease (CKD), and cardiovascular disease overlap in many ways. Therefore, prevention of cardiovascular and kidney disease events is a major focus of type 2 diabetes, CKD, and obesity management.

Glucagon-like peptide-1 (GLP-1) receptor agonists have emerged as an important new advancement in the management of cardiovascular-kidney-metabolic syndrome. Although research has demonstrated that GLP-1 receptor agonists significantly reduce major adverse cardiovascular events (MACE) and composite kidney outcomes in individuals with type 2 diabetes, questions remain.

Composite kidney outcomes in previous trials were assessed as secondary outcomes, and reported effects were mostly driven by a lower risk of new-onset macroalbuminuria. It is unclear whether GLP-1 receptor agonists reduce the risk of important clinical outcomes, including kidney failure, and whether patients without diabetes could benefit from GLP-1 receptor agonist treatment for cardiovascular and kidney outcomes.

Researchers led by **Sunil V. Badve, MBBS, MD, DNB, PhD,** conducted a literature search and meta-analysis of aggregate data from randomized controlled trials to illuminate these issues. Their results were published in *Lancet Diabetes & Endocrinology* [doi:10.1016/S2213-8587(24)00271-7].

Eligible studies for inclusion were randomized controlled trials, had at least 500 participants with type 2 diabetes, compared a GLP-1 receptor agonist with placebo, included at least 12 months of follow-up, and reported a primary clinical kidney or cardiovascular outcome. Studies were identified using MEDLINE, Embase, and the Cochrane Central Register of Controlled Trials. In addition, authors of the FLOW trial provided their data.

The primary kidney disease outcome was a composite of kidney failure (kidney replacement therapy or a persistent estimated glomerular filtration rate [eGFR] <15 mL/min/1.73 m^2), a sustained reduction in eGFR from baseline by 50% or more, or death due to kidney disease.

When the eGFR reduction data were not available, researchers analyzed the nearest reported equivalent. When data on the composite kidney outcome were not available, they included kidney failure as the primary outcome.

The primary cardiovascular outcome was MACE (cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke). Secondary outcomes comprised kidney failure, a 50% or more (or nearest equivalent) sustained reduction in eGFR, individual components of MACE, all-cause death, and hospitalization for heart failure.

Key adverse outcomes included medullary thyroid cancer, pancreatic cancer, acute pancreatitis, severe hypoglycemia, and retinopathy. Subgroup analyses were conducted for age, sex, BMI, cardiovascular disease, eGFR, type of GLP-1 receptor agonist, frequency of administration, and median duration of follow-up.

The researchers used a random-effects approach on the assumption that the true effect could vary among studies. They also performed leave-1-out meta-analyses for the primary composite kidney and MACE outcomes to examine the influence of each study on the overall effect size estimate. In addition, heterogeneity across studies was estimated with the I^2 test. Subgroup analyses were performed to compare overall treatment estimates across participants with or without type 2 diabetes.

The researchers analyzed 11 trials from 21 full-text articles including 85,373 participants, of whom 29,386 were female and 55,987 were male. The median sample size was 6,068 participants (range, 3,183-17,604). Median follow-up duration was 25.2 months (range, 15.9-64.8). Participants' key baseline characteristics were well-balanced between groups. The mean baseline eGFR was 77.2 mL/min/1.73 m^2.

The primary outcomes were a 5-component kidney disease outcome including cardiovascular death (1 trial), a 3-component MACE outcome (8 trials), and a 4-component MACE outcome including hospitalization for unstable angina (2 trials).

Among participants with type 2 diabetes (n=67,769), GLP-1 receptor agonists reduced the composite kidney outcome by 18% compared with placebo (hazard ratio [HR], 0.82; 95% CI, 0.73-0.93; I^2=26.41%) and reduced kidney failure by 16% (HR, 0.84; 95% CI, 0.72-0·99; I^2=0%). In addition, GLP-1 receptor agonists reduced MACE by 13% (HR, 0.87; 95% CI, 0.81-0.93; I^2=49·75%) and all-cause death by 12% (HR, 0.88; 95% CI, 0.83-0.93; I^2=0%) compared with placebo.

The effect remained consistent for the composite kidney outcome (HR, 0.81; 95% CI, 0.72-0.92; I^2=23·11%), kidney failure (HR, 0.84; 95% CI, 0.72-0.98; I^2=0%), MACE (HR, 0.86; 95% CI, 0.80-0.92; I^2=48·9%), and all-cause death (HR, 0.87; 95% CI, 0.82-0.91; I^2=0%) when the SELECT trial, which enrolled participants with no history of diabetes, was included. There was no evidence of heterogeneity between this trial and those including participants with type 2 diabetes ($P_{heterogeneity}$>0.05).

Among participants with type 2 diabetes, GLP-1 receptor agonists reduced the composite kidney outcome by 18% compared with placebo and reduced kidney failure by 16%.

The risk of serious adverse events, including acute pancreatitis and severe hypoglycemia, did not differ between the GLP-1 receptor agonist and placebo groups (risk ratio [RR], 0.95; 95% CI, 0.90-1.01; I^2=88·5%). However, treatment discontinuation due to adverse events occurred more often in the GLP-1 receptor agonist groups (RR, 1.51; 95% CI, 1.18-1.94; I^2=96·3%).

The authors acknowledge some limitations of their study. Definitions of kidney disease outcomes were not consistent across trials. Event rates of kidney failure were low in all trials except FLOW, and the reduction in risk of the composite kidney disease outcome may have been due to the outcome of sustained reduction in eGFR by 50% or more (or the nearest equivalent).

Kidney disease was not the primary outcome in any of the included trials except FLOW. Subgroup analyses according to participant-level baseline characteristics were not conducted due to the unavailability of data. Subgroup analyses by diabetes status were also limited because the SELECT trial was the only trial that enrolled participants without diabetes. Lastly, all trials included were industry funded.

In conclusion, the authors said that the study provides high-certainty evidence that GLP-1 receptor agonists significantly reduce the risk of clinically important cardiovascular and kidney outcomes. "Taken together," they wrote, "these results and the breadth of the benefits observed support an important role for GLP-1 receptor agonists as kidney-protective and heart-protective medications that could play an important role in addressing the global burden of noncommunicable diseases, particularly in people with type 2 diabetes, chronic kidney disease, or overweight and obesity." ●

FDA Approves First Xenotransplant Trial of Gene-Edited Pig Kidney

United Therapeutics announced that the FDA has granted the company approval to begin a first-in-human clinical study of a gene-edited pig kidney. The study focuses on UKidney, which is derived from a 10-gene–edited source pig.

The purpose of the multicenter, open-label study is to determine the efficacy and safety of UKidney to support FDA approval of a Biologics License Application. The study will initially enroll 6 patients and expand to up to 50 participants.

Participants will come from 2 groups: patients with end-stage renal disease (ESRD) who have been assessed and determined to be ineligible for a conventional allogeneic kidney transplant for medical reasons and patients with ESRD who are on the kidney transplant waitlist but are more likely to die or go without a transplant than receive a deceased donor kidney transplant within 5 years.

The first xenotransplant in the trial is expected to occur in mid-2025.

Monlunabant Fails, Ozempic Triumphs for Novo Nordisk

In its financial report for 2024, Novo Nordisk announced that a phase 2 trial of the small molecule oral cannabinoid receptor 1 inverse agonist monlunabant failed to meet its primary end point.

The trial examined the efficacy and safety of a once-daily 10-mg and 25-mg dose of monlunabant versus placebo at improving urine albumin-creatinine ratio after 16 weeks in 254 individuals with diabetic kidney disease. The most common adverse events were gastrointestinal, but neuropsychiatric side effects were also reported and were more frequent with monlunabant than placebo. Currently, the drug is being evaluated for further clinical development for kidney disease.

The disappointing news was tempered by the label expansion for Ozempic (semaglutide) in the United States and European Union, extending the drug's use to kidney indications based on positive results from the FLOW trial. FLOW showed that the glucagon-like peptide-1 receptor agonist helped cut the risk of death from chronic kidney disease and major cardiac events by 24%.

Travere Aims to Expand Use of Sparsentan to FSGS

Travere Therapeutics completed a Type C meeting with the FDA and plans to submit a supplemental New Drug Application requesting traditional approval of Filspari (sparsentan) for focal segmental glomerulosclerosis (FSGS) by the end of the first quarter of 2025.

If approved, sparsentan could become the first and only FDA-approved medicine for the treatment of FSGS, a rare kidney disorder and leading cause of kidney failure that affects more than 40,000 patients in the United States.

The phase 3 DUPLEX trial showed that sparsentan delivered clinically meaningful benefit at 108 weeks with significant proteinuria reduction, higher rates of partial and complete remission, and a lower rate of end-stage renal disease compared with the active control. The phase 2 DUET study demonstrated a greater than 2-fold reduction in proteinuria with sparsentan compared with irbesartan.

Currently, sparsentan is indicated to slow kidney function decline in adults with primary immunoglobulin A nephropathy at risk for disease progression.

KidneyVault Renal Perfusion System Used in 4 Successful Transplants

Paragonix Technologies announced that its KidneyVault Portable Renal Perfusion System has been used in human kidney transplants for the first time. The cases included the successful transport of 4 donor kidneys to 4 separate medical institutions across the country in a 24-hour period last December.

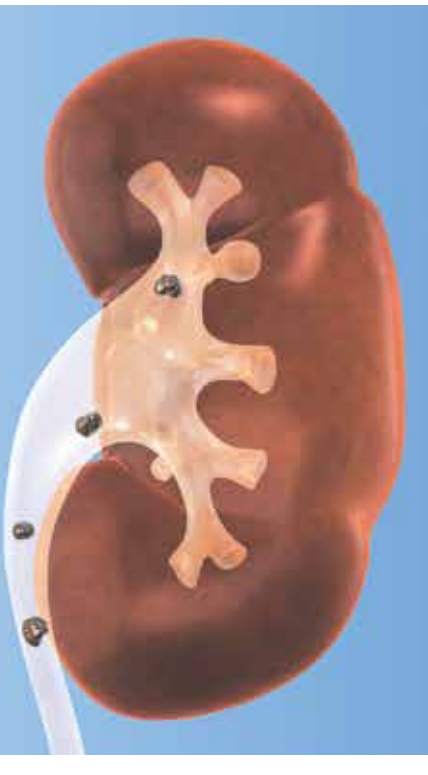
Updates to the national kidney allocation policy in recent years have enabled broader distribution and increased the volume of transplant offers. However, extended transport times result in longer cold ischemia times, requiring the use of perfusion to sustain the viability of donor kidneys.

Approved by the FDA in October 2024, KidneyVault is a lightweight device designed for convenient end-to-end hypothermic perfusion. Organ procurement organizations and transplant centers can remotely monitor the device and view perfusion parameters, temperature conditions, and other critical data in real time.

ABO-101 Receives 2 FDA Designations for Treating PH1

Arbor Biotechnologies announced that the FDA has granted orphan drug designation (ODD) and rare pediatric disease designation (RPDD) to ABO-101 to treat primary hyperoxaluria type 1 (PH1). The rare genetic kidney disease, which often presents in children, is associated with an overproduction of oxalate and can cause kidney stones, kidney damage, and kidney failure.

The ODD and RPDD programs support the development and evaluation of new treatments for serious and life-threatening rare diseases affecting fewer than 200,000 people or children younger than 18 years, respectively.



ACUTE KIDNEY INJURY

Urine Output Thresholds for Defining and Staging Pediatric AKI

Clinical Journal of the American Society of Nephrology. 2024;19(10):1230-1239.

Although pediatric acute kidney injury (AKI) is associated with considerable morbidity and mortality, a precise definition, particularly regarding urine output (UO) thresholds, remains elusive. **Adriana Torres de Melo Bezerra Girão** and colleagues wanted to understand the optimal thresholds for defining and staging AKI in neonates and children aged 1 to 24 months and compare them with currently used Kidney Disease: Improving Global Outcomes (KDIGO) criteria.

They conducted a prospective cohort study from 2018 to 2023 of patients who had cardiac surgery at a reference center in Brazil, had indwelling urinary catheters up to 48 hours after surgery, and had at least 2 serum creatinine measurements, including 1 before surgery. The primary study outcome was a composite of severe AKI (stage 3 AKI diagnosed solely by serum creatinine criterion), kidney replacement therapy, or hospital mortality.

Of the 1,024 patients included in the study, 772 were younger children (aged 1 to 24 months) and 253 were neonates. The lowest UO at 24 hours as a continuous variable demonstrated good discriminatory capacity for the composite outcome in both groups (area under the curve–receiver operating characteristic [AUC-ROC], 0.75; 95% CI, 0.70-0.81 for neonates and AUC-ROC, 0.74; 95% CI, 0.68-0.79 for younger children). In the neonate group, the optimal thresholds were 3.0, 2.0, and 1.0 mL/kg per hour. In the group of younger children, the best thresholds were 1.8, 1.0, and 0.5 mL/kg per hour.

Those optimal thresholds were then used for modified AKI staging for each age group. In the group of younger children, the modified criteria had discriminatory capacity comparable to that of the adult KDIGO criteria; the net improvement with the reclassification was near zero.

However, in the neonate group, the modified criterion was associated with discriminatory capacity superior to that of the current KDIGO criteria (AUC-ROC, 0.74; 95% CI, 0.67-0.80 vs AUC-ROC, 0.68; 95% CI, 0.61-0.75; $P<0.05$). The modified criterion was also associated with a net improvement compared with the neonatal KDIGO criteria (AUC-ROC, 0.74; 95% CI, 0.67-0.80 vs AUC-ROC, 0.68; 95% CI, 0.61-0.75; $P<0.05$).

In summary, the study results suggest that KDIGO criteria for the definition and staging of AKI in neonates may need adjustment.

CHRONIC KIDNEY DISEASE

Intensive Home Blood Pressure Lowering in Advanced CKD

American Journal of Kidney Diseases. doi:10.1053/j.ajkd.2024.08.010

When efforts at intensive blood pressure (BP) lowering are initiated for patients with advanced chronic kidney disease (CKD), there is a potential risk of AKI, hyperkalemia, and end-stage renal disease (ESRD). **Elaine Ku, MD,** and colleagues conducted a nonblinded, randomized, controlled pilot trial to help determine whether lower home systolic BP (SBP) targets can be safely achieved in patients with CKD through titration of BP medications using in-home–measured BP.

The study examined 108 patients with advanced CKD (estimated glomerular filtration [eGFR] ≤30 mL/min/1.73 m^2) and hypertension who were randomized to either a target SBP goal of less than 120 mm Hg (n=66) or a less intensive goal (n=42). Antihypertensive medications were titrated to achieve the target home SBP range within the first 4 months of the study. The medications were maintained through the end of the study period. A wireless Bluetooth-enabled monitor was used to measure home BP and transmit real-time readings to clinicians.

Efficacy and safety were evaluated. The primary efficacy outcome was the difference in achieved clinic SBP between the 2 study groups from months 4 through 12. The safety outcomes comprised hyperkalemia, a composite outcome of falls or syncope, and onset of a need for dialysis or kidney transplantation.

The mean clinic SBP at month 12 was 124.7 mm Hg in the intensive SBP goal group and 138.2 mm Hg in the less intensive SBP goal group. The achieved mean clinic SBP in the intensive goal arm was 11.7 mm Hg (95% CI, 7.5-16; $P<0.001$) lower than that achieved in the less intensive goal group, on average, over months 4 through 12. There was no statistically significant difference in safety outcomes between the 2 groups (all $P>0.05$).

The study found that a clinic SBP goal of less than 120 mm Hg can be safely achieved through real-time home BP monitoring in the study population. However, the sample size was small, so larger trials are needed to determine optimal BP targets for patients with advanced CKD and to assess the risks and benefits associated with more intensive BP control.

Genetic Testing in CKD of Unknown Origin

Nephrology Dialysis Transplantation. doi:10.1093/ndt/gfae270

The underlying cause of CKD is unknown in at least 20% of patients. Massive parallel sequencing (MPS) could help with diagnosis in such patients, but prospective data from routine clinical practice are limited.

Amber de Haan, MD, PhD, and colleagues wanted to understand the diagnostic yield and relevance of MPS-based gene panel testing in patients with unexplained CKD in a real-world context. Their prospective cohort study also examined barriers to genetic testing implementation.

Study participants comprised patients with CKD of unknown origin (eGFR <60 mL/min/1.73 m^2 without underlying clinical diagnosis) with onset before age 50 years. Participants had MPS-based multigene panel testing at 11 hospitals (academic and nonacademic) across the Netherlands. When a pathogenic variant was identified, the researchers verified that the variant likely explained the clinical phenotype.

Of 340 participants, 59 (17%) had a diagnostic variant identified. The most common variants occurred in *NPHP1* (n=13), *COL4A3* (n=12), *COL4A4* (n=5), *COL4A5* (n=6), and *PAX2* (n=5). In 73% of patients, a genetic diagnosis resulted in at least 1 clinical consequence.

To gain insight into barriers to gene panel testing, the researchers distributed an online survey to all Dutch nephrologists and residents. The barriers most frequently reported by 71 survey respondents were genetic illiteracy (53%), difficulties with test selection (51%), and lack of time (43%).

The findings support the relevance of MPS in diagnosing adults with unexplained CKD and highlight the need to better educate nephrologists about genetics to increase clinical implementation of MPS-based diagnostic testing.

Effects of Exercise on Cognitive Function in Patients With CKD

Clinical Journal of the American Society of Nephrology. 2024;19(11):1461-1472.

Individuals who have CKD are at risk for cognitive impairment. Physical activity may improve cognitive function. Therefore, **Ellen Bradshaw** and colleagues wanted to determine the efficacy of exercise in improving cognitive function in people with CKD and the potential harm exercise might cause. They conducted a systematic review and meta-analysis of randomized controlled trials.

The literature review identified randomized controlled trials that enrolled patients with CKD and included an exercise intervention that worked large-muscle groups and a validated outcome measure of cognitive function. The analyses included 19 trials and 1,160 participants.

The researchers first assessed harm from exercise. There were 94 reports of harm in the intervention groups and 83 in control groups.

Next, they conducted a random-effects meta-analysis with subsequent planned subgroup analyses to examine heterogeneity between CKD stages and treatments; different exercise types, durations, and intensities; and different outcome methodologies. This was followed by rating the quality of the evidence.

In the primary analysis, exercise was shown to have a statistically significant, although small, effect on cognition in patients with CKD (effect size, 0.22; 95% CI, 0.00-0.44; $P=0.05$). However, the quality of the evidence was low. The subgroup analyses revealed that the type of exercise moderated its effect on cognition ($\chi^2=7.62$; $P=0.02$), with aerobic exercise having

only positive effects (effect size, 0.57; 95% CI, 0.21-0.93; *P*=0.002).

In conclusion, the effects of exercise on cognitive function were small but clinically significant. The effects were also positive, particularly in the case of aerobic exercise. Although the quality of evidence in this study was rated as low, exercise may be recommended to prevent cognitive decline. The authors note that studies are needed to determine the intensity and duration of exercise required to maximize the efficiency of such exercise interventions.

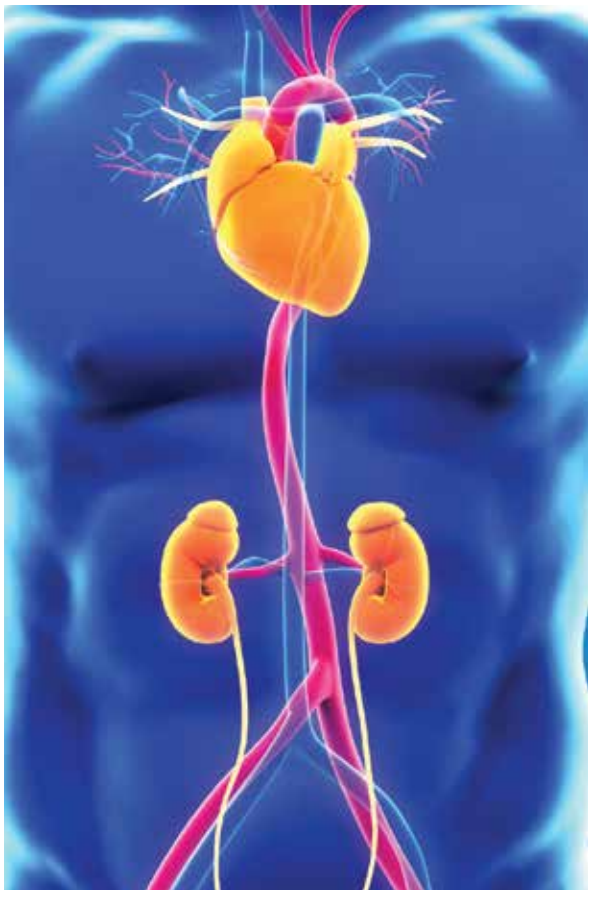
Spironolactone and Cardiovascular Outcomes in CKD

Nature Medicine. 2024;30(12):3634-3645.

With CKD, there is substantial risk of progression to ESRD and vascular events. Finerenone, a nonsteroidal mineralocorticoid receptor antagonist (MRA), provides cardiorenal protection for individuals who have CKD and diabetes. However, it is unclear whether the steroidal MRA spironolactone provides comparable protection.

To examine the question, **F. D. Richard Hobbs, FMedSci,** and colleagues conducted a prospective, randomized, open, blinded end point trial. The study evaluated the effectiveness of 25 mg spironolactone plus usual care versus usual care alone for reducing adverse cardiovascular outcomes in stage 3b CKD in a cohort of older adults in the community.

The cohort comprised 1,434 adults, mean (SD) age 74.8 (8.1) years, from English primary care. Of them, 1,372 (96%) were included in the primary analysis, with 677 randomized to spironolactone and 695 randomized to usual care. The primary outcome was the time from randomization until the first occurrence of death; hospitalization for heart disease, stroke, heart failure, transient ischemic attack, or peripheral arterial disease; or first onset of any condition not noted at baseline.



During 3 years of follow-up, the primary end point occurred in 113 (16.7%) participants in the spironolactone group and 111 (16.0%) participants in the usual care group. No significant difference between the groups was observed (hazard ratio [HR], 1.05; 95% CI, 0.81-1.37).

Two-thirds of participants in the spironolactone group stopped treatment within 6 months, most often due to a decrease in eGFR that met prespecified stop criteria (n=239; 35.4%), followed by withdrawal due to treatment side effects (n=128; 18.9%) and hyperkalemia (n=54; 8.0%).

Spironolactone was frequently discontinued because of safety concerns, and there was no evidence that it reduced adverse cardiovascular outcomes. In summary, spironolactone should not be used for patients with stage 3b CKD unless there is another explicit treatment indication.

Effects of Canagliflozin on Iron Metabolism in Patients With CKD

Nephrology Dialysis Transplantation. doi:10.1093/ndt/gfae198

Previous studies of people with heart failure have shown that sodium-glucose cotransporter-2 inhibitors (SGLT2i) increase iron use and exacerbate erythropoiesis. In a post hoc analysis of data from the CREDENCE trial, **Akihiko Koshino, MD, PhD,** and colleagues studied the effects of canagliflozin on iron metabolism in participants with CKD and sought to determine whether iron deficiency modified the effects of canagliflozin on hemoglobin and cardiorenal outcomes.

The researchers measured the serum iron, total iron binding capacity (TIBC), transferrin saturation (TSAT), and ferritin of 4,401 randomized participants at baseline and 12 months. They used analysis of covariance to evaluate the effects of canagliflozin on iron markers, compared with placebo. Mixed-effect models and Cox regression models were used to study interactions between baseline iron deficiency (TSAT <20%) and the effects of canagliflozin on hemoglobin and cardiorenal outcomes, respectively.

At baseline, 2,416 (54.9%) participants had iron markers measured; 924 (38.2%) were found to have iron deficiency. Canagliflozin increased TIBC by 2.1% (95% CI, 0.4-3.8; *P*=0.014) and decreased ferritin by 11.5% (95% CI, 7.1-15.7; *P*<0.001) compared with placebo but had no clear effect on serum iron or TSAT. In addition, canagliflozin increased hemoglobin over the trial period by 7.3 g/L (95% CI, 6.2-8.5; *P*<0.001) in participants with iron deficiency and by 6.7 g/L (95% CI, 5.2-8.2; *P*<0.001) in participants without iron deficiency (*P*-interaction=0.38).

The relative effect of canagliflozin on the primary outcome of doubling of serum creatinine, kidney failure, or death due to cardiovascular disease or kidney failure (HR, 0.70; 95% CI, 0.56-0.87) remained consistent regardless of iron deficiency (*P*-interaction=0.83). Canagliflozin's effects on other cardiovascular and mortality outcomes were also consistent regardless of iron deficiency (all *P*-interactions ≥0.10).

In sum, iron deficiency is prevalent among individuals with type 2 diabetes and CKD, and canagliflozin increased TIBC and decreased ferritin in such patients, implying increased iron utilization. In addition, the drug improved hemoglobin levels and clinical outcomes regardless of iron deficiency.

DIALYSIS

Outcomes of Incremental Versus Standard Peritoneal Dialysis

BMC Nephrology. doi:10.1186/s12882-024-03669-w

The efficacy and safety of incremental peritoneal dialysis (IPD) compared with standard full-dose peritoneal dialysis (SPD) are uncertain. IPD refers to the use of less than SPD in patients with ESRD. To provide clarity, **Shuang Xu** and colleagues conducted a systematic review of studies comparing mortality, peritonitis, technique survival, anuria-free survival, and residual renal function (RRF) between IPD and SPD.

The researchers included 10 studies in the analysis. All comparative studies from the PubMed, Embase, CENTRAL, Scopus, and Web of Science databases published from inception to September 5, 2023, and reporting on given outcomes were eligible for inclusion.

Qualitative synthesis was used to account for the heterogeneity of definitions of IPD. Most of the included studies did not demonstrate a difference in patient survival with IPD compared with SPD, nor did meta-analysis of crude mortality data reveal a difference. Peritonitis and technique survival did not differ significantly between IPD and SPD in most studies. However, data regarding RRF was conflicting, with some studies finding that IPD was associated with the preservation of RRF while others did not.

In summary, IPD could provide a safe alternative to SPD for patients receiving incident dialysis. There appears to be no significant difference between the 2 modalities regarding patient survival, peritonitis, and technique survival. However, the impact of IPD on RRF remains unclear.

Serum Phosphate, Difelikefalin, and Pruritus Severity in CKD

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Steven N. Fishbane, MD, and colleagues conducted a post hoc analysis of data from 3 phase 3 studies (KALM-1, KALM-2, and open-label Study 3105) involving difelikefalin, a novel antipruritic agent approved for the treatment of moderate to severe CKD-associated pruritus (CKD-aP) in adults receiving hemodialysis.

CKD-aP is associated with elevated serum phosphate (sP). This analysis examined the role of sP in the pathogenesis of CKD-aP as well as whether difelikefalin relieves CKD-aP in patients with and without elevated sP.

The analysis included patients with moderate to severe CKD-aP undergoing hemodialysis with baseline sP data. Eight hundred forty-five participants were sourced from the KALM-1 and KALM-2 studies, and 220 participants were from Study 3105.

The researchers assessed the correlation between 24-hour Worst Itching Intensity Numerical Rating Scale (WI-NRS) score and sP. Among participants from KALM-1 and KALM-2, baseline characteristics in the overall population were similar in patients with sP ≤5.5 and >5.5 mg/dL. There was no significant correlation between WI-NRS and sP at baseline or in week 12. Similarly, no correlation was found between WI-NRS and sP at baseline or between their change from baseline to week 12 among patients receiving placebo (all *P*<0.05).

More participants receiving placebo with baseline sP ≤5.5 mg/dL experienced clinically meaningful (≥3-point) reductions in WI-NRS scores from baseline to week 12 than those receiving placebo with baseline sP >5.5 mg/dL (least squares mean, 37.2% vs 27.4%; odds ratio, 0.63; 95% CI, 0.41-0.97; *P*=0.04).

A greater percentage of patients receiving difelikefalin achieved a ≥3-point WI-NRS reduction from baseline to week 12 compared with those receiving placebo. This was similar between sP ≤5.5 and >5.5 mg/dL subgroups (least squares means, 51.1% vs 57.6%; *P*=0.20). No significant relationships between sP and WI-NRS were observed in patients receiving difelikefalin in Study 3105 at any time point.

In conclusion, there was no observed correlation between the severity of pruritus and sP or the response to placebo or difelikefalin among patients with CKD-aP receiving hemodialysis. Regardless of baseline sP, difelikefalin relieved itch when compared with placebo.

Cardiovascular Safety, Efficacy of Denosumab Versus Oral Bisphosphonates in Patients on Dialysis

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Although individuals receiving dialysis have high rates of fracture morbidity, few data regarding optimal management of osteoporosis are available. Therefore, **Soichiro Masuda, MD,** and colleagues sought to determine the risk for cardiovascular events and fracture prevention benefits of denosumab versus oral bisphosphonates in dialysis-dependent patients.

The researchers conducted an observational study emulating a target trial using data from a Japanese administrative claims database spanning from April 2014 to October 2022. Participants were dialysis-dependent adults aged 50 years and older receiving denosumab or oral bisphosphonates for osteoporosis. The follow-up period was 3 years. The safety outcome was major adverse cardiac events (MACE), and the effectiveness outcome was a composite of all fractures.

The study included a total of 1,032 participants, 658 receiving denosumab and 374 receiving oral bisphosphonates. The average participant age was 74.5 years and 62.9% were women.

The weighted 3-year risk difference for MACE was 8.2% (95% CI, -0.2% to 16.7%) with a weighted 3-year risk ratio of 1.36 (95% CI, 0.99-1.87). The weighted 3-year risk difference for composite fractures was -5.3% (95% CI, -11.3% to -0.6%) with a weighted three-year risk ratio of 0.55 (95% CI, 0.28-0.93).

Denosumab was found to lower the risk for fractures by 45% and increase the risk for MACE by 36% compared with bisphosphonates. However, the authors warn that their estimates are imprecise and confirmational studies are needed.

DIABETES

Effects of SGLT2i Versus GLP-1RA in Veterans with Type 2 Diabetes

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To examine kidney end points between patients with type 2 diabetes 36 months after they began taking an SGLT2i or glucagon-like peptide 1 receptor agonist (GLP-1RA), **Candis M. Morello, PharmD,** and colleagues conducted a retrospective cohort study. Secondary goals of the study included comparing changes in eGFR, HbA1c, weight, and urine albumin-creatinine ratio (UACR).

The study included 29,146 propensity score–matched veterans with type 2 diabetes and baseline eGFR >20 mL/min/1.73 m^2 who started taking an SGLT2i or GLP-1RA (n=14,573 for each group) between April 1, 2009, and September 1, 2020.

The researchers used Cox proportional hazard models to assess the effectiveness of each therapy in achieving a composite end point (decline of ≥40% in eGFR from baseline, ESRD event, and all-cause mortality) and its components, adjusting for baseline characteristics. They used spline models to evaluate eGFR changes and linear mixed-effects models to assess changes in HbA1c, weight, and UACR.

The primary analysis took an intent-to-treat (ITT) approach, which was followed by a per-protocol (PP) approach, excluding participants who discontinued or changed therapy during the study period. In both analyses, participants who initiated SGLT2i therapy had a 35% (HR, 0.65; 95% CI, 0.62-0.68) and 34% (HR, 0.66; 95% CI, 0.62-0.69) reduction in the hazard of experiencing the composite end point compared with participants who initiated GLP-1RA therapy, respectively, adjusting for baseline characteristics.

In both ITT and PP analyses, between 6 and 36 months, an improved chronic eGFR slope was found with SGLT2i compared with GLP-1RA (+1.19 mL/min/1.73 m^2; 95% CI, 0.93-1.45 and +1.29 mL/min/1.73 m^2; 95% CI, 1.01-1.57). The annual differences in chronic eGFR slope in both analyses were +0.97 mL/min/1.73 m^2 per year (95% CI, 0.82-1.11) and +1.08 mL/min/1.73 m^2 per year (95% CI, 0.92-1.25), respectively.

HbA1c, weight loss, and UACR improved for both groups.

In summary, in a cohort of veterans with type 2 diabetes, the initiation of an SGLT2i was associated with a reduced hazard of mortality, worsening eGFR, or development of ESRD, as well as improved glycemic, metabolic, and renal end points compared with GLP-1RA initiation. ●

Sarah Tolson

Navigating Medicare's Phosphate Binder Challenge: Insights From the Field

During the latter part of 2024, I met with dialysis program administrators to assess the impact of Medicare's change requests 13686 and 13865 on their programs. These changes, which implement system modifications for the 2025 End-Stage Renal Disease (ESRD) Prospective Payment System (PPS), have significant implications for compliance, documentation, and billing—particularly for phosphate binders.

My discussions included administrators from a variety of dialysis programs, ranging from hospital-based and nursing home–based programs to small rural and pediatric centers, with both for-profit and nonprofit structures represented. This column highlights the most frequently voiced concerns and challenges program administrators face under the 2025 ESRD PPS requirements.

BILLING CHALLENGES, REIMBURSEMENT SURPRISES

One universal challenge reported was the difficulty of documenting phosphate binders in a way that seamlessly integrates with billing processes. Dialysis-specific electronic health records (EHRs) are designed to track and report medications administered during dialysis treatments, but oral medications taken at home, such as phosphate binders, historically have not been separately billable on dialysis claims. Even with prior experience managing oral calcimimetic documentation, dialysis EHR systems still struggle to efficiently capture and communicate the necessary data for phosphate binders, leading to administrative burdens and potential reimbursement issues.

Adding to the complexity, most programs entered supply contracts for phosphate binders before the end of 2024, yet the Centers for Medicare & Medicaid Services (CMS) did not release its allowed reimbursement amounts until January 2025. When these figures became available, several program administrators contacted me, questioning whether the CMS had published incorrect rates—only to realize that their contracted rates were nearly double the Medicare reimbursement amount. Without prior access to these figures, many programs inadvertently overpaid for essential medications, creating financial strain.

STRAINED RESOURCES

Another widespread concern was the financial viability of covering phosphate binder costs, particularly in states where Medicaid functions as a secondary payer and only issues payment when Medicare reimburses less than the Medicaid-allowed amount. Programs with a significant Medicare Advantage patient population faced additional financial pressures because many contracts provided a flat per-treatment payment for dialysis, with no added reimbursement for phosphate binders. In some cases, these agreements barely covered operational costs, let alone the additional expenses of these medications.

In response, many programs have opted to provide patients with only generic phosphate binders, regardless of patient preferences. This raises an ethical dilemma: In healthcare, we strive to provide care regardless of a patient's ability to pay, yet here, programs are forced to determine whether they can afford to supply the necessary medication.

In discussing these concerns, it is important to acknowledge that program administrators are navigating an increasingly complex landscape of financial constraints, regulatory requirements, and patient needs. Many administrators expressed frustration that, despite their best efforts to ensure compliance, they still found themselves facing unexpected financial shortfalls. Others pointed to the added administrative burden of tracking and reconciling medications, which pulls valuable time and resources away from direct patient care. These ongoing challenges make it clear that dialysis programs are being asked to do more with less, putting additional strain on already stretched teams.

COUNTING ON RESILIENCE

Despite these challenges, one thing remains clear: Dialysis programs have a history of adaptability and perseverance. When the ESRD PPS was first implemented in 2011, programs found creative solutions to sustain operations despite increased administrative demands and reduced reimbursement. Similarly, when calcimimetics lost Transitional Drug Add-On Payment Adjustment status, dialysis programs innovated with ways to ensure patients continued receiving calcimimetics when necessary. The current challenges with phosphate binders will require the same resourcefulness, and I have no doubt that the dialysis community will rise to the occasion once again.

Although uncertainty remains, the dedication of dialysis program administrators to problem-solving and patient care is unwavering. The resilience that has carried this industry through past payment model changes will continue to drive solutions, ensuring that patients receive the medications they need. The road ahead may be difficult, but history has shown that dialysis programs don't just survive change—they find ways to thrive. ●

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