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Practical News, Trends, and Analysis

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Effects of Patiromer Treatment in Patients With CKD and Hyperphosphatemia

Because phosphate excretion becomes impaired as kidney function declines, patients with chronic kidney disease (CKD) commonly develop hyperphosphatemia, defined as elevated serum phosphate levels >4.5 mg/dL. An analysis of data from a US health care system estimated the prevalence of hyperphosphatemia at approximately 7% among patients with estimated glomerular filtration rates of 30 to 39 mL/min/1.73 m^2 (CKD stage 3b), approximately 21% among those with eGFR 20 to 29 mL/min/1.73 m^2 (CKD stage 4), and more than 80% in patients with eGFR <20 mL/min/1.73 m^2 (CKD stage 4/5).

Patients with hyperphosphatemia face increased risks for mortality. The Kidney Disease: Improving Global Outcomes (KDIGO) guidelines recommend that serum phosphate in patients with CKD stage 3 and above should be lowered to within 2.5 to 4.5 mg/dl (normal range). Recommended treatment for lowering serum phosphate in patients with hyperphosphatemia includes use of phosphate binders. However, the KDIGO guidelines call for caution when managing serum phosphate in patients with CKD not on dialysis, and suggest consideration of the risk-benefit ratio of phosphate-lowering therapies. Phosphate binders are not approved for the treatment of patients with CKD not on dialysis in the United States.

Patiromer, a nonabsorbed, sodium-free potassium binder, uses calcium

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Disparities in Rates of Prescriptions for SGLT2 Inhibitors Among US Veterans

Since 2018, based on cardiovascular benefits seen in large clinical trials, recommendations for the treatment of type 2 diabetes mellitus in patients with chronic kidney disease (CKD) with estimated glomerular filtration rate (eGFR) ≥30 mL/min/1.73 m^2 have included use of sodium-glucose cotransporter-2 (SGLT2) inhibitors. In 2019, results from the CREDENCE (Canagliflozin and Renal Events in Diabetes with Established Nephropathy) trial demonstrated reductions in kidney end points in patients with CKD stages 2-3 who were randomized to canagliflozin

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Hemodiafiltration Offers Survival Benefit in Patients With Kidney Failure

The incidence of kidney failure is increasing worldwide. Patients with kidney failure are commonly treated with hemodiafiltration or hemodialysis. While practice differences across the globe may favor one method over the other, hemodialysis is used more often overall.

There have been four randomized, controlled trials examining possible survival benefits associated with hemodiafiltration versus hemodialysis. Of those four trials, three were inconclusive and the fourth demonstrated a survival benefit for hemodiafiltration. Results of a meta-analysis of individual patient data from the four trials indicated a survival benefit with hemodiafiltration when a convection volume was delivered at a high dose, with a putative threshold of at least 23 liters per session in postdilution mode.

Due to the inconsistency and limitations of the previously published studies, **Peter J. Blankestijn, MD,** and colleagues conducted a pragmatic, multinational, randomized, controlled trial among patients with kidney failure who had received high-flux hemodialysis for at least 3 months. Results were reported online in the *New England Journal of Medicine* [doi:10.1056/NEJMoa2304820].

The primary outcome of interest was death from any cause. Secondary outcomes included cause-specific mortality, composite fatal and nonfatal cardiovascualr events, kidney transplantation, and recurrent hospitalizations for any cause and for causes re-

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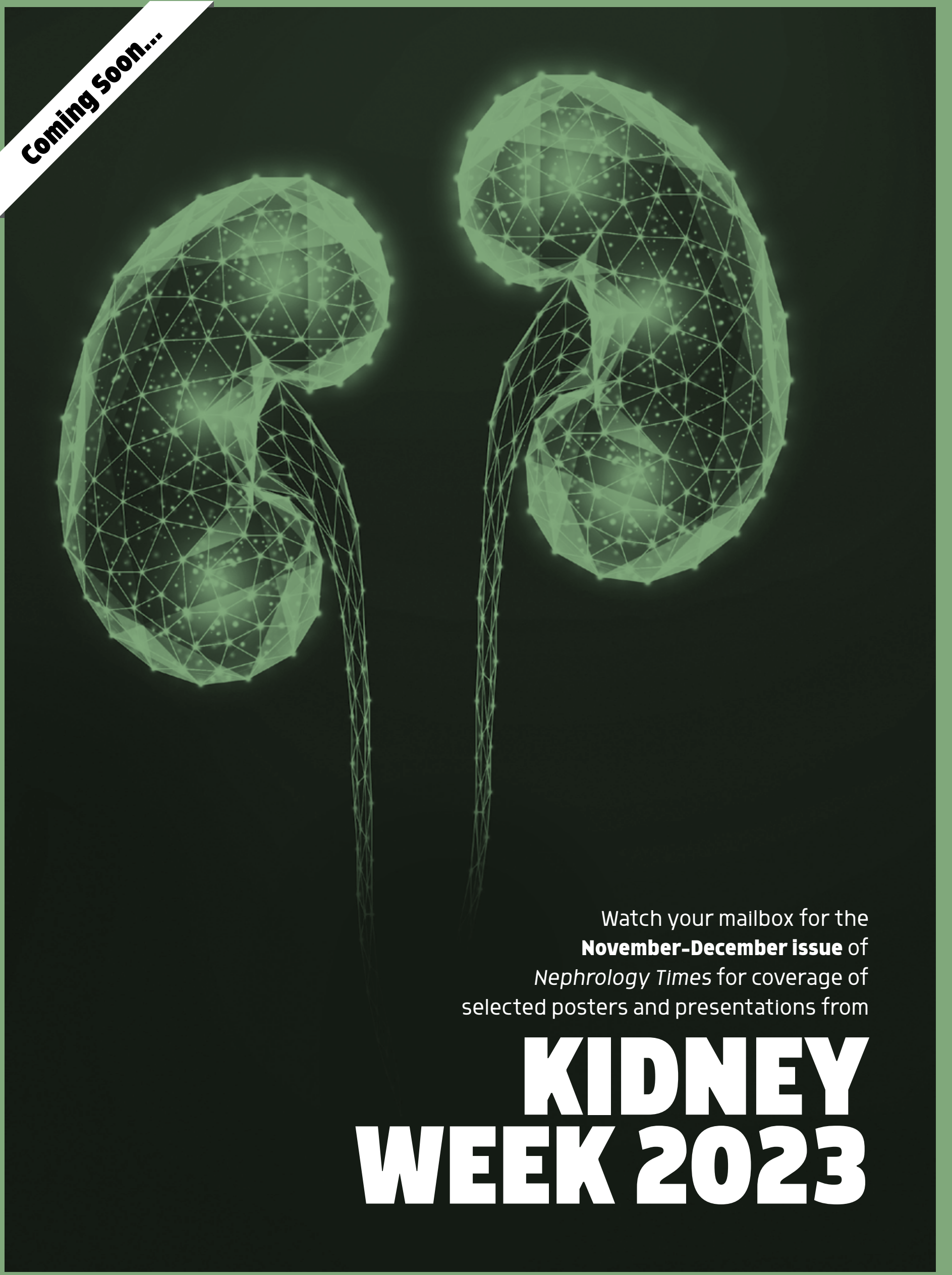
Coming Soon...
Watch your mailbox for the
November–December issue of
Nephrology Times for coverage of
selected posters and presentations from
KIDNEY
WEEK 2023

Support the Chronic Kidney Disease Improvement in Research and Treatment Act (HR 5027)

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For a few years I've written about the importance of the federal government investing in a dialysis moonshot. Nothing big has happened, at least so far. Recent surveys and, separately, by coincidence, a bill introduced by two members of the United States House Committee on Ways and Means, underscore that chronic kidney disease (CKD) awareness, detection, and treatment remains a big problem. Legislation before Congress is targeted to fix this issue. First, consider the poll data.

A survey conducted by the Global Coalition on Aging on a cohort of US adults (n=1000) asked about understanding and perception of CKD.[1] Only 58% of respondents had awareness of CKD, and this awareness was lower among elderly respondents, even though we know they have a higher prevalence of CKD.

In a separate survey of health care providers (HCPs) sponsored by Bayer Pharma,[2] 84% of respondents thought that patients with type 2 diabetes mellitus (T2DM) and CKD are unprepared for their diagnosis and that better communication about CKD is needed. The poll also reported that 89% of HCPs don't think patients with T2DM and CKD understand that they are at high risk of cardiovascular disease (CVD).

Writing about the lack of awareness and difficulty in treating CKD,[3] Rep. Carol Miller (R-WV) and Rep. Terri Sewell (D-AL) have introduced the Chronic Kidney Disease Improvement in Research and Treatment Act (HR 5027) to "expand access to prevention, education, and treatment efforts that will help patients and providers more effectively recognize and treat this silent killer."

They go on: "The Chronic Kidney Disease Improvement in Research and Treatment Act would incentivize innovation in kidney care. It will require Medicare to provide a long-term, sustainable payment pathway for new drugs, biologics, medical devices, and other technologies that can help diagnose and treat kidney disease. It would also help to ensure Medicare Advantage plans support access to innovative therapies and treatments that are not currently covered. By expanding access to cutting-edge treatment options, these provisions will lower costs and result in better care for our nation's kidney community."

Lack of awareness of CKD remains a major issue. The National Kidney Foundation has done a lot, such as promotion of estimated glomerular filtration rate (eGFR), the kidney risk equation, the kidney heat map, and so on. Likewise, the International Society of Nephrology has championed World Kidney Day each March. Still, if we believe the surveys I've cited, it doesn't seem to be enough. Unlike CVD, where awareness and education are high among HCPs and the general population, we don't have a similar situation with CKD. For example, the importance of measuring urinary albumin excretion (UACR) is not widely recognized or implemented. While this might change with its adoption as a Healthcare Effectiveness Data and Information Set measure later this year, there is very little promotion of UACR among the primary care community.

Does education of HCPs about CKD make a difference? Research is limited. A cursory search of PubMed revealed very little original research over the past 10 years. However, insightful conversations I had recently with Dr. Manisha Jhamb, an associate chief of nephrology in the Renal Division at the University of Pittsburgh, point to three things that seem to make a difference: outreach directly to primary care practices, use of the electronic medical record to identify at-risk patients, and use of academic detailing (individualized contact with HCPs either through eConsults or personalized emails) advising them on what therapies to consider and how to manage the complexities of treatment, such as the initial dip in eGFR one sees with initiation of a renin-angiotensin-aldosterone system inhibitor or sodium-glucose cotransporter-2 (SGLT2) inhibitor, or managing acute hyperkalemia.

The problem is that most health systems and health insurers are not motivated to increase awareness about CKD, because with greater awareness comes earlier detection and treatment, both of which increase cost to the system. However, this approach is short-sighted and doesn't consider the later consequences of CKD progression—heart failure hospitalizations, vascular complications, and even end-stage kidney disease (ESKD). In addition, the saying "more people die with CKD than progress to end-stage kidney disease" isn't a punchline, it is true and supported by good data. The human cost of not managing CKD remains high.

The recently introduced bill HR 5027 would help increase awareness and education and provide pathways for patients to access newer preventive treatments for CKD, such as SGLT2 inhibitors. It would also push Medicare Advantage plans to cover these newer treatments—something that would be a major benefit to seniors. The first part of the dialysis moonshot is to prevent the need for dialysis. Of course, we also need innovations in ESKD treatment. So, I am all for HR 5027 and will write to my congressional representative. You should too! ■

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Disparities in Rates of Prescriptions for SGLT2 Inhibitors

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compared with placebo. SGLT2 inhibitors are considered first-line therapy for patients with type 2 diabetes and CKD.

Treatment with SGLT2 inhibitors has been adopted by the Veterans Affairs (VA) Health Care System for patients with type 2 diabetes and comorbid CKD, atherosclerotic cardiovascualr disease (ASCVD), or heart failure. However, studies have reported underutilization of those agents. Other studies have spotlighted racial and ethnic disparities in prescription rates for SGLT2 inhibitors, possibly contributing to the underutilization.

L. Parker Gregg, MD, MSCS, and colleagues conducted a retrospective cohort study to examine factors associated with prevalent SGLT2 inhibitor prescription and disparities in patterns of SGLT2 inhibitor prescription by race and sex. They also examined facility-level variation in prescription patterns among patients with comorbid CKD, type 2 diabetes, and ASCVD with indications for treatment with an SGLT2 inhibitor. Results were reported in the *American Journal of Kidney Diseases* [2023;82(1):53-62].

The study cohort included a national sample of US veterans with comorbid CKD, type 2 diabetes, and ASCVD who had a primary care visit between January 1, 2020, and December 31, 2020. The study exposures were race, sex, and location of individual VA. The outcome of interest was prescription for a SGLT2 inhibitor.

Associations of race and sex with SGLT2 inhibitor prescription were assessed using multivariable logistic regression. Median rate ratios (MRR) were used to quantify facility-level variation in SGLT2 inhibitor prescription, expressing the likelihood that two randomly selected facilities would differ in their use of SGLT2 inhibitors among similar patients.

The researchers utilized national data from the US VA Corporate Data Warehouse to identify 174,443 patients with CKD, type 2 diabetes, and ASCVD across 130 VA locations and their affiliated outpatient clinics. The index date was the most recent primary care visit within the study period.

Of the 174,443 eligible patients, 11.5% (n=20,024) were prescribed an SGLT2 inhibitor. Veterans who received a prescription for an SGLT2 inhibitor were younger than those who were not prescribed an SGLT2 inhibitor (72.0 years vs 75.9 years; $P<.001$). The cohort was predominantly male in both groups.

The two groups differed in race, with SGLT2 inhibitor users comprising 80.0% White and 12.3% Black or African American patients; the non-SGLT2 inhibitor group included 79.7% White and 12.6% Black or African American patients ($P<.001$).

Patients in the SGLT2 inhibitor group were more likely to have systolic heart failure (26.5% vs 20.3%) and ischemic heart disease (86.3% vs 80.7%) but less likely to have peripheral arterial disease (23.7% vs 26.5%) and ischemic cerebrovascular disease (25.8% vs 28.0%), compared with the non-SGLT2 inhibitor group ($P<.001$ for all comparisons). Patients in the SGLT2 inhibitor 2 group were also more likely to be prescribed statins, high-intensity statins, insulin, biguanides, thiazolidinediones, dipeptidyl-peptidase 4 inhibitors, glucagon-like peptide receptor agonists, ACEI or ARB, and beta-blockers ($P<.001$ for each).

In the multivariable model, Black or African American patients were less likely to be prescribed an SGLT2 inhibitor than White patients (adjusted odds ratio [aOR], 0.87; 95% CI, 0.83-0.91; $P<.001$). Women were nearly half as likely to receive a prescription for an SGLT2 inhibitor compared with men (aOR, 0.59; 95% CI, 0.52-0.67; $P<.001$). Factors associated with higher odds of being prescribed an SGLT2 inhibitor were younger age, ischemic heart disease, use of concomitant medications, higher body mass index (BMI), higher hemoglobin A1c, and higher number of visits with a primary care provider, cardiologist, or endocrinologist. In those with more nephrology visits in the preceding 12 months, the odds of SGLT2 inhibitor prescription were lower.

Analyses of disparities by race demonstrated that Black and African American patients were less likely than White patients to receive a prescription for an SGLT2 inhibitor among subgroups by age, sex, comorbidities, or clinical characteristics. There were no differences between Black or African American and White patients among women, those without hypertension, or those with heart failure, BMI of <18.5 kg/m^2, an estimated glomerular filtration rate of 30 to 44 mL/min/1.73 m^2, hemoglobin A1c of >9%, or who were receiving care at a teaching facility.

The rates of SGLT2 inhibitor prescriptions varied across individual VA facilities; the mean facility-level rate was 11.2% of patients being prescribed an SGLT2 inhibitor. Following adjustment for covariates, the MRR was 1.58 (95%CI, 1.48-1.67), indicating a residual 58% variation in treatment with SGLT2 inhibitors for two similar patients treated at two random facilities.

Facility-level variation was examined among Black or African American patients (MRR, 1.55; 95% CI, 1.47-1.68), White patients (MRR, 1.57; 95% CI, 1.47-1.66), women (MMR, 1.40; 95% CI, 1.28-1.51), and men (MMR, 1.57; 95% CI, 1.48-1.67).

Limitations to the study cited by the researchers included not assessing albuminuria as a key risk factor for progression of CKD, having only one measurement of eGFR prior to the index date, and the lack of clinical data from 2021 for analysis.

In summary, the authors said, "The prescription rate of SGLT2 inhibitors for likely eligible patients was low, with substantial variation between individual facilities. Ischemic heart disease, concomitant medication prescription, higher BMI, and higher hemoglobin A1c were independently associated with SGLT2 inhibitor prescription. There were evident racial and sex disparities in SGLT2 inhibitor prescription that persisted among subgroups. The underlying reasons for racial and sex disparities must be identified and addressed to ensure equitable access to these important medications. Further health services research should address the barriers to SGLT2 inhibitor prescription to increase guideline-based practice and improve long-term cardiovascular and kidney outcomes in patients with CKD." ■

TAKEAWAY POINTS

- Researchers reported results of a retrospective cohort study among US veterans examining factors associated with sodium-glucose cotransporter-2 (SGLT2) inhibitor prescription and disparities by race and sex and facility-level variation in prescription patterns.
- Black or African American patients were less likely to receive a prescription for an SGLT2 inhibitor compared with White patients (odds ratio, 0.87; 95% CI, 0.83-0.91).
- There was an unexplained 58% variation in treatment between Veterans Affairs facilities, independent of patient and facility characteristics.

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Effects of Patiromer Treatment

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as the exchange ion and may also reduce serum phosphate. Three clinical trials (AMETHYST-DN, OPAL-HK, and TOURMALINE) have shown the efficacy of patiromer for hyperkalemia in patients who are eligible for treatment with renin-angiotensin-aldosterone system (RAAS) inhibitors.

David A. Bushinsky, MD, and colleagues conducted a post hoc pooled analysis of individual-level data from the three trials of patiromer to characterize the effect of patiromer on serum phosphate in patients with CKD, hyperkalemia, and hyperphosphatemia. Results were reported in the *American Journal of Kidney Diseases* [2023;82(1):97-104].

The study cohorts included patients with CKD and hyperkalemia who were treated with patiromer (8.4-33.6 g/day). The analysis outcome of interest was mean changes from baseline in serum phosphate, serum potassium, serum calcium, and serum magnesium after 2 to 4 weeks of treatment. Descriptive statistics were used to summarize pooled data on the study outcomes from the three studies.

The analysis included 578 patients: 61.8% (n=357) were male, mean age was 65.6 years, 80.1% (n=463) had diabetes, mean eGFR was 39.1 mL/min/1.73 m^2, and 37.7% (n=218) had stage 4/5 CKD. At baseline, mean serum potassium was 5.4 mEq/L and mean serum phosphate was 3.9 mg/dL.

A total of 492 patients (85.1%) had baseline serum phosphate levels of ≤4.5 mg/dL, and 86 patients (14.9%) had a baseline serum phosphate level of >4.5 mg/dL (above the threshold for hyperphosphatemia). Of the 86 patients with baseline serum phosphate level >4.5 mg/dL, 50 (58.1%) had a baseline serum phosphate level >4.8 mg/dL, and 24 (27.9%) had a baseline serum phosphate level >5.1 mg/dL. Of the patients with baseline serum phosphate level >4.5 mg/dL, mean baseline serum potassium level was 5.5 mEq/L and mean baseline serum phosphate level was 5.0 mg/dL. Those with baseline serum phosphate level ≤4.5 mg/dL had a mean baseline serum potassium of 5.4 mEq/L and baseline serum phosphate of 3.6 mg/dL.

The proportion of patients with CKD stage 4/5 was higher among those with baseline serum phosphate level >4.5 mg/dL than among patients with baseline serum phosphate level ≤4.5 mg/dL (75.6% vs 31.1%). The proportion of patients with CKD stage 4/5 increased with increasing baseline serum phosphate level.

Following 4 weeks of treatment, reductions from baseline in serum potassium were similar in patients with serum phosphate >4.5 mg/dL and those with serum phosphate ≤4.5 mg/dL: mean –0.71 (95% CI, –0.83 to –0.59) mEq/L and mean –0.84 (95% CI, –0.90 to –0.78) mEq/L, respectively.

In patients with concomitant hyperphosphatemia treated with patiromer, mean serum phosphate decreased into the normal range within 2 weeks. At 4 weeks of treatment, mean reduction in serum phosphate was –0.62 (95% CI, –0.87 to –0.36) mg/dL. Patients with serum phospahte ≤4.5 mg/dl had a mean reduction in serum phospahte of –0.07 (95% CI, –0.13 to –0.00). Among those with baseline serum phosphate >4.2 mg/dL, >4.5 mg/dL, >4.8 mg/dL, and >5.1 mg/dL, the reductions after 4 weeks of treatment with patiromer were –0.48 mg/dL, –0.62 mg/dL, –0.73 mg/dL, and –0.83 mg/dL, respectively. Reductions in serum phosphate over 4 weeks of treatment with patiromer were typically greater in patients with higher baseline serum phosphate.

At week 4, treatment with patiromer reduced serum phosphate compared with baseline in both patients with serum phosphate ≤4.5 mg/dL and those with serum phosphate >4.5 mg/dL. Serum phosphate remained in the normal levels in patients with baseline serum phosphate <4.2 mg/dL, while levels of serum potassium declined.

There were also reductions in serum magnesium across 4 weeks of treatment with patiromer compared with baseline. Irrespective of baseline serum phosphate, mean serum magnesium remained within the normal range. Over the 4 weeks of treatment with patiromer, mean serum calcium remained at similar concentrations in patients with serum phosphate >4.5 mg/dL and serum phosphate ≤4.5 mg/dL, with mean changes from baseline to week 4 of 0.04 and 0.00 mg/dL, respectively.

Treatment-emergent adverse events (TEAEs) were reported in 32.4% of patients (n=187). The most common TEAEs reported by preferred term were constipation (5.7%, n=33) and diarrhea (2.9%, n=17). Most of the reported TEAEs were mild or moderate. For nine patients, the TEAEs were severe. All severe TEAES occurred in patients with serum phosphate ≤4.5 mg/dL. Seventy-six patients (13.1%) had TEAEs determined to be related to patiromer. There were no severe TEAEs considered related to patiromer. Thirteen serious TEAEs were reported in nine patients, and 20 patients discontinued treatment due to TEAEs.

In citing limitations to the analysis results, the researchers noted that due to the post hoc nature of the analyses, the findings should be considered exploratory in nature. In addition, the findings were only considered in patients treated with patiromer with no comparisons made with placebo.

The researchers said, "In conclusion, in this post hoc analysis of these three clinical trials evaluating patiromer for the treatment of hyperkalemia in patients with NDD-CKD, 14.9% of patients also had hyperphosphatemia (serum phosphate >4.5 mg/dL) at baseline. In patients treated with patiromer, there was a reduction in both serum potassium and serum phosphate levels to within the normal range after 2 weeks, which was sustained for up to 4 weeks. Patiromer was well tolerated in patients with hyperkalemia and NDD-CKD, and the most common adverse events were mild or moderate gastrointestinal events. Future placebo-controlled trials in both NDD-CKD and stage 5 CKD are needed to assess the ability of patiromer to concomitantly normalize serum phosphate in hyperkalemic patients with CKD to manage hyperphosphatemia." ■

TAKEAWAY POINTS

- Researchers reported results of a post hoc analysis of data from three trials of patiromer in patients with nondialysis-dependent chronic kidney disease, hyperkalemia, and hyperphosphatemia.
- After 2 weeks of treatment with patiromer, there were reductions in serum phosphate levels from baseline, and the reduction was sustained during 4 weeks of treatment.
- There were also reductions in serum potassium from baseline at 2 weeks of treatment, sustained during the 4-week treatment period.

Hemodiafiltration Offers Survival Benefit in Patients

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lated to infection. Cardiovascular events were defined as death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, therapeutic coronary procedure, therapeutic carotid procedure, and vascular intervention or peripheral limb amputation.

The trial intervention was high-dose hemodiafiltration with on-line production of substitution fluid and ultrapure bicarbonate-based dialysis fluid at a convection volume of at least 23 liters per session in postdilution mode. The comparison group received conventional hemodialysis by means of high-flux dialysis membranes and ultrapure bicarbonate-based dialysis fluid.

Cox proportional-hazards models were used to estimate hazard ratios (HR) and corresponding 95% CIs for the primary and key secondary outcomes involving single events. The Anderson-Gill model was applied for recurrent outcomes of hospitalizations for any cause and for cause-specific reasons. Both models included the trial site as a random effect. Competing risk analyses with kidney transplantation as the competing event were conducted for the primary outcomes.

Trial enrollment occurred from November 2018 through April 2021. A total of 1360 patients underwent randomization in a 1:1 ratio to receive either high-dose hemodiafiltration or continuation of high-flux hemodialysis; 683 patients were assigned to receive high-dose hemodiafiltration and 677 to receive high-flux hemodialysis. At baseline, the two groups were well balanced in demographics, coexisting illnesses, laboratory values, and medications. Median follow-up was 30 months for both groups. Loss to follow-up occurred in 18 patients in the hemodiafiltration group and in 12 patients in the hemodialysis group.

The target volume of at least 23 liters per session for high-dose convection was achieved in 92% of delivered hemodiafiltration sessions. The mean convection volume among the patients was stable during the study period. The Kt/V value (K is urea clearance by the dialyzer, t is treatment time, and V is urea distribution volume) was higher in the hemodiafiltration group than in the hemodialysis group and remained higher during the study period.

The primary outcome of death from any cause occurred in 17.3% of patients (n=118) in the hemodiafiltration group (7.13 events per 100 patient-years) compared with 21.9% of patients (n=148) in the hemodialysis group (9.19 events per 100 patient-years; HR, 0.77; 95% CI, 0.65-0.93; *P*=.005). Of the 266 deaths, 25.6% (n=68) were attributed to cardiovascular

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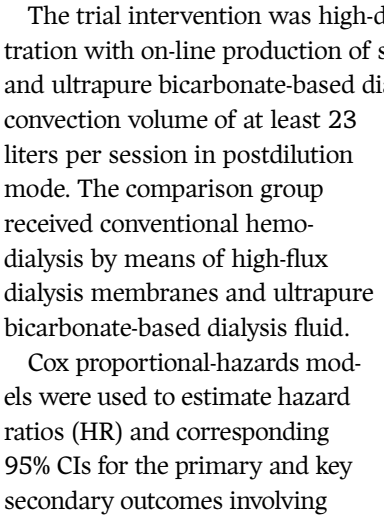

NATIONAL KIDNEY FOUNDATION SPRING CLINICAL MEETINGS

MAY 14-18, 2024

LONG BEACH, CA

Major Meetings

American Society of Nephrology Kidney Week 2023
November 2-5, 2023
Philadelphia, Pennsylvania
www.asn-online.org/education/kidneyweek

American Nephrology Nurses Association 2024 National Symposium
April 14-17, 2024
Orlando, Florida
www.annanurse.org/education-events/events/national-symposium

National Kidney Foundation Spring Clinical Meetings 2024
May 14-18, 2024
Long Beach, California
www.kidney.org/spring-clinical

American Transplant Congress 2024
May 31-June 5, 2024
Philadelphia, Pennsylvania
www.myast.org/american-transplant-congress/american-transplant-congress-information

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Among patients with no history of cardiovascular disease at baseline, the risk of death was lower in the hemodiafiltration group (HR, 0.58; 95% CI, 0.42-0.79).

disease, 9.8% (n=26) to COVID-19, and 21.1% (n=56) to other infections.

Among patients with a history of cardiovascular disease at baseline, the risk of death was similar in the two study groups (HR, 0.99; 95% CI, 0.76-1.28). Among patients with no history of cardiovascular disease at baseline, the risk of death was lower in the hemodiafiltration group (HR, 0.58; 95% CI, 0.42-0.79). Among patients with diabetes mellitus, the risk of death was similar in the two groups (HR, 0.97; 95% CI, 0.72-1.31). Among patients without diabetes mellitus, the risk of death was lower in the hemodiafiltration group compared with the hemodialysis group (HR, 0.65; 95% CI, 0.48-0.87).

The two groups were similar in the risk of death from cardiovascular causes (HR, 0.81; 95% CI, 0.49-1.33) and the composite outcome of fatal or nonfatal cardiovascular outcomes (HR, 1.07; 95% CI, 0.86-1.33). For infection-related death, including death from COVID-19, there was an apparent reduction in favor of the high-dose hemodiafiltration group (HR, 0.69; 95% CI, 0.49-0.96).

The two groups were also similar in the risks of recurrent hospitalization, including for nonfatal hospitalization (HR, 1.11; 95% CI, 0.98-1.25), hospitalization for infection including COVID-19 infection (HR, 1.06; 95% CI, 0.86-1.30), and hospitalization for infection that excluded COVID-19 (HR, 0.97; 95% CI, 0.74-1.26).

Limitations to the study findings cited by the authors included the sample size being smaller than anticipated due to the COVID-19 pandemic that limited participant recruitment, and the overall risk of death being lower than that used for determine the sample size.

In summary, the researchers said, “In our trial, at a median follow-up of 30 months after randomization, patients with kidney failure who received high-dose hemodiafiltration had a lower risk of death than those who received conventional high-flux hemodialysis.” ■

TAKEAWAY POINTS

- Researchers reported results of a multinational, randomized, controlled trial to determine whether high-dose hemodiafiltration offers survival benefits compared with hemodialysis in a population of patients with kidney failure.
- Patients were randomized in a 1:1 ratio to receive either high-dose hemodiafiltration or to continue conventional high-flux hemodialysis.
- Patients in the hemodiafiltration group had a lower risk of death from any cause compared with patients in the conventional hemodialysis group.

Conference Coverage

San Diego, California | June 3-7, 2023

AMERICAN TRANSPLANT CONGRESS

The American Transplant Congress is the joint annual meeting of the American Society of Transplant Surgeons and the American Society of Transplantation. The Congress provides a forum for the exchange of new scientific and clinical information related to solid organ and tissue transplantation. Presentations and posters provide information on advances in research and care to transplant physicians, scientists, nurses, organ procurement professionals, pharmacists, and other transplant professionals.

The American Transplant Congress was held June 3-7 in San Diego, California, providing a showcase for the latest research and advances made by the transplant community in the past year. This is Part Two of our coverage of the meeting.

SARS-CoV-2 Vaccination in Adolescent Solid Organ Transplant Recipients

Results of previous analyses have demonstrated that adolescent solid organ transplant recipients who receive three doses of SARS-CoV-2 mRNA vaccine experience high seroconversion rates and antibody persistence for up to 3 months. There are few data available on the long-term antibody durability in that patient population.

During a poster session at the American Transplant Congress 2023, **J. McAteer** and colleagues reported results of an analysis of antibody responses 6 months following the third vaccine dose of the BNT 162b2 mRNA vaccine among adolescent solid organ transplant recipients. The poster was titled *Anti-Spike Antibody Durability After SARS-CoV-2 Vaccination in Adolescent Solid Organ Transplant Recipients.*

The analysis included participants in a multicenter, observational cohort who received the third dose of the vaccine. Participants were analyzed for antibodies to the SARS-CoV-2 spike protein receptor-binding domain (Roche Elecsys anti-SRAS-CoV-2-S positive: ≥0.08, maximum: >2500 U/mL). Samples were collected at 1, 3, and 6 months following dose three.

The observational cohort included 34 adolescent solid organ transplant recipients. Of those, 100% (n=34) had positive antibody titers 6 months after dose three, with a median of 2500 U/mL. Twenty-four percent (n=8/34) had decreased titers at 6 months compared with 3 months (mean decrease of 617 U/mL) and 6% (n=2/34) had increased titers (mean increase of 312 U/mL). The remaining 24 study participants (70%, n=24/34) had stable titers of >2500 U/mL from 3 to 6 months after the third dose.

Four of the 34 participants (12%) had breakthrough infection between 3 and 6 months after dose three; all of those four participants had antibody titers of >2500 U/mL at both the 3 and the 6 month time intervals. Four of the 34 (12%) reported infection at 6 to 12 months after dose three. Mean 6-month antibody titers (U/mL) were 927 among those infected 6 to 12 months after dose three versus 2174 among those not infected post dose three. At 3 months, mean antibody levels (U/mL) were 1275 among those infected 6 to 12 months after dose three (n=4) versus 2345 (n=26) among those not infected after dose three.

"In this observational cohort, antibody titers remained positive 6 months following dose three, indicating antibody durability among adolescent solid organ transplant recipients," the authors said. "Antibody titers remained stable after receipt of dose three, with only a small subset of participants experiencing a decrease in titers compared to their 3-month post-dose three levels. Lower antibody titers at both 3 and 6 months post dose three may be associated with increased risk of breakthrough infection >6 months post dose three."

Source: McAteer J, Abedon RR, Kalluri DD, et al. Anti-spike antibody durability after SARS-CoV-2 vaccination in adolescent solid organ transplant recipients. Poster A128. Abstract of a poster presented at the American Transplant Congress 2023; June 3-7, 2023; San Diego, California.

Dialysis Provider Referral Decisions for Patients With Past Nonadherence

Compared with dialysis, kidney transplant improves patient survival and quality of life. However, not all patients on maintenance dialysis are referred for transplant evaluation. Guidelines from Kidney Disease: Improving Global Outcomes (KDIGO) highlight the importance of assessing dialysis patient adherence to treatment and advise referral of patients with past nonadherence to a transplant center.

To identify dialysis providers' beliefs regarding the causes and implications of nonadherence, **J. McDonnell** and colleagues at Emory University, Atlanta, Georgia, conducted a study to identify dialysis clinic provider processes leading up to referral or nonreferral to a transplant center. Results were reported during a poster session at the American Transplant Congress 2023 in a poster titled *A Grounded Theory Approach to Understanding Dialysis Providers' Transplant Referral Decisions for Patients With Past Non-Adherence.*

The study included in-depth interviews with 39 dialysis clinic providers in Georgia, North Carolina, and South Carolina from June to August 2022. Interview questions focused on clinics' processes leading up to referral or nonreferral to a transplant center. Using purposive sampling to ensure diversity by participant role, years of experience, and county median household income, the researchers recruited dialysis social workers, nurse managers, nephrologists, and administrators for the study. The semistructured telephone interviews were recorded and transcribed. A novel theoretical model of provider beliefs about nonadherence was crafted using a grounded theory approach.

Without specific prompting, interview participants cited patient nonadherence (to medications, diet or fluid intake restrictions, dialysis attendance, and completion of dialysis session) as a key barrier to transplant referral. Provider beliefs related to nonadherence were classified into three domains: (1) causes of nonadherence; (2) implications of nonadherence for referral decisions; and (3) waitlist eligibility for patients with past nonadherence.

Some providers named patient limited social and financial resources as causes of nonadherence; other causes mentioned included disinterest in transplant or an inability to self-manage. Some respondents felt that referred patients with past nonadherence would be ruled ineligible for waitlisting at the transplant center. Respondents' beliefs were consistent across forms of nonadherence in all three domains.

"How dialysis providers respond to patient nonadherence may be affected by their beliefs about the causes and implications of nonadherence," the authors said. "Though KDIGO guidelines advise referring patients with past nonadherence to a transplant center for evaluation–and for intervention as needed–dialysis providers may delay referral or opt not to refer based on their beliefs about nonadherence."

Source: McDonnell J, Urbanski M, Pastan S, et al. A grounded theory approach to understanding dialysis providers' referral decisions for patients with past non-adherence. Poster A147. Abstract of a poster presented at the American Transplant Congress 2023; June 3-7, 2023; San Diego, California.

Managing Vitamin D Deficiency in Kidney Transplant Recipients

In patients with chronic kidney disease, vitamin D deficiency is associated with secondary hyperparathyroidism. Levels of 1,25-dihydroxyvitamin D (calcitriol) decrease progressively as kidney function declines. The 2009 Kidney Disease: Improving Global Outcomes Transplant Recipient Guidelines recommends minimizing life-long sun exposure for kidney transplant recipients. The guidelines also call for the use of appropriate ultraviolet light block agents and treatment similar to the strategies recommended for the general population to correct vitamin D deficiency and insufficiency.

In 2018, Brigham and Women's Hospital, Boston, Massachusetts, completed a retrospective cohort study that analyzed kidney allograft biopsies performed within 3 months of kidney transplantation. Results of the study demonstrated that the risk of graft failure was significantly higher in kidneys with calcium oxalate deposition. Based on those findings, the center modified its policy on supplementing vitamin D in early transplantation.

In an oral abstract session at the American Transplant Congress 2023, **R. Anumolu** and colleagues from Brigham and Women's Hospital reported results of an analysis of levels of vitamin D in patients at the center. The presentation was titled *A Single-Center Cross-Sectional Analysis of Vitamin D Management in Kidney Transplant Recipients: Are We Sufficiently Addressing Deficiency?*

The single-center, cross-sectional analysis included 338 patients who received a kidney transplant in the last 5 years. The protocol at Brigham and Women's Hospital is to check S-25(OH)D and intact parathyroid hormone (iPTH) levels at 3 and 12 months posttransplant. The analysis included patient demographics and frequency of monitoring vitamin D and iPTH.

Of the analysis cohort, 81.8% had vitamin D checked at 3 months, and 60.4% had vitamin D checked at 12 months posttransplant. PTH was checked in 79.6% of the cohort at 3 months and in 59.7% at 12 months. At the 3-month mark, 36.5% of the kidney transplant recipients were vitamin D deficient (<21 ng/mL), and 31.5% were vitamin D insufficient (21-29 ng/mL). At 12 months, 25.5% were vitamin D deficient, and 29.2% were insufficient.

At the 3-month mark, only 31.9% of the kidney transplant recipients had vitamin D levels above 30 ng/mL. By 12 months, 45.3% had levels above 30 ng/mL.

In summary, the authors said, "At our center, we identified that although there is an overall improvement across the racial demographics in terms of vitamin D levels, a considerable portion of the population, particularly African Americans remain either insufficient or deficient. Given that low vitamin D levels are associated with a variety of increased risks, malignancies, and immune dysregulation, we need to pay closer attention to the African American population and evaluate what measures can be taken to improve outcomes."

Source: Anumolu R, Martinez-Yamada S, Schreiber B, Chandraker A. A single-center cross-sectional analysis of vitamin D management in kidney transplant recipients: are we sufficiently addressing deficiency? Abstract 572. Abstract of an oral presentation at the American Transplant Congress 2023; June 3-7, 2023; San Diego, California.

Treating BK Virus Infection Post-transplant: A Single-Center Study

Kidney transplant recipients who develop BK anemia of diabetic nephropathy/nephropathy (DNanemia) are at increased risk for graft failure. Results of previous studies have suggested graft loss in that patient population to be up to 15%. There is no definite treatment against BK DNanemia, and there are limited data available to support the use of leflunomide to prevent graft failure.

Y. Natori and colleagues at the University of Miami and the Miami Transplant Institute, Miami, Florida, conducted a single-center, retrospective cohort study to examine the efficacy of leflunomide in transplant recipients with BK DNanemia. Results of the study were reported during a poster session at the American Transplant Congress 2023 in a poster titled *BK Virus Infection in the Current Era: Risk Factors and Outcomes of Large Kidney Transplant Cohort*.

The study included all adult kidney and kidney-pancreas transplant recipients at the center between January 1, 2016, and December 31, 2019. The center provides routine monitoring for BK virus at 1, 3, 6, 9, and 12 months post-transplant and annually thereafter. They also monitor following decrease in allograft function.

When BK virus load exceeds 3000 copies/ml, patients are switched from mycophenolate to leflunomide and their tacrolimus trough level is decreased to 3-5. Assessed outcomes include graft failure and mortality 1-year post-transplant. The current study utilized multiple logistic analysis with stepwise backward elimination to identify risk factors for BK DNanemia.

A total of 694 transplant recipients were included in the analysis. Of those, 23.0% (n=160) developed BK DNanemia at a median of 118.5 days post-transplant. Risk factors predicting BK DNanemia identified in multivariant analysis were rejection within 3 months after transplant, organ donor of White race, cytomegalovirus negative serostatus donor, and urinary leakage at the time of transplant.

Patients undergoing the center's treatment protocol were less likely to develop graft loss within 1-year (5.6% vs 10.9%; P=.048) and had a trend to have lower 1-year morality following transplant (2.5% vs 6.2%; P=.073).

"Risk factors for developing BK DNanemia are equivocal to previous studies, and rates of development at our center remain the same as in other transplant centers," the authors said. "However, this study revealed a decreased rate of graft loss and patient mortality at 1 year with the current leflunomide protocol and a decrease in calcineurin inhibitor (tacrolimus). Further prospective multicenter studies need to be performed best to determine long-term outcomes of BK DNanemia in renal allograft using this immunosuppressive regimen."

Source: Natori Y, Mendez Castaner L, Anjan S, et al. BK virus infection in the current era: risk factors and outcomes of large kidney transplant cohort. Poster B070. Abstract of a poster presented at the American Transplant Congress 2023; June 3-7, 2023; San Diego, California.

Risk of Infection Among Transplant Recipients With DGF

In deceased-donor kidney transplant recipients, delayed graft function (DGF) is a common complication and a known risk factor for allograft rejection, decreased graft survival, and increased health care costs. DGF is an inflammatory process modulating the immune system. While the increased risk of rejection associated with DGF is well known, there are few data available on the association between DGF and increased risk for infection.

During an oral abstract session at the American Transplant Congress 2023, **E. A. Alshaikh** and colleagues at the University of Wisconsin Hospital and Clinics reported results of an analysis of all adult deceased donor kidney transplant recipients at the center between 2010 and 2018. The presentation was titled *Delayed Graft Function Among Kidney Transplant Recipients Is Associated With Increased Risk of Infections*.

The primary outcomes of interest were BK viremia, cytomegalovirus (CMV) viremia, pneumonia, and urinary tract infections (UTIs) in the first year following the transplant. Secondary outcomes included whether the association of DGF was independent of rejection, determined by developing models that treated rejections as a censoring event.

The analysis included data on 1512 decreased donor kidney transplant recipients. Of those, 31% (n=468) had DGF. The recipients in the DGF group had donors with higher body mass index (BMI), higher terminal serum creatinine, higher Kidney Donor Profile Index, higher number of human leukocyte antigen mismatches, and were more likely to be a donor after cardiac death donor.

Recipients in the DGF group also had higher BMI, were more likely to be female, more likely to have diabetes as a cause of end-stage renal disease. They were also more likely to have received induction with depleting agents, and were less likely to be the recipient of a preemptive transplant.

In a model adjusting for multiple baseline characteristics, there was a significant association between DGF and increased risk of BV viremia (hazard ratio [HR], 1.34; 95% CI, 1.0-1.81; P=.05) and UTI (HR, 1.70; 95% CI, 1.31-2.19; P<.001. There was no significant association between DGF and CMV or pneumonia. In models censored at the time of rejection, outcomes were similar: BK viremia, HR, 1.33; 95% CI, 0.99-1.80; P=.06) and UTI, HR, 1.72; 95% CI, 1.33-2.23; P<.001.

"DGF is associated with an increased risk of early infection complications, mainly UTI," the authors said. "Close monitoring and appropriate management are warranted for better outcomes in this unique population."

Source: Alshaikh EA, Astor BC, Muth B, et al. Delayed graft function among kidney transplant recipients is associated with increased risk of infections. Abstract 219. Abstract of an oral presentation at the American Transplant Congress 2023; June 3-7, 2023; San Diego, California.

Pretransplant Dialysis Modality and Atrial Fibrillation Post-transplant

In the first 3 years following kidney transplantation, 7% of recipients experience new onset atrial fibrillation (AF). According to **L. Pozo Garcia** and colleagues, there are few data available on the association of pretransplant dialysis modality and incident AF in patients receiving their first kidney transplant.

During a poster session at the American Transplant Congress 2023 the researchers reported results of a study examining the association between dialysis modality and incident AF in a population of kidney transplant recipients. The poster was titled *Association of Pretransplant Dialysis Modality With Incident Atrial Fibrillation Following Kidney Transplantation*.

The study utilized data from the United States Renal Data System, the United Network for Organ Sharing, and Medicare Parts A and B to retrospectively identify patients ≥18 years of age with no previously diagnosed AF undergoing their first kidney transplant between January 1, 2005, and September 30, 2012. Inpatient and outpatient Medicare claims based on *International Classification of Diseases, Ninth Revision* codes were used to further identify patients with newly diagnosed AF post-transplant with follow-up through September 30, 2015.

Dialysis modality routinely used prior to transplant was the exposure of interest. The association of modality with incident AF over up to 3 years posttransplant was estimated using multivariable Cox regression. Death was considered a competing risk.

The cohort included 43,621 eligible patients. Of those, 84.9% (n=37,055) used hemodialysis and 15.1% (n=6566) used peritoneal dialysis prior to kidney transplantation. Mean age of the overall cohort was 51 years, 60.8% were male, 33% were obese, 29.90% had diabetes as the cause of end-stage renal disease, 55.6% identified as White, and 35.8% as Black. Heart failure was identified in 25.2%, 20.9% had coronary artery disease, and 4.3% had been diagnosed with arrhythmias other than AF. Mean dialysis vintage was 4.3 years.

Atrial fibrillation was more likely in those in the hemodialysis group compared with those in the peritoneal group (adjusted cause-specific hazard ratio [HR], 1.18; 95% CI, 1.05-1.31). The incidence of AF more than doubled the likelihood of graft failure (HR, 2.82; 95% CI, 2.70-2.95). There was an association between older age and a higher incidence of AF (HR, 1.05; 95% CI, 1.04-1.5). Being female and non-White was associated with a lower risk of AF.

There was an association between longer dialysis vintage and higher risk of AF (HR, 1.05; 95% CI, 1.03-1.08). There were also associations between comorbidities such as coronary artery disease, valvular heart disease, heart failure and the presence of other arrhythmias and higher risk of AF. The risk of AF was also increased with the presence of transplant factors such as previous solid organ transplant (HR, 1.45; 95% CI, 1.22-1.68), female donor (HR, 1.10; 95% CI, 1.02-1.18), and human leukocyte antigen mismatch (4-6 vs 0, HR, 1.26; 95% CI, 1.09-1.43). There was an association between having a living donor and a lower risk of AF (HR, 0.75; 95% CI, 0.60-0.91).

"Prekidney transplantation hemodialysis as compared with peritoneal dialysis was associated with higher risk of newly diagnosed AF after a first kidney transplant," the authors said.

Source: Pozo Garcia L, Liu S, Lenihan C, Winkelmayer WC, Khairallah P. Association of pretransplant dialysis modality with incident atrial fibrillation following kidney transplantation. Poster C191. Abstract of a poster presented at the American Transplant Congress 2023; June 3-7, 2023; San Diego, California.

Kidney Transplantation in Patients With Severe Pulmonary Hypertension

There is an association between severe pulmonary arterial hypertension (PAH), defined by a pulmonary artery systolic pressure (PASP) >50 mmHg, and high perioperative mortality. PAH is generally considered a contraindication to kidney transplantation.

During an oral abstract session at the American Transplant Congress 2023, **D. Kumar** and colleagues at VCU Health, Richmond, Virginia, described the clinical course of kidney transplant candidates referred to the center who were found to have a diagnosis of severe PAH. The presentation was titled *Kidney Transplantation Improves Survival In Patients With Treated Severe Pulmonary Hypertension Compared to Dialysis: A Single Center Approach.*

The researchers identified all patients with severe PAH on initial pretransplant workup between November 2013 and August 2022. Eligible patients had undergone ultrafiltration and/or medical therapy for PAH prior to kidney transplantation. Patients' perioperative course, renal function, graft and patient survival were examined following kidney transplantation. The study was designed to compare kidney transplant recipient survival with survival among patients who remained on the kidney transplant waitlist or were delisted prior to transplantation.

The study cohort included 32 patients who were diagnosed with severe PAH on pretransplant screening echocardiogram. The findings were confirmed by elevated PASP (mean PASP 67 mm Hg). Mean age of the cohort was 55 years and 69% (n=22) were Black.

The patients with PAH were confirmed to have an elevated pulmonary capillary wedge pressure and elevated right atrial pressure on right heart catheterization (RHC). Thirty patients (94%) were subjected to a median of four ultrafiltration sessions with an average weight loss of 4.33 kg at the end of the sessions.

Results of repeat assessment of pulmonary hypertension and volume status showed a marked decline in PASP from an average of 67 mm Hg to 43 mm Hg ($P<.0001$), a decline in PCWP from 25 mm Hg to 11 mm Hg ($P<.0001$), and a decline in right arterial pressure from 15 mm Hg to 6 mm Hg ($P<.0001$). In seven patients who underwent pre- and postultrafiltration measurement of B-natriuretic peptide, there was a significant decline from a mean 1147 pg/mL to 370 pg/mL ($P=.0045$).

Seventeen of the 32 patients (53%) received a kidney transplant. Of those, 76% (n=13) received a deceased donor kidney transplant. Mean estimated glomerular filtration rate at 3, 6, 9, and 12 months posttranspaint was 72, 72, 75, and 75 mL/min/1.73 m^2, respectively. At median follow-up of 88 months, kidney transplant recipients had a patient survival rate of 88%, compared with a patient survival rate of 53% among those who remained on maintenance dialysis ($P=.0003$).

"In this single center study, we report that severe PAH should not be considered an absolute contraindication to kidney transplant," the researchers said. "A better elucidation of the etiology of PAH with a RHC [right heart catheterization] should be considered. Postcapillary PAH can be a significant contributor to elevations in PASP especially in the dialysis population. Using a multidisciplinary approach, PAH could be improved with optimal volume removal and PDE5 [phosphodiesterase 5] inhibitor therapy leading to successful short- and long-term posttransplant outcomes and a significant improvement in morality with kidney transplants as compared to chronic dialysis."

Source: Kumar D, Moinuddin I, Raju N, Thomas D, Tripath S, Gupta G. Kidney transplantation improves survival in patients with treated severe pulmonary hypertension compared to dialysis: a single center approach. Abstract 392. Abstract of a presentation at the American Transplant Congress 2023; June 3-7, 2023; San Diego, California.

Outcomes Among Elderly Kidney Transplant Recipients

Decisions regarding eligibility for kidney transplantation may include concerns related to age among elderly candidates. The Edward Hines Jr. Veterans Administration (VA) transplant center (Hines, Illinois) is one of several transplant centers serving veterans across the United States.

During a poster session at the American Transplant Congress 2023, **M. Samra** and colleagues reported results of an analysis of outcomes of kidney transplants at the center among veterans ≥65 years of age. The poster was titled *Kidney Transplant Outcomes in an Elderly Veteran Population.*

A total of 65 kidney transplants were performed during the study period. Of those, 31 met inclusion criteria for the current analysis. Mean age of the analysis cohort was 70 years, all were male, and 65% (n=20) were Black. Ninety percent (n=28) were receiving maintenance hemodialysis prior to transplant, with a mean dialysis vintage of 4 years.

Nineteen percent (n=6) had cytomegalovirus (CMV) viremia, defined as polymerase chain reaction >200 units/mL at any time in the posttransplant study period. The incidence of BK viremia was 10% (n=3) during the study period. Seven patients (23%) experienced delayed graft function. The 30-day all-cause rehospitalization rate was 42% (n=13). At 1 year after transplant, patient and graft survival was 100%.

In summary, the authors said, "The data illustrate that patients over the age of 65 can be safely transplanted and have good graft and patient survival as observed in this veteran cohort. They were found to have higher rates of 30-day all-cause rehospitalization at 42%, but comparable rates of CMV and BK viremia incidence. It is important to note the utilization of higher KDPI donor kidneys as well as hepatitis C and B kidneys known as marginal kidneys, resulting in excellent outcomes."

Source: Samra S, Joyce C, Thorndyke AS, et al. Kidney transplant outcomes in an elderly veteran population. Poster D179. Abstract of a poster presented at the American Transplant Congress 2023; June 3-7, 2023; San Diego, California.

Living Liver Donation After Living Donor Kidney Donation

In recent years, living donor kidney donation has gained widespread acceptance and has an established safety profile for donors. As laparoscopic liver donation is increasingly used, previous kidney donors are considering liver donation. However, according to **R. Raj** and colleagues at the Cleveland Clinic in Ohio, there is a concern for the safety of previous kidney donors being considered for living liver donation.

The researchers conducted a study examining sequential liver donation after kidney donation at the Cleveland Clinic and the center's strategy to ensure donor safety. Results were reported during an oral abstract session at the American Transplant Congress 2023 in a presentation titled *A Safe Strategy for Sequential Living Donor Liver Donation Following Living Donor Kidney Donation.*

The analysis included data on living liver donation from 2012 to 2022. The data were used to identify patients who donated liver following kidney donation. The Cleveland Clinic evaluates previous kidney donors for a left lobe organ donation to ensure an adequate functional liver reserve. Kidney donors must wait at least 1 year after kidney donation before being evaluated for liver donation.

Of the 209 living donor liver transplants performed during the study period, 18 involved liver donors following kidney donation. Mean age was 47 years, 55% were female, mean body mass index was 25 kg/m^2, and 88% (n=16) were White. The average interval between kidney donation and liver donation was 47 months. Twelve of the 18 procedures (66%) were performed laparoscopically and six (34%) were open.

Mean hospital length of stay was 5 days. Three donors had in-hospital complications: two with superficial wound infections and one with postoperative blood product requirement. Seventeen of the 18 donors were altruistic donors.

Prior to liver donation, mean estimated glomerular filtration rate (GFR) was 69 mL/min/1.73 m^2; post liver donation, mean GFR remained stable and no patient noticed any decline in GFR.

Mean age of the liver recipients was 30 years; seven were pediatric recipients. Thirty-three percent of the liver procedures were left lateral segment grafts and the remaining 11 were full left lobes. Mean graft-to-recipient weight ratio was 1.3 and functional liver reserve for donors was 71. Median Model for End-Stage Liver Disease score was 15. At 1 year post procedure, graft survival was 84%.

In summary, the authors said, "We are reporting the largest single center experience of sequential liver donation after kidney donation. We have established a protocol for maximizing donor safety by using left lobe in this subset of donors. With this strategy, we have achieved excellent donor and recipient outcomes."

Source: Raj R, Khalil M, Calderon E, et al. A safe strategy for sequential living donor liver donation following living donor kidney donation. Abstract 96. Abstract of a presentation at the American Transplant Congress 2023; June 3-7, 2023; San Diego, California.

Kidney-Lung Transplant in a Patient With Positive Cross Match

When considering human leukocyte antigen (HLA)-incompatible multiorgan transplant, positive cross match is generally considered a contraindication. According to **S. Metwally,** and colleagues, there are no reported cases of successful combined lung-kidney transplants across a positive cross match.

During a poster session at the American Transplant Congress 2023, the researchers described the case of a 58-year-old woman with end-stage renal disease and respiratory failure due to severe pulmonary arterial hypertension who was waitlisted for a lung-kidney transplant. The poster was titled *A Successful Double Lung and Kidney Transplant Despite Strongly Positive T and B-Cell Cross March.*

The patient was highly sensitized (100% calculated panel reactive antibody [cPRA]) and despite multiple attempts at desensitization, the PRA did not decrease. Due to the severity of respiratory failure, the patient required continuous hospitalization and her waitlist period, which spanned more than a year, was complicated by multiple respiratory and blood stream infections.

Despite a strongly positive flow cytometry T and B cell cross match, due to the patient's critical illness the decision was made to proceed with combined lung-kidney transplant. Desensitization and induction consisted of pre- and postoperative plasmapheresis (PP)/eculizumab (ECU), intraoperative basiliximab/steroids, and postoperative anti-thymocyte globulin (rATG) and intravenous immunoglobulin (IVIg). At the time of the transplant, multiple donor-specific antibodies (DSA) were present in high titers; peak DSA titer was 1:128.

The kidney allograft had prompt graft function, while the lungs had primary graft dysfunction grade 1 disproportionately affecting the first implanted lung, with improvement by day 4. Multiple infectious complications complicated the posttransplant course of treatment. By 6 months posttransplant, both allografts were functioning well with no biopsy evidence of rejection and with declining DSA titers.

In this unique case of a highly sensitized recipient undergoing a successful combined lung-kidney transplant, the patient was treated with an intensive immunomodulatory therapy that included three rounds of desensitization pre- and posttransplant. In addition to PP, IVIg, bortezomib, and rATG, the posttransplant induction regimen included tacrolimus, mycophenolate, and prednisone. The therapy was designed to passively remove DSA with peritransplant PP, inhibit HLA antibody-triggered complement activation with ECU, and prevent T cell activation with basiliximab.

The authors said, "Using an intensive immunomodulatory regiment, multiorgan transplants can be successfully performed despite positive cross match. The long-term outcomes and the risks of infectious complications should be further studied to optimize treatment regimens for such transplants."

Source: Metwally S, Portocarrero Caceres J, Friedewald J, et al. A successful double lung and kidney transplant despite strongly positive T and B-cell cross match. Poster B167. Abstract of a poster presented at the American Transplant Congress 2023; June 3-7, 2023; San Diego, California.

Pancreas/Kidney Transplantation During the COVID-19 Pandemic

The optimal long-term treatment option among patients with diabetes and chronic kidney disease is a simultaneous pancreas/kidney transplant to achieve independence from insulin and dialysis. Simultaneous pancreas/kidney transplant is an option for patients with type 1 diabetes mellitus as well as for patients with type 2 diabetes mellitus. In the past, outcomes between the two types of diabetes were similar. However, a recent registry analysis demonstrated an increased mortality among patients with type 2 diabetes following the emergence of COVID-19.

A. C. Gruessner and colleagues conducted a study to examine the potential risk factors for those differences in patient and graft survival. Results of the study were reported during an oral abstract session at the American Transplant Congress 2023 in a presentation titled *COVID-19 Caused Higher Mortality in Simultaneous Pancreas/Kidney Transplants in Patients With DM Type 2.*

The study included data on all reported primary simultaneous pancreas/kidney transplants performed between January 1. 2017, and December 31, 2021. The Kaplan-Meier method was used to assess patient and graft survival. Cox regression with time-dependent variables was used to develop a risk assessment model.

During the study period, 3112 patients with type 1 diabetes and 899 patients with type 2 diabetes received a simultaneous pancreas/kidney transplant. Patients with type 2 diabetes were more likely to be male, were older, were not White, and were obese. Patient and graft survival were significantly lower among the patients with type 2 diabetes compared with those with type 1 diabetes. When graft survival was assessed with "dying with a functional graft censored," the differences between the two groups were attenuated and graft outcomes became equivalent.

General viral or COVID-19-related causes were detected in 25 recipients with type 1 diabetes and in 21 recipients with type 2 diabetes. In multivariable Cox regression for patient survival, there was a significant impact of older patient age and higher body mass index (BMI). There was no interaction between age and BMI. All other factors did not reach statistical significance. The mortality risk was highest for transplants performed in 2020; there was a slight decrease in mortality after 2020.

In conclusion, the authors said, "Differences in simultaneous pancreas/kidney transplant outcome between type 1 and type 2 diabetes mellitus recipients was due to an increased mortality in type 2 diabetes mellitus patients. Adjusted for potential risk factors, only older age and obesity stood out. Black race did not reach significance. Those are the same risk factors for recipients infected with COVID-19 which were more prevalent in type 2 diabetes mellitus recipients. Hence, poorer outcomes in type 2 diabetes mellitus patients during the COVID-19 pandemic was more related to the infection that the diabetes type. Even though outcome in simultaneous pancreas/kidney transplants during the COVID-19 pandemic was excellent, type 2 diabetes mellitus patients with increased BMI and older age had higher mortality rate."

Source: Gruessner AC, Saggi SJ, Gruessner RW. COVID-19 caused higher mortality in simultaneous pancreas/kidney transplants in patients with DM type 2. Poster 407. Abstract of a poster presented at the American Transplant Congress 2023; June 3-7, 2023; San Diego, California.

Stability of Renal Function in Transplant Recipients Treated With SGLT2i

Researchers at St. Michael's Hospital, Toronto, Ontario, Canada, led by **A. Angieli,** conducted a single-center retrospective chart review designed to examine the safety and efficacy of sodium-glucose cotransporter 2 inhibitors (SGLT2i), in a population of kidney transplant recipients with type 2 diabetes mellitus or new onset diabetes after transplantation (NODAT).

Results were reported during an oral abstract session at the American Transplant Congress 2023. The presentation was titled *Are Sodium-Glucose Cotransporter-2 Inhibitors (SGLT2i) Safe to Use in Kidney Transplant Recipients With Diabetes?*

Patients with type 2 diabetes mellitus or NODAT who received a kidney transplant prior to December 31, 2020, and started SGLT2i posttransplant prior to March 31, 2021, were included in the analysis. The SGLT2i start date was considered baseline. The review included available data 24 months prior to and following initiation of SGLT2i. Data were collected from the date of recent transplantation and up to March 31, 2021.

The primary end point was the effects of SGLT2i use on stability of renal function using serum creatinine and estimated glomerular filtration rate (eGFR). Secondary end points were comparison of A1c, urine albumin-creatinine ratio (UACR), and adverse events at baseline and quarterly following start of SGLT2i.

The cohort included 125 kidney transplant recipients. Of those, 42% (n=52) developed NODAT, and 58% (n=73) had diabetes mellitus. Mean age at transplant was 55 years, 27% (n=33) were female, and mean study follow-up was 1.8 years.

The rate of change in eGFR in periods following initiation of SGLT2i was not different from the preinitiation period rate of change (slope difference, -0.26 mL/min/1.73 m^2; 95% CI, -0.08 to 0.27; P=.33). There was no significant increase in acute kidney injury (pre 8%, post 10.4%; P=.51). Rates of change in A1c were 0.02% prior to SGLT2i initiation and -0.06% following initiation of SGLT2i, resulting in a decrease in A1c over a postinitiation period of -0.09 (95% CI, -0.0017 to -0.0001; P=.03). The post-SGLT2i slope in UACR compared with pre-SGLT2i slope was reduced by -0.11 log units (95% CI, -0.16 to -0.05; P<.01).

Before initiation of SGLT2i, 18.4% of the cohort (n=23) experienced at least one cardiovascular event, compared with 12% (n=15) who experienced at least one cardiovascular event following initiation of SGL2i. The 24-month survival probability of at least one cardiovascuair event post-SGLT2i initiation was 83.9%.

The risk of developing new genital mycotic infections among all patients was 4%. The incidence of urinary tract infections was 13.6% (n=17) prior to SGLT2i initiation and 12% (n=15) following initiation of SGLT2i. The 24-month survival probability for UTIs following initiation of SGLT2i was 85.7%.

In conclusion, the authors said, "In our retrospective analysis, SGLT2i use in kidney transplant recipients with type 2 diabetes mellitus or NODAT appears to be safe and efficacious as renal function remained stable and glycemic control improved. There was a low risk of new genital mycotic infections after SGLT2i start. The reduction in UACR, cardiovascular, and UTI events will be further evaluated in subsequent analyses."

Source: Angieli A, Montada-Atiin T, Nisenbaum R, Dacouris N, Nash M, Zaltzman J. Are sodium-glucose cotransporter-2 inhibitors (SGLT2i) safe to use in kidney transplant recipients with diabetes? Abstract 472. Abstract of an oral presentation at the American Transplant Congress 2023; June 3-7, 2023; San Diego, California.

Adequacy of Dietary Intake Among Patients Receiving Maintenance Hemodialysis

An estimated 14.9% of the population of the United States is affected by chronic kidney disease (CKD), and approximately 88% of Americans with CKD are unaware that they have reduced kidney function. In 2020, according to data from the United States Renal Disease Data System, 802,759 people in the United States had end-stage kidney disease.

The term protein-energy wasting (PEW) was coined in 2008 by the International Society of Renal Nutrition and Metabolism to describe a complex combination of malnutrition, cachexia, and inflammation in individuals with CKD. The worldwide prevalence of PEW in those receiving maintenance hemodialysis is 28% to 54%, and the risk of risk of morbidity and mortality in that patient population is elevated.

Several biochemical, clinical, and nutritional parameters are used to diagnose PEW. According to **Terry Brown, MBA, MPH, RD, LD,** and colleagues, research is needed to assess the various PEW components, such as reduced dietary energy and protein intake and anthropometrics (BMI, BMI category, waist circumference, waist-to-hip ratio) to identify appropriate nutrition interventions for patients receiving maintenance hemodialysis at risk of malnutrition.

The researchers conducted a secondary analysis of clinical and demographic data for 142 adults from the Rutgers Nutrition and Kidney Disease (RNKD) database to explore whether those with ESKD on maintenance hemodialysis meet the National Kidney Foundation Kidney Disease Outcomes Quality Initiative 2020 (NKF-KDOQI 2020) guidelines for nutritional adequacy on dialysis treatment day. The study also examined the relationship between dietary energy and protein intake and anthropometrics. Results were reported in the *Journal of Renal Nutrition* [2023;33(2):355-362].

Continuous variables (age, dialysis vintage, BMI, waist-to-hip ratio, waist circumference, and self-reported dietary intake of protein, fat, carbohydrate, and energy) were reported using the mean standard deviation or median interquartile range. Categorical variables (sex, race, ethnicity, CKD etiology, and BMI category) were described using total count and percentage.

The RNKD database is a compilation of four cross-sectional studies conducted in the Northeast and/or Midwest regions of the United States and includes data from a convenience sample of 210 study participants with stage 5 CKD undergoing maintenance hemodialysis from September 2012 to December 2018. Of those 210 participants, 142 had complete data and were included in the current analysis. Median age was 55.7 years and dialysis vintage ranged from 3 to 411 months, with a median duration of 42 months. A total of 119 participants were Black (83.8%) and 111 were of non-Hispanic ethnicity (78.2%).

Seventy-five percent of the study cohort had a BMI of 25 to 29 or ≥30 kg/m^2, consistent with the Centers for Disease Control and Prevention definition for overweight (n=51, 35.9%) or obesity (n=56, 39.4%). Median waist circumference for men was 103.0 cm, exceeding the recommended standard for optimal health of 102 cm; the waist-hip-ratio was within normal limits at 1.0. For women, mean waist circumference and waist-to-hip ratio exceeded the recommended standard for optimal health of 88 cm and 0.85, respectively.

Dietary energy intake, dietary protein intake, and macronutrients were based on a 24-hour recall that reflected intake on a dialysis day. Median dietary energy intake was 1342 kcals or 18 kcal/kg, and median dietary protein intake was 56 g or 0.7 g/kg. Those values did not meet the NKF-KDOQI 2020 recommendations of 25 to 35 kcal/kg and 1.0 to 1.2 g of protein/kg to maintain stable nutritional status.

Dietary energy intake was significantly higher among men than women, as was dietary protein intake; however, dietary intake was suboptimal in both men and women. The macronutrient composition was 16.4% of kcal from protein, 37.3% from fat, and 45.7% from carbohydrates. The percent of energy from carbohydrates and proteins did not meet established guidelines of 20% protein, 50% to 60% carbohydrates, and 25% to 35% fats. Fat intake exceeded recommendations.

From the total sample data, there was a significant weak positive correlation between dietary energy intake and waist-to-hip ratio (r=0.18; *P*=.03), indicating that sample data from those with a higher waist-to-hip ratio had higher self-reported dietary energy intake. There were no significant correlations between dietary energy intake and BMI or waist circumference. There were no correlations between dietary energy intake and BMI, waist circumference, waist-to-hip ratio, or BMI category based on sex.

There was a significant weak positive correlation between dietary protein intake and waist-to-hip ratio (r=0.18; *P*=.037), suggesting that sample data from those with a higher waist-to-hip ratio also consumed higher amounts of dietary protein intake. There was no significant correlation between dietary protein intake and BMI or waist circumference. For both men and women, there were no significant relationships between dietary protein intake and BMI or waist circumference. There was a significant moderate, positive relationship between dietary protein intake and waist-to-hip ratio in women, but not in men, suggesting that women with higher waist-to-hip ratio also had higher self-reported dietary protein intake. There was no significant relationship between dietary protein intake and BMI category.

Limitations to the study findings cited by the authors included the self-reported dietary intake results may not have accurately reflected usual intake because the data were collected at one point in time, and the possibility that participants may have underreported dietary intake.

In conclusion, the researchers said, "Clinicians should be aware that many patients with ESKD receiving maintenance hemodialysis may have inadequate energy and protein intake, especially on a dialysis day. Also, individuals with a higher BMI may consume less energy and protein than their normal-weight counterparts and there may be gender-related differences in waist-to-hip ratio and dietary intake. Based on the results of this study, waist-to-hip ratio may be a useful tool to assist clinicians in identifying patients who may be a risk for suboptimal nutritional intake, which could be an indication of PEW." ■

TAKEAWAY POINTS

- Researchers reported results of a study examining whether people receiving maintenance hemodialysis met the National Kidney Foundation Kidney Disease Outcomes Quality Initiative 2020 guidelines for nutritional adequacy on a dialysis day.
- The results suggested that the nutritional intake in that patient population was inadequate to meet the guidelines on a dialysis day.
- In women, there was a significant positive correlation between dietary protein intake and waist-to-hip ratio.

Eating Patterns and Prevalence of Diabetic Kidney Disease

The increasing prevalence of diabetes mellitus has significant impact on economic and health systems worldwide. Diabetes is a complex, chronic illness that requires continuous care with multifactorial risk-reduction strategies beyond glycemic control. The increase in the number of individuals with diabetes has had a corresponding impact on the development of diabetic kidney disease, affecting approximately 40% of patients with type 2 diabetes. Patients with diabetic kidney disease face increases in cardiovascular risks and costs of health care.

There is no ideal percentage of calories from carbohydrates, protein, and fat for patients with diabetes, creating a critical role for medical nutrition therapy. Individual nutrition therapy is based on the patient's health status, skills, resources, food preferences, and health goals.

Cíntia Corte Real Rodrigues, MSc, and colleagues in Brazil conduced a cross-sectional study to examine the relationship between eating patterns and diabetic kidney disease in patients with type 2 diabetes. Results were reported in the *Journal of Renal Nutrition* [2023;33(2):261-268].

Eligible participants with type 2 diabetes were >30 years of age at diabetes onset with no previous episode of ketoacidosis or documented ketonuria and had not used insulin in the 5 years since diabetes diagnosis. Outpatients consecutively treated at the endocrinology division of a university hospital and tertiary referral center in southern Brazil were recruited for study participation.

Patients underwent clinical and nutritional evaluation. A validated quantitative food frequency questionnaire was used to obtain dietary information, and eating patterns were identified by cluster analysis. Diabetic kidney disease was defined as estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2 and/or persistently elevated urinary albumin concentration (albuminuria ≥14 mg/L).

The study cohort included 329 patients with type 2 diabetes. Of those, 72% were White, 62% were women, and mean age was 62 years. Mean duration of diabetes was 10 years (range, 5-19 years), mean body mass index (BMI) was 30.9 kg/m^2, and mean glycated hemoglobin was 8.7%. Forty-seven percent of the cohort had diabetic kidney disease.

Based on cluster analysis, four eating patterns were identified: (1) healthy, a pattern of higher intake of dairy products, fruits, and vegetables; (2) snacks, a pattern with high intake of dairy products, whole breads, vegetables, and low-calorie products; (3) processed foods, a pattern with high intake of refined carbohydrates and processed meats; and (4) red meat, a pattern with high intake of red meat.

The healthy and red meat patterns had a higher proportion of unprocessed foods compared with snacks and processed food patterns. The processed foods pattern had the highest proportion of processed foods, and those in the snack pattern category had the highest proportion of ultraprocessed foods (P<.001 for all comparisons). There was no difference in culinary ingredients among the four patterns.

Participants in the red meat pattern group had higher total energy intake, lipids, proteins, and potassium and lower intake of total carbohydrates compared with participants in the other three pattern groups (P<.001 for all comparisons). The processed foods and red meat patterns had a higher glycemic load and sodium intake compared with the healthy and snack patterns (P<.001 for all comparisons).

Patients in the healthy pattern group were significantly older than those in the processed foods group (P=.011), but not the other groups. Those in the red meat group had a lower proportion of women (P=.009) and a greater proportion of sedentary individuals compared with the other groups (P=.024). Compared with other groups, the snacks group had the lowest proportion of patients with low socioeconomic status (P=.033).

There was no significant difference among the groups in glycated hemoglobin values. However, more patients in the processed foods pattern group were treated with the maximum daily dose of glycemic agents (P=.011). Those in the processed foods group also had significantly higher fasting plasma glucose compared with snack eaters, but not compared with the other groups. The red meat group had the most patients with diabetic kidney disease compared with the other groups (P=.032).

The researchers utilized Poisson regression models to test for possible associations between eating patterns and diabetic kidney disease (as an outcome). Following adjustment for age, male sex, sedentarism, fasting plasma glucose, total energy intake, White race, BMI, duration of diabetes, and hypertension, there was a positive prevalence ratio (PR) for diabetic kidney disease in the snacks group and the red meat group (PR, 1.48; 95% CI, 1.10-1.99; P=.010 and PR, 1.93; 95% CI, 1.29-2.89; P=.001, respectively).

> The processed foods and red meat patterns have a higher glycemic load and sodium intake compared with the healthy and snack patterns (P<.001 for all comparisons).

Limitations to the study cited by the authors included the cross-sectional study design that limited the ability to establish a causal relationship between the variables and study outcomes; the lack of data on the blood nitrogen urea; and using eGFR to define diabetic kidney disease rather than a direct measurement of GFR.

In summary, the researchers said, "The snacks and red meat patterns were associated with a higher prevalence of diabetic kidney disease than the healthy pattern in our study. These results suggest that targeted guidance regarding food choice (ultraprocessed foods, type, and amount of meat) can be given to patients with diabetes. In this sense, lifelong nutritional strategies (reeducation or related support system) for patients with diabetic kidney disease about the concepts of healthy snacking habits (for optimizing a nutrient-dense snack regimen) should be reinforced. However, the effect of these orientations as protection from renal function decline needs to be tested in a randomized clinical trial." ■

TAKEAWAY POINTS

- Researchers in Brazil conducted a cross-sectional study to examine the relationships between eating patterns and diabetic kidney disease in a population of adult patients with type 2 diabetes mellitus.
- Four eating patterns were identified: healthy, snacks, processed foods, and red meat.
- Those in the snacks and red meat groups had higher prevalence of diabetic kidney disease compared with those in the healthy eating pattern group.

Outcomes of Machine Perfusion Compared With Hypothermia in Kidney Donors

In a population of kidney transplant recipients the use of therapeutic hypothermia (34 to 35 degrees C) has been shown to reduce relative risk of delayed graft function by 38% compared with the use of normothermia in brain-dead organ donors, a benefit particularly pronounced among high-risk donors. Results were similar in another study examining the protective effect of ex situ kidney hypothermic machine perfusion compared with static cold storage. However, according to **Darren Malinoski, MD,** and colleagues, the logistics of machine perfusion are complex and costly.

There are few data available on the clinical and cost effects of the use of machine perfusion of kidneys from brain-dead donors. The researchers conducted a pragmatic, adaptive, prospective, randomized trial to examine whether targeted mild hypothermia is as effective as machine perfusion of kidneys from brain-dead donors identified as eligible for machine perfusion of their kidneys. The trial also sought to determine whether the combination of the two strategies would be superior to either strategy alone. The trial also tested the hypothesis that finding that mild hypothermia was noninferior to machine perfusion would lead to cost savings and streamlined logistics. Results were reported in the *New England Journal of Medicine* [2023; 388(5):418-426].

The trial was conducted between August 10, 2017, and May 21, 2020, in seven states (Arizona, Colorado, Minnesota, North Dakota, Oregon, South Dakota, and Texas). Organ assignments were managed by six organ-procurement organizations in their respective service areas.

At the six organ-procurement facilities, brain-dead kidney donors were randomly assigned to undergo therapeutic hypothermia (hypothermia group), ex situ hypothermic machine perfusion (machine perfusion group), or both (combination-therapy group). The primary outcome of interest was delayed graft function in the kidney transplant recipients, defined as the initiation of dialysis during the first 7 days after transplantation. The noninferiority of hypothermia was determined if the upper boundary of the 95% CI fell below 1.4, a margin based on what was considered a clinically meaningful difference according to common practice. Secondary outcomes included graft survival at 1 year after transplantation.

A total of 910 donors (1820 kidneys) met inclusion criteria. Of those, 1349 kidneys from 725 donors were transplanted: 359 from the hypothermia group, 511 from the machine-perfusion group, and 479 from the combination-therapy group. In the machine-perfusion group, one patient received two kidneys, resulting in 511 kidneys transplanted into 510 patients. Two organ-procurement organizations performed machine perfusion in all kidney donors, and the remaining four performed machine-perfusion selectively.

After the enrollment of 600 donors, the researchers performed the first prespecified interim analysis. At that time, the hypothermia group met the prespecified criteria for inferiority as compared with both the machine-perfusion group and the combination-therapy group. The data and safety monitoring board recommended that the hypothermia group be dropped for inferiority after January 19, 2020, and that the randomization plan be changed accordingly. Subsequent donors were randomly assigned to either normothermia or hypothermia, and the design was revised to lower the maximum planned sample size to 1200 donors and to add a futility stopping rule for the remaining comparison between machine perfusion and combination therapy.

After the second prespecified interim analysis following enrollment of 800 donors, the data and safety monitoring board recommended that the trial be stopped for expected futility in showing the superiority of combination therapy over machine perfusion alone. There was no pause in enrollment and randomization during the interim analyses.

Donor characteristics were similar among the three treatment groups. Overall, mean age was 42 years, 62% were male, Kidney Donor Profile Index score was 46.40, and 80% met standard donation criteria.

Recipients did not undergo randomization. Recipient characteristics were also well balanced among the three treatment groups. The mean cold-ischemia time in the hypothermia group was 16.7 hours, compared with 19.3 hours in the machine-perfusion group and 19.1 hours in the combination-therapy group.

Delayed graft function occurred in 30% of patients in the hypothermia group (109/359), in 19% of patients in the machine-perfusion group (99/510), and in 22% of patients in the combination therapy group (103/479). In the primary efficacy analysis, the model-adjusted odds ratio was 2.21 (95% CI, 1.57-3.10) for hypothermia as compared with machine perfusion, 1.93 (95% CI, 1.39-2.69) for hypothermia as compared with combination therapy, and 1.14 (95% CI, 0.82-1.60) for combination therapy as compared with machine perfusion.

Hypothermia was inferior to machine perfusion in protecting kidney-graft recipients from delayed graft function, and combination therapy was not superior to machine perfusion. Adjusted risk ratios for delayed graft function were 1.72 (95% CI, 1.26-1.96) for hypothermia as compared with machine perfusion, 1.57 (95% CI, 1.26-1.96) for hypothermia as compared with combination therapy, and 1.09 (95% CI, 0.85-1.40) for combination therapy as compared with machine perfusion.

At 1 year posttransplant, the frequency of kidney graft survival was similar among the three groups. Among all 1348 kidney recipients, 45 died within 1 year of transplantation; 2% (n=8) were in the hypothermia group, 4% (n=9) were in the machine-perfusion group, and 4% (n=18) were in the combination therapy group. A total of 10 adverse events were reported among the donors, including cardiovascular instability (9 donors) and organ loss in one donor caused by machine-perfusion malfunction.

The open design of the study, where all health care providers were aware of group assignments, was cited by the authors as a limitation to the findings.

In summary, the researchers said, "We found that machine perfusion of kidneys obtained from brain-dead donors provided better protection against delayed graft function than targeted mild hypothermia alone. The combination of hypothermia and machine perfusion was not superior to machine perfusion alone in decreasing the incidence of delayed graft function." ■

TAKEAWAY POINTS

- Researchers reported results of a study examining the effect of hyperthermia as compared with machine perfusion on outcomes following kidney transplantation.
- At six US organ-procurement facilities, brain-dead donors were randomly assigned to undergo hypothermia, ex situ kidney hypothermic kidney perfusion, or both.
- Machine perfusion provided better protection against delayed graft function than targeted mild hypothermia alone. There was no additional protection with combination therapy.

Controlling Gout in Adult Kidney Transplant Recipients

The most common solid organ transplant is kidney transplant. In 2021, there were more than 24,600 kidney transplants performed in the United States. Common comorbidities experienced by kidney transplant recipients include hyperuricemia and consequent gout. The prevalence rate of gout in the United States among kidney transplant recipients is approximately 12-fold higher than that in the general nontransplanted population.

Reduced urate excretion related to chronic renal impairment as well side effects associated with medications such as calcineurin inhibitors and diuretics are potential contributors to the increased prevalence of gout. Management of gout in kidney transplant recipients is challenging due to potential adverse effects and drug interactions that lead to underutilization of conventional urate lowering therapies in that patient population.

Pegloticase is a recombinant modified mammalian urate oxidase that is indicated for the treatment of chronic gout in adults refractory to conventional therapy. Results of two replicate phase 3 studies for pegloticase monotherapy demonstrated the sustained reduction of serum uric acid in 43.5% of participants in 6 months. Pegloticase has been shown to be safe and effective in a small number of patients with kidney and kidney-pancreas transplants. However, there are no formal clinical trials examining the efficacy and safety of pegloticase in kidney transplant recipients with gout.

Abdul Abdellatif, MD, FASN, and colleagues conducted an open-label, phase 4 trial (PROTECT NCT04087720) designed to examine the safety and efficacy of pegloticase in 20 kidney transplant recipients >1 year prior to enrollment. Inclusion criteria were uncontrolled gout and a functioning kidney transplant. Results were reported online in *Clinical Transplantation* [doi.org/10.1111/ctr:14993].

The primary end point was the proportion of treatment responders in the intention-to-treat population during month 6. Treatment response was defined as serum uric acid <6 mg/dL for more than 80% the evaluations during month 6 (weeks 20, 21, 22, 23, and 24). Safety evaluations included all incidences of adverse events and serious adverse events. Infusion reactions, anaphylaxis, gout flare, and major cardiovascular events were considered events of special interest.

The intention-to-treat population included 20 participants who entered the open-label treatment period that included pegloticase treatments every 2 weeks for a total of 12 infusions. Of the 20 participants, 70% (n=14) completed the 24-week open-label treatment period and received all 12 pegloticase treatments.

Mean age at baseline was 53.9 years, 85% were male, mean time from kidney transplantation was 14.7 years, and mean time from gout diagnosis was 7.9 years. Eleven participants (55%) reported a history of visible gout tophi and 18 (90%) reported gout flares within the previous 12 months. All participants were on stable doses of two or more immunosuppressive drugs and 17 (85%) were CKD stage 3a or 3b. Fourteen participants (70%) were on a therapy regimen of two or more immunosuppressive drugs consisting of a calcineurin inhibitor (CNI) or mTOR inhibitor-based protocol (tacrolimus, cyclosporin, or rapamycin), an antimetabolite (mycophenolate or azathioprine), and prednisone. Four (20%) were on a CNI and prednisone without an antimetabolite, and two (10%) were on an antimetabolite and prednisone without a CNI or mTOR inhibitor.

Sixteen of 18 study participants (88.9%; 95% CI, 65.3%-98.6%) reached and maintained a serum uric acid level of <6 mg/dL for at least 80% of the measurements during month 6. Participants who completed treatment or discontinued treatment for non-serum uric acid monitoring reasons but continued with follow-up study monitoring achieved substantial and sustained reduction in serum uric acid during ongoing treatment. Among responders, reduction in serum uric acid was observed by the week 2 visit.

Per study protocol, the two participants with two consecutive serum uric acid values >6 mg/dL were considered nonresponders; they were among the four participants who were not receiving an antimetabolite as part of their immunosuppression regimen. There was a mean increase in serum uric acid at 3-month follow-up visits; the increase was expected after treatment discontinuation.

All participants who received at least one dose of pegloticase and had a post-pegloticase sample available for pharmacokinetic analysis were included in the pharmacokinetics population. Measurable serum concentrations of pegloticase were maintained in serum uric acid responders through month 6. Median predose pegloticase concentration following initiation of treatment ranged from 0.97 µg/L at week 2 (n=20) to 1.59 µg/mL at week 14 (n=15). Median postdose pegloticase concentration ranged from 1.57 µg/mL at week 1 (n=18) to 3.60 µg/mL at week 14 (n=16) across visits.

Pegloticase immunogenicity, evaluated by the incidence of anti-pegloticase antibodies, showed consistency with the pharmacokinetic results with substantially increased anti-drug antibodies titers and decreased serum pegloticase concentrations in the two nonresponders only. All other anti-pegloticase antibody titer measures were not meaningfully greater than baseline levels and considered negative for induction of anti-pegloticase antibodies.

Eighty percent of participants (n=16/20) experienced treatment-emergent adverse events; 90% were considered mild to moderate in intensity. During the treatment period, 45% (n=9/20) experienced gout flares. The percentage of gout flares decreased from 35% (n=7/2) during the first month of treatment to 0% (n=0/16) during month 6. Most gout flares were mild or moderate.

Seven serious adverse events deemed unrelated to pegloticase were reported in 25% of participants (n=5/20). None of the serious adverse events led to investigator-directed discontinuation of the study drug. There were no anaphylaxis, infusion reactions, or major cardiovascular events reported.

Limitations to the study findings cited by the authors included the open-label design, lack of a control group, the small cohort size, and the wide variation in the immunosuppression regimens used by the participants.

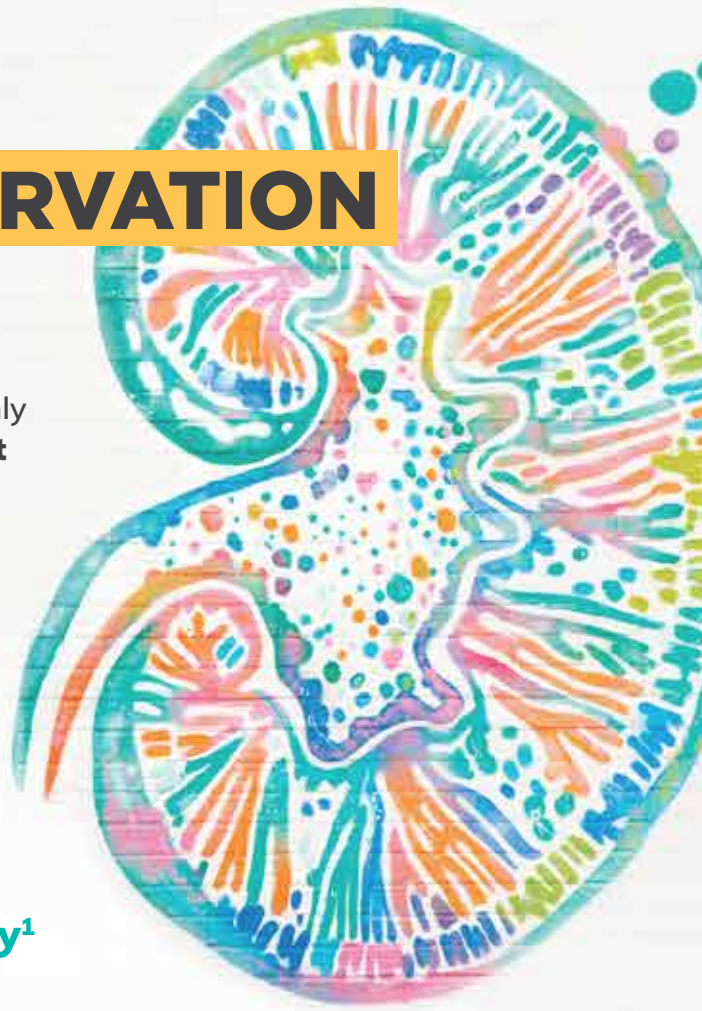
In conclusion, the researchers said, "Pegloticase was well tolerated in this trial of adult participants with uncontrolled gout who had a history of kidney transplantation with an increased proportion achieving durable response compared to participants treated with pegloticase without an immunomodulator. Pegloticase immunogenicity showed consistency with the pharmacokinetic and serum uric acid results for the two participants that did not respond with appropriately decreased serum uric acid concentrations. The proportion of patients with gout flares declined over the 6-month treatment period to 0% in month 6. There were no infusion reactions, anaphylaxis, or new safety concerns identified. Data from this open-label trial suggest pegloticase is a potentially safe and effective option to manage gout in kidney transplant patients who are at high risk of developing gout and have failed other urate-lowering therapies." ■

TAKEAWAY POINTS

- Researchers reported results of an open-label phase 4 trial assessing the efficacy and safety of pegloticase in adult kidney transplant recipients with uncontrolled gout.
- The primary end point of serum uric level <6 mg/dL for >80% of the time during month 6 was achieved by 88.9% of the study cohort.
- Pegloticase was well tolerated; there were no infusion reactions, anaphylaxis, or new safety concerns identified.

For adults with active lupus nephritis[1]

HELP MAKE KIDNEY PRESERVATION POSSIBLE WITH LUPKYNIS[1,a]



Results from LUPKYNIS in combination with MMF and low-dose steroids in the only clinical trial program to include **3 years of continuous lupus nephritis treatment and follow-up.**[1,b]

Safety and tolerability similar to MMF and low-dose steroids alone[1]

3 years of consistent safety with a comparable proportion of patients experiencing adverse events between groups.

- 86% in the LUPKYNIS plus MMF and low-dose steroids group experienced AEs vs 80% on MMF and low-dose steroids alone

Steroid sparing with doses at or below 2.5 mg/day[1]

At year 3, 76% of patients maintained 2.5 mg/day or less of steroids.[1,3]

[a]Kidney preservation as defined by evaluating the slope of the mean change in corrected eGFR of each arm from month 12 to month 36.[1]

[b]The AURORA 1 Phase 3 trial was a randomized, double-blind, placebo-controlled trial of LUPKYNIS 23.7 mg BID in combination with MMF (target 2 g/day) and corticosteroids (n=179) vs placebo BID in combination with MMF and corticosteroids (n=178) in adults with class III or IV (alone or in combination with class V) or class V lupus nephritis. AURORA 2 was a Phase 3, double-blind, 2-year continuation study of AURORA 1. Patients who completed AURORA 1 were eligible to enroll in the AURORA 2 extension. Patients entered the study voluntarily and continued to receive the same double-blind study drug treatment assigned by randomization in the AURORA 1 study. Randomization remained masked for the duration of the study; however, randomization criteria employed to enroll in AURORA 1 were not maintained in AURORA 2.[1,2]

[c]Both kidney preservation and kidney function decline were defined by evaluating the slope of the mean change in corrected eGFR of each arm from month 12 to month 36. Slopes of the change in eGFR were: –0.2 mL/min/1.73 m^2 with LUPKYNIS plus MMF and low-dose steroids (95% CI: –3.0, 2.7) and –5.4 mL/min/1.73 m^2 with MMF and low-dose steroids over 2 years (95% CI: –8.4, –2.3).[1]

[d]Renal function was assessed with corrected eGFR (Chronic Kidney Disease Epidemiology Collaboration equation) using a prespecified ceiling of 90 mL/min/1.73 m^2. Analysis of AURORA 2 patients includes data from pretreatment baseline of AURORA 1, 12 months in AURORA 1, and up to 24 months in AURORA 2.[1,2]

AE=adverse event; BID=twice daily; CI=confidence interval; eGFR=estimated glomerular filtration rate; LN=lupus nephritis; MMF=mycophenolate mofetil.

INDICATION

LUPKYNIS is indicated in combination with a background immunosuppressive therapy regimen for the treatment of adult patients with active lupus nephritis (LN). *Limitations of Use*: Safety and efficacy of LUPKYNIS have not been established in combination with cyclophosphamide. Use of LUPKYNIS is not recommended in this situation.

IMPORTANT SAFETY INFORMATION

BOXED WARNINGS: MALIGNANCIES AND SERIOUS INFECTIONS

Increased risk for developing malignancies and serious infections with LUPKYNIS or other immunosuppressants that may lead to hospitalization or death.

CONTRAINDICATIONS: LUPKYNIS is contraindicated in patients taking strong CYP3A4 inhibitors because of the increased risk of acute and/or chronic nephrotoxicity, and in patients who have had a serious/severe hypersensitivity reaction to LUPKYNIS or its excipients.

WARNINGS AND PRECAUTIONS

Lymphoma and Other Malignancies: Immunosuppressants, including LUPKYNIS, increase the risk of developing lymphomas and other malignancies, particularly of the skin. The risk appears to be related to increasing doses and duration of immunosuppression rather than to the use of any specific agent.

Serious Infections: Immunosuppressants, including LUPKYNIS, increase the risk of developing bacterial, viral, fungal, and protozoal infections (including opportunistic infections), which may lead to serious, including fatal, outcomes.

Nephrotoxicity: LUPKYNIS, like other calcineurin inhibitors (CNIs), may cause acute and/or chronic nephrotoxicity. The risk is increased when CNIs are concomitantly administered with drugs associated with nephrotoxicity.

Hypertension: Hypertension is a common adverse reaction of LUPKYNIS therapy and may require antihypertensive therapy.

Neurotoxicity: LUPKYNIS, like other CNIs, may cause a spectrum of neurotoxicities: severe include posterior reversible encephalopathy syndrome (PRES), delirium, seizure, and coma; others include tremor, paresthesia, headache, and changes in mental status and/or motor and sensory functions.

Hyperkalemia: Hyperkalemia, which may be serious and require treatment, has been reported with CNIs, including LUPKYNIS. Concomitant use of agents associated with hyperkalemia may increase the risk for hyperkalemia.

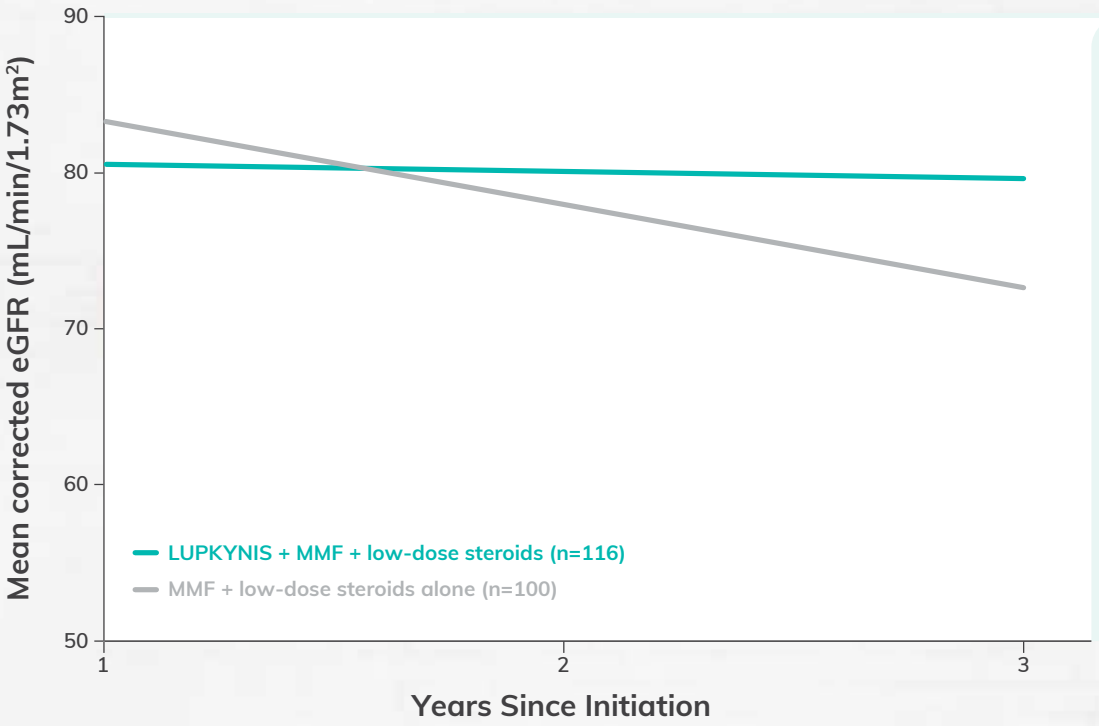
QTc Prolongation: LUPKYNIS prolongs the QTc interval in a dose-dependent manner when dosed higher than the recommended lupus nephritis therapeutic dose. The use of LUPKYNIS in combination with other drugs that are known to prolong QTc may result in clinically significant QT prolongation.

Stable eGFR throughout the extension study[1]

Kidney function was preserved in patients treated with LUPKYNIS throughout the extension study[1,c,d]

- Slope change with MMF and low-dose steroids alone likely reflects the natural progression of lupus nephritis

Kidney Function Over Time[1]



Rate of decline in eGFR (slope) over 2-year period:
−0.2 mL/min/1.73m²
(95% CI: −3.7, 2.7)

Rate of decline in eGFR (slope) over 2-year period:
−5.4 mL/min/1.73m²
(95% CI: −8.4, −2.3)

96% less eGFR loss over 2 years with LUPKYNIS

5.2 eGFR slope difference vs MMF + low-dose steroids alone[1]

To learn more about the AURORA 2 Study, scan the code or visit LUPKYNISLongTerm.com

Immunizations: Avoid the use of live attenuated vaccines during treatment with LUPKYNIS. Inactivated vaccines noted to be safe for administration may not be sufficiently immunogenic during treatment with LUPKYNIS.

Pure Red Cell Aplasia: Cases of pure red cell aplasia (PRCA) have been reported in patients treated with another CNI immunosuppressant. If PRCA is diagnosed, consider discontinuation of LUPKYNIS.

Drug-Drug Interactions: Avoid co-administration of LUPKYNIS and strong CYP3A4 inhibitors or with strong or moderate CYP3A4 inducers. Reduce LUPKYNIS dosage when co-administered with moderate CYP3A4 inhibitors. Reduce dosage of certain P-gp substrates with narrow therapeutic windows when co-administered.

ADVERSE REACTIONS

The most common adverse reactions (≥3%) were glomerular filtration rate decreased, hypertension, diarrhea, headache, anemia, cough, urinary tract infection, abdominal pain upper, dyspepsia, alopecia, renal impairment, abdominal pain, mouth ulceration, fatigue, tremor, acute kidney injury, and decreased appetite.

SPECIFIC POPULATIONS

Pregnancy/Lactation: May cause fetal harm. Advise not to breastfeed.

Renal Impairment: Not recommended in patients with baseline eGFR ≤45 mL/min/1.73 m² unless benefit exceeds risk. If used in this population, reduce LUPKYNIS dose.

Hepatic Impairment: For mild or moderate hepatic impairment, reduce LUPKYNIS dose. Avoid use with severe hepatic impairment.

Please see Brief Summary of Prescribing Information including Boxed Warning on adjacent pages.

References: 1. Saxena A, Ginzler EM, Gibson K, et al. Safety and efficacy of long-term voclosporin treatment for lupus nephritis in the Phase 3 AURORA 2 clinical trial. *Arthritis Rheumatol.* Published online July 19, 2023. doi:10.1002/art.42657 **2.** Rovin BH, Teng YKO, Ginzler EM, et al. Efficacy and safety of voclosporin versus placebo for lupus nephritis (AURORA 1): a double-blind, randomised, multicentre, placebo-controlled, phase 3 trial. *Lancet.* 2021;397(10289):2070-2080. doi:10.1016/S0140-6736(21)00578-X
3. Aurinia Pharma U.S., Inc. Data on file.

Aurinia™

US-LUP-2300205 09/23

Lupkynis® (voclosporin) capsules 7.9 mg

LUPKYNIS® (voclosporin) capsules, BRIEF SUMMARY
SEE PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION

BOXED WARNINGS: MALIGNANCIES AND SERIOUS INFECTIONS

Increased risk for developing malignancies and serious infections with LUPKYNIS or other immunosuppressants that may lead to hospitalization or death.

INDICATIONS AND USAGE

LUPKYNIS is indicated in combination with a background immunosuppressive therapy regimen for the treatment of adult patients with active lupusnephritis (LN). Limitations of Use: Safety and efficacy of LUPKYNIS have not been established in combination with cyclophosphamide. Use of LUPKYNIS is not recommended in this situation.

CONTRAINDICATIONS

LUPKYNIS is contraindicated in patients taking strong CYP3A4 inhibitors because these medications can significantly increase exposure to LUPKYNIS which may increase the risk of acute and/or chronic nephrotoxicity and also in patients who have had a serious/severe hypersensitivity reaction to LUPKYNIS or its excipients.

WARNINGS AND PRECAUTIONS

Lymphoma and Other Malignancies: Immunosuppressants, including LUPKYNIS, increase the risk of developing lymphomas and other malignancies, particularly of the skin. The risk appears to be related to the intensity and duration of immunosuppression rather than to the use of any specific agent.

Serious Infections: Immunosuppressants including LUPKYNIS, increase the risk of developing bacterial, viral, fungal, and protozoal infections including opportunistic infections. These infections may lead to serious, including fatal, outcomes. Viral infections reported include cytomegalovirus and herpes zoster infections.

Nephrotoxicity: LUPKYNIS, like other calcineurin inhibitors (CNIs), may cause acute and/or chronic nephrotoxicity. The risk is increased when CNIs are concomitantly administered with drugs associated with nephrotoxicity. Consider the risks and benefits of LUPKYNIS treatment in light of the patient's treatment response and risk of worsening nephrotoxicity, including in the following situations: 1) Longer treatment duration beyond one year. Safety and efficacy of LUPKYNIS have not been established beyond one year. 2) Co-administration with drugs associated with nephrotoxicity. The risk for acute and/or chronic nephrotoxicity is increased when LUPKYNIS is concomitantly administered with drugs associated with nephrotoxicity.

Hypertension: Hypertension is a common adverse reaction of LUPKYNIS therapy and may require antihypertensive therapy.

Neurotoxicity: LUPKYNIS, like other CNIs, may cause a spectrum of neurotoxicities. The most severe include posterior reversible encephalopathy syndrome (PRES), delirium, seizure, and coma; others include tremor, paresthesia, headache, mental status changes, and changes in motorand sensory functions.

Hyperkalemia: Hyperkalemia, which may be serious and require treatment, has been reported with CNIs including LUPKYNIS. Concomitant use of agents associated with hyperkalemia may increase the risk for hyperkalemia.

QTc Prolongation: LUPKYNIS prolongs the QTc interval in a dose-dependent manner after single dose administration at a dose higher than the recommended lupus nephritis therapeutic dose. The use of LUPKYNIS in combination with other drugs that are known to prolong QTc may result in clinically significant QT prolongation.

Immunizations: Avoid the use of live attenuated vaccines during treatment with LUPKYNIS. Inactivated vaccines noted to be safe for administration may not be sufficiently immunogenic during treatment with LUPKYNIS.

Pure Red Cell Aplasia: Cases of pure red cell aplasia (PRCA) have been reported in patients treated with another CNI immunosuppressant. If PRCA is diagnosed, consider discontinuation of LUPKYNIS.

ADVERSE REACTIONS

Clinical Trials Experience

A total of 355 patients with LN were treated with voclosporin in the Phase 2 and 3 clinical studies of whom 224 were exposed for at least 48 weeks. A total of 267 patients received at least 1 dose of LUPKYNIS 23.7 mg twice a day with 184 exposed for at least 48 weeks. A total of 88 patients received at least 1 dose of voclosporin 39.5 mg twice a day with 40 exposed for 48 weeks. Patients received background treatment with MMF 2 g daily and an IV bolus of corticosteroids.

Adverse Reactions in ≥3% of Patients Treated with LUPKYNIS 23.7 mg BID and ≥2% Higher than Placebo in Studies 1 and 2

Adverse Reaction	LUPKYNIS 23.7 mg twice a day (n=267)	Placebo (n=266)
Glomerular filtration rate decreased*	26%	9%
Hypertension	19%	9%
Diarrhea	19%	13%
Headache	15%	8%
Anemia	12%	6%
Cough	11%	2%
Urinary tract infection	10%	6%
Abdominal pain upper	7%	2%
Dyspepsia	6%	3%
Alopecia	6%	3%
Renal Impairment*	6%	3%
Abdominal Pain	5%	2%
Mouth ulceration	4%	1%
Fatigue	4%	1%
Tremor	3%	1%
Acute kidney injury*	3%	1%
Decreased appetite	3%	1%

**See Specific Adverse Reactions below (Nephrotoxicity)*

Other adverse reactions reported in less than 3% of patients in the LUPKYNIS 23.7 mg group and at a 2% higher rate than in the placebo group through Week 48/52 included gingivitis and hypertrichosis. Studies 1 and 2 were integrated to represent safety through 48/52 weeks for placebo (n=266), LUPKYNIS 23.7 mg twice a day (n=267), and voclosporin 39.5 mg twice a day (n=88). Exposure adjusted incidence rates were adjusted by study for all the adverse events reported in this section.

DRUG INTERACTIONS

Effect of Other Drugs on LUPKYNIS

Strong and Moderate CYP3A4 Inhibitors: Voclosporin is a sensitive CYP3A4 substrate. Co-administration with strong or moderate CYP3A4 inhibitors increases voclosporin exposure, which may increase the risk of LUPKYNIS adverse reactions. Co-administration of LUPKYNIS with strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, clarithromycin) is contraindicated. Reduce LUPKYNIS dosage when co-administered with moderate CYP3A4 inhibitors (e.g., verapamil, fluconazole, diltiazem). Avoid food or drink containing grapefruit when taking LUPKYNIS.

Strong and Moderate CYP3A4 Inducers: Voclosporin is a sensitive CYP3A4 substrate. Co-administration with strong or moderate CYP3A4 inducers decreases voclosporin exposure, which may decrease the efficacy of LUPKYNIS. Avoid co-administration of LUPKYNIS with strong or moderate CYP3A4 inducers.

Effect of LUPKYNIS on Other Drugs

Certain P-gp Substrates

Voclosporin may be a P-gp inhibitor. Co-administration of voclosporin increases exposure of P-gp substrates, which may increase the risk of adverse reactions of these substrates. For certain P-gp substrates with a narrow therapeutic window, reduce the dosage of the substrate as recommended in its prescribing information, if needed.

OATP1B1 Substrates

The effect of LUPKYNIS on OATP1B1 substrates (e.g., statins) has not been studied clinically. However, voclosporin is an OATP1B1 inhibitor in vitro, and information suggests an increase in the concentration of these substrates is possible. Monitor for adverse reactions of OATP1B1 substrates when used concomitantly with LUPKYNIS.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

Avoid use of LUPKYNIS in pregnant women unless benefit outweighs risk. The available data on the use of LUPKYNIS in pregnant patients are insufficient to determine whether there is a drug-associated risk for major birth defects, miscarriage, or adverse maternal or fetal outcomes. There are risks to the mother and fetus associatedwith systemic lupus erythematosus (SLE). LUPKYNIS may be usedin combination with a background immunosuppressive therapy regimen that includes mycophenolate mofetil (MMF). MMF used in pregnant women and men whose female partners are pregnant can cause fetal harm (major birth defects and miscarriage). Refer to the MMF prescribing information for more information on its use during pregnancy. The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Clinical Considerations

Disease-Associated Maternal and/or Embryo/Fetal Risk: Pregnant women with SLE are at increased risk of adverse pregnancy outcomes, including worsening of the underlying disease, premature birth, miscarriage, and intrauterine growth restriction. Maternal LN increases the risk of hypertension and preeclampsia/eclampsia. Passage of maternal autoantibodies across the placenta may result in adverse neonatal outcomes, including neonatal lupus and congenital heart block.

Lactation

There are no available data on the presence of voclosporin in human milk, the effects on the breastfed infant, or the effects on milk production. Voclosporin is present in milk of lactating rats. When a drug is present in animal milk, it is likely that the drug will be present in human milk. Given the serious adverse reactions seen in adult patients treated with LUPKYNIS such as increased risk of serious infections, advise patients that breastfeeding is not recommended during treatment and for at least 7 days after the last dose of LUPKYNIS (approximately 6 elimination half-lives).

Females and Males of Reproductive Potential

LUPKYNIS may be used in combination with a background immunosuppressive therapy regimen that includes MMF. If LUPKYNIS is administered with MMF, the information for MMF regarding pregnancy testing, contraception, and infertility also applies to this combination regimen. Refer to MMF prescribing information for additional information.

Pediatric Use: The safety and efficacy of LUPKYNIS in pediatric patients has not been established.

Geriatric Use: Clinical studies of LUPKYNIS did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger patients. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

Renal Impairment

Use of LUPKYNIS is not recommended in patients with a baseline eGFR ≤45 mL/min/1.73 m^2 unless the benefit exceeds the risk. If used in patients with severe renal impairment at baseline, LUPKYNIS should be used at a reduced dose. No dosage adjustment is recommended in patients with mild or moderate renal impairment at baseline. Monitor eGFR closely. After initiating therapy, dosing adjustments should be made based on eGFR.

Hepatic Impairment

In patients with mild and moderate hepatic impairment, reduce the LUPKYNIS dosage. Avoid LUPKYNIS in patients with severe hepatic impairment.

OVERDOSAGE

Experience with LUPKYNIS overdose is limited. Symptoms of accidental overdose with LUPKYNIS may include tremor, headache, nausea and vomiting, infections, urticaria, lethargy, and increases in blood urea nitrogen, serum creatinine, and alanine aminotransferase levels.

To report SUSPECTED ADVERSE REACTIONS, contact Aurinia Pharma U.S., Inc. at 1-833-672-0028 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

This brief summary is based on LUPKYNIS Prescribing Information (FPI-0009) issued January 2021.

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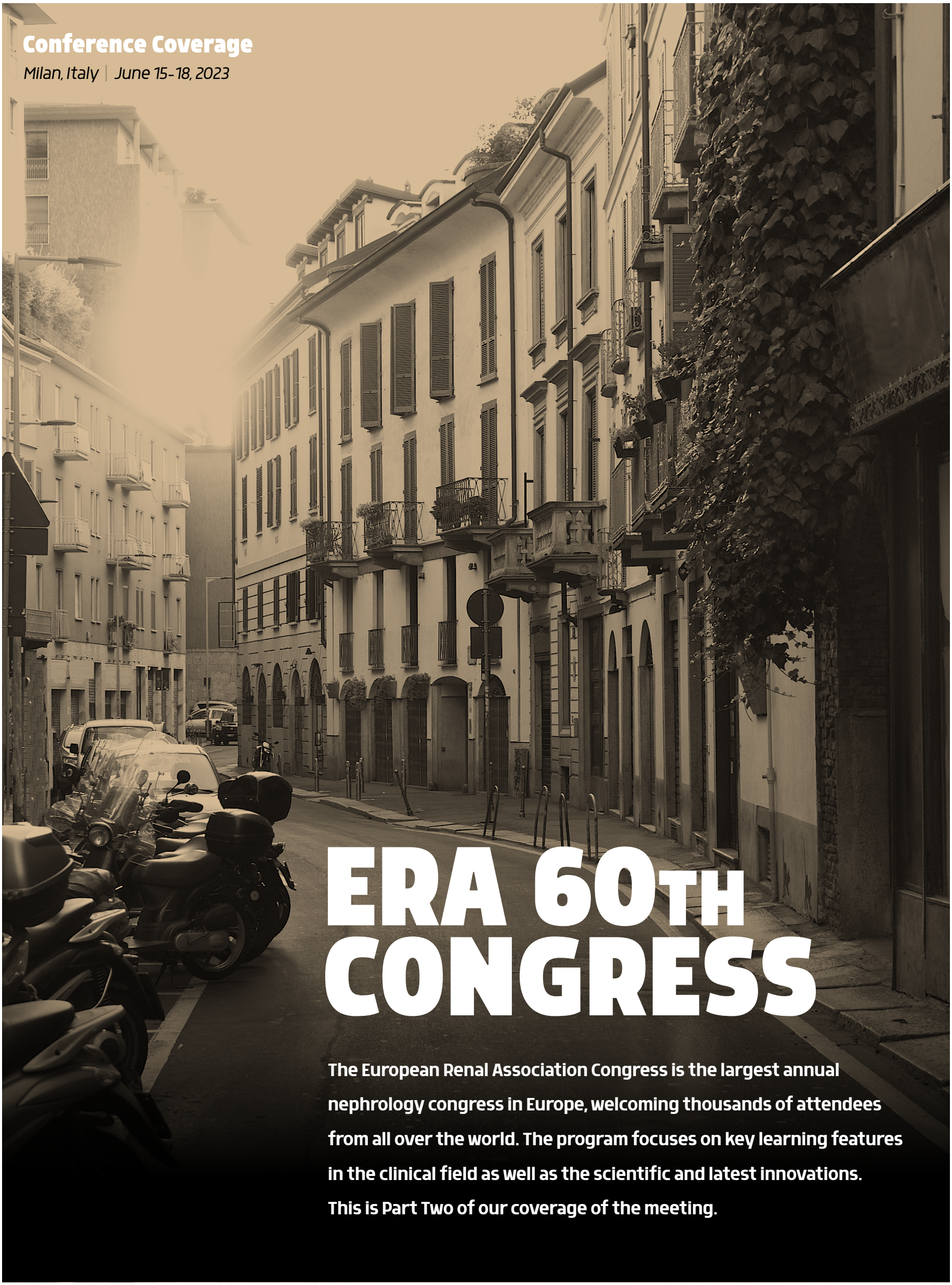
Additional information can be found at LUPKYNISpro.com.



ERA 60TH CONGRESS

The European Renal Association Congress is the largest annual nephrology congress in Europe, welcoming thousands of attendees from all over the world. The program focuses on key learning features in the clinical field as well as the scientific and latest innovations. This is Part Two of our coverage of the meeting.

Intradialytic Hypertension and Adverse Outcomes in Dialysis Patients

During hemodialysis, the pattern of systolic blood pressure is typically characterized by a rapid decrease during the start of dialysis, followed by a more gradual decline later in the session. Patients receiving hemodialysis who experience a deviation from the typical blood pressure trend with a rise in blood pressure during hemodialysis have been shown to be at increased risk for mortality and morbidity.

According to **Jeanmar De Castro** and **Trisha Michelle Manalaysay** at the Southern Philippines Medical Center, Section of Adult Nephrology, Davao City, The Philippines, this deviation may be a modifiable risk marker for short-term adverse events in patients receiving hemodialysis. The researchers conducted a study examining the association of intradialytic hypertension with short-term (30 day) clinical outcomes. Results were reported at the ERA 60th Congress in a presentation titled *Association Between Intradialytic Hypertension Frequency and Short-Term Clinical Outcomes Among ESRD Patients Receiving Hemodialysis.*

All patients at the tertiary hospital who were 18 years of age and older and who had at least 1 year of hemodialysis were included in the prospective cohort study (n=81). The researchers collected data from patients within a 30-day observation period and recorded the occurrence of events within the next 30-day follow-up period. The data collection was conducted from July 2022 to August 2022.

Average age of the study participants was 49.18 years. The majority (55.56%) were male and the most common cause of end-stage renal disease was glomerular disease. The incidence of intradialytic hypertension was 49.38%. Of the 81 participants, 16% had short-term outcomes. Of those, 13.5% were hospitalized within the follow-up period, and 63.6% had intradialytic hypertension. Two point four percent of the cohort died during the follow-up period. All of those who died had intradialytic hypertension.

There were significant associations between concomitant heart failure ($P<.001$), having non-tunneled catheter vascular access ($P=.004$), high intradialytic frequency ($P<.001$), and interdialytic weight gain of at least 2 kilograms ($P=.029$) and hospitalization and mortality within 30 days.

In conclusion, the authors said, "The results of this study recommend that prompt attention should be given to ESRD patients who exhibit intradialytic hypertension as this may be a risk marker for adverse short-term events within 30 days. In line with this, setting of dry weight, screening for heart failure, conversion to permanent arteriovenous fistula access, and tailoring of antihypertensive medications for better blood pressure control should be assessed with vigilance in the dialysis unit."

Source: De Castro J, Manalaysay TM. Association between intradialytic hypertension frequency and short-term clinical outcomes among ESRD patients receiving hemodialysis. #4319. Abstract of a presentation at the European Renal Association 60th Congress; June 15-18, 2023; Milan, Italy.

Variability in Heart Rate at Rest and After Stress by Dialysis Modality

In patients with end-stage kidney disease (ESKD), the leading causes of cardiovascular mortality are cardiac arrhythmias and sudden death. Autonomic dysfunction contributes to the arrhythmogenic background of patients with ESKD.

Danai Faitatzidou and colleagues in Greece conducted a study comparing linear and nonlinear heart rate variability (HRV) indices between patients on hemodialysis and patients on peritoneal dialysis, both at rest and in response to mental- and physical-stimulation maneuvers. Results of the study were reported at the ERA 60th Congress in a presentation titled *Heart Rate Variability at Rest and in Response to Physical and Mental Stress: A Comparative Study Between Hemodialysis and Peritoneal Dialysis Patients.*

The overall study cohort included 34 patients receiving hemodialysis, 34 patients on peritoneal dialysis matched for age, sex, and dialysis vintage, as well as 17 controls matched for age and sex. Linear and nonlinear HRV indices were used to examine autonomic function. Heart rate was recorded continuously with Finometer-PRO at rest and during orthostatic, mental-arithmetic, sit-to-stand, and handgrip exercise tests.

There were no significant between-group differences in resting HRV indices, with the exception of the detrended fluctuation analysis alpha 1 (DFA-a1) index. During the mental-arithmetic test, all HRV indices were similar between the hemodialysis group and the peritoneal dialysis group. Results of the physical stress tests were also similar between the two groups.

Patterns of HRV responses to orthostatic and handgrip exercise tests were similar between the two dialysis groups Following the sit-to-stand test, RMSSD, SD1, SD2, and DFA-a2 indices were higher compared to rest only in hemodialysis patients, indicating a greater difficulty in hemodialysis patients in recovering normal autonomic nervous system (ANS) function following a physical stress test.

"HRV indices at rest and after mental and physical stimulation did not differ between hemodialysis and peritoneal dialysis patients," the researchers said. "However, the ANS response following the sit-to-stand test was more impaired in hemodialysis. These findings suggest that ANS dysfunction is not largely affected by dialysis modality, but small differences in normal ANS recovery may exist."

Source: Faitatzidou D, Dipla K, Theodorakopoulou M, et al. Heart rate variability at rest and in response to physical and mental stress: a comparative study between hemodialysis and peritoneal dialysis patients. #6044. Abstract of a presentation at the European Renal Association 60th Congress; June 15-18, 2023; Milan, Italy.

In 16 of the 22 hemodialysis patients, blood volume was higher than in the controls. In the hemodialysis group, the median blood volume was 89.3 mL/kg, compared with 79.9 mL/kg in the control group ($P<.037$).

Fluid Overload in Patients Receiving Hemodialysis

Managing fluid overload in patients receiving hemodialysis is a major challenge. Patients experiencing fluid overload may develop hypervolemia. **Vårin Vinje** and colleagues in Demark conducted a study to test the hypothesis that patients on hemodialysis reaching dry weight could have undetected hypervolemia and low hemoglobin concentration due to hemodilution.

Results of the study were reported during a presentation at the ERA 60th Congress. The presentation was titled *Intravascular Volumes and the Influence on Anemia in Patients Undergoing Maintenance Hemodialysis.*

The overall study cohort included 22 patients on hemodialysis and 22 healthy controls. Using a carbon monoxide(CO)-rebreathing method, blood volume, plasma volume, red blood cell volume, and total hemoglobin mass were determined in hemodialysis patients reaching dry weight and in the control group. For validation purposes, blood volume measurements were also obtained by a dual-isotope labeling technique.

In 16 of the 22 hemodialysis patients, blood volume was higher than in the controls. In the hemodialysis group, the median blood volume was 89.3 mL/kg, compared with 79.9 mL/kg in the control group ($P<.037$). Median plasma volume was 54.7 mL/kg in the hemodialysis group compared with 44.0 mL/kg in the control group ($P<.001$).

Hemoglobin was lower in the hemodialysis group ($P<.001$). There was no difference in total hemoglobin mass between the two groups ($P=.11$). Changes in hemoglobin levels during and following dialysis were seen in the hemodialysis group. There was a correlation between blood volume measured by the CO-rebreathing test and the dual-isotope labelling technique in the control group ($r=0.83$; $P=.015$), but not in the hemodialysis group ($r=0.25$; $P=.60$)

"The hemodialysis group had increased blood volume at dry weight due to high plasma volume, indicating a hypervolemic state. The total hemoglobin mass was similar between hemodialysis patients and controls, unlike hemoglobin, which emphasizes that hemoglobin is an inaccurate marker of anemia among hemodialysis patients," the researchers said.

Source: Vinje V, Bomholt T, Hornum M, et al. Intravascular volumes and the influence on anemia in patients undergoing maintenance hemodialysis. #3712. Abstract of a presentation at the European Renal Association 60th Congress; June 15-18, 2023; Milan, Italy.

Spironolactone in Patients With CKD at High Risk for Hyperkalemia

Patients with chronic kidney disease (CKD) and albuminuria treated with mineralocorticoid receptor antagonists (MRA) experience reductions in blood pressure, albuminuria, and the rate of disease progression. However, according to **Frederik Husum Mårup** and colleagues, only a small fraction of patients with CKD are treated with an MRA despite the apparent benefits. The underuse of the agents may be due, in part, to a concern regarding hyperkalemia, a complication that when severe may cause life-threatening arrythmias.

International guidelines and results of previous studies have excluded patients at high risk of severe hyperkalemia, including patients with preexisting high serum potassium, from treatment with an MRA. For the current study, the researchers sought to examine whether the risk of hyperkalemia can be predicted by baseline levels of potassium or estimated glomerular filtration rate (eGFR). The study exposure was introduction of spironolactone on plasma potassium levels; the study population included closely monitored, high-risk patients excluded from other studies. The effect of spironolactone on eGFR and albuminuria were also of interest.

Results of the study were reported at the ERA 60th Congress. The presentation was titled *Potassium Levels and eGFR Do Not Predict Severe Hyperkalemia Following Spironolactone Introduction in Patients With CKD at High Risk of Hyperkalemia.*

Eligible patients had eGFR 25 to 60 mL/min/1.73 m^2 receiving maximal tolerated renin-angiotensin-aldosterone system blockade and a history of at least two episodes of hyperkalemia, defined as plasma potassium level >4.5 mmol/L within 24 months of study inclusion. Spironolactone was initiated at 25 mg daily following dietary counseling on avoidance of foods rich in potassium. If tolerated, the dose was increased to 50 mg after 2 weeks. Total follow-up was 4 weeks, with measurements of plasma potassium, eGFR, blood pressure, and spot urine albumin-to-creatinine ratio.

The cohort included 58 patients. Mean age was 65 years, 47 were male, and 23 had diabetes. Forty-eight patients reached a spironolactone dose of 50 mg. Following initiation of spironolactone, mean eGFR declined from 39 mL/min/1.73 m^2 at baseline to 34 mL/min/1.73 m^2 ($P<.001$) at week 4, and albuminuria was reduced from a median of 1276 mg/g to 654 mg/g. There was no significant change in blood pressure. Mean plasma potassium increased 0.5 mmol/L (from 4.7 mmol/L to 5.2 mmol/L).

Seventeen patients developed severe hyperkalemia, and four were briefly admitted with a plasma potassium level >6.2 mmol/L. There was no difference from baseline in plasma potassium or eGFR among the subcohort who developed severe hyperkalemia compared with those who did not develop severe hyperkalemia (4.70 vs 4.67 mmol/L; $P=.83$ and 36.2 vs 40.1 mL/min/1.73 m^2; $P=.13$, respectively). There was no correlation between baseline plasma potassium and plasma potassium at maximum spironolactone dose. There was no significant correlation between the change in plasma potassium and baseline eGFR.

In summary, the authors said, "Short-term treatment with spironolactone in patients with CKD at high risk of hyperkalemia leads to similar reductions in albuminuria and eGFR when compared with low-risk cohorts. With dietary counseling, 30% of patients will develop severe hyperkalemia within 4 weeks. Importantly, and contrary to common belief, neither baseline plasma potassium levels nor baseline eGFR were associated with the development of severe hyperkalemia. Thus, excluding patients from MRA treatment based solely on eGFR and plasma potassium levels is not appropriate. Instead, we believe an empirical approach based on dietary counseling and close monitoring of plasma potassium should be used."

Source: Mårup FH, Peters C, Nielsen S, et al. Potassium levels and eGFR do not predict severe hyperkalemia following spironolactone introduction in patients with CKD at high risk of hyperkalemia. #3068. Abstract of a presentation at the European Renal Association 60th Congress; June 15-18, 2023; Milan, Italy.

Sarcopenia and Mortality Risk in Kidney Transplant Recipients

Older adults and patients receiving maintenance dialysis are at increased risk for sarcopenia. However, there are few data available on the risk among kidney transplant recipients.

Akihiro Kosoku and colleagues conducted a single-center prospective cohort study to examine the association between sarcopenia and all-cause mortality in a population of kidney transplant recipients. Results of the study were reported at the ERA 60th Congress in a presentation titled *Sarcopenia as a Predictor of Mortality in Kidney Transplant Recipients.*

At baseline, study participants were evaluated for muscle mass, muscle strength, and physical performance, using a hand dynamometer, the 10-meter walk test, and bioelectrical impedance analysis, respectively. Sarcopenia was defined according to the Asia Working Group for Sarcopenia 2019 criteria.

To reduce bias between the sarcopenia and nonsarcopenia groups, the researchers used propensity score matching, adjusting for age, sex, and body mass index. After follow-up of 5 years, the Kaplan-Meier method and Cox proportional hazards model were used to assess patient survival in the matched cohort.

The total cohort included 212 patients, with a median age of 54 years, median transplant vintage of 79 months, and 16% (n=33) had sarcopenia at baseline. Following 1:1 propensity score matching, a matched cohort was generated. The overall incidence density rates of morality in the matched cohort were 48.8 per 1000 person-years in the sarcopenia group and 6.75 per 1000 person-years in the nonsarcopenia group.

Using the Kaplan-Meier method, the estimated survival curves indicated that cumulative survival in the sarcopenia group was significantly lower than that in the nonsarcopenia group (log rank test, $P=0.25$). Mortality risk was also significantly higher in the sarcopenia group that in the nonsarcopenia group (hazard ratio, 7.59; 95% CI, 1.93-61.7).

"Sarcopenia was a significant predictor of mortality in kidney transplant recipients," the authors said.

Source: Kosoku A, Iwai T, Kabei K, Nishide S, Machida Y, Uchida J. Sarcopenia as a predictor of mortality in kidney transplant recipients. #4089. Abstract of a presentation at the European Renal Association 60th Congress; June 15-18, 2023; Milan, Italy.

Cancer Status and Mortality Risk Among Elderly Hemodialysis Patients

Chronic kidney disease and older age are associated with an increased risk for malignancy. According to **Hyunjeong Cho** and colleagues, there are few data available on whether elderly patients with active cancer or a history of cancer face the same risk of mortality following initiation of hemodialysis as do elderly patients without a cancer history.

The researchers performed an analysis designed to examine prognosis according to cancer status in a population of elderly patients initiating hemodialysis. Results were reported at the ERA 60th Congress in a presentation titled *Cancer Status and Mortality in Elderly Incident Hemodialysis Patients.*

Using the retrospective cohort of the Korean Society of Geriatric Nephrology, the analysis included data on 2085 patients >70 years of age who initiated hemodialysis between 2010 and 2017. The Kaplan-Meier survival estimator and Cox proportional hazards regression analysis were used to assess the primary outcome of all-cause mortality.

At baseline, 12.6% (n=262) had a history of previous cancer and 2.6% (n=55) had active cancer. During 3.2 years of follow-up, 65.1% (n=1357) died. The incidence of all-cause mortality was significantly higher in the active cancer group compared with the previous cancer group and the no cancer group (85.5% vs 68.3% vs 64.0%; $P<.002$).

Kaplan-Meier analysis showed a significant difference in all-cause mortality among the three groups ($P<.001$, by log-rank test). Following adjustment for various clinical factors, results of multivariate Cox regression analysis revealed a strong association between active cancer and all-cause mortality (hazard ratio [HR], 1.89; 95% CI, 1.36-2.64; $P<.001$). There was no association between previous cancer and an increased risk of overall mortality (HR, 1.07; 95% CI, 0.90-1.28; $P=.448$).

"Active cancer was associated with high mortality in incident older hemodialysis patients. But patients with a history of previous cancer had a similar mortality risk compared with patients without a cancer history," the researchers said. "Therefore, our study suggests that older cancer survivors may be able to maintain dialysis successfully."

Source: Cho H, Park M, Sun I0, et al. Cancer status and mortality in elderly incident hemodialysis patients. #5686. Abstract of a presentation at the European Renal Association 60th Congress; June 15-18, 2023; Milan, Italy.

Management of Elderly Patients With Kidney Failure

Patients with kidney failure are commonly treated with dialysis. However, more than half of geriatric patients who initiate dialysis die within the first year of treatment. Current guidelines call for presenting comprehensive conservative management (CM) as an alternative option for elderly patients with kidney failure.

Results of a 2022 meta-analysis demonstrated that dialysis treatment had a median survival time of 20 to 67 months, compared with 6 to 31 month survival benefit with CM. However, according to Fiammetta Zanetti and colleagues, the distinction disappears in patients ≥80 years of age, suggesting that outcomes may be similar in both strategies in older patients.

The researchers conducted a study to examine and compare the survival of elderly patients who elected to undergo either conservative therapy or dialysis. Results of a preliminary analysis of data from the prospective observational study were reported at the ERA 60th Congress in a presentation titled *Kidney Failure Management in the Elderly: A Preliminary Survival Analysis*.

The study was conducted across three nephrology units in Veneto, Italy. A total of 117 patients in predialysis or CM clinics were enrolled. Inclusion criteria were age 75 or more years, estimated glomerular filtration rate (eGFR) >15 mL/min/1.73 m^2, and no history of dialysis therapy or CM (personalized pharmacological therapy plus adherence to a low-protein diet).

Medical records and interviews were used to collect baseline socio-demographic data, comorbidities, and results of blood and urine tests. The 36-item Short Form Survey questionnaire, the Barthel questionnaire, and the Mini-Mental State Examination were used to assess quality of life, functional status, and global cognitive functioning, respectively. Survival was evaluated at 3 and 9 months after follow-up initiation, defined as the date of the first dialysis session or when eGFR dropped below 10 mL/min/1.73 m^2 in patients in the CM group. Follow-up continued until the ninth month, death, change in treatments, discontinued medical follow-up, voluntary study discontinuation, or the end of the project.

Of the 117 patients enrolled, 64 initiated follow-up. Of those, 47 were in the CM group and 17 were in the dialysis group. Patients in the CM group were older than those in the dialysis group (median age, 82.5 years vs 78.9 years; P=.028). There were other statistically significant differences at baseline, including median levels of blood urea nitrogen, creatinine, parathyroid hormone, hemoglobin, and total cholesterol (all P<.05).

Eleven patients died during follow-up: 10 in the CM group and one in the dialysis group. One patient had no available date of death and was excluded from additional analyses. Kaplan-Meier curves and Log Rank Test revealed no significant difference in survival between the two groups (P=.25).

Because less that 50% of both groups died during follow-up, median survival time was undefined. In the CM group, unadjusted survival rates at 3 and 9 months were 91.3% and 78.2%, respectively.

"In this study, we found that middle-term survival in the elderly is comparable to dialysis therapy and CM," the researchers said. "Despite limitations, these results provide valuable information for clinical decision-making. Our results suggest that well-organized CM can be a reasonable option for elderly patients with kidney failure."

Source: Zanetti F, Fanton G, Martino F, et al. Kidney failure management in the elderly: a preliminary survival analysis. #3659. Abstract of a presentation at the European Renal Association 60th Congress; June 15-18, 20323; Milan. Italy.

Effect of SGLT2 Inhibitor in Patients With Heart Failure and CKD

In patients with diabetes and heart failure, the risk of hospitalization for heart failure is significantly reduced with treatment with sodium-glucose cotransporter 2 (SGLT2) inhibitors. According to **Maria Eleni Alexandrou** and colleagues, the data on SCLT2 inhibitors in patients with chronic kidney disease (CKD) and heart failure are unclear.

The researchers conducted a systematic review and meta-analysis designed to examine the effect of SGLT2 inhibitors on heart failure events among patients with CKD and across subgroups defined by baseline kidney function. Results of the analysis were reported during the ERA 60th Congress in a presentation titled *Effects of Sodium-Glucose Co-Transporter 2 Inhibitors on Heart Failure in Chronic Kidney Disease; A Systematic review and Meta-Analysis.*

The review included randomized, controlled trials that included data on the effect of SGLT2 inhibitors on the primary outcome of risk for hospitalization for heart failure, as well as secondary outcomes including time to hospitalization or an urgent visit related to heart failure in patients with prevalent CKD at baseline, and across subgroups stratified by baseline estimated glomerular filtration rate. (eGFR)

The meta-analysis included 12 studies representing 89,191 participants. Among patients with CKD, the risk for heart failure events was reduced by 32% with treatment with SGLT2 inhibitors compared with placebo (hazard ratio [HR], 0.68; 95% CI, 0.63-0.73). In the subgroup of patients with eGFR <60 mL/min/1.73 m^2, the reduction in heart failure events was more prominent than in patients with eGFR ≥60 mL/min/1.73 m^2 (HR, 0.68; 95% CI, 0.62-0.74 vs HR, 0.76; 95% CI, 0.69-0.83, respectively).

In subgroup analyses according to type of SGLT2 inhibitor, the treatment effect was consistent among all agents studied. In sensitivity analysis of data from studies that included only patients with diabetic kidney disease, the effect of SGLT2 inhibitor use was even more pronounced in the subgroup with eGFR <60 mL/min/1.73 m^2 (HR, 0.62; 95% CI, 0.54-0.70).

"Treatment with SGLT2 inhibitors led to a significant reduction in heart failure events in patients with CKD," the researchers said. "These findings may change the landscape of heart failure treatment in patients with advanced CKD."

Source: Alexandrou ME, Tsitouridis A, Theodorakopoulou MT, et al. Effects of sodium-glucose co-transporter 2 inhibitors on heart failure in chronic kidney disease: a systematic review and meta-analysis. #6355. Abstract of a presentation at the European Renal Association 60th Congress; June 15-18, 2023; Milan, Italy.

Vaccination Status and Post-COVID-19 Conditions in Hemodialysis Patients

Patients receiving maintenance hemodialysis are at increased risk for post-COVID-19 complications and a high mortality rate during the 1-year period following diagnosis of COVID-19, particularly in the first 3 months following diagnosis. Results of previous studies have shown that vaccinated individuals who experience breakthrough infection are less likely to report post-COVID-19 complications compared with unvaccinated individuals.

Oxidative stress has been shown to be a key component in post-COVID-19 complications, However, there are few data available of oxidant/antioxidant status in patients on hemodialysis who develop post-COVID-19 complications. **Lesya Korol** and colleagues in the Ukraine conducted a study designed to examine the oxidant/antioxidant markers in patients on hemodialysis with post-COVID-19 conditions according to vaccination status.

Results were reported during the ERA 60th Congress. The presentation was titled *Effect of Vaccination on Oxidant/Antioxidant Status in Hemodialysis Patients With Post-COVID Conditions*.

The cross-sectional, observational cohort study included 106 patients on hemodialysis. Mean age was 52.4 years, and mean dialysis vintage was 68 months (range, 29-134 months). Study participants were stratified into three groups according to vaccination status and the presence of post-COVID-19 conditions: group 1, 36 hemodialysis patients fully vaccinated against COVID-19 with either Pfizer-BNT-162b2 or Moderna-mRNA-1273 vaccine who had experienced a post-vaccination SARS-CoV-2 infection and had at least one post-COVID symptom; group 2, 35 fully vaccinated hemodialysis patients who had never been infected with COVID-19 (vaccinated control group); and group 3, 35 unvaccinated hemodialysis patients who had experienced COVID-19 infection and had post-COVID-19 conditions (unvaccinated control group).

Three months following recovery from COVID-19, concentrations of malondialdehyde in serum (MDAs) and erythrocytes (MDAe), sulfhydryl groups (SH-groups), serum catalase activity (CTs), serum transferrin, and ceruloplasmin levels were measured. Data were expressed as a median and interquartile range, and compared with the Kruskal-Wallis test.

The highest concentrations of MDAs and ceruloplasmin, and lowest serum levels of CTs and transferrin were seen in patients in group 1, compared with patients in group 2 and group 3.

"Our findings suggest a significant oxidative imbalance in hemodialysis patients with post-COVID-19 syndrome, most likely due to the synergistic effects of the virus and the vaccine," the researchers said. "The use of antioxidant supplements might be a possible strategy to treat post-COVID-19 conditions in hemodialysis patients."

Source: Karol L, Stepanova N, Ostapenko T, Rysyev, Marchenko V, Belousova O. Effect of vaccination on oxidant/antioxidant status in hemodialysis patients with post-COVID conditions. #2518. Abstract of a presentation at the European Renal Association 60th Congress; June 15-18, 2023; Milan, Italy.

Health-Related Quality of Life in Older Adults With CKD

In patients with advanced chronic kidney disease (CKD), there is an association between lower health-related quality of life (HRQoL) and increased risk of mortality. For older adults with CKD, symptoms such as pain, fatigue, and cognitive impairment (described as geriatric syndromes) negatively affect function and reduce the ability to execute daily tasks. These geriatric syndromes may be a potential target for interventions aimed at improving HRQoL, with the ultimate goal of improving clinical outcomes.

Christine K. Liu, MD, and colleagues performed a secondary analysis of data from a parallel-group randomized controlled clinical trial examining the cross-sectional and longitudinal associations of geriatric syndromes with HRQoL in older adults with CKD. Results of the analysis were reported online in *Kidney 360* [2023;4(4):p e457-e465].

The analysis included data from the Aerobics, Weights, and Renal Disease Study that evaluated a 12-month intervention in adults ≥55 years of age with CKD stage 3b-4. Participants were assessed for baseline geriatric syndromes (cognitive impairment, poor appetite, dizziness, fatigue, and chronic pain) as well as diabetes, hypertension, coronary artery disease, cancer, or chronic obstructive pulmonary disease. HRQoL was assessed with the Short Form Health Survey-36 (SF-36), EuroQol 5-Dimensions 5-Level (EQ-5D-5L), and the EuroQol Visual Analogue Scale (EQ-VAS). Multiple linear regression was used to examine the cross-sectional and longitudinal associations of geriatric syndromes and medical conditions with HRQoL.

The cohort for the current analysis included 99 patients. Mean age was 68.0 years, 25.3% were women, and 61.6% were Black. Mean estimated glomerular filtration rate was 33.3 mL/min/1.73 m^2. Sixty-seven percent of the cohort had 12-month HRQoL data available. The two randomization groups (exercise intervention and health education) were similar in baseline characteristics (all $P<.05$).

At baseline, 73% of the overall cohort had cognitive impairment, 53% had fatigue, and 49% had chronic pain. The mean number of geriatric syndromes was 2.0. Three participants had zero baseline geriatric syndromes. Ninety-three percent had hypertension, 59% had diabetes, and 30% had cardiovascular disease. The mean number of medical conditions was 2.1. Sixty-two percent of the participants had two or more geriatric syndromes, and 49% had at least two geriatric syndromes and at least two medical conditions concurrently.

There were significant associations between the number of geriatric syndromes at baseline and scores in the SF-16 domains for general health and role limitations because of physical health, physical functioning, EQ-5D-5L, and EQ-VAS (all P values $<.05$). The number of medical conditions was associated only with the baseline scores on the SF-36 domains for role limitations because of physical health, physical functioning, and EQ-5D-5L.

When the model included both geriatric syndromes and medical conditions concurrently, the association between the number of geriatric conditions and all HRQoL outcomes remained significant. However, the number of medical conditions was only associated with the SF-36 physical functioning domain. Participants with two or more geriatric syndromes consistently had the lowest least square mean values for scores on the SF-36 for general health and role limitations because of physical health and physical functioning (all P values $<.05$).

Sixty-seven participants had complete 12-month follow-up assessments; the remaining 32 were lost to follow-up, study drop out, or inability to complete follow-up testing. There were no differences in any of the 12-month changes in the HRQoL scores in univariate comparison by randomization strata. In multivariable models assessing associations between geriatric syndromes and medical conditions and 12-month changes in HRQoL, there were no associations between the number of geriatric syndromes, the number of medical conditions, and geriatric syndromes and medical conditions concurrently with any HRQoL scores.

The authors cited some limitations to the study, including the lack of specific criteria for geriatric syndromes, limiting the sample to patients with CKD stage 3b-4, and using only three SF-36 domains.

In summary, the researchers said, "Geriatric syndromes are highly symptomatic conditions and typically have a multifactorial etiology. Common examples are pain and fatigue, and many geriatric syndromes affect function. In this secondary analysis of a clinical trial with older adults with CKD stage 3b-4, we found that most persons concurrently had multiple geriatric syndromes and multiple medical conditions. We demonstrated that the number of geriatric syndromes was more likely to be associated with HRQoL, compared with the number of medical conditions. Given geriatric conditions focus on symptoms and their functional effect, clinically our results suggest that geriatric syndromes may be a way to address HRQoL in this population. Future studies of HRQoL in older adults with CKD should include assessments for geriatric syndromes. More research is needed to determine whether addressing geriatric syndromes improves HRQoL." ■

TAKEAWAY POINTS

- Researchers reported results of a secondary analysis of a trial evaluating a 12-month exercise intervention in individuals >55 years of age with chronic kidney disease (CKD) stage 3b-4.
- In that patient population, geriatric syndromes (cognitive impairment, poor appetite, dizziness, fatigue and chronic pain) were common and associated with poor health-related quality of life.
- Addressing geriatric conditions may aid in improving health-related quality of life in older adults with CKD.

Rate of Testing for Kidney Health Fails to Meet Recommendations

A study conducted by the National Kidney Foundation (NKF) and the National Committee for Quality Assurance (NCQA) has found that fewer than 40% of patients with diabetes have been given recommendations for at least annual kidney health screening tests. Among Black Americans and socioeconomically disadvantaged groups, the rate of recommended testing is even lower.

The NKF and NCQA have developed the Kidney Health Evaluation Measure for People With Diabetes (KED) initiative. Operating as a component of the Healthcare Effectiveness Data and Information Set, KED is a tool for the Centers for Medicare & Medicaid Services to identify areas for improvement and set targets for enhanced care.

In a press release, **Joseph Vassalotti, MD,** chief medical officer at the NKF, said, "Kidney health testing is pivotal to ensuring timely diagnosis and equitable treatment of chronic kidney disease (CKD). Based on this knowledge, we want health care professionals, policymakers, and communities to use KED guidance as an important step in the road map to counter the significant public health challenge posed by undetected and untreated CKD."

KED is based on recommendations from the American Diabetes Association and the NKF. The measure calls for annual testing for kidney disease among individuals with diabetes at least once annually, using both a blood test to measure kidney function (or estimated glomerular filtration rate) and a urine albumin test to measure kidney damage (or urine to albumin-creatinine ratio).

The NKF-NCQA study also highlights the disparities in KED fulfillment among Black Americans and socioeconomically disadvantaged groups, stressing the need to address the disparities to ensure equitable care for all.

Rural Health System Partners With Fresenius Medical Care

In a recent press release, Fresenius Medical Care announced it has launched an on-site dialysis program with Sarah Bush Lincoln, a regional health system in Mattoon, Illinois. The program provides dialysis services with the NxStage VersiHD home hemodialysis system to patients in the community who previously had to travel as far as 100 miles to receive care.

Timothy Pflederer, medical director of the dialysis program at Sarah Bush Lincoln and former president of the Renal Physicians Association, said, "Rural communities across the country struggle with providing access to high-quality health care, especially when more complex procedures like dialysis are needed. Utilizing the smaller, simpler NxStage system makes it possible to provide dialysis to hospitalized patients in their own community, closer to home and loved ones. This is an added benefit of the NxStage VersiHD in rural hospitals as patients who choose home dialysis have better outcomes than those who require dialysis in an outpatient facility."

Following implementation of the NxStage VersiHD in partnership with Fresenius Medical Care in September 2022, Sarah Bush Lincoln's dialysis volumes grew significantly higher than anticipated.

Joseph Turk, executive vice president and global head of home therapies at Fresenius Medical Care, said, "It is incredible to see the immediate impact Sarah Bush Lincoln and the local community are experiencing since launching an on-site dialysis program. Now the patients can receive treatments, work on their rehabilitation, and have family visits all in one location. We always strive to make a positive impact on patients' lives. It is very rewarding to see how our system helps dialysis providers and hospitals improve efficiency and patient experience."

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CONFERENCE COVERAGE **KIDNEY WEEK 2022**

Risk Profile Improved With Tolvaptan for ADPKD

Among patients with autosomal dominant polycystic kidney disease (ADPKD), the expected rate of decline in estimated glomerular filtration rate (eGFR) is calculated using the 2015 ADPKD risk classification system developed by Irazabal et al. The system is based on patient height-adjusted kidney volume (htTKV) and age. Patients with typical image findings on MRI (class 1) can be categorized for anticipated slope of eGFR decline from slow progressors (subclass 1A) through rapid progressors (subclass 1E).

For most, but not all patients, subclass assignment remains stable over time, dependent on htTKV growth. **Neera K. Dahl, MD, PhD,** and colleagues performed an analysis of data from the TEMPO 3:4 trial to examine the effects of tolvaptan on ADPKD risk subclass over time. Results of the analysis were reported during a poster session at the American Society of Nephrology Kidney Week 2022 in a poster titled *Tolvaptan Modifies Patient Risk Class Distribution Over Time in Autosomal Dominant Polycystic Kidney Disease (ADPKD): An Analysis of Data From the TEMPO 3:4 Trial.*

The post hoc analysis was designed to compare changes in risk subclass between patients randomized to tolvaptan or placebo. Baseline MRI and age were used to identify patients in subclasses 1B to 1E. The Cochran-Mantel-Haenszel mean score statistic was used compare the proportions of participants (completers only) in both treatment arms in each baseline subclass who shifted to a different subclass over 36 months.

Most of the participants in the TEMPO 3:4 placebo arm remained in their baseline subclass; some progressed to a higher risk subclass and a smaller proportion dropped into a lower risk subclass. In the tolvaptan arm, the proportion of participants who progressed to a higher risk subclass was smaller than the proportion of participants who dropped into a lower risk subclass.

In baseline subclasses 1C and 1D, participants in the placebo arm were statistically more likely to progress to a higher risk subclass than those in the tolvaptan arm subclasses 1C ($P<.001$) and 1D ($P=.0087$).

In summary, the researchers said, "Reduction of htTKV growth by tolvaptan in ADPKD improved the population risk profile during the 3-year period of treatment with tolvaptan or placebo."

Source: Dahl NK, Chebib FT, Rahbari-Oskoui FF, et al. Tolvaptan modified patient risk class distribution over time in autosomal dominant polycystic kidney disease (ADPJD): an analysis of data from the TEMPO 3:4 trial. Th-P0413. Abstract of a poster presented at the American Society of Nephrology Kidney Week 2022; November 3, 2022; Orlando, Florida. Funding was provided by Otsuka Pharmaceutical Development & Commercialization Inc.

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NKF Survey Reveals Awareness Gap Among Patients

The National Kidney Foundation (NKF) recently conducted a national survey on patient awareness regarding minimally invasive options for creation of access for hemodialysis. The survey was conducted in partnership with Medtronic. Survey responses came from more than 400 patients with end-stage kidney disease (ESKD).

The responses demonstrated that despite the availability of minimally invasive treatment options for the development of an arteriovenous (AV) fistula, most patients with ESKD undergo open surgery to have a fistula created.

In a press release from NKF, **Joseph Vassalotti, MD,** chief medical officer at NKF said, "Blood access is one of the greatest challenges faced by people treated with hemodialysis both at home or in a clinic. Hemodialysis access complications can include infection and mechanical complications that are related to frequent use, typically three times weekly. A mature AV fistula as a hemodialysis access generally has lower complication rates than hemodialysis catheters."

Terry Litchfield, a kidney patient advocacy advocate, said, "Minimally invasive AV fistula creations are an emerging technology, so there is great opportunity to help kidney patients who will require dialysis to learn more and discuss with their physician if they are a candidate for this type of fistula creation. Patient feedback on using minimally invasive technology to create a fistula has been positive. For example, hemodialysis patients have said that they appreciate that a fistula can be created through an outpatient procedure rather than an open surgery."

Results of the survey revealed patient concerns regarding dialysis access via fistula include the ability to return to an active lifestyle, the appearance of the fistula, and recovery time and side effects. According to the press release, those concerns are directly addressed with use of minimally invasive AV fistula creation procedures such as the Ellipsys™ system procedure from Medtronic.

Dr. Vassalotti added, "Shared decision making between the patient and nephrology care team about the options for kidney failure replacement therapy is very important...Our goal is that kidney patients can have multiple interactions with their care team, supported by educational materials from NKF and others that leave them feeling well informed about the full scope of treatment options."

Humana and Interwell Health Announce Care Partnership

Humana Inc. and Interwell Health have announced a value-based agreement in 13 states for most Humana Medicare Advantage HMO and PPO members with chronic kidney disease as well as members nationwide who are living with end-stage kidney disease.

Eligible Humana members have access to 1700 network nephrologists, renal care coordinators, and in-home virtual support from dietitians, nurses, social workers, pharmacists, and care coordinators. The 13 states where the program is available are Arizona, Arkansas, Colorado, Kansas, New Mexico, New York, North Carolina, Ohio, Oklahoma, Pennsylvania, South Carolina, Texas, and West Virginia.

In a recent press release, **Carl Davey,** senior vice president at Humana, said, "At Humana, we

are committed to providing the highest levels of support and care for our members. With millions of Americans currently living with chronic kidney disease, we continue to expand our programs, and this latest collaboration helps our members have access to value-based, coordinated chronic kidney disease care, as well as a vast amount of resources tailored to meet their specific needs throughout each stage of their health care journey."

George Hart, MD, chief medical officer at Interwell Health, added, "This agreement is key to helping even more patients with kidney disease live their best lives. We are proud of our close collaboration with Humana that is demonstrating a way to improve outcomes while lowering the total cost of care. Our success is due in large part to our ability to fully activate a passionate, multidisciplinary care team that works in partnership with our network of high-preforming nephrologists across the country."

Researchers Develop New Membrane for Dialysis Machines

The Canadian Light Source, a national research facility at the University of Saskatchewan, has developed a membrane for dialysis machines designed for safer treatment and improved quality of life for patients with kidney failure.

Amira Abdelrasoul, PhD, P Eng, associate professor at the University's College of Engineer-

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ing, was the lead researcher on the project. In a report in the journal *Membranes*, the development team described how the new membrane maintains a reduction in blood clotting and has a neutral surface that is biocompatible, leading to improved outcomes for patients.

"This will lead to less cell destruction and means that we could regulate inflammation to prevent any tissue damage," Dr. Abdelrasoul said in a recent press release. "It has a more stable hydration layer that is 10 times better than commercial ones. This is the best we have ever achieved."

The research group filed a provisional patent for one of the top-performing membrane materials they have developed.

"This achievement could lead to a reduction in physical and psychological symptoms that patients experience and improve their quality of life," Dr. Abdelrasoul added.

Variation in Kidney Health Screening Rates

Using data from Medicare's Data Sharing for Performance Measurement (Qualified Entity Program), Vizient, Inc. has published a report on care utilization and quality. The report is titled "Measuring Care Utilization and Quality for Those With Chronic Kidney Disease by Payer and Community Vulnerability." The authors sought to evaluate the cost and quality of care provided to patients with chronic kidney disease (CKD) and end-stage renal disease (ESRD) by payer, based on four indicators of resource use and quality. They utilized the Vizient Vulnerability Index™ to examine outcomes based on levels of social determinants of health.

In a recent press release, **Madeleine McDowell, MD,** senior principal, Advanced Analytics and Informatics at Vizient, said, "Chronic kidney disease affects more than 35 million adults, and the CDC reports as many as nine out of 10 people with CKD do not even know they have it. If not carefully managed, CKD can progress to ESRD requiring regular dialysis. By analyzing prevalence rates of CKD and ESRSD and health equity data, we were able to identify stark differences in high social need communities both in overall rates of disease and in severity of disease. Most importantly, we found communities with the lowest rates of screening had the highest rates of dialysis, underscoring the importance of early and regular screening in high social need communities."

The report's findings indicate that CKD-related outcomes are worse for patients living in the most socially challenged areas where the prevalence of patients on dialysis is seven times higher than in the least socially challenged neighborhoods. Further, communities with low levels of kidney health screenings had the highest rates of dialysis. In neighborhoods with a high prevalence of CKD, there were 5.1 dialysis patients per 1000 beneficiaries in low screening communities compared with 2.9 per 1000 beneficiaries in communities with high screening rates. ■

Sarah Tolson

Empowering Excellence: Advantages of Continued Training for Billing Staff

In the rapidly evolving landscape of renal health care, an area that demands unwavering attention is that of effective collections practices. When collections waver, a facility's financial health teeters. Yet, with regular training and a vigilant eye on detailed reports, nephrology practices and dialysis facilities can preempt potential downfalls, ensuring that their critical services continue without interruption.

For any health care facility, including dialysis centers and nephrology practices, maintaining financial stability is intrinsically tied to delivering exceptional patient care. Revenue slowdown or substantial financial losses can have cascading effects, from reduced ability to update equipment to difficulties in retaining staff. Effective collections ensure a consistent influx of revenue, allowing for uninterrupted, high-quality care.

As the landscape of insurance and reimbursement evolves, what worked even a year ago might now be obsolete. It's not enough to be familiar with billing; administrators and billing staff significantly benefit from an in-depth understanding of current policies, regulatory changes, and compliance mandates. Training keeps staff updated, minimizing the risk of inefficient and outdated practices that can slow down or reduce reimbursements.

In addition to keeping current with changing policies and regulations, keeping a pulse on accounts receivable is another imperative skill to provide consistent training on. Regular analysis of reports isn't just a managerial duty. Good billing staff should be able to identify and work to correct issues based on basic report analysis. Discrepancies or anomalies can be early indicators of larger underlying problems. For example:

- ***Aging Reports:*** Delays in collections might initially seem like minor lags, but aging reports can highlight problematic patterns. If 90-day outstanding balances are growing, it could be a sign of billing issues, noncompliance, or ineffective follow-ups.
- ***Reimbursement Analysis:*** Reviewing reimbursement trends by payer and by service type are great ways to identify changes that could lead to cash-flow issues. Any abrupt or gradual decrease in reimbursements needs to be analyzed immediately. Are certain procedures being underbilled? Is there a pattern of denials for specific services or from specific payers? Are all billable services being captured for billing?
- ***Payer Mix Reports:*** A sudden change in the payer mix may have a negative impact on collections. Some insurers might require authorization, have tight timely filing deadlines, or have longer processing times.

CONTINUED TRAINING IS A MUST

While it's tempting to view training of billing staff as a one-time initiative for new hires, the dynamics of health care billing and collections necessitate ongoing instruction. A few areas of importance are:

- ***Skill Enhancement:*** As in any other field, accounts receivable follow-up and collections also see innovation in terms of technology, methods, and best practices. By providing consistent training, you ensure your team's proficiency and efficiency improves over time, leading to faster and more effective collections.
- ***Error Minimization:*** Well-trained staff can identify and rectify errors proactively. This can significantly reduce claim denials and rejections, which are often costly both in terms of money and time.
- ***Streamline Processes:*** It seems as though obtaining payment from an insurance company takes more effort each year. Streamlining the processes used by billing staff frees up more time for collecting from insurance companies.

EMPOWERING WITH TOOLS AND TECHNOLOGY

While training is the bedrock of effective collections, the importance of equipping your team with tools that allow for efficiency cannot be overstated. Advances in health care administrative technology allow for automation of many of the labor-intensive tasks such as charge entry, payment posting, eligibility verification, and claim status checks. Automating as many processes as make sense for the size of your organization will give time back to billing staff that can be used for functions that drive reimbursement. Simple tools such as providing two to three monitors at a biller's workstation can realize an increase in efficiency. By integrating training with technology, facility and practice administrators can ensure that they are not only identifying issues but are also well equipped to address them. ■

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

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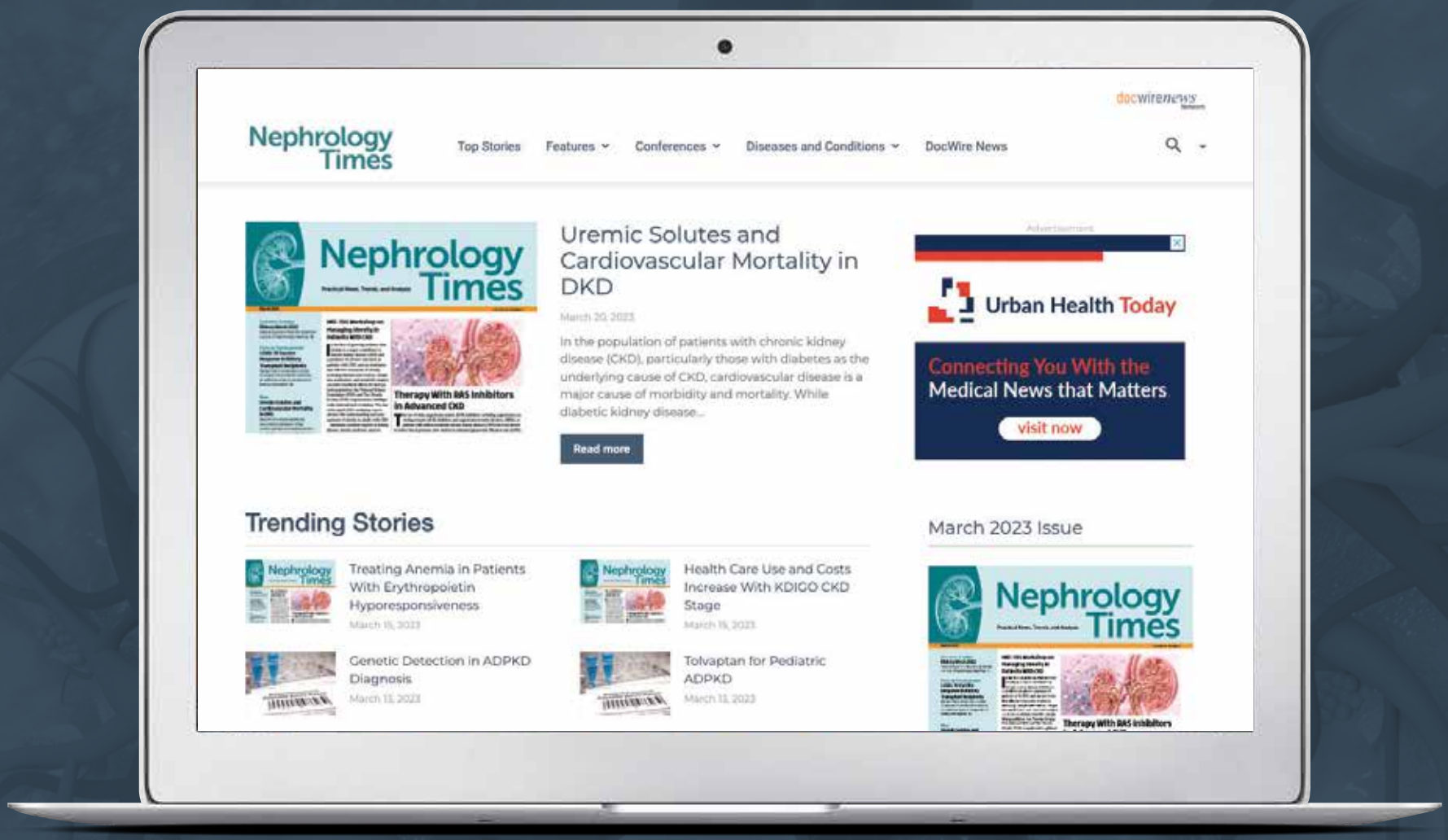

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