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Dietary Potassium Intake and Abdominal Aortic Calcification

Among patients with chronic kidney disease (CKD), the leading cause of mortality is cardiovascular disease. The high rate of cardiovascular disease-related mortality in that patient population is associated in part with accelerated development of arterial calcification in CKD.

Arterial calcification is an active process of mineralization and deposition of calcium-phosphate salts, and can occur in the intimal and medial layer of arteries as a consequence of aging. In patients with CKD, arterial calcification becomes more extensive. Hypertension and diabetes, as well as hyperphosphatemia and uremic toxins promote the development of arterial calcification in patients with CKD.

Results of recent animal studies have suggested that reduced dietary potassium intake promoted arterial calcification and increased arterial stiffness, while increased dietary potassium intake attenuated both arterial calcification and stiffness. There are limited data in humans on the relationship of dietary potassium and arterial clarification and stiffness.

Yuping Xie, MD, MS, and colleagues conducted cross-sectional analyses to test the hypothesis that higher dietary potassium would be associated with less abdominal aortic calcification (AAC) and lower arterial stiffness among adults in the United States. Results were reported in the *Journal of Renal Nutrition* [2023;33(5):657-663].

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Risk of Cardiovascular Events in Patients With CKD and Type 2 Diabetes

A 2004 landmark study demonstrated an association between chronic kidney disease (CKD) and an increased risk of cardiovascular events. There were associations between lower levels of estimated glomerular filtration rate (eGFR) and higher risk of mortality from any cause, cardiovascular events, and hospitalizations. It is well established that the risk of kidney outcomes is modifiable in patients with type 2 diabetes.

According to **Rajv Agarwal, MD, MBBS, MS,** and colleagues, the modifiability of cardiovascular risk associated with CKD in patients with type 2 diabetes in a broad population, even in those with an eGFR of ≥60 mL/min/1.73 m^2 and defined by albuminuria, is unclear. The FIDELITY (Finerenone in Chronic Kidney Disease and Type 2 Diabetes: Combined FIDELIO-DKD and FIGARO-DKD) trial analysis is a prespecified pooled analysis of two phase 3 trials examining the efficacy and safety of finerenone, a selective, nonsteroidal mineralocorticoid receptor antagonist.

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Hypokalemia and Hyperkalemia Increase Risk of Adverse Outcomes in Older Adults

Serum potassium disturbances are common among individuals with chronic kidney disease (CKD) stages 4-5. Patients may experience hyperkalemia due to impaired urinary potassium excretion and the use of renin-angiotensin-aldosterone system (RAAS) inhibitors for cardiorenoprotection, or they may experience hypokalemia due to treatment with nonpotassium-sparing diuretics or malnourishment.

Both hyperkalemia and hypokalemia are associated with muscle paralysis and potentially fatal cardiac arrhythmias. Further, there is an association between hypokalemia and increased rate of decline in kidney function in those with CKD, likely via chronic interstitial nephritis and fibrosis (hypokalemic nephropathy).

Serum potassium disturbances may be related to progression to kidney failure requiring kidney replacement therapy (KRT) and mortality. Older patients with CKD

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KRYSTEXXA **can change the course** of uncontrolled gout[1]

KRYSTEXXA with methotrexate:

>80%
relative improvement in patient response;
71% (71/100) vs 39% (20/52) complete response compared to KRYSTEXXA alone[1]*

87%
relative reduction in infusion reactions;
4% (4/96) vs 31% (15/49) compared to KRYSTEXXA alone[1]

A 52-week, randomized, double-blind trial conducted in adult patients with chronic gout refractory to conventional therapy to evaluate administration of KRYSTEXXA 8 mg Q2W co-administered with 15 mg oral methotrexate QW and 1 mg oral folic acid QD vs KRYSTEXXA alone.[1,2]

QD, every day; QW, every week; Q2W, every 2 weeks.

*Complete sUA response: The primary efficacy endpoint was the proportion of responders, defined by patients achieving and maintaining sUA <6 mg/dL for at least 80% of the time during Month 6.[1]

INDICATION

KRYSTEXXA® (pegloticase) is indicated for the treatment of chronic gout in adult patients who have failed to normalize serum uric acid and whose signs and symptoms are inadequately controlled with xanthine oxidase inhibitors at the maximum medically appropriate dose or for whom these drugs are contraindicated.

Limitations of Use: KRYSTEXXA is not recommended for the treatment of asymptomatic hyperuricemia.

IMPORTANT SAFETY INFORMATION

WARNING: ANAPHYLAXIS AND INFUSION REACTIONS, G6PD DEFICIENCY ASSOCIATED HEMOLYSIS AND METHEMOGLOBINEMIA

- **Anaphylaxis and infusion reactions have been reported to occur during and after administration of KRYSTEXXA.**
- **Anaphylaxis may occur with any infusion, including a first infusion, and generally manifests within 2 hours of the infusion. Delayed hypersensitivity reactions have also been reported.**
- **KRYSTEXXA should be administered in healthcare settings and by healthcare providers prepared to manage anaphylaxis and infusion reactions.**
- **Premedicate with antihistamines and corticosteroids and closely monitor for anaphylaxis for an appropriate period after administration of KRYSTEXXA.**
- **Monitor serum uric acid levels prior to each infusion and discontinue treatment if levels increase to above 6 mg/dL, particularly when 2 consecutive levels above 6 mg/dL are observed.**
- **Screen patients at risk for glucose-6-phosphate dehydrogenase (G6PD) deficiency prior to starting KRYSTEXXA. Hemolysis and methemoglobinemia have been reported with KRYSTEXXA in patients with G6PD deficiency. KRYSTEXXA is contraindicated in patients with G6PD deficiency.**

CONTRAINDICATIONS:

- In patients with G6PD deficiency.
- In patients with history of serious hypersensitivity reactions, including anaphylaxis, to KRYSTEXXA or any of its components.

Dissolve years of urate deposition[3]
ChangeTheCourse.com

WARNINGS AND PRECAUTIONS

Gout Flares: An increase in gout flares is frequently observed upon initiation of anti-hyperuricemic therapy, including KRYSTEXXA. Gout flare prophylaxis with a non-steroidal anti-inflammatory drug (NSAID) or colchicine is recommended starting at least 1 week before initiation of KRYSTEXXA therapy and lasting at least 6 months, unless medically contraindicated or not tolerated.

Congestive Heart Failure: KRYSTEXXA has not been formally studied in patients with congestive heart failure, but some patients in the pre-marketing placebo-controlled clinical trials experienced exacerbation. Exercise caution in patients who have congestive heart failure and monitor patients closely following infusion.

ADVERSE REACTIONS

The most commonly reported adverse reactions (≥5%) are:

KRYSTEXXA co-administration with methotrexate trial:
KRYSTEXXA with methotrexate: gout flares, arthralgia, COVID-19, nausea, and fatigue; KRYSTEXXA alone: gout flares, arthralgia, COVID-19, nausea, fatigue, infusion reaction, pain in extremity, hypertension, and vomiting.

KRYSTEXXA pre-marketing placebo-controlled trials:
gout flares, infusion reactions, nausea, contusion or ecchymosis, nasopharyngitis, constipation, chest pain, anaphylaxis, and vomiting.

Please see Brief Summary of Prescribing Information for KRYSTEXXA on following page.

References: 1. KRYSTEXXA (pegloticase) [prescribing information] Horizon. **2.** Botson J, et al. *J Clin Rheumatol*. 2022;28:e129-e134. **3.** Data on File. Horizon, March 2022.

KRYSTEXXA®
pegloticase

HORIZON.

KRYSTEXXA® (pegloticase) injection, for intravenous use

Brief Summary - Please see the KRYSTEXXA package insert for Full Prescribing Information.

WARNING: ANAPHYLAXIS and INFUSION REACTIONS, G6PD DEFICIENCY ASSOCIATED HEMOLYSIS and METHEMOGLOBINEMIA

See full prescribing information for complete boxed warning.

- **Anaphylaxis and infusion reactions have been reported to occur during and after administration of KRYSTEXXA.**
- **Anaphylaxis may occur with any infusion, including a first infusion, and generally manifests within 2 hours of the infusion. However, delayed hypersensitivity reactions have also been reported.**
- **KRYSTEXXA should be administered in healthcare settings and by healthcare providers prepared to manage anaphylaxis and infusion reactions.**
- **Pre-medicate with antihistamines and corticosteroids and closely monitor for anaphylaxis for an appropriate period of time after administration of KRYSTEXXA.**
- **Monitor serum uric acid levels prior to each infusion and discontinue treatment if levels increase to above 6 mg/dL, particularly when 2 consecutive levels above 6 mg/dL are observed.**
- **Screen patients at risk for G6PD deficiency prior to starting KRYSTEXXA. Hemolysis and methemoglobinemia have been reported with KRYSTEXXA in patients with G6PD deficiency. KRYSTEXXA is contraindicated in patients with G6PD deficiency.**

INDICATIONS AND USAGE

KRYSTEXXA® (pegloticase) is indicated for the treatment of chronic gout in adult patients refractory to conventional therapy.

Gout refractory to conventional therapy occurs in patients who have failed to normalize serum uric acid and whose signs and symptoms are inadequately controlled with xanthine oxidase inhibitors at the maximum medically appropriate dose or for whom these drugs are contraindicated.

Limitations of Use:
KRYSTEXXA is not recommended for the treatment of asymptomatic hyperuricemia.

CONTRAINDICATIONS

KRYSTEXXA is contraindicated in:

- Patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency *[see Warnings and Precautions]*
- Patients with history of serious hypersensitivity reactions, including anaphylaxis, to KRYSTEXXA or any of its components

WARNINGS AND PRECAUTIONS

Anaphylaxis

In a 52-week controlled trial, which evaluated KRYSTEXXA co-administered with methotrexate compared to KRYSTEXXA alone, patients were pre-treated with standardized infusion reaction prophylaxis and were discontinued from treatment with KRYSTEXXA if serum uric acid levels increased to above 6 mg/dL at 2 consecutive visits after the initiation of KRYSTEXXA therapy to reduce the risk of anaphylaxis. One patient randomized to the group treated with KRYSTEXXA co-administered with methotrexate (1%) experienced anaphylaxis during the first infusion and no patients experienced anaphylaxis in the group treated with KRYSTEXXA alone *[see Adverse Reactions]*.

During pre-marketing clinical trials with KRYSTEXXA alone, KRYSTEXXA was not discontinued following 2 consecutive serum uric acid levels above 6 mg/dL. Anaphylaxis was reported with a frequency of 6.5% (8/123) of patients treated with KRYSTEXXA every 2 weeks and 4.8% (6/126) for the every 4-week dosing regimen. There were no cases of anaphylaxis in patients receiving placebo. Anaphylaxis generally occurred within 2 hours after treatment.

Diagnostic criteria of anaphylaxis were skin or mucosal tissue involvement, and, either airway compromise, and/or reduced blood pressure with or without associated symptoms, and a temporal relationship to KRYSTEXXA or placebo injection with no other identifiable cause. Manifestations included wheezing, peri-oral or lingual edema, or hemodynamic instability, with or without rash or urticaria, nausea or vomiting. Cases occurred in patients being pre-treated with one or more doses of an oral antihistamine, an intravenous corticosteroid and/or acetaminophen. This pre-treatment may have blunted or obscured symptoms or signs of anaphylaxis and therefore the reported frequency may be an underestimate.

KRYSTEXXA should be administered in a healthcare setting by healthcare providers prepared to manage anaphylaxis. Patients should be pre-treated with antihistamines and corticosteroids. Anaphylaxis may occur with any infusion, including a first infusion, and generally manifests within 2 hours of the infusion. However, delayed type hypersensitivity reactions have also been reported. Patients should be closely monitored for an appropriate period of time for anaphylaxis after administration of KRYSTEXXA. Patients should be informed of the symptoms and signs of anaphylaxis and instructed to seek immediate medical care should anaphylaxis occur after discharge from the healthcare setting.

The risk of anaphylaxis is higher in patients whose uric acid level increases to above 6 mg/dL, particularly when 2 consecutive levels above 6 mg/dL are observed. Monitor serum uric acid levels prior to infusions and discontinue treatment if levels increase to above 6 mg/dL. Because of the possibility that concomitant use of oral urate-lowering therapy and KRYSTEXXA may potentially blunt the rise of serum uric acid levels, it is recommended that before starting KRYSTEXXA patients discontinue oral urate-lowering medications and not institute therapy with oral urate-lowering agents while taking KRYSTEXXA.

Infusion Reactions

In a 52-week, controlled trial which evaluated KRYSTEXXA co-administered with methotrexate compared to KRYSTEXXA alone *[see Adverse Reactions]*, patients were pre-treated with standardized infusion reaction prophylaxis and were discontinued from treatment with KRYSTEXXA if serum uric acid levels increased to above 6 mg/dL at 2 consecutive visits after the initiation of KRYSTEXXA therapy to reduce the risk of infusion reactions. Infusion reactions were reported in 4% of patients in the KRYSTEXXA co-administered with methotrexate group compared to 31% of patients treated with KRYSTEXXA alone experienced infusion reactions *[see Adverse Reactions]*. In both treatment groups, the majority of infusion reactions occurred at the first or second KRYSTEXXA infusion and during the time of infusion. Manifestations of these infusion reactions were similar to that observed in the pre-marketing trials.

During pre-marketing 24-week controlled clinical trials with KRYSTEXXA alone, KRYSTEXXA was not discontinued following 2 consecutive serum uric acid levels above 6 mg/dL. Infusion reactions were reported in 26% of patients treated with KRYSTEXXA 8 mg every 2 weeks, and 41% of patients treated with KRYSTEXXA 8 mg every 4 weeks, compared to 5% of patients treated with placebo. These infusion reactions occurred in patients being pre-treated with an oral antihistamine, intravenous corticosteroid and/or acetaminophen. This pre-treatment may have blunted or obscured symptoms or signs of infusion reactions and therefore the reported frequency may be an underestimate.

Manifestations of these reactions included urticaria (frequency of 10.6%), dyspnea (frequency of 7.1%), chest discomfort (frequency of 9.5%), chest pain (frequency of 9.5%), erythema (frequency of 9.5%), and pruritus (frequency of 9.5%). These manifestations overlap with the symptoms of anaphylaxis, but in a given patient did not occur together to satisfy the clinical criteria for diagnosing anaphylaxis. Infusion reactions are thought to result from release of various mediators, such as cytokines. Infusion reactions occurred at any time during a course of treatment with approximately 3% occurring with the first infusion, and approximately 91% occurred during the time of infusion.

KRYSTEXXA should be administered in a healthcare setting by healthcare providers prepared to manage infusion reactions. Patients should be pre-treated with antihistamines and corticosteroids. KRYSTEXXA should be infused slowly over no less than 120 minutes. In the event of an infusion reaction, the infusion should be slowed, or stopped and restarted at a slower rate.

The risk of infusion reaction is higher in patients whose uric acid level increases to above 6 mg/dL, particularly when 2 consecutive levels above 6 mg/dL are observed. Monitor serum uric acid levels prior to infusions and discontinue treatment if levels increase to above 6 mg/dL. Because of the possibility that concomitant use of oral urate-lowering therapy and KRYSTEXXA may potentially blunt the rise of serum uric acid levels, it is recommended that before starting KRYSTEXXA patients discontinue oral urate-lowering medications and not institute therapy with oral urate-lowering agents while taking KRYSTEXXA.

G6PD Deficiency Associated Hemolysis and Methemoglobinemia

Life threatening hemolytic reactions and methemoglobinemia have been reported with KRYSTEXXA in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency. Because of the risk of hemolysis and methemoglobinemia, do not administer KRYSTEXXA to patients with G6PD deficiency *[see Contraindications]*. Screen patients at risk for G6PD deficiency prior to starting KRYSTEXXA. For example, patients of African, Mediterranean (including Southern European and Middle Eastern), and Southern Asian ancestry are at increased risk for G6PD deficiency.

Gout Flares

In a 52-week, randomized, double-blind trial which evaluated KRYSTEXXA co-administered with methotrexate compared to KRYSTEXXA alone, patients were administered gout flare prophylaxis similar to that in the pre-marketing, placebo-controlled trials. In this trial, the percentages of patients with any flare for the first 3 months were 66% and 69% for the group treated with KRYSTEXXA co-administered with methotrexate and the group treated with KRYSTEXXA alone, respectively. In the group treated with KRYSTEXXA co-administered with methotrexate, the percentages of patients with any flare for the subsequent 3 month increments of treatment were 27% during Month 6, 8% during Month 9 and 9% during Month 12. In the group treated with KRYSTEXXA alone, the percentages of patients with any flare were 14% during Month 6, 9% during Month 9 and 21% during Month 12.

During pre-marketing, 24-week controlled clinical trials with KRYSTEXXA alone, the frequencies of gout flares were high in all treatment groups, but more so with KRYSTEXXA treatment during the first 3 months of treatment, and decreased in the subsequent 3 months of treatment. The percentages of patients with any flare for the first 3 months were 74%, 81%, and 51%, for KRYSTEXXA 8 mg every 2 weeks, KRYSTEXXA 8 mg every 4 weeks, and placebo, respectively. The percentages of patients with any flare for the subsequent 3 months were 41%, 57%, and 67%, for KRYSTEXXA 8 mg every 2 weeks, KRYSTEXXA 8 mg every 4 weeks, and placebo, respectively. Patients received gout flare prophylaxis with colchicine and/or nonsteroidal anti-inflammatory drugs (NSAIDs) starting at least one week before receiving KRYSTEXXA.

Gout flares may occur after initiation of KRYSTEXXA. An increase in gout flares is frequently observed upon initiation of anti-hyperuricemic therapy, due to changing serum uric acid levels resulting in mobilization of urate from tissue deposits. Gout flare prophylaxis with a non-steroidal anti-inflammatory drug (NSAID) or colchicine is recommended starting at least 1 week before initiation of KRYSTEXXA therapy and lasting at least 6 months, unless medically contraindicated or not tolerated. KRYSTEXXA does not need to be discontinued because of a gout flare. The gout flare should be managed concurrently as appropriate for the individual patient *[see Dosage and Administration]*.

Congestive Heart Failure

KRYSTEXXA has not been formally studied in patients with congestive heart failure, but some patients in the pre-marketing, 24-week controlled clinical trials experienced exacerbation of congestive heart failure. Two cases of congestive heart failure exacerbation occurred during the trials in patients receiving treatment with KRYSTEXXA 8 mg every 2 weeks. No cases were reported in placebo-treated patients. Four subjects had exacerbations of pre-existing congestive heart failure while receiving KRYSTEXXA 8 mg every 2 weeks during the open-label extension study.

Exercise caution when using KRYSTEXXA in patients who have congestive heart failure and monitor patients closely following infusion.

Re-treatment with KRYSTEXXA

No controlled trial data are available on the safety and efficacy of re-treatment with KRYSTEXXA after stopping treatment for longer than 4 weeks. Due to the immunogenicity of KRYSTEXXA, patients receiving re-treatment may be at increased risk of anaphylaxis and infusion reactions. Therefore, patients receiving re-treatment after a drug-free interval should be monitored carefully *[see Adverse Reactions]*.

ADVERSE REACTIONS

The following serious adverse reactions are discussed in greater detail in other sections of the label:

- Anaphylaxis *[see Warnings and Precautions]*
- Infusion Reactions *[see Warnings and Precautions]*
- G6PD Deficiency Associated Hemolysis and Methemoglobinemia *[see Warnings and Precautions]*
- Gout Flares *[see Warnings and Precautions]*
- Congestive Heart Failure *[see Warnings and Precautions]*

Clinical Trials Experience

Because clinical studies are conducted under widely varying and controlled conditions, adverse reaction rates observed in clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug, and may not predict the rates observed in a broader patient population in clinical practice.

Co-administration with Methotrexate

A 52-week, randomized, double-blind trial was conducted in adult patients with chronic gout refractory to conventional therapy to evaluate administration of KRYSTEXXA 8 mg every 2 weeks co-administered with weekly administration of oral methotrexate 15 mg, compared to KRYSTEXXA alone. In this trial, patients who were able to tolerate two weeks on methotrexate 15 mg were then randomized to receive four additional weeks on either methotrexate 15 mg or matching placebo prior to initiating KRYSTEXXA therapy. A total of 152 subjects were randomized, and of these, 145 subjects completed the 4-week methotrexate run-in period and received KRYSTEXXA (96 subjects received KRYSTEXXA co-administered with methotrexate and 49 received KRYSTEXXA plus placebo) during the treatment period. All patients received pre-treatment with an oral antihistamine, intravenous corticosteroid and acetaminophen. These patients were between the ages of 24 and 83 years (average 55 years); 135 patients were male and 17 and were female; 105 patients were White/Caucasian, 22 were Black/African American,

14 were Asian, 5 were Native Hawaiian/Other Pacific Islander and 5 identified as Other; 28 were Hispanic or Latino. Common co-morbid conditions among the enrolled patients included hypertension (63%), osteoarthritis (25%), hyperlipidemia (24%), gastroesophageal reflux disease (22%), obesity (20%), type 2 diabetes (18%) and depression (16%). Patients with an eGFR <40 mL/min/1.73 m² were excluded from this trial.

The most commonly reported adverse reaction during the methotrexate pre-treatment periods was gout flare. The most commonly reported adverse reactions that occurred in ≥ 5% in either treatment group during the KRYSTEXXA co-administered with methotrexate or KRYSTEXXA alone period are provided in Table 1.

Table 1. Adverse Reactions Occurring in 5% or More of Patients in Either the KRYSTEXXA Co-administered with Methotrexate or KRYSTEXXA Alone Treatment Period

Adverse Reaction	KRYSTEXXA with Methotrexate (N=96) n (%)	KRYSTEXXA Alone (N=49) n (%)
Gout flare	64 (67%)	35 (71%)
Arthralgia	13 (14%)	5 (10%)
COVID-19	9 (9%)	3 (6%)
Nausea	5 (5%)	6 (12%)
Fatigue	5 (5%)	2 (4%)
Infusion reaction	4 (4%)[a]	15 (31%)
Pain in extremity	1 (1%)	3 (6%)
Hypertension	1 (1%)	3 (6%)
Vomiting	0	4 (8%)

[a] Included one case of anaphylaxis

KRYSTEXXA ALONE

The data described below reflect exposure to KRYSTEXXA in patients with chronic gout refractory to conventional therapy in two replicate randomized, placebo-controlled, double-blind 24-week clinical trials: 85 patients were treated with KRYSTEXXA 8 mg every 2 weeks; 84 patients were treated with KRYSTEXXA 8 mg every 4 weeks; and 43 patients were treated with placebo. These patients were between the ages of 23 and 89 years (average 55 years); 173 patients were male and 39 were female; and 143 patients were White/Caucasian, 27 were Black/African American, 24 were Hispanic/Latino and 18 were all other ethnicities. Common co-morbid conditions among the enrolled patients included hypertension (72%), dyslipidemia (49%), chronic kidney disease (28%), diabetes (24%), coronary artery disease (18%), arrhythmia (16%), and cardiac failure/left ventricular dysfunction (12%).

During the pre-marketing placebo-controlled clinical trials, the most commonly reported adverse reactions that occurred in greater than or equal to 5% of patients treated with KRYSTEXXA 8 mg every 2 weeks are provided in Table 2.

Table 2. Adverse Reactions Occurring in 5% or More of Patients Treated with KRYSTEXXA Compared to Placebo

Adverse Reaction	KRYSTEXXA 8 mg every 2 weeks (N=85) n[a] (%)	Placebo (N=43) n (%)
Gout flare	65 (77%)	35 (81%)
Infusion reaction	22 (26%)	2 (5%)
Nausea	10 (12%)	1 (2%)
Contusion[b] or Ecchymosis[b]	9 (11%)	2 (5%)
Nasopharyngitis	6 (7%)	1 (2%)
Constipation	5 (6%)	2 (5%)
Chest Pain	5 (6%)	1 (2%)
Anaphylaxis	4 (5%)	0 (0%)
Vomiting	4 (5%)	1 (2%)

[a] If the same subject in a given group had more than one occurrence in the same preferred term event category, the subject was counted only once.

[b] Most did not occur on the day of infusion and could be related to other factors (e.g., concomitant medications relevant to contusion or ecchymosis, insulin dependent diabetes mellitus).

Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity. The observed incidence of antibody positivity in an assay is highly dependent on several factors including assay sensitivity and specificity and assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, the comparison of the incidence of antibodies to pegloticase with the incidence of antibodies to other products may be misleading.

In a 52-week, randomized, double-blind trial which evaluated KRYSTEXXA co-administered with methotrexate compared to KRYSTEXXA alone, approximately 26% of patients had pre-existing antibodies to pegloticase. Patients with an increase in titer from baseline or who were negative at baseline and developed an anti-pegloticase response at one or more post dose time points was 30% and 51%, for the KRYSTEXXA co-administered with methotrexate and KRYSTEXXA alone treatment groups, respectively. Patients with higher antibody titers were more likely to have faster clearance and lower efficacy.

During pre-marketing 24-week controlled clinical trials with KRYSTEXXA alone, anti-pegloticase antibodies developed in 92% of patients treated with KRYSTEXXA every 2 weeks, and 28% for placebo. Anti-PEG antibodies were also detected in 42% of patients treated with KRYSTEXXA. High anti-pegloticase antibody titer was associated with a failure to maintain pegloticase-induced normalization of uric acid. The impact of anti-PEG antibodies on patients' responses to other PEG-containing therapeutics is unknown.

There was a higher incidence of infusion reactions in patients with high anti-pegloticase antibody titer: 53% (16 of 30) in the KRYSTEXXA every 2 weeks group compared to 6% in patients who had undetectable or low antibody titers.

Postmarketing Experience

The following adverse reactions have been identified during postapproval use of KRYSTEXXA. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship.

General disorders and administration site conditions: asthenia, malaise, peripheral swelling

DRUG INTERACTIONS

Methotrexate

KRYSTEXXA 8 mg every 2 weeks has been studied in patients with chronic gout refractory to conventional therapy taking concomitant oral methotrexate 15 mg weekly. Co-administration of methotrexate with KRYSTEXXA may increase pegloticase concentration compared to KRYSTEXXA alone.

PEGylated products

Because anti-pegloticase antibodies appear to bind to the PEG portion of the drug, there may be potential for binding with other PEGylated products. The impact of anti-PEG antibodies on patients' responses to other PEG-containing therapeutics is unknown.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

There are no adequate and well-controlled studies of KRYSTEXXA in pregnant women. Based on animal reproduction studies, no structural abnormalities were observed when pegloticase was administered by subcutaneous injection to pregnant rats and rabbits during the period of organogenesis at doses up to 50 and 75 times, respectively, the maximum recommended human dose (MRHD). Decreases in mean fetal and pup body weights were observed at approximately 50 and 75 times the MRHD, respectively *[see Data]*.

All pregnancies have a background risk of birth defect, loss or other adverse outcomes. In the US general population, the estimated background risk of major birth defects and miscarriage in clinical recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data

Animal Data

In 2 separate embryo-fetal developmental studies, pregnant rats and rabbits received pegloticase during the period of organogenesis at doses up to approximately 50 and 75 times the maximum recommended human dose (MRHD), respectively (on a mg/m² basis at maternal doses up to 40 and 30 mg/kg twice weekly, in rats and rabbits, respectively). No evidence of structural abnormalities was observed in rats or rabbits. However, decreases in mean fetal and pup body weights were observed at approximately 50 and 75 times the MRHD in rats and rabbits, respectively (on a mg/m² basis at maternal doses up to 40 and 30 mg/kg every other day, in rats and rabbits, respectively). No effects on mean fetal body weights were observed at approximately 10 and 25 times the MRHD in rats and rabbits, respectively (on a mg/m² basis at maternal doses up to 10 mg/kg twice weekly in both species).

Lactation

Risk Summary

It is not known whether this drug is excreted in human milk. Therefore, KRYSTEXXA should not be used when breastfeeding unless the clear benefit to the mother can overcome the unknown risk to the newborn/infant.

Pediatric Use

The safety and effectiveness of KRYSTEXXA in pediatric patients less than 18 years of age have not been established.

Geriatric Use

Of the total number of patients treated with KRYSTEXXA 8 mg every 2 weeks in the controlled studies, 34% (29 of 85) were 65 years of age and older and 12% (10 of 85) were 75 years of age and older. No overall differences in safety or effectiveness were observed between older and younger patients, but greater sensitivity of some older individuals cannot be ruled out. No dose adjustment is needed for patients 65 years of age and older.

Renal Impairment

No dose adjustment is required for patients with renal impairment. In a 52-week, randomized, double-blind trial which evaluated KRYSTEXXA co-administered with methotrexate compared to KRYSTEXXA alone, 85% of patients had chronic kidney disease based on estimated glomerular filtration rate (eGFR) of ≥ 40 to < 90 mL/min/1.73 m² at baseline. In the pre-marketing 24-week controlled clinical trials with KRYSTEXXA alone, a total of 32% (27 of 85) of patients treated with KRYSTEXXA 8 mg every 2 weeks had a creatinine clearance of ≤62.5 mL/min. No overall differences in efficacy were observed.

OVERDOSAGE

No reports of overdosage with KRYSTEXXA have been reported. The maximum dose that has been administered as a single intravenous dose is 12 mg as uricase protein. Patients suspected of receiving an overdose should be monitored, and general supportive measures should be initiated as no specific antidote has been identified.

PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Anaphylaxis and Infusion Reactions

- Anaphylaxis and infusion reactions can occur at any infusion while on therapy. Counsel patients on the importance of adhering to any prescribed medications to help prevent or lessen the severity of these reactions.
- Educate patients on the signs and symptoms of anaphylaxis, including wheezing, peri-oral or lingual edema, hemodynamic instability, and rash or urticaria, nausea or vomiting.
- Educate patients on the most common signs and symptoms of an infusion reaction, including urticaria (skin rash), erythema (redness of the skin), dyspnea (difficulty breathing), flushing, chest discomfort, chest pain, and rash.
- Advise patients to seek medical care immediately if they experience any symptoms of an allergic reaction during or at any time after the infusion of KRYSTEXXA *[see Warnings and Precautions, Adverse Reactions]*
- Advise patients to discontinue any oral urate-lowering agents before starting on KRYSTEXXA and not to take any oral urate-lowering agents while on KRYSTEXXA.

Glucose-6-phosphate dehydrogenase (G6PD) Deficiency

Inform patients not to take KRYSTEXXA if they have a condition known as G6PD deficiency. Explain to patients that G6PD deficiency is more frequently found in individuals of African, Mediterranean, or Southern Asian ancestry and that they may be tested to determine if they have G6PD deficiency, unless already known *[see Warnings and Precautions, Contraindications]*.

Gout Flares

Explain to patients that gout flares may initially increase when starting treatment with KRYSTEXXA, and that medications to help reduce flares may need to be taken regularly for the first few months after KRYSTEXXA is started *[see Warnings and Precautions, Adverse Reactions]*. Advise patients that they should not stop KRYSTEXXA therapy if they have a flare.

Manufactured by:
Horizon Therapeutics Ireland DAC
Dublin, Ireland

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Cardiovascular-Kidney-Metabolic Syndrome: A New Look for an Old Syndrome

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BOSTON, MASSACHUSETTS

The concept of cardiovascular-kidney-metabolic (CKM) syndrome published recently by Ndumele and colleagues in *Circulation*[1] as a presidential advisory reflects an axis that has long been recognized.[2] However, while this review is a masterpiece of pulling together an enormous amount of information and organizing it into practical approaches to managing CKM syndrome, it has several limitations that need to be highlighted.

Ndumele et al define CKM syndrome as a "systemic disorder with connections among heart disease, kidney disease, diabetes, and obesity." Heart disease encompasses heart failure (HF), atrial fibrillation, coronary heart disease, stroke, and peripheral artery disease. The Ndumele review emphasizes the importance of an integrated approach among the specialties that are involved in managing CKM syndrome. It also emphasizes the role of adverse social determinants of health in determining CKM outcomes.

The growing number of therapeutic options for CKM syndrome and its components necessitates a detailed understanding of CKM-related therapies. The intricacies of using multiple agents in guideline-directed medical therapy (GDMT) for HF, GDMT for chronic kidney disease (CKD) with type 2 diabetes, and an emerging multitude of therapies for adiposity are not for the faint of heart.

An easy-to-remember staging of CKM syndrome is provided in the review:

- Stage 0, no CKM risk factors
- Stage 1, excess or dysfunctional adiposity
- Stage 2, metabolic risk factors (hypertriglyceridemia, hypertension, diabetes, metabolic syndrome) or moderate- to high-risk CKD
- Stage 3, subclinical cardiovascular disease (CVD) in CKM syndrome or risk equivalents (high predicted CVD risk or very high-risk CKD)
- Stage 4, clinical CVD in CKM syndrome; in addition, risk-enhancing factors influence the likelihood of progression along CKM stages

Ndumele and colleagues propose that patients with CKD and albuminuria should receive an angiotensin-converting enzyme inhibitor (ACEi) or an angiotensin receptor blocker (ARB); they recommend sodium-glucose cotransporter 2 inhibitors (SGLT2i) in patients with or without diabetes, and for patients with residual albuminuria on ACEi or ARB they recommend finerenone that "can be used on background SGLT2i."

In the paper, Ndumele and colleagues leave the clinician wondering about whether SGLT2i should be used concurrently with ACEi or ARB. The answer is yes, because three landmark trials have demonstrated this approach (CREDENCE, EMPA Kidney, and DAPA-CKD).[3-5] SGLT2i therapy showed benefit in the background of ACEi and/or ARB. The same is also true, incidentally, for the use of the nonsteroidal mineralocorticoid receptor antagonist finererone, which demonstrated efficacy when used in the context of background renin-angiotensin-aldosterone system (RAAS) inhibition. The pyramid approach advocated by Kidney Disease: Improving Global Outcomes and the American Diabetes Association guidelines, and the pillars of care approach advocated by others, emphasizes the importance of layering therapies on top of each other.

We must get this approach right because there is already profound underutilization of SGLT2i (and nonsteroidal mineralocorticoid receptor antagonists [nsMRAs]) therapy in patients with CKM syndrome. Adding ambiguity isn't going to help. The underutilization of SGLT2i therapy is emphasized in two separate analyses. Among individuals with type 2 diabetes mellitus (T2DM) and an estimated glomerular filtration rate of >30 ml/min/1.73m^2, only 14% of individuals were being treated with an SGLT2i.[6] In a second study among 105,799 patients with atherosclerotic cardiovascular disease, HF, and T2DM across 130 Veterans Administration facilities, 14.6% received an SGLT2i.[7] Underutilization is even worse for nsMRA therapy.

Ndumele et al recommend SGLT2i therapy in all CKD patients with or without diabetes, but this statement isn't supported by evidence. It is hard to justify using SGLT2is in kidney transplant patients because these patients were excluded from the pivotal SGLT2i trials.[8] Likewise, evidence about whether patients with genetic kidney disease, including autosomal dominant polycystic kidney disease, benefit from SGLT2is is also lacking.[9] The evidence is strongest for CKD patients with albuminuria, particularly those with T2DM.

One important caveat not mentioned by the authors is that SGLT2i therapy is contraindicated in patients with type 1 diabetes mellitus (T1DM) who have CKD. While it is true that T2DM is much more common than T1DM, the risk of inducing euglycemic ketoacidosis (commonly defined as ketoacidosis with a blood sugar <250 mg/dL) in T1DM patients treated with SGLT2is isn't trivial. In the inTANDEM trial in T1DM using the SGLTi sotagliflozin, and in the DEPICT-2 trial using dapagliflozin, a three- to five-fold higher rate of diabetic ketoacidosis was observed.[10,11] Therefore, a more nuanced statement by Ndumele and colleagues cautioning against the use of SGLTi in T1DM would have been worthwhile.

The Ndumele review recommends "for patients with residual albuminuria on ACE or ARB, finerenone, which can be used on background SGLT2i." The evidentiary basis for this approach is lacking. In the pivotal FIGARO[12] and FIDELIO[13] trials (and the prespecified FIDELITY pooled analysis[14]), the question of whether finerenone is effective in patients with residual albuminuria wasn't examined. Rather, patients were recruited and then placed on maximal doses of ACEi or ARB. Despite maximal use of RAAS blockade, additional kidney and cardiac protection was observed with finernone. The use of finerenone in T2DM patients with CKM stage 2-3 who have a potassium level <5.0 mEq/L would have been a more supportable statement.

In summary, there are many strengths and some weaknesses in the American Heart Association's presidential statement by Ndumele and colleagues. The most important take-home messages for me are that while gaps remain, there is now a large amount of data that has deepened our understanding of CKM syndrome, its interconnections, and how it should be managed. The emergence of

several new classes of medications provides exciting opportunities to reduce morbidity and mortality from CKM syndrome. ■

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Risk of Cardiovascular Events in Patients With CKD

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Using data from the pooled analysis, Dr. Agarwal et al tested whether the risk of cardiovascular disease associated with CKD, as defined jointly by eGFR and albuminuria, was modifiable with finerenone in patients with type 2 diabetes. The researchers also estimated the population-wide benefit in the United States if all eligible patients were treated with finerenone. Results were reported in *JAMA Cardiology* [doi:10.1001/jamacardio.2023.1505].

To simulate the number of composite cardiovascular events that may be prevented per year with finerenone at a population level, the analysis combined the data from the pooled analysis and data from the National Health and Nutrition Examination Survey (NHANES). Data were analyzed over 4 years of consecutive NHANES data cycles (2015-2016 and 2017-2018).

The key outcome in the current analysis was a composite cardiovascular outcome of time to cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for heart failure. Cox proportional hazards models, stratified by study, region, eGFR, and albuminuria categories at screening, and history of cardiovascular disease were used to analyze the outcome. Analyses were performed in the full analysis set that comprised all randomly assigned patients with the exception of those with critical Good Clinical Practice violations.

The current subanalysis utilized the FIDELITY study sample as a model. The model included 13,026 patients with CKD and type 2 diabetes. Mean age was 64.8 years, 69.8% (n=9088) were male, and 30.2% (n=3938) were female. There was a broad range of eGFR and urine albumin to creatinine ratio (UACR) values. Self-reported race and ethnicity categories were Asian (22.2%; n=2894), Black or African American (4.0%; n=522), Hispanic (16.1%; n=2099), White (68.1%; n=8869), and other or not reported (5.7%; n=741). Mean eGFR was 57.6 mL/min/1.73 m^2 and median UACR was 515 mg/g.

Based on Kidney Disease: Improving Global Outcomes risk scores, 10.2% of the cohort (n=1323/13,026) was categorized as at moderate risk, 41.0% (n=5345/13,026) as at high risk, and 48.3% (n=6288/13,026) as at very high risk. The cohort was largely balanced in characteristics at baseline between eGFR and UACR categories. However, the prevalence of a history of atherosclerotic cardiovascular disease increased with lower eGFR and was higher in patients with UACR less than 300 mg/g compared with those with UACR 300 mg/g or greater (52.6%; n=2279/4329 and 42.1%; n=3655/8692, respectively).

Median follow-up in the FIDELITY trial was 3 years. During the follow-up period, the incidence rate of cardiovascular events was higher among patients in lower eGFR and higher UACR categories. Among patients in the placebo arm with an eGFR of 90 mL/min/1.73 m^2 or greater, the incidence rates per 100 patient-years were 2.38 (95% CI, 1.03-4.29) in patients with UACR less than 300 mg/g and 3.78 (95% CI, 2.91-4.75) in those with UACR of 300 mg/g or greater. In those with eGFR less than 30 mL/min/1.73 m^2, the incidence rates increased to 6.54 (95% CI, 4.19-9.40) versus 8.74 (95% CI, 6.78-10.93), respectively.

Overall, there was an association between finerenone and a reduction in the risk of cardiovascular events versus placebo (hazard ratio, 0.86; 95% CI, 0.78-0.95; *P*=.002). The association between finerenone and reduction in the risk of cardiovascular events remained across ranges of eGFR and UACR. There was no significant interaction between the outcome of finerenone versus placebo across eGFR and UACR groups (*P* for interaction=.66).

Results of modeling the predictive probability of a cardiovascular event at 4 years demonstrated a higher risk for patients with higher levels of albuminuria in patients with eGFR less than 60 mL/min/1.73 m^2 as well as those with eGFR 60 mL/min/1.73 m^2 or greater. There was an association between finerenone and a reduction in risk of cardiovascular events across the range of UACR in both eGFR groups.

There was a higher risk of cardiovascular events at 4 years seen in patients with UACR of 300 mg/g or greater with lower levels of eGFR.

In the simulation of prevention of cardiovascular events in the United States, in the overall FIDELITY study population, based on differences in incidence rates per 100 patient-years between the finerenone and placebo arms, the total excess number of cardiovascular events that would be prevented per 10,000 patient-years was 67 (95% CI, 24-111). Based on the 6.4 million estimated individuals with albuminuric CKD and type 2 diabetes eligible for finerenone and the differences in incidence rates per 100 patient-years between the finerenone and placebo arms, the simulated total number of preventable cardiovascular events per year was estimated at 38,359 events (95% CI, 31.741-44.852), including the prevention of approximately 14,000 hospitalizations for heart failure.

Limitations to the study findings included exclusion of patients receiving dialysis or those with stage 5 CKD and those with UACR less than 30 mg/g at screening from the FIDELITY trial, as well as the lack of inclusion of significant numbers of Black and Hispanic patients.

In summary, the authors said, "Results of the present subanalysis of the FIDELITY trial suggest that CKD-associated composite cardiovascular risk, driven in part by reduction in hospitalization for heart failure, was modifiable with finerenone treatment. Identifying patients with moderately to severely increased albuminuria and eGFR of 60 or greater and treating them to reduce cardiovascular risk will have public health implications." ■

TAKEAWAY POINTS

- Researchers performed a subanalysis of data from the FIDELITY trial to examine whether cardiovascular risk is modifiable in patients with chronic kidney disease (CKD) and type 2 diabetes.
- There was an association between finerenone treatment and a reduction in cardiovascular risk in patients with CKD, type 2 diabetes, estimated glomerular filtration rate >25 mL/min/1.73 m^2, and moderately to severely increased albuminuria.
- A simulation model suggested that over 1 year, finerenone may prevent 38,359 cardiovascular events.

Hypokalemia and Hyperkalemia Increase Risk

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stages 4-5 are at high risk of kidney failure and mortality. The relationship between potassium level and the combined outcome of death or KRT may differ in older patients compared with younger individuals.

According to **Esther N. M de Rooij, MD,** and colleagues, there are few data available on the relationship between serum potassium and death or the occurrence of kidney failure requiring KRT in older people with CKD stage 4-5. The researchers conducted a prospective observational cohort study designed to examine that relationship in patients ≥65 years of age with CKD stage 4-5. Results were reported in the *American Journal of Kidney Diseases* [2023;82(3):257-266].

The study exposure was serum potassium measured every 3 to 6 months and categorized according to seven prespecified categories: ≤3.5, >3.5 to ≤4.0, >4.0 to ≤4.5, >4.5 to ≤5.0, >5.0 to ≤5.5, >5.5 to ≤6.0, and >6.0 mmol/L. The outcome of interest was the combined outcome of death before KRT or initiation of KRT.

Cox proportional hazards and restricted cubic spine analyses were used to assess the association between categorical and continuous time-varying potassium and death or KRT. The analyses were adjusted for age, sex, diabetes, cardiovascular disease, RAAS inhibition, estimated glomerular filtration rate (eGFR), and subjective global assessment (SGA).

Data from the European Quality (EQUAL) study were utilized for the current study. Patients ≥65 years of age were followed for 8 years from their first eGFR <20 mL/min/1.73 m^2 measurement.

Of the 1736 EQUAL study participants, 1714 met eligibility requirements (at least one available serum potassium measurement). At baseline, mean age was 76 years, 66% were men, 42% had diabetes, 47% had cardiovascular disease, and 54% used RAAS inhibitors. Mean eGFR was 17 mL/min/1.73 m^2, mean SGA was 6.0, and mean serum potassium level was 4.6 mmol/L.

Distribution of potassium levels in the seven potassium categories was as follows: 2%, 13%, 28%, 33%, 17%, 5%, and 2%, respectively. In the lowest category (≤3.5 mmol/L), the mean value was 3.3 mmol/L, and in the highest category (>6.0 mmol/L) the mean value was 6.3 mmol/L. Compared with the reference category (>4.5 to ≤5.0 mmol/L), patients in the lowest potassium category had lower SGA scores, more often had diabetes, and less often had cardiovascular disease. Patients in the highest serum potassium

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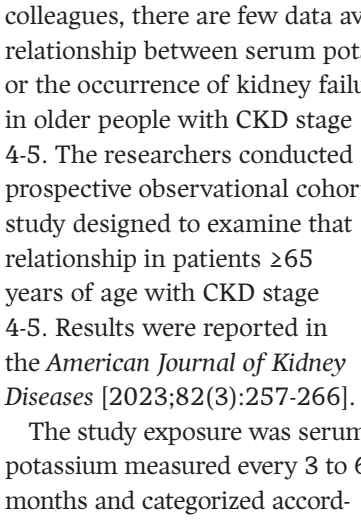

NATIONAL KIDNEY FOUNDATION SPRING CLINICAL MEETINGS

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category were more often men, had a lower eGFR, and less often had cardiovascular disease.

During follow-up, 6091 potassium measurements were performed (average, 3.6 measurements per participant). The distribution of serum potassium during follow-up was similar to the distribution at baseline. Of the total cohort, 7% (n=126) experienced serum potassium ≤3.5 mmol/L, and 13% (n=230) and 3% (n=59) experienced serum potassium >5.5 to ≤6.0 mmol/L and >6.0 mmol/L during follow-up, respectively. Compared with normal serum potassium levels, the low or high levels were less often persistent for two or more consecutive visits.

Median time to death or initiation of KRT was 2.6 years. Twenty-four percent of participants died (n=414), 1% (n=15) had a preemptive kidney transplantation, and 34% (n=580) initiated dialysis during 3851 person-years, yielding an overall crude combined death or KRT start rate of 26.2 (95% CI, 24.6-27.8) per 100 patient-years. Among older patients with an eGFR <20 mL/min/1.73 m^2, KRT initiation was more common than death before KRT. Of the 414 deaths before start of KRT, 26% (n=109) were due to cardiovascular disease.

In the lowest serum potassium category of ≤3.5 mmol/L, the absolute rates of combined death or initiation of KRT were 40 (95% CI, 28-54) per 100 person-years. The rates were 22 (95% CI, 20-24) per 100 person-years in the reference category (>4.5 to ≤5.0 mmol/L), and 59 (95% CI, 40-85) per 100 person-years in the highest serum potassium category (>6.0 mmol/L).

Adjusted hazard ratios for death or initiation of KRT according to the serum potassium categories were 1.6 (95% CI, 1.1-2.3), 1.4 (95% CI, 1.1-1.7), 1.1 (95% CI, 1.0-1.4), 1.0 (reference), 1.1 (95% CI, 0.9-1.4), 1.8 (95% CI, 1.4-2.3), and 2.2 (95% CI, 1.50-3.3). Hazard ratios were lowest at a potassium level of approximately 4.9 mmol/L.

The researchers cited some limitations to the study findings, including missing data, the inability to adjust for time-dependent confounding due to limited follow-up data on confounders, only updating serum potassium as a time-dependent variable, and using all-cause mortality rather than sudden cardiac death as the primary outcome.

"In conclusion," the authors said, "We found a U-shaped relationship between serum potassium and the combined outcome of death or KRT start in patients aged ≥65 years with an incident eGFR <20 mL/min/1.73 m^2 during 8 years of follow-up. Our results indicate a serum potassium level of approximately 4.9 mmol/L to be associated with the lowest hazard of death or KRT start. Compared with this optimum level, low (≤3.5 mmol/L) and high (>6.0 mmol/L) serum potassium concentrations were a 1.6- and 2.2-fold stronger hazard for death or KRT start after multivariable adjustment, respectively. This relatively high level may stress the importance of preventing both high and low serum potassium in older patients with CKD stages 4-5." ■

TAKEAWAY POINTS

- In older adults with chronic kidney disease stages 4-5, both hypokalemia and hyperkalemia may increase the risk of death or decline in kidney function leading to the need for kidney replacement therapy (KRT).
- Results of a prospective observational cohort study demonstrated a U-shaped relationship between serum potassium and death or initiation of KRT.
- A serum potassium level of approximately 4.9 mmol/L was associated with the lowest hazard of death or KRT start.

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Dietary Potassium Intake

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The analyses included data on participants >40 years of age from the National Health and Nutrition Examination Survey (NHANES) 2013-2014. Dietary potassium intake was categorized into quartiles: quartile 1, <1911 mg/day; quartile 2, 1911-2461 mg/day; quartile 3, 2462-3119 mg/day; and quartile 4, >3119 mg/day.

The primary outcome of interest was AAC quantified using the Kauppila scoring system. AAC scores were categorized into no AAC (AAC=0, reference group), mild/moderate (AAC >0 to ≤6), and severe AAC (AAC >6). The secondary outcome was arterial stiffness that was examined using pulse pressure as a surrogate.

Potential cofounders included age, sex, race/ethnicity, body mass index (BMI), poverty, smoking status, hypertension, diabetes mellitus, lipid profile, kidney function, serum markers of mineral bone disease, prescription antihypertensive or antihyperlipidemic use, daily caloric intake, and level of physical activity.

Following exclusion of NHANES participants with extreme dietary potassium intake (n=49), those with missing potassium dietary intake data (n=500), and missing covariate data (n=173), the primary analysis of dietary potassium intake and AAC included data on 2418 participants. The secondary analysis of dietary potassium intake and pulse pressure included data on 2186 participants.

In the primary analysis cohort, 20% had mild/moderate calcification and 8% had severe calcification. Patient morbidities included diabetes (16.8%), hypertension (59.7%), CKD stage 1-2 (7.6%), and CKD stage 3-5 (9.1%).

Compared with participants with no AAC, those with mild/moderate or severe AAC were significantly older, less physically active, and more likely to be smokers, diabetic, or hypertensive. They were also more likely to have lower BMI, lower estimated glomerular filtration rate (eGFR), and take antihyperlipidemic medications. There were statistically significant but not clinically meaningful differences in serum phosphate levels: those with severe AAC had higher levels compared with the reference group. Mean serum potassium level was 4.0 mg/dL; there was no significant difference in serum potassium among the AAC groups.

Mean dietary potassium intake was 2654 mg/day among all participants. Mean dietary potassium intake among those in quartile 1 was 1511 mg/day; in quartile 2, 2185 mg/day; in quartile 3, 2767 mg/day; and in quartile 4, 3821 mg/day. Daily potassium intake was lower in women than in men. Participants with albuminuria were more likely to have a lower dietary potassium intake. Those with poverty, low BMI, low daily caloric intake, and low physical activity had a lower daily potassium intake. There was a positive association between serum potassium and dietary potassium intake ($P<.001$).

Compared with the reference group, those in the AAC groups had lower daily potassium intake; the difference did not reach statistical significance ($P=.20$). When examined as a continuous variable in either unadjusted or fully adjusted models, there was no association between dietary potassium intake and AAC.

When dietary potassium intake was examined within quartiles, there was a nonlinear association with AAC. In the unadjusted model, compared with quartile 1, dietary potassium intake in quartile 2 was associated with 35% lower odds of severe AAC (odds ratio, 0.65; 95% CI, 0.44-0.96; $P=.01$). The association remained significant in the fully adjusted model. There were no associations between dietary potassium intake and AAC in comparisons of other quartiles with the first.

In the fully adjusted model, there were significant associations between age, BMI, hypertension, diabetes, smoker, and eGFR and severe AAC. Age, sex, race-ethnicity, hypertension, diabetes, eGFR, albuminuria, and CKD did not modify the association between dietary potassium intake and AAC.

In secondary analyses, compared with participants in the reference group who had a mean pulse pressure of 50.4 mm Hg, pulse pressure was significantly higher in those with mild/moderate AAC (58.7 mm Hg) or severe AAC (69.7 mm Hg) (P for trend<.001). in the fully adjusted model, per 1000 mg higher in dietary potassium intake, pulse pressure was 1.47 mm Hg lower (95% CI, –2.47 to –0.47; $P=.007$).

The authors cited some limitations to the study findings, including the cross-sectional design that did not allow for inference of causation between dietary potassium intake and arterial calcification and stiffness, the small number of participants with CKD stage 4 or 5, and not differentiating the dietary potassium source (plant vs animal).

In conclusion, the researchers said, "In a population of adults over 40 years of age, there was not a linear association between dietary potassium intake and AAC. There was a negative relationship when comparing dietary potassium in quartile 2 to quartile 1, suggesting that there might be an optimal level of dietary potassium intake that is beneficial for the prevention of arterial calcification. Additionally, dietary potassium intake was negatively associated with pulse pressure. These findings support the potential important benefits of dietary potassium intake on arterial calcification and stiffness. Further large and prospective studies are needed to validate our findings." ■

TAKEAWAY POINTS

- Researchers reported results of a study testing the hypothesis that higher dietary potassium intake would be associated with less abdominal aortic calcification (AAC) and lower arterial stiffness.
- There was no linear association between dietary potassium intake and AAC. When comparing dietary potassium intake in quartiles of participants, there was an association between higher dietary potassium intake and less severe AAC.
- There was a significant association between higher dietary potassium intake and lower pulse pressure.

Conference Coverage

Philadelphia, Pennsylvania | November 2-5, 2023

KIDNEY WEEK 2023

The American Society of Nephrology Kidney Week 2023 included presentations and posters highlighting the latest findings in kidney health research, as well as sessions on advances in the care of patients with kidney and related disorders. This is part one of our coverage of Kidney Week 2023. Part two will appear in our January/February 2024 issue.

Gout Control Projected to Improve Patient Health and Reduce Costs

One in four patients with stage 3-5 chronic kidney disease (CKD) is affected by gout, an independent predictor for progression of CKD. Oral urate-lowering therapies do not adequately manage gout in some patients with CKD.

Brad A. Marder and colleagues conducted a study designed to examine the potential benefits of pegloticase treatment in patients with CKD with refractory gout. Results of the study were reported during a poster session at the American Society of Nephrology Kidney Week 2023 in a poster titled *Projected Benefits of Gout Control on the Health and Economic Burden of CKD Patients With Uncontrolled Gout*.

Gout burden in a virtual US CKD population was projected using a validated microsimulation model. In the baseline scenario, individuals were assigned an estimated glomerular filtration rate (eGFR), albuminuria status, and serum urate level. Those with gout were assigned complication risks for stroke, diabetes, and hypertension, as well as direct and indirect costs, use/efficacy of oral urate-lowering therapy probability (use, 29.2%-41.9% [based on eGFR]; efficacy, 48.3%), and utility weight.

In the intervention scenario, those with uncontrolled gout (defined as serum urate >6 mg/dL) despite oral urate-lowering therapy and two or more gout flares per year were "treated" with pegloticase, assuming a 71% serum urate-lowering efficacy rate (serum urate <6 mg/dL) through simulation end. Health and economic benefits were projected through 2035.

Results of the simulation suggested that the prevalence of comorbid gout and CKD would rise from 8.2 million in 2023 to 10.5 million in 2035; 28% of those patients would have uncontrolled gout. The annual costs of management of gout in patients with CKD were projected to increase from $39.1 billion in 2023 to $50.4 billion in 2035.

Use of pegloticase in all patients with CKD and uncontrolled gout was projected to result in 301,000 fewer cases of uncontrolled gout, a gain of 208,000 quality-adjusted life-years, and avoidance of 53,000 complications by 2035. Compared with the baseline scenario (nontreatment), the costs in the intervention scenario were $23.4 billion lower in 2035.

"Gout prevalence in CKD patients is projected to markedly increase over the next 12 years," the researchers said. "This microsimulation suggests that intervention could result in health and quality of life improvement in CKD patients with uncontrolled gout, with associated cost reductions."

Source: Marder BA, Card-Gowers J, Retat L, et al. Projected benefits of gout control on the health and economic burden of CKD patients with uncontrolled gout. FR-P0921. Abstract of a poster presented at the American Society of Nephrology Kidney Week 2023; November 3, 2023; Philadelphia, Pennsylvania. Funding for this study was provided by Horizon Therapeutics plc.

Incident CKD After Hospitalization for COVID-19

Results of previous studies have suggested an association between COVID-19 and accelerated decline in estimated glomerular filtration rate (eGFR) in hospitalized patients. However, according to **Spencer Krichevsky** and colleagues, those studies were limited by cohort size, duration of follow-up, and geo-specificity. There is also a lack of data on characterization of incident chronic kidney disease (CKD) in nonhospitalized patients with CKD.

The researchers conducted an analysis of electronic health record data from 77 health systems in the United States in the National COVID Cohort Collaborative. They reported results of the analysis during a poster session at the American Society of Nephrology Kidney Week 2023 in a poster titled *Risk Factors for Post-COVID-19 Incident CKD in the National COVID Cohort Collaborative*.

The analysis included data on adults diagnosed with COVID-19 between March 1, 2020, and October 1, 2022, without pre-COVID-19 CKD. The cohort was evaluated for post-COVID-19 CKD through December 31, 2022. Diagnosis codes or outpatient eGFR measurements were used to identify CKD.

Risk factors were analyzed using multivariable models. Risk factors of interest were demographics (age, sex, race/ethnicity), geographical region (Midwest, Northeast, South, West), hospitalization, acute kidney injury (AKI), and a reported diagnosis of long COVID-19.

Of 3.7 million patients, 2% (n=76,000) had incident post-COVID-19 CKD. Of those, 73% (n=55,000) were not assigned a CKD diagnosis code but met requirements for eGFR-based CKD. In multivariable models, there were associations between incident CKD and older age, male sex, and Black of Native Hawaiian or Pacific Islander race (compared with White race).

The event rates for incident CKD for patients hospitalized during the COVID-19 diagnosis were significantly higher than among those never hospitalized for COVID-19 (11.4 vs 28.7 per 1000 patient-years). Among hospitalized patients, those with AKI (vs no AKI) had an even higher rate of incident CKD (98.3 vs 21.2 per 1000 patient-years).

In multivariable analyses, when compared with patients who were never hospitalized with COVID-19, the incidence of CKD was much higher in those who were hospitalized and developed AKI (hazard ratio [HR], 3.82; $P<.001$). Compared with the Midwest, the adjusted odds ratios for incident CKD were higher in the West (1.32; $P<.001$) and South (1.03; $P<.001$) and lower in the Northeast (0.94; $P<.001$).

In a subcohort of 1.5 million patients evaluated at U09.9-reporting sites, there was an association between long COVID-19 and a moderately higher HR for incident CKD (1.14; $P<.001$).

In conclusion, the researchers said, "In one of the largest studies on this topic, we observe that incident CKD in patients with COVID was underdiagnosed and influenced by geographical region, hospitalizations, and AKI. Patients with long COVID had higher rates of CKD compared with those without."

Source: Krichevsky S, Koraishy FM, Ellison DH. Risk factors for post-COVID-19 incident CKD in the National COVID Cohort Collaborative. TH-P0112. Abstract of a poster presented at the American Society of Nephrology Kidney Week 2023; November 2, 2023; Philadelphia, Pennsylvania.

Blood Pressure Control and Mortality After AKI

Approximately 20% to 25% of hospital admissions are complicated by acute kidney injury (AKI) events. AKI-related events are associated with increased rates of long-term mortality. Effective blood pressure control following AKI may have beneficial effects on outcomes, but there are few data available on appropriate blood pressure targets and the optimal timing of initiation of blood pressure-lowering medication.

Benjamin R. Griffin and colleagues at the University of Iowa Hospital & Clinics, Iowa City, conducted a retrospective cohort analysis of data on US veterans with in-hospital AKI. Results of the analysis were reported during a poster session at the American Society of Nephrology Kidney Week 2023. The poster was titled *Time to Blood Pressure Control and Blood Pressure Targets Significantly Impact Mortality Among Veterans Following AKI*.

The cohort included veterans admitted to the hospital from 2013 to 2018 who experienced an in-hospital AKI event. Eligible patients had one or more blood pressure measurement within 30 days of hospital discharge. Systolic blood pressure was treated as time dependent and categorized as <120, 120-129, and 130-139 mm Hg, relative to >140 mm Hg.

The primary outcome of interest was time to death. Cox proportional hazards regression models were adjusted for demographics, chronic lung disease, unexplained weight loss, dementia, congestive heart failure, hematocrit, blood urea nitrogen, bilirubin, and albumin. Hazard ratios (HRs) were calculated at seven different time points to evaluate the impact of blood pressure control over time (30, 60, 120, 180, 270, and 365 days after discharge).

The cohort included 97,376 veterans. Of those, 15% (n=14,819) died within 1 year of hospital discharge. Rates of hypertension, congestive heart failure, and diabetes were high in the overall cohort (85%, 28%, and 19%, respectively). Relative to uncontrolled blood pressure, HRs for mortality were significantly reduced for all blood pressure categories <140 mm Hg. The lowest HRs were in the group with blood pressure 130-139 mm Hg. Relative to uncontrolled blood pressure, HRs were lowest at the 30-day mark for all blood pressure categories and increased over time.

In summary, the authors said, "Among post-AKI veterans, blood pressure control within 30 days of discharge was associated with reduced mortality, but this benefit was attenuated over time. All blood pressure targets were superior to blood pressure >140 mm Hg, but the 130-139 mm Hg group had the lowest risk of death at each time point. These findings highlight the importance of achieving blood pressure control promptly post-AKI and suggest that targeting a systolic blood pressure of 130-139 is ideal."

Source: Griffin BR, Sarrazin MV, Masaaki Y, et al. Time to blood pressure control and blood pressure targets significantly impact mortality among veterans following AKI. FR-P0105. Abstract of a poster presented at the American Society of Nephrology Kidney Week 2023; November 3, 2023; Philadelphia, Pennsylvania.

Deprived Neighborhoods and Disparities in Access to Living Donor Kidney Transplantation

The optimal treatment for patients with end-stage kidney disease (ESKD) is living donor kidney transplantation, which offers improved health outcomes. Deprived neighborhoods are defined as those with low socioeconomic status, limited social cohesion, and reduced access to health care. According to **Byoungjum Kim** and colleagues, there are few data available on the role of neighborhood deprivation in assess to living donor kidney transplantation.

The researchers conducted an analysis using data from the Scientific Registry of Transplant Recipients to identify 510,674 non-Hispanic White, non-Hispanic Black, non-Hispanic Asian, and Hispanic kidney transplant candidates ≥18 years of age who were listed for a first kidney transplant from 1995 to 2021. Results were reported during a poster session at the American Society of Nephrology Kidney Week 2023 in a poster titled *Neighborhood Deprivation and Access to Living Donor Kidney Transplantation: Reducing Health Care Disparities*.

Using population weights from the American Community Survey, the National Cancer Institute's Neighborhood Deprivation Index was averaged at the ZIP code level. The likelihood of living donor kidney transplant across tertiles was determined using proportional hazards models, adjusting for clinical and neighborhood-level factors.

Results of the analysis revealed that candidates for living donor kidney transplant who resided in high-deprivation neighborhoods had a lower access to living donor kidney transplantation compared with those in low-deprivation neighborhoods (adjusted hazard ratio [aHR], 0.80; 95% CI, 0.79-0.82). Black candidates residing in high-deprivation neighborhoods had 37% lower access to living donor kidney transplantation compared with candidates in low-deprivation neighborhoods (aHR, 0.63; 95% CI, 0.60-0.67). Asian and Hispanic candidates living in high-deprivation neighborhoods had 22% (aHR, 0.778; 95% CI, 0.70-0.88) and 21% (aHR, 0.79; 95% CI, 0.75-0.83), respectively, lower access to living donor kidney transplantation compared with White candidates.

"Neighborhood deprivation is associated with decreased access to living donor kidney transplantation, particularly among Black candidates. Identification of structural factors impacting health care access in disadvantaged neighborhoods can be used by policymakers and health care providers to develop interventions to address barriers and disparities in living donor kidney transplantation access," the researchers said.

Source: Kim B, Menon G, Li Y, et al. Neighborhood deprivation and access to living donor kidney transplantation: reducing health care disparities. TH-P0881. Abstract of a poster presented at the American Society of Nephrology Kidney Week 2023; November 2, 2023; Philadelphia, Pennsylvania.

PTH and Calcium Levels and Mortality in Peritoneal Dialysis Patients

Patients with chronic kidney disease (CKD) and mineral bone disorder (MBD) face a high symptom burden, including fractures, vascular calcification, and cardiovascular disease, as well as increased risk of morbidity and mortality. According to **Kosaku Nitta** and colleagues, there are few data available on CKD-MBD among patients receiving peritoneal dialysis.

The researchers conducted a data analysis to examine calcium and parathyroid hormone (PTH) control, as well as associations with mortality in patients on peritoneal dialysis. Results of the analysis were reported during a poster session at the American Society of Nephrology Kidney Week 2023 in a poster titled *International Variations in Serum PTH and Calcium Levels and Their Mortality Associations in Peritoneal Dialysis Patients: Results From PDOPPS*.

Data from eight countries (Australia and New Zealand [A/NZ], Canada, Japan, Thailand, South Korea, the United Kingdom, and the United States) participating in the Peritoneal Dialysis Outcomes and Practice Patterns Study (PDOPPS) 2014-2022 were included in the analysis. Eligible participants had received peritoneal dialysis for at least 3 months. Cox regression adjusted for potential confounders was used to examine the association between baseline PTH and albumin-adjusted calcium ($calcium^{Alb}$) and all-cause mortality.

Mean age of the eligible patients ranged from 54.6 years in South Korea to 63.5 years in Japan. PTH was measured at baseline in 12,642 patients, and serum $calcium^{Alb}$ was measured at baseline in 14,244 patients. Median PTH ranged from 161 pg/mL in Japan to 363 pg/mL in the United States. Mean $calcium^{Alb}$ ranged from 9.1 mg/dL in South Korea and the United States to 9.8 mg/dL in A/NZ.

The relationship between PTH and mortality was U-shaped, with the lowest risk at PTH 300 to 599 pg/mL. The risk of mortality was nearly 20% higher at serum $calcium^{Alb}$ 9.6 mg/dL than at 8.4 mg/dL.

"A large proportion of peritoneal dialysis patients in the multinational study have calcium or PTH levels in ranges associated with substantially higher mortality," the authors said. "These observations point to the need to substantially improve MBD management in peritoneal dialysis to optimize patient outcomes."

Source: Nitta K, Bieber B, Karaboyas A, et al. International variations in serum PTH and calcium levels and their mortality associations in peritoneal dialysis patients: results from PDOPPS. TH-P0161. Abstract of a poster presented at the American Society of Nephrology Kidney Week 2023; November 2, 2023; Philadelphia, Pennsylvania.

Obesity, Metabolic Syndrome, and Diabetes and CKD in Men and Women

Previous studies have documented associations between chronic kidney disease (CDK), obesity, and metabolic syndrome. However, there are few data available on how those associations vary across obesity/metabolic phenotypes in males and females.

Chyng-Wen Fwu and colleagues conducted an analysis of data from the 2003-2020 cycles of the National Health and Nutrition Examination Survey for 8586 men and 8420 nonpregnant women ≥20 years of age. Results were reported during a poster session at the American Society of Nephrology Kidney Week 2023 in a poster titled *Association of Obesity, Metabolic Syndrome, and Diabetes With CKD in Men and Women: National Health and Nutrition Examination Survey (NHAMES), 2003-2020*.

CKD was defined as albuminuria or estimated glomerular filtration rate <60 mL/min/1.73 m^2; metabolic syndrome was defined as three of the following: hypertension, prediabetes, hypertriglyceridemia, low high-density lipoprotein cholesterol, and/or central obesity; and obesity was defined as body mass index ≥30 kg/m^2. CKD, metabolic syndrome, and obesity were defined by physical examination and/or results from fasting laboratory samples.

Diabetes was defined by self-report, prior diagnosis, and/or high fasting glucose or hemoglobin A1c. Participants without diabetes were further categorized based on four obesity/metabolic phenotypes: (1) metabolically healthy nonobese (MHNO); (2) metabolically unhealthy nonobese (MUNO); (3) metabolically healthy obese (MHO): and (4) metabolically unhealthy obese (MUO).

The relationship between CKD and obesity/metabolic phenotypes was examined using multivariable-adjusted logistic regression models.

Among participants with diabetes, the prevalence of CKD was 36.7% for men and 35.9% for women (95% CI, 33.6%-39.8% and 32.2%-39.9%, respectively). In the MUNO group, the prevalence of CKD was 13.2% for men and 21.0% for women (95% CI, 10.6%-16.5% and 18.0%-24.3%, respectively). In the MUO group, the prevalence was 10.9% for men and 14.8% for women (95% CI, 9.1%-13.1% and 12.9%-16.9%, respectively). In the MHNO group, the prevalence was 5.6% for men and 9.6% for women (95% CI, 4.9%-6.5% and 8.5%-10.9%, respectively). In the MHO group, the prevalence was 4.6% for men and 8.4% for women (95% CI, 3.4%-6.2% and 6.6%-10.7%, respectively).

There was an association between CKD and the metabolically unhealthy phenotypes in men (adjusted odds ratio [aOR], MUNO 1.94; 95% CI, 1.41-2.687 and MUO 1.83; 95% CI, 1.40-2.38). In women, there was an association between CKD and the MUNO group only (aOR, 1.50; 95% CI, 1.12-1.99).

In conclusion, the authors said, "These findings suggest different associations between metabolic syndrome and CKD between males and females. Understanding how sex-specific differences such as sex hormones modulate the interaction between obesity/metabolic phenotypes and CKD may provide additional avenues for prevention and treatment."

Source: Fwu C-W, Barthold J, Kimmel PL, et al. Association of obesity, metabolic syndrome, and diabetes with CKD in men and women: National Health and Nutrition Examination Survey (NHANES), 2003-2020. TH-P0923. Abstract of a poster presented at the American Society of Nephrology Kidney Week 2023; November 2, 2023; Philadelphia, Pennsylvania.

Serum Creatinine Improvement and Outcomes in Hepatorenal Syndrome

Hepatorenal syndrome (HRS) is a severe form of acute kidney injury. It is life-threatening but potentially reversible. In the phase 3 CONFIRM study, more patients with HRS in the group treated with terlipressin achieved verified reversal of HRS compared with those in the placebo group (29.1% vs 15.8%, respectively; *P*=.012).

Juan Carlos Q. Velez and colleagues conducted a post hoc analysis of patient data from CONFIRM to determine whether an improvement in serum creatinine of >30% was associated with improved clinical outcomes. The researchers reported results of the analysis during a poster session at the American Society of Nephrology Kidney Week 2023 in a poster titled *Improvement in Serum Creatinine Was Associated With Favorable Clinical Outcomes in Patients With Hepatorenal Syndrome: A Post Hoc Analysis of the CONFIRM Study*.

Adults with cirrhosis, ascites, HRS, and a serum creatinine level of ≥2.25 mg/dL with projected doubling in serum creatinine within 2 weeks were enrolled in the CONFIRM study. Patients treated intravenously with terlipressin 1 mg every 6 hours were matched with patients in the placebo arm. Patients in both arms received recommended albumin. Patients from the CONFIRM intent-to-treat population were analyzed based on improvement (>30% vs ≤30%) in serum creatinine level from baseline (day 0 or a prestudy value if day 0 value is missing) to the end of treatment for length of intensive care unit (ICU) stay; incidence of renal replacement therapy (RRT); RRT-free survival at days 30, 60, and 90; and survival at day 90.

More patients in the terlipressin group had a >30% improvement in serum creatinine from baseline to end of treatment than patients in the placebo group (43.7% vs 21.8%, respectively; *P*<.001). Of patients admitted to the ICU, mean length of stay was numerically shorter among patients who had a >30% improvement in serum creatinine versus those who had a ≤30% improvement in serum creatinine (5.8 days vs 9.4 days, respectively; *P*=.673).

At day 90, RRT was required in fewer patients in the >30% improvement in serum creatinine group (18.3% vs 40.3%; *P*<.001). Overall, a higher proportion of patients (n=300; terlipressin + placebo combined) who achieved a >30% improvement in serum creatinine were alive (67.0% vs 42.9%; *P*<.001); and alive and RRT-free by day 90 (55.0% vs 20.4%; *P*<.001).

"Significantly more patients in the terlipressin group achieved a >30% improvement in serum creatinine versus placebo. Patients with a >30% improvement in serum creatinine had significant improvements in clinical outcomes through day 90," the authors said.

Source: Velez JCQ, Mujtaba MA, Elsiesy H, Jamil K. Improvement in serum creatinine was associated with favorable clinical outcomes in patients with hepatorenal syndrome: a post hos analysis of the CONFIRM study. TH-P0052. Abstract of a poster presented at the American Society of Nephrology Kidney Week 2023; November 2, 2023; Philadelphia, Pennsylvania.

Sex Disparities in the United States in Living Kidney Donor Transplantation

The prevalence of chronic kidney disease in the United States is higher among women than men (16.2% vs 13.4%). Results of studies conducted in Asia and Mexico examining sex disparities in kidney transplantation suggested that women comprised 62% to 69% of donors but were recipients of living kidney donor transplantation in only 20% of cases. Sociocultural or biological factors did not fully explain those disparities.

According to **Fausto R. Cabezas** and colleagues, outdated data on sex disparities in the United States indicate a lower rate of living kidney donor transplantation in women. The researchers conducted a data analysis to assess the current trend of living kidney donor transplantation in the United States. Results were reported during a poster session at the American Society of Nephrology Kidney Week 2023 in a poster titled *Ongoing Sex Disparities in Living Kidney Transplantation: A UNOS Analysis*.

The researchers queried the United Network for Organ Sharing (UNOS) database for all single-organ living kidney donor transplants from 2011 to 2022. Changes and risk factors were characterized using comprehensive univariate and multivariate analyses.

Of the 60,865 identified living kidney donor transplants, women were 36.0% of recipients and 63.5% of donors. The likelihood of receiving a living kidney donor transplant decreased with increasing age. Compared with White women, Black women were more likely to be donors than to receive a living kidney donor transplant (odds ratio [OR], 1.4; 95% CI, 1.3-1.5; *P*<.001).

Female recipients had longer times on the transplant waitlist and were more likely to have a higher Calculated Panel Reactive Antibody score (OR, 6.2; 95% CI, 6.2-8.3; *P*<.001).

In summary, the authors said, "Females are more likely to be donors than living kidney transplant recipients and face longer times on the transplant waiting list. Black females were more likely to be donors and less likely to be recipients compared with White females. The sex disparities in kidney transplant listing and living kidney donor transplant remain. However, sociocultural factors, as well as biological factors influencing such disparities are yet to be elucidated. Data-informed policy is warranted to bridge the sex disparities in living kidney donor transplantation."

Source: Cabezas FR, Sasidharan SR, Abushawer MW, et al. Ongoing sex disparities in living kidney transplantation: a UNOS analysis. TH-P0882. Abstract of a poster presented at the American Society of Nephrology Kidney Week 2023; November 2, 2023; Philadelphia, Pennsylvania.

Renal Effects of SGLT2 Inhibitors in Patients With Acute Heart Failure

In patients with heart failure, sodium-glucose cotransporter-2 (SGLT2) inhibitors improve renal and cardiovascular outcomes. There is growing evidence that SGLT2 inhibition decreases the risk of acute kidney injury (AKI). **Jananya Wattanakul** and colleagues, of the Bhumibol Adulyadej Hospital, Bangkok, Thailand, conducted a study to examine the effect of SGLT2 inhibitors on biomarkers of tubular injury in patients with acute heart failure.

Results of the study were reported during a poster session at the American Society of Nephrology Kidney Week 2023. The poster was titled *SGLT2 Inhibitor Dapagliflozin Reduces Biomarkers of Tubular Injury in Patients With Acute Heart Failure*.

The study cohort included patients who were hospitalized for acute heart failure. Patients were randomized to receive dapagliflozin added to standard therapy or to a control group for 28 days. The primary outcome of interest was the change of urinary biomarkers ([TIMP-2] × [IGFBP7]) by NephroCheck from baseline. Secondary outcomes included the incidence of AKI, change in serum creatinine from baseline, adverse events (AEs), and 28-day mortality.

Thirty-two patients underwent randomization. After 7 days, compared with the control group, dapagliflozin significantly reduced urinary biomarkers ([TIMP-2] × [IGFBP7]): dapagliflozin, -0.03 (ng/mL)^2 per 1000 versus control, +0.04 (ng/mL)^2 per 1000; *P*=.022. The trend continued to the end of the study period.

Compared with the control group, there was a trend toward a decrease in AKI events in the dapagliflozin group (33.3% vs 46.2%; *P*=.0513). The two groups were similar in change in serum creatinine, AEs, and 28-day mortality.

"Initiation of SGLT2 inhibitors in patients with acute heart failure significantly decreased the urinary AKI risk markers TIMP-2 and IGFBP7 and supported the protective effect of SGLT2 inhibitors on renal tubular injury," the researchers said.

Source: Wattanakul J, Gojaseni P, Chittinandana A. SGLT2 inhibitor dapagliflozin reduces biomarkers of tubular injury in patients with acute heart failure. TH-P0059. Abstract of a poster presented at the American Society of Nephrology Kidney Week 2023; November 2, 2023; Philadelphia, Pennsylvania.

Conference Coverage

Philadelphia, Pennsylvania | November 2-5, 2023

Voclosporin in Black Patients With Lupus Nephritis: AURORA Studies

Black patients with lupus nephritis commonly have more severe disease, are often refractory to treatment, and experience worse long-term outcomes. Treatment with voclosporin in conjunction with low-dose glucocorticoids and mycophenolate mofetil (MMF) has been shown to have significant benefit across ancestries and classes of lupus nephritis.

During a poster session at the American Society of Nephrology Kidney Week 2023, **Gabriel Contreras** and colleagues reported on outcomes of up to 3 years of follow-up in patients identifying as Black who were treated with voclosporin during the phase 3 AURORA studies. The poster was titled *Long-term Safety and Efficacy of Voclosporin in Black Patients With Lupus Nephritis.*

Inclusion criteria for the parent AURORA 1 study were biopsy-proven lupus nephritis, urine protein creatinine ratio (UPCR) ≥15 g/g (≥2 g/g for Class V), and estimated glomerular filtration rate (eGFR) >45 mL/min/1.73 m^2. Participants who completed AURORA 1 were eligible to enter AURORA 2, a continuation study on the same blinded therapy of voclosporin or placebo in combination with MMF and glucocorticoids for an additional 2 years.

Study outcomes of programmed complete renal response (CRR; UPCR ≤0.5 g/g, stable eGFR, low-dose steroids, and no rescue medication), partial renal response (PRR; reduction in UPCR of ≥50% from baseline), and safety were assessed in a subgroup of patients who self-identified as Black or mixed Black.

In the voclosporin arm of AURORA 1, 14.5% of participants (26/179) self-identified as Black or mixed Black; in the control arm, 10.6% of participants (19/178) self-identified as Black or mixed Black. The two arms were similar in baseline characteristics. At 1 year, CRR rates numerically favored voclosporin (46.2% vs 15.8%; odds ratio [OR], 3.92; *P*=.0597). PRR rates also favored voclosporin at 1 year (69.2% vs 47.4%; OR, 2.62; *P*=.1422).

A total of 18 patients in the voclosporin arm and seven in the control arm in the Black subgroup continued into AURORA 2. At 3 years, response rates continued to numerically favor voclosporin (CRR, 44.4% vs 14.3%; OR, 4.17; *P*=.2276 and PRR, 66.7% vs 42.9%; OR, 1.67; *P*=.6094).

Over the 3-year period, there were greater reductions in mean UPCR in the voclosporin arm (change from baseline, -3.4 g/g vs -1.5 g/g; *P*=.0349). Over the 3 years of treatment, mean eGFR remained stable and in the normal range.

"Black patients treated with a voclosporin-based regimen achieved higher rates of renal response than patients treated with MMF and glucocorticoids alone," the researchers said. "For patients entering the continuation study, the response was largely durable for up to 3 years."

Source: Contreras G, Baker MG, Hodge LS, Yap E. Long-term safety and efficacy of voclosporin in Black patients with lupus nephritis. SA-P0876. Abstract of a poster presented at the American Society of Nephrology Kidney Week 2023; November 4, 2023; Philadelphia, Pennsylvania. Funding was provided by Aurinia Pharmaceuticals Inc.

Dialysis Facility Staffing Ratios and Kidney Transplantation

Studies have shown that higher patient-to-nurse ratios at dialysis facilities are associated with worse patient outcomes in older adults. Researchers at the University of California, San Francisco, led by **Alexandra Bicki,** conducted a retrospective analysis of data from the US Renal Data System of patients 12 to 30 years of age who initiated dialysis from 2005 to 2019 at dialysis facilities in the United States.

The primary exposure was patient-to-nurse ratio at the dialysis facility. The relationship of the primary exposure to receipt of kidney transplant (living or deceased donor) was examined using Cox models.

Results of the analysis were reported during a poster session at the American Society of Nephrology Kidney Week 2023. The poster was titled *Higher Dialysis Facility Patient-to-Nurse Staffing Ratio Is Associated With Lower Hazard of Kidney Transplantation Among Adolescents and Young Adults.*

The analysis included data on 51,419 individuals. Of those, 74% were ≥22 years of age, and 84% initiated therapy with hemodialysis. Median staffing ratio was 14 patients per one nurse. During a median follow-up of 2.4 years, 53% of patients <22 years of age versus 34% of those ≥22 years of age received a kidney transplant.

In adjusted analysis, each doubling of patient-to-nurse ratio at a facility resulted in a 15% lower hazard of transplantation (hazard ratio [HR], 0.85; 95% CI, 0.84-087). There was an interaction (*P*<.001) by age at dialysis initiation: the association between higher patient-to-nurse ratio and access to transplantation was more pronounced in patients 12 to 21 years of age (HR, 0.79; 95% CI, 0.77-0.82) compared with patients 22 to 30 years of age (HR, 0.96; 95% CI, 0.94-0.99)

"Adolescents and young adults receiving care from facilities with higher patient-to-nurse ratios had lower hazard of transplantation compared [with] those receiving care [from] facilities with lower staffing ratios," the authors said. "Low dialysis nurse staffing ratios may represent a crucial facility characteristic that promotes successful kidney transplantation, particularly for adolescents."

Source: Bicki A, Mcculloch CE, Grimes BA, Ku E. Higher dialysis facility patient-to-nurse is associated with lower hazard of kidney transplantation among adolescents and young adults. TH-P0897. Abstract of a poster presented at the American Society of Nephrology Kidney Week 2023; November 3, 2023; Philadelphia, Pennsylvania.

Real-world Efficacy of Tolvaptan Among Patients With ADPKD

Results of clinical trials among patients with autosomal dominant polycystic kidney disease (ADPKD) at risk of rapid progression demonstrated that tolvaptan led to a slower decline in kidney function compared with placebo. **Ronald D. Perrone** and colleagues conducted a study to assess the real-world effectiveness of tolvaptan by comparing annual rate of change in kidney function, as measured by estimated glomerular filtration rate (eGFR), in adults with ADPKD treated with and without tolvaptan.

The researchers reported results of the study during a poster session at the American Society of Nephrology Kidney Week 2023. The poster was titled *Kidney Function Decline in Autosomal Dominant Polycystic Kidney Disease (ADPKD) Patients: Assessment of Real-world Effectiveness of Tolvaptan.*

Using medical records of patients with ADPKD treated with tolvaptan for ≥2 years, 57 nephrologists in the United States completed a web-based survey (May 2019 to September 2022) to identify patients with ADPKD who were treated with tolvaptan (cases). A control group included a cohort of patients with ADPKD in Mayo class 1C to 1E who were not being treated with tolvaptan. Patients in the control group were identified from the CRISP, HALT-PKD (data provided by NIDDK CR, a program of the National Institute of Diabetes and Digestive and Kidney Diseases), and OVERTURE studies.

Mixed models were used to compare decline in kidney function between cases and controls, including treatment, time, and treatment-by-time interactions as fixed effects and patient-specific intercepts and slopes (for time) as random effects.

The surveys included data on 149 patients with ADPKD treated with tolvaptan. Of those, 110 were matched with controls for age, sex, and chronic kidney disease (CKD) stage. Among the 110 matched pairs, 60% were male, average age was 43 years, and 76% had CKD stage 3a or earlier.

At baseline, mean eGFR was 60 mL/min/1.73 m^2 among cases and 63 mL/min/1.73 m^2 among controls. The annual change in eGFR was -2.23 mL/min/1.73 m^2 among cases compared with -3.62 mL/min/1.73 m^2 among controls, with a statistically significant difference of 1.40 mL/min/1.73 m^2 per year (95% CI, 0.05-2.74; *P*=.042).

In a second analysis, matching cases and controls on baseline age, sex, and eGFR resulted in 98 matched pairs. In that subpopulation, there was an association between treatment with tolvaptan and a trend in reduction of decline rate by 1.18 mL/min/1.73 m^2 per year (95% CI, -0.22 to 2.50; *P*=.097).

In conclusion, the researchers said, "In the current analysis, tolvaptan showed real-world effectiveness in slowing decline in eGFR when compared with matched historical controls, consistent with its efficacy in clinical trials."

Source: Perrone RAD, Nunna S, Gandhi HK, Fernandes A, Garbinsky D, Zhou X. Kidney function decline in autosomal dominant polycystic kidney disease (ADPKD) patients: assessment of real-world effectiveness of tolvaptan. TH-P0421. Abstract of a poster presented at the American Society of Nephrology Kidney Week 2023; November 2, 2023; Philadelphia, Pennsylvania. Funding was provided by Otsuka Pharmaceutical Development & Commercialization, Inc.

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Dahl et al., Journal of the American Society of Nephrology[1]

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Reference
1. Dahl et al. The Journal of the American Society of Nephrology (2023) DOI: 10.1681/ASN.0000000000000249

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Predicting Future eGFR in People With Type 2 Diabetes and CKD

Approximately 40% of individuals with type 2 diabetes develop chronic kidney disease (CKD). Key to prevention of CKD in patients with type 2 diabetes is early awareness and identification of those at risk of rapid progression. CKD is characterized by progressive loss of kidney function, assessed by sequential estimated glomerular filtration rate (eGFR), a measurement that can vary between individuals.

According to **Mariella Gregorich, MS,** and colleagues, a clinically useful prediction model of future eGFR measurements based on routinely collected laboratory data could aid clinicians in implementing interventions designed to slow the course of kidney function decline. The researchers conducted a prognostic study to develop and externally validate a model to predict future trajectories in eGFR in adults with type 2 diabetes and CKD. Results were reported online in *JAMA Network Open* [doi:10.1001/jamanetworkopen.2023.1870].

The study utilized baseline and follow-up data collected between February 2010 and December 2019 from three European multinational cohorts: PROVALID (Prospective Cohort Study in Patients With Type 2 Diabetes Mellitus for Validation of Biomarkers); GCKD (German Chronic Kidney Disease); and DIACORE (Diabetes Cohorte). The total cohort included 4637 participants 18 to 75 years of age with type 2 diabetes and mildly to moderately impaired kidney function (baseline eGFR ≥30 mL/min/1.73 m^2). Data analysis occurred between June 30, 2021, and January 21, 2023.

The primary outcomes and measures were 13 variables available from routine clinical care visits: age; sex; body mass index (BMI); smoking status (never or ever); hemoglobin A1c (mmol/mol and percentage); hemoglobin and serum cholesterol levels; mean arterial pressure; urinary albumin-creatinine ratio; and intake of glucose-lowering, blood pressure-lowering, or lipid-lowering medications (yes/no). Baseline was defined as the individual's first study visit.

The primary outcome of interest was repeated measurements of eGFR recorded at baseline and at follow-up visits. The eGFR values were calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation from 2021 that includes the person's age, sex, and serum creatinine level. A linear mixed-effects model for repeated eGFR measurements at study entry up to the last recorded follow-up visit (up to 5 years after baseline) was fit and externally validated.

Of the 4637 adults with type 2 diabetes and CKD in the overall study cohort, mean age at baseline was 63.5 years, 2680 (57.8%) were men and 1957 (42.2%) were women, and all were White. The development cohort included 3323 individuals from the PROVALID and GCKD studies (mean age, 63.2 years, 1864 men [56.1%], and 1459 [43.9%] women). The external validation cohort included 1314 individuals from the DIACORE study (mean age, 64.5 years, 816 [62.1%] men. and 498 [37.9%] women; mean follow-up, 5.0 years).

The median rate of decline in eGFR, estimated using individual-specific linear regression analysis, was similar across cohorts (PROVALID: median, –1.45 mL/min/1.73 m^2 per year; GCKD: median, –1.43 mL/min/1.73 m^2 per year; DIACORE: median, –1.28 mL/min/1.73 m^2 per year).

Prior to updating the random effects coefficients using baseline eGFR values, the overall conditional R2 was 0.90, and the marginal R2 was 0.20. Age was the most important predictor, with a decrease in marginal R2 of 0.10 (95% CI, 0.08-0.10). The time-specific predicted R2 values ranged from 0.74 (95% CI, 0.59-0.84) at year 1 to 0.47 (95% CI, 0.25-0.68) at year 5. The C statistic ranged from 0.84 (95% CI, 0.78-0.88) at year 1 to 0.75 (95% CI, 0.67-0.82) at year 5, with lower values seen after the first follow-up year.

With the exception of BMI, smoking status, mean arterial pressure, serum cholesterol, glucose-lowering medication, and lipid-lowering medication, there was an association between all other study variables and significant decreases in eGFR; age had the greatest reduction (estimate, –0.30; 95% CI, –0.32 to –0.28). However, there was an association between the interaction of the six variables and significant decreases in eGFR. Compared with the main effect size estimates, the magnitude of the standardized interaction effects was low.

In the external validation cohort, measurements of eGFR were available from year 2 to year 5 after baseline. Overall, updating the random effects with baseline eGFR yielded excellent agreement between the predicted and the observed eGFR values in the validation cohort, particularly in the early follow-up years. The externally validated R2 ranged from 0.70 (95% CI, 0.63-0.76) at year 1 to 0.58 (95% CI, 0.53-0.63) at year 5. The C statistic ranged from 0.83 (95% CI, 0.81-0.85) at year 1 to 0.79 (95% CI, 0.77-0.80) at year 5. The calibration slope was highest at follow-up year 4 and lowest at follow-up year 5, suggesting stable predictive capabilities of the model in individuals the model has not been trained on. The assessment of time-specific calibration slopes revealed an almost perfect calibration at up to 4 years after baseline and only minimal shrinkage at 5 years after baseline.

The prediction model for an individual's eGFR at future follow-up time points, visualization of model results, and risk assessment for rapid progression was implemented as an online risk calculator.

The researchers cited some limitations to the study findings, including the three large-scale cohort studies being conducted in Europe, necessitating the use of the CKD-EPI equation to estimate GFR; the lack of standardization of creatinine assays across cohorts; the limited available data at later time points; and the lack of data on routine use of medications approved for the treatment of CKD shortly before or after 2010 and 2011.

"This prognostic study used a linear mixed-effects model to predict eGFR trajectories among adults with type 2 diabetes and CKD; this model naturally circumvented the inherent issues related to eGFR slope estimation and fully incorporated the observed data into model estimation," the researchers said. "Despite its complexity, the prediction model was robust, well calibrated, and suitable for implementation in a web-based application, revealing the potential of a publicly available online tool that can be used by patients, caregivers, and primary health care professionals to predict individual eGFR trajectories and disease progression up to 5 years after baseline." ■

TAKEAWAY POINTS

- Researchers utilized data from three multinational cohort studies to develop and externally validate a model to predict future trajectories in estimated glomerular filtration rate (eGFR) in adults with type 2 diabetes and chronic kidney disease.
- The model was robust and well calibrated and capable of predicting decline in kidney function up to 5 years after baseline.
- The prediction model is publicly available and suitable for implementation in an accompanying web-based application.

Meta-analysis of HIF-PHIs versus ESAs or Placebo in CKD With Anemia

Individuals with chronic kidney disease (CKD) often experience anemia, a complication associated with increased incidence of cardiovascular disease, hospitalizations, and mortality The current mainstays of treatment for anemia associated with CKD are erythropoiesis-stimulating agents (ESAs), typically epoetin and darbepoetin, in combination with iron supplementation.

ESAs decrease the need for blood transfusions; however, high-dose ESAs have been associated with increased risk for cardiovascular events, progression to kidney failure, and death. Due in part to concerns regarding the safety of ESAs, anemia may be untreated or delayed in patients with CKD stage 3b to 5 who are not receiving dialysis.

Hypoxia-inducible factor prolyl hydroxylase inhibitors (HIF-PHIs) have emerged as potential alternative treatment for anemia in CKD. HIF-PHIs activate HIF transcription factors, leading to functional activation of early-response target genes encoding proteins such as erythropoietin and the erythropoietin receptor. Further, HIF-PHIs are administered orally and increase endogenous erythropoietin within or near the physiologic range while improving iron homeostasis.

Qiyan Zheng, MD, and colleagues conducted a systematic review and meta-analysis to assess the cardiac and renal adverse effects of HIF-PHIs among patients with CKD and anemia. Results were reported in the *American Journal of Kidney Diseases* [2023;81(4):434-445].

The researchers searched PubMed, Embase, Web of Science, Cochrane Library database, and, to include randomized controlled trials that were completed but unpublished, the ClinicalTrials.gov website. The search timeframe was from time of database inception to March 2021, with no language restrictions applied.

Eligible studies were randomized controlled trials that met the following population, intervention, comparison outcomes, and study criteria: (1) study population consisting of non-dialysis dependent patients with CKD and anemia; (2) use of HIF-PHI; (3) placebo or ESA as comparator; and (4) primary outcomes of cardiac adverse events and kidney-related adverse events.

Cardiac adverse events included cardiovascular death, myocardial infarction, unstable angina pectoris, ischemic stroke, heart failure, arrhythmia, or other cardiac and valvular disease, or major adverse cardiovascular events. Kidney-related adverse events were worsening of CKD or decrease in estimated glomerular filtration rate (eGFR), kidney failure or initiation of dialysis, acute kidney injury, nephritis, azotemia, or renal disorders or kidney-related adverse events. Secondary outcomes searched for included the incidence of hypertension and hyperkalemia, the number of patients who progressed to kidney failure or started dialysis, severe adverse events, drug-related serious adverse events, and death.

The Mantel-Haenszel method was used to pool dichotomous variables, presented as risk ratios (RRs). Analyses of subgroups assessed varying interventions times and HIF-PHIs, as well as phase 2 versus phase 3 trials.

The initial search identified 13,384 articles. Of those, 3954 were duplicates, and 9430 titles and abstracts were then screened. Full-text screening included 112 articles, resulting in 23 eligible articles included in the analysis (15,144 participants). Most included trials were judged to have a low or unclear risk of bias for random sequence generation, allocation concealment, incomplete outcome data, selective reporting, and other bias. Ten were judged to be at high risk of bias for masking of participants and personnel, and 10 were judged to be at high risk of bias for masking of outcomes due to the open-label design of the studies.

Twenty trials representing 14,561 reported cardiac adverse events. In pooled results, there was no significant difference in the risk of cardiac adverse events seen in the HIF-PIH group compared with the placebo group (RR, 1.02; 95% CI, 0.89-1.16; I^2=0%) or the ESA group (RR, 1.06; 95% CI, 0.98-1.14; I^2=10%). In a sensitivity analysis that excluded three studies that did not report the total number of cardiac adverse events, there was no significant change in the overall effect size and heterogeneity.

The subgroup analysis of intervention time (<52 or ≥52 weeks) on outcomes demonstrated an association between the HIF-PHIs group and a significantly lower risk of cardiac adverse events in the short term (<52 weeks) compared with the placebo group. There was no statistically significant difference in the long term (≥52 weeks). There were no significant differences in additional subgroup analyses for each of the HIF-PHI drugs (roxadustat, daprodustat, vadadustat, and molidustat) and the trial phases (phase 2 and phase 3).

A total of 22 trials reported kidney-related adverse events (13,437 participants). In meta-analysis, there were no statistically significant differences in the risk of kidney-related adverse events seen in the HIF-PHIs group compared with the placebo group (RR, 1.09; 95% CI, 0.98-1.20; I^2=0%) or the ESA group (RR, 1.00; 95% CI, 0.94-1.06; I^2=0). In sensitivity analyses excluding eight studies that did not report the total number of kidney-related adverse events, there was no significant change in overall effect size and heterogeneity. There were no significant differences in the incidence of kidney-related adverse events in subgroup analysis of intervention times (<52 or ≥52 weeks), HIF-PHI drugs ((roxadustat, daprodustat, vadadustat, and molidustat), and the trial phases (phase 2 and phase 3).

Hypertension events were reported in 19 trials, with pooled results showing a higher risk of hypertension in the HIF-PHIs groups compared with the placebo group. When compared with ESA group, the risk of hypertension was lower in the HIF-PHIs group. Seventeen trials reported hyperkalemia, with pooled results showing a higher risk of hyperkalemia in the HIF-PHIs group compared with the placebo group. There was no significant difference in risk when compared with the ESA group.

The inconsistency in reporting criteria of cardiac and kidney-related adverse events and dosage of HIF-PHIs across trials was cited as a limitation to the study. Also cited as study limitation were not evaluating specific laboratory indicators related to cardiac and kidney function, and the inconsistency in dosage of HIF-PHIs in the included trials. In summary, the researchers said, "According to the current evidence, HIF-PHIs did not significantly increase the risk of cardiac or kidney-related adverse events, kidney failure events, serious adverse events, or death in patients with anemia and CKD who are not receiving dialysis. HIF-PHIs were associated with an increased risk of hypertension and hyperkalemia compared with placebo, but they were associated with a lower risk of hypertension and a similar risk of hyperkalemia compared with ESA treatment. Further research should consider the limitations of our study to explore the impacts of cardiac and kidney-related adverse events of HIF-PHIs for anemia of CKD." ■

TAKEAWAY POINTS

- Researchers reported results of a review and meta-analysis of the adverse effects on cardiac and renal outcomes in patients with nondialysis-dependent chronic kidney disease (CKD) and anemia receiving hypoxia-inducible factor prolyl hydroxylase inhibitors (HIF-PHIs).
- Trials included in the analysis compared HIF-PHIs to placebo or to erythropoiesis-stimulating agents (ESA).
- There were no statistically significant differences in the occurrence of cardiac- and kidney-related adverse events in the HIF-PHIs groups compared with placebo or ESA groups.

Solid Organ Transplants From Deceased Donors With Primary Brain Tumors

Recipients of solid organ transplants face a small risk of disease transmission from donor to recipient, and active malignancy is usually a contraindication to organ donation. However, because primary brain tumors rarely spread beyond the central nervous system, the use of organs from patients with primary brain tumors is generally accepted.

According to **George H. B. Greenhall, MBChB,** and colleagues, there are varying opinions regarding the safety of organ transplants from donors with brain tumors. International guidelines reflect this uncertainty, with wide variation in risk stratification, and guidelines in the United States are notably more conservative than in Europe.

The researchers conducted a cohort study in England and Scotland to determine the risk of cancer transmission associated with organ transplants from deceased donors with primary brain tumors. The researchers also sought to examine the association between brain tumors and organ usage and posttransplant survival. Results of the study were reported in *JAMA Surgery* [2023;158(5):504-513].

The study was conducted from January 1, 2000, to December 31, 2016; follow-up continued to December 31, 2020. The researchers utilized linked data on deceased donors and solid organ transplant recipients with valid national patient identifier numbers from the UK Transplant Registry, the National Cancer Registration and Analysis Services (England), and the Scottish Cancer Registry.

The study exposure was a history of primary brain tumor in the organ donor, identified from all three data sources using disease codes. The primary outcome of interest was transmission of brain tumor from the organ donor into the transplant recipient. Secondary outcomes included organ utilization, and survival of kidney, liver, heart, and lung transplants and their recipients. Tumor grade and treatment history in donors with brain tumors were key covariates.

The study population included 13,274 solid organ donors. Of those, 2% (n=282) had primary brain tumors. Median age of the cohort with a primary brain tumor was 42 years, 55% (n=154) were female, and 45% (n=128) were male. Compared with donors without brain tumors, those in the brain tumor cohort were younger, had fewer comorbidities (eg, hypertension [15%, 42/282 vs 25%, 3230/12,992]) and lifestyle risk factors (eg, smoking [24%, 69/282 vs 46%, 5970/12,991]). Donors with brain tumors also had more favorable organ risk markers (median terminal creatinine, 65 µmol/L vs 75 µmol/L). Median time from brain tumor diagnosis to death was 8 days. Of the 282 tumors, 74% (n=210) had a histological diagnosis, and 8% (n=22) were confirmed on biopsy at the time of organ retrieval.

There were a total of 887 transplants utilizing 1014 organs donated from the 282 donors with primary brain tumors. Of those, 88% (n=778) were included in the analysis for the primary study outcome. There were 262 transplants from donors with high-grade brain tumors, including 81 from donors with grade 3 tumors and 142 from donors with grade 4 tumors. Sixty-three percent of transplants (n=490) were from donors with prior neurosurgical intervention or radiotherapy. Donors defined as high risk by Organ Procurement and Transplantation Network (OPTN) guidelines generated 605 transplants, including 60 transplants from donors with glioblastoma and no history of neurosurgery or radiotherapy which may be considered as intermediate risk by OPTN criteria.

Median age of recipients of transplants from donors with brain tumors was 48 years, and 61% (n=476) were male. Recipient characteristics of recipients of transplants from brain tumors were similar to recipients of transplants from donors without brain tumors.

Over a median follow-up of 6 years, there were 83 posttransplant malignancies (excluding nonmelanoma skin cancer) in 79 recipients of transplants from donors with brain tumors. Of 45 tumors in recipients of kidney transplant, 33% (n=15) were reported to National Health Services Blood and Transplant. No recipient tumors had a histological type matching that of the donor brain tumor.

The 10-year survival of transplants from donors with brain tumors was 65% (95% CI, 59%-71%) for single kidney transplants, 69% (95% CI, 60%-76%) for liver transplants, 73% (95% CI, 59%-83%) for heart transplants, and 46% (95% CI, 29%-61%) for lung transplants. Nine transplants from donors with brain tumors (6 kidney, 2 liver, 1 heart) were excluded from the matched survival analysis due to lack of follow-up data (n=2), incomplete matching variables (n=4), or no available matches (n=3). Compared with matched controls, there was no evidence of a difference in transplant survival. Results were similar in separate analysis of patient and graft survival.

The researchers cited some limitations to the study findings, including the inability to incorporate data from the Welsh and Northern Ireland cancer registries, and the possibility that the risk stratification of the tumors in the study may be oversimplified.

In conclusion, the authors said, "This cohort study has three principal findings. First, results suggest that the risk of cancer transmission from donors with primary brain tumors was lower than that previously thought. No transmission occurred despite many donors having high-grade tumors or undergoing prior surgical intervention, both of which are considered as increasing the risk of transmission. Second, results suggest that donors with brain tumors were a source of good-quality organs, as evidenced by favorable risk markers and excellent transplant outcomes. Third, there may have been an aversion by transplant clinicians or their patients to use some organs from donors with high-grade brain tumors. The variation in utilization between organs may reflect differences in risk tolerance, although it is interesting that the rate of lung utilization was so low, considering the high mortality of patients on the waiting list for lung transplants.

"Taken together, these observations suggest that it may be possible to expand organ usage from donors with primary brain tumors without negatively impacting outcomes. Although this is likely to result in a modest increase in the number of transplants in the United Kingdom, our findings may be particularly relevant to counties with more conservative guidelines, including the United States. Our findings should help transplant clinicians when discussing the risks and benefits of accepting an organ offer. Analysis of pooled data could help to refine risk estimates in this area." ■

TAKEAWAY POINTS

- Researchers reported results of a study examining the risk of cancer transmission associated with solid organ transplants from donors with primary brain tumors.
- Despite many donors having high-risk tumors or undergoing prior surgical interventions, there were no cancer transmissions from donor to recipient.
- As shown by favorable risk markers and good transplant outcomes, deceased donors with primary brain tumors were a source of good-quality organs in this study cohort.

Vaccine-Preventable Infections in Solid Organ Transplant Recipients

In immunocompromised patients, including sold organ transplant recipients, infectious diseases are key causes of morbidity and mortality. Vaccination is a proven and efficient method of preventing communicable diseases. However, transplant recipients may be at risk for suboptimal vaccine coverage due to decreased immunogenicity of vaccines in the post-transplant setting, as well as underimmunization due to logistic complications prior to transplant, vaccine hesitancy, and imperfect financial coverage.

According to **Laura N. Walti, MD,** and colleagues, the actual burden of vaccine-preventable infections among recipients of solid organ transplants is unclear. The researchers conducted a cohort study designed to examine the incidence rate of vaccine-preventable infections among individuals who underwent solid organ transplant from May 2008 to June 2019 in Switzerland. Follow-up continued until December 2019. Results were reported online in *JAMA Network Open* [doi:10.1001/jamanetworkopen.2023.10687].

The study exposure was solid organ transplant. The primary outcomes of interest were the incidence rate of vaccine-preventable illnesses in solid organ transplant recipients (hepatitis A and B, diphtheria, *Haemophilus influenzae* infection, influenza, measles, mumps, pertussis, pneumococcal disease, poliomyelitis, meningococcal disease, rubella, tetanus, tick-borne encephalitis [TBE], and varicella zoster virus [VZV] infection).

The study utilized age-adjusted standardized incidence ratios (SIRs) to examine whether vaccine-preventable infections occurred more frequently in solid organ transplant recipients compared with the general population. Factors associated with occurrence of vaccine-preventable infections among solid organ transplant recipients were explored, and associated morbidity and mortality were assessed.

The study included 4967 solid organ transplant recipients (56.0% kidney, n=2784; 22.1% liver, n=1100; 9.1% lung, n=454; 7.8% heart, n=385; and 4.9% combined, n=244) based on data from the nationwide Swiss Transplant Cohort Study (STCS). All six transplant centers in Switzerland participate in the STCS, and for the analyzed period approximately 93% of transplant recipients in Switzerland were included.

Median age of the study cohort was 54 years, 64.2% (n=3191) were male, and 35.8% (n=1776) were female. Three percent (n=151) were African, 3.7% (n=184) were Asian, 91.6% (n=4551) were White, 1.3% (n=64) were other race/ethnicity, and 2.3% (n=17) had unknown race/ethnicity.

The researchers identified 668 vaccine-preventable infections in 593 solid transplant recipients (11.9%). Most occurred more than 1 year after transplant. The most common vaccine-preventable infections were influenza (360 episodes [53.9%] in 333 patients [6.7%]), VCV (282 episodes [42.2%] in 269 patients [5.4%]), and invasive pneumococcal disease (IPD; 10 episodes [1.5%] in 9 patients [0.2%]).

Noninvasive pneumococcal infections outnumbered invasive cases; this finding was similar for H influenzae. There were no cases of hepatitis A, measles, mumps, poliomyelitis, rubella, diphtheria, or tetanus identified in the solid organ transplant recipients. The incidence rate of vaccine-preventable infection was higher in recipients of a lung or heart transplant compared with recipients of a kidney or liver transplant. The incidence rate of influenza was highest in recipients of a lung transplant (40.46 [95% CI, 31.97-51.70] per 1000 person-years) and lowest in recipients of a liver transplant (8.82 [95% CI, 6.13-12.67] per 1000 person-years).

Patient characteristics associated with increased risk of occurrence of vaccine-preventable infection were age ≥65 years (incidence rate ratio [IRR], 1.29; 95% CI, 1.02-1.62) and lung or heart transplant compared with kidney transplant (lung transplant: IRR, 1.77; 95% CI, 1.38-2.26; heart transplant: IRR, 1.40; 95% CI, 1.05-1.88). There was an association between liver transplant and a decreased risk of vaccine-preventable infection (IRR, 0.62; 95% CI, 0.48-0.80) compared with kidney transplant. There was no association between the type of induction treatment and occurrence of vaccine-preventable infections.

There was no association between rejection treatment and an increased risk for vaccine-preventable infections in the following 3 months (hazard ratio, 1.26; 95% CI, 0.90-1.76). Compared with kidney transplant recipients, there was an increased risk for influenza among lung transplant recipients (IRR, 2.51; 95% CI, 1.88-3.34) and an increased risk for VZV among heart transplant recipients (IRR, 1.72; 95% CI, 1.16-2.55).

Influenza had the highest incidence rate among solid organ transplant recipients at 16.55 per 1000 person-years (95% CI, 14.86-18.46 per 1000 person-years), followed by VZV (12.83 per 1000 person-years; 95% CI, 11.40-14.44 per 1000 person-years) and IPD (0.45 per 1000 person-years; 95% CI, 0.23-0.90 per 1000 person-years).

Only data on notifiable vaccine-preventable infections were available for the general population. The overall incidence of notifiable vaccine-preventable infections was higher in the solid organ transplant population (30.57 per 1000 person-years; 95% CI, 28.24-33.10 per 1000 person-years) than in the general population (0.71 per 1000 person-years). Of the notifiable vaccine-preventable infections, the most common was influenza (0.56 per 1000 person-years), followed by IPD (0.11 per 1000 person-years) and TBE (0.02 per 1000 person-years).

SIRs were used to compare incidence rates among solid organ transplant recipients with those in the general population. Notifiable vaccine-preventable infections occurred more frequently in the solid organ transplant recipient population than in the general population (SIR, 27.84; 95% CI, 25.00-31.00). Age-adjusted incidence rates for laboratory-confirmed influenza, IPD, and invasive H influenzae were significantly higher in the solid organ transplant population. There were no significant differences between the two groups in incidence rates for invasive meningococcal disease and TBE.

The researchers cited some limitations to the findings, including the inability to provide data on pre- and posttransplant vaccination of the solid organ transplant patients, as well as the lack of detailed data on demographics other than age.

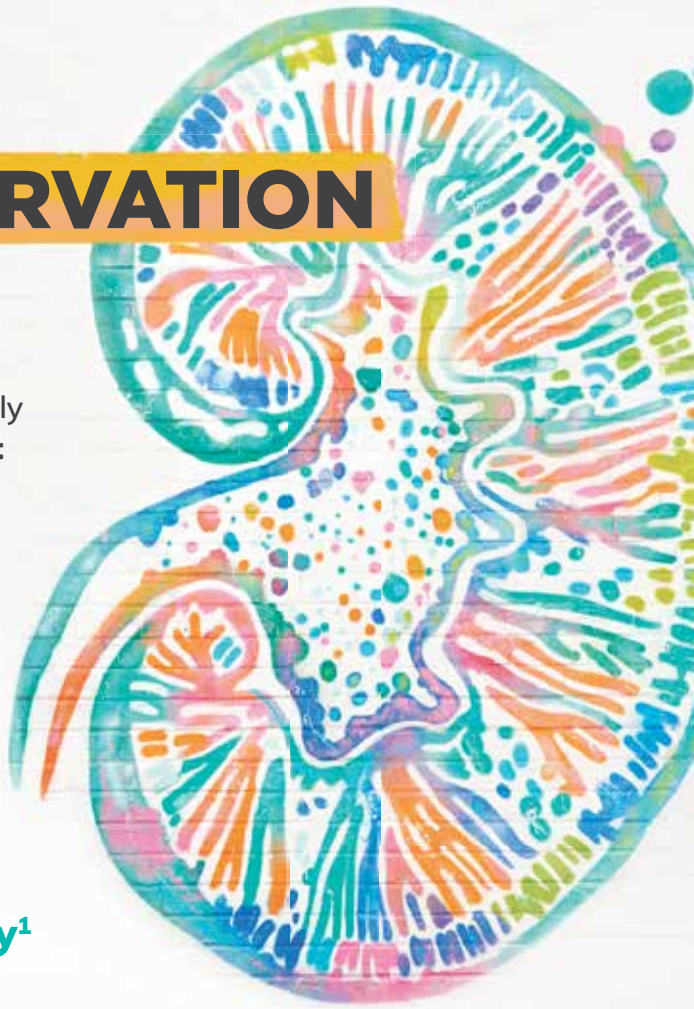
In conclusion, the authors said, "This study found that vaccine-preventable infections were common after solid organ transplant. Despite current efforts, 11.9% of recipients experienced vaccine-preventable infections. The overall incidence rate of notifiable vaccine-preventable infections in the solid organ transplant population was higher than that in the general population, including the incidence rates for influenza, IPD, and H influenzae infection. These findings suggest that efforts for optimization of vaccine strategies in solid organ transplant recipients should focus on vaccine-preventable infections with either a high incidence in this particular population or a higher incidence rate compared with the general population." ■

TAKEAWAY POINTS

- Swiss researchers reported results of a nationwide cohort study designed to assess the incidence rates of vaccine-preventable infections among a population of solid organ transplant recipients.
- Among the 4967 solid organ transplant recipients in the study, 11.9% (n=533) experienced at least one vaccine-preventable infection.
- The overall incidence rate of notifiable vaccine-preventable infection was higher among the cohort of solid organ transplant recipients than that in the general population (30.57 per 1000 person-years vs 0.71 per 1000 person-years).

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 in combination with MMF and corticosteroids.**[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/1.73m^2/yr with LUPKYNIS plus MMF and low-dose steroids (95% CI: –3.0, 2.7) and –5.4 mL/min/1.73m^2/yr with MMF and low-dose steroids (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]

[e]These changes in slope are annualized based on generalized linear model analysis of individual patient slopes.

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.

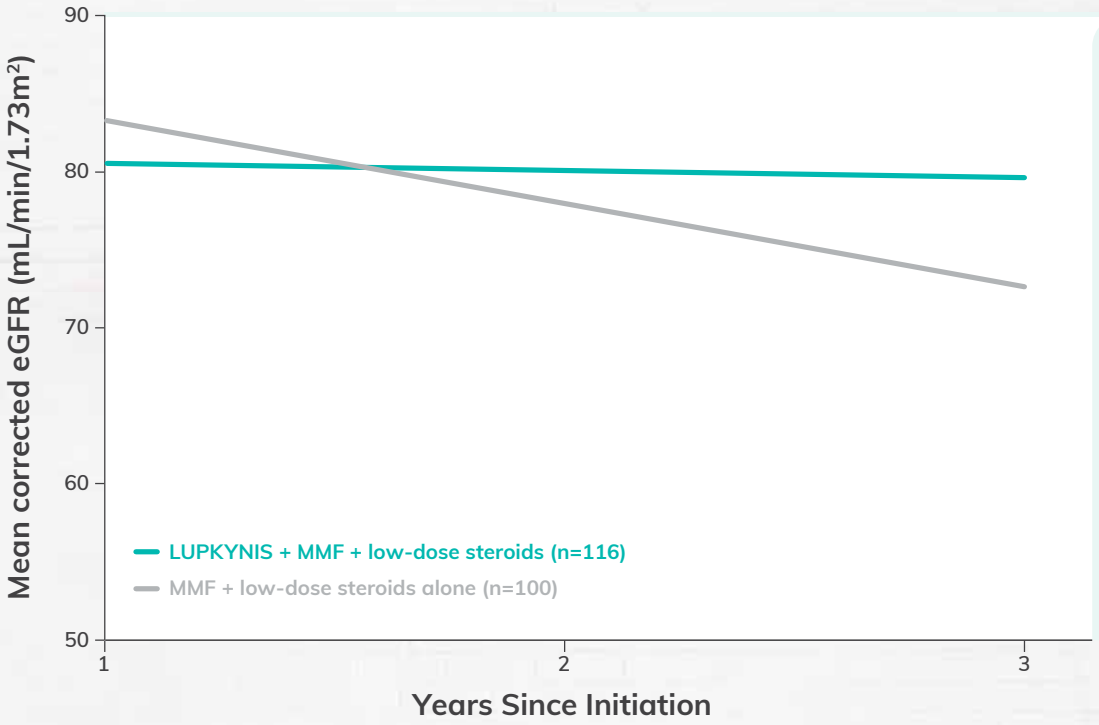
QTc Prolongation: LUPKYNIS prolongs the QTc interval in a dose-dependent manner when dosed higher than the recommended lupus nephritis therapeutic dose. The use of LUPKYNIS in combination with other drugs that are known to prolong QTc may result in clinically significant QT prolongation.

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):
–0.2 mL/min/1.73m²/yr[e]
(95% CI: –3.0, 2.7)

Rate of decline in eGFR (slope):
–5.4 mL/min/1.73m²/yr[e]
(95% CI: –8.4, –2.3)

96% less eGFR loss over an additional 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-2300268 11/23

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.

INDICATION 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.

Incidence, Risk of Community-Acquired AKI Among US Veterans

Community-acquired acute kidney injury (CA-AKI) is AKI that develops outside of the hospital setting. The causes of CA-AKI are thought to be heterogeneous and can include volume depletion due to poor oral intake, urinary obstruction, or exposure to nephrotoxic medications.

According to **Clarissa J. Diamantidis, MD, MHS,** and colleagues, there are no standard definitions for detection of AKI outside of the acute hospital setting. They also note that because accurate measurement of kidney function requires the availability of serial creatinine laboratory values, the detection of reduction of kidney function outside of the acute hospital setting is difficult.

Using laboratory and administrative data from the Veterans Health Administration (VA), the researchers conducted a retrospective cohort study to quantify the incidence of CA-AKI among VA primary care users between 2013 and 2017 and to identify the patient factors associated with the risk of developing CA-AKI. Results were reported in the *American Journal of Kidney Diseases* [2023;82(3):300-310].

Eligible study participants were VA primary care users from 2013 to 2017 who had recorded outpatient serum creatinine measurement and no history of chronic kidney disease (CKD) stage 5 or end-stage kidney disease. The study predictors were sociodemographics, comorbidities, medication use, and health care utilization.

The outcome of interest was annual incidence of CA-AKI defined as a ≥1.5-fold relative increase in serum creatinine on either a subsequent outpatient serum creatinine measurement or inpatient serum creatinine measurement obtained within ≤24 hours of hospital admission. Index serum creatinine was defined as the preceding outpatient serum creatinine ≥24 hours apart and ≤12 months from the outcome serum creatinine in each cohort year.

The cohort included 5,375,435 distinct US veterans contributing 14,129,977 veteran-years of observation among VA primary care users between 2013 and 2017. There were approximately 2.5 million veterans in the 2013 to 2015 cohort, 2.9 million in the 2016 cohort, and 3.5 million in the 2017 cohort.

The mean age of the overall cohort was 63 years, most (92%-93%) were male, and 75% were White. More than half lived in urban settings, and the median driving distance to the nearest VA facility was 11 miles. Median estimated glomerular filtration rate (eGFR) was 82 mL/min/1.73 m^2 and approximately 7% had a diagnosis code for CKD.

More than 30% had diabetes, and 63% had hypertension. Approximately 30% had a prescription for a proton-pump inhibitor, 38% for a nonsteroidal anti-inflammatory drug, 26% for a diuretic, and 40% for a renin-angiotensin-aldosterone system (RAAS) blocker. In the year prior, approximately half of all veterans had zero hospital days and six outpatient encounters per year, and approximately 1% had a nephrology encounter.

The cumulative incidence of CA-AKI was approximately 1.9% per year. Overall, 26.9% of CA-AKI was detected at hospital admission. Seventy-nine percent of CA-AKI was stage 1, 15% was stage 2, and 6% was stage 3. In 29.7% of veterans, a diagnosis code for AKI was detected; 69.4% of inpatient CA-AKI at hospital admission had a documented diagnosis, and 14.5% of outpatient CA-AKI cases reported this diagnosis. Results of a post hoc analysis examining the frequency of repeated episodes of CA-AKI demonstrated that only 8% of veterans (n=18,630) had an observed repeat of AKI during the study period.

There were associations between higher risk of CA-AKI and eGFR <15 mL/min/1.73 m2 (hazard ratio [HR], 2.70; 95% CI, 2.32-3.14), higher levels of outpatient health care utilization (HR, 2.38; 95% CI, 2.31-2.46), female sex (HR, 1.26; 95% CI, 1.24-1.28), or other/missing rural residence (HR, 1.37; 95% CI, 1.27-1.47). Medications associated with a higher risk of CA-AKI were RAAS blockers (HR, 1.45; 95% CI, 1.44-1.47) and diuretics (HR, 1.33; 95% CI, 1.32-1.34).

There were numerous comorbidities associated with increased risk of CA-AKI: metastatic cancer (HR, 1.93; 95% CI, 1.88-1.98), HIV/AIDS (HR, 1.84; 95% CI, 1.77-1.91), diabetes (HR, 1.48; 95% CI, 1.47-1.50), alcohol or drug use disorder (HR, 1.42; 95% CI, 1.40-1.44), liver disease (HR, 1.41; 95% CI, 1.39-1.43), heart

TAKEAWAY POINTS

- Researchers reported results of a retrospective cohort study designed to estimate the incidence and risk factors of community-acquired acute kidney injury (CA-AKI).
- Using data from the Veterans Health Administration, the analysis demonstrated a cumulative incidence of CA-AKI of approximately 2.1% annually.
- Factors associated with increased risk of CA-AKI included high health care utilization, female sex, chronic illness, cancer, rural location, and use of renin-angiotensin-aldosterone system inhibitors or diuretics.

failure (HR, 1.37; 95% CI, 1.35-1.39), sickle cell anemia (HR, 1.30; 95% CI, 1.03-1.64), kidney stones (HR, 1.31; 95% CI, 1.28-1.34), cancer (HR, 1.27; 95% CI, 1.25-1.28), weight loss (HR, 1.24; 95% CI, 1.21-1.28), hypertension (HR, 1.23; 95% CI, 1.21-1.25), and tobacco use (HR, 1.19; 95% CI, 1.18-01.21).

There was an association between acute myocardial infarction and a lower hazard of CA-AKI (HR, 0.81; 95% CI, 0.78-0.84).

In a sensitivity analysis that limited the analytic cohort to veterans with two or more serum creatinine measures (n=12,062,827), the annual incidence of CA-AKI was approximately 2.1% in all cohort years, with the exception of 2017 when it was 1.8%. There were no significant changes in the factors associated with incidence of CA-AKI.

The cumulative incidence of CA-AKI was approximately 1.9% per year. Overall, 26.9% of CA-AKI was detected at hospital admission.

In citing limitations to the study, the authors included using data from the VA, limiting the generalizability to other populations that have a higher proportion of females; the lack of a standardized definition of CA-AKI; and assessing medication use at a single time point

In summary, the researchers said, "CA-AKI affects one of every 50 primary care users in the VA. The majority of CA-AKI events occurred in the outpatient setting, so studies on AKI in the hospital likely dramatically underestimate the true incidence of CA-AKI. Under-recognition of CA-AKI represents a missed opportunity to prevent and manage the long-term consequences of CA-AKI. Therefore, comprehensive investigations using longitudinal health data are critically needed to determine the impact of CA-AKI on long-term clinical outcomes in the US population." ■

National Kidney Foundation: New Organ Procurement Transplant Law Is Game Changer

*Statement from **Kevin Longino,** CEO of the National Kidney Foundation and a transplant recipient, on the signing of the US Organ Procurement and Transplantation Network (OPTN) Act into law.*

This is a game changer!

The Securing US Organ Procurement and Transplantation Network (OPTN) Act will help improve the transplant system by promoting innovation, transparency, and accountability across the system. It will improve equity and access to transplantation for all Americans. Modernize the technology that matches donors to recipients and create a more efficient system to maximize the number of organs that can be transplanted.

Make no mistake, reforms to the governance of the OPTN will save lives, strengthen accountability, and increase transparency. Provisions in this law will strengthen data collection, and reporting, and will allow patients to make informed decisions about where and how they receive their care.

Far too many kidney patients do not have access to organ transplantation, either because they are too sick to get a transplant, are uneducated about transplant as an option, or are poorly served by the system that is in place. They often wait 3 to 5 years for a transplant, and in some areas of the country up to 10 years or longer. For communities of color, the kidney disease journey is fraught with obstacles. African Americans are four times more likely to experience kidney failure, less likely to access options like home dialysis, and are less likely to be approved for a transplant. Organ donation—both deceased donors and living donors—is lower in communities of color, often due to lack of awareness or distrust in the medical system. As a result of these barriers, Black and Hispanic patients wait on average 18 to 24 months longer for a transplant than White patients.

The National Kidney Foundation is honored to join President Biden at today's signing ceremony. We'd also like to thank Senators Ron Wyden, Chuck Grassley, Ben Cardin, Todd Young, and Bill Cassidy along with Representatives Larry Bucshon and Robin Kelly, for introducing this legislation and securing its unanimous passage in the House and Senate. Their hard work helped make this bill a reality. We look forward to working with the OPTN as it implements these important reforms and to continue to strengthen our nation's organ procurement and transplantation system as we work toward kidney equity for all.

AOPO Supports the OPTN Act

In a late September press release, the Association of Organ Procurement Organizations (AOPO) expressed support for the President's signing of the Securing the US Organ Procurement and Transplantation Network (OPTN) Act (H.R. 2544) into law.

The legislation is a crucial piece of the Health Resources and Services Administration (HRSA) Modernization Initiative that is designed to enhance the OPTN's capabilities and effectiveness to improve service to patients, donors, and donor families in the United States.

Colleen McCarthy, president of AOPO, said, "As the national voice of OPOs, which provide compassionate care to donors and donor families every day, AOPO recognizes the profound potential for system enhancement to transform countless lives. Our unwavering focus is on patient-centric solutions that will result in increased organ donation and transplants for those in need.

AOPO is ready to collaborate with HRSA, Congress, and other stakeholders to further advance OPTN modernization and enhance the organ donation and transplantation system, according to the press release. They added that H.R. 2544 represents a significant milestone. AOPO is committed to implementing additional system-wide reforms aimed at achieving the ambitious goal of 50,000 annual organ transplants in 2026.

AKF Raises Awareness of Two Rare Kidney Diseases

The American Kidney Fund (AKF) has launched educational awareness campaigns for two rare kidney diseases: complement 3 glomerulopathy (C3G) and IgA nephropathy (IgAN). Both C3G and IgAN are related to improper function of the immune system.

The campaigns are sponsored by Novartis and will provide patients with information on the diseases and connect them to resources to understand and manage their conditions.

In a recent press release, LaVarne A. Burton, president and CEO of AKF, said, "Knowledge is power when it comes to managing kidney disease and staying as healthy as possible. We are grateful to Novartis for their support as we launch these educational campaigns and are pleased to share information and resources that will help people with C3G or IgAN and their families advocate for themselves."

The campaign included dedicated web pages that are accessible from the AKF's website (KidneyFund.org). The pages will include information on diagnosis, symptoms, and management of C3G and IgAN, as well as resources for building and managing relationships with a medical team, nutrition considerations, and strategies for coping with the mental health effects of these disease on patients and their families.

Also in development are patient-facing educational videos and a downloadable guide. The C3G page will also feature a video series highlighting patient experiences with C3G to help build a support community for individuals diagnosed with the disease.

Somatus Receives 2023 Certification Renewal

The Validation Institute has renewed the certification of the claim from Somatus that patients with chronic kidney disease (CKD) who receive Somatus Transitions of Care Assessment (TCA) services have fewer hospital readmissions than similar patients who do not receive TCA services. Somatus is the nation's largest value-based kidney care company. The Validation Institute validates performance claims made by solutions providers.

NKF Presents Health Equity Community Engagement Awards

Amber Paulus, PhD, RN, CPHQ

Janet Diaz Martinez, PhD, RN, LDN

The National Kidney Foundation (NFK) has announced the recipients of the 2023 NKF Health Equity Community Engagement Award. The award includes research funding to individuals working to make a difference in disparities in kidney health. The recipients for 2023 are **Amber Paulus, PhD, RN, CPHQ,** and **Janet Diaz Martinez, PhD, RN, LDN.**

Dr. Paulus's project, Designing Equitable Care for Kidneys (DECK): Community-Based Screening for Social Determinants of Health and Kidney Disease Risk Factors, focuses on identifying social determinants of health that impact kidney disease risk factors. The grant award is supported by Chinook Therapeutics.

Dr. Martinez's project, Caridad Awareness and Education (CARE), helps create patient educational materials on chronic kidney disease (CKD) to increase awareness of and screening for CKD. The initiative aims to address education gaps among Latino/a adults, a community that is disproportionately affected by kidney disease.

In a press release from Somatus, **Joe Kimura, MD,** chief medical officer said, "As we continue to deliver our whole-person care model at scale, our care teams are doing the necessary work to keep our patients from experiencing unplanned readmissions and remain healthier at home."

In the 2023 analysis of more than 14,000 TCAs conducted in patients with stage 3 CKD (in addition to patients with stage 4 CKD and end-stage kidney disease included in the previous analysis), TCA participants' likelihood of hospital readmission for postattribution discharges was 49% lower than that among similar nonparticipants.

NKF Announces Young Investigator Research Grant Recipients

The National Kidney Foundation (NKF) has announced the five recipients of the 2023 NKF Young Investigator Research Grant Program. The program provides support to young researchers who are working to advance research in kidney disease and improve patient care. This year's recipients are:

Korey Bartolomeo, DO, who has received the Satellite Dialysis Young Investigator Grant to continue his work investigating the mechanisms underlying APL1-associated kidney diseases related to the inheritance of two copies of high-risk APOL1 kidney disease risk variants. Dr. Bartolomeo is a nephrologist in Cleveland, Ohio, and is affiliated with the Cleveland Clinic.

Dipal Patel, MD, PhD, is the recipient of the NKF Young Investigator Research Grant for her work leveraging electronic health records to implement and incorporate patient-related symptoms into clinical care. Dr. Patel is an assistant professor of medicine in Baltimore, Maryland, and is affiliated with Johns Hopkins University.

Leonela Villegas, MD, has been awarded the NKF Young Investigator Research Grant to continue her research on the experience and impact of readmissions on the caregivers of children with chronic kidney disease. Her work seeks to identify the factors contributing to readmissions and improve clinical care for that vulnerable patient population. Dr. Villegas is an assistant professor at the Connecticut Children's Medical Center in Hartford.

The Joseph M. Krainin MD Memorial Young Investigator Award was presented to **Anvesha Srivastava, MD**, for her pilot study focusing on the interplay between genetic variations and microRNA expression in chronic kidney disease progression. Dr. Srivastava is a postdoctoral fellow at George Washington University.

Stella Kilduff, MD, was awarded the NKF Young Investigator Grant for research investigating the impact of metabolic acidosis on kidney transplant recipients, with the aim of identifying mechanisms and potential therapeutic targets to improve patient outcomes. Dr. Kilduff is affiliated with The Ann & Robert H. Lurie Children's Hospital in Chicago, Illinois.

In a recent press release, **Sylvia Rosas, MD, MSCE,** NKF president, said, "These exceptional young investigators have

continued on page 30

continued from page 29

demonstrated remarkable dedication to advancing kidney disease research. Their works hold great promise for improving our understanding of kidney disease and enhancing patient care. At NKF we understand that kidney disease affects individuals throughout their lifespan and are pleased that reviewers recommended for funding several awards focused on children with kidney disease. In addition, we look forward to learning more about the impact of genes in kidney disease progression as well as the use of artificial intelligence to address patient symptoms."

Rimidi Launches CKD Module

In a recent press release, Rimidi, a clinical management platform, announced the launch of a chronic kidney disease (CKD) module, designed to give providers better visibility of the status of their population of patients with CKD to improve patient management. The module will combine clinically relevant data from the electronic health record with patient-generated data from connected devices and patient surveys into a streamlined, problem-oriented view that will allow for improved risk stratification and chronic disease management.

Lucienne Ide, MD, PhD, founder and CEO of Rimidi, said, "Given that Rimidi already supports disease management and remote patient monitoring for diabetes and hypertension, two common risk factors for CKD, developing a full CKD module was a natural platform progression. As we continue to see innovations in connected devices and systems for treating and assessing CKD progression, being able to analyze and interpret all relevant data in a unified platform will drive clinical efficiency, coordination, and positive impact for CKD patients."

Initiatives planned for 2024 include integration of additional data from connected medical devices used in renal care to further support patient-centered and data-driven care delivery.

FDA Approves Rivfloza™ for Patients With PH1

Novo Nordisk, Inc. announced that the US Food and Drug Administration (FDA) has approved Rivfloza™ (nedosiran) injection 80 mg, 128 mg, or 160 mg, a once monthly subcutaneous ribonucleic acid interference (RNAi) therapy, to lower urinary oxalate levels in children ≥9 years of age and adults with primary hyperoxaluria type 1 (Ph1) and relatively preserved kidney function.

Ph1 is a progressive metabolic disorder that primarily affects the kidneys and can lead to progressive kidney damage. An estimated 2000 individuals in the United States are living with PH1.

In a press release, **Blandine Lacroix,** senior vice president, strategy and rare disease at Novo Nordisk, said, "The FDA approval of Rivfloza builds on Novo Nordisk's legacy of advancing research, fostering innovation, and creating strategic partnerships to expand treatment options in rare diseases. We are committed to driving change on behalf of people living with rare diseases and helping address the significant unmet needs of the PH1 community. We look forward to making our first RNAi treatment available to people living with PH1 and the health care professionals partnering on their care." ■

COVID-19

Patients With COVID-19 and AKI Face Increased Mortality Risk

Journal of Clinical Medicine.
doi.org/10.3390/jcm12155127

In the face of the high number of patients with severe COVID-19 who develop acute kidney injury (AKI), **Nabil Bouguezzi, MD,** and colleagues in Tunisia conducted a retrospective, observational study designed to determine the frequency, risk factors, and impact of AKI on mortality in critically ill patients with COVID-19. Risk factors for AKI and clinical outcomes were identified using univariate and multivariate analyses.

A total of 465 consecutive COVID-19 patients were admitted to the medical intensive care unit (ICU) at Farhat Hached University Hospital, Sousse 4000, Tunisia, during the study period. Median age was 64 years, median Simplified Acute Physiology Score was 31, and 52.5% (n=244) required invasive mechanical ventilation (IMV).

The overall mortality rate among patients admitted to the ICU was 49%. Of the 465 patients in the study cohort, 49.2% (n=229) developed AKI. Factors independently associated with AKI were positive fluid balance (odds ratio [OR], 2.78; 95% CI, 1.88-4.11; *P*<.001), right heart failure (OR, 2.15; 95% CI, 1.25-3.67; *P*=.005), and IMV use (OR, 1.55; 95% CI, 1.01-2.40; *P*=.044).

In multivariate analysis among the patients with AKI, age (OR, 1.05; 95% CI, 1.02-1.09; *P*=.012), IMV use (OR, 48.23; 95% CI, 18.05-128.89; *P*<.001), and septic shock (OR, 3.65; 95% CI, 1.32-10.10; *P*=.012) were independently associated with mortality.

In conclusion, the researchers said, "The present study revealed a high proportion of AKI among critically ill COVID-19 patients. This complication seems to be linked to a severe cardiopulmonary interaction and fluid balance management, thus accounting for a poor outcome."

Mortality Risk Among Patients With Kidney Disease and COVID-19

Cureus. doi:10.7759/cureus.41043

Results of previous studies have suggested a link between preexisting kidney disease and higher rates of mortality among patients with COVID-19 infection. Kidney disease is prevalent in the rural midwestern region of the United States, an area with significant impact associated with COVID-19 in a population that includes significant numbers of Medicare or Medicaid beneficiaries.

Kailey J. Kowalski and colleagues conducted a retrospective cohort study to identify patients with acute kidney injury (AKI), chronic kidney disease (CKD), and end-stage renal disease (ESRD) with and without COVID-19. Physician-submitted codes from the *International Classification of Diseases, Tenth Revision* into Freeman Health System's electronic medical records were gathered from April 2020 to January 2021. Excluding variables such as sex and age, the data were analyzed and compared to determine whether the mortality rate in patients with varying stages of kidney disease and COVID-19 was higher than the mortality rate in patients with kidney diseases alone.

Among patients with COVID-19 and any degree of kidney disease, encompassing both CKD and AKI, the 95% CI of the mortality rate was between 30.21% and 37.63%. That metric was significantly higher than the 95% CI of COVID-19 infection (6.70%-9.96%; *P*<.0001) or kidney disease alone (10.89%-13.01%; *P*<.0001).

Among the CKD plus COVID-19 cohort, the highest rate of mortality was in patients with AKI (38.13% and 49.02%). The statistical support in the sample was not sufficient to assert that COVID-19 increased mortality in patients with ESRD.

"Based on our results, patients with kidney disease and COVID-19 are at higher risk for mortality when compared with patients with kidney disease alone," the researchers said. "Further studies are warranted into individual comorbidities affecting kidney disease patient outcomes with COVID-19."

ANEMIA

Benefits and Risks of Long-term Use of HIF-PHIs for Anemia of CKD

Pediatric Nephrology.
doi.org/10.1007/s00467-023-06031-8

In several countries, including the United States, hypoxia-inducible factor prolyl hydroxylase inhibitors (HIF-PHIs) have been approved as supplement or alternative for the clinical treatment of anemia in patients with chronic kidney disease (CKD). Hemoglobin levels are effectively increased via activation of HIF by HIF-PHIs by inducing multiple HIF downstream signaling pathways, suggesting that HIF-PHIs have effects beyond erythropoietin. **Jia He, MD,** and colleagues presented a review of the potential benefits and risks associated with treatment with HIF-PHIs for patients with anemia of CKD.

Results of multiple clinical trials have demonstrated the efficacy and safety of these agents in the short-term treatment of anemia in patients with CKD. However, according to the researchers, there are few data available on the benefits and risks of long-term use of HIF-PHIs (more than 1 year). Areas of concern include the risk of progression of kidney disease, cardiovascular events, retinal diseases, and tumor growth.

The authors said, "This review aims to summarize the current potential risks and benefits of HIF-PHIs in CKD patients with anemia and further discuss the mechanism of action and pharmacological properties of HIF-PHIs, in order to provide direction and theoretical support for future studies."

CHRONIC KIDNEY DISEASE

Detecting Hyperechoic Crystal Deposits in Patients With CKD

Journal of Nephrology.
doi.org/10.1007/s40620-023-01605-z

Ultrasonography examination enables detection of hyperechoic crustal deposits in the kidney medulla of patients with gout. Patients with chronic kidney disease (CKD) commonly experience hyperuricemia. There are few data available on whether hyperechoic crystal deposition can be detected by ultrasonography in patients with CKD.

Daorina Bao, Nan Lv, Xiufang Duan and colleagues at the Institute of Nephrology, Peking University, Beijing, China, recently conducted an observational study of 515 consecutive patients with CKD. The researchers collected and analyzed clinical, biochemical, and pathological data. A total of 234 patients (45.4%) were found to have hyperuricemia and 25 patients (4.9%) had a history of gout. Hyperechoic crystal deposits in kidney medulla were found in 8.5% of the cohort (n=44).

Compared with patients without hyperechoic crystal deposits, those with deposits were more likely to be male, younger, and have a history of gout. They were also more likely to present with higher serum uric acid level, lower estimated glomerular filtration rate, lower urine pH, lower 24-hour excretion of urinary citrate and uric acid, and a higher percentage of ischemic nephropathy (all *P*<.05).

Results of multivariable logistic analyses demonstrated associations between the hyperechoic depositions and age, serum uric acid level, square-root-transformed 24-hour urine uric acid excretions, and ischemic nephropathy.

"Hyperechoic crystal deposition can be detected in kidney medulla by ultrasonography; in CKD patients their presence was associated with hyperuricemia as well as with ischemic nephropathy," the authors said.

Rethinking Management of Hyperkalemia in CKD

Journal of Renal Nutrition.
doi.org/10.1053/j.jrn.2022.12.003

Potassium disorders, common electrolyte abnormalities in patients with chronic kidney disease (CKD), are associated with poor clinical outcomes. Management of these patients requires maintaining serum

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potassium levels within the physiologically normal range.

A core strategy for the management of chronic hyperkalemia in patients with CKD includes restriction of dietary potassium. However, recent evidence has challenged this regimen, suggesting a paradigm shift toward fostering more liberal, plant-based dietary patterns.

According to **Keiichi Sumida, MD, MPH, PhD,** and colleagues, the emergence of novel potassium binders and an improved understanding of gastrointestinal processes involved in potassium homeostasis (gastrointestinal potassium wasting) may facilitate a shift in thinking and incorporation of heart-healthy potassium-enriched food sources.

"Nevertheless, uncertainty regarding the risk-benefit of plant-based diets in the context of potassium management in CKD remains, requiring well-designed clinical trials to determine the efficacy of dietary potassium manipulation toward improvement of clinical outcome sin patients with CKD," the researchers said.

DIABETES

CONUT Score Predicts Adverse Outcomes in Patients With DKD

Frontiers in Physiology.
doi.org/10.3389/fphys.2023.1231448

The Controlled Nutritional Status (CONUT) score is calculated from albumin, total cholesterol, and lymphocyte count. It is a useful indicator for assessment of immune-nutritional status and is associated with the prognosis of various diseases. However, there are few data available on the relationship between CONUT score and renal outcomes, cardiovascular disease, and all-cause mortality in patients with diabetic kidney disease (DKD).

Quingyu Huo, MD, and colleagues at Xinqiao Hospital, Army Medical University (Third Military Medical University), Chongqing, China, conducted a retrospective single-center study that enrolled 336 patients with biopsy-confirmed DKD from August 2009 to December 2018. Outcomes of interest were progression to end-stage renal disease (ESRD), cardiovascular disease events, and death.

The association between confounding factors and outcomes was estimated using univariate and multivariate Cox regression analysis. The outcomes of patients according to the median CONUT score were compared using the Kaplan-Meier curve.

Follow-up continued for a median of 5.1 years. Results of Kaplan-Meier analysis demonstrated that the incidence of ESRD, cardiovascular disease events, and all-cause mortality was significantly higher among patients in the high CONUT group (CONUT score >3) compared with those in the low CONUT group (CONUT score <3). In the multivariate COX regression, the CONUT score was an independent predictor of ESRD (hazard ratio [HR], 1.129; 95% CI, 1.037-1.228; *P*=.005), cardiovascular disease events (HR, 1.159; 95% CI, 1.057-1.271; *P*=.002), and all-cause mortality (HR, 1.299; 95% CI, 1.143-1.478; *P*<.001).

In summary, the authors said, "The CONUT score is an independent risk factor for ESRD, cardiovascular disease events, and overall death in patients with diabetic kidney disease."

HYPERKALEMIA

Findings From DIALIZE China Reported

Clinical Therapeutics.
doi.org/10.1016/j.clinthera/2023.04.014

The DIALIZE China (Reduce Incidence of Predialysis Hyperkalemia With Sodium Zirconium Cyclosilicate in Chinese Subjects) study was designed to evaluate the use of sodium zirconium cyclosilicate (SZC) for the management of hyperkalemia in patients in China undergoing hemodialysis

(NCT04217590). **Zhaohui Ni, MD,** and colleagues reported results of the double-blind study.

The study cohort included adults in China with kidney failure and predialysis hyperkalemia, (predialysis serum potassium concentration >5.4 mmol/L after the long interdialytic interval (LIDI) and >5.0 mmol/L after ≥1 short interdialytic interval) who were receiving hemodialysis three times weekly. Participants were randomized to placebo or SZC 5 grams once daily on nondialysis days.

Doses were titrated toward maintaining normokalemia for 4 weeks (titration period) in 5-gram increments up to 15 grams. The primary efficacy outcome of interest was the proportion of responders during the 4-week valuation period following the titration period. Responders were defined as those with a predialysis serum potassium concentration of 4.0 to 5.0 mmol/L for at least three of four hemodialysis visits following the LIDI who did not require urgent rescue therapy.

A total of 143 adults were randomized to SZC (n=67) or placebo (n=67). The mean age was 55 years. The proportion of responders was significantly higher in the SZC group than in the placebo group: 37.3% vs 10.4%, respectively (estimated odds ratio [OR], 5.10; 95% CI, 1.90-15.12; *P*<.001). The probability of all predialysis serum potassium concentrations being 3.5 to 5.5 mmol/L was significantly higher with SZC versus placebo (estimated OR, 6.41; 95% CI, 2.71-15.12; *P*<.001).

The proportion of patients who achieved a serum

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potassium concentration of 3.5 to 5.5 mmol/L on at least three of four LIDI visits during evaluation was higher in the SZC group than in the placebo group (73.1% vs 29.9%, respectively). Serious adverse events were reported in 9.1% and 11.9% of patients in the SZC group and placebo group, respectively.

In conclusion, the researchers said, "SZC treatment for predialysis hyperkalemia is effective and well tolerated in Chinese patients with kidney failure receiving hemodialysis."

LUPUS NEPHRITIS

New and Emerging Therapies for Lupus Nephritis

BioDrugs. doi.org/10.1007/s40259-023-00597-3

Women of childbearing age are the most common population at risk for lupus nephritis (LN), a severe complication associated with systemic lupus erythematosus (SLE). Women with SLE/LN face increased risk for the progression of chronic kidney disease (CKD), cardiovascular disease, and pregnancy complications. Current management of LN includes the use of drug that carry significant toxicities, making the overall efficacy of treatment low.

Ajinath Kale, PhD, and colleagues provided a review of recent drug approvals as well as the upcoming pipeline of novel medications being tested in clinical trials to improve the effectiveness in terms of LN disease activity, LN relapse, and progression of LN-related CKD. The review includes three areas: (1) drugs with the potential to achieve those treatment goals by modulating SLE activity as the driving force of LN (belimumab, obinutuzumab, anifrolumab, among others); (2) drugs with SLE-nonspecific renoprotective effects by targeting nonimmune mechanisms of progression of LN (dapagliflozin, empagliflozin); and (3) drugs with dual immunosuppressive and antiproteinuric effects (voclosporin).

"Increasing the number of possible drug options will help to improve the management of LN in terms of efficacy and safety, and enable a more personalized treatment approach," the authors said. ■

Major Meetings

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

American Society of Nephrology Kidney Week 2024
October 23–27, 2024
San Diego, California
www.asn-online.org/education/kidneyweek

Sarah Tolson

Facing the Tide: Navigating the Rising Costs and Regulatory Changes in the 2024 ESRD PPS

Those involved in the dialysis industry since 2020 have faced a substantial increase in costs for supplies and labor due to the public health emergency (PHE). As a participant in this industry, you are likely aware that these costs have not subsided.

The company I work for specializes in revenue cycle management for small, independent dialysis programs. Our clients range from hospital-based and freestanding facilities to those providing care in nursing homes, traditional in-center dialysis facilities, and home programs. They cater to a diverse demographic spectrum, from elderly, indigent patients to affluent, middle-aged individuals, including residents of Indian reservations and pediatric patients. Despite their differences, a common thread unites these programs: deep care for their patients and grappling with labor and supply costs that have significantly outpaced reimbursement increases in the End Stage Renal Disease (ESRD) Prospective Payment System (PPS).

ESRD PPS BASE RATE INCREASE

The new base rate for CY 2024 is set at $271.02, which is a 2% increase from CY 2023. The Centers for Medicare & Medicaid Services (CMS) projects the updates to the ESRD PPS for CY 2024 will result in an overall reimbursement increase of 2.1% over CY 2023 reimbursement. CMS anticipates hospital-based dialysis facilities will see a 3.1% increase, whereas the reimbursement increase for freestanding dialysis programs will be approximately 2%. The information I have reviewed from renal associations as well as commentary from my clients indicates the underlying driver for requesting a higher increase to the market basket adjustment is to adequately cover costs for dialysis treatments and ensure continued access to care for patients with ESRD who need dialysis treatments. Despite 90 comments urging a higher market basket adjustment to account for labor cost spikes during and post-PHE, CMS believes the current adjustment adequately reflects the average change in service costs, including labor.

TRANSITIONAL PEDIATRIC ESRD ADD-ON PAYMENT ADJUSTMENT

The introduction of a 30% add-on payment adjustment for pediatric ESRD patients is a welcome development. The labor requirements for pediatric hemodialysis are *significantly* higher than adult hemodialysis. As such, pediatric dialysis programs are really feeling the financial squeeze. However, this adjustment is temporary, and concerns remain about the adequacy of future payment adjustments, given the history with post-transitional drug add-on (TDAPA).

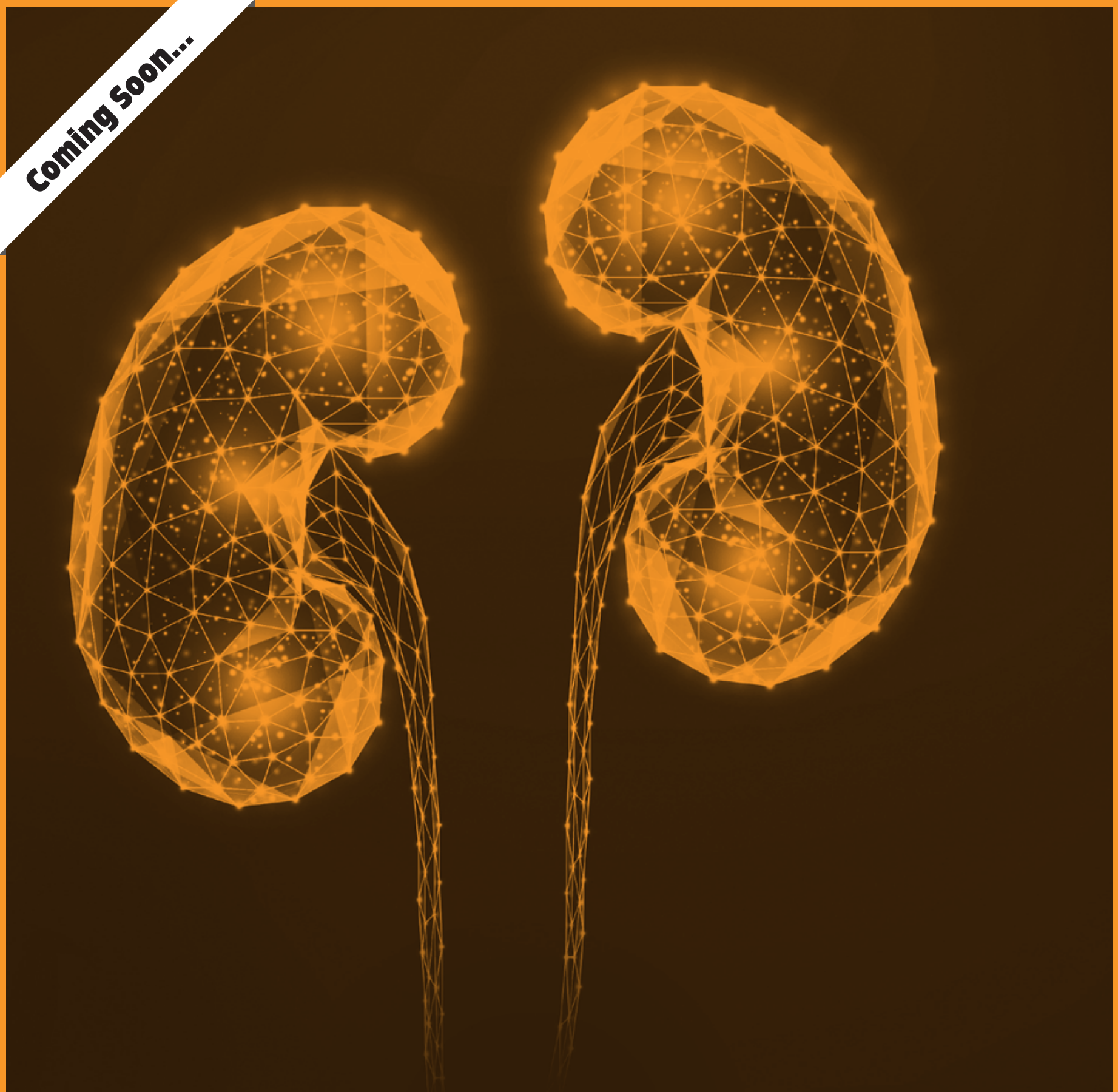
TIME ON MACHINE AND WASTAGE REPORTING REQUIREMENTS

Beginning in January 2025, CMS will require dialysis programs to report JW and/or JZ modifiers when billing for medications on a dialysis claim to allow CMS to gather data more easily regarding medication waste. Additionally, CMS will require dialysis facilities to include the amount of time a patient spent on dialysis during a billing period on the claim form to assess patient-level resource usage. These reporting requirements will increase the administrative burden related to documenting reporting medication amounts and time on dialysis in medical records as well as on billing claim forms. Dialysis facility administrators should begin to review their processes, electronic health records, and billing software to identify any changes that need to be made to meet these new requirements. Additionally, it is important to work with individuals whose workflows will be impacted to ensure they have a complete understanding of how to comply with these reporting changes.

TDAPA PAYMENT ADJUSTMENT, OUTLIER AND LVPA UPDATES

CMS has set the post-TDAPA payment adjustment amount at 65% of TDAPA expenditure levels. This new adjustment provides a bit of clarity on what to expect after the TDAPA period ends. The outlier policy was updated by adjusting the adult and pediatric Medicare allowable payment amounts and fixed dollar loss amounts in an attempt to increase outlier payments to the goal of 1% of ESRD PPS claims. Lastly, CMS has made modifications to the low-volume payment adjustment (LVPA) to provide flexibilities in qualification of dialysis programs as they relate to temporary closure and reopening or exceeding treatment thresholds during a disaster or other emergency. ■

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.



Watch your mailbox for the **May–June issue** of *Nephrology Times* for coverage of selected posters and presentations from the National Kidney Foundation's

SPRING CLINICAL MEETINGS 2024