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Patient Experience Is Driving the Development of New Outcomes for Fluid Overload Treatment

By Bridget M. Kuehn

A decade ago, Christine Gwinn started noticing her clothes suddenly and inexplicably became tight during a fly-fishing trip in Colorado. Over the next 6 weeks, fluid buildup caused her weight to skyrocket from 120 to 200 pounds. Her physicians diagnosed her with focal segmental glomerulosclerosis (FSGS). Initial treatment with diuretics and fluid restriction were not effective, so Gwinn was started on emergent dialysis to alleviate the fluid buildup and protect her kidneys.

"When it's that kind of dramatic change, finding something that works is critical," Gwinn said. Eventually, she started taking prednisone. It worked well but had many side effects.

Now, Gwinn is part of a team effort to spur the development of new treatments for fluid buildup associated with nephrotic disease that better meet patients' needs. Gwinn is a member of the Stakeholder Engagement Committee for Prepare-NS (1), a US Food and Drug Administration (FDA)-funded study recruiting patients with nephrotic disease to share their experiences.

"The goal of the project is to create a set of outcome measures to capture the clinical benefit of new nephrotic syndrome treatments," said Co-Principal Investigator John Devin Peipert, PhD, assistant professor of medical social sciences at Northwestern University's Feinberg School of Medicine (Chicago, IL). "Patients are in the best position to tell you about their experience of that symptom, the severity of the symptom, the frequency, and how it impacts their life."

What's the catch?

Current treatments for fluid overload associated with nephrotic disease focus on either treating the underlying condition causing kidney dysfunction or using diuretics to help the kidneys remove the salt and water causing the buildup, said

Continued on page 7

Team-Based Care Is Essential for Diabetic Kidney Disease

By Bridget M. Kuehn

The emergence of a new generation of kidney-protecting therapies for diabetes, including sodium-glucose cotransporter-2 inhibitors, glucagon-like peptide 1 receptor agonists, and finerenone, will require better use of team-based care, according to a flurry of recent recommendations.

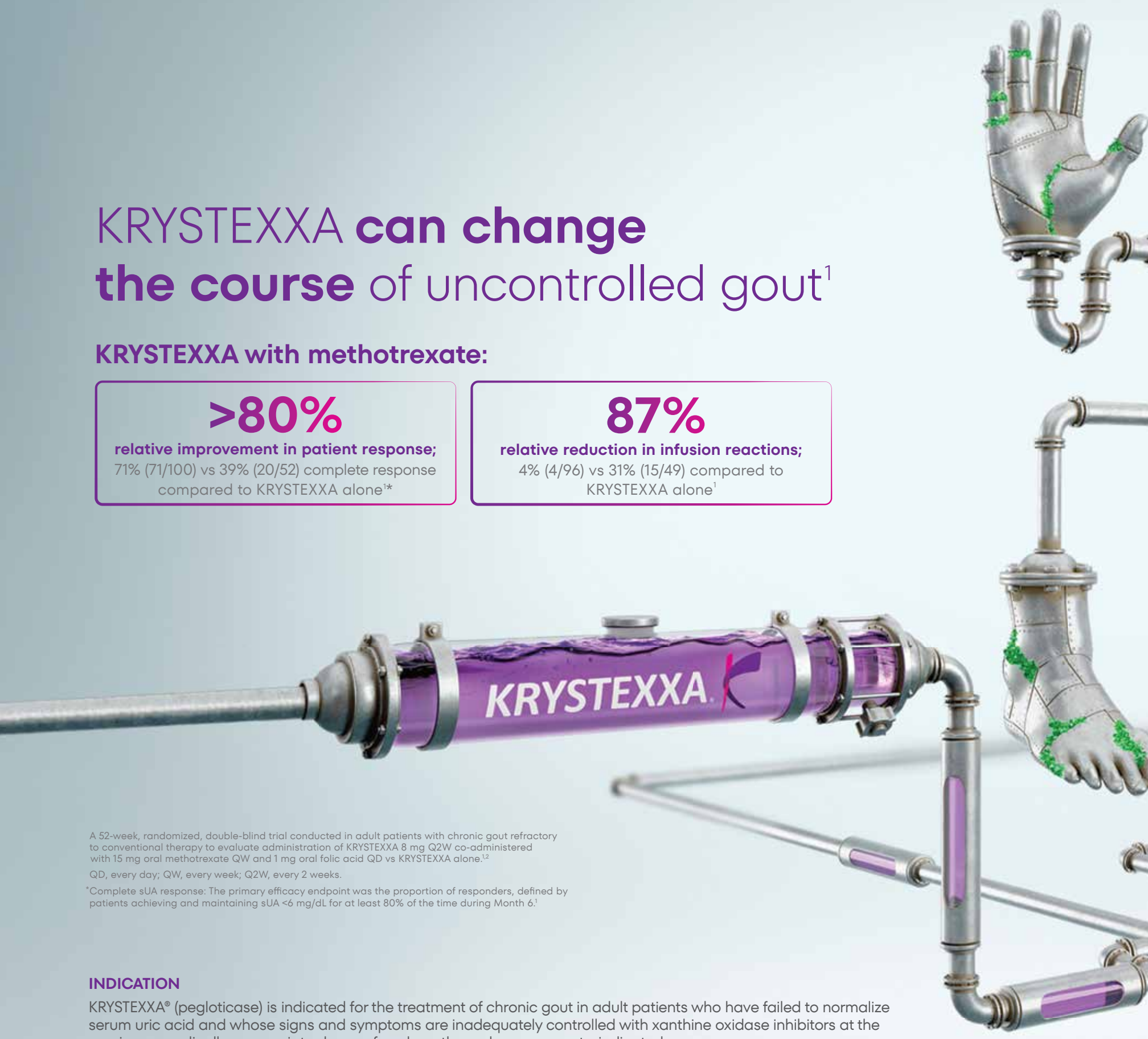
In recent months, Kidney Disease: Improving Global Outcomes (KDIGO) updated its diabetic kidney disease guidelines (1), and the American Diabetes Association (ADA) and KDIGO released a consensus report (2) on diabetic kidney disease management. According to the guidelines, making the most of the new practice-changing therapies along with lifestyle modifications and more traditional therapies will require new multidisciplinary, comprehensive models of care. The recommendations echo those of the ASN Diabetic Kidney Disease Collaborative Task Force (3) calling for the transformation of the care of patients with diabetic kidney disease.

"With the breakthrough therapies we now have, nephrology is poised to be completely transformed as a specialty," Katherine Tuttle, MD, chair of the ASN Diabetic Kidney Disease Collaborative Task Force and professor of medicine at the University of Washington in Spokane, said in an interview. "Instead of focusing on end stage and kidney failure, we now have the opportunity to focus on early diagnosis and treatment that [preserve] kidney function for a lifetime."

Continued on page 10

Inside

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.

HORIZON.

KRYSTEXXA®
pegloticase

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.

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Fluid Overload Treatment

Continued from cover

Eloise Salmon, MD, a Prepare-NS co-investigator and clinical assistant professor in the Division of Pediatric Nephrology at the University of Michigan (Ann Arbor). The effectiveness of these approaches varies from patient to patient, she noted. For patients like Gwinn, the questions are often, "What's the catch?" with a given treatment, and "How will it affect day-to-day life?"

"I've gone through a number of different treatments in the past 10 years," Gwinn said. "Some have worked; some haven't, and everything comes with a side effect. The more information you have, the better you can assess your options."

It is also important for children with nephrotic disease and their caregivers to have as much information as possible and have medications that meet their needs. "Children are especially resilient, but often under that tough exterior, they are suffering from edema and are impacted in ways health care professionals don't see or understand," said Kelly Helm, a parent of a patient with nephrotic disease, co-chair of the Stakeholder Engagement Committee for Prepare-NS, and executive director of patient engagement at NephCure Kidney International (King of Prussia, PA). "The effects of edema are often painful and exhausting, which limits kids' physical capabilities and ability to carry out their normal daily lives. Additionally, edema impacts the way they look and for some, impacts their interactions with peers."

The FDA has funded the Prepare-NS study with a pilot grant (2) as part of its Patient-Focused Drug Development efforts. In addition to patient perspectives, the study team has gathered input from various stakeholders, including nephrologists, industry representatives, payors, and regulators. The shared goal is to create patient-reported clinical trial outcome measures that investigators and the FDA can use to evaluate whether a new drug provides meaningful patient benefits.

"There is an unmet need for safe and effective treatments for rare kidney diseases that cause the nephrotic syndrome," said Kirtida Mistry, MBBCh, DCH, MRCPCH, senior physician in the Division of Cardiology and Nephrology at the FDA's Center for Drug Evaluation and Research (CDER), in an e-mailed comment.

The Prepare-NS team will work closely with the FDA staff to create a clinical outcome assessment over the course of about 5 years, according to Robyn Bent, RN, MS, director of Patient-Focused Drug Development at CDER. At the end of the process, they will have a core set of clinical outcome assessments that are publicly available for free or at a low cost, she said.

"Patient-reported outcomes are a relatively new concept," said Patrick Nachman, MD, co-chair of the Stakeholder Engagement Committee and director of the Division of Nephrology and Hypertension at the University of Minnesota in Minneapolis. "The FDA is encouraging all stakeholders, physicians, investigators, patients, patient advocates, [and] pharmaceutical companies to think about clinical trial development outside of the traditional metrics or end points used in clinical trials."

Traditional clinical outcome assessments might focus on changes in patient weight or a clinician assessment of fluid overload, noted Salmon. But those assessments only capture one point in time and may differ from the measures most important to patients, she said. Nachman said that other common traditional end points in nephrology studies are kidney diseases' progression, needing dialysis or a transplant, and patient survival. But he said those end points take a long time to happen.

"As nephrologists, we obsess over the proteinuria levels, creatinine, and glomerular filtration rate," said Barbara Gillespie, MD, vice president and therapeutic head of nephrology at LabCorp Drug Development and adjunct professor in the Division of Nephrology and Hypertension at the University of North Carolina (Chapel Hill). "But patients, when they come to the clinic, they are ready to talk about their leg swelling, not their lab value."

Meaningful measures

To find out what is important to patients with fluid overload, Salmon and her co-investigators are starting with a qualitative study. The team is recruiting patients or caregivers of individuals with FSGS, minimal change disease, membranous nephropathy, or unbiopsied childhood with nephrotic syndrome to participate in the first phase. Prospective participants will complete a screening questionnaire on the https://www.prepare-ns.org/ website. Patients selected to participate will complete a 30- to 60-minute interview by telephone or Zoom with one of the study coordinators. Patients who do not qualify for the study's first phase are still encouraged to register and may be selected to participate in later stages of the study.

"Hopefully, we'll get a global sense of how edema affects the patient and [his or her] daily activities," Salmon said. For example, Peipert noted that swelling could lead to fatigue or limit patients' daily activities. The team will use the information to design and validate patient-centered outcome measures.

Gillespie said that patient-centered outcomes are critical because they can help new therapies win FDA approval. For example, she noted that the FDA approved difelikefalin, a drug used to treat pruritis in dialysis patients, based on a patient-reported outcome—itch-related quality of life measured on a rating scale (3, 4). She noted that there is a misperception that patient-reported outcomes can only be used as a secondary outcome or only in the FDA's accelerated approval pathways. But the difelikefalin approval provides a clear precedent in the field of nephrology that a patient-reported outcome can be a primary end point, Gillespie said.

"In clinical trials, we want to be confident we are asking the questions that matter to patients," Gillespie said. She noted that other efforts are underway in nephrology to develop patient-centered outcomes, including the Standardised Outcomes in Nephrology initiative (5). That initiative is developing standardized outcomes for hemodialysis, transplantation, peritoneal dialysis, children and adolescents with kidney diseases, glomerular disease, and polycystic kidney disease.

Nachman noted that quality-of-life measures have long been used as secondary end points in studies but that the shift to using well-tested and validated patient-reported outcomes as a primary end point is an exciting development. It is also a shift that patients, their caregivers, physicians, researchers, and pharmaceutical companies all welcome, he said.

"You can go to the FDA and say we have a validated tool; we have demonstrated that our new treatment is improving how the patients are functioning and feeling," he said.

> **As nephrologists, we obsess over the proteinuria levels, creatinine, and glomerular filtration rate. But patients, when they come to the clinic, they are ready to talk about their leg swelling, not their lab value.**
>
> **—Barbara Gillespie**

The Prepare-NS team encourages patients with nephrotic disease to register and has flyers available that nephrologists can post in their practices to help patients learn more. Ultimately, the Prepare-NS team hopes the study will result in new and better treatment options for patients with fluid overload.

"Patient-reported outcomes from both caregivers and the pediatric patients themselves are essential in providing not only optimal treatments but also implementing holistic patient-centered care," Helm said. ■

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ASN Executive Vice President's Update

Five Big Hairy Audacious Goals for US Nephrology

By Tod Ibrahim

During the past decade, the term "moonshot" has replaced BHAG (pronounced "bee hag," which is an acronym for big hairy audacious goal) in popular culture. I prefer the clarity of BHAG. Jim Collins introduced BHAG in his 1994 book (coauthored with Jerry I. Porras), *Built to Last: Successful Habits of Visionary Companies* (1). According to Collins and Porras, BHAGs are clear, compelling, and more likely to stimulate progress, like the moon mission. Serving as a unifying focal point of effort—often creating immense team spirit—BHAGs have a clear finish line and are engaging, tangible, energizing, and highly focused (2).

Influenced by ASN President Michelle A. Josephson, MD, FASN; the late ASN Councilor Barbara T. Murphy, MD, MB BAO BCh, FRCPI (who would have served as the society's president last year); and ASN Policy and Advocacy Committee Chair Roslyn B. Mannon, MD, FASN, I cannot think *big* about nephrology or aim high with future *goals* without first acknowledging that kidney transplantation is the optimal therapy for most people with kidney failure. Because transplantation entails a surgical procedure, some see kidney transplant as a surgical specialty, but it is integral to nephrology. Transplant is nephrology, and this intertwining makes both stronger, more significant, and likelier to succeed in maximizing access to transplantation for every person with kidney diseases who might benefit.

At least five BHAGs would galvanize the kidney and transplant communities in the United States to speak with one voice as never before:

1. Developing a national clearinghouse to help patients match with a transplant program that meets their needs would improve access and care.
2. Forming the National Center for Kidney Health and Transplantation at the National Institutes of Health (NIH) would advance research.
3. Embracing a fellowship in transplant nephrology accredited by the Accreditation Council for Graduate Medical Education (ACGME) would strengthen education.
4. Creating the Division of Kidney Health and Transplantation at the Centers for Disease Control and Prevention (CDC) would increase kidney health awareness, surveillance, and prevention.
5. Establishing the Office of Kidney Health and Transplantation at the Department of Health & Human Services (HHS) would coordinate, align, and bolster these efforts to improve care; advance research; strengthen education; and increase awareness, surveillance, and prevention.

To meet *Built to Last*'s definition, these five BHAGs should have grabbed you in the gut, and they should require little or no explanation (2). Context, however, is important, so the rest of this editorial will briefly describe each of the five BHAGs for US nephrology.

Improving care by developing a national clearinghouse to help match patients with transplant programs. People with kidney diseases and their nephrologists struggle to navigate the current system to find a transplant program, creating barriers to access transplant care. This challenge is especially acute for transplant candidates living in rural areas with already limited access to transplant facilities. Also, transplant candidates who might be deemed higher risk—a designation that often overlaps with populations who are socioeconomically disadvantaged or who face systemic racism in access to other areas of care—struggle to navigate the current system.

A centralized, national online clearinghouse would help match patients with transplant programs by uploading information from electronic health records (EHRs) for prospective patients and urging transplant center decision-makers to input their baseline criteria for accepting patients. The patient's information would be compared with the program's criteria and suggest likely matches. This clearinghouse would:

- Create a pathway to transplant for many patients for whom one does not presently exist.
- Decrease redundancy, administrative burdens, and paperwork (such as nephrology care teams or patients having one-off interfaces sharing the same information with multiple transplant centers to attempt to identify a good fit).
- Reduce transplant coordinator effort (such as fielding many one-off interactions regarding patients who may or may not be a good fit).
- Increase transplant center transparency to better understand—and improve—patients' access to transplant nationwide.

Pioneering research funded by the Agency for Healthcare Research and Quality (AHRQ) aims to help empower patients with more of this type of information, but this effort is in its infancy (3). Eventually, this AHRQ proof-of-concept platform could be expanded into a nationwide matching clearinghouse to help patients identify the transplant center(s) that are the optimal fit, including integration with EHRs at dialysis facilities, nephrology clinics, and transplant centers nationwide.

Advancing research by forming the NIH National Center for Kidney Health and Transplantation. With 27 institutes and centers, NIH is the world's leading research agency, seeking "fundamental knowledge about the nature and behavior of living systems and the application of that knowledge to enhance health, lengthen life, and reduce illness and disability" (4). In fiscal year 2021, NIH spent an estimated $700 million (1.6%) on kidney research and $201 million (0.47%) on organ transplantation research of its $42.94 billion total budget (5, 6).

Most of the funding for kidney research comes from the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), whereas organ transplantation research is funded across 18 different institutes and centers. By spending an estimated $18.13 for each American with kidney diseases—compared with an estimated $305.57 for each American with cancer—NIH significantly underfunds kidney research (7).

In the early 1970s, the federal government made two decisions that helped determine the future of both oncology and nephrology. As part of the "war on cancer," the government in 1971 declared that "the amount spent on cancer is grossly inadequate" and directed broad authority to the National Cancer Institute (NCI)—established in 1937—to pursue "new scientific leads" (8). From 1971 to 1979, the overall budget for NIH increased by more than 160%, with the budgets for NCI and NIDDK increasing by more than 300% and 50%, respectively (9).

By establishing the Medicare End-Stage Renal Disease (ESRD) Program in 1972, the government ensured that every American had access to lifesaving dialysis. In making this remarkable commitment, however, the government focused on treating people with kidney failure rather than finding cures to kidney diseases, reimagining dialysis, improving kidney transplants, or aligning incentives to promote kidney health and care. The National Center for Kidney Health and Transplantation is an important step toward embracing transplant as the optimal therapy for kidney failure, investing holistically across the entire research continuum, and improving access to and outcomes in kidney transplantation and research.

Strengthening education by embracing an ACGME-accredited fellowship in transplant nephrology. The federal government pays more than $16 billion annually for medical education, including fellowship training, through the Medicare program (10). This federal funding, however, is only available to ACGME-accredited residency and fellowship programs. ACGME currently accredits fellowships in transplant hepatology (since 2007), advanced heart failure and transplant cardiology (2013), and interventional pulmonology (2024) but not transplant nephrology (11). The American Society of Transplantation (AST) accredits nearly 70 transplant nephrology fellowship programs in the United States and Canada (12). Therefore, Medicare helps fund additional training in transplant hepatology, transplant cardiology, and interventional pulmonology but provides no support for transplant nephrology.

ACGME accreditation would raise the profile of kidney transplantation and nephrology among residents, faculty, and institutions that sponsor medical education; provide a pathway for federal funding of transplant nephrology fellows; emphasize the bond between kidney transplantation and ne-phrology; and help implement the final recommendations from the ASN Task Force on the Future of Nephrology (13). Starting July 1, 2023, ACGME will become responsible for overseeing J-1 visa holders in non-accredited fellowship programs (such as transplant nephrology). This policy change means that the directors of these programs will need to navigate two accreditation processes (ACGME and AST).

Increasing awareness, surveillance, and prevention by creating the CDC Division of Kidney Health and Transplantation. To accomplish its vision of "equitably protecting health, safety, and security," the CDC relies on 10 centers and institutes, including the National Center for Chronic Disease Prevention and Health Promotion (14). In turn, this center includes eight divisions focused on cancer, diabetes, heart disease, nutrition (and physical activity and obesity), oral health, population health, reproductive health, and smoking.

The Division of Diabetes Translation includes the CDC's Chronic Kidney Disease Surveillance System (15). While kidney diseases are housed within the CDC Division of Diabetes Translation, the agency's efforts related to transplantation are organized within the CDC's National Center for Emerging and Zoonotic Infectious Diseases' Division of Healthcare Quality Promotion (16). Given the magnitude of kidney diseases as a public health issue, the inequities and disparities in kidney health, the distinct approaches to prevention and care management, the bond between nephrology and transplantation, and the amount the federal government pays through Medicare to treat Americans with kidney failure, the CDC should equate kidney health and transplantation with cancer, diabetes, and heart disease.

In addition to raising the profile of kidney diseases, kidney failure, and kidney transplantation—which would help increase awareness in the public and private sectors, likely leading to more prevention—a freestanding CDC Division of Kidney Health and Transplantation in the National Center for Chronic Disease Prevention and Health Promotion would help coordinate the agency's many efforts related to improving kidney health and increasing transplantation. This focused approach could also lead to new efforts, such as establishing a national registry for people with kidney diseases. The absence of such a real-time database was a major challenge in the CDC's response to the COVID-19 pandemic.

This division would also help the CDC prepare for the next pandemic. During the early months of COVID-19, a sharp increase in acute kidney injury cases occurred, resulting in mortality rates never seen before—often in otherwise healthy people (17). Moreover, a Division of Kidney Health and Transplantation would help the CDC ensure that people receiving dialysis and people with a transplant are prioritized during the first rounds of future vaccines and therapeutics, as was the case during the pandemic for residents of long-term care facilities (18).

Helping to coordinate these efforts by establishing the HHS Office of Kidney Health and Transplantation. Nearly 50 years after declaring war on cancer and providing "Medicare for all" for every US citizen with kidney failure, the federal government focused on Advancing American Kidney Health (19). Through three priorities, this initiative shifted the emphasis from treating kidney failure to promoting kidney health. First, the initiative prioritized preventing kidney failure via better diagnosis, treatment, and incentives for preventive care. Second, the initiative focused on increasing patient choice, which includes encouraging higher value-based care, educating patients about treatment alternatives, and advancing the development of artificial kidneys. And third, the initiative is committed to enhancing access to kidney transplants.

Unfortunately, the oversight, administration, and delivery of care for the more than 37 million Americans with kidney diseases, kidney failure, and kidney transplants are spread across the federal government, particularly at HHS and the Department of Veterans Affairs (VA). The government recognized this problem in 1987 and created the Kidney Interagency Coordinating Committee (KICC) "to encourage communication and collaboration to shape a more coordinated federal response to CKD [chronic kidney disease]" (20).

Despite KICC's efforts, this decentralized approach—especially at HHS—impedes the government's ability to accomplish Advancing American Kidney Health's three priorities. For example, the Centers for Medicare & Medicaid Services (CMS) retired the use of a 1-year outcome metric for transplant centers in 2019, acknowledging that it resulted in "unintended consequences" and impeded patients' access to transplant. The Health Resources and Services Administration (HRSA), however, continues to use a 1-year outcome metric to grade the very same transplant centers. These types of misaligned, duplicative policies detract from the ability of nephrologists and other kidney health professionals to focus on doing what is best for patients.

With an annual budget of $2.4 trillion (21), HHS's massive department influences kidney policy through nearly every component of the agency, including the Immediate Office of the Secretary as well as the following entities (in alphabetical order):

- Administration for Strategic Preparedness and Response
- AHRQ
- Agency for Toxic Substances and Disease Registry
- CDC
- CMS and the Center for Medicare & Medicaid Innovation
- Food and Drug Administration (FDA)
- HRSA
- Indian Health Service
- NIH

The HHS Office of Kidney Health and Transplantation would help ensure that each of these components works synergistically toward the shared goals of improving access and care; advancing research; strengthening education; and increasing awareness, surveillance, and prevention. Besides improving coordination within HHS, the Office of Kidney Health and Transplantation would offer an ideal home for the Kidney Innovation Accelerator (KidneyX), the public-private partnership between ASN and HHS launched in 2018 to "accelerate innovation in the prevention, diagnosis, and treatment of kidney diseases."

KidneyX is building on the success of the Kidney Health Initiative (KHI), a partnership started in 2012 among ASN, the FDA, and approximately 100 member organizations "to catalyze innovation and the development of safe and effective patient-centered therapies for people living with kidney diseases." Through its Patient and Family Partnership Council (PFPC), KHI has also helped ensure that "the patient's voice, experience, and involvement is meaningful and effective" in helping bring new drugs, devices, biologics, and food products to market.

The HHS Office of Kidney Health and Transplantation would amplify the patient voice even further than the KHI PFPC. It would offer people with kidney diseases, kidney failure, and kidney transplants a centralized opportunity to share their experiences to drive access, accelerate innovation, and benefit from scientific advancements.

Eventually, the success of these five BHAGs—particularly the HHS Office of Kidney Health and Transplantation—could lead to a larger national effort like the bipartisan National Nanotechnology Initiative (NNI), which focuses on research, development, commercialization, and awareness as well as expanding the workforce. In addition to HHS, the kidney version of NNI would include other federal government agencies and departments that already fund kidney research, such as VA, the Department of Defense, and the National Science Foundation.

For the record, none of these five BHAGs is originally my idea. They have evolved in discussions with ASN leaders, members, and staff as well as other stakeholders during my 16 years with the society. The time is now to think big, aim high, and galvanize the kidney and transplant communities in the United States to speak boldly with one voice as never before. ■

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Team-Based Care Is Essential for Diabetic Kidney Disease

Continued from cover

Multi-organ effects

Approximately one in three (4) or one in four (5) patients with diabetes has chronic kidney disease (CKD), and too many patients go undiagnosed until their kidney disease has progressed to a late stage when they have fewer treatment options. "It is an extremely common condition and probably more common than most clinicians realize because screening, detection, and awareness have been so low," said Tuttle, who co-authored the KDIGO guidelines and task force recommendations.

The development of kidney diseases in patients with diabetes can also have severe consequences for patients' heart health, said Prakash Deedwania, MD, a cardiologist and professor of medicine at the University of California, San Francisco, in an interview. Most patients with end stage kidney disease die from cardiovascular causes, he noted, in a review of the intersecting renal-cardio and metabolic consequences of diabetes (6). He noted in the interview that by the time patients reach stage 4 of kidney diseases, they already have substantial vascular damage and far fewer treatment options. But treating patients with diabetes for heart disease earlier by using lipid-lowering therapy can halt or reverse diabetic nephropathy (6).

Physicians are important, no doubt about it . . . but we need to recognize that there are other members of the team who have a lot to offer, too.

Deedwania and Tuttle agree that more early screening for kidney diseases in patients with diabetes is essential. The ADA-KDIGO consensus guideline recommends annual screening for CKD in patients with diabetes starting at diagnosis (2). Deedwania noted that physicians obtain information about a patient's glomerular filtration rate from routine testing. They can use that information to identify people during the earliest stages of kidney diseases, educate them about the condition and its consequences, and work with them to prevent progression. "That is the time to intervene," Deedwania said.

But Tuttle acknowledged that successful screening efforts for kidney diseases in patients with diabetes would likely lead to an influx of new patients at a time when the United States is facing a growing shortage of nephrologists and other physicians (7). "We do not have a workforce that is prepared for it," she said. Traditionally, primary care clinicians primarily manage patients with diabetes, but Deedwania said they cannot do it alone.

So far, many newer medications for patients with diabetes and kidney diseases have been under-utilized, said Joshua Neumiller, PharmD, professor of pharmacotherapy at Washington State University in Spokane and a co-author of the ADA-KDIGO consensus report. He noted that patients with diabetes and kidney diseases have many risk factors that need to be managed, including lifestyle optimization. They may be treated simultaneously by diabetes specialists, cardiologists, and nephrologists. They may also need complex medication management. "We have to come together as a team to ensure we're treating the individual in a holistic fashion to manage all of their risk factors the best we can," Neumiller said.

Dream team

Tuttle and Deedwania agree that advanced practice clinicians could play a key role in multidisciplinary teams for patients with diabetes affecting multiple organ systems. Teams might include primary care physicians, cardiologists, diabetologists, endocrinologists, nurse practitioners, pharmacists, nurses, diabetes educators, dieticians, and social workers.

"Physicians are important, no doubt about it, and we have certain training that makes us particularly adept at diagnosis and complex management, but we need to recognize that there are other members of the team who have a lot to offer, too," Tuttle said. "We need to move beyond the paternalism that it always has to be a physician."

Tuttle suggested that a nephrologist could be a team leader and focus on tasks such as complex diagnostic workups or condition management difficulties. Other team members could handle more routine tasks such as follow-up and medication management. Dieticians can help address lifestyle factors, whereas social workers can help patients overcome barriers such as insurance access. "It is going be a huge task, but we view team care as a way forward to deliver high-quality, reliable care to large numbers of patients with a limited nephrology workforce," Tuttle said.

Tuttle also emphasized the importance of patient engagement in team-based care. Patients with diabetic kidney disease have innovative ideas based on their lived experience and know what will work best for them, she said. "They are the ultimate stakeholder," she said.

The ADA-KDIGO consensus report also emphasizes the need for patient-centered, whole-person care. Neumiller noted that engaging patients in shared decision-making about their treatment options improves patient engagement and medication adherence because patients have a "buy-in" in the care plan.

Some preliminary efforts are underway to develop multidisciplinary diabetic kidney disease clinics. Tuttle said one approach might be to emulate the anticoagulation clinic model, which uses advanced practice clinicians and pharmacists to aid anticoagulant medication management for patients with cardiovascular disorders. A recent pilot study showed that a pharmacist-led intervention, including an interactive workbook, improved patients' understanding of their kidney test results, boosted kidney function screening, and enabled the administration of appropriate kidney-protecting medications (8). "The evidence is building, and there's a lot of interest in formally studying these interventions in people with chronic kidney disease," Neumiller said.

Clinical pharmacists can play a crucial role in educating patients about their medications, their side effects, and how to mitigate them. They can help adjust background therapies to minimize hypoglycemia risk and assist with medication titrations for new medicines, Neumiller said. He said they could regularly check in with patients and serve as a hub, communicating any medication changes to all the team clinicians.

Until more formal team models are in place, Neumiller recommended that nephrologists check in with the pharmacists in their organization about what services are available. He noted that his institution has a pharmacotherapy clinic where pharmacists can help patients access expensive medications or those requiring preauthorization, which can be a barrier for time-strapped physicians. He also suggested that the physicians tap into existing services such as diabetes educators at their institution.

Deedwania, Neumiller, and Tuttle acknowledged that substantial barriers to instituting new diabetic kidney disease models remain. The biggest hurdle may be reimbursement, Deedwania said. He noted that current payment models do not reimburse for care by multiple physicians during a single visit. The Centers for Medicare & Medicaid Services has created new payment models for CKD that incentivize team-based care. However, Tuttle said they focus more on the later stages of kidney diseases. New payment models and investment from health care systems are needed, she said.

"We now have the opportunity with the therapies we have to save lives, kidneys, and hearts," Tuttle said. "We have a moral and ethical obligation to do so, and it will take a lot of voices speaking loudly to policymakers and health care systems." ■

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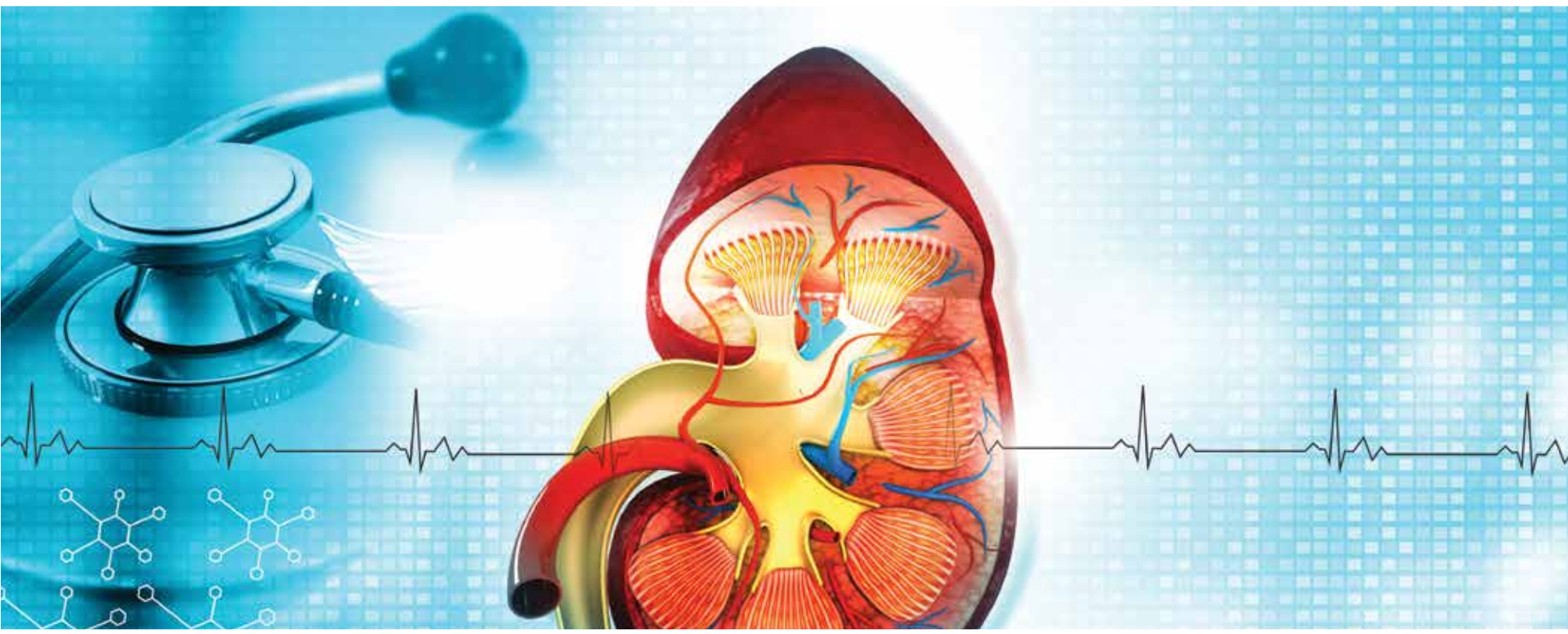

KIDNEY AND CARDIOVASCULAR DISEASES

Exploring Cardiorenal Developments

The heart and the kidney share immense metabolic demands, overlapping stressors, and devastating diseases. Cardiovascular disease remains the predominant cause of death for people with kidney diseases. In turn, the development of chronic kidney disease portends poor outcomes and may limit guideline-directed medical therapies for people with cardiovascular disease.

Thankfully, kidney and cardiovascular diseases are also joined by a growing number of therapeutic options: angiotensin-converting enzyme inhibitors, angiotensin receptor blockers (alone or in combination with neprilysin inhibitors), glucagon-like peptide 1 receptor agonists, mineralocorticoid receptor antagonists, and of course, sodium-glucose cotransporter-2 inhibitors. Nephrologists and cardiologists now welcome our shared patients to the kitchen of many cooks. However, the need for dedicated cardio-nephrologists rises with the growing complexities of advanced heart failure management, cardiothoracic surgery, and other cardiovascular disease treatments.

In this special issue of *Kidney News*, we explore cardiorenal topics for the nephrologist that range from the common (e.g., loop diuretic choice in heart failure) to the critical (e.g., combined kidney-heart transplant and complications of left ventricular assist devices). We also highlight the experience of model cardio-nephrology clinical and training centers across the United States. ■

Kidney News *thanks Daniel Edmonston, MD, MHS, for editing this special issue. Dr. Edmonston is assistant professor of medicine (nephrology), Duke University School of Medicine, and faculty member, Duke Clinical Research Institute, in Durham, NC.*

The author reports no conflicts of interest.

LVADs and the Kidney

By Carl P. Walther and Sankar D. Navaneethan

When the heart is chronically failing to provide adequate circulation despite numerous evidence-based medical and procedural options, left ventricular assist devices (LVADs) can be placed. Implantation of these devices is usually permanent (destination therapy), although some recipients may go on to receive heart transplants (bridge to transplant) (1); rarely is there sufficient heart recovery to enable LVAD removal (bridge to recovery) (2).

Although kidney health and function are important and affected across the spectrum of heart disease and cardiovascular procedures, perhaps nowhere is the kidney more challenged than in LVAD recipients. First, consider the kidney substrate: Kidney damage may accrue at each stage of the life course leading to advanced heart failure and LVAD implantation. Diabetes and atherosclerosis injure both the heart and the kidney; the aging process causes fibrosis in both organs; acute kidney injury (AKI) episodes accumulate from prior cardiovascular procedures and surgeries; and chronic heart failure, punctuated with acute decompensations, causes congestive nephropathy and later, with failure of forward flow, ischemia.

From this environment, the kidney enters the perioperative period. LVADs are placed once all less-invasive measures have been exhausted; prior to implantation, many patients require one or more inotropes or even temporary mechanical circulatory support with a balloon pump, a percutaneous microaxial pump, or veno-arterial extracorporeal membrane oxygenation. From this state of chronic and acute stress and damage, the kidney is then put through the prototypical insult of major cardiac surgery. Ischemia-reperfusion injury, inflammatory cascade activation and oxidative stress, hemolysis, and nephrotoxic exposures may all be at play (Table 1). Once the LVAD is in place, macrocirculation usually normalizes, with cardiac output returning to normal and elevated central venous pressures declining (except when the feared complication of right ventricular failure develops). This usually increases estimated kidney function (at least for a time and with the caveat that kidney function estimates are likely to be highly confounded in these patients), and in some people, this results in persistent normalization of estimated kidney function (in the majority, there is no evidence of persistent kidney function improvement) (3). Potential mechanisms for beneficial and harmful effects on the kidney with LVAD support are shown in Figure 1.

Nephrology expertise is essential for accurate etiologic and prognostic deconstruction of AKI syndrome. This may require integration of relevant information ranging from distant kidney events to operating room details and potentially gathering information with tools from manual urine microscopy to interpretation of tissue inhibitor of metalloproteinases-2 (TIMP-2) ·

Continued on page 12 >

LVADs and the Kidney

Continued from page 11

insulin-like growth factor-binding protein 7 (IGFBP7) scores to image-based venous congestion assessments. Kidney replacement therapy (KRT) decisions (need, timing, and therapy parameters) are the most conspicuous nephrology service, and these decisions necessarily use subjective judgment on the part of the nephrologist and close collaboration with intensivists. KRT management throughout the recovery course is a challenge requiring close collaboration as well, particularly when the patient no longer has invasive hemodynamic monitors. Fluid removal in this case requires consideration of the pump speed, flow rate, and pulsatility index, along with appropriate hemodynamic measurements based on whether the aortic valve opens (in which case usual oscillometric or auscultatory measurements can be used) or does not (requiring measurement using Doppler ultrasound and a manual sphygmomanometer) (4).

The era of precision nephrology holds great promise for individualized diagnoses and targeted therapies in many areas. The realm of durable mechanical circulatory support will be a particular challenge, given the extreme clinical complexity of kidney insults and the limited access to kidney tissue for study because of the tenuousness (and anti-coagulation) of the patients. Despite these challenges, noninvasive diagnostic and investigative tools—primarily being developed in other realms—should enable improvements in kidney diagnostic and prognostic precision and even provide mechanistic insights soon. Precise pathophysiologic diagnostics, plus effective targeted therapies for cardiac surgery-associated AKI, are urgently needed to improve the health of LVAD recipients. ■

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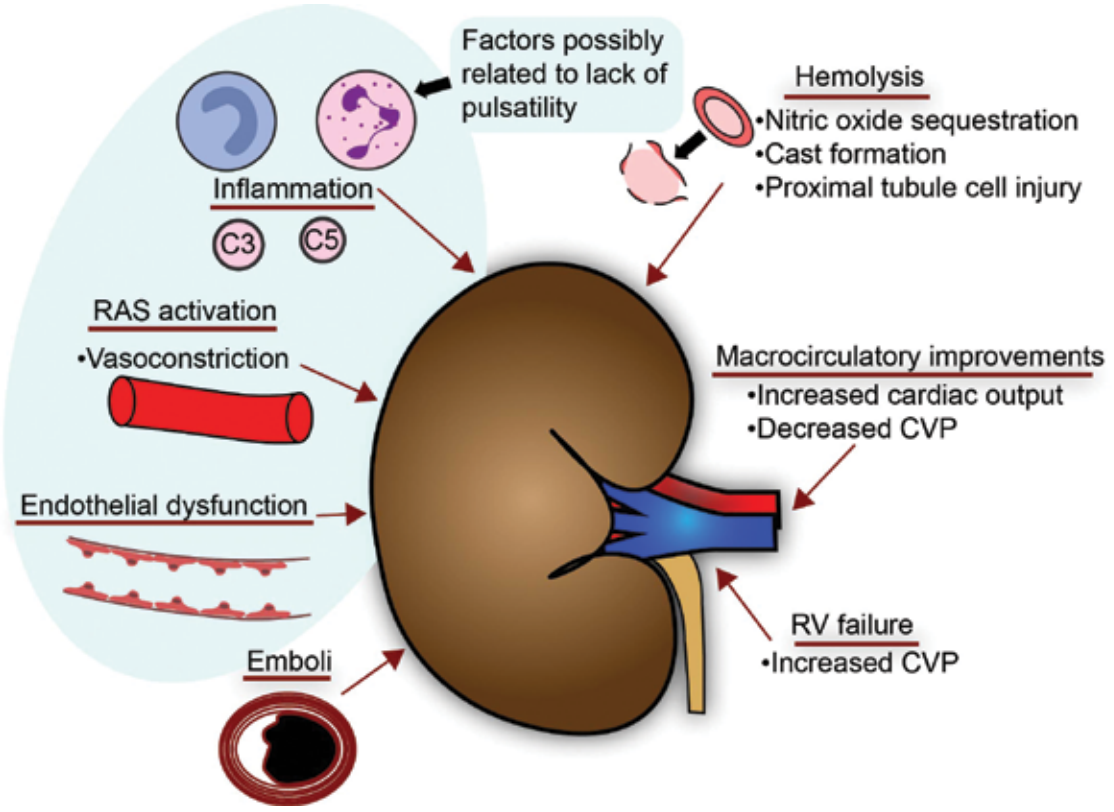
The authors report no conflicts of interest.

Figure 1. Potential mechanisms for LVAD effects (beneficial and harmful) on the kidneys



CVP, central venous pressure; RAS, renin-angiotensin system; RV, right ventricle. The figure is reprinted from Walther et al. (4).

Table 1. Categories and mechanisms of potential AKI with LVAD implantation

Category of injury	Causes
Ischemia and ischemia-reperfusion injury	CPB initiation and discontinuation, microcirculatory dysfunction, temperature changes, intraoperative bleeding, aortic cross clamping for additional procedures
Inflammation	CPB, surgical tissue injury
Hemolysis	CPB, LVAD pump
Microemboli	Cholesterol emboli, thromboemboli, gaseous emboli with CPB
Nephrotoxic exposures	Antibiotics

CPB, cardiopulmonary bypass.

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Natriuretic Response Prediction Equation
Worth Its Weight in Salt?

By Nayan Arora

Law number 7 in the classic novel, *The House of God*, is age + blood urea nitrogen (BUN) equals Lasix dose (1). Limited data to guide diuretic therapy, the mainstay of treatment for patients admitted with decompensated heart failure, have given rise to similar urban legends uttered throughout hospital wards. Providers have traditionally relied on changes in weight and measurement of fluid intake and output for therapeutic decision-making. However, these variables can be notoriously difficult to obtain with accuracy and can result in therapeutic inertia, as data are collected within a 24-hour period. Furthermore, weight changes and fluid balance have shown considerable discrepancy and are not associated with 6-month survival (2, 3). Consequently, residual congestion is common and associated with adverse outcomes (4).

Whereas the aforementioned parameters are markers of total fluid balance, the variable of interest is natriuresis. Net negative sodium balance correlates with improved survival regardless of documented fluid balance. Negative sodium balance, even in patients with documented positive fluid balance, was associated with improved 6-month survival, whereas positive sodium balance was associated with worse survival, even among patients with negative fluid balance (3). Numerous studies have demonstrated the benefit of monitoring spot urine sodium values to gauge natriuretic response and allow rapid escalation of loop diuretics to achieve the desired therapeutic effect (5–10); however, measuring net sodium output remains challenging, as 24-hour urine collections on every hospitalized patient are neither feasible nor practical.

In the *Journal of the American College of Cardiology*, Rao et al. (11) proposed a natriuretic response prediction equation (NRPE), which utilizes a spot urine sodium 2 hours post-loop diuretic administration, along with glomerular filtration rate and serum/urine creatinine values to predict cumulative 6-hour natriuresis. This group previously demonstrated the ability of the NRPE to accurately predict cumulative sodium output with an area under the curve (AUC) of >0.9 compared with 6-hour urine collections (12). In this single-center study, the authors attempted to validate these findings in two cohorts: one to assess natriuretic response, categorized as poor, suboptimal, and excellent, defined as sodium output of <50 mmol, <100 mmol, and >150 mmol, respectively, and in the second, to utilize a nurse-driven protocol to guide loop diuretic titration using the NRPE among adult patients admitted with acute decompensated heart failure (ADHF). In 409 patients in the validation cohort, the authors again demonstrated excellent ability of the NRPE to predict a 6-hour natriuretic response with an AUC of 0.92 (95% confidence interval [CI], 0.89–0.95), 0.9 (95% CI, 0.87–0.93), and 0.9 (95% CI, 0.87–0.93) for a poor, suboptimal, and excellent response, respectively. The NRPE outperformed markers such as spot urine sodium concentration and net fluid output. Among 161 patients using the NRPE to guide diuretic therapy, significant improvement in net fluid output (–1.1 ± 0.9 L vs. –2.1 ± 0.9 L) and weight loss (–0.3 ± 0.3 kg vs –2.5 ± 0.3 kg) was seen after initiation.

An important limitation to the study is lack of information regarding validity in patients treated with continuous infusions of loop diuretics, as well as adjunctive agents, such as thiazide diuretics and acetazolamide, interventions that are common in hospitalized patients. Additionally, the protocol prioritizes maximizing loop diuretic therapy before consideration of adjunctive agents for sequential nephron blockade, although it is currently unknown if one strategy is superior to the other. Nonetheless, this study provides a potential new tool to guide diuretic therapy among patients with ADHF. However, it would be prudent to demonstrate improvement in hard outcomes, such as rehospitalization, before widespread implementation. ■

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The author reports no conflicts of interest.

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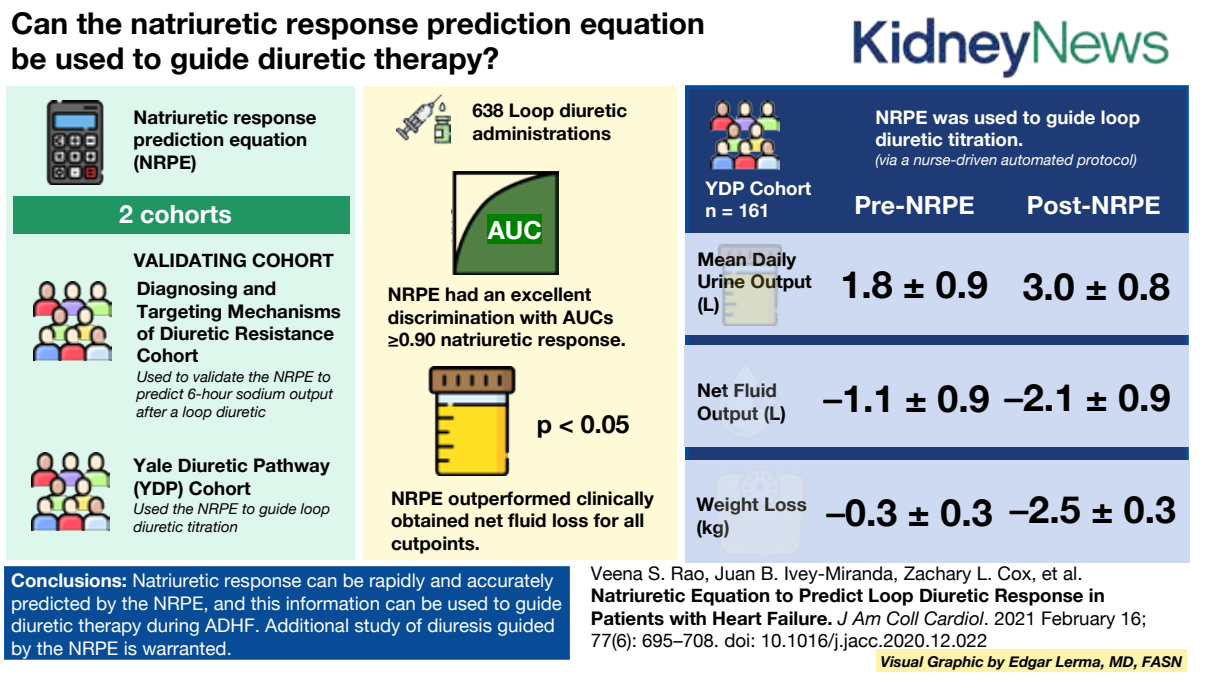
[T]his study provides a potential new tool to guide diuretic therapy among patients with ADHF.



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Cardio-nephrology Services around the United States: Experience of Three Centers of Excellence

The population of patients with or at risk for concomitant kidney and heart disease is large, continues to grow, and has poor clinical outcomes. The interaction of kidney and heart disease leads to unique pathophysiology, disease manifestations, and treatment, necessitating specialized care that may not be addressed adequately by either cardiology or nephrology alone. The creation of a cardiorenal service at several centers has led to providing excellent clinical service, advanced fellowship education, and grounds for research (Table 1). In this article, we invited leaders from a few of the US centers' cardiorenal (or nephrocardiology) services to take us through their journey into the creation and advancement of this process.

The Columbia University Irving Medical Center Nephrocardiology Experience

Jacob Stevens, MD, is an assistant professor of medicine; director, Acute Care Nephrology; and associate program director, Internal Medicine Residency, Columbia University Irving Medical Center, New York, NY.

Dr. Stevens reports being a consultant with Health Advances (for hyperoxaluria; 2021), receiving honoraria from the National Institutes of Health/ASN Kidney Innovation Accelerator (KidneyX) COVID-19 Innovation Prize (for Kidney Replacement Therapy Dashboards; 2021), and having a patent on an aptamer-based creatinine sensor that is owned and licensed by Columbia University (ongoing).

The Columbia University Irving Medical Center is a 738-adult inpatient bed tertiary care hospital in the Washington Heights neighborhood of New York City (1). One floor of the hospital is geographically dedicated to cardiology and cardiothoracic surgical patients, representing nearly 22% of all hospital beds (102 cardiology beds and 59 cardiac intensive care unit [ICU] beds in total of which 28 are cardiology care unit beds and 31 are cardiothoracic surgical ICU beds). There are four dedicated cardiothoracic surgical operating rooms and >1000 cardiothoracic surgeries, requiring cardiopulmonary bypass, performed annually.

The high burden of cardiovascular disease in patients with chronic kidney disease and end stage kidney disease (ESKD) and the high incidence of peri-procedural acute kidney injury (AKI) result in a high volume of patients who are admitted to our cardiac services requiring nephrology consultation. Given our high total nephrology consult census (typically 100–130 patients total for all services) and a high percentage of consults coming from the cardiac floor, a dedicated nephrocardiology consult team was formed in 2007–2008 (in addition to our ESKD, general floor, ICU, and transplant consult teams). In a typical calendar year, this consult team receives 450–500 consults, and our daily service census typically ranges between 15 and 20 patients (approximately 10%–15% of the cardiac floor), with the majority coming from the four ICUs on this floor.

There are several benefits to having a dedicated nephrocardiology consult service (Table 1). First, we provide continuity for both patients and teams by having a dedicated geographical team, and often, we are the only providers in the hospital who have followed a patient from their pre-procedure course in the cardiac care unit, post-operatively in the cardiothoracic ICU (CTICU), and then later as they are transferred out of the ICU to the cardiac floor. This team facilitates peri-operative renal replacement therapy planning (2, 3). Additionally, with a dedicated subgroup—approximately 12 of our 31 nephrology attendings staffing this service—we develop an expertise for the unique challenges of these cardiac patients (e.g., advanced heart failure requiring mechanical support, diuretic refractory cardiorenal syndrome, performing intermittent hemodialysis on patients with a left ventricular assist device without a pulse pressure, or performing continuous renal replacement therapy while on extracorporeal membrane oxygenation). Additionally, given the smaller subset of our attendings who rotate on this service, we develop relationships with the cardiac primary teams that foster collaboration and build trust that extends beyond the patient floors. This results in clinical research collaborations (4–7) and the formation of the multidisciplinary Hypertension Center. Finally, having a dedicated high-volume nephrocardiology consult service provides a unique learning opportunity for our seven general nephrology fellows, two transplant fellows, and one glomerular fellow. They quickly learn the fundamental principles involved in caring for patients with heart disease who are critically ill (from the nuances of volume status exams to diuretic refractory cardiorenal syndrome, severe peri-operative AKI, and refractory hyponatremia).

The Northwell Health Cardiorenal Service Experience

Nupur N. Uppal, MD, is an associate professor of medicine and director of Cardiorenal Services, North Shore University Hospital at Northwell Health, Manhasset, and the Donald and Barbara Zucker School of Medicine at Hofstra/Northwell, Hempstead, NY.

Dr. Uppal reports no conflicts of interest.

North Shore University Hospital at Northwell Health in Manhasset, NY, is a 786-adult inpatient bed quaternary care primary teaching hospital for the Zucker School of Medicine at Hofstra/Northwell training medical students, residents, nephrology and cardiology fellows, including interventional cardiology, advanced heart failure, and transplant cardiology fellows. It offers all medical and surgical specialties, with recent advancement in heart and lung transplantation. Here, we established the cardiorenal service in 2014 as a distinct inpatient clinical service that comprises a group of seven nephrologists from our faculty who work in close association with cardiologists, cardiothoracic surgeons, and cardiac intensivists.

The inpatient cardiorenal service at North Shore University Hospital is run by the nephrology attending and a fellow in training. It serves to take consultations from regular medical floors, telemetry units, and cardiac and CTICUs. There is a dedicated phone number that is transferred to the attending rotating on the service for weekdays, weeknights, and weekends, which ensures the ease in reaching out to the attending directly and warrants 24/7 availability of the service. The consultants carry a portable point-of-care ultrasound (POCUS) device that aids as a bedside tool for volume assessment during rounds.

Over the past 8 years, the service has expanded tremendously. During the initial years of the service, the majority of consultations were for optimization of kidney function in patients undergoing percutaneous coronary interventions and management of patients with acute cardiorenal syndrome, including diuretic augmentation and use of renal replacement therapies for volume management. In recent years, our center's cardiology and cardiac surgery programs have expanded, leading to growth in the census of the service as well as additional consultations to manage AKI after procedures, including transcatheter aortic valve replacement, open heart valvular surgeries, VADs, and mechanical circulatory assist devices. Lately, the service also manages kidney issues and electrolyte abnormalities that develop in the peri-operative period for patients receiving heart transplantation, lung transplantation, as well as multiple organ transplantation, such as simultaneous heart, lung, and kidney transplantation. Kidney transplant recipients are followed by the kidney transplant team after the transplantation.

The creation of inpatient service eventually led to development of an outpatient cardiorenal specialist service that consists of eight nephrologists who specifically manage patients with coexisting heart and kidney diseases. These nephrologists receive direct consultations, and the secretarial staff at the office has a list of the dedicated attendings to whom they assign cardiorenal patients for evaluation and management. The office also has a dedicated exam room with a POCUS machine.

The cardiorenal service has been advantageous for patients, consultant specialists, as well as nephrology and cardiology trainees (8). The co-management of patients by a specific group of nephrologists and cardiologists builds a strong relationship among patients and physicians, ensuring regular follow-ups and better patient care. When hospitalized, the patients are under the care of the same group of physicians who communicate well with each other. This prevents polypharmacy and incorrect medication dosing and promotes shared medical decision-making, leading to better patient health.

This service has established an association and trust among the nephrology and cardiol-

ogy specialists that foster an ease to consult each other and advocate persistent communication between each other. It has led to collaboration among nephrologists, cardiologists, medical specialists, and renal pathologists and has enhanced the educational experience for trainees. The fellows, along with the attendings, participate in multidisciplinary team discussions and integrated journal clubs and grand rounds (usually held every 3–4 months by faculty and fellows of either advanced heart failure or nephrology), which keep them up to date with advances in cardiorenal medicine and promote unceasing learning. The service creates opportunities for future research and organization of conferences, further culminating in combined publications. Several nephrologists from the group have gained recognition at national societies, are national experts in the field of POCUS, and have presented at national cardiology conferences. The nephrologists have attained an expertise in management of kidney manifestations that arise after various cardiac procedures. This has led to an increase in interest among trainees to pursue their careers in this growing field of cardiorenal medicine.

The University of Washington Kidney-Heart Service Experience

Nisha Bansal, MD, MAS, is a professor, Division of Nephrology, Department of Medicine; an Arthur Stach Family Endowed Professor; director, Nephrology Clinical and Research Education; and director, Kidney Heart Service, University of Washington, Seattle, WA.

***Dr. Bansal reports being an associate editor for* Kidney360.**

The University of Washington (UW) launched the Kidney-Heart Service in August 2020 (9). The UW Medical Center (UWMC) is a large, 630-bed academic medical center in Seattle, WA, that serves as a catchment area for people in a five-state region (Washington, Wyoming, Alaska, Montana, and Idaho) and is the primary site for the most complex and intensive cardiology care, including heart transplantation, cardiac device implantation, and cardiothoracic surgery. The UW Kidney-Heart Service functions as a specialized, inpatient consultation service and is staffed by three nephrologists who have a specialized clinical and scientific expertise in cardiorenal disease. In designing this new service, our mission was to excel in clinical care, education, and scholarship (Table 1).

The service has focused on nephrology consultation to patients admitted to cardiology or cardiothoracic services on the floors or the ICUs. The average daily census varies between 10 and 20 patients. Since our inception, we have launched several key clinical initiatives. We have developed effective and streamlined communication strategies between the UW Kidney-Heart Service and Cardiology/Cardiothoracic Surgery Inpatient Services. All attendings on the UW Kidney-Heart Service have trained in POCUS and have incorporated this practice into routine clinical decision-making. In collaboration with our cardiology colleagues, we also have revised, updated, and promoted wider use of their evidence-based diuretic algorithm, which was developed to improve diuretic efficacy, reduce rates of diuretic resistance, decrease the risk of AKI and need for dialysis, and reduce length of stay. This updated algorithm focuses on a "sequential nephron blockade" and use of objective measures to guide diuresis.

Although early, the initial results of these clinical initiatives are promising. Prior to the launch of the Kidney-Heart Service, patients admitted to UWMC with heart failure who developed AKI had three times longer lengths of stay, a three to four higher rate of in-hospital death, and significantly higher rates of readmission within 30 days as compared with patients with heart failure without AKI (9). Since the launch of the UW Kidney-Heart Service, we have observed a 3-day reduction in average length of stay in patients with heart failure and AKI as well as a modest decline in rates of inpatient acute dialysis following launch of the UW Kidney-Heart Service (9).

To fulfill our educational mission, we developed a specialized curriculum that includes core topics such as: volume and hemodynamic assessment, physiology of diuretic resistance, diuretic pharmacokinetics and management, cardiorenal physiology, kidney diseases in patients with durable and non-durable mechanical circulatory support, electrolyte disorders, and acid-base disorders. Nephrology fellows, cardiology fellows, internal medicine residents, and advanced practice provider students rotate on the service, allowing for cross-disciplinary training.We have made several strides to advance quality improvement and research in cardiorenal diseases. We continue to collect longitudinal electronic medical record data on patients seen by the Kidney-Heart Service, which forms the basis for several ongoing quality improvement projects. Patients seen by the service are recruited directly into several research studies. For example, we have received funding for a National Institutes of Health (NIH) R01 grant, "Kidney Injury in Patients with Acute Decompensated Heart Failure," as well as an NIH administrative supplement to study bioethical issues in patients admitted with acute decompensated heart failure and AKI (9).

In summary, the UW Kidney-Heart Service is an innovative model to advance clinical care, education, and scholarship in cardiorenal disease.

Table 1. Advantages of a cardio-nephrology service

Advantages of a dedicated cardio-nephrology service	Examples
Clinical expertise	• Volume assessment including POCUS • Peri-operative risk stratification and management for cardiac procedures and surgeries • Diuretic resistance, including sequential nephron blockage and novel therapies • Management of kidney diseases in relation to advanced heart failure therapies, including ventricular assist devices • AKI and dialysis management in cardiogenic shock • Electrolyte disorders in patients with cardiorenal disease • Goal-directed medical therapy (including SGLT2i and MRAs) in patients with cardiorenal disease • Pre-peri and post-heart transplant management
Education	• Focused learning on high-yield topics in cardiorenal disease from experts • Opportunities for cardiology and nephrology fellows to work together directly
Scholarship	• Recruitment of patients directly into studies, including clinical trials • Opportunities for quality improvement
Other	• Promotes collaboration • Enhances nephrology-cardiology communication • Continuity of care (including inpatient-outpatient)

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Heart and Kidney: When Do We Perform Combined Transplants?

By Xingxing S. Cheng

Historically, candidacy for simultaneous heart-kidney (SHK) transplantation, or transplantation of both the heart and kidney from the same deceased donor into the same candidate, has only been considered for patients who have end-stage heart failure as the primary disease process. In this setting, kidney diseases, which may or may not be a result of heart failure, are frequently milder than that which would prompt consideration for kidney transplantation in a non-heart transplant candidate. This has been the approach undertaken by the newly considered eligibility criteria for SHK under deliberation at the Organ Procurement & Transplantation Network (OPTN) (1). These eligibility criteria have largely followed the same framework as established for simultaneous liver-kidney transplantation in 2017 on the grounds of transparency and consistency (2). In specific terms, sustained acute kidney injury lasting 6 weeks or longer or chronic kidney disease (defined as estimated glomerular filtration rate [eGFR] ≤60 mL/min for 6 months and eGFR ≤30 mL/min at the time of listing) is sufficient to qualify the heart transplant candidate for SHK transplantation. Additional priority is granted for heart transplant recipients who develop kidney failure and meet usual kidney transplant eligibility within 1 year after heart transplant (the "safety net" provision).

Eligibility is only half of the equation. We have recently pointed out how the current *allocation*, or how patients who meet eligibility criteria for an organ or organ combination are *prioritized* for said organ or organ combination, is systemically biased against candidates for kidney transplant alone who suffer real harm from the delay in transplant (3, 4). SHK further decreases access to kidneys in that it preferentially draws high-quality kidneys (5) but yields poorer kidney graft outcomes, owing to the disease acuity of SHK candidates (6). Currently, allocation priority for SHK is determined by the patient's severity of heart disease: Any time the patient is offered a heart, the kidney will be offered, regardless of the severity of the kidney disease, the urgency of the next-sequence kidney transplant candidate (who may be highly sensitized, a child, a prior kidney transplant donor, or a dialysis patient running out of access), or the likelihood that the kidney even survives the SHK transplant. Wait time or urgency for kidney transplant does not factor into allocation priority for SHK at all. A candidate on dialysis for many years and running out of access, who has stable heart disease that puts him or her into a lower allocation tier for the heart, will not be granted additional priority. The current allocation system is ethically unjustifiable and disadvantages all patients with kidney diseases, except the minority who happen to have high-acuity failure of non-kidney organs (6).

The establishment of eligibility criteria for SHK at the OPTN level is, therefore, only a start to the conversation. As OPTN works out how to incorporate combined organ transplants into the allocation system, we need sustained efforts from the nephrology and kidney diseases community to engage with the OPTN to advocate for the needs of all patients with kidney diseases who may benefit from a kidney transplant. ■

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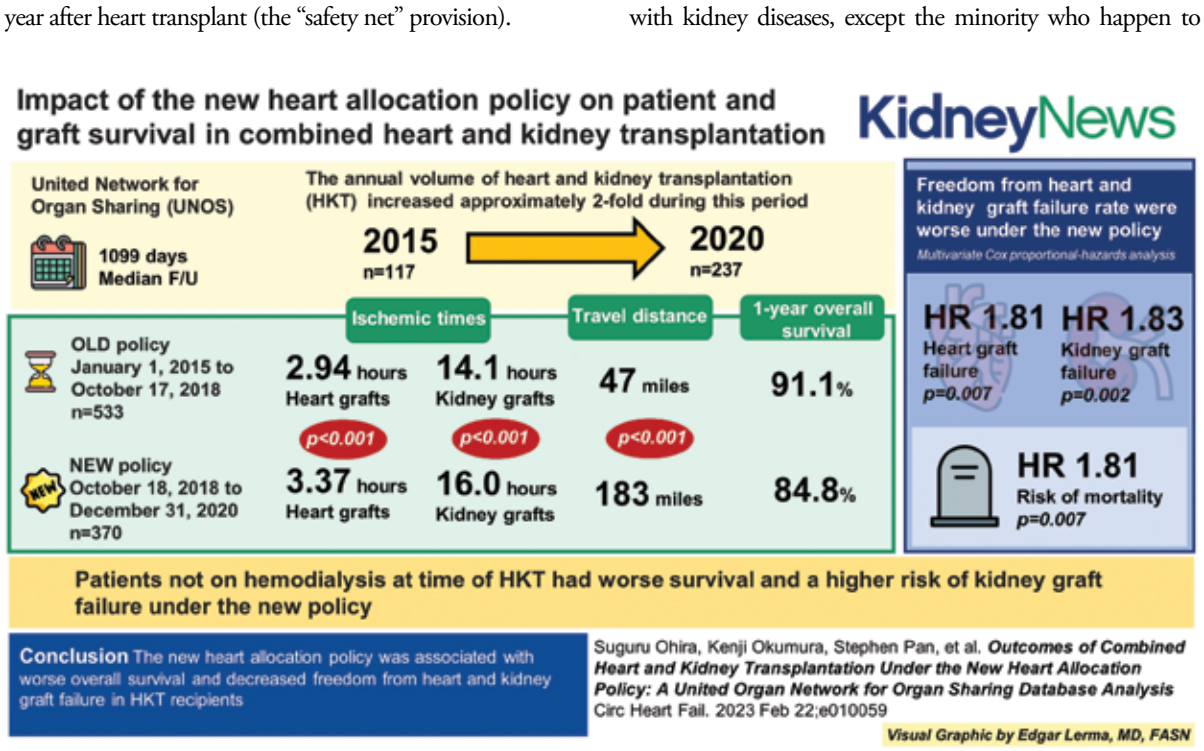

Torsemide versus Furosemide: No Difference after All?

By Klodia Hermez and James E. Novak

Although various loop diuretics have long been considered equivalent for treating congestive heart failure (CHF), recent, small studies have suggested that torsemide may be superior to furosemide for decreasing mortality and hospitalization rates, possibly by reducing renin-angiotensin-aldosterone system activation and myocardial fibrosis (1). The Torsemide Comparison with Furosemide for Management of Heart Failure (TRANSFORM-HF) trial was a multi-center, open-label, pragmatic trial in which 2859 patients hospitalized for CHF were randomized to either torsemide or furosemide and were followed for up to 1 year after discharge (2). Based on previous data, the authors powered the trial to detect a 20% reduction in mortality with torsemide.

Eligible patients were those hospitalized with worsening chronic CHF or a new diagnosis of CHF, plus ejection fraction ≤40% or elevated natriuretic peptide levels. Patients were discharged with either torsemide or a bioequivalent dose of furosemide (a ratio of 1 mg torsemide to 2–4 mg furosemide). Those with end stage kidney disease were excluded from the study. Furthermore, the approximately 35% of patients with chronic kidney disease (CKD) included mostly mild CKD, with a mean estimated glomerular filtration rate of 59 mL/min/1.73 m^2. More than 90% of patients were adherent to diuretics at 6 months, but patients in the torsemide group had been prescribed a higher dose than those in the furosemide group after only 1 month. The primary end point of all-cause mortality was roughly identical at 26% in both torsemide and furosemide groups. All-cause hospitalization rates were similar. On the heels of recent advances in CHF management, it is no surprise that a hint of torsemide's preferential benefit sparked intense interest. The rise of the sodium-glucose cotransporter-2 inhibitors (SGLT2is), for example, is largely due to their proven value in reducing cardiovascular mortality, CHF hospitalization, and CKD progression (3, 4). In the TRANSFORM-HF study, curiously, only 6% of patients were prescribed SGLT2i, 19% sacubitril-valsartan, 35% mineralocorticoid receptor blockers, and 40% angiotensin-converting enzyme inhibitors. The aggregate enrollment of patients with both a reduced and preserved ejection fraction possibly accounts for this low utilization rate of evidence-based medical therapy.

So, how does TRANSFORM-HF impact the practice of nephrology? As cardiorenal syndrome is a major cause of acute kidney injury in hospitalized patients, both cardiologists and nephrologists target effective decongestion, which is associated with improved post-discharge outcomes. The current standard of care for patients hospitalized with acute, decompensated CHF includes conversion of oral to intravenous loop diuretics with a stepwise increase in dose, administered as either bolus or continuous infusion (5, 6). Diuretic resistance should be addressed by increasing the loop diuretic dose or adding a thiazide-type diuretic. Although TRANSFORM-HF did not show significant differences in mortality or rehospitalization for patients with CHF who were prescribed torsemide versus furosemide, further investigation into the potential differences among specific drugs within diuretic classes may yet uncover unexpected benefits and is worth examining. ■

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Prevention of Cardiac Surgery-Associated Acute Kidney Injury

Commentary on the 2023 STS/SCA/AmSECT Guidelines

By Pey-Jen Yu, Karl Bocchieri, and Hugh Cassiere

Acute kidney injury (AKI) occurs in 5%–42% of patients undergoing cardiac surgery, making it one of the most common peri-operative complications in this patient population (1). Even subtle declines in postoperative kidney function confer an increased risk of postoperative mortality and persistent kidney injury (2, 3).

The Society of Thoracic Surgeons (STS), Society of Cardiovascular Anesthesiologists (SCA), and American Society of Extracorporeal Technology (AmSECT) recently published their consensus Clinical Practice Guidelines for the Prevention of Adult Cardiac Surgery-Associated Acute Kidney Injury (4). This is a pragmatic guideline with seven recommendations (Table 1).

The new cardiac surgery-associated (CSA)-AKI guidelines reinforce standard cardiac surgical practices for most institutions. For example, avoidance of hyperthermic perfusion (>37°C) remains a class I recommendation to prevent cerebral hyperthermia. Elements of the Kidney Disease: Improving Global Outcomes (KDIGO) bundle, such as peri-operative discontinuation of angiotensin-converting enzyme inhibitors and angiotensin-receptor blockers, avoiding hyperglycemia, and close hemodynamic monitoring, are already part of existing guidelines to avoid hypotension and infection and to optimize systemic perfusion. The use of minimally invasive extracorporeal circulation is currently a class IIA recommendation to reduce blood loss and transfusion.

Select recommendations continue to evolve and expand on prior recommendations. Notably, the new CSA-AKI guidelines officially recommend against using dopamine and mannitol for adult cardiac surgery patients. Furthermore, although prior guidelines have recommended adjusting the pump flow rate during cardiopulmonary bypass (CPB) based on oxygenation and metabolic parameters, the new CSA-AKI guidelines specify the use of goal-directed perfusion targeting oxygen delivery (DO_2) ≥270 mL/min/m^2 as a class I recommendation.

The one element in the new CSA-AKI guidelines that may deviate from current practices is its recommendation that fenoldopam may be used to reduce the risk of CSA-AKI as long as hypotension can be avoided (class IIB). The literature supporting this recommendation is conflicting. A prospective randomized clinical trial looking at attenuating immediate postoperative AKI showed no benefit and significantly more hypotension (5). It is also acknowledged by the authors of the new guidelines that KDIGO does not support using fenoldopam to prevent or treat AKI. Therefore, we would hesitate to adopt the use of fenoldopam to reduce the risk of CSA-AKI without more substantive evidence to support its use in this patient population.

The new CSA-AKI guidelines affirm existing clinical practices for the care of adult cardiac surgery patients. They also highlight the need for continued research for novel ways to reduce the incidence of CSA-AKI, as it remains a significant source of morbidity and mortality in patients undergoing cardiac surgery. ■

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The authors report no conflicts of interest.

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Table 1. Summary of recommendations from the 2023 STS/SCA/AmSECT Clinical Practice Guidelines for the Prevention of Adult Cardiac Surgery-Associated Acute Kidney Injury

Recommendation	Class of recommendation, level of evidence
Avoid hyperthermic perfusion (>37°C).	Class I, level B-R
Use goal-directed oxygen-delivery strategy on CPB (avoid nadir DO_2 <270 mL/min/m^2).	Class I, level B-R
Adopt KDIGO practice guidelines for patients at high risk of AKI.	Class IIA, level B-R
Fenoldopam infusion during CPB and perioperatively may be reasonable if hypotension is avoided.	Class IIB, level B-R
Consider use of minimally invasive extracorporeal circulation.	Class IIB, level B-R
Use of dopamine infusion is not recommended.	Class III, level A
Use of mannitol to prime CPB is not recommended.	Class III, level B-R

Most US Adults with T2D Meet Criteria for GLP-1 RAs or SGLT2is, but Few Receive Them

More than 80% of American adults with type 2 diabetes (T2D) meet criteria for treatment with glucagon-like peptide-1 receptor agonists (GLP-1 RAs) or sodium-glucose cotransporter-2 inhibitors (SGLT2is), but few actually receive these medications, according to a research letter in the *Annals of Internal Medicine*.

The researchers analyzed data on 1330 adults with T2D from the National Health and Nutrition Examination Survey 2017–2020. Of these adults, 82.3% of patients met recommended criteria for GLP-1 RA or SGLT2i treatment. Criteria were met by all patients with established or high risk for atherosclerotic cardiovascular disease (ASCVD), heart failure, or chronic kidney disease (CKD). Ninety-seven percent of patients aged 65 years or older met treatment criteria, as did 70% of younger patients. Treatment criteria were met by 94.5% of Medicare patients.

Only 9.1% of patients were receiving either of these medications between 2017 and 2020, a time when they were not recommended for first-line treatment in many patients who would now be considered eligible. Treatment rates were 5.3% for SGLT2is and 3.7% for GLP-1 RAs.

Based on level A evidence, a 2022 consensus report by the American Diabetes Association and the European Association for the Study of Diabetes recommended GLP-1 RA treatment for patients with T2D with established or high risk for ASCVD. The report also recommended SGLT2is for patients with established ASCVD, CKD, or heart failure or high risk for ASCVD.

This study suggests that most US adults with T2D would meet those treatment criteria, including nearly all Medicare beneficiaries. During the period studied, only approximately 9% of eligible patients were receiving GLP-1 RAs or SGLT2is.

"However, at current drug pricing, using these two new medications as first-line agents among all eligible patients with T2D may not be cost-effective," the researchers conclude. "[A]n assessment of cost-effectiveness may assist better targeting of interventions to achieve the greatest effect at a sustainable cost" [Tang S, et al. Recommended and prevalent use of glucagon-like peptide-1 receptor agonists and sodium-glucose cotransporter-2 inhibitors in a national population-based sample. *Ann Intern Med*, published online ahead of print February 28, 2023. doi: 10.7326/M22-3051; https://www.acpjournals.org/doi/10.7326/M22-3051].

"No Opioids" for Major Urologic Cancer Surgery?

A "no-opioid" strategy greatly reduces the percentage of patients receiving opioid prescriptions after surgery for renal, bladder, or prostate cancer, reports a study in *JAMA Surgery*.

The cohort study included 647 opioid-naive patients undergoing open or minimally invasive radical cystectomy, radical or partial nephrectomy, or radical prostatectomy at the authors' referral center between 2017 and 2021. In a pre-intervention period (2017–2018), 202 patients were treated, 100 during an initial feasibility study or lead-in period (2019), and 384 during the intervention period (2020–2021). The no-opioid intervention consisted of a pre-admission educational handout and post-discharge instructions for using non-opioid analgesics, without a routine opioid prescription. Acetaminophen and ibuprofen were the main non-opioid analgesics used.

The rate of opioid prescriptions at discharge decreased from 80.9% in the pre-intervention period to 57.9% during the lead-in period and to 2.2% in the intervention period. Median tablets prescribed were 14, 4, and 0, respectively. For procedures performed during the intervention period, mean and median opioid dose was 0 tablets for prostate and bladder surgery. The mean number of tablets prescribed was 0.6 for open surgery and 0.3 for robotic kidney surgery.

The intervention did not increase calls or unplanned clinic or emergency department visits due to pain. Patient surveys from the no-opioid period showed low pain scores (mean 2.5) and high satisfaction scores. Of 10 patients in the intervention group who received additional opioid prescriptions, 8 had undergone kidney surgery.

The no-opioid intervention—focused on pre-operative instruction and non-opioid alternatives—greatly reduced the use of opioid medications after major abdominopelvic surgery. The experience suggests that routine discharge opioid prescriptions can be eliminated with good pain control, low complication rates, and high patient satisfaction [Mian BM, et al. Implementation and assessment of no opioid prescription strategy at discharge after major urologic cancer surgery. *JAMA Surg*, published online ahead of print February 8, 2023. doi: 10.1001/jamasurg.2022.7652; https://jamanetwork.com/journals/jamasurgery/fullarticle/2801213].

No Reduction in Recurrent Kidney Stones with Hydrochlorothiazide

In patients with recurring kidney stones, hydrochlorothiazide does not reduce the incidence of further recurrences compared with placebo, reports a clinical trial in *The New England Journal of Medicine*.

The trial enrolled 416 adult patients with recurrent kidney stones with at least two episodes over the past 10 years and any previous stone containing at least 50% calcium oxalate and/or calcium phosphate. Patients were randomly assigned to receive once-daily hydrochlorothiazide at a dose of 12.5, 25, or 50 mg or placebo. A primary composite end point of symptomatic or radiologic kidney stone recurrence was evaluated at a median follow-up of 2.9 years.

No dose of hydrochlorothiazide was effective in reducing the risk of recurrent kidney stones. Compared with the 59% incidence with placebo, recurrence rates with hydrochlorothiazide were 59% at the 12.5-mg dose, 56% at the 25-mg dose, and 49% at the 50-mg dose. The symptomatic recurrence rate was similar across groups, with a 34% rate in the placebo group. The radiologic recurrence rate—a composite of stone growth or new stone formation—was lowest in the hydrochlorothiazide 25- and 50-mg dose groups.

Patients receiving hydrochlorothiazide had higher rates of hypokalemia, gout, new-onset diabetes, skin allergy, and plasma creatinine >150% of baseline. Serious adverse events were no more common with hydrochlorothiazide versus placebo.

Kidney stones are a common and frequently recurrent problem. Hydrochlorothiazide is widely prescribed to prevent recurrent stones, despite limitations of the research on this issue.

This randomized, placebo-controlled trial finds no significant reduction in the frequency of recurrent kidney stones in high-risk patients taking hydrochlorothiazide. This is so across the range of once-

Continued on page 22

No Reduction in Recurrent Kidney Stones

Continued from page 21

daily doses studied. The researchers note the lack of effectiveness despite decreased urinary calcium excretion in the hydrochlorothiazide group [Dhayat NA, et al. Hydrochlorothiazide and prevention of kidney-stone recurrence. *N Engl J Med* 2023; 388:781–791. doi: 10.1056/NEJMoa2209275]. ■

High Rates of Burnout in Dialysis Patient Care Technicians

Close to 60% of US dialysis patient care technicians (PCTs) meet criteria for burnout, suggests a national survey study in the *American Journal of Kidney Diseases*.

A survey was sent to members of the National Association of Nephrology Technicians/Technologists in the spring of 2022. The survey included Likert scale (0–4) items related to professional fulfillment and two key burnout domains: work exhaustion and interpersonal disengagement, and a yes or no question assessing turnover intention. Burnout was a combined score of 1.3 or higher for work exhaustion and interpersonal disengagement. Professional fulfillment was defined by a score of 3 or higher.

Responses were received from 228 PCTs: 83.9% women, 42.6% between 35 and 49 years of age, and 64.6% White. Nearly three-fourths (72.8%) of respondents reported working 40 or more hours per week.

Median scores were 2.3 for work exhaustion, 1.0 for interpersonal disengagement, and 2.6 for professional fulfillment. Burnout criteria were met by 57.5% of respondents, whereas only 37.3% met the cutoff for professional fulfillment. Factors related to burnout and professional fulfillment included salary for 66.5% of respondents, supervisor support for 64.0%, respect from other staff members for 57.8%, sense of purpose at work for 54.5%, and weekly working hours for 52.9%.

In response to the turnover question, just 52.6% of respondents said they planned to be working as a dialysis PCT in 3 years. In free-text comments, the PCTs re-emphasized issues related to excessive work burden and lack of respect.

The findings raise concerns about the very high burnout risk among US dialysis PCTs, with correspondingly low rates

of professional fulfillment. Turnover is a critical concern, as nearly half of respondents do not plan to continue working as PCTs in the future. The researchers conclude: "Because of the critical, frontline role of dialysis PCTs in the care of patients receiving in-center hemodialysis, strategies to improve morale and reduce turnover are imperative" [Plantinga LC, et al. Professional fulfillment, burnout, and turnover intention among US dialysis patient care technicians: A national survey. *Am J Kidney Dis*, published online ahead of print March 9, 2023. doi: 10.1053/j.ajkd.2022.12.017; https://www.ajkd.org/article/S0272-6386(23)00559-0/fulltext].

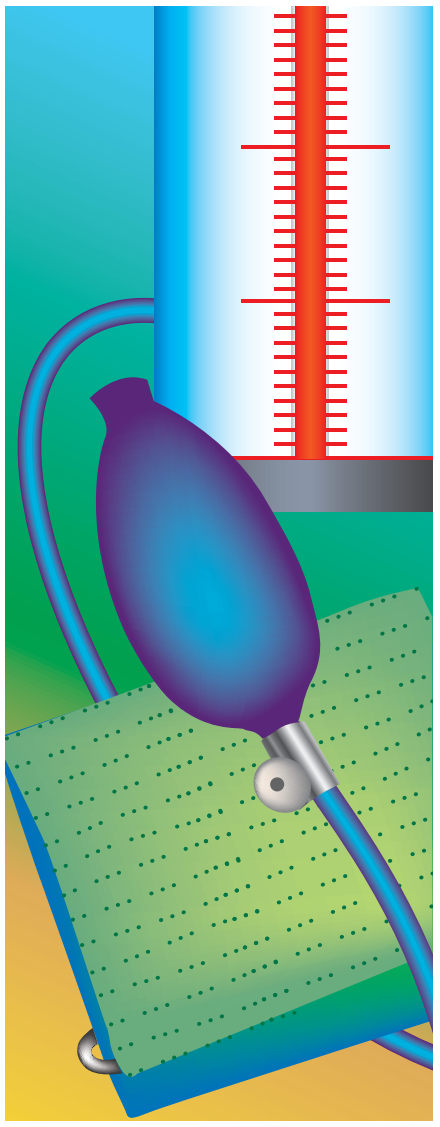
Hypertension Is Under-Recognized in Young Children with Kidney Diseases

In pediatric patients with chronic kidney disease (CKD), hypertensive blood pressure (BP) is less likely to be recognized and treated in children aged <7 years compared with older age groups, reports a study in *Hypertension*.

The researchers examined the relationship between age and recognition and control of hypertension in 902 children with non-dialysis-dependent CKD, drawn from the Chronic Kidney Disease in Children (CKiD) study. A total of 3550 annual study visits were classified into groups corresponding to early, middle, and later childhood and adolescence: aged 0 to <7 years, 7 to <13 years, and 13–18 years. Analyses adjusted for potential confounders, including sex, glomerular diagnosis, estimated glomerular filtration rate (eGFR), nephrotic-range urine protein:creatinine ratio, and obesity.

The median age was 10.73 in the cohort overall and 4.62 years in the aged 0 to <7 years group. The median eGFR was 49 mL/min/1.73 m^2 and was similar across age groups. A glomerular diagnosis was present in 47% of the oldest age group and 9% of the youngest.

Clinic BP readings consistent with stage 1 or 2 hypertension were present in 32% of children aged 0 to <7 years, 22% of the aged 7 to <13 years group, and 16% of the aged 13–18 years group. Among patients with hypertensive BP readings, rates of unrecognized, untreated hypertension were 45.8% in the youngest age group, 29.3% in the aged 7 to <13 years group, and 20.8% in the oldest age group. Rates of recognized but uncontrolled hypertension were 35.5%, 50.7%, and 56.4%, respectively.



On adjusted analysis, children aged 0 to <7 years were twice as likely to have unrecognized hypertensive BP (odds ratio [OR], 2.11) compared with patients aged 13–18 years. Among patients with unrecognized hypertension, the youngest age group was less likely to receive antihypertensive medication (OR, 0.51).

Younger age is associated with poorer control of hypertension among children with CKD. The new analysis finds an increased prevalence of undiagnosed, untreated hypertensive BP in patients with CKD aged 0 to <7 years compared with older children and adolescents. The researchers conclude, "Efforts to improve BP control in young children with CKD are needed to minimize development of cardiovascular disease and slow CKD progression" [Douglas CE, et al. Effect of age on hypertension recognition in children with chronic kidney disease: A report from the Chronic Kidney Disease in Children study. *Hypertension*, published online ahead of print March 2, 2023. doi: 10.1161/HYPERTENSIONAHA.122.20354; https://www.ahajournals.org/doi/10.1161/HYPERTENSIONAHA.122.20354].

ASN and AAKP Advocates Urge Congress to Support Kidney Health

This March, advocates from ASN and the American Association of Kidney Patients (AAKP) headed to Capitol Hill as part of Kidney Health Advocacy Day (KHAD) to advocate for policies to increase support and funding for kidney health programs. Currently in the middle of its annual funding process, officially known as appropriations, for fiscal year 2024 (FY24), it is imperative for members of Congress to hear how increasing funding for kidney health innovation and care for American service members living with kidney diseases is crucial for improving the care for the 37 million Americans living with kidney diseases. During KHAD, advocates from AAKP and ASN raised two key requests of Congress:

- Accelerate innovation in the prevention, diagnosis, and treatment of kidney diseases by increasing funding for Kidney Innovation Accelerator (KidneyX).
- Support American services members with kidney diseases by increasing funding for the Veterans Health Administration (VHA) National Kidney Program and by increasing funding for the Department of Defense Congressionally Directed Medical Research Programs.

KidneyX, a public-private accelerator between ASN and the Department of Health and Human Services, aims to accelerate innovation in the prevention, diagnosis, and treatment of kidney diseases through a series of prize competitions. To date, KidneyX has awarded 67 prizes across five competitions for solutions ranging from dialysis-accessible clothing to groundbreaking prototypes of artificial kidney and xenotransplant technology.

ASN committed the first $25 million to KidneyX, and Congress has appropriated $5 million each year for KidneyX since its first Congressional appropriation in 2019, now totaling $20 million. During KHAD, advocates from AAKP and ASN urged Congress to provide KidneyX $25 million in the FY24 appropriations bill to expand the number of innovators it supports and accelerate the development of transformative technologies, particularly the world's first artificial kidney.

Advocates also requested that Congress support American service members and veterans living with kidney diseases. Advocates requested increased funding for the VHA Kidney Program to ensure its mission to "improve the quality and consistency of healthcare services delivered to veterans with kidney disease nationwide" (1). Federal funding would also support VA health care facilities that offer outpatient dialysis care to service members in 70 locations (2). Additionally, advocates requested increased funding for the Department of Defense Congressionally Directed Medical Research Programs, which, among other hallmarks, supports "groundbreaking research; the next generation of researchers and established scientists; and research development, including basic, translational, and clinical research" (3). Currently, the program funds extensive research of polycystic kidney disease and other rare kidney diseases.

Lastly, with the recent announcement of the Public Health Emergency (PHE) expiring on May 11, 2023, it is essential that

Congress understands the implications of this decision for individuals who are immunocompromised and immunosuppressed and ensure they retain access to life-saving care. Patients with kidney diseases and kidney failure are at the highest risk of contracting and experiencing severe outcomes, such as death, from COVID-19. Furthermore, patients with kidney transplants must take immune-suppressing medication, making vaccines less effective and this population particularly vulnerable to severe outcomes from COVID-19. Ending the PHE will have a significant impact on the lives of these patients by abruptly removing funding for testing and diagnostic tools and potentially risking gaps in the delivery of life or death therapies, particularly antivirals such as nirmatrelvir and ritonavir—the only COVID-19 therapeutics effective in most transplant recipients. ASN and AAKP advocates raised these implications with policymakers and the need to continue to provide people with kidney diseases and kidney failure access to valuable care.

ASN will continue advocating for these key priorities throughout the year and encourages kidney health professionals and patients with kidney diseases to amplify these requests through ASN's Legislative Action Center (https://www.asn-online.org/policy/lac.aspx). ■

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Hemodialysis Access Planning Just Got a Little More Help

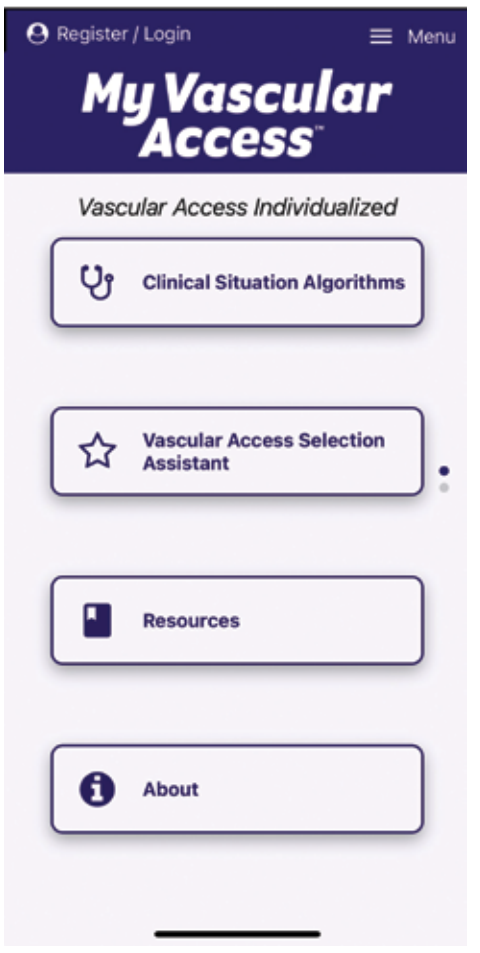
By Sonia Talathi and Yana Etkin

Physicians involved in managing the ever-growing population of patients with end stage kidney disease (ESKD) continue to debate what is the "best" vascular access for hemodialysis (HD). With the initiation of the "Fistula First Breakthrough Initiative" in 2003, there was a strong directive to increase the rates of arteriovenous fistula (AVF) use and decrease the rate of catheter use. As advocated by national guidelines, physicians believed that an AVF was the preferred access choice for most patients. This initiative was somewhat successful, and the rates of AVF use in the United States increased from 35% in 2003 to 63% in 2017 but still fell short of the original goal set out by the Centers for Medicare & Medicaid Services of 66% (1). The data to support the advantages of AVF have always been clear: fewer infectious and thrombotic complications, better patency, and lower rates of reinterventions. However, as we created more AVFs in the past two decades, the drawback has become apparent. The maturation process could be as long as 4 months, requiring multiple interventions and a primary failure rate between 30% and 50% (2).

It became clear that AVF is not the "gold standard" for HD access. A "one size fits all" strategy is not ideal in this complex patient population, and a more patient-centered approach to the creation of vascular access is needed. In 2019, the Kidney Disease Outcomes Quality Initiative (KDOQI) ESKD Life-Plan was developed, which advocates for "right access in the right patient at the right time for the right reasons" (3). The Life-Plan encourages physicians (nephrologists, vascular surgeons, interventional radiologists, etc.) to not only consider arterial and venous anatomy when planning HD access but also to take into consideration other factors including comorbidities, life expectancy, and patient preference. There is a significant shift from previous recommendations, as Life-Plan does not emphasize a strong preference for AVF utilization. Although this individualized approach provides an opportunity for more patient-centered care, it makes the decision-making process more challenging.

My Vascular Access (a website and application) was developed by Kidney CARE Network International to aid physicians and patients in developing the most appropriate individualized vascular access life plan. *My Vascular Access* uses two algorithms and integrates the recommendations from KDOQI guidelines, along with patient-specific information, such as age, functional status, and vascular anatomy. The first algorithm approaches the problem based on the clinical situation. After choosing from a set of pre-selected clinical situations and answering questions related to the patient-specific data, the algorithm then provides feedback regarding which access type to consider. The second algorithm on the app allows providers to input data, such as age, need for dialysis, functional status, body mass index, and size of veins and arteries, and gives a list of possible access types, ranked by appropriateness.

Figure 1.



The app is based on the latest available clinical data and expert opinion from vascular access experts composed of surgeons, nephrologist, and interventionalists. The recommendations were generated by the algorithms based on a consensus process of a large data set that was validated by access experts and published in the *Journal of Vascular Surgery* in a 2017 article, titled "Establishing patient-specific criteria for selecting the optimal upper extremity vascular access procedure" (4). The study used the RAND/University of California Los Angeles Appropriateness Method (RAM) to assess 3816 clinical scenarios for the suitability of AVF vs. AV graft (AVG). Eleven vascular access experts rated the appropriateness of each scenario, and 864 clinical scenarios were then created in which the experts were given the option to choose between AVF or AVG as the first access operation. Interestingly, in 25% of those scenarios, AVG was rated more appropriate than AVF. There are, of course, limitations to this study. Only upper-extremity AV access was taken into account, and the option of Hemodialysis Reliable Outflow (HeRO) catheters or leg grafts was not included. Furthermore, all possible combinations of clinical scenarios could not be included for the feasibility study.

The first human HD was performed approximately 100 years ago, and the first AVF was created nearly 60 years ago (5). Despite tremendous advances in medical care since then, creating and maintaining well-functioning HD access continue to be challenges. A clear answer of AVF vs. AVG in terms of survival, morbidity, and cost benefit would require a large, multicenter randomized trial. Until this trial is available, the decision is based on the clinical judgment of the providers caring for the patient. The *My Vascular Access* app aids in this decision-making and allows providers to easily identify patients who may fall into the gray zone of whether or not they will benefit from an AVF. It uses a data-centered approach to take the guesswork out of optimizing vascular access in our most challenging patients. Appropriate patient selection can avoid unnecessary interventions and surgical procedures, which have been increasing in frequency (6). *My Vascular Access* can be a useful tool for every provider who takes care of patients on HD. As we continue our journey to develop the optimal strategy for HD access planning, we need to integrate the best available evidence and tools as well as individual patients' circumstances and preferences.

My Vascular Access is available through the app store on your smart phone (Figure 1) or via www.myvascularaccess.com.

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The authors report no conflicts of interest.

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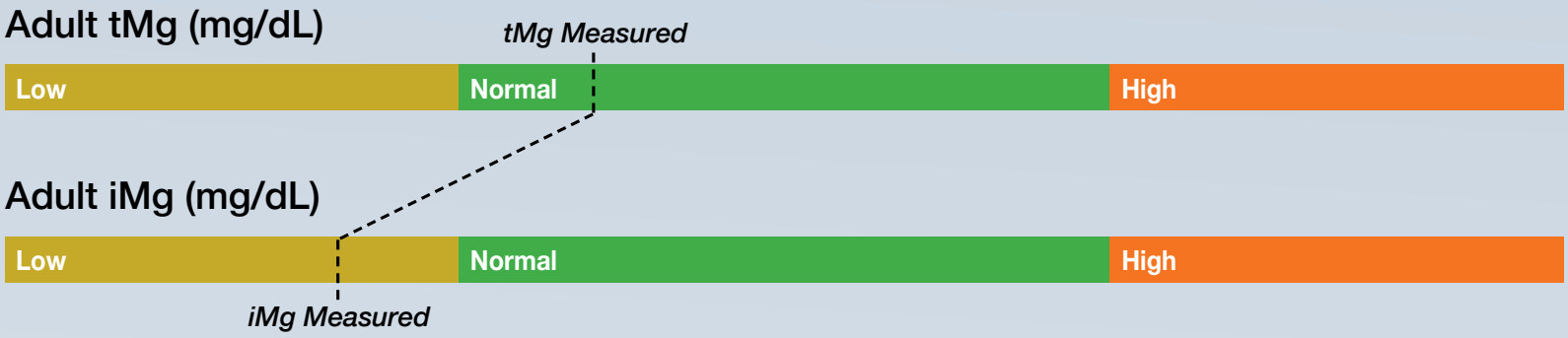
ICU Patient Studies Show Critical Importance of iMG

Patients Undergoing Continuous Renal Replacement Therapy (CRRT)

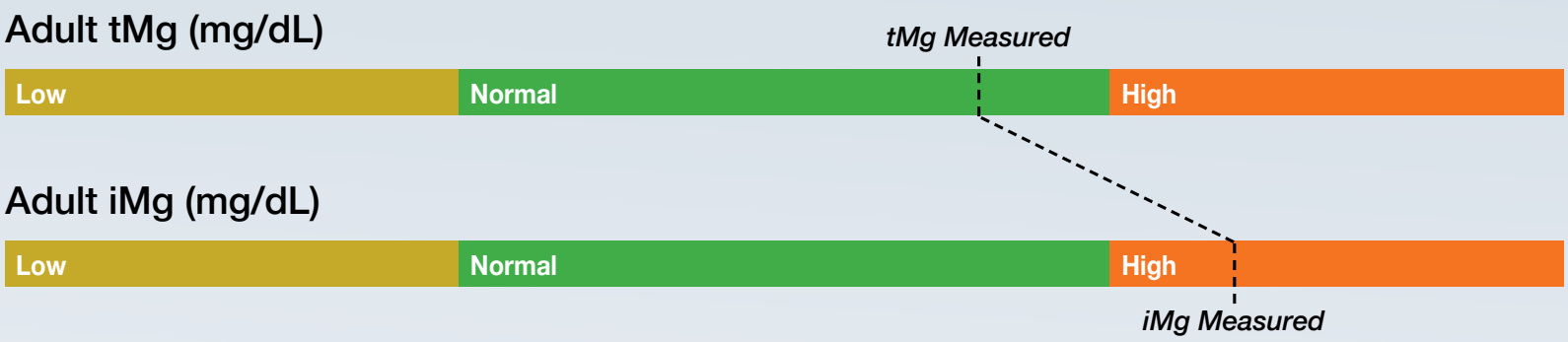
Hutten et. al.[1] found that patients receiving CRRT with citrate anticoagulation had normal tMg levels, but low iMg levels. This is due to magnesium ions being bound by citrate, and the citrate-magnesium complex being measured as tMg. These patients are actually hypomagnesemic but would not be recognized as such if only tMg were measured.



1.Hutten et al., Ionized and not total magnesium as a discriminating biomarker for hypomagnesaemia in continuous venovenous haemofiltration patients. *Nephrol Dial Transplant*, 2021.

Surgical ICU Patients

Yeh et. al.[2] found that 21% of tMg tests which were reported as normal were hypermagnesemic based on iMg. This exposes patients to potential risks associated with undetected hypermagnesemia, including prolonged days on the ventilator, muscle weakness, QT prolongation, and cardiac arrhythmia. In addition, there were many patients with low tMg and normal iMg, which led to unnecessary Mg supplementation and repeat blood draws.



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