ASN American Society of Nephrology

KidneyNews

December 2021 | Vol. 13, Number 12

Nephrologists Campaign to Replace Urine Anion Gap with Urine Ammonium Test

By Eric Seaborg

If there is a better test, why not use it?

That is the question a group of nephrologists are asking directors of their laboratories about diagnosing metabolic acidosis. They are advocating that measuring a patient's urine ammonium level is more helpful than trying to estimate it from the urine anion gap (UAG).

More than 170 nephrologists signed a public letter making this request to "directors of clinical laboratories," first published on Twitter as the introductory step in a campaign to make urine ammonium tests more available.

The letter notes that the test would be valuable "not only in the diagnosis of renal tubular acidosis…but also in managing acidosis in progressive [chronic kidney disease] CKD…and in evaluating and treating patients with kidney stones, where it will give us clues about the acid load the patients consume."

Although the test is available at some reference labs, many institutions do not even offer physicians the option to request to send out the test.

Many nephrologists realize that "the urine anion gap is not a good test," said David S. Goldfarb, MD, clinical chief of nephrology at New York University Langone Health and one of the leaders of the ammonium test campaign. "We are hoping that nephrologists will read this [letter] and say, 'Yeah, why are we satisfied with a urine anion gap measurement which is clearly not satisfactory?' If we can demonstrate that nephrologists are interested in this test, then perhaps it won't be such a big deal for [laboratories] to perform it."

The start of UAG

The use of the UAG as an indirect measure of ammonium rests on surprisingly flimsy ground, according to a recent review in *JASN* by Jaime Uribarri, MD, of the Icahn School of Medicine at Mount Sinai in New York City, and Man S. Oh, MD, of the State University of New York Downstate Health Sciences University in Brooklyn (1). Uribarri said the widespread use of the UAG grew out of "two papers in the 1980s [that] reported a strong inverse correlation between UAG and urine ammonium excretion in patients with metabolic acidosis. [The authors] postulated that the UAG could be used as an indirect measure of urine ammonium" (2, 3).

Continued on page 11

Steroid-Free Immunosuppression May Reduce Posttransplant Diabetes Risk

In older and obese adults undergoing kidney transplantation, immunosuppression without the use of steroids is associated with a lower risk of posttransplant diabetes mellitus, suggests a study in *Kidney Medicine* (1).

The retrospective analysis included data on adult kidney-only transplant patients from 2005 to 2016 with Medicare billing claims, drawn from the US Renal Data System. Incidence of posttransplant diabetes was analyzed, including the impact of age and obesity (body mass index 30 kg/m^2 or greater). The impact of immunosuppression was analyzed by inverse propensity weighting, with thymoglobulin (TMG) or alemtuzumab (ALEM) plus mycophenolic acid plus prednisone as the reference regimen.

Overall incidence of posttransplant diabetes was 12.7%. Incidence was higher in older patients: 16.7% for patients aged 55 years or older versus 10.1% in patients younger than 55. Obese patients were also at higher risk of posttransplant diabetes: 17.1% versus 10.9%.

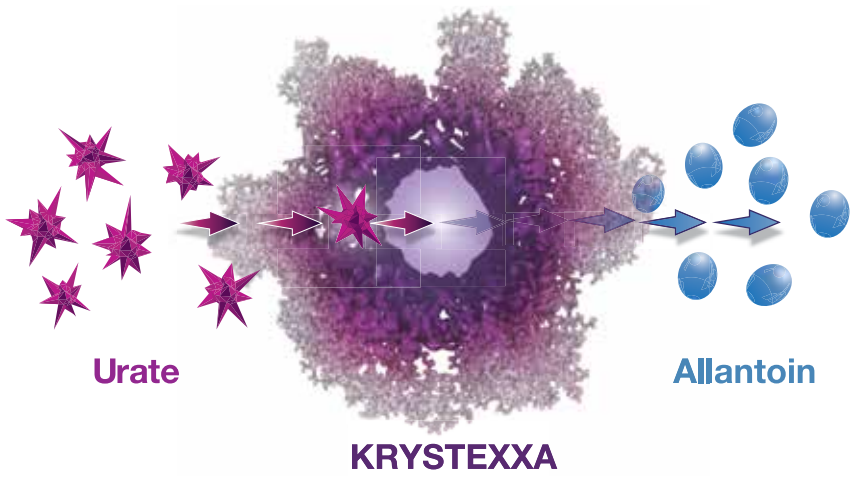
Patients whose immunosuppressive regimen did not include steroids were less likely to develop posttransplant diabetes. Incidence was 8.4% in patients receiving TMG/ALEM with no prednisone and 9.7% for those receiving anti-interleukin 2 receptor antibodies with no prednisone compared to 13.1% for those receiving TMG/ALEM with triple therapy.

With adjustment for donor and recipient characteristics,

Continued on page 11

Inside

KRYSTEXXA (PEGLOTICASE) IS A RECOMBINANT INTO ALLANTOIN[1]



Artist's renditions.

RENAL EXCRETION OF ALLANTOIN IS UP TO 10 TIMES MORE EFFICIENT THAN EXCRETION OF URIC ACID[2]

INDICATION AND IMPORTANT SAFETY INFORMATION

INDICATIONS AND USAGE

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.

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

IMPORTANT SAFETY INFORMATION

WARNING: ANAPHYLAXIS AND INFUSION REACTIONS

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-type hypersensitivity reactions have also been reported. KRYSTEXXA should be administered in healthcare settings and by healthcare providers prepared to manage anaphylaxis and infusion reactions. Patients should be premedicated with antihistamines and corticosteroids. Patients should be closely monitored for an appropriate period of time for anaphylaxis after administration of KRYSTEXXA. Monitor serum uric acid levels prior to infusions and consider discontinuing treatment if levels increase to above 6 mg/dL, particularly when 2 consecutive levels above 6 mg/dL are observed.

The risk of anaphylaxis and infusion reactions is higher in patients who have lost therapeutic response.

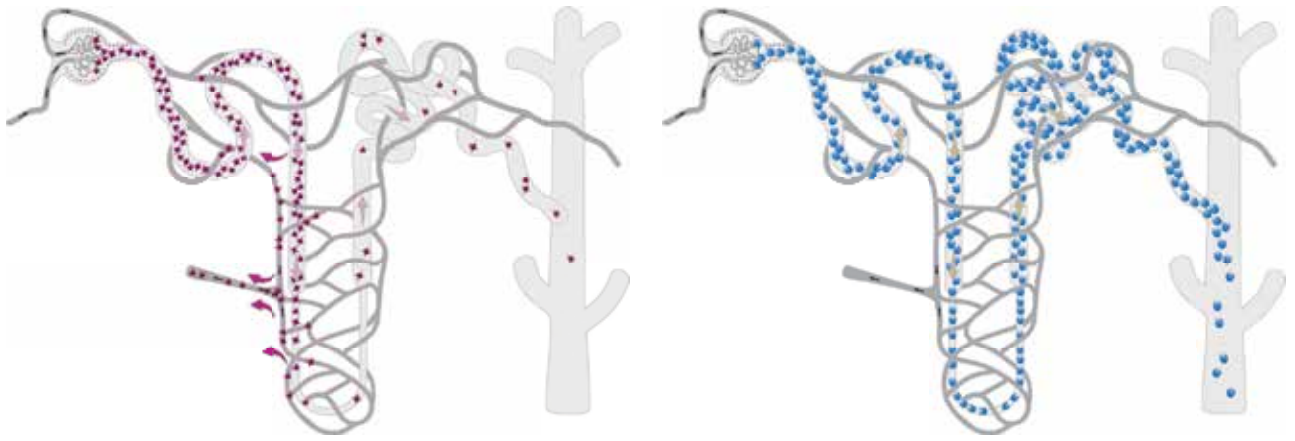
Concomitant use of KRYSTEXXA and oral urate-lowering agents may blunt the rise of sUA levels. Patients should discontinue oral urate-lowering agents and not institute therapy with oral urate-lowering agents while taking KRYSTEXXA.

In the event of anaphylaxis or infusion reaction, the infusion should be slowed, or stopped and restarted at a slower rate.

References: 1. KRYSTEXXA (pegloticase) [prescribing information] Horizon. **2.** McDonagh EM, et al. *Pharmacogenet Genomics*. 2014;24:464-476. **3.** Terkeltaub R, et al. *Arthritis Res Ther*. 2006;8(suppl 1):S4.

HORIZON

URICASE ENZYME THAT CONVERTS URATE



Only 10% of uric acid filtered through the kidney is excreted[3]

vs

Nearly all of allantoin filtered through the kidney is excreted[2,3]

TO LEARN MORE, VISIT KRYSTEXXAHCP.COM

Inform patients of the symptoms and signs of anaphylaxis, and instruct them to seek immediate medical care should anaphylaxis occur after discharge from the healthcare setting.

CONTRAINDICATIONS: G6PD DEFICIENCY ASSOCIATED HEMOLYSIS AND METHEMOGLOBINEMIA

Screen patients for G6PD deficiency prior to starting KRYSTEXXA. Hemolysis and methemoglobinemia have been reported with KRYSTEXXA in patients with G6PD deficiency. Do not administer KRYSTEXXA to these patients.

GOUT FLARES

An increase in gout flares is frequently observed upon initiation of anti-hyperuricemic therapy, including treatment with KRYSTEXXA. If a gout flare occurs during treatment, KRYSTEXXA need not be discontinued. 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 studied in patients with congestive heart failure, but some patients in the clinical trials experienced exacerbation. Exercise caution when using KRYSTEXXA in patients who have congestive heart failure and monitor patients closely following infusion.

ADVERSE REACTIONS

The most commonly reported adverse reactions in clinical trials with KRYSTEXXA are gout flares, infusion reactions, nausea, contusion or ecchymosis, nasopharyngitis, constipation, chest pain, anaphylaxis and vomiting.

Please see Brief Summary of Prescribing Information, including Boxed Warning, for KRYSTEXXA on the following page.

KRYSTEXXA®
pegloticase

KRYSTEXXA® pegloticase

(pegloticase injection), for intravenous infusion

Brief Summary - Please see the KRYSTEXXA package insert for Full Prescribing 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. However, delayed-type hypersensitivity reactions have also been reported.**
- **KRYSTEXXA should be administered in healthcare settings and by healthcare providers prepared to manage anaphylaxis and infusion reactions.**
- **Patients should be pre-medicated with antihistamines and corticosteroids.**
- **Patients should be closely monitored for an appropriate period of time for anaphylaxis after administration of KRYSTEXXA.**
- **Monitor serum uric acid levels prior to infusions and consider discontinuing 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. Do not administer KRYSTEXXA to patients with G6PD deficiency.**

INDICATIONS AND USAGE

KRYSTEXXA® (pegloticase) is a PEGylated uric acid specific enzyme 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.

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

CONTRAINDICATIONS

Glucose-6-phosphate dehydrogenase (G6PD) deficiency

WARNINGS AND PRECAUTIONS

Anaphylaxis

During pre-marketing clinical trials, 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. 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 consider discontinuing 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

During pre-marketing controlled clinical trials, 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 consider discontinuing 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

During the controlled treatment period with KRYSTEXXA or placebo, 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.

Congestive Heart Failure

KRYSTEXXA has not been formally studied in patients with congestive heart failure, but some patients in the clinical trials experienced exacerbation. 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.

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

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 6-month 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.

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.

The most common adverse reactions that occurred in ≥5% of patients treated with KRYSTEXXA 8 mg every 2 weeks are provided in Table 1.

Table 1. Adverse Reactions Occurring in 5% or More of Patients Treated with KRYSTEXXA Compared to Placebo

Adverse Reaction (Preferred Term)	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

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.

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.

Postmarketing Experience

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

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.

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. 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).

General Information

Provide and instruct patients to read the accompanying Medication Guide before starting treatment and before each subsequent treatment.

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.
- 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.
- 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.

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. Advise patients that they should not stop KRYSTEXXA therapy if they have a flare.

Manufactured by:
Horizon Therapeutics Ireland DAC
Dublin, Ireland
US License Number 2022

Distributed by:
Horizon Therapeutics
Deerfield, IL 60015

ASN American Society of Nephrology

KidneyNews

ASN Kidney News is published by the American Society of Nephrology
1401 H Street, NW, Suite 900, Washington, DC 20005. Phone: 202-640-4660

www.asn-online.org

Postmaster: Please send address changes to *ASN Kidney News*, c/o Customer Service, American Society of Nephrology 1401 H Street, NW, Suite 900, Washington, DC 20005.

Publications mail agreement No. 40624074. Return undeliverable Canadian addresses to PO Box 503, RPO West Beaver Creek, Richmond Hill ON L4B 4R6

ASN Kidney News (ISSN print 1943-8044 and online 1943-8052) is an official publication of the American Society of Nephrology, 1401 H Street, NW, Suite 900, Washington DC 20005, and is published monthly 11 times a year except November. Periodicals postage paid at Washington, DC and at additional mailing offices. Subscription rates: $12 per year. To order, please email bhenkel@asn-online.org. Subscription prices subject to change. Annual ASN membership dues include $12 for *ASN Kidney News* subscription.

★ WINNER OF 3 DESIGN AWARDS ★

GD USA 2018 WINNER · WINNER 2019 APEX AWARDS FOR PUBLICATION EXCELLENCE · GD USA 2020 WINNER

We're United 4 Kidney Health

ASN IN REVIEW

Earlier this year, the American Society of Nephrology (ASN) launched "We're United 4 Kidney Health," an initiative that repositions nephrology as a specialty that embraces kidney health through early intervention, transplantation, innovation and patient choice, and equity. We're United 4 Kidney Health presents a rallying cry that shows how the kidney community can advance the field by embracing four priorities:

1. INTERVENE EARLIER to prevent, diagnose, coordinate care, and educate.
2. TRANSFORM TRANSPLANT and increase access to donor kidneys.
3. ACCELERATE INNOVATION and expand patient choice.
4. ACHIEVE EQUITY and eliminate disparities.

ASN is committed to a world without kidney diseases, and the society made significant accomplishments across these four priorities in 2021. Through the broader ASN Alliance for Kidney Health, the campaign's priorities will advance more in the future.

Intervene earlier

NTDS Transforming Dialysis Safety

Preventing or slowing the progression of kidney diseases and related comorbidities is the best way to improve the lives of the more than 37 million Americans living with kidney diseases. Nearly 800,000 Americans have kidney failure, a life-threatening condition for which there is no cure. Kidney failure is most commonly managed by dialysis, a therapy that has changed little in the 50 years since the federal government established the Medicare End-Stage Renal Disease (ESRD) Program. Dialysis has poor survival rates; more than 50% percent of people who start dialysis die within 5 years.

Diabetes is the leading cause of kidney diseases, and approximately one in three adults with diabetes develops diabetic kidney disease (DKD). ASN established the Diabetic Kidney Disease Collaborative (DKD-C) to increase coordination among health professionals and other stakeholders to deliver appropriate therapies for people living with DKD. Through DKD-C, ASN hosted three strategy conferences attended by nephrologists, primary care physicians, pharmacists, nurses, endocrinologists, cardiologists, industry, healthcare systems, and payors to define barriers and facilitate strategies that would increase access to new treatments. ASN also developed a DKD Education Module available on the society's website.

AKI!Now: Promoting Excellence in the Prevention and Treatment of Acute Kidney Injury (AKI) is helping transform the delivery of AKI care, reduce morbidity and mortality, and improve long-term outcomes. Through *AKI!Now*, ASN identified challenges and opportunities to improve post-AKI care, including the development of tests and supportive strategies that build capacity for the delivery of care. The *AKI!Now* compendium promotes collaborative and inclusive research that facilitates the translation of new discoveries, including augmented and artificial intelligence, in the development of novel therapies.

Nephrologists Transforming Dialysis Safety (NTDS)—ASN's partnership with the Centers for Disease Control and Prevention (CDC)—enhances the quality of life for people with kidney failure by engaging nephrologists and other health professionals to continuously improve the safety of life-sustaining dialysis. NTDS is eliminating preventable infections in dialysis facilities in the United States by conducting human factors assessments to determine better practices that prevent the spread of infections in dialysis facilities, designing electronic checklists to engage patients as observers of infection-prevention processes, and hosting a Targeting Zero Infections webinar series.

Additionally, NTDS partnered with Northwest Kidney Centers to develop a Pop-Up Leadership Academy—Leading Together: Creating a Culture of Collaboration—for dialysis facility medical directors and nurse managers. The academy aims to foster a team environment that focuses on the delivery of excellent patient care by ensuring physicians, nursing leaders, and staff at all levels are engaged in their work; communication is clear, direct, honest, and open; and collaboration is proactive and effective.

Throughout the SARS-CoV-2 (causing Coronavirus disease 2019 [COVID-19]) pandemic, the kidney community increasingly learned about the impact of SARS-CoV-2 infection on kidneys. According to the Centers for Medicare & Medicaid Services (CMS), people on dialysis are the most vulnerable population covered by Medicare, and people with kidney failure are most at risk among Medicare beneficiaries for severe outcomes from COVID-19, including hospitalization and death. Additionally, people with healthy kidneys who contract more severe COVID-19 often experience kidney damage.

To coordinate efforts addressing the pandemic, ASN established a COVID-19 Response Team in spring 2020. Through the COVID-19 Response Team, ASN collaborates with external partners, including the chief medical officers of dialysis organizations, to share safety practices, testing, therapeutics, vaccines and efficacy, and data. Successful advocacy efforts resulted in the Network Administrator Model for vaccine distribution to kidney failure patients in dialysis facilities through Fresenius Medical Care and DaVita, as well as the approval of a third vaccine dose for immunosuppressed people with kidney diseases.

The COVID-19 Response Team also partnered with KidneyX—a public-private partnership between ASN and the US Department of Health and Human Services (HHS)—to award 15 innovators with a COVID-19 Kidney Care Challenge prize, all aiming to reduce transmission of SARS-CoV-2 among people with kidney diseases. ASN also developed education and collated external resources on monoclonal antibody therapies, compassion fatigue, and other important topics. Additionally, ASN published original research and other information from the kidney community related to COVID-19 across the society's peer-reviewed journals and ASN *Kidney News*.

Transform transplant

A kidney transplant is the optimal therapy for most people with kidney failure, yet transplantation is out of reach for many people. Each day, 12 Americans die on the 100,000-person kidney transplant waitlist. The second priority of the We're United 4 Kidney Health campaign revolves around fundamentally improving the current transplant system.

After many years of advocacy, ASN and the kidney community celebrated the passage of the Comprehensive Immunosuppressive Drug Coverage for Kidney Transplant Patients Act in December of 2020. Taking effect in 2023, this legislation indefinitely extends Medicare coverage of immunosuppressive drugs for kidney transplant recipients. This success helped propel early momentum for ASN to help transform transplant and increase access to donor kidneys in 2021.

ASN helped secure the introduction of the Living Donor Protection Act in Congress. This legislation will remove barriers to donation and increase access to life-saving transplants by ensuring that insurance companies offering life, disability, and long-term care plans do not deny or limit coverage or raise premiums based on an individual's status as a living organ donor. In March, the Biden administration, as advocated for by ASN, allowed the organ procurement organizations metric final rule to take effect, which will apply new standards of accountability, provide greater transparency to the transplant waitlist, and address elimination based on financial criteria or secondary insurance for transplant recipients.

ASN also established a Task Force on Transplant Nephrology Compensation to evaluate transplant nephrologists' work, which, at times, is undervalued and undercompensated. The task force has been collecting data on different financial structures within institutions across the nation to better understand the nuances in funding. Based on this analysis, the task force will submit its observations and recommendations for publication by the end of the year.

During Kidney Week 2021, ASN hosted an educational symposium describing the new payment models on the delivery of posttransplant care, the major immunologic and non-immunologic threats to long-term graft survival, and advances in non-invasive monitoring of kidney transplant function. ASN also partnered with the American Society of Transplantation to host an early program on kidney transplantation updates during 2021.

Additionally, ASN expanded "Cross-Publication Collections," bringing together articles from the society's journals (as well as related content in ASN *Kidney News*) on specific nephrology topics, including transplantation, for reader convenience.

Accelerate innovation

Several ASN efforts have helped accelerate innovation and expand patient choice, including KidneyX, which incentivizes innovators to fill unmet patient needs through a series of prize competitions. Including the COVID-19 Kidney Care Challenge, KidneyX has funded more than 60 innovators for solutions ranging from patient-created tools to the first concepts of an artificial kidney. In September, KidneyX announced the six Artificial Kidney Prize phase 1 winners who are splitting a $4 million prize.

The Kidney Health Initiative—a public-private partnership among ASN, the US Food and Drug Administration (FDA), and more than 100 member organizations to advance regulatory kidney science—continues to produce valuable patient-centered resources for the community. These resources include publications on patient-reported outcome measurements for vascular access and dialysis-associated muscle cramping as well as a series in *CJASN* on integrating patient preferences into the design and evaluation of innovations.

Advocacy by ASN and the rest of the kidney community secured $5 million in congressional appropriations for KidneyX and $2.13 billion for the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) in fiscal year (FY) 2021 (October 1, 2020–September 30, 2021). ASN submitted written testimony on FY 2022 funding to Congress requesting the National Institutes of Health receive an increase of 7.3% for a total of $46.11 billion: providing a real growth of 5% after accounting for the biomedical research and development price index. ASN advocated that NIDDK receive a proportional funding increase or $157 million in FY 2022.

ASN also supported the Patient Access to ESRD New Innovative Devices Act, which would direct CMS to provide a 3-year temporary add-on payment adjustment through the ESRD Prospective Payment System—more commonly known as "the bundle"—that provides reimbursement for dialysis care. This bill would increase patient access to new products by removing bureaucratic red tape and allowing new and innovative devices for kidney failure that meet approval standards set by the FDA to be reimbursed by Medicare. Without a clear and assured mechanism to add innovative new devices to the payment bundle for dialysis services, there is little incentive to develop novel technologies for people with kidney failure.

In addition to launching the ASN Home Dialysis Task Force—an organization-wide initiative to increase access to and the use of home dialysis therapies through education, training, advocacy, and other means—ASN supported the introduction of key legislation to accelerate innovation and expand patient choice, including the Improving Access to Home Dialysis Act. This legislation would allow CMS to pay professional staff to work with kidney patients directly in their homes to assist them in learning how to properly implement home dialysis.

To communicate the latest scientific and medical breakthroughs with the kidney community, ASN added "early access" to the publication process for *JASN* and *CJASN*, bringing unedited and unformatted manuscript content to readers expeditiously. A full summary of recent advances through the innovation pipeline were highlighted during a special session at Kidney Week 2021, "Accelerating Up the Innovation Curve in Kidney Medicine."

Achieve equity

The fourth priority centers on achieving equity and eliminating disparities. The roots of disparities in kidney medicine are multifactorial, and these disparities are linked to social determinants of health and systemic racism on a national level. The entire kidney community must begin to address these disparities.

ASN has attempted to meet this goal through a variety of initiatives, including a letter to the White House Office of Management and Budget encouraging the Biden administration to adopt a blueprint for addressing equity across the federal government. For example, ASN recommended HHS conduct a more systematic assessment of social determinants of health data, including the most common non-clinical barriers to home dialysis, such as housing or financial insecurity, minimal caregiver support, other mental and certain physical illnesses, or advanced age. This information will help identify barriers to equitable care and develop policies to overcome these barriers.

ASN and the National Kidney Foundation championed a joint Task Force on Reassessing the Inclusion of Race in Diagnosing Kidney Diseases that released its interim and final reports in 2021. Timed with two publications in *The New England Journal of Medicine,* the task force's final report outlined new race-free approaches to diagnosing kidney diseases. The task force recommended the adoption of the new estimated glomerular filtration rate (eGFR) 2021 Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) creatinine equation that estimates kidney function without a race variable and the increased use of cystatin C combined with serum (blood) creatinine as a confirmatory assessment of GFR or kidney function. Also, the task force recommended that more research funding is dedicated to exploring new approaches for precise and unbiased GFR estimation as well as for the estimation of physiologic function in other areas of medicine.

The ASN Loan Mitigation Pilot Program opened its first round of applications in summer 2021. ASN has committed $2.7 million to the 5-year pilot program to reduce the loan burden of those entering the field of nephrology and increase interest in the specialty. The first year of the program centered on individuals who are historically underrepresented in medicine with the intention of strengthening the specialty's reflection of the patient population it serves. Six individuals selected this year will receive $50,000 over the course of 3 years toward the repayment of eligible student loans.

To further guarantee that achieving equity and eliminating disparities remain core principles of ASN, the society established a Health Care Justice Committee to identify opportunities to promote justice in healthcare and society and influence social determinants of health. The committee is focusing its activities on education, clinical care and innovation, and scholarship and advocacy.

Supporting the fourth priority of the We're United 4 Kidney Health campaign, the ASN Kidney Week Education Committee devoted ePosters, oral abstracts, and educational sessions for content related to race and equity. For example, the Race and Ethnicity in Kidney Diseases: Joint ASN-JSN session that featured representatives from ASN and the Japanese Society of Nephrology discussed considerations regarding race and ethnicity relevant to their settings.

ASN's 2022 outlook

The achievements of 2021 provide renewed hope, enthusiasm, and momentum that greater triumphs await the kidney community in 2022 and beyond. ASN and the broader ASN Alliance for Kidney Health will continue to focus on meeting their shared mission of "elevating care by educating and informing, driving breakthroughs and innovation, and advocating for policies that create transformative changes in kidney medicine throughout the world."

If you are interested in supporting the We're United 4 Kidney Health campaign and making the campaign's priorities a reality, please visit www.4KidneyHealth.org to learn more.

ASN Kidney Week 2021 content is available on the virtual meeting platform until Friday, January 7, 2022.

In adult patients with CKD associated with T2D

With KERENDIA, a different pathway leads to different possibilities[1,2]

KERENDIA offers a different path forward

- KERENDIA is the first and only selective MRA with a nonsteroidal structure
- KERENDIA blocks MR overactivation, which is thought to contribute to inflammation and fibrosis that can lead to CKD progression
- In adults with CKD associated with T2D, KERENDIA is proven to slow CKD progression and reduce CV risk

INDICATION:

- KERENDIA is indicated to reduce the risk of sustained eGFR decline, end-stage kidney disease, cardiovascular death, non-fatal myocardial infarction, and hospitalization for heart failure in adult patients with chronic kidney disease (CKD) associated with type 2 diabetes (T2D)

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS:

- Concomitant use with strong CYP3A4 inhibitors
- Patients with adrenal insufficiency

WARNINGS AND PRECAUTIONS:

- ***Hyperkalemia:*** KERENDIA can cause hyperkalemia. The risk for developing hyperkalemia increases with decreasing kidney function and is greater in patients with higher baseline potassium levels or other risk factors for hyperkalemia. Measure serum potassium and eGFR in all patients before initiation of treatment with KERENDIA and dose accordingly. Do not initiate KERENDIA if serum potassium is >5.0 mEq/L

  Measure serum potassium periodically during treatment with KERENDIA and adjust dose accordingly. More frequent monitoring may be necessary for patients at risk for hyperkalemia, including those on concomitant medications that impair potassium excretion or increase serum potassium

MOST COMMON ADVERSE REACTIONS:

- Adverse reactions reported in ≥1% of patients on KERENDIA and more frequently than placebo: hyperkalemia (18.3% vs. 9%), hypotension (4.8% vs. 3.4%), and hyponatremia (1.4% vs. 0.7%)

DRUG INTERACTIONS:

- ***Strong CYP3A4 Inhibitors:*** Concomitant use of KERENDIA with strong CYP3A4 inhibitors is contraindicated. Avoid concomitant intake of grapefruit or grapefruit juice
- ***Moderate and Weak CYP3A4 Inhibitors:*** Monitor serum potassium during drug initiation or dosage adjustment of either KERENDIA or the moderate or weak CYP3A4 inhibitor and adjust KERENDIA dosage as appropriate
- ***Strong and Moderate CYP3A4 Inducers:*** Avoid concomitant use of KERENDIA with strong or moderate CYP3A4 inducers

Learn more about KERENDIA and the FIDELIO-DKD trial

USE IN SPECIFIC POPULATIONS

- ***Lactation:*** Avoid breastfeeding during treatment with KERENDIA and for 1 day after treatment
- ***Hepatic Impairment:*** Avoid use of KERENDIA in patients with severe hepatic impairment (Child Pugh C) and consider additional serum potassium monitoring with moderate hepatic impairment (Child Pugh B)

Please read the Brief Summary of the KERENDIA Prescribing Information on the following page.

CKD=chronic kidney disease; CV=cardiovascular; MR=mineralocorticoid receptor; MRA=mineralocorticoid receptor antagonist; T2D=type 2 diabetes.

References: 1. KERENDIA (finerenone) [prescribing information]. Whippany, NJ: Bayer HealthCare Pharmaceuticals, Inc; July 2021. **2.** Bakris GL, et al; FIDELIO-DKD Investigators. *N Engl J Med*. 2020;383(23):2219-2229.

Kerendia®
(finerenone) tablets
10 mg • 20 mg

BAYER

PP-KER-US-0016-1 10/21

KERENDIA (finerenone) tablets, for oral use
Initial U.S. Approval: 2021

BRIEF SUMMARY OF PRESCRIBING INFORMATION
CONSULT PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Kerendia® is indicated to reduce the risk of sustained eGFR decline, end-stage kidney disease, cardiovascular death, non-fatal myocardial infarction, and hospitalization for heart failure in adult patients with chronic kidney disease (CKD) associated with type 2 diabetes (T2D).

4 CONTRAINDICATIONS

Kerendia is contraindicated in patients:

- Who are receiving concomitant treatment with strong CYP3A4 inhibitors *[see Drug Interactions (7.1)]*.
- With adrenal insufficiency.

5 WARNINGS AND PRECAUTIONS

5.1 Hyperkalemia

Kerendia can cause hyperkalemia *[(see Adverse Reactions (6.1)]*.

The risk for developing hyperkalemia increases with decreasing kidney function and is greater in patients with higher baseline potassium levels or other risk factors for hyperkalemia. Measure serum potassium and eGFR in all patients before initiation of treatment with Kerendia and dose accordingly *[see Dosage and Administration (2.1)]*. Do not initiate Kerendia if serum potassium is > 5.0 mEq/L.

Measure serum potassium periodically during treatment with Kerendia and adjust dose accordingly *[see Dosage and Administration (2.3)]*. More frequent monitoring may be necessary for patients at risk for hyperkalemia, including those on concomitant medications that impair potassium excretion or increase serum potassium *[see Drug Interactions (7.1), 7.2)]*.

6 ADVERSE REACTIONS

The following serious adverse reactions are discussed elsewhere in the labeling:

- Hyperkalemia *[see Warnings and Precautions (5.1)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety of Kerendia was evaluated in the randomized, double-blind, placebo-controlled, multicenter pivotal phase 3 study FIDELIO-DKD. In this study, 2827 patients received Kerendia (10 or 20 mg once daily) and 2831 received placebo. For patients in the Kerendia group, the mean duration of treatment was 2.2 years.

Overall, serious adverse reactions occurred in 32% of patients receiving Kerendia and in 34% of patients receiving placebo. Permanent discontinuation due to adverse reactions occurred in 7% of patients receiving Kerendia and in 6% of patients receiving placebo. Hyperkalemia led to permanent discontinuation of treatment in 2.3% of patients receiving Kerendia versus 0.9% of patients receiving placebo.

The most frequently reported (≥ 10%) adverse reaction was hyperkalemia *[see Warnings and Precautions (5.1)]*. Hospitalization due to hyperkalemia for the Kerendia group was 1.4% versus 0.3% in the placebo group.

Table 3 shows adverse reactions in FIDELIO-DKD that occurred more commonly on Kerendia than on placebo, and in at least 1% of patients treated with Kerendia.

Table 3: Adverse reactions reported in ≥ 1% of patients on Kerendia and more frequently than placebo in the phase 3 study FIDELIO-DKD

Adverse reactions	Kerendia N = 2827 n (%)	Placebo N = 2831 n (%)
Hyperkalemia	516 (18.3)	255 (9.0)
Hypotension	135 (4.8)	96 (3.4)
Hyponatremia	40 (1.4)	19 (0.7)

Laboratory Test

Initiation of Kerendia may cause an initial small decrease in estimated GFR that occurs within the first 4 weeks of starting therapy, and then stabilizes. In a study that included patients with chronic kidney disease associated with type 2 diabetes, this decrease was reversible after treatment discontinuation.

7 DRUG INTERACTIONS

7.1 CYP3A4 Inhibitors and Inducers

Strong CYP3A4 Inhibitors

Kerendia is a CYP3A4 substrate. Concomitant use with a strong CYP3A4 inhibitor increases finerenone exposure *[see Clinical Pharmacology (12.3)]*, which may increase the risk of Kerendia adverse reactions. Concomitant use of Kerendia with strong CYP3A4 inhibitors is contraindicated *[see Contraindications (4)]*. Avoid concomitant intake of grapefruit or grapefruit juice.

Moderate and Weak CYP3A4 Inhibitors

Kerendia is a CYP3A4 substrate. Concomitant use with a moderate or weak CYP3A4 inhibitor increases finerenone exposure *[see Clinical Pharmacology (12.3)]*, which may increase the risk of Kerendia adverse reactions. Monitor serum potassium during drug initiation or dosage adjustment of either Kerendia or the moderate or weak CYP3A4 inhibitor, and adjust Kerendia dosage as appropriate *[see Dosing and Administration (2.3) and Drug Interaction (7.2)]*.

Strong and Moderate CYP3A4 Inducers

Kerendia is a CYP3A4 substrate. Concomitant use of Kerendia with a strong or moderate CYP3A4 inducer decreases finerenone exposure *[see Clinical Pharmacology (12.3)]*, which may reduce the efficacy of Kerendia. Avoid concomitant use of Kerendia with strong or moderate CYP3A4 inducers.

7.2 Drugs That Affect Serum Potassium

More frequent serum potassium monitoring is warranted in patients receiving concomitant therapy with drugs or supplements that increase serum potassium *[see Dosage and Administration (2.3) and Warnings and Precautions (5.1)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no available data on Kerendia use in pregnancy to evaluate for a drug-associated risk of major birth defects, miscarriage or adverse maternal or fetal outcomes. Animal studies have shown developmental toxicity at exposures about 4 times those expected in humans. *(see Data)*. The clinical significance of these findings is unclear.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Data

Animal Data

In the embryo-fetal toxicity study in rats, finerenone resulted in reduced placental weights and signs of fetal toxicity, including reduced fetal weights and retarded ossification at the maternal toxic dose of 10 mg/kg/day corresponding to an $AUC_{unbound}$ of 19 times that in humans. At 30 mg/kg/day, the incidence of visceral and skeletal variations was increased (slight edema, shortened umbilical cord, slightly enlarged fontanelle) and one fetus showed complex malformations including a rare malformation (double aortic arch) at an $AUC_{unbound}$ of about 25 times that in humans. The doses free of any findings (low dose in rats, high dose in rabbits) provide safety margins of 10 to 13 times for the $AUC_{unbound}$ expected in humans.

When rats were exposed during pregnancy and lactation in the pre- and postnatal developmental toxicity study, increased pup mortality and other adverse effects (lower pup weight, delayed pinna unfolding) were observed at about 4 times the $AUC_{unbound}$ expected in humans. In addition, the offspring showed slightly increased locomotor activity, but no other neurobehavioral changes starting at about 4 times the $AUC_{unbound}$ expected in humans. The dose free of findings provides a safety margin of about 2 times for the $AUC_{unbound}$ expected in humans.

8.2 Lactation

Risk Summary

There are no data on the presence of finerenone or its metabolite in human milk, the effects on the breastfed infant or the effects of the drug on milk production. In a pre- and postnatal developmental toxicity study in rats, increased pup mortality and lower pup weight were observed at about 4 times the $AUC_{unbound}$ expected in humans. These findings suggest that finerenone is present in rat milk *[see Use in Specific Populations (8.1) and Data]*. When a drug is present in animal milk, it is likely that the drug will be present in human milk. Because of the potential risk to breastfed infants from exposure to KERENDIA, avoid breastfeeding during treatment and for 1 day after treatment.

8.4 Pediatric Use

The safety and efficacy of Kerendia have not been established in patients below 18 years of age.

8.5 Geriatric Use

Of the 2827 patients who received Kerendia in the FIDELIO-DKD study, 58% of patients were 65 years and older, and 15% were 75 years and older. No overall differences in safety or efficacy were observed between these patients and younger patients. No dose adjustment is required.

8.6 Hepatic Impairment

Avoid use of Kerendia in patients with severe hepatic impairment (Child Pugh C).

No dosage adjustment is recommended in patients with mild or moderate hepatic impairment (Child Pugh A or B).

Consider additional serum potassium monitoring in patients with moderate hepatic impairment (Child Pugh B) *[see Dosing and Administration (2.3) and Clinical Pharmacology (12.3)]*.

10 OVERDOSAGE

In the event of suspected overdose, immediately interrupt Kerendia treatment. The most likely manifestation of overdose is hyperkalemia. If hyperkalemia develops, standard treatment should be initiated.

Finerenone is unlikely to be efficiently removed by hemodialysis given its fraction bound to plasma proteins of about 90%.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Finerenone was non-genotoxic in an in vitro bacterial reverse mutation (Ames) assay, the in vitro chromosomal aberration assay in cultured Chinese hamster V79 cells, or the in vivo micronucleus assay in mice.

In 2-year carcinogenicity studies, finerenone did not show a statistically significant increase in tumor response in Wistar rats or in CD1 mice. In male mice, Leydig cell adenoma was numerically increased at a dose representing 26 times the $AUC_{unbound}$ in humans and is not considered clinically relevant. Finerenone did not impair fertility in male rats but impaired fertility in female rats at 20 times AUC to the maximum human exposure.

17 PATIENT COUNSELING INFORMATION

Advise patients of the need for periodic monitoring of serum potassium levels. Advise patients receiving Kerendia to consult with their physician before using potassium supplements or salt substitutes containing potassium *[see Warnings and Precautions (5.1)]*.

Advise patients to avoid strong or moderate CYP3A4 inducers and to find alternative medicinal products with no or weak potential to induce CYP3A4 *[see Drug Interactions (7.1)]*.

Avoid concomitant intake of grapefruit or grapefruit juice as it is expected to increase the plasma concentration of finerenone *[see Drug Interactions (7.1)]*.

Advise women that breastfeeding is not recommended at the time of treatment with KERENDIA and for 1 day after treatment *[see Use in Specific Populations (8.2)]*.

Manufactured for:

Bayer HealthCare Pharmaceuticals Inc.
Whippany, NJ 07981

Manufactured in Germany 6711200BS1A

Urine Anion Gap

Continued from cover

The influence of those papers continued "despite four other published studies that did not support that association. Urine ammonium excretion…has no consistent relationship to UAG either theoretically or in reality," Uribarri said. "UAG ultimately depends on the intake of its three determinants—sodium, potassium, and chloride—without any a priori reason why this should correlate with urine ammonium."

Uribarri and Oh said the authors of the original articles followed a flawed experimental process in which they induced metabolic acidosis by using oral loads of ammonium chloride, so it should have come as no surprise that ammonium secretion increased as UAG increased—thereby producing the inverse correlation as an artifact. "We concluded that there is no evidence that UAG is a good index of urine ammonium and therefore clinical laboratories should start measuring this parameter directly since it is not technically difficult," Uribarri told *Kidney News*.

Uribarri said the comments he has received on the article have been entirely positive, with no one raising counterarguments to question it.

Adapting plasma ammonia tests

"We know urinary anion gap doesn't work," agrees John C. Lieske, MD, medical director of the renal testing laboratory at the Mayo Clinic in Rochester, MN. Lieske's lab is one of the few that offers urine ammonium testing.

Although there is no off-the-shelf test for urine ammonium, laboratories commonly offer plasma ammonia tests, which can be adapted. Lieske's laboratory adapted a plasma ammonia enzymatic kit that runs on a Roche analyzer.

"The concentration of ammonia in the urine is about 100 times more than it is in blood, and so it is really fairly straightforward. We checked with a couple of labs when we were looking into this. You just dilute the urine 1 to 100 and run it with the same reagents that you would run the blood test. It works just fine. Plasma ammonia is commonly measured and I would think it is available at most big centers because it is something that we follow in patients with liver disease."

He said there is no large regulatory burden in adapting an off-the-shelf test for a different matrix or analyte, but there is more work in verifying and documenting the test's accuracy. Lieske said that if you don't use a test "exactly as the package insert says, there is an extra layer of validation you have to do. All labs have to verify that their methods work a couple of times a year through various surveys… where we compare answers with different laboratories. So, there are various ways that this would get verified that you are doing it correctly."

Goldfarb said that "most major medical centers in the United States measure a plasma ammonia level," so they already have the kits and reagents on hand to measure it in the urine as the Mayo Clinic does.

The question of volume

One hurdle to the implementation of a new test is the question of whether the expected volume will justify its expense. "Every test requires a certain amount of maintenance," Lieske said. "If people are going to order this once a month, that is not really worth it. But if they were going to order a lot of these, I think the lab would be more receptive to doing it. So there is a certain chicken-and-egg thing that comes up with this sort of testing."

The letter to laboratory directors addresses this issue head on: "One argument of the clinical labs is that the test may not be ordered in sufficient volume to justify them developing the required complex proficiency and validation tests. We believe the test is not being ordered, not because clinicians do not think it worthwhile, but because of its limited availability. If at least a number of clinical laboratories were available to perform the test as a 'send-out,' we all would order UNH4 [ammonium] with greater frequency."

The campaigners are urging nephrologists to talk to the staff of their laboratories about offering the test and started by talking to their own laboratory people.

"The clinical laboratory asked me if I would be satisfied with the laboratory handling it as a send-out to Mayo Clinic, and I said, 'sure enough,'" Uribarri added. "I am waiting now because they have to put it [into] the electronic medical records. It has to be in the system so you can click on it."

Goldfarb agreed that "we'll be happy for the send-out for now." His laboratory director expressed interest in the proposal and contacted a major referral laboratory about its policy on the test. "That's positive for me" that the laboratory director was invested enough in his request to research it, Goldfarb said.

The Mayo Clinic Laboratories could handle the increase in volume if a number of institutions began offering the test as a send-out, Lieske explained.

Goldfarb said that NYU Langone Health's campaign is in its preliminary stages. He plans to ask nationwide laboratory networks like Quest and LabCorp to offer the test and perhaps contact laboratory organizations to enlist their help. "We are going to demonstrate that nephrologists care about this test," he said. "It can be sent to a number of places that are actually doing the test, so it is not a big deal. It is not going to cost very much. The fact that it is not available is somewhat inexplicable." ■

References

1. Uribarri J, Oh MS. The urine anion gap: Common misconceptions. *J Am Soc Nephrol* 2021; 32:1025–1028. doi: 10.1681/ASN.2020101509
2. Batlle DC, et al. The use of the urinary anion gap in the diagnosis of hyperchloremic metabolic acidosis. *N Engl J Med* 1988; 318:594–599. doi: 10.1056/NEJM198803103181002
3. Goldstein MB, et al. The urine anion gap: A clinically useful index of ammonium excretion. *Am J Med Sci* 1986; 292:198–202. doi: 10.1097/00000441-198610000-00003

Letter to Directors of Clinical Laboratories (September 2021)

Calculation of the urine anion gap (UAG) was suggested in the 1980s as an easy way to indirectly estimate urine ammonium (NH4) in patients with hyperchloremic metabolic acidosis. This calculation was used by necessity because clinical laboratories were not measuring UNH4 at that time. Despite significant technological advances ever since, most clinical laboratories in this country still do not measure UNH4. The UAG has fallen short as a surrogate for UNH4 for many reasons, and its shortcomings have been recently reviewed in detail (1). The undersigned believe that direct measurement of UNH4 is a test [that] is long overdue. It has value not only in the diagnosis of renal tubular acidosis, as mentioned above, but also in managing acidosis in progressive [chronic kidney disease] CKD (2, 3), and in evaluating and treating patients with kidney stones, where it will give us clues about the acid load the patients consume (4). One argument of the clinical labs is that the test may not be ordered in sufficient volume to justify them developing the required complex proficiency and validation tests. We believe the test is not being ordered, not because clinicians do not think it worthwhile, but because of its limited availability. If at least a number of clinical laboratories were available to perform the test as a "send-out," we all would order UNH4 with greater frequency. We therefore petition you to make UNH4 a readily available test to which clinicians throughout the country have access. We, the undersigned ([174 of us]), are nephrologists who strongly support this initiative and appreciate your consideration of our request.

Sincerely,

Jaime Uribarri, MD, Professor of Medicine, Icahn School of Medicine at Mt. Sinai

David S. Goldfarb, MD, Professor of Medicine, NYU Grossman School of Medicine, NYU Langone Health

Kalani Raphael, MD, Professor of Medicine, Oregon Health & Science University

Anna Zisman, MD, Associate Professor of Medicine, University of Chicago

References

1. Uribarri J, Oh MS. The urine anion gap: Common misconceptions. *J Am Soc Nephrol* 2021; 32:1025–1028. doi: 10.1681/ASN.2020101509
2. Raphael KL, et al. Urine ammonium predicts clinical outcomes in hypertensive kidney disease. *J Am Soc Nephrol* 2017; 28:2483–2490. doi: 10.1681/ASN.2016101151
3. Vallet M, et al. Urinary ammonia and long-term outcomes in chronic kidney disease. *Kidney Int* 2015; 88:137–145. doi: 10.1038/ki.2015.52
4. Asplin JR. Evaluation of the kidney stone patient. *Semin Nephrol* 2008; 28:99–110. doi: 10.1016/j.semnephrol.2008.01.001

Steroid-Free Immunosuppression

Continued from cover

TMG/ALEM without steroids was associated with a lower risk of posttransplant diabetes across groups. The adjusted hazard ratio (HR) was 0.63 in patients younger than 55 compared to 0.69 in older patients and 0.67 in obese patients compared to 0.69 in non-obese patients. In contrast, anti-interleukin 2 receptor antibodies with no steroid were protective only in older patients (HR 0.76) and non-obese patients (HR 0.63). Mammalian target of rapamycin inhibitor-based immunosuppression was associated with an increased rate of posttransplant diabetes, with an adjusted HR of 1.40.

Patients who develop diabetes mellitus after kidney transplantation are at risk of increased morbidity and mortality, especially older and obese patients. Previous evidence suggests that the choice of an immunosuppressive regimen might be a modifiable risk factor for posttransplant diabetes. This study of Medicare-insured kidney transplant recipients finds a lower risk of posttransplant diabetes in those receiving steroid-free immunosuppressive regimens.

Although the protective effect of steroid avoidance is apparent in both older and obese recipients, the effects of concomitant cell depletion may differ.

"These data support consideration of the risk of non-immune complications along with rejection risk when selecting immunosuppression regimens in kidney transplant recipients to minimize patient morbidity from immunosuppression associated side effects," the authors state. ■

Reference

1. Axelrod DA, et al. Posttransplant diabetes mellitus and immunosuppression selection in older and obese kidney transplant recipients. *Kidney Med* [published online ahead of print October 22, 2021]. https://www.sciencedirect.com/science/article/pii/S259005952100220X.

Kidney News *thanks Editorial Board members Hajeong Lee, MD, PhD, Maria Soler Romeo, MD, PhD, Jia H. Ng, MD, and Mayuri Trivedi, MBBS, DM, for this series of articles from around the world.*

Interventional Nephrology in Spain: A Challenge and a Responsibility That Depend on Many

By Jose Ibeas

One of the areas with the most promising potential in nephrology is interventional nephrology. However, paradoxically, it is possibly one of the areas most historically neglected by the specialty itself. Its resurgence in recent years, although not an easy process, reflects a history that is common to the entire nephrology community. In Spain, we have not been oblivious to this process, and now it has become one of the greatest challenges in our specialty.

Diagnostic and interventional nephrology is defined as a discipline that uses imaging and interventional procedures in the kidney patient. Although these techniques were mainly developed by visionary nephrologists to fill the gap necessary in clinical practice, they were progressively introduced into other specialities such as radiology, vascular surgery, or urology, as both demand for care increased, and nephrologists lost interest in favor of other growing areas of nephrology. This aspect was evident in the different countries where interventional nephrology was practiced, from the United States to Spain (1, 2). In this way, interventionism was not prioritized within the speciality of nephrology, unlike other areas, and therefore, no training or assessment of training was dedicated to it. That is why other specialities, such as radiology or vascular surgery, had to take it on, thereby increasing their waiting list and affecting both their organizational system and nephrology itself.

In the 1990s, nephrologists' interest in interventional nephrology began to resurface to optimize patient care. Nephrologists started to train through informal programs, mainly in the United States, thereby giving rise to variable levels of training. Doctors tried to find a standardized model of program formation, which didn't occur until the American Society of Diagnostic and Interventional Nephrology (ASDIN) was created in 2000. As procedures were carried out, the results were shown to be equal or superior to those of other specialities (3). Once again, this demonstrated nephrologists' ability to perform procedures in various settings (4–7). However, this phase generated debates surrounding who should perform these techniques: the professionals of the specialities who were experts in the technique or the pathology specialist. In this case, the nephrologists, through their knowledge and daily work with the pathology, could capitalize on their autonomy, patient care, and waiting times, taking into account the indispensable collaboration with the specialists who have expertise in the technique.

In fact, today, most specialities have progressively begun to carry out the procedures associated with their pathologies (8). This patient-centered approach can improve the care process, resource management, and above all, innovation. This will undoubtedly redefine the borders of biotechnology with the subsequent benefit for health systems and especially, the patient. The way to bring all of this about is by creating models of academic interventional nephrology, from basic to translational science, from research to clinical research, patient centered, and multidisciplinary (9). In this context, there is inevitably an overlap with other specialities. Therefore, interventional nephrology programs should involve sharing of expertise among disciplines, namely those with which they share knowledge of the pathology, albeit from different perspectives, skills, and training.

In Spain, as a result of recognition of the need to boost interventional nephrology, the Spanish Society of Nephrology (or Sociedad Española de Nefrología [S.E.N.]) approved the creation of the Diagnostic and Interventional Nephrology Working Group in 2014 so as to promote interventional nephrology dissemination in Spain and establish and agree on the use of techniques in the speciality (10). The fundamental objective of this working group is to incorporate diagnostic procedures based on ultrasound and to recover the specific techniques required in the speciality as well as the central role that nephrologists need to play, based mainly on kidney pathology and its complications, kidney replacement therapy, and cardiovascular risk. In this way, the number of trained nephrologists would be increased, with proven training and set standards, and certification of training centers would be established.

To find out what the starting point was, the group sent out a survey in 2015 in all of the country's nephrology departments (11). Although the participation rate was not very high (35.8%), it was similar to other surveys (12) and could be considered representative of Spain, thereby allowing us to gain an overall picture of the situation.

The survey demonstrated that 30% of non-tunneled catheters were still being placed without ultrasound, despite this being recommended by the guidelines of the working group (13); that less than 30% used ultrasound in the native or transplanted kidney; and that the placement of tunneled catheters did not reach 40%. Use of ultrasound of the arteriovenous fistula (AVF) reached 56%, and that associated with the measurement of cardiovascular risk was around 20%. Ultrasound-guided native and transplanted kidney biopsies were found in 35.8% and 46% of cases, respectively. Peritoneal catheter placement was performed in 31% of the centers (Table 1) (2, 11). Thus, the implementation of interventional nephrology was heterogeneous and relatively scarce. These results are consistent with those of other countries, in which nephrologists complain of a lack of training in diagnostic and interventional techniques (2, 11). However, it was shown that all the techniques had been successfully implemented and consolidated in the training programs of several centers.

These previous observations confirmed the need to standardize the training and procedures associated with the use of ultrasound, which is precisely on what all diagnostic and interventional procedures are based. For this reason, the working group created a consensus document specifically for ultrasound training in nephrology (14). The indisputable usefulness of POCUS (point of care ultrasound) in the vast majority of specialities and in nephrology in particular lies in its diagnostic, monitoring, and support capacity in interventional procedures. This includes the management of vascular access for hemodialysis, peritoneal catheter, measurement of cardiovascular risk, ultrasound of the urinary tract, measurement of volume with the pulmonary and cava ultrasound, parathyroid ultrasound, basic echocardiography, or AVF ultrasound-guided cannulation. In addition, it provides support for interventional procedures such as kidney biopsy and tunneled and non-tunneled catheter placement for hemodialysis and peritoneal dialysis. The aim of this document is to lay the foundations for standardizing both this training and the procedures themselves.

S.E.N. aims to establish routine practice standards, and for this purpose, a regulatory framework for both training and continuous education is required in order to make kidney patient management diligent, efficient, and comprehensive in the long term. The training program for the speciality of nephrology already establishes kidney ultrasound, kidney biopsy, and the placement of non-tunneled catheters as basic tools (15). In the new program being developed, interventional nephrology is now included among the skills to be learned. At the same time, the S.E.N. 2016–2020 strategic program (16) highlights reassessment of the speciality of nephrology as a priority, defending its competencies and developing emerging areas such as interventional nephrology.

Although interventional nephrology is now being introduced as a part of the speciality training program, its implementation, although progressive, is still slow and scarce, thereby making it necessary to develop strategies aimed at facilitating it. This means the standardization of training programs and accreditation of centers. In Spain, training programs such as the masters in diagnostic and interventional nephrology at the University of Alcalá (17) or the Parc Taulí University Hospital Vascular Access Training Program (18) have appeared. Numerous centers are beginning to standardize this training, but the curriculum also needs to be standardized. In fact, in Europe, this recognition has been obvious, as the European Commission has awarded a large grant to finance the creation of a consortium made up of 8 reference centers; 2 scientific societies, namely the European Renal Association-European Dialysis and Transplant Association (ERA-EDTA) and the Vascular Access Society (VAS); and 2 companies involved in e-learning and simulation, respectively. The aim is to set up the foundations of a pan-European curricular model in interventional nephrology: the multidisciplinary-based Nephrology Partnership for Advancing Technology in Healthcare (N-PATH) project (19).

Once we recognize that training is the bottleneck, it is as necessary for it to be standardized as it is for trainers to have expert knowledge, and at this point, it is important to recognize that the best way to move forward, as noted above, is with multidisciplinary collaboration. The technical skills

Table 1. Interventional nephrology in Spain

Interventional nephrology procedures	n	%
US-guided jugular temporary catheter insertion	48	68.6
NK biopsy	53	75.7
Radiology	34	64.1
Nephrology	19	35.9
KT biopsy	26	37.1
Radiology	14	53.8
Nephrology	12	46.1
Tunneled HD catheter insertion	27	38.6
PD catheter insertion	18	25.7
AVF Angioplasty	2	2.9
Diagnostic sonography		
NK US (nephrologist)	20	28.6
KT US (nephrologist)	16	22.8
AVF US	60	85.7
Radiology	21	35
Nephrology	39	65
Carotid US (cIMT by nephrologist)	15	21.5
Femoral US (nephrologist)	9	12.8
Abdominal aorta US (nephrologist)	6	8.5

Survey of all of the country's nephrology departments (n = number of centers; %, with respect to the total). US, ultrasound; NK, native kidney; KT, kidney transplant; HD, hemodialysis; PD, peritoneal dialysis; AVF, arteriovenous fistulae; cIMT, carotid intima-medial thickness.

of interventional radiologists and vascular surgeons acquire a fundamental value in this multidisciplinary training. The field of knowledge that the nephrologist needs is only a small part of what these specialities require, as well as being of a low level of complexity compared to the procedures performed by surgeons and radiologists. Nevertheless, it is the basis of interventional nephrology. Turning this knowledge into greater autonomy, optimization of resources, and reduction of waiting times determines an increase in efficiency and therefore, in cost. Furthermore, what can be interpreted as overlapping skills, if properly resized, still complements task distribution and can bring about not only greater efficiency but above all, can benefit the patient's well-being.

In summary, interventional nephrology is an indispensable tool in nephrology practice that has already proven its efficiency. It is slowly but surely becoming more present in our field. It has the recognition of national scientific societies, as in our case, in Spain and in Europe, which value its need and therefore standardized training. In the future, it seems necessary to be included on the curricular fellow nephrology plan, with adequate multidisciplinary training in which training programs are agreed upon and endorsed by scientific societies. Why? Because, ultimately, the nephrologist is responsible for leading multidisciplinary teams to optimize kidney patient care and promote collaboration in training and research. ■

Jose Ibeas, MD, PhD, is with the Department of Nephrology, Parc Taulí University Hospital, Parc Taulí Research and Innovation Institute (I3PT), Autonomous University of Barcelona, Sabadell, Barcelona, Spain. He is also past president of the Vascular Access Society (VAS), vice president of the Spanish Multidisciplinary Group on Vascular Access (GEMAV), secretary of the Working Group on Vascular Access of the Spanish Society of Nephrology (S.E.N.), and on the council of the Working Group on Diagnostic and Interventional Nephrology of S.E.N.

The author reports no conflicts of interest.

References

1. Sachdeva B, Abreo K. The history of interventional nephrology. *Adv Chronic Kidney Dis* 2009; 16:302–308. doi: 10.1053/j.ackd.2009.06.002
2. Sosa Barrios H, et al. Performance of diagnostic and interventional nephrology in Spain. *Nefrologia (Engl Ed)* 2018; 38:459–462. doi: 10.1016/j.nefro.2017.11.019
3. Niyyar VD, Beathard G. Interventional nephrology: Opportunities and challenges. *Adv Chronic Kidney Dis* 2020; 27:344–349. e1. doi: 10.1053/j.ackd.2020.05.013
4. Beathard GA, et al. Effectiveness and safety of dialysis vascular access procedures performed by interventional nephrologists. *Kidney Int* 2004; 66:1622–1632. doi: 10.1111/j.1523-1755.2004.00928.x
5. The new nephrologist. *Am J Kidney Dis* 2000; 35:978–979. doi: 10.1016/s0272-6386(00)70275-7
6. Asif A. Peritoneal dialysis access-related procedures by nephrologists. *Semin Dial* 2004; 17:398–406. doi: 10.1111/j.0894-0959.2004.17355.x
7. Rivera M, et al. Interventional nephrology: A one-center experience for 15 years. *J Am Soc Nephrol* 2006; 17:754.
8. Thakar CV. Interventional nephrology: What, who, why? *Adv Chronic Kidney Dis* 2020; 27:167. doi: 10.1053/j.ackd.2020.05.016
9. Roy-Chaudhury P, et al. Academic interventional nephrology: A model for training, research, and patient care. *Clin J Am Soc Nephrol* 2012; 7:521–524. doi: 10.2215/CJN.08360811
10. Rivera Gorrín M, et al. Creation of the Working Group on Diagnostic and Interventional Nephrology of the Spanish Society of Nephrology. *Nefrologia* 2016; 36:325–326. doi: 10.1016/j.nefro.2015.11.004
11. Sosa Barrios RH, et al. Diagnostic and interventional nephrology in Spain: A snapshot of current situation. *J Vasc Access* 2019; 20:140–145. doi: 10.1177/1129729818783965
12. Rope RW, et al. Education in nephrology fellowship: A survey-based needs assessment. *J Am Soc Nephrol* 2017; 28:1983–1990. doi: 10.1681/ASN.2016101061
13. Ibeas J, et al. Spanish clinical guidelines on vascular access for haemodialysis. *Nefrologia* 2017; 37 (Suppl 1):1–191. doi: 10.1016/j.nefro.2017.11.004
14. Rivera Gorrín M, et al. Consensus document for ultrasound training in the specialty of nephrology. *Nefrologia (Engl Ed)* 2020; 40:623–633. doi: 10.1016/j.nefro.2020.05.008
15. Sociedad Española de Nefrología (S.E.M.) Guía de formación de especialistas en nefrología [Nephrology specialists training guide]. 2008. Accessed September 9, 2021. https://www.senefro.org/modules.php?name=webstructure&idwebstructure=21
16. Sociedad Española de Nefrología (S.E.M.) Sociedad Española de nefrología 2016–2020 [Spanish Society of Nephrology strategic plan 2016–2020]. Accessed September 9, 2021. https://www.senefro.org/contents/webstructure/Plan_estrate_gico_de_la_S.E.n.pdf
17. Universidad de Alcalá Nefrología Diagnóstica e Intervencionista [Diagnostic and interventional nephrology]. Accessed September 9, 2021. https://www.uah.es/es/estudios/estudios-oficiales/grados/Master-Propio-en-Nefrologia-Diagnostica-e-Intervencionista/
18. Parc Taulí Hospital Universitari. Vascular access program. Accessed September 9, 2021. https://www.tauli.cat/en/hospital/pav
19. Nephrology Partnership for Advancing Technology in Healthcare (N-PATH). New paradigms of learning and knowledge sharing. Accessed September 9, 2021. https://npath.eu

Living and Deceased Kidney Donation in Canada

By Aninda Dibya Saha and Ana Konvalinka

Kidney transplantation is the optimal treatment for end stage kidney disease. There are two types of kidney donors—living or deceased—and their proportions vary in different countries. This summary focuses on the living and deceased donation of all organs in Canada, which uses a voluntary opt-in system, where an individual who is eligible to become an organ donor may choose to opt-in to a national or provincial registry.

The total number of kidney transplants performed in Canada in 2019, the last year with data available, was 1483 (1) (including 53 kidney-pancreas transplants but excluding Quebec). The number of total living donors in Canada increased only modestly in the last decade, from 557 living donor transplants in 2010 to 614 in 2019 (2). The living donation rate declined slightly during this time (3). In contrast, the number of deceased donors nearly doubled during the same time, from 466 donors in 2010 to 820 donors in 2019, with a similar trend also being observed for the number of kidney transplants from deceased donors (1, 2) (Figure 1). The increase in deceased donors has been driven by the higher prevalence of donation after circulatory death (DCD) donors, which increased from <10% of all deceased donors in 2010 to 29% of all deceased donors in 2019 (2). DCD was launched in 2006 and was accompanied by strong advocacy efforts and the implementation of a legal framework, leading to its success (2, 4, 5, 6) (Figure 2).

Efforts directed at increasing awareness and living kidney donation are warranted globally.

There is an interesting sex bias when it comes to the composition of living compared to deceased donors in Canada. Excluding Quebec (data unavailable), 62% of living donors in Canada were female, whereas a similar proportion of deceased donors (61%) were male. Furthermore, of the living organ donors, 57% were unrelated to the transplant recipient (2). Interestingly, although living donation has been stagnant since 2010 (3), at 16.3 donors per million population, Canada has one of the higher living donation rates compared to most other countries with available data (7). Overall, Canada's deceased donor transplantation has increased markedly, mostly due to increased DCD donors. Efforts directed at increasing awareness and living kidney donation are warranted globally.

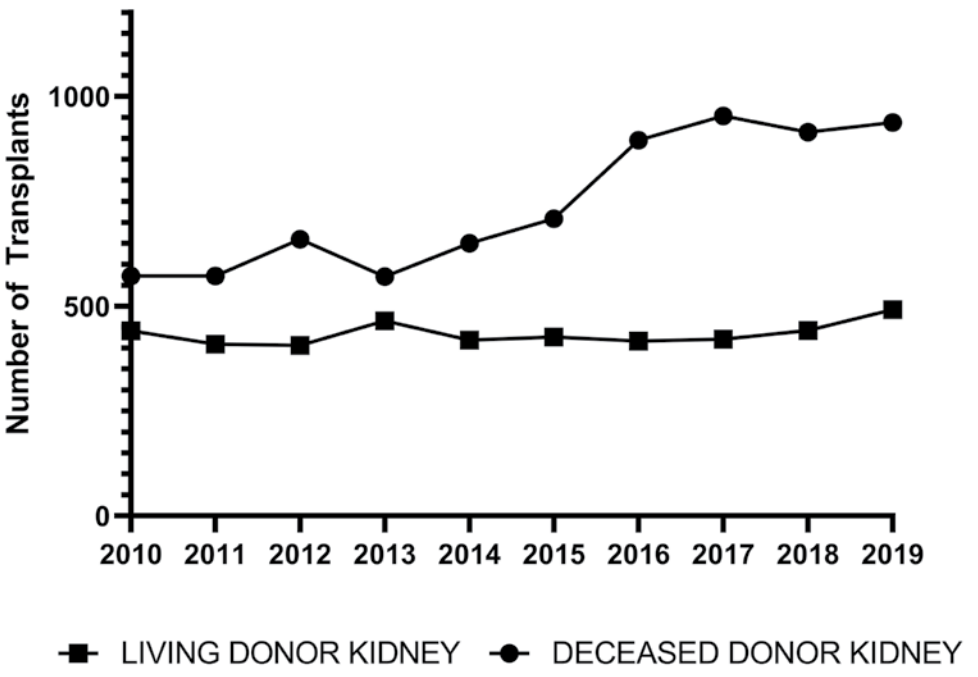
Aninda Dibya Saha is with the Institute of Medical Science, University of Toronto, and Toronto General Hospital Research Institute, University Health Network, Toronto, ON, Canada. Ana Konvalinka is with the Institute of Medical Science, University of Toronto; Toronto General Hospital Research Institute, University Health Network; Division of Nephrology, Department of Medicine, Toronto General Hospital, University Health Network, University of Toronto; Soham and Shaila Ajmera Family Transplant Centre, Toronto General Hospital, University Health Network; and Department of Laboratory Medicine and Pathobiology, University of Toronto, Toronto, ON, Canada.

The authors report no conflicts of interest.

References

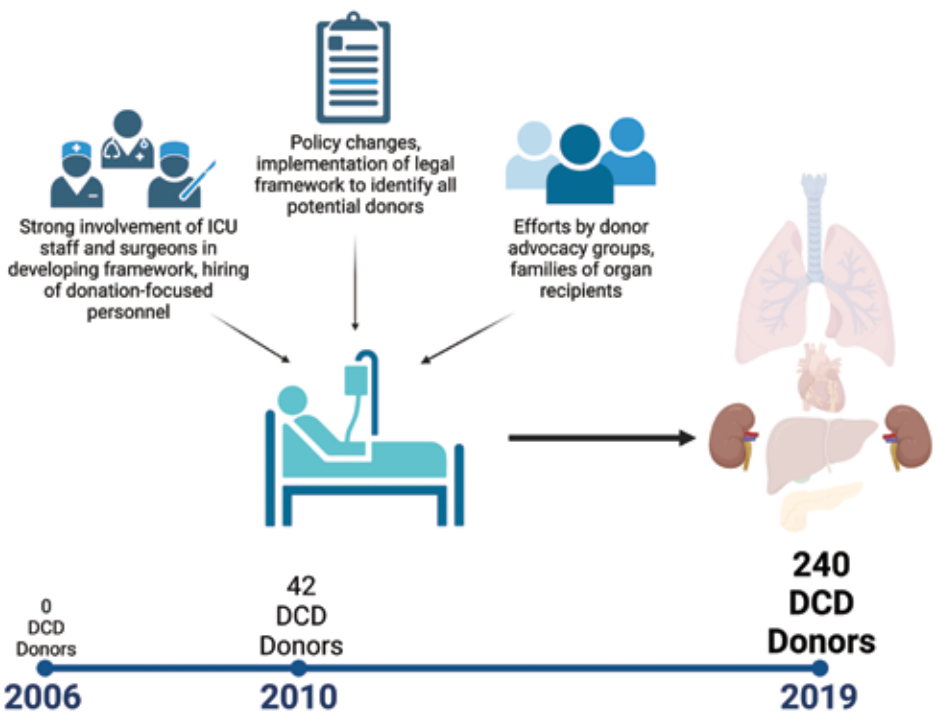
1. Canadian Institute for Health Information. CORR transplants by organ type: Quick stats. 2021. https://www.cihi.ca/en/corr-transplants-by-organ-type-quick-stats
2. Canadian Institute for Health Information. Annual statistics on organ replacement in Canada: Dialysis, transplantation and donation, 2010 to 2019. 2020. https://www.cihi.ca/sites/default/files/document/corr-dialysis-transplantation-donation-2010-2019-snapshot-en.pdf
3. Canadian Institute for Health Information. Treatment of end-stage organ failure in Canada, Canadian Organ Replacement Register, 2010 to 2019: Donors—data tables. 2020. https://www.cihi.ca/sites/default/files/document/end-stage-kidney-disease-transplants-2010-2019-data-tables-en.xlsx
4. Shemie SD, et al. National recommendations for donation after cardiocirculatory death in Canada: Donation after cardiocirculatory death in Canada. *CMAJ* 2006; 175:S1. doi: 10.1503/cmaj.060895
5. Rao V, et al. Effect of organ donation after circulatory determination of death on number of organ transplants from donors with neurologic determination of death. *CMAJ* 2017; 189:E1206–E1211. doi: 10.1503/cmaj.161043
6. Shemie SD. Trends in deceased organ donation in Canada. *CMAJ* 2017; 189:E1204–E1205. doi: 10.1503/cmaj.170988
7. International Registry in Organ Donation and Transplantation. IRODaT–2020 preliminary numbers in organ donation and transplantation. Donation & Transplantation Institute, 2021. https://tpm-dti.com/irodat-2020-preliminary-numbers-in-organ-donation-and-transplantation/

Figure 1. Number of kidney transplants performed in Canada



The number of kidney transplants performed in Canada from living donor (squares) and deceased donor (circles) kidneys, between 2010 and 2019, excluding Quebec (data unavailable). Data obtained from Canadian Institute of Health Information (1).

Figure 2. Reasons for the increased number of DCD donors in Canada



Infographic outlining the reasons for the increased number of DCD donors in Canada as a result of explicit measures implemented in 2006. Created with BioRender.com.

Increasing Living Donor Kidney Transplantation in the UK: A Strategy to Meet the Needs of 2030

By Rachel K.Y. Hung

It is well established that the best treatment for kidney failure is kidney transplantation and that it should be the treatment of choice for all eligible patients. The greatest economic impacts of kidney transplantation, both living and deceased, are savings to the National Health Service (NHS; the universal health service in the United Kingdom) in dialysis costs (1). Living donor kidney transplantation (LDKT) maximizes the opportunity to avoid dialysis via preemptive transplantation. It has a higher success rate of graft survival (as compared to deceased donor kidney transplantation), while adding to the overall supply of organs.

Donation rates have generally plateaued in the last few years. During 2019–2020, LDKT represented 29% of the UK kidney transplant program. In 2020–2021, however, there was an overall decrease in living donors by 58%, with a comparable drop of White and non-White donors, but a 61% decrease in the number of Black and minority ethnic (BAME) living donors (2, 3). Although the drop in donation in 2020 may be explained by the impact of the COVID-19 pandemic and suspension of the UK Live Kidney Shared Scheme (a paired and pooled scheme whereby a willing donor cannot donate to the recipient of his or her choice and instead gives to another recipient in return for a reciprocal donation), the number of living donors from the BAME community has always been lower than that for White and non-White donors (4).

The NHS Blood and Transplant (NHSBT) task force published a report with an action plan to make living donation an expected part of care, where clinically appropriate, for all of society by 2030 (5) (Figure 1). The plan involves execution by the NHSBT, transplant and nontransplant centers, commissioners, and community leaders in a bid to increase the number of living donors and reduce time on the waitlist. In particular, non-directed altruistic kidney donors were found to most benefit long-waiting patients who are immunologically complex and/or from BAME background (5).

To achieve the best overall outcome, the advantages of living donor kidney transplantation must be shared unambiguously with the public.

To achieve the best overall outcome, the advantages of LDKT must be shared unambiguously with the public. Furthermore, grassroots organizations can help increase awareness of living donation among BAME communities in a culturally relevant way to ensure maximum engagement from the target audiences in order to enable more donations and life-saving transplants in the United Kingdom. ■

Rachel K.Y. Hung, MD, is a specialist trainee in renal medicine at King's College London, United Kingdom.

The author reports no conflicts of interest.

References

1. Kerr M, et al. Estimating the financial cost of chronic kidney disease to the NHS in England. *Nephrol Dial Transplant* 2012; 27:iii73–iii80. doi: 10.1093/ndt/gfs269
2. NHS Blood and Transplant. Organ donation and transplantation—activity figures for the UK as of 9 April 2021. 2021. https://nhsbtdbe.blob.core.windows.net/umbraco-assets-corp/24212/annual-stats.pdf
3. NHS Blood and Transplant. Organ and tissue donation and transplantation. Activity report 2020/21. 2021. https://nhsbtdbe.blob.core.windows.net/umbraco-assets-corp/23461/activity-report-2020-2021.pdf
4. NHS Blood and Transplant. Organ donation and transplantation data for Black, Asian, Mixed Race and Minority Ethnic (BAME) communities. Report for 2020/2021 (1 April 2016–31 March 2021). 2021. https://nhsbtdbe.blob.core.windows.net/umbraco-assets-corp/24488/bame-transplant-activity-report-2020_2021.pdf
5. NHS Blood and Transplant et al. Organ donation and transplantation 2030: Meeting the need. A ten-year vision for organ donation and transplantation in the United Kingdom. Accessed October 10, 2021. https://nhsbtdbe.blob.core.windows.net/umbraco-assets-corp/23463/meeting-the-need-2030.pdf

Figure 1.

Organ Donation and Transplantation 2030: Meeting the Need to Increase Living Donors for Kidney Transplantation in the United Kingdom

NHS Blood and Transplant

Background

- 29% of UK's kidney transplant program are living donors.
- Black and minority ethnic (BAME) groups have lower numbers of living donors.
- Further action is required to increase the numbers of living donors in the UK.

The NHSBT Report

- The organ donation and transplantation task force by the NHS Blood and Transplant (NHSBT) published an action plan.
- The NHSBT's aim is to make living donation an expected part of care, where clinically appropriate, for all of society by 2030.

The Action Plan

Government

- Maximize transplant opportunities via UK Living Kidney Sharing Scheme.
- Address health inequalities (e.g., funding recently launched via the Community Investment Programme to enable grass roots organizations to champion organ donation in a culturally relevant way).
- Overcome barriers to donation (including financial) to enable more access to donation.

Transplant Centers

- Improve donor and recipient well-being and experience through better clinical pathways and data quality.
- Remove unnecessary variation in clinical practice by strengthening leadership.
- Recognize donors for their gift of donation through the Living Donor Pin recognition scheme.
- Conduct world-class research to improve donor and recipient outcome.

Community

- Promote awareness among the community, e.g., grass roots organizations like Africa Advocacy, to drive public awareness and engagement in living donation among Black people in the UK & religious leaders to engage their community about the religious stance on living donation.

Living and Deceased Donation in Australia

By Kate Wyburn

Australia, like many countries around the world, has experienced a decline in living donor transplantation compared to deceased donors. The 2020 Australia and New Zealand Dialysis and Transplant Registry Annual Report (1) (reflecting complete data to 2019) reports that a total of 1104 kidney transplants were performed in 2019, an overall rate of 11.6 transplants per 100 dialysis-years (of people on dialysis aged 15–64 years). Living donor kidneys accounted for 22% of all kidney transplants performed in Australia in 2019. Of the 12,815 (prevalent) people with functioning kidney transplants, 30% (3797) originated from living kidney donors, and living kidney donors were more likely to be female (57.2%) (2010–2019).

The overall proportion of living donor procedures compared to deceased donor transplants fell from 29% in 2014 to 21% in 2018 (2). However, this was predominantly due to the steady overall increase in deceased organ donors, as the actual number of living donor kidney transplants remained relatively steady over that time (range 238–271), with a peak of 354 living donor transplants performed in 2008. The Organ and Tissue Authority, an independent agency within the Australian Government health portfolio, was formed in 2009; since then, deceased donors have more than doubled. In 2008, there were 259 deceased organ donors, and in 2019, there were 548. Donation after circulatory death (DCD) has increased over that time and currently accounts for approximately one-third of deceased donors in Australia.

While the overall proportion of living versus deceased kidney donors is now 22%, the proportion of living donors for recipients aged less than 25 years is generally greater than 40%. Additionally, 46% of all first kidney transplants in 2019 from living donors were performed preemptively (1). Preemptive transplantation is not available to people waitlisted for deceased donor kidneys in Australia.

The Australian and New Zealand Kidney Paired Kidney Exchange (ANZKX) program has been responsible for a significant proportion of the living donor kidney transplants (Figure 1). The program has evolved with strong clinical oversight to maximize its impact on, for example, continuous matching, inclusion of ABO incompatible matching, hepatitis B core antibody positive donors, and human leukocyte antigen (HLA) compatible pairs. Started in Australia in 2010 and extended to include New Zealand in 2019, ANZKX has facilitated over 400 kidney transplants since inception and now results in approximately 50 kidney transplants each year (3). ■

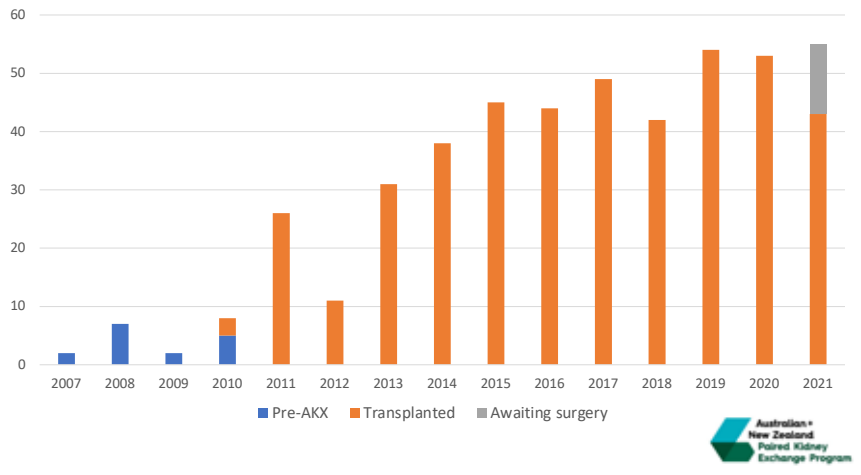
Kate Wyburn, BSc (Hons), MBBS, PhD, is with the Renal Department, Royal Prince Alfred Hospital, and is clinical professor at The University of Sydney, Australia.

The author reports no conflicts of interest.

References

1. Australia and New Zealand Dialysis and Transplant Registry. ANZDATA 43rd Annual Report 2020 (Data to 2019). Chapter 8: Kidney Donation. 2020. https://www.anzdata.org.au/wp-content/uploads/2020/09/c08_donation_2019_ar_2020_v1.0_20201222.pdf
2. Australia and New Zealand Organ Donation Registry. ANZOD Annual Report 2021. Section 5: Deceased Donor Kidney Donation. 2021. https://www.anzdata.org.au/wp-content/uploads/2021/08/s05_kidney_2021_v0.5_20210802.pdf
3. Australian and New Zealand Kidney Paired Kidney Exchange (ANZKX) Program. 2021. https://www.donatelife.gov.au/ANZKX

Figure 1. AKX / ANZKX transplant numbers



Findings

Increased Dose Versus Added Drug for BP Control: Randomized Trial

In older adults requiring intensification of antihypertensive therapy, adding a new medication leads to a greater reduction in blood pressure (BP), but maximizing dosage provides a more sustainable effect, reports a study in *Annals of Internal Medicine*.

The observational study included 178,562 patients requiring intensified antihypertensive treatment in the Veterans Health Administration (VA) system between 2011 and 2013. All patients were aged 65 years or older, had systolic BP (SBP) of 130 mm Hg or higher, and were taking one or more antihypertensive medications at less than maximum dose. Mean age was 75.8 years, and 98.1% of patients were men. The intensification strategy chosen was maximizing dosage in 74.5% of patients and adding a new medication in 25.5%. At 3 months, sustained intensification was achieved in 65.0% of patients receiving a maximized dose compared to 49.8% of those receiving a new medication. The average treatment effect was 15.2% at 3 months and 15.1% at 12 months.

In contrast, patients receiving a new medication had a slightly greater reduction in BP. The 3-month change in SBP was –4.9 mm Hg with adding a new medication versus –3.8 mm Hg with maximizing dose. Average treatment effect was –0.8 mm Hg at 3 months and –1.1 mm Hg at 12 months. For both outcomes, there was no interaction between intensification strategy and cardiovascular conditions.

Designed to emulate a clinical trial, the analysis helps address the lack of evidence on best strategy for older adults when intensified antihypertensive therapy is needed. In this VA population, adding a new medication provides a slightly greater reduction in SBP but a less-sustained effect.

By comparison, dose maximization is a more commonly followed strategy that provides greater sustainability. The researchers conclude, "Trials of different strategies of dose intensification are certainly feasible and would ultimately provide the most definitive support for our findings" [Aubert CE, et al. Adding a new medication versus maximizing dose to intensify hypertension treatment in older adults: A prospective observational study. *Ann Intern Med*, published online ahead of print October 5, 2021. doi: 10.7326/M21-1456; https://www.acpjournals.org/doi/10.7326/M21-1456]. ■

PCI Shows Benefits for Dialysis Patients with STEMI

For dialysis patients with ST-elevation myocardial infarction (STEMI), the benefits of percutaneous coronary intervention (PCI) are similar to those in non-dialysis patients, reports a study in the *American Journal of Kidney Diseases*.

Using the National Inpatient Sample, the researchers identified 413,500 adult hospitalizations for STEMI between 2016 and 2018. Of these, 4220 hospitalizations were for patients receiving dialysis—a rate of 1.07%. Dialysis patients with STEMI were older (65.2 versus 63.4 years), more likely to be women (42.4% versus 30.6%), and less likely to be White (41.1% versus 71.7%). Dialysis patients also had higher rates of comorbid cardiovascular and non-cardiovascular conditions.

Outcomes were compared for propensity score-matched cohorts of 2425 dialysis patients and 326,725 non-dialysis patients undergoing PCI, as well as 2420 dialysis patients and 325,955 non-dialysis patients who did not undergo PCI. The average treatment effect of PCI was estimated for in-hospital mortality and other outcomes.

Among STEMI patients, those on dialysis were less likely to undergo angiography (73.1% versus 85.4%) and less likely to undergo PCI (57.5% versus 79.8%). PCI was associated with lower mortality among dialysis patients (15.7% versus 27.1%), as well as non-dialysis patients (5.0% versus 17.4%). The average treatment effect was about the same between groups: –8.6% and –8.2%, respectively. The average marginal effect, accounting for clustering within hospitals, was –9.4% versus –7.9%. Other treatment effects of PCI were also similar for dialysis and non-dialysis patients, including major complications and discharge disposition. In both groups, PCI was associated with longer hospital stays and higher costs.

The study confirms that dialysis patients with STEMI are much less likely to undergo PCI compared to non-dialysis patients. However, despite their increased clinical risks, the in-hospital mortality benefit of PCI in dialysis patients appears similar to that for non-dialysis patients. The researchers conclude, "Further studies are needed to optimize STEMI care in the growing dialysis population" [Kawsara A, et al. Treatment effect of percutaneous coronary intervention in dialysis patients with ST-elevation myocardial infarction. *Am J Kidney Dis*, published online ahead of print October 15, 2021. doi: 10.1053/j.ajkd.2021.08.023; https://www.ajkd.org/article/S0272-6386(21)00922-7/fulltext]. ■

Scan this code to unmask a hidden culprit

THERE MAY BE A HIDDEN CULPRIT IN IgA NEPHROPATHY

A better understanding of the pathophysiology of IgA-related autoimmune diseases, including nephropathy, may help provide targets for future treatment exploration. Investigate further at **HiddenCulprit.com**

calliditas THERAPEUTICS

National Economy and Policies on End Stage Kidney Care in South Asia and South East Asia

By Hemant Mehta, Wasiyeeullah Shaikh, Sanjiv Jasuja, and Gaurav Sagar

The South East Asian region (SEAR) and South Asian countries (SACs) are divided as high and high-middle economies (HEs), low and lower-middle economies (LEs), and countries not classified due to lack of data (1) (Figure 1). The association between kidney disease and economic status is complex and directly affects therapeutic management. A rising burden of hypertension and diabetes mellitus in the region, with a high prevalence of smoking (11.8% in India), leads to the inter-related comorbidities for cardiovascular diseases and chronic kidney disease (CKD).

The overall higher morbidity and mortality of end stage kidney disease (ESKD) patients are due to poor availability of medical insurance, lack of government funding, limited means for out-of-pocket payment coupled with illiteracy, lack of awareness of dialysis, limited deceased donor transplant acceptance, and administrative delays (2). Moreover, patients are afraid of any type of dialysis, and it prompts them to use alternative medicines. Also, due to prevailing myths about dialysis—could cause death, expensive, inability to work, burden on family, etc.—patients try to avoid it. Furthermore, there is extreme social and economic disparity among people, and consequently, those with means can avail the best medical care in the same or other countries (3).

The choice of kidney replacement therapy depends on both state policy and funding.

The choice of kidney replacement therapy (KRT) depends on both state policy and funding. A "peritoneal dialysis (PD)-first" policy is a strategy used in Hong Kong, where it is subsidized, and Thailand (4), where it is free if the patients opts for the PD-first policy; however, the patient has to pay if hemodialysis (HD) is chosen as the first therapy. In Nepal, Indonesia, Vietnam, and Philippines, entire costs of PD for suitable patients are covered; in Sri Lanka and Myanmar, PD is partially covered. In India, Pakistan, and Bangladesh, funding is available only to state employees and below poverty-line patients (1, 5).

There is great contrast in and diversity of care available to patients in the developing world who have ESKD (6). Most patients have no or only meager resources to pay the recurring cost of ESKD care (7).

The lower frequency of HD sessions implemented is a reflection of poor socioeconomic status coupled with poor education (8). The average distribution of dialysis schedules in a week between HEs and LEs, respectively, is as follows: >2 HD sessions (84% vs. 25%), 2 HD sessions (16% vs. 64%), and <2 HD sessions (0.2% vs.

Table 1. ESKD hemodialysis session frequency in SEAR and SACs

Distribution of HD frequency	Overall						Higher economies (HE)/ lower economies (LE)					
	N	Mean	SD	Median	Min	Max	N	Mean	SD	Median	Min	Max
<2/week	15	6.8	12.4	2	0	48	6/9	0.2/11.2	0/10	0.4/14.7	0/0	1/48
2/week	15	44.9	34	50	1	92	6/9	15.9/64.2	3.9/62	25.1/24.1	1/16	65/92
>2/week	15	48.3	38.6	36	2	99	6/9	83.9/24.6	95.5/12	25/25.2	35/2	99/80

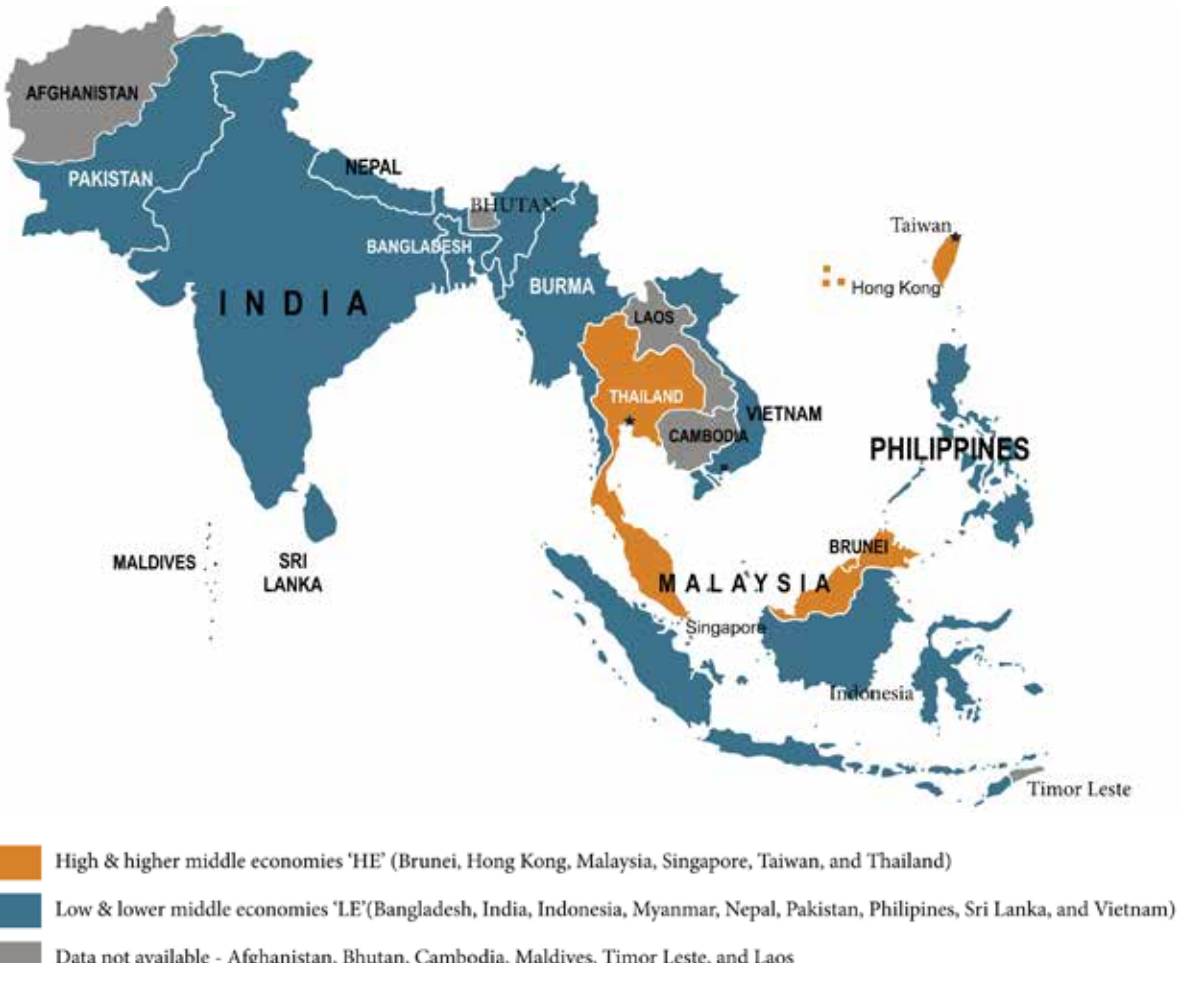
Adapted from Alexander et al. (1).

Table 2. What a few countries are doing to mitigate the problem of kidney care services in South East Asia

Country	Funding for medications (dialysis medications/transplant medications), yes or no
Afghanistan	No/No
Bangladesh	No/No
Bhutan	Yes/No
India	No/No
Nepal	Yes/No
Pakistan	No/No
Sri Lanka	No/Yes

Table 2 adapted from Divyaveer et al. (12). Vietnam has launched a cooperation program with the World Health Organization (WHO) to support the country in strengthening its health system (11). Indonesia set up a renal registry with initial pharmacy sponsorship and aided uptake by tying dialysis center licenses to mandatory participation in the registry (11). Sindh Institute of Urology and Transplantation in Karachi, Pakistan, provides free lifelong kidney care to all, with 35% state funding and the rest through philanthropy (13, 14). Ministry of Health and Family Welfare, Government of India, has a national dialysis program under the National Health Mission (15).

Figure 1. South Asia and Southeast Asia regional depiction based on economy



Alexander S, et al. Impact of national economy and policies on end-stage kidney care in South Asia and Southeast Asia. *International Journal of Nephrology*, Article ID 66659012021. https://doi.org/10.1155/2021/6665901

11.2%). HD sessions of <2/week were 56 times more common in LEs (median LE 14.7 vs. HE 0.4) (1) (Table 1).

The preventive measures for CKD are more cost effective at the community level, with successful implementation of a comprehensive yet inexpensive screening program to prevent CKD and treatment with low-cost medicines for hypertension and diabetes (9). In Taiwan, a kidney health promotion project, costing $15 million/year since 2003, has reduced the annual incidence of ESKD from a peak of 432 per million in 2005 to 361 per million in 2010 (10). An International Society of Nephrology (ISN) Global Kidney Policy Forum (Focus on South East Asia and Oceania 2019) recommended "developing appropriate solutions and driving innovation towards patient-centered, self-sufficient care" to give priority to preventive measures (11).

Equitable kidney care will be achieved by investment in people and processes (12) (Table 2). ■

Hemant Mehta, MD, DM (Nephrology), DNB (Nephrology), is a nephrologist with Lilavati Hospital and Research Center, Mumbai, India; executive director of the Association of Vascular Access & Interventional Renal Physicians (AVATAR Foundation); and patron of the Interventional Nephrology Forum (INForm). Wasiyeeullah Shaikh, DNB (Medicine), DNB (Nephrology), is with Holy Family Hospital, Mumbai, India. Sanjiv Jasuja, MD (Medicine), DNB (Nephrology), MNAMS, and Gaurav Sagar, MD (Medicine), DNB (Nephrology), MNAMS, are with Apollo Indraprastha Hospital, New Delhi, India.

The authors report no conflicts of interest.

References

1. Alexander S, et al. Impact of national economy and policies on end-stage kidney care in South Asia and Southeast Asia. *Int J Nephrol* 2021; 2021:6665901. doi: 10.1155/2021/6665901
2. Luyckx VA, et al. Dialysis funding, eligibility, procurement, and protocols in low- and middle-income settings: Results from the International Society of Nephrology collection survey. *Kidney Int Suppl (2011)* 2020; 10:E10–E18. doi: 10.1016/j.kisu.2019.11.005.
3. Jha V, et al. The state of nephrology in South Asia. *Kidney Int* 2019; 95:31–37. doi: 10.1016/j.kint.2018.09.001
4. Kwong VW-K, et al. Peritoneal dialysis in Asia. *Kidney Dis (Basel)* 2015; 1:147–156. doi: 10.1159/000439193
5. Tang SCW, et al. Dialysis care and dialysis funding in Asia. *Am J Kidney Dis* 2020; 75:772–781. doi: 10.1053/j.ajkd.2019.08.005
6. Kher V. End-stage renal disease in developing countries. *Kidney Int* 2002; 62:350–362. doi: 10.1046/j.1523-1755.2002.00426.x
7. Bharati J, Jha V. Global dialysis perspective: India. *Kidney360* 2020; 1:1143–1147. https://kidney360.asnjournals.org/content/1/10/1143
8. Dhaidan FA. Prevalence of end stage renal disease and associated conditions in hemodialysis Iraqi patients. *Int J Res Med Sci* 2018; 6:1515–1518. https://msjonline.org/index.php/ijrms/article/view/4941
9. Mani MK. Experience with a program for prevention of chronic renal failure in India. *Kidney Int* 2005; 67 (Suppl 94):S75–S78. doi: 10.1111/j.1523-1755.2005.09419.x
10. Jha V, et al. Chronic kidney disease: Global dimension and perspectives. *Lancet* 2013; 382:260–272. doi: 10.1016/S0140-6736(13)60687-X
11. International Society of Nephrology. ISN Global Kidney Policy Forum Series: Focus on South East Asia and Oceania 2019. April 12, 2019. https://www.theisn.org/wp-content/uploads/2021/06/Melbourne-2019-GKPF-Conclusions.pdf
12. Divyaveer SS, et al. International Society of Nephrology Global Kidney Health Atlas: Structures, organization, and services for the management of kidney failure in South Asia. *Kidney Int Suppl (2011)* 2021; 11:E97–E105. doi: 10.1016/j.kisu.2021.01.006
13. Jha V. Current status of end-stage renal disease care in India and Pakistan. *Kidney Int Suppl* 2013; 3:P157–P160. https://www.kisupplements.org/article/S2157-1716(15)31134-5/fulltext
14. Mazhar F, et al. Problems associated with access to renal replacement therapy: Experience of the Sindh Institute of Urology and Transplantation. *Exp Clin Transplant* 2017; 15 (Suppl 1):46–49. doi: 10.6002/ect.mesot2016.O27
15. Ministry of Health & Family Welfare, Government of India. National Dialysis Programme under National Health Mission. April 5, 2016. https://main.mohfw.gov.in/sites/default/files/Pradhan%20Mantri%20National%20Dialysis%20Programme%20under%20NHM_0.pdf

Glomerular Disease Corner

Managing Crescentic IgA Nephropathy

By Haresh Selvaskandan

Immunoglobulin A nephropathy (IgAN) is the most common glomerular disorder reported following biopsy worldwide (1–3). A wide variety of histopathological findings can be seen in IgAN, including crescents. Crescents are defined as two or more cell layers in Bowman's space (4). Their presence indicates active inflammation and predicts a poor prognosis in IgAN (4). The temptation to employ immunosuppression in crescentic IgAN is often strong, given the common practice in other glomerular disorders, but is it appropriate in IgAN? Let's consider a case study and explore the evidence for immunosuppression in crescentic IgAN.

The case

A 34-year-old man presents with fatigue and is found to have blood++ and protein++ in his urine on dipstick testing. His creatinine is elevated at 2.0 mg/dL, having been 1.9 mg/dL 4 months previously (only value known). His urine protein:creatinine ratio is 350 mg/g. A biopsy demonstrates diffuse mesangial IgA deposits with associated hypercellularity. Thirty percent of his glomeruli (4/13) demonstrates fibro-cellular crescents, and there is minimal interstitial fibrosis. There are no C1q or IgM deposits noted, and his immunology is negative, consistent with a diagnosis of IgAN, with a MEST-C score of M1 E0 S0 T0 C2.

Initial management

Thirty percent to 40% of those with IgAN reach kidney failure within 20 years of diagnosis (5, 6). Measures to reduce this risk include renin-angiotensin system inhibition, blood pressure control, smoking cessation, dietary salt restriction, and weight optimization. These standard interventions are not to be underestimated—they work and do reduce risk of progressive disease (7).

With the increasing evidence base for sodium-glucose co-transporter-2 (SGLT2) inhibitors in chronic kidney disease (CKD), many clinicians feel comfortable initiating them for IgAN. The evidence arises from a subgroup analysis of 270 IgAN patients enrolled in the DAPA-CKD study (which successfully demonstrated the efficacy of dapagliflozin in reducing risk of kidney failure and mortality in CKD) (8, 9). The pre-specified analysis, which included more patients with IgAN than any other IgAN trial to date, confirmed the benefits of dapagliflozin in IgAN. The findings need to be interpreted with an element of caution. More patients receiving placebo reached the composite renal endpoint than expected, perhaps due to suboptimal deployment of standard interventions, which were not optimized prior to randomization as a requirement for the trial (8, 9). Although SGLT2 inhibitors are safe and are likely to have a role in managing IgAN, their benefits beyond standard interventions are not immediately clear.

There are no other safe treatments available for reducing risk of IgAN progression. The only option that Kidney Disease: Improving Global Outcomes (KDIGO) lists for those who have proteinuric IgAN despite 6 months of optimal standard interventions is a course of corticosteroids. This is not without risks.

The risks of immunosuppressive therapy in IgAN

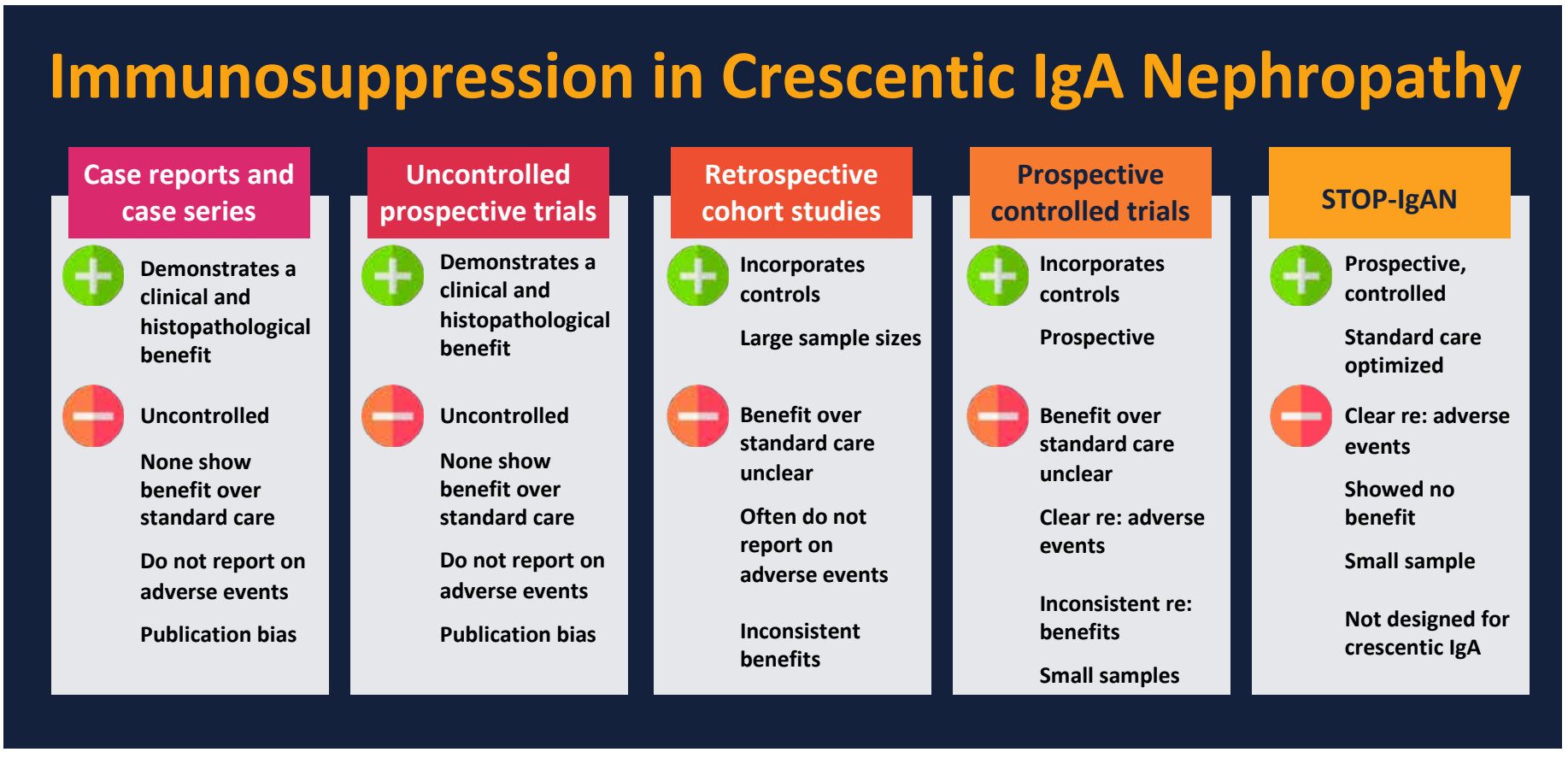
The evidence base for immunosuppression, including corticosteroids, comes from a group of small, randomized clinical trials from over 10 years ago (10–12). The main drawback of these trials was that they did not deploy optimized standard interventions prior to commencing immunosuppression, so it was unclear if immunosuppression truly conferred an added benefit. TESTING and STOP-IgAN were randomized controlled trials (RCTs) designed to answer this question (13, 14). They included a 6-month run-in period of optimized standard interventions, after which patients were randomized to either receive immunosuppression or not. Both trials found minimal benefits for immunosuppression but significant risks for adverse events; TESTING was prematurely halted because of this. A second iteration of TESTING is under way, employing lower doses of immunosuppression and *Pneumocystis jirovecii* prophylaxis.

Although it is possible that some with IgAN may benefit from corticosteroids, at present, there are no effective methods to determine who they may be, and it is clear from STOP-IgAN and TESTING that these benefits come at a cost. In keeping with this, draft KDIGO guidelines advise these risks be very carefully considered, and corticosteroids only be trialed in those who have proteinuric disease despite standard treatment (>1 gram/day), if their estimated glomerular filtration rate (eGFR) is above 30, with a low risk of adverse events related to steroids, and accepting benefits may be minimal.

This is crescentic IgAN—does that change the risk vs. benefit profile?

Crescents are a component of the MEST-C score, which describes five histopathological lesions in IgAN that are associated with a poor prognosis, independent of traditional prognostic markers (15, 16). The presence of crescents (in at least 25% of glomeruli, defined as C2 in the MEST-C score) confers a hazard ratio (HR) of 2.29 (1.35–3.91) for end stage kidney disease or 50% decline in eGFR (4). The prognostic value of crescents has been validated internationally. Despite this, consensus is that crescents alone should not influence management. This is reflected in the draft KDIGO 2020 guidelines and is based on the evidence base available.

A number of papers have sought to address the value of immunosuppression in crescentic IgAN. The vast majority are case reports/series or uncontrolled trials reporting success, including resolution of crescents on serial biopsies. None were set up to detect the risks of immunosuppression, all were uncontrolled, and all were prone to publication bias with few negative reports available. To address these shortcomings, a number of retrospective analyses of crescentic IgAN have been conducted. These results are more variable. The largest two (7143 patients total, including Caucasians and Asians) found those who received some form of immunosuppression developed kidney failure less often than those who did not. However, benefits were either minimal (HR of 1.31 vs. 1.51), or confidence intervals were wide (4, 17). Furthermore, it was unclear if these benefits were beyond that of standard interventions. Other analyses of different cohorts reported no benefit to immunosuppression in crescentic IgAN, including one with a sample size of 1152 (18).



Icons made by www.freepik.com from www.flaticon.com.

The results of TESTING and STOP-IgAN are likely applicable to our case study; both included a subgroup of crescentic IgAN patients with similar characteristics. TESTING excluded crescentic patients if >50% of crescents were present, and STOP-IgAN excluded crescentic patients if they also had evidence of rapidly progressive disease. TESTING ultimately included 144 crescentic patients (55% of participants), and STOP-IgAN included 22 (14%); crescents are more commonly seen in Chinese patients, who accounted for >95% of those in TESTING. A subgroup analysis of crescentic patients in STOP-IgAN also found no benefit of immunosuppression and in fact found crescents associated with kidney failure in the immunosuppressed group but not in the standard intervention group (limited sample size to be noted) (19).

Only two RCTs specifically investigated immunosuppression in crescentic IgAN. One (n = 20) found a benefit to 5-year renal survival but was not set up to detect adverse events related to immunosuppression (20). The other (n = 15) found no benefit to serum creatinine and proteinuria at 3 years, but more than 30% in the steroid group withdrew due to side effects (21). Neither trial optimized standard interventions prior to initiating immunosuppression.

The literature therefore is at best mixed with regard to the benefits of using immunosuppression in crescentic IgAN, but the risk of adverse events remains clear and significant. This risk-benefit profile would strongly suggest avoiding immunosuppression in stable or slowly progressive crescentic IgAN.

Are there any exceptions?

There are instances in which immunosuppression is suggested for the management of IgAN by KDIGO draft guidelines, notably in the context of rapidly progressive disease and variant forms of IgAN (e.g., co-presentation with minimal change disease). However, it is important to note that the presence or absence of crescents in any of the above scenarios should not influence management decisions.

Our patient doesn't have a variant form of IgAN nor does he have crescentic glomerulonephritis (GN)—is there anything more we can do?

Yes! With the introduction of surrogate end points for clinical trials, such as eGFR slopes and proteinuria, the number of clinical trials investigating novel and repurposed treatments of IgAN has rapidly increased. Enrolling this patient in any of the available clinical trials would be the most appropriate next step. These developments, combined with advances in laboratory methods investigating the mechanisms of IgAN, are likely to drive the management of IgAN into the era of personalized and precision medicine in the not-too-distant future. ■

Haresh Selvaskandan, MBChB (Hons), MRCP (UK), ESE (Neph), MRes, BSc (Hons), is a GlomCon Fellow and a Higher Specialist Trainee in nephrology (Nephrology Fellow)/Kidney Research UK Clinical Research Fellow with the John Walls Renal Unit, University Hospitals of Leicester, and Department of Cardiovascular Sciences, University of Leicester, UK.

Dr. Selvaskandan is a Kidney Research UK-funded clinical research fellow based at the Mayer IgA nephropathy Laboratories of the University of Leicester.

References

1. Nakai S, et al. An overview of regular dialysis treatment in Japan (as of 31 December 2004). *Ther Apher Dial* 2006; 10:476–497. doi: 10.1111/j.1744-9987.2006.00440.x
2. Chembo CL, et al. Long-term outcomes for primary glomerulonephritis: New Zealand glomerulonephritis study. *Nephrology (Carlton)* 2015; 20:899–907. doi: 10.1111/nep.12538
3. Murugapandian S, et al. Epidemiology of glomerular disease in southern Arizona: Review of 10-year renal biopsy data. *Medicine (Baltimore)* 2016; 95:e3633. doi: 10.1097/MD.0000000000003633
4. Haas M, et al. A multicenter study of the predictive value of crescents in IgA nephropathy. *J Am Soc Nephrol* 2017; 28:691–701. doi: 10.1681/ASN.2016040433
5. Wyatt RJ, Julian BA. IgA nephropathy. *N Engl J Med* 2013; 368:2402–2414. doi: 10.1056/NEJMra1206793
6. Reid S, et al. Non-immunosuppressive treatment for IgA nephropathy. *Cochrane Database Syst Rev* 2011; CD003962. doi: 10.1002/14651858.CD003962.pub2
7. Selvaskandan H, et al. New strategies and perspectives on managing IgA nephropathy. *Clin Exp Nephrol* 2019; 23:577–588. doi: 10.1007/s10157-019-01700-1
8. Barratt J, Floege J. SGLT-2 inhibition in IgA nephropathy: The new standard of care? *Kidney Int* 2021; 100:24–26. doi: 10.1016/j.kint.2021.04.002
9. Wheeler DC, et al. A pre-specified analysis of the DAPA-CKD trial demonstrates the effects of dapagliflozin on major adverse kidney events in patients with IgA nephropathy. *Kidney Int* 2021; 100:215–224. doi: 10.1016/j.kint.2021.03.033
10. Pozzi C, et al. Corticosteroids in IgA nephropathy: A randomised controlled trial. *Lancet* 1999; 353:883–887. doi: 10.1016/s0140-6736(98)03563-6
11. Manno C, et al. Randomized controlled clinical trial of corticosteroids plus ACE-inhibitors with long-term follow-up in proteinuric IgA nephropathy. *Nephrol Dial Transplant* 2009; 24:3694–3701. doi: 10.1093/ndt/gfp356
12. Lv J, et al. Combination therapy of prednisone and ACE inhibitor versus ACE-inhibitor therapy alone in patients with IgA nephropathy: A randomized controlled trial. *Am J Kidney Dis* 2009; 53:26–32. doi: 10.1053/j.ajkd.2008.07.029
13. Rauen T, et al. Intensive supportive care plus immunosuppression in IgA nephropathy. *N Engl J Med* 2015; 373:2225–2236. doi: 10.1056/NEJMoa1415463
14. Lv J, et al. Effect of oral methylprednisolone on clinical outcomes in patients with IgA nephropathy: The TESTING randomized clinical trial. *JAMA* 2017; 318:432–442. doi: 10.1001/jama.2017.9362
15. Trimarchi H, et al. Oxford classification of IgA nephropathy 2016: An update from the IgA Nephropathy Classification Working Group. *Kidney Int* 2017; 91:1014–1021. doi: 10.1016/j.kint.2017.02.003
16. Barbour SJ, et al. Evaluating a new international risk-prediction tool in IgA nephropathy. *JAMA Intern Med* 2019; 179:942–952. doi: 10.1001/jamainternmed.2019.0600
17. Chen T, et al. Identification and external validation of IgA nephropathy patients benefiting from immunosuppression therapy. *EBioMedicine* 2020; 52:102657. doi: 10.1016/j.ebiom.2020.102657
18. Zhang X, et al. A validation study of crescents in predicting ESRD in patients with IgA nephropathy. *J Transl Med* 2018; 16:115. doi: 10.1186/s12967-018-1488-5
19. Schimpf JI, et al. Renal outcomes of STOP-IgAN trial patients in relation to baseline histology (MEST-C scores). *BMC Nephrol* 2018; 19:328. doi: 10.1186/s12882-018-1128-6
20. Roccatello D, et al. Steroid and cyclophosphamide in IgA nephropathy. *Nephrol Dial Transplant* 2000; 15:833–835. doi: 10.1093/ndt/15.6.833
21. Kanno Y, et al. A comparison of corticosteroid and warfarin therapy in IgA nephropathy with crescent formation: Preliminary trial. *Clin Exp Nephrol* 2003; 7:48–51. doi: 10.1007/s101570300006

PRN Antihypertensive Medications in Hospitalized Patients: Doing More Harm than Good?

By Priyanka Athavale and Charlie M. Wray

Titrating blood pressure (BP) medications in the outpatient setting is one of the most fundamental practices in medicine. Unfortunately, managing hypertension in the inpatient setting may not be as evidence based or as straightforward as we think. For decades, our response to elevated BP in hospitalized patients has been to give intravenous or oral medications pro re nata (PRN). Although this intervention does a decent job at lowering BP to an acceptable range, the question of whether or not it is actually helping the patient, or more importantly not doing any harm, remains an important one.

A recent study in the journal *Hypertension* examined data from over 4000 propensity-matched hospitalized patients who, in addition to their scheduled antihypertensives, also received PRN antihypertensives and compared adverse outcomes to those who only received scheduled antihypertensives. The authors found that patients who received PRN antihypertensives were more likely to experience immediate lowering of systolic BP, acute kidney injury, ischemic events, and longer hospital stays (1). Although these findings may be new to many, the literature around this topic has been growing in recent years.

A similar analysis published in the *Journal of the American Medical Association Internal Medicine* examined inpatient antihypertensive use in over 20,000 patients admitted for non-cardiac reasons and similarly found that individuals treated with PRN antihypertensives had higher rates of acute kidney injury and myocardial ischemia compared to a matched cohort (2). So the answer is to increase the patient's daily regimen, right? Not quite, as there is little evidence that intensifying antihypertensives at discharge is associated with improved BP control or reduced cardiac events. For example, a recent study by Anderson et al. (3) found that an antihypertensive regimen that was intensified during hospitalization led to increased readmission rates and more serious adverse events within 30 days of discharge.

Despite the widespread practice of treating asymptomatic hypertension in the hospital, there is growing evidence to support that this may have unintended side effects. Although institutions often use standardized order-sets to treat hypertension in the inpatient setting, these studies show that such practices should be reexamined and potentially modified. Instead of reflexively treating elevated BPs, careful consideration of the underlying cause of hypertension should be the initial treatment (4). Additionally, instead of making such decisions on their own, inpatient providers should look to other resources to help guide their decision-making process. For instance, the use of electronic health records of outpatient medications and BP trends and clinical pharmacists are resources that can be leveraged to support optimal treatment of inpatient hypertension.

All told, this growing body of literature may be ushering in a paradigm shift in how we think about hypertension management in the hospitalized patient. Simply put, PRN antihypertensives and aggressive uptitration of antihypertensives in the inpatient setting may, in fact, do more harm than good. ■

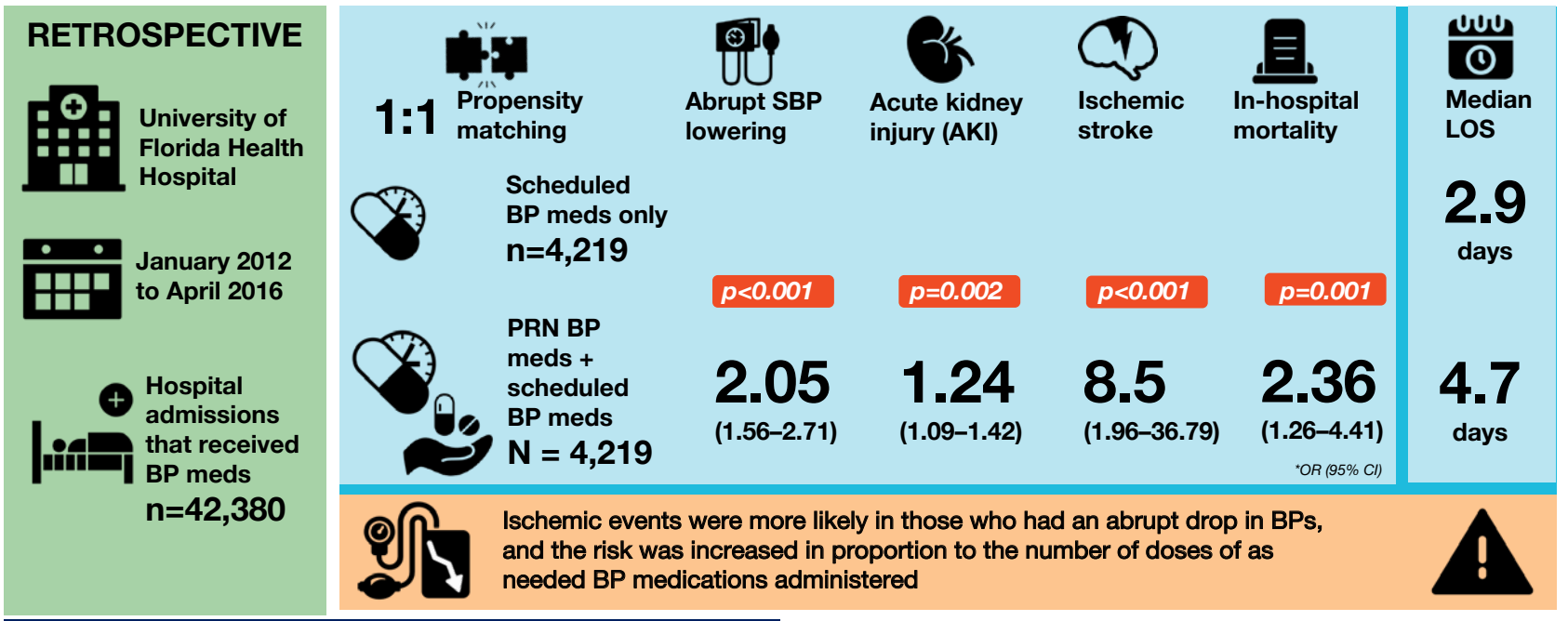
Priyanka Athavale, MD, MS, is with the Department of Medicine, University of California, San Francisco. Charlie M. Wray, DO, MS, is with the Department of Medicine, San Francisco Veterans Affairs Hospital, San Francisco, CA.

The authors report no conflicts of interest.

References

1. Mohandas R, et al. Pro re nata antihypertensive medications and adverse outcomes in hospitalized patients: A propensity-matched cohort study. *Hypertension* 2021; 78:516–524. doi: 10.1161/HYPERTENSIONAHA.121.17279
2. Rastogi R, et al. Treatment and outcomes of inpatient hypertension among adults with noncardiac admissions. *JAMA Intern Med* 2021; 181:345–352. doi: 10.1001/jamainternmed.2020.7501
3. Anderson TS, et al. Clinical outcomes after intensifying antihypertensive medication regimens among older adults at hospital discharge. *JAMA Intern Med* 2019; 179:1528–1536. doi: 10.1001/jamainternmed.2019.3007
4. Anderson TS, Wray CM. Web exclusive. Annals for hospitalists inpatient notes—inpatient hypertension—to treat or tolerate? *Ann Intern Med* 2020; 172:HO2–HO3. doi: 10.7326/M20-1021

Association between PRN Use of Antihypertensive Medications and Adverse Outcomes in Hospitalized Patients



Mohandas R, et al. ***Pro Re Nata Antihypertensive Medications and Adverse Outcomes in Hospitalized Patients: A Propensity-Matched Cohort Study***. Hypertension. 2021;78:516–524. DOI: 10.1161/HYPERTENSIONAHA.121.17279.

SGLT2 Inhibitors Continue to Show Kidney, Heart Benefits at Kidney Week

By Bridget M. Kuehn

Results from two major trials of sodium glucose co-transporter 2 (SGLT2) inhibitors, a class of drugs initially developed as a treatment for type 2 diabetes mellitus, add to evidence that the drugs may offer kidney-protecting benefits. The results were presented during the High-Impact Clinical Trials session at Kidney Week 2021.

The Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease (DAPA-CKD) trial found that the SGLT2 inhibitor dapagliflozin provided heart and kidney benefits regardless of the cause of underlying kidney disease. Results from the Empagliflozin Outcome Trial in Patients with Chronic Heart Failure with Reduced Ejection Fraction (EMPEROR-Reduced) trial of the SGLT2 inhibitor empagliflozin showed the drug reduced serious complications from heart failure and kidney disease in patients with and without chronic kidney disease. Results from the Finerenone in Reducing Kidney Failure and Disease Progression in Diabetic Kidney Disease (FIDELIO-DKD) trial were also presented during the session and suggested that finerenone, a non-steroidal mineral corticoid receptor antagonist, may reduce kidney and heart harm in patients with chronic kidney disease and diabetes, adding to the potential options for this often hard-to-treat group.

"It's an extremely exciting time in nephrology to finally have additional options for the treatment of our patients," said session co-moderator Linda Awdishu, PharmD, a professor of clinical pharmacy at the University of California, San Diego.

SGLT2s shine

Results from DAPA-CKD (1) showed dapagliflozin improved cardiovascular and kidney outcomes for patients with type 2 diabetes mellitus and chronic kidney disease, but whether the results extended to other types of chronic kidney disease were not clear, said David Wheeler, MD, professor of kidney medicine at University College London.

At Kidney Week, Wheeler presented results of a prespecified secondary analysis including 4304 participants of the DAPA-CKD trial that showed the heart and kidney benefits of dapagliflozin were consistent across all types of kidney diseases. Patients with polycystic kidney disease and immune system disease requiring immunosuppressive therapy were excluded.

"We've shown that these renal and cardiovascular mortality benefits are present regardless of the underlying cause of chronic kidney disease and regardless of the presence or absence of type 2 diabetes," Wheeler said. "Dapagliflozin was well tolerated with a safety profile that was consistent with that seen in other populations."

Wheeler noted, "Importantly, none of the nondiabetic patients developed ketoacidosis or hyperglycemia in the study." He also reported during the press briefing that they did not see an excess of amputations in patients taking the drug compared with placebo. The US Food and Drug Administration (FDA) had initially warned of a potential risk of foot and leg amputation with the SGLT2 inhibitor canagliflozin, but that warning was later removed based on newer data (2).

"Safety information from recent clinical trials also suggests that the risk of amputation, while still increased with canagliflozin, is lower than previously described, particularly when appropriately monitored," according to the FDA statement.

Rajiv Agarwal, MBBS, professor of medicine at the Indiana University School of Medicine, said he believed that SGLT2 inhibitors do not increase the risk of amputation.

"Anybody who has had a previous amputation will be at risk of a future amputation," Agarwal said. "These drugs don't enhance that risk."

Daniel Weiner, MD, associate medical director of dialysis and associate professor at Tufts University, said that during the Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE) trial of canagliflozin (3), he and his colleagues paid a lot of attention to diabetic foot wounds, something he said should be standard of care in vulnerable patient populations. "In these vulnerable populations with diabetes and kidney diseases we should be looking at feet regularly," Weiner said. He added in a follow-up interview by e-mail that he believes agents in this class of drugs have similar risk and benefit profiles.

The EMPEROR-Reduced trial (4) has previously shown that empagliflozin reduces cardiovascular death and heart failure hospitalization and slows kidney function decline in patients with heart failure with reduced ejection fraction. Now, data presented at Kidney Week and published in *Circulation* (5) show the benefits extend to patients with chronic kidney disease. The data found empagliflozin reduced the risk of cardiovascular death and heart failure hospitalization by one-quarter; reduced total heart failure hospitalizations by 30%; and reduced a composite of dialysis, transplant, and kidney death by one-half.

"Empagliflozin slows kidney function decline in patients with and without chronic kidney disease across the spectrum," said Faiez Zannad, MD, PhD, a cardiologist and professor of therapeutics at the University of Lorraine in France, during the High-Impact Clinical Trials session. Additionally, the data found the treatment was well tolerated by patients, with and without chronic kidney disease.

Diabetes options

Treatment options for patients with kidney disease and diabetes have long been limited, but the growing data on the benefits of SGLT2 inhibitors are promising. The results from FIDELIO-DKD suggest finerenone may be another promising option—if it is approved by the FDA.

In the FIDELIO-DKD trial, which was published in *The New England Journal of Medicine* (6), 5734 patients with chronic kidney disease and type 2 diabetes mellitus from 48 countries were randomized to receive either finerenone or placebo. All of the patients were treated with a renin-angiotensin system blockade prior to randomization. It found that finerenone reduced a composite of kidney failure, a sustained 40% decrease in estimated glomerular filtration rate from baseline, or death by 18%, said Agarwal, a study co-author, during a press briefing. The drug also reduced a composite of death from cardiovascular causes, nonfatal cardiac events, and hospitalization for heart failure by 14%.

"This is an exciting discovery because we've had many other [failures] in this high-risk population of patients with diabetes and chronic kidney disease," Agarwal said.

As expected, patients in the finerenone group had a higher rate of hyperkalemia compared with the placebo group (18.3% vs. 9%), but only 2.3% of patients in the finerenone group permanently discontinued this drug because of hyperkalemia compared with 0.9% in the placebo group, Agarwal said. He noted that the rate of discontinuation because of hyperkalemia was much higher with spironolactone in the AMBER trial (7).

"An ideal drug would cause no hyperkalemia, but if you look at absolute risk it's a fraction of what we saw when we used spironolactone in this vulnerable population," Agarwal said.

Too small a proportion of patients in the FIDELIO trial (4% in the placebo and 5% in the treatment group) were taking an SGLT2 inhibitor to determine what role SGLT2 inhibitors might play in combination with finerenone, Agarwal said. Wheeler noted during the press briefing that he and his colleagues saw benefits in the small proportion of patients in the DAPA-CKD trial who were taking a mineralocorticoid receptor antagonist along with dapagliflozin.

Agarwal said dual therapy with an SGLT2 inhibitor and a renin-angiotensin-aldosterone system (RAAS) inhibitor is well-established clinical practice. If finerenone were to be approved by the FDA, it might become part of a stepwise approach or as part of a triple therapy for high-risk patients.

"If we were to be [FDA] approved, then definitely you're going to individualize therapy," he said.

Among the other trials presented during the High-Impact Clinical Trials session were the following:

- A trial showing that using citrate for anticoagulation during continuous kidney replacement therapy extended filter life compared with heparin but was inconclusive regarding a mortality benefit. Heparin was associated with more bleeds, and citrate was associated with more infections (abstract FR-OR57).
- Results from the Reducing the Burden of Dialysis Catheter Complications: A National Approach (REDUCCTION) trial found a safety bundle designed to reduce catheter-related bloodstream infections did not significantly reduce these infections (abstract FR-OR56).
- A cluster randomized trial of oral protein supplementation during dialysis for patients with normal serum albumin did not find a mortality benefit for patients with normal serum albumin (abstract-FR-OR55). ■

References

1. Heerspink HJL, et al. Dapagliflozin in patients with chronic kidney disease. *N Engl J Med* 2020; 383:1436–1446. doi: 10.1056/NEJMoa2024816
2. US Food and Drug Administration. FDA removes boxed warning about risk of leg and foot amputations for the diabetes medicine canagliflozin (Invokana, Invokamet, Invokamet XR). August 26, 2020. https://www.fda.gov/drugs/drug-safety-and-availability/fda-removes-boxed-warning-about-risk-leg-and-foot-amputations-diabetes-medicine-canagliflozin
3. Perkovic V, et al. Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. *N Engl J Med* 2019; 380:2295–2306. doi: 10.1056/NEJMoa1811744
4. Packer M, et al. Cardiovascular and renal outcomes with empagliflozin in heart failure. *N Engl J Med* 2020; 383:1413–1424. doi: 10.1056/NEJMoa2022190
5. Zannad F, et al. Cardiac and kidney benefits of empagliflozin in heart failure across the spectrum of kidney function: Insights from the EMPEROR-Reduced trial. *Circulation* 2021; 143:310–321. doi: 10.1161/CIRCULATIONAHA.120.051685
6. Bakris GL, et al. Effect of finerenone on chronic kidney disease outcomes in type 2 diabetes. *N Engl J Med* 2020; 383:2219–2229. doi: 10.1056/NEJMoa2025845
7. Agarwal R, et al. Patiromer versus placebo to enable spironolactone use in patients with resistant hypertension and chronic kidney disease (AMBER): A phase 2, randomised, double-blind, placebo-controlled trial. *Lancet* 2019; 394:1540–1550. doi: 10.1016/S0140-6736(19)32135-X

Managing Obesity in Chronic Kidney Disease

By Vishnu P. Parvathareddy

The global burden of chronic kidney disease (CKD) is increasing, and obesity is recognized as an independent risk factor for CKD. Healthy lifestyle changes are essential for long-term well-being and are proven to assist with weight loss and long-term weight maintenance. Even a moderate degree of weight loss decreases metabolic demands on the kidneys, reduces proteinuria, and potentially aids in delaying CKD progression. The benefits of different diets used for weight loss are uncertain in those with CKD. Thus, clinical practice guidelines recommend consumption of a healthy, balanced diet along with 150–300 min of moderate-intensity physical activity per week or 75–150 min of vigorous activity per week for those with non-dialysis-dependent CKD (1). Sodium-glucose cotransporter-2 (SGLT2) inhibitors offer both cardiovascular and kidney benefits in patients with or without diabetes and are associated with weight loss. Similarly, glucagon-like peptide 1 (GLP1) agonists lower cardiovascular events and albuminuria and also lead to weight loss (2).

Obtaining a detailed history and review of medications would help clinicians identify reasons for weight gain and potential alternatives for treatment that are weight-neutral/weight-loss medications (Table 1). Several weight-loss medications approved by the US Food and Drug Administration (FDA) have not been studied in patients with CKD (Table 2). Bariatric (metabolic) surgery offers durable weight loss and results in improved outcomes. Bariatric surgery in patients with CKD is associated with reduced progression to end stage kidney disease (ESKD) or enables selected ESKD patients with severe obesity to become candidates for kidney transplantation (3). However, there are also risks of acute kidney injury, nephrolithiasis, and oxalate nephropathy, particularly in malabsorptive procedures that should be recognized. Future studies should address the safety and efficacy of FDA-approved weight-loss medications and various bariatric procedures in CKD patients. As experimental studies advance our understanding of the pathophysiology of obesity, additional clinical trial data would help in the development of evidence-based recommendations for managing obesity in CKD. It is also critical to incorporate education about obesity management into nephrology training programs. ■

Vishnu P. Parvathareddy, MD, CPE, is with the Selzman Institute for Kidney Health, Section of Nephrology, Department of Medicine, Baylor College of Medicine, Houston, TX.

The author reports no conflicts of interest.

References

1. Jensen MD, et al. 2013 AHA/ACC/TOS guideline for the management of overweight and obesity in adults: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and The Obesity Society. *Circulation* 2014; 129:S102–S138. doi: 10.1161/01.cir.0000437739.71477.ee
2. Brown E, et al. Weight loss variability with SGLT2 inhibitors and GLP-1 receptor agonists in type 2 diabetes mellitus and obesity: Mechanistic possibilities. *Obes Rev* 2019; 20:816–828. doi: 10.1111/obr.12841
3. American Association of Clinical Endocrinologists/American College of Endocrinology. AACE/ACE algorithm for the medical care of patients with obesity. 2016; 1–10. https://deansomerset.com/wp-content/uploads/2016/06/AACE-ObesityAlgorithm-2016.pdf

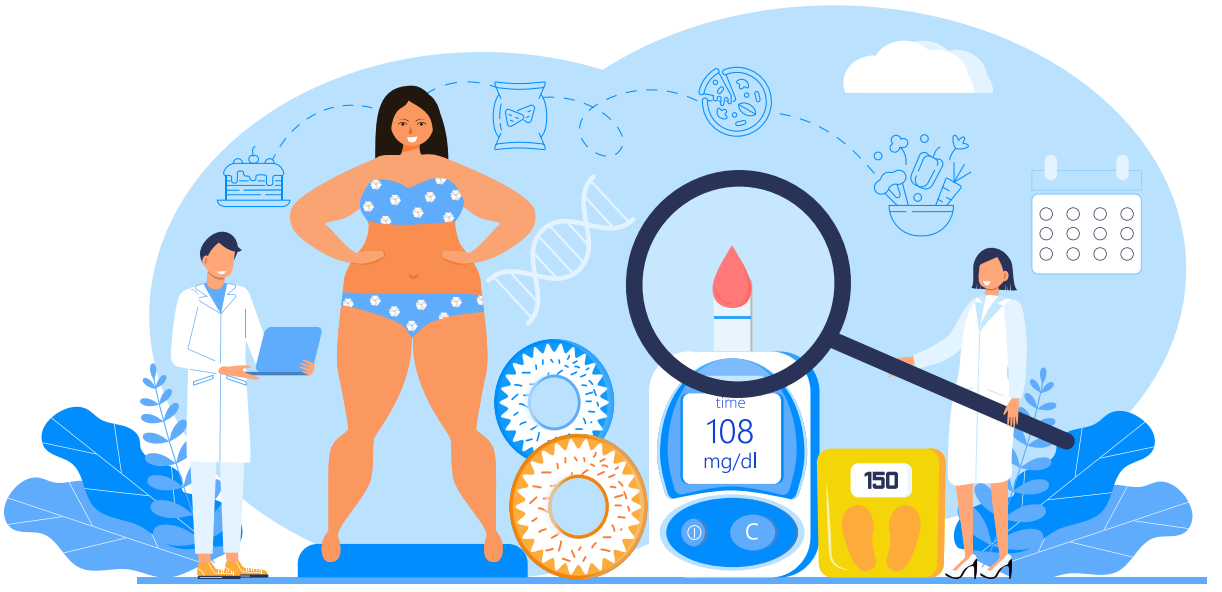


Table 1. Commonly used medications that cause weight gain and potential alternatives

Medications causing weight gain	Potential alternatives
Oral hypoglycemics	
Short-acting insulin: lispro, aspart, glulisine *Sulfonylureas* *Thiazolidinediones* *Meglitinides*	*Long-acting insulin:* Levemir, glargine, degludec *Biguanides:* metformin *SGLT2 inhibitors* *GLP1 agonists* *DPP4 inhibitors* *Alpha-glucosidase inhibitor:* acarbose
Antihypertensives	
Beta blockers: propranolol, metoprolol, atenolol *Calcium channel blockers* *Alpha adrenergic blockers* *Alpha adrenergic agonists:* methyldopa	*Angiotensin-converting enzyme inhibitors* *Angiotensin receptor blockers* *Beta blockers:* carvedilol, nebivolol
Antidepressants	
Tricyclics *Monoamine oxidase inhibitors* *SSRI:* paroxetine, fluvoxamine	*SSRI:* citalopram, duloxetine, fluoxetine *NDRI:* bupropion *Serotonin modulator:* nefazodone *SNRI:* venlafaxine
Antipsychotics	
Risperidone Clozapine Haloperidol Fluphenazine Olanzapine Quetiapine Lithium Chlorpromazine	Ziprasidone Aripiprazole
Antiseizures	
Carbamazepine Valproic acid Gabapentin	Topiramate Zonisamide Lamotrigine Levetiracetam Phenytoin
Contraceptives	
Depo medroxyprogesterone Hormonal IUD	Copper IUD Oral contraceptive pill
Antihistamines	
Diphenhydramine Meclizine Cyproheptadine	Cetirizine Fexofenadine Loratadine

DPP4 inhibitors, dipeptidyl peptidase 4 inhibitors; GLP1 agonists, glucagon-like peptide 1 agonists; SGLT2 inhibitors, sodium-glucose cotransporter-2 inhibitors; SSRI, selective serotonin reuptake inhibitors; NDRI, norepinephrine dopamine reuptake inhibitor; SNRI, selective serotonin and norepinephrine reuptake inhibitor; IUD, intrauterine device.

Table 2. Weight-loss medications

Medication	Mechanism of action	Dose adjustment in CKD	Expected % weight loss	Side effects	Contraindications
Phentermine	Increase in norepinephrine; increased energy expenditure	CrCl 15–29, 15 mg/day; CrCl <15, avoid	5%–7%	Elevated blood pressure, palpitations, dry mouth, tremors, insomnia, anxiety	Uncontrolled hypertension, hyperthyroidism, recent history of coronary artery disease, angle-closure glaucoma, drug abuse, agitation, psychosis; drug interactions with: MAOI, alcohol, other sympathomimetics, and adrenergic blockers
Phentermine Topamax	Norepinephrine release (phentermine) GABA receptor modulator (Topamax)	CrCl 30–50, 7.5/46 mg/day; CrCl <30, avoid	10%–12%	In addition to above, paresthesia, dysgeusia, constipation, dizziness	In addition to above, nephrolithiasis, mood disorders
Orlistat	Lipase inhibitor	No dose adjustment is needed, as it is not renally excreted.	5%	Flatulence, fecal incontinence, steatorrhea, malabsorption of fat-soluble vitamins, promotes gallstones and kidney stones	Chronic malabsorption syndrome, cholestasis; interaction with warfarin, oral contraceptives, cyclosporine, thyroid hormones, and seizure medications
Naltrexone/ bupropion ER	Opiate antagonist (naltrexone); norepinephrine dopamine reuptake inhibitor (bupropion)	CrCl 30–50, 8/90 mg BID; CrCl <30, avoid	5%–10%	Headache, nausea, constipation, dizziness, dry mouth, increased risk for suicidal ideation; bupropion reduces seizure threshold	Uncontrolled hypertension, seizure disorder, drug/alcohol withdrawal, purging/bulimia nervosa; drug interactions with opioid pain meds, antiseizure meds, MAOI
Liraglutide	GLP1 analog	CrCl <30, use with caution	8%–10%	Diarrhea, dyspepsia, abdominal pain, hypoglycemia, dizziness; reduces absorption of concomitantly administered oral medications as it delays gastric emptying	Personal/family history of medullary thyroid carcinoma or type 2 multiple endocrine neoplasia syndrome; pancreatitis/gallbladder disease

All weight-loss medications are relatively contraindicated while pregnant or breastfeeding. CrCl, creatinine clearance; MAOI, monoamine oxidase inhibitors; GABA, gamma-aminobutyric acid; ER, extended release; BID, twice/day.

COVID-19 Wellness Module Offered through ASN Website

By Karen Blum

A new wellness module offered through ASN's website aims to promote balanced mental health among people who work in dialysis facilities. It conveys that feelings of compassion fatigue experienced during the ongoing COVID-19 pandemic are understandable and offers resources and strategies on how to cope and move forward.

"We're just beginning to see the mental health fallout of COVID," said Daniel Cukor, PhD, a coauthor of the new module and director of behavioral health at the Rogosin Institute in New York. There's a great shift happening now in hesitancy over returning to work in the general population, he said, which is extending into the nephrology community. "Some of that is burnout, people feeling really overwhelmed with healthcare responsibilities at their job. Many people have been through challenging times over the last year and a half, and they're re-evaluating whether they have the desire to continue doing that type of work."

The module, "Pursuing Mental Wellness: The Impact of COVID-19 on Dialysis Facility Staff," features seven lessons offered via text and videos to help clinicians identify compassion fatigue and how it can appear in healthcare settings. It also offers tips, strategies, and resources that individuals and organizations can use to foster resilience. Some nephrologists and their colleagues also share information about how they remained positive and overcame pandemic fatigue, such as by practicing gratitude and spending time outdoors. One nephrology fellow said his program director purchased jewelry made by a kidney transplant recipient to serve as a morale booster.

Compassion fatigue is different from traditional burnout, said nephrologist Matthew Sinclair, MD, a coauthor of the module, medical instructor at Duke University School of Medicine, and a staff physician with the Durham Veterans Administration Medical Center in North Carolina. It's more of a posttraumatic stress disorder-type response to the ongoing pressure of working in a high-acuity environment, he said. Symptoms include emotional, mental, or physical exhaustion; a reduced sense of meaning in work; and decreased interaction with others.

People who work in dialysis centers already had ongoing stressors, Sinclair said. Patients receive years of ongoing care, often from the same personnel, and are dependent on staff for treatment. Nephrologists have multiple responsibilities, and non-physicians spend the bulk of their time directly in the clinics.

The COVID-19 pandemic then compounded these issues, with dialysis clinic staffs often having to set up separate shifts for COVID-19-positive patients, working extra hard to prevent the spread of COVID-19, and worrying about contracting the virus themselves or bringing it home to their families.

ASN and the authors wanted to emphasize to the dialysis community that these feelings are being experienced by a lot of people, Sinclair said. "This isn't just focused on one particular provider or aspect of health care—the lessons could be widely applicable to anybody who takes care of patients during COVID," he said.

"For people who are going through some of these experiences of feeling burnt out, disengaged from their work, and not as empathetically connected to their patients, I hope this will be a first stop that they can go to begin to get some resources to understand what's going on inside and link that to get professional mental health help if warranted," Cukor said. "We don't want good people leaving healthcare just because they're feeling burdened and overwhelmed at the moment….We want those people to be able to build up their reserves and re-engage in a healthful way with our patient community."

Other coauthors of the wellness module are Vineeta Kumar, MD; Jeffrey Silberzweig, MD; and Felicia Speed, LMSW, PhD. To review the free course, see https://rise.articulate.com/share/ciYQC-LTODyPV591tbL7Eo-LAI4eelbmd#/.

Steps you can take to combat compassion fatigue

- Take time off from work.
- Identify things that are truly important or valuable in your life.
- Find new hobbies or interests unrelated to medicine.
- Talk to a family member, friend, colleague, or mental health professional.
- Exercise, and eat well.
- Get sufficient sleep.

Blood Pressure Management in Special Populations: Patients with End Stage Kidney Disease and Kidney Transplant Recipients

By Emily Dryer

KDIGO (Kidney Disease: Improving Global Outcomes) recently updated its guidelines for hypertension management in patients with chronic kidney disease (CKD). While awaiting forthcoming trials for better evidence, the guidelines are a reminder to use an individualized approach to all patients, including patients with end stage kidney disease (ESKD) and kidney transplant recipients (KTRs) (1).

The patient with ESKD

A major challenge in managing hypertension in the ESKD population lies in finding balance between attaining euvolemia while minimizing risk of complications from both hypertension and hypotension (2). Establishing blood pressure (BP) targets for this population is also challenging. A high burden of cardiovascular disease and wide pulse pressure are common in dialysis patients, both of which carry increased risk of morbidity and mortality. It is unclear if achievement of any given BP target provides morbidity and mortality benefits. It is also unclear if any benefit is derived from the choice of antihypertensive agent targeting the specific comorbid condition (3).

BP targets

Based on current evidence, definitive recommendations on target BP in the ESKD population cannot be made. Individualized treatment planning must be based on volume management, BP trends, history of intradialytic hypotension, and comorbid conditions (Figure 1). Published recommendations have suggested targeting a pre-dialysis BP of <140/90 and a post-dialysis BP of <130/90, but in other guidelines, no target is identified due to lack of clinical trial data (3). The Blood Pressure in Dialysis pilot study evaluated feasibility and safety to inform a larger randomized controlled trial (RCT) assessing clinical outcomes based on varying BP targets in dialysis patients (4). Feasibility was demonstrated in this study, and defining BP targets will depend on the completion of large RCTs in the future.

Pharmacologic approach

Although not discussed in the 2021 KDIGO Practice Guidelines, the 2017 KDIGO recommendations suggest that pharmacologic selection for BP management in ESKD patients should be based on the patient's medical history and comorbid conditions. The general consensus is to use beta blockers as first-line therapy due to vulnerability of dialysis patients to coronary artery disease and serious arrhythmias (5). Drug pharmacodynamics and dialyzability are important considerations (Table 1). Reduction in pill burden can promote improved medication adherence (2).

The kidney transplant recipient

The difficulty in establishing BP management guidelines in the KTR population lies in the lack of studies designated specifically to this population. Guidelines created for the CKD population have been generalized to include KTRs, which may limit applicability. Special considerations in this population include the impact of BP on allograft function and rejection. Interactions between antihypertensive therapy and immunosuppressive therapy, especially calcineurin inhibitors (CNIs), must also be considered (6).

BP targets

There are no completed RCTs in KTRs; thus, a definitive guideline on a BP target cannot be made. 2021 KDIGO recommendations suggest adult KTRs should be treated to a BP goal of <130/80 using standardized office BP measurement (Figure 2). A lower target, as suggested for CKD patients, may not be appropriate for KTRs without further data on the risks and benefits of targeting such BP in this population (1).

Pharmacologic selection

Calcium channel blockers (CCBs) are recommended as first-line therapy in KTRs, as they increase renal blood flow by counteracting CNI-induced vasoconstriction. Non-dihydropyridine CCBs increase levels of CNIs and thus should be used cautiously (1). For those who additionally have cardiovascular disease, diabetes, or ongoing proteinuria, consider renin-angiotensin-aldosterone system (RAAS) inhibitors. RAAS inhibition should not be initiated in the immediate posttransplant period due to risk of hyperkalemia and changes in serum creatinine (particularly in combination with CNIs) as well as posttransplant anemia (7, 8).

The guidelines on hypertension management in ESKD patients and KTRs are vague due to paucity of clinical trial data available for these populations, and additional research is needed to better understand their needs. Generalization and application of guidelines created for larger populations should be approached with caution. ■

Emily Dryer, DO, is a clinical nephrology fellow at the University of Alabama at Birmingham.

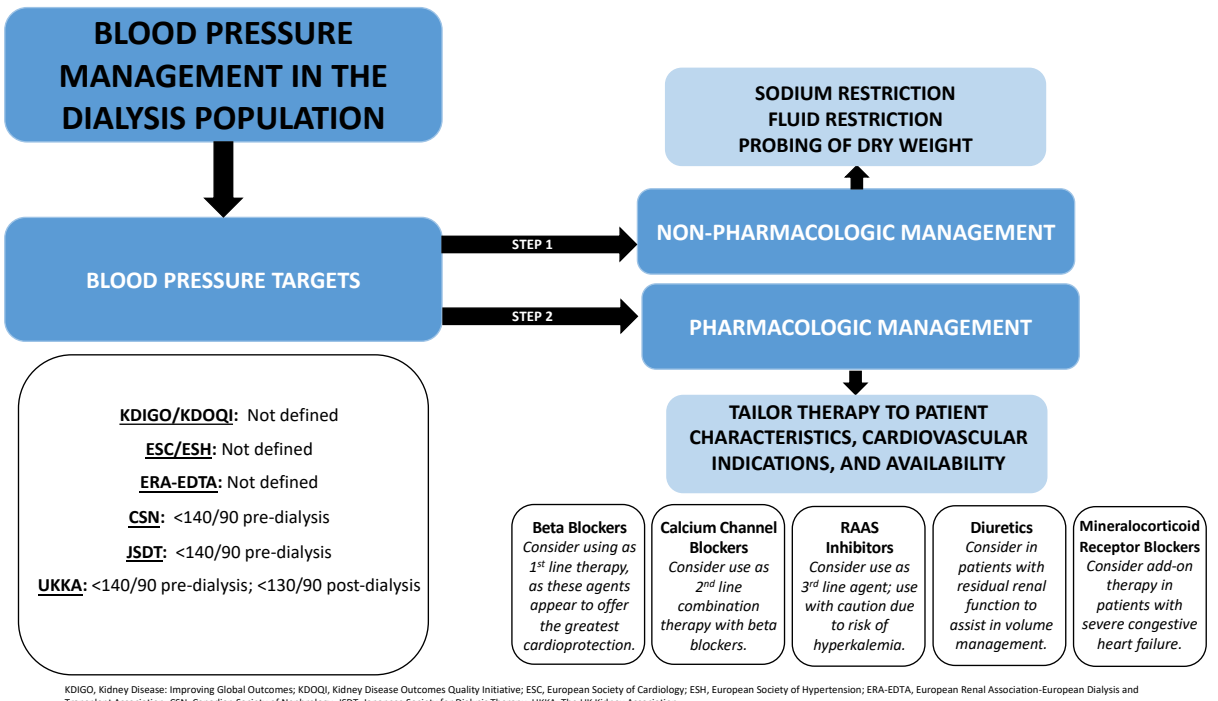
The author reports no conflicts of interest.

Table 1. Dialyzable antihypertensive drugs

Antihypertensive drug	Usual dosage	Removal with dialysis	Supplement dose for dialysis
ACE INHIBITORS			
Benazepril	5–40 mg daily	20%–50%	5–10 mg
Captopril	12.5–50 mg TID	50%	12.5–25 mg
Enalapril	2.5–10 mg Q12H	50%	2.5–5 mg
Lisinopril	2.5–10 mg daily	50%	2.5–5 mg
Ramipril	5–10 mg daily	20%	2.5 mg
BETA BLOCKERS			
Atenolol	25 mg daily	50%	25–50 mg
Nadolol	80–100 mg BID	50%	80 mg
ALPHA AGONISTS			
Clonidine	0.1–0.3 mg BID to TID	5%	None
NITRATES			
Hydralazine	25–50 mg BID to TID	25%–40%	None

ACE, angiotensin-converting enzyme; TID, three times/day; Q12H, every 12 h; BID, twice/day.

Figure 1. Managing BP in the dialysis population

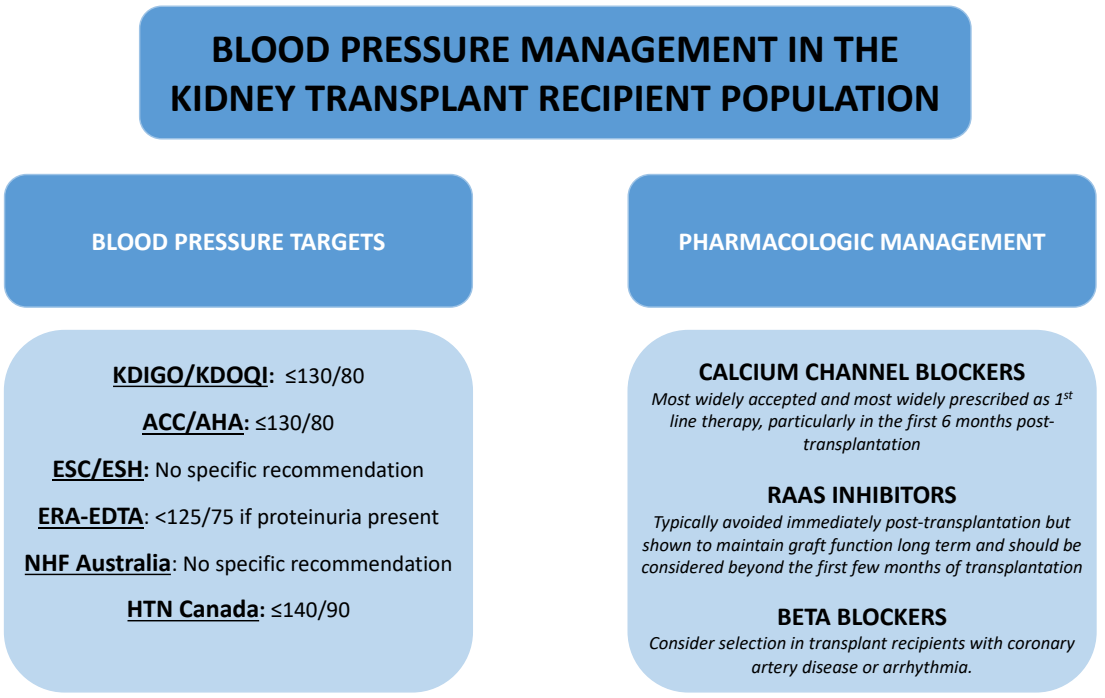


KDIGO, Kidney Disease: Improving Global Outcomes; KDOQI, Kidney Disease Outcomes Quality Initiative; ESC, European Society of Cardiology; ESH, European Society of Hypertension; ERA-EDTA, European Renal Association-European Dialysis and Transplant Association; CSN, Canadian Society of Nephrology; JSDT, Japanese Society for Dialysis Therapy; UKKA, The UK Kidney Association.

References

1. Kidney Disease: Improving Global Outcomes (KDI-

Figure 2. Managing BP in the kidney transplant population



KDIGO, Kidney Disease: Improving Global Outcomes; KDOQI, Kidney Disease Outcomes Quality Initiative; ACC, American College of Cardiology; AHA, American Heart Association; ESC, European Society of Cardiology; ESH, European Society of Hypertension; ERA-EDTA, European Renal Association-European Dialysis and Transplant Association; NHF Australia, National Heart Foundation of Australia; HTN Canada, Hypertension Canada.

GO) Blood Pressure Work Group. KDIGO 2021 clinical practice guideline for the management of blood pressure in chronic kidney disease. *Kidney Int* 2021; 99:S1–S87. doi: 10.1016/j.kint.2020.11.003
2. Flythe JE, et al. Blood pressure and volume management in dialysis: Conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference. *Kidney Int* 2020; 97:861–876. doi: 10.1016/j.kint.2020.01.046
3. McCallum W, Sarnak MJ. Blood pressure target for the dialysis patient. *Semin Dial* 2019; 32:35–40. doi: 10.1111/sdi.12754
4. Miskulin DC, et al. BP in dialysis: Results of a pilot study. *J Am Soc Nephrol* 2018; 29:307–316. doi: 10.1681/ASN.2017020135
5. Georgianos PI, Agarwal R. Pharmacotherapy of hypertension in chronic dialysis patients. *Clin J Am Soc Nephrol* 2016; 11:2062–2075. doi: 10.2215/CJN.00870116
6. Ari E, et al. Hypertension in kidney transplant recipients: Where are we today? *Curr Hypertens Rep* 2021; 23:21. doi: 10.1007/s11906-021-01139-4
7. Wadei HM, Textor SC. Hypertension in the kidney transplant recipient. *Transplant Rev (Orlando)* 2010; 24:105–120. doi: 10.1016/j.trre.2010.02.001
8. Aziz F, et al. Hypertension guidelines: How do they apply to kidney transplant recipients? *Transplant Rev (Orlando)* 2018; 32:225–233. doi: 10.1016/j.trre.2018.06.002

New Dietary Approaches to Managing Kidney Disease

By Bridget M. Kuehn

Kidney patients have long complained that the diet recommended for them is bland, tasteless, and hard to follow. But that old advice is being challenged by new research that may offer more palatable alternatives to old dietary approaches to managing kidney disease.

During the Diet and CKD [Chronic Kidney Disease]: What to Eat, When to Eat, How to Eat session at Kidney Week 2021, a panel of speakers highlighted evidence backing the health benefits of plant-based diets, time-restricted eating, and culturally sensitive dietary interventions for Black, Latinx, or Hispanic patients with kidney disease.

Rethinking diet dogma

Juan-Jesus Carrero, PhD Medicine, PhD Pharm, MBA, MSc, professor of cardio-renal epidemiology in the Department of Medical Epidemiology and Biostatistics at the Karolinska Institute in Sweden, explained that the traditional kidney diet has emphasized avoiding plant foods because of concerns about electrolyte abnormalities, hyperphosphatemia, hyperkalemia, and protein malnutrition.

"Patients do not like these recommendations which are difficult to adhere to," Carrero said. Patients report feeling deprived of healthy eating—lacking motivation to eat the recommended foods—and have difficulties eating away from home. "I would like us all to rethink these old dogmas and discuss whether plant-based diets can be of benefit for our patients," he said.

Advice to restrict potassium-rich produce can inadvertently deprive patients of other nutrients that may be beneficial for patients with kidney disease, Carrero said. He noted that it may not account for hidden sources of dietary potassium from processed foods and that potassium content in foods may also vary by how much a person eats or how the food is cooked. For example, boiling food can reduce potassium levels by 75%, he said. Potassium absorption may also be affected by the combination of foods that patients eat.

"Dietary potassium restriction as a means to prevent hyperkalemia and CKD may have been well intended, but it is not supported by strong evidence," he said.

In a recent review, Carrero and colleagues highlighted the benefits of plant-based diets for patients with CKD, such as increased fiber intake, beneficial effects on gut microbiota, heart health benefits of plant-based fats, reduced acidosis, and potentially better control of hyperphosphatemia because plant phosphorous may not be as bioavailable (1).

Carrero said slow and careful changes with close monitoring may enable patients to transition to more plant-based diets. Fresh produce prepared at home is best, he said. Distributing fruits and vegetables throughout the course of the day and controlling portions may minimize risks. He said more research is needed on plant-based diets in CKD.

On the clock

Meal timing may also be a useful intervention to improve patient health, said Michelle Gumz, PhD, associate professor in the Division of Nephrology, Hypertension, and Renal Transplantation, College of Medicine at the University of Florida, Gainesville. Gumz highlighted how disruption of the circadian clock that keeps the body entrained to the 24-hour light-dark cycle may contribute to an increased risk of CKD, hypertension, or cardiovascular disease.

We live in a 24-7 society in an environment that is not in sync with our internal [clock]," Gumz said. "These pathological states can further disrupt the clock, and this can lead to a vicious cycle."

For example, shift work has been associated with a 2- to 3-fold increased risk of CKD, and individuals who do not have the typical nightly dip in blood pressure associated with normal circadian rhythms are at greater risk of cardiovascular and kidney events, she noted.

The body's circadian rhythms are controlled by a central clock in the brain that is entrained to both light and the timing of food intake, Gumz explained. Peripheral clocks in the organs and tissues of the body are entrained by foods. Both the central and peripheral clock are controlled by a cycle of gene expression that regulates the expression of 50% of the genes in the body, including many important for cardiovascular and kidney health, she noted.

"If your eating circadian rhythm is out of sync with the light-dark cycle, those eating patterns can entrain the peripheral clocks," Gumz explained. "This will result in misalignment between the brain and the peripheral clocks. This can lead to metabolic dysfunction and is likely to increase cardiometabolic risk factors."

For example, a recent study showed that women who have inconsistent eating patterns have higher blood pressure, higher body mass index, and worse blood sugar control (2). But several ways to restore healthy circadian clock function have been studied, including time-restricted eating, noted Gumz. Another recent study showed that patients with metabolic syndrome who restricted their eating to a 10-hour window for 12 weeks lost weight, lowered their blood pressure, and improved their lipid profile (3).

"Timing of food intake can alter blood pressure and cardiovascular risks," Gumz said. She said more study is needed to see if time-restricted eating helps restore a normal pattern of nighttime blood pressure dips in patients with kidney disease.

Addressing diet disparities

Diet is considered a modifiable factor in kidney disease, but dietary modifications are not easy, said Crystal Tyson, MD, assistant professor of medicine in the Division of Nephrology at Duke University Medical Center in Durham, NC. Socioeconomic, environmental, behavioral, and cultural, as well as the patient's kidney disease and co-morbid conditions all need to be factored into dietary interventions. Overall, she noted that Americans' diets are poor and that Black, Hispanic, and Latinx individuals have a greater prevalence of poor dietary scores than their White and Asian counterparts.

"Improving diet in US racial and ethnic minorities may reduce disparities in kidney outcomes," she said.

The DASH (Dietary Approaches to Stop Hypertension) diet is one of the most studied dietary patterns, particularly among people of Black race, Tyson said. A study by Tyson and her colleagues found that Black individuals with CKD who were more adherent to the diet had low blood pressure, but overall adherence was low (4). Focus groups conducted by the team at Duke with Black patients with CKD found the participants thought the DASH diet was culturally compatible, but they expressed some concern that it wasn't consistent with previous dietary advice they had received about eating fruits and vegetables, salt, or protein. Other barriers included inadequate cooking skills and concerns about how to buy or use unfamiliar foods.

"Interventions should include cost-effective and time-efficient strategies to follow a healthy diet and emphasize food sources that are convenient and accessible in the local

Continued on page 28 >

New Dietary Approaches

Continued from page 27

environment," Tyson said. They should also provide instructions on measuring serving sizes, cooking tips, and resources about new foods and address kidney-related diet concerns.

Nimrit Goraya, MD, a nephrologist at Baylor Scott & White Health in Temple, TX, also highlighted some barriers to healthy food access in racial and ethnic minority communities. Food insecurity, which has been linked (5) to a higher risk of CKD and progression to end-stage kidney disease, disproportionately (6) affects Black and Hispanic or Latinx households. The pandemic has increased food insecurity in the United States, particularly among these groups, she said.

Living in "food deserts" without easy access to supermarkets can also be a barrier to healthy eating. Goraya explained that individuals who live in areas with limited access to food resources may purchase energy-dense foods from gas stations or bodegas. This leads to individuals having a higher dietary acid load, which may contribute to higher acid excretion and CKD progression.

Making healthy foods easily available through vouchers or food banks can facilitate healthier eating, Goraya said. Family-based interventions that work to build trust in communities and engaging trusted community leaders can also help. For example, church-based programs have demonstrated success. Counseling on how to prepare healthy foods can also help, she said.

It is important to avoid stereotypes about what racial and ethnic minorities eat and to focus on individualized interventions. "Dietary patterns are diverse within cultures, and the breadth of that diversity should be recognized," Tyson said. Because of this, it is important to address a patient's individual needs and preferences, she said.

References

1. Carrero JJ, et al. Plant-based diets to manage the risks and complications of chronic kidney disease. *Nat Rev Nephrol* 2020; 16:525–542. doi: 10.1038/s41581-020-0297-2
2. Makarem N, et al. Variability in daily eating patterns and eating jetlag are associated with worsened cardiometabolic risk profiles in the American Heart Association Go Red for Women Strategically Focused Research Network. *J Am Heart Assoc* 2021; 10:e022024. doi: 10.1161/JAHA.121.022024
3. Wilkinson MJ, et al. Ten-hour time-restricted eating reduces weight, blood pressure, and atherogenic lipids in patients with metabolic syndrome. *Cell Metab* 2020; 31:92–104.e5. doi: 10.1016/j.cmet.2019.11.004
4. Tyson CC, et al. DASH diet and blood pressure among Black Americans with and without CKD: The Jackson Heart Study. *Am J Hypertens* 2019; 32:975–982. doi: 10.1093/ajh/hpz090
5. Banerjee T, et al. Food insecurity, CKD, and subsequent ESRD in US adults. *Am J Kidney Dis* 2017; 70:38–47 [erratum in *Am J Kidney Dis* 2017; 70:736]. doi: 10.1053/j.ajkd.2016.10.035
6. Belanger MJ, et al. Covid-19 and disparities in nutrition and obesity. *N Engl J Med* 2020; 383:e69. doi: 10.1056/NEJMp2021264

High-Impact Trials Offer Potential Solutions to Clinical Conundrums

By Bridget M. Kuehn

A reduced dose of the inexpensive oral methylprednisolone reduced the risk of kidney failure by 41% over 4 years in patients with immunoglobulin A (IgA) nephropathy in the Therapeutic Evaluation of Steroids in IgA Nephropathy Global (TESTING) study presented during Kidney Week 2021. The drug, however, was associated with an increased risk of severe infection, particularly in the first months of treatment. The TESTING trial results were among several results that promise to help solve "clinical conundrums" in the field of nephrology, presented during the High-Impact Clinical Trials session at Kidney Week 2021.

"These are exciting times in the field of nephrology," said Wendy St. Peter, PharmD, professor with the College of Pharmacy at the University of Minnesota in Minneapolis, who co-moderated the High-Impact Clinical Trials session at the meeting.

Steroid balancing act

IgA nephropathy is a common cause of kidney disease in younger adults and is a consequence of autoimmune attacks on the kidneys (1). Most studies' use of corticosteroids in these patients have not been adequately powered to assess kidney outcomes, said Vlado Perkovic, MBB, PhD, the TESTING trial's co-senior author and dean of medicine, University of New South Wales in Australia. To help fill this gap, the trial initially planned to randomize 503 patients with IgA to a full dose of methylprednisolone starting at 0.6–0.8 mg/kg/day to a maximum dose of 48 mg/day for 2 months, followed by gradual weaning from the drug over 4 to 7 months or placebo.

However, the identification (2) of an increased incidence of serious infections, including four that were fatal, in patients taking methylprednisolone led to the change in the trial protocol in which 241 patients were randomized to a reduced dose of methylprednisolone of 0.4 mg/kg/day to a maximum of 32 mg/day, followed by weaning. When the results from both steroid groups were analyzed after an average of 4 years of follow-up, there was a 47% reduction in a composite endpoint of 40% decline in estimated glomerular filtration rate (eGFR) or kidney failure compared with the placebo group and a 41% reduction in kidney failure, according to the data presented by Perkovic. A subgroup analysis of the lower dose group compared with placebo found a 73% reduction in the composite endpoint over an average of 2.5 years' follow-up. Perkovic noted that one patient in the lower dose group also died of a serious infection.

In the full dose group, for every 100 patients treated, methylprednisolone would precipitate about 12 fewer primary outcome kidney events but about 12 serious adverse events, Perkovic said. In the reduced dose group, for every 100 treated, there would be almost 17 fewer primary outcome kidney events with 2.4 serious events, he said. Perkovic said the results support existing guidelines that recommend nephrologists discuss the benefits and risks of corticosteroids with patients with IgA nephropathy who are at a high risk of kidney events.

"We provide additional data that will help inform those conversations by providing more precision about the risks and benefits of different approaches," Perkovic said. "[The results] suggest this should be offered to high-risk people."

The evidence shows that a lower dose of methylprednisolone is effective at reducing kidney-related events and resulted in fewer serious adverse events than higher doses, St. Peter said. "This is good news for patients with IgA nephropathy and their nephrologists who want them to get the benefits from an effective treatment but with less risk of a severe infection or other serious side effects that are common with higher steroid doses," she added.

New options for old challenges

Other high-impact studies presented during the session offered promising new options to solve longstanding challenges in nephrology, including a treatment for RNA inhibitor-reduced oxalate levels in patients with primary hyperoxaluria type 1 (PH1); a potential oral alternative to injectable therapies for anemia in patients with chronic kidney disease (CKD); and an inexpensive, older drug that may help control hypertension in patients with stage 4 CKD.

An injectable RNA inhibitor called lumasiran reduced urinary oxalate levels by one-third in patients with PH1 who were not on dialysis and by 42% among those on dialysis, according to results from the Evaluate Lumasiran in Patients with Advanced Primary Hyperoxaluria Type 1 (ILLUMINATE-C) study presented at Kidney Week by its lead author Mini Michael, MD, MMed, associate professor at Baylor College of Medicine in Houston, TX. PH1 is a rare condition associated with oxalate overproduction, kidney disease, and multi-organ damage. The trial enrolled 21 patients and followed them for 6 months.

"[Oxalate] changes of this magnitude may change long-term patient outcomes," Michael said. She and her colleagues are continuing to follow patients to assess longer term outcomes.

"It is exciting to see a new therapy which has the potential to change the dynamic of a rare and serious disease [like PH1] that mainly affects the kidneys but can result in multi-organ damage," St. Peter said. She noted the condition often results in the need for dialysis, kidney transplant, or liver and kidney transplant. She said one remaining question is whether lumasiran will reduce kidney disease progression, the need for dialysis, or the need for kidney and liver transplantation.

Oral daprodustat may be an alternative to injectable erythropoiesis-stimulating agents (ESAs) for treating anemia in patients with CKD, according to a presentation by Ajay Singh, MBBS, MBA, a nephrologist at Brigham and Women's Hospital and Harvard University in Boston, MA. The results of the Anemia Studies in Chronic Kidney Disease: Erythropoiesis Via a Novel Prolyl Hydroxylase Inhibitor Daprodustat (ASCEND) trials in patients on dialysis (3) and not on dialysis (4) were published in *The New England Journal of Medicine* simultaneously. The trials enrolled 6800 patients and showed that daprodustat was non-inferior to ESAs for treating anemia patients with CKD who were receiving dialysis and those who did not require dialysis. It was also non-inferior to ESAs when the researchers looked at major adverse cardiovascular adverse events.

In a press briefing about the results, Singh noted that many patients currently don't have access to ESA treatment. Additionally, patients may be more likely to comply with and tolerate an oral medication, he said.

"The nephrology community has been hoping that the new hypoxia-inducible factor prolyl hydroxylase inhibitor would represent a new era in the treatment of anemia in CKD, with better efficacy and/or safety than ESAs," St. Peter said. "It's a little disappointing that daprodustat was only shown to be non-inferior and not superior in efficacy or safety endpoints as ESAs. Regardless, it would be nice to have an oral option for anemia management, particularly in non-dialysis-dependent patients with CKD."

The Chlorthalidone in Chronic Kidney Disease (CLICK) study (5) randomized 160 patients with stage 4 CKD and hypertension to chlorthalidone or placebo and found the low-cost medication reduced systolic blood pressure by 11 mm Hg within 4 weeks, according to a presentation by Rajiv Agarwal, MD, of the Indiana University School of Medicine in Indianapolis. It also lowered albuminuria by one-half over 12 weeks.

"The results of the CLICK study dispelled the myth that thiazide diuretics are not effective for blood pressure man-

agement when eGFR is less than 30 mL/min/1.73 m^2," St. Peter said. "This study sets the stage for chlorthalidone to become a main component of blood pressure management in patients with stage 4 CKD."

St. Peter cautioned, however, that clinicians need to do more frequent monitoring in patients already receiving a loop diuretic because the combination increased the risk of hypokalemia and increased serum creatinine due to a combination diuretic effect.

Other studies presented during the High-Impact Clinical Trials session included the following:

- The EMPEROR-Preserved (Empagliflozin Outcome Trial in Patients with Chronic Heart Failure with Preserved Ejection Fraction) trial, presented by Faiez Zannad, showed that empagliflozin reduced cardiovascular death and heart failure hospitalization and slowed kidney decline in patients with heart failure with preserved ejection fraction with and without CKD (6).
  The ADVOCATE (A Phase 3 Clinical Trial of CCX168 [Avacopan] in Patients with ANCA [Anti-Neutrophil Cytoplasmic Autoantibody]-Associated Vasculitis) trial showed that patients with ANCA-associated vasculitis taking avacopan had better recovery of kidney function than patients taking prednisone, as explained by David Jayne (7). The US Food and Drug Administration approved use of avacopan for ANCA-associated vasculitis (8).
- Five-year follow-up results from the Ellipsys Vascular Access System pivotal trial of an ultrasound-guided, percutaneous outpatient technique for creating an arteriovenous fistula show that patients' use of the fistula remained above 90% at 5 years, and only one-half to one-quarter of patients needed a second procedure, said Jeffrey Hull, MD, director of the Richmond Vascular Center in Virginia, during a press briefing about the results.
- Another study presented by Aditi Sinha, MD, MBBS, PhD, professor of pediatrics at the All India Institute of Medical Sciences in New Delhi, showed no benefit to extending prednisone treatment for longer than 12 weeks for very young children with nephrotic syndrome. The open-label, multi-center study that randomized 172 children younger than 4 years with nephrotic syndrome to 12 or 24 weeks of prednisone found the proportions of patients who achieved sustained remission, relapse rates, or time-to-first relapse were not significantly different between the groups. Adverse effects were similar in the two groups, she said.

References

1. National Institute of Diabetes and Digestive and Kidney Diseases. IgA nephropathy. https://www.niddk.nih.gov/health-information/kidney-disease/iga-nephropathy
2. Lv J, et al. Effect of oral methylprednisolone on clinical outcomes in patients with IgA nephropathy: The TESTING randomized clinical trial. *JAMA* 2017; 318:432–442. doi: 10.1001/jama.2017.9362
3. Singh AK, et al. Daprodustat for the treatment of anemia in patients undergoing dialysis. *N Engl J Med* [published online ahead of print November 5, 2021]. doi: 10.1056/NEJMoa2113379; https://www.nejm.org/doi/10.1056/NEJMoa2113379
4. Singh AK, et al. Daprodustat for the treatment of anemia in patients not undergoing dialysis. *N Engl J Med* [published online ahead of print November 5, 2021]. doi: 10.1056/NEJMoa2113380; https://www.nejm.org/doi/10.1056/NEJMoa2113380
5. Agarwal R, et al. Chlorthalidone for hypertension in advanced chronic kidney disease. *N Engl J Med* [published online ahead of print November 5, 2021]. doi: 10.1056/NEJMoa2110730; https://www.nejm.org/doi/10.1056/NEJMoa2110730
6. Anker SD, et al. Empagliflozin in heart failure with a preserved ejection fraction. *N Engl J Med* 2021; 385:1451–1461. doi: 10.1056/NEJMoa2107038
7. Jayne DRW, et al. Avacopan for the treatment of ANCA-associated vasculitis. *N Engl J Med* 2021; 384:599–609. doi: 10.1056/NEJMoa2023386
8. US Food and Drug Administration. FDA approves add-on drug for adults with rare form of blood vessel inflammation. October 13, 2021. https://www.fda.gov/drugs/news-events-human-drugs/fda-approves-add-drug-adults-rare-form-blood-vessel-inflammation

Nephrology Teams Can Help Address Patients' Psychosocial Needs

By Karen Blum

Patients with chronic kidney disease have a high symptom burden that can impact their outlook on life and self-confidence to manage disease. With the recognition of these features, nephrology teams can offer targeted solutions to help patients improve their quality of life, according to a presentation at Kidney Week 2021.

More than 60% of patients receiving dialysis reported feeling depressed, worried, or frustrated in a recent survey (1), said Daniel Cukor, PhD, director of behavioral health at the Rogosin Institute in New York. "There's a really high emotional toll being a patient with end stage renal disease [ESRD]," he said.

About 6% of patients in the general population experience depression, according to another study looking at the prevalence of depression in patients with different medical conditions (2). However, depression among people with ESRD is estimated to range from 22% to 37%, akin to prevalence in patients with ovarian or brain cancers or those who experienced heart attack, hypertension, or type 2 diabetes.

There are four models of thinking that explain why the emotional toll is so high for patients with kidney disease, Cukor said.

1) Coping model. This involves a patient's interpretation of whether he or she has the power, ability, or resources to respond to, adjust to, or fight a particular event or challenge. This evaluation determines a person's ability to cope. The greater the threat or challenges, the larger the coping response an individual must mount in response.

The demands for ESRD are multifaceted. Kidney failure taxes the body and spirit. Treatments, although life saving, also pose a high burden on patients. Additionally, some patients may have lifestyle changes imposed on them, such as needing to stop work or travel. This may impact future plans, such as how they were going to spend their retirement years.

To help, Cukor said, clinical teams can provide support to decrease the amount of demand on patients while increasing the available psychological resources. They can conduct patient-centered team meetings to really hear about what's bothering patients and their families; connect them to any needed resources and to patient ambassador programs; and offer support groups or family counseling sessions.

2) Cognitive behavioral model. In this model, patients believe that bad things, such as needing dialysis, are internal (meaning because of them), widespread, and unlikely to change in the future. These are hallmarks of depressive thinking.

If patients think managing their condition is too hard, it can launch a negative, vicious cycle where they begin to isolate from friends and family, to skip clinical visits, or to not maintain open communication with the care team. Turning that around to a more positive outlook, patients will engage more and feel more mastery over their condition.

Clinical teams can support patients here by offering cognitive behavioral therapy, which includes a process called cognitive restructuring—a careful evaluation of people's thoughts and whether they contribute to a positive or negative cycle and helping people reframe and think more positively about their situation. Psychologists or counselors with the program also could help people accept that their life may be different now and offer existential coaching, helping patients work to derive meaning and enjoyment from activities they still are able to do.

3) Learned helplessness. If a patient's life revolves around dialysis—waking up in the morning and prepping for treatment, going to dialysis, and then recovering from treatment multiple times a week—it can be very challenging and demanding. As a result, other rewarding life activities, including socializing, tend to fade out because all of the person's energy is consumed by the dialysis cycle and thinking it's never going to get better. Patients tend to give up on everything else and have a negative outlook.

In this case, clinical teams can offer better patient engagement, finding strategies to partner with patients to keep their motivation high and keep them active in care. Motivational interviewing can help people understand for themselves what their drivers are. They also could consider pharmacological or non-pharmacological treatments for depression. Teams can help patients start rescheduling some of the activities they've given up that they enjoyed, such as calling or visiting a friend or going out to dinner. "If [people] look at [their] week, and it's not only medical related, [they] tend to feel a lot better and a lot more engaged in their care," Cukor said.

4) Symptom burden. A high symptom burden has been reported in patients from a 2005 survey of 162 dialysis patients from three centers (3). In that study, over 50% of patients reported mood or sexual issues, sleep difficulties, pain, and skin and gastrointestinal issues.

Poor sleep, in particular, can lead to a cycle of fatigue, napping, decreased satisfaction with sleep, and anticipatory anxiety related to sleep, Cukor said. Symptom burden also can lead to a cycle of depression where patients aren't sleeping well, aren't active, feel tired, and don't have energy for preferred activities. Pain, too, can start a cycle of not sleeping well or feeling anxious or depressed.

Symptoms should be thought of as interconnected gears, with one factor having the power to impact others. Clinical teams should focus on the interference caused by symptoms, to help patients return to more positive health cycles. Helping someone with pain, for example, may allow that person to get better sleep, which can in turn lead to improved mood.

"Targeting symptoms as clinical entities that are worth treating is really important," Cukor said. "They're not just merely comorbidities but are real difficulties that people are going through. Even if you can't solve all of them, if you can alleviate some of them, that would be quite a significant contribution to the patient's quality of life."

References

1. Flythe JE, et al. Symptom prioritization among adults receiving in-center hemodialysis: A mixed methods study. *Clin J Am Soc Nephrol* 2018; 13:735–745. doi: 10.2215/CJN.10850917
2. Gold SM, et al. Comorbid depression in medical diseases. *Nat Rev Dis Primers* 2020; 6:69. doi: 10.1038/s41572-020-0200-2
3. Weisbord SD, et al. Prevalence, severity, and importance of physical and emotional symptoms in chronic hemodialysis patients. *J Am Soc Nephrol* 2005; 16:2487–2494. doi: 10.1681/ASN.2005020157

CORPORATE SUPPORTERS 2021

The ASN Corporate Support Program recognizes supporters year round for their generous contributions to the Society. Through this program, supporters help ASN lead the fight against kidney diseases. ASN gratefully acknowledges the following companies for their contributions in 2021.

DIAMOND LEVEL

Akebia Therapeutics
AstraZeneca
natera
Otsuka
Visterra
Otsuka Group of Companies

PLATINUM LEVEL

Bayer
CareDx
Fresenius Medical Care
Travere Therapeutics
Vifor Pharma

GOLD LEVEL

Alnylam Pharmaceuticals, Inc.
Baxter
Cara Therapeutics, Inc.
GSK
Horizon Therapeutics
Mallinckrodt Pharmaceuticals
OPKO Renal
Reata Pharmaceuticals
Vertex Pharmaceuticals Inc.

SILVER LEVEL

Ardelyx
Aurinia Pharma U.S.
CVS Kidney Care
Novartis Pharmaceuticals Company

As of September 24, 2021

Clinical Trials in Critical Care Presented at Kidney Week 2021

By Karen Blum

Recent clinical trials in fluid therapies, COVID-19 treatment, and sepsis management were presented at Kidney Week 2021 to keep nephrologists up to date in critical care medicine: The Balanced Solutions in Intensive Care Study (BaSICS) trial (1, 2) of balanced solution versus 0.9% saline in critically ill patients; the Efficacy and Safety of Baricitinib for the Treatment of Hospitalized Adults with COVID-19 (COV-BARRIER) trial (3); and the Vitamin C, Thiamine, and Steroids in Sepsis (VICTAS) trial (4) of vitamin C, thiamine, and hydrocortisone on ventilator- and vasopressor-free days in sepsis.

BaSICS

There has been much debate over several decades regarding the use of fluids in the intensive care unit (ICU). Although saline solution has remained the primary fluid over time, recent evidence from observational and randomized controlled trials suggests that administration of balanced crystalloids results in better outcomes such as reduced mortality and acute kidney injury (AKI). Additionally, infusion rate has been commonly neglected as an aspect of fluid therapy delivery in randomized controlled trials. BaSICS, published as two reports in the *Journal of the American Medical Association* (*JAMA*) (1, 2), compared the effects of each fluid type as well as two different infusion speeds.

BaSICS enrolled 11,052 patients in 75 ICUs across Brazil. Participants were randomized to receive either Plasma-Lyte or 0.9% saline and then further randomized to receive these fluids at either 333 mL/hour or 999 mL/hour. Patients included in the study were admitted to an ICU and required at least 1 L of fluid expansion. They also were not expected to be discharged the next day and had at least one risk factor for AKI, such as age over 65 or presence of sepsis.

Baseline characteristics were similar. The mean age of participants was 61, 44% were women, 50% required elective surgery as the reason for ICU admission, and 40% were admitted for medical reasons. Of note, 30% of patients had a Kidney Disease: Improving Global Outcomes (KDIGO) score of 1 or greater at the time of enrollment. Sixty percent were hypotensive, and 44% required some means of mechanical ventilation.

The study found no difference in 90-day mortality rates between those who received balanced solution (26.4%) and saline (27.2%). There also was no difference in 90-day mortality rates between those who received slower infusion (26.6%) and faster infusion (27%). Furthermore, there were no significant differences found in any of the secondary endpoints related to AKI with need for kidney replacement therapy or AKI with KDIGO scores of 2 or higher on day 3 or 7.

Therefore, the findings do not support the use of balanced solution over normal saline or a slower infusion rate, said M. Elizabeth Wilcox, MD, PhD, an associate professor of medicine at the University of Toronto and a staff intensivist with University Health Network. There may be harm for traumatic brain injury patients with the administration of balanced solution, but further study is required, she said.

COV-BARRIER

Some patients with COVID-19 develop intense, hyperinflammatory states leading to multiorgan failure and ICU admission. Baricitinib, a selective JAK1/JAK2 inhibitor with a known anti-inflammatory profile, was identified as a potential intervention for the treatment of COVID-19. Since then, several small cohort studies have provided some evidence of clinical improvement with its use, Wilcox said.

COV-BARRIER was a phase 3, randomized, double-blind controlled trial that enrolled 1525 patients with COVID-19 and at least one elevated inflammatory marker at 101 centers across 12 countries. Patients were randomized to receive either standard-of-care therapy, including dexamethasone, or 4 mg of baricitinib daily for up to 14 days or until hospital discharge. Follow-up was conducted 28 and 60 days after the last dose of the study drug.

The median patient age was 58, and 37% were women. Approximately 88%–90% of patients required supplemental oxygen, noninvasive ventilation, or high-flow oxygen delivered by nasal cannula. All participants had at least one preexisting comorbid condition.

Twenty-eight percent of patients in the baricitinib group and 31% of patients in the control group progressed to the primary composite endpoint of receiving high-flow oxygen, noninvasive ventilation, invasive mechanical ventilation, or death at 28 days. All-cause mortality was reduced at 28 days (8% vs. 13%) and at 60 days (10% vs. 15%) for the baricitinib group. Additionally, the frequency of serious adverse events, including infections and venous thromboembolism, was similar between groups.

Results suggest that baricitinib reduces both 28- and 60-day mortality when given in addition to standard of care.

"This has very important implications in terms of it being a possible treatment option to reduce overall deaths in the context of a global burden of mortality during a pandemic," Wilcox said. A dose-adjusting study may be of use, she said, as would potentially using a loading dose to prevent rapid progression events.

VICTAS

Despite hundreds of pharmacologic agents and bundled approaches to care for sepsis studied, approximately one-third of patients hospitalized do not survive their diagnosis, Wilcox said. In 2017, the combination of hydrocortisone, vitamin C, and thiamine (HAT) received attention because of a single study (5) that reported a 32% absolute reduction in mortality in nearly 50 patients treated with the regimen compared with historical controls. In 2020, accumulating evidence from several additional studies failed to re-demonstrate a mortality benefit.

VICTAS was intended to be a definitive trial exploring the effects of this combination therapy on ventilator- and vasopressor-free days in sepsis patients, Wilcox said. The multi-center, double-blind, randomized controlled trial enrolled 501 patients with sepsis and respiratory or cardiovascular dysfunction from 43 US hospitals. Patients were randomized to an intervention group in which they received 1.5 g of vitamin C, 100 mg of thiamine, and 50 mg of hydrocortisone or received placebo within 4 hours of randomization and every 6 hours after, up to 96 hours, or until they died or were discharged from the ICU. The trial was stopped early after changes in funder priorities.

Participants in the two groups were similar, with a median age of 62. Thirty percent were Black, and 46% were female. Patients were fairly ill, with a median sequential organ failure assessment (SOFA) score of 9. The primary source of infection was pneumonia in almost 40% of patients.

No statistically significant differences were seen between the intervention and control groups' ventilatory- or vasopressor-free days, which were 25 or 26 days in each group, respectively. Mortality rates also were largely similar, with a 40.5% mortality rate in the intervention group and a 37.8% mortality rate in the control group at 180 days. These results were consistent with recent randomized studies finding no greater effectiveness of HAT as compared to placebo, but they also confirmed that HAT is safe for this patient population, Wilcox said.

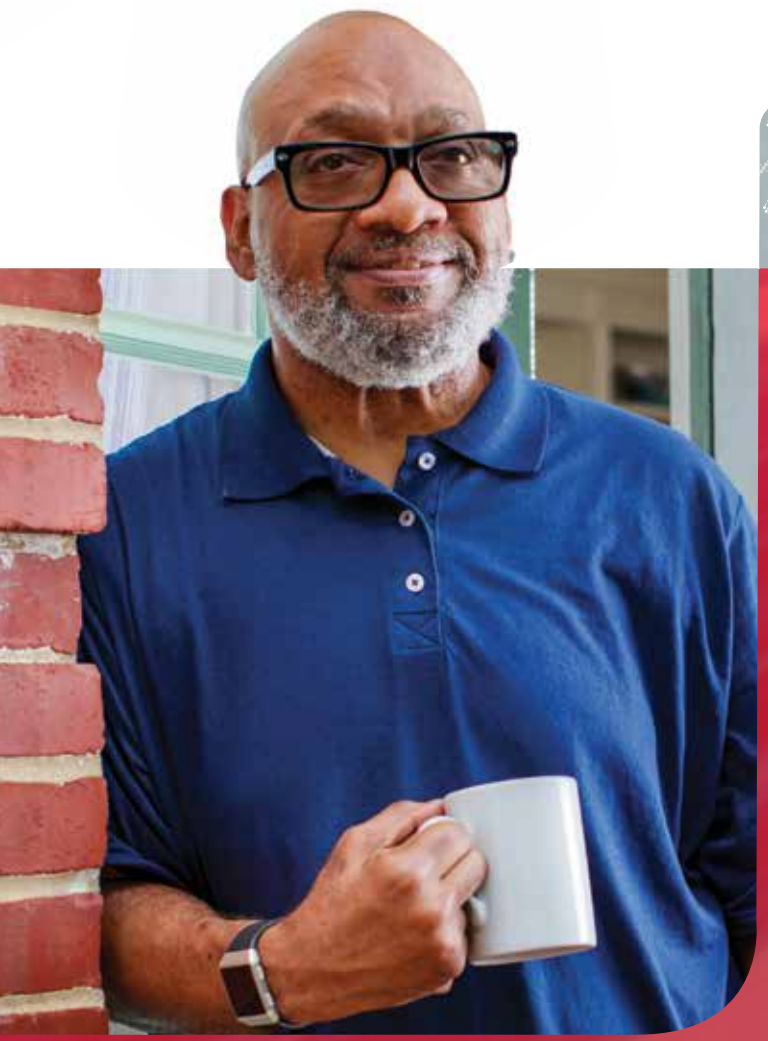
"Underpowered trials fail to provide certainty in their conclusions," she said. "Therefore, it really isn't going to be able to settle the debate over HAT treatment in sepsis. Another study may or may not be funded to answer that question." ■

References

1. Zampieri FG, et al. Effect of intravenous fluid treatment with a balanced solution vs 0.9% saline solution on mortality in critically ill patients: The BaSICS randomized clinical trial. *JAMA* 2021; 326:1–12. doi: 10.1001/jama.2021.11684
2. Zampieri FG, et al. Effect of slower vs faster intravenous fluid bolus rates on mortality in critically ill patients: The BaSICS randomized clinical trial. *JAMA* 2021; 326:830–838. doi: 10.1001/jama.2021.11444
3. Marconi VC, et al. Efficacy and safety of baricitinib for the treatment of hospitalised adults with COVID-19 (COV-BARRIER): A randomised, double-blind, parallel-group, placebo-controlled phase 3 trial. *Lancet Respir Med* [published online ahead of print August 31, 2021]. doi: 10.1016/S2213-2600(21)00331-3; https://www.thelancet.com/journals/lanres/article/PIIS2213-2600(21)00331-3/fulltext
4. Sevransky JE, et al. Effect of vitamin C, thiamine, and hydrocortisone on ventilator- and vasopressor-free days in patients with sepsis: The VICTAS randomized clinical trial. *JAMA* 2021; 325:742–750. doi: 10.1001/jama.2020.24505
5. Marik PE, et al. Hydrocortisone, vitamin C, and thiamine for the treatment of severe sepsis and septic shock: A retrospective before-after study. *Chest* 2017; 151:1229–1238. doi: 10.1016/j.chest.2016.11.036

AlloSure® KIDNEY

CareDx®
Your Partner in Transplant Care



Patrick G., kidney transplant recipient

It's time for innovation

DETECT ALLOGRAFT INJURY EARLIER

AlloSure is the leading dd-cfDNA test in transplant, used by over 80% of centers by volume.

PROVEN EXPERIENCE IN TRANSPLANT SPECIFIC cfDNA

1 in 3
newly transplanted kidney patients use AlloSure

>160
Centers
Actively Using AlloSure

14
Center
Prospective Validation Trial

Learn more at: **caredx.com/allosure**