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New KDIGO Blood Pressure Guideline Emphasizes Standardized Measurement, Tight Control

By Bridget M. Kuehn

When Alfred Cheung, MD, co-chair of the Kidney Disease Improving Global Outcomes (KDIGO) 2021 Clinical Practice Guideline update on the Management of Blood Pressure (1), and his colleagues were preparing to release their new guideline on blood pressure management in patients with chronic kidney disease (CKD), they knew it might "ruffle some feathers."

But after careful consideration, their workgroup came to a conclusion that they should make the right recommendation to shoot for a target systolic blood pressure of less than 120 for patients with CKD, a recommendation supported by the results of the Systolic Blood Pressure Intervention Trial (SPRINT) (2) and a large meta-analysis (3). Because all large outcome trials in hypertension were using standardized, not routine, blood pressure, they also made that target contingent on using standardized office-based blood pressure. They expected both recommendations would be controversial—and they were right.

Standardized blood pressure measurements, which require a series of steps to ensure a reliable reading, were used in SPRINT and are also recommended by the American College of Cardiology/American Heart Association (ACC/AHA)'s 2017 guideline for the management of high blood pressure (4). But this set of procedures for measuring blood pressure is far from routine in clinics crunched for time and under pressure to move patients efficiently through the office. Instead, most routine blood pressure measurements skip many of the steps, which can result in readings that can be as much as 10–30 points higher and sometimes lower than a standardized measurement for the same patient (5).

"You are slowing down the clinic workflow, although not by much," explained Cheung, who is also Chief of the Division of Nephrology & Hypertension at the University of Utah. "Many people do not like to do that. But we are adjusting patients' medications based on these often unreliable measurements if we stick to routine measurement techniques."

Clinical impact

Without a reliable measurement, Cheung said, it is impossible to recommend a blood pressure target, so he and his colleagues were willing to "push the envelope" in the hope that over time more practices will adopt the recommendations despite some obstacles.

"If you measure blood pressure carefully, we are comfortable making the target below 120 mm Hg systolic with individualization as needed," he said. The 120 target is not recommended for patients with a kidney transplant or those on dialysis or pediatric patients.

Cheung and his colleagues felt confident in the recommendation because SPRINT for the first time provided evidence of a 25% risk reduction in cardiovascular events

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CKD Regression, Death More Likely than Kidney Failure with Advancing Age, Study Finds

For adults with chronic kidney disease (CKD), disease regression is at least as common as disease progression or kidney failure, especially as the competing risk of death increases with age, according to results of a study published in *JAMA Network Open* (1).

The new analysis documents regression of incident CKD across different ages and degrees of severity. Ping Liu, PhD, and coauthors note that as the risk of death increases with advancing age, the likelihood of CKD regression decreases to a lesser extent relative to the risk of CKD progression or kidney failure. "Therefore, the aging of the general population may not necessarily translate into increased CKD burden for patients and health services," the authors state. "[The] findings suggest that CKD regression should be considered in the allocation of health resources and in patient counseling." Ping Liu is affiliated with the Department of Medicine, Cumming School of Medicine, University of Calgary, Calgary, Alberta, Canada.

The researchers used linked administrative and laboratory databases to identify adult residents of Ontario, Canada, with incident CKD. Women accounted for 55.2% of those studied. Based on estimated glomerular filtration rate (eGFR), CKD was classified as mild (eGFR 45 to 59 mL/min/1.73 m^2) in 81,320 patients, moderate (30 to 44 mL/min/1.73

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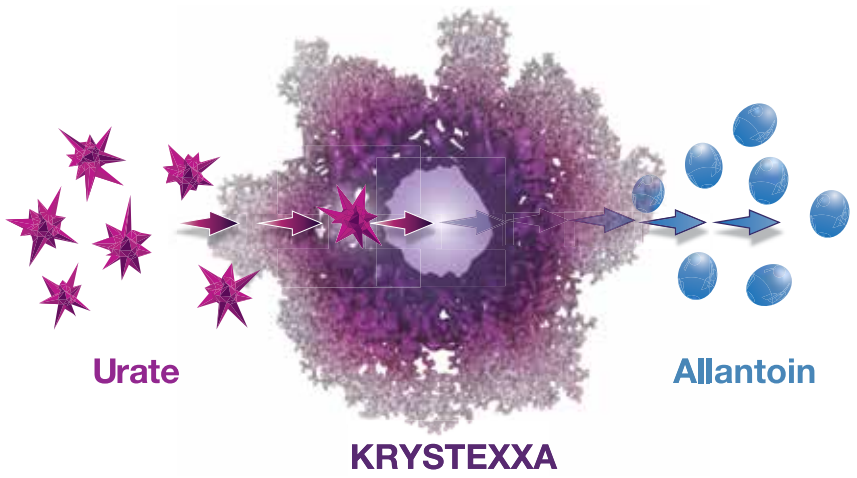
Inside

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.

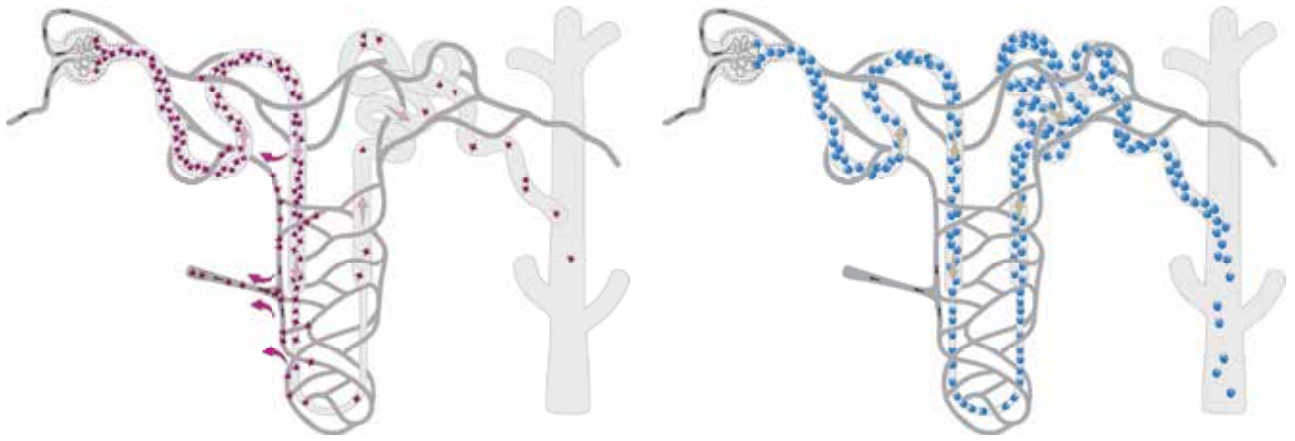
Concomitant use of KRYSTEXXA and oral urate-lowering agents may blunt the rise of sUA levels. Patients should discontinue oral urate-lowering agents and not institute therapy with oral urate-lowering agents while taking KRYSTEXXA.

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.

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New KDIGO Blood Pressure Guideline

Continued from page 1

or deaths from cardiovascular causes in patients with CKD who were shifted to the lower target of 120 mm Hg compared with a 140-mm Hg target. It also found a 27% reduction in overall mortality, as well as cognitive benefits, all with an apparently overall neutral effect on kidney health, Cheung noted. He acknowledged that some clinicians may be concerned that tight control could lead to more adverse events, particularly in older patients, but he said the risk/benefit analysis did not support those concerns.

"We think the risk/benefit ratio is really in favor of tight blood pressure control," he said.

In fact, a new large meta-analysis of 58 randomized trials enrolling almost 300,000 participants published earlier this year (6) did not find an association between anti-hypertensive treatment and falls. The study did not look specifically at patients with CKD. It did find an association with mild hyperkalemia, hypotension, fainting, and acute kidney injury. The estimated association with kidney injury was small and somewhat uncertain, said senior author James Sheppard, PhD, university research lecturer at the University of Oxford, in an interview.

"Acute kidney injury can be problematic but also quite mild and reversible if given the right treatment," he said.

Sheppard said he thought the new KDIGO guideline was balanced, based on good quality data, and did a good job highlighting some populations for whom the risks and benefits of intensive blood pressure lowering may be less well understood or where the risks may outweigh the benefits. Like the guideline, he emphasized the importance of taking an individualized approach to blood pressure management.

"Ultimately, it is up to the individuals [as to] what treatment they take," he said. "The important thing is to give them as much information as possible so they can make an informed decision."

If the new guideline is implemented widely, it could have a dramatic effect on reducing cardiovascular events and death in patients with CKD, according to an analysis by Kathryn Foti, PhD, a postdoctoral fellow in the Department of Epidemiology at the Johns Hopkins Bloomberg School of Public Health, and her colleagues (7). Under the new guidelines, 69.5% of adults with CKD would be eligible for blood pressure-lowering therapy, compared with 49.8% under the 2012 KDIGO guideline or 55.6% under the American College of Cardiology/American Heart Association (ACC/AHA) 2017 guideline. It may also have an impact on improving health equity. Both hypertension and CKD are more prevalent in Black people, Foti said.

"There is a real opportunity to improve blood pressure control, particularly in high-risk patients," Foti said. "If we are able to effectively implement this guideline, there are implications for getting closer to health equity."

Additionally, the number of patients with CKD and albuminuria eligible for treatment with an angiotensin converting enzyme inhibitor (ACEi) or an angiotensin II receptor blocker (ARB) would increase to 78.2% under the new KDIGO guideline from 71% under the previous version. Despite the previous guideline, Foti noted that only about 39% of eligible patients with albuminuria are currently taking an ACEi or ARB, based on data from the National Health and Nutrition Examination Survey. Foti attributed this low use of ACEi/ARB to the fact that often albuminuria is not measured and noted that more consistently measuring it may lead to more guideline-directed care.

Cheung noted that the recommendations on ACEi/ARBs are not much different from previous recommendations and focus primarily on the blood pressure-lowering benefits. Cheung and colleagues provide a table that helps organize the information in the revised guideline.

Preparation key

Preparation is key to ensuring a reliable blood pressure measurement, said Cheung. He noted that standardized office-based blood pressure measurement requires that the patient is resting quietly with no one talking to him or her for at least 5 minutes before the blood pressure is taken. Otherwise, he cautioned, the reading could be skewed by, for example, a patient running upstairs or getting into an argument with his or her spouse just before the reading. Patients should also avoid caffeine, exercise, or smoking 30 minutes before a reading.

The patient should be seated with his or her feet on the ground and arm resting at heart level, according to the guideline. The blood pressure cuff should be large enough to fit properly, Cheung said. An average of two or more readings obtained on two or more occasions is also recommended.

"Once the nurses and medical assistants are trained, it becomes second nature," he said.

The guideline recommends using an automated blood pressure machine, if possible, but Cheung said that is not essential, especially in low-resource settings. The guidelines also recommend complementing standardized office blood pressure readings with home-based blood pressure readings or 24-hour blood pressure readings.

"It'll be nice if you have an automated machine, but it is far less important," he said. "We are not trying to ask everybody to buy fancy machines."

Sheppard also emphasized the importance of an accurate blood pressure reading in treatment decisions.

"Blood pressure measurement is a real problem and has been for decades now," he noted. He added that blood pressure measurements are meticulously taken during clinical research following standardized office-based blood pressure measurement but that clinicians do not always have time for gold-standard measurements. In such circumstances, he emphasized the need to double-check with out-of-office measurements.

"Ultimately, we are using these readings to make a decision about a patient taking lifelong treatment, and so you want to be sure you are basing it on good quality measures," Sheppard said. ■

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CKD Regression

Continued from page 1

m^2) in 35,929 patients, and severe (15 to 29 mL/min/1.73 m^2) in 12,237 patients. Those in the mild CKD group had a mean age of 72.4 years, compared with 77.1 years for those in the moderate group, and 76.6 years for those in the severe group.

The researchers analyzed rates of CKD progression and regression by age, based on a sustained increase or decrease in the eGFR category for more than 3 months or a 25% or greater increase or decrease in eGFR, respectively. Other outcomes included kidney failure (eGFR less than 15 mL/min/1.73 m^2) and death. The analysis included measures to minimize the effects of regression of CKD after acute kidney injury or owing to the effects of variability in eGFR measurements.

For individuals 65 or under, annual CKD incidence was 180 per 100,000 population. For those 85 or older, annual CKD incidence increased to 7250 per 100,000 population. In all three categories of mild, moderate, or severe kidney disease, the 5-year probability of regression was similar to that of progression: 14.3% versus 14.6% in the mild CKD group, 18.9% versus 16.5% in the moderate CKD group, and 19.3% versus 20.4% in the severe CKD group.

In patients with moderate CKD, 5-year mortality increased from 9.6% for those under 65 to 48.4% for those 85 or older. The aging-related increase in the severe CKD group was from 10.8% to 60.2%. When the competing risk of death was considered, the risk of disease progression or kidney failure decreased significantly: from 32.3% at age under 65 to 9.4% at age 85 or older in patients with the moderate CKD group and from 55.2% to 4.7% in those with severe CKD. Aging had a lesser effect on the probability of CKD progression: from 22.5% at age under 65 to 15.4% at age 85 or older in the moderate CKD group and from 13.9% to 18.7% in the severe CKD group.

"The burden CKD is expected to increase worldwide as the global population ages, potentially increasing the demand for nephrology services," the authors state. "Understanding whether CKD inevitably progresses or may regress can inform clinical decision-making and health policy." ■

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The Launch of "We're United 4 Kidney Health"

ASN and the Kidney Health Community Build a Movement

By O. N. Ray Bignall II

The American Society of Nephrology (ASN) is reinforcing what those of us in kidney care have been experiencing for years: There is too much focus on kidney failure rather than kidney health.

The COVID-19 pandemic put even more urgency on kidney health, as well as its disparities in diagnosis and treatment. In order to move from kidney disease to kidney health, ASN created a roadmap and rallying cry to mobilize the kidney care community and work toward a world without kidney diseases by embracing four priorities:

1) **Intervene Earlier** to prevent, diagnose, treat, 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 launching a campaign that shares these learnings and engages the kidney professional community in achieving these goals. This campaign has four principles:

1 **A Rallying Cry.** "We're United 4 Kidney Health" captures the ambitious goal of the campaign: the embrace of early intervention and health over end-state treatment and diseases; the unity across kidney health professions and the powerful diversity of our patients and providers; and the four priorities that move us from kidney diseases to kidney health.

2 **Kidney Professionals Telling the Story.** They are the eyes, ears, and mouthpiece for an often-disadvantaged community and hidden diseases. They share their stories, their passion, and their progress. I was proud to join my colleagues from across the nation, including Mukta Baweja, MD; Eugene Lin, MD, MS, FASN; Alejandro Diez, MD, FASN; and Sri Lekha Tummalapalli, MD, MBA, to share this important work. Through this campaign, we look forward to joining with many other members of the kidney health community to tell our stories.

3 **Personal and Group Commitment.** ASN wants to demonstrate personal commitment to this effort and understand that this will take the entire kidney care community to be successful. Kidney care professionals are encouraged to go to 4KidneyHealth.org to join the movement in supporting the four priorities needed to reach a future without kidney diseases.

4 **Substance and Action.** We are expanding our network over time, collecting best practices to share with the community, and activating desired behaviors that drive progress.

As members of the kidney health community, we have the future in our hands. ASN has built this foundation, a powerful launching pad, but now we need to put a man on the moon. I get most excited about the promise of where we can go from here, leaving behind old ways of doing things that no longer serve us and our patients. However, these priorities can only be accomplished if we all work together. Indeed, kidney health is foundational to the health of the rest of the body: to create homeostasis, balance. Kidneys are complex and essential, and we need to attract the best and brightest minds to advance the field.

Unfortunately, we face a workforce problem in nephrology. And simply relying on the stereotype of the nephrologist as "the smartest doctor in the hospital" is an uninspiring and reductive trope that fails to capture the imagination of many young physicians today. After all, medical students and residents are more than just "smart": They are deeply committed to advancing research and discovery, innovative medical education, and the passionate pursuit of justice through advocacy and equity. They are committed to all these pursuits, and we should be, too.

As a physician-advocate, the campaign's goal to "achieve equity and eliminate disparities" resonates with me, my patients, and many of the young people considering and entering nephrology today. Historically excluded communities are disproportionately affected by kidney diseases and kidney health disparities, including racial and ethnic minorities, houseless persons, and those who face socioeconomic challenges. Kidney health education and advocacy are key weapons in the arsenal of the kidney health professional: They are every bit as potent as the latest pharmaceutical or therapeutic device. Reaching communities where kidney health disparities are ravaging the population is one of our field's greatest charges. In doing so, we can combat the narrative of hopelessness in the face of kidney disease and expand awareness, acceptance, and adherence in the promotion of kidney health.

That links directly to another goal: "transform transplant and expand access to donor kidneys." The single biggest thrill I have as a pediatric nephrologist is when I have the privilege of telling the parents of a child living with kidney failure that they will receive the gift of life—an organ donation. Not only is it important to expand opportunities to receive this gift, but increasing opportunities for health-disparate communities is a priority of nephrologists worldwide. Focused outreach to minority and health-disparate communities and exercising our platform as trusted messengers to combat medical misinformation are crucial tools for the 21st century nephrologist.

"Intervening earlier" is essential to promote "kidney health" rather than "kidney diseases." Coordinating care with other healthcare providers is one of the most exciting aspects of my job, especially working in teams to care for patients referred to me. But today, our impact is limited in early intervention. Nephrology needs new approaches, specifically accelerated innovation so patients have meaningful choices: In too many cases of kidney disease today, our ability to intervene early is limited in impact because we don't have a fix. I am excited to see the remarkable pace of research and discovery taking place in basic, translational, clinical, and community-engaged research programs throughout the field, and I am optimistic that our impact will grow in the decades ahead.

I hope the kidney health community is as excited as I am for nephrology's future. I invite everyone to join this movement, make progress with these four priorities, and move society toward a world without kidney diseases. ■

O. N. Ray Bignall II, MD, FAAP, FASN, is Director of Kidney Health Advocacy and Community Engagement in the Division of Nephrology and Hypertension at Nationwide Children's Hospital and Assistant Professor of Pediatrics at The Ohio State University College of Medicine, Columbus, OH. He is an alumnus of ASN's Policy and Advocacy Committee, the inaugural Chair of ASN's Health Care Justice Committee, and a member of the Kidney News *Editorial Board.*

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- **39%** RRR in the primary composite of sustained eGFR decline, ESKD, and CV or renal death[1,3†]
- **31%** RRR in all-cause mortality[1,3‡]

*The FDA granted its "Breakthrough Therapy" designation to FARXIGA in their review of FARXIGA in CKD.[2]
†14.5% vs 9.2% with placebo in adults with eGFR ≤75 to ≥25 mL/min/1.73 m^2; HR 0.61 (95% CI: 0.51–0.72); *P*<0.0001.[1,3]
‡6.8% vs 4.7% with placebo in adults with eGFR ≤75 to ≥25 mL/min/1.73 m^2; HR 0.69 (95% CI: 0.53–0.88); *P*=0.0035.[1,3]

Study design: DAPA-CKD was a randomized, double-blind, placebo-controlled, multicenter clinical trial of 4304 adults with eGFR 25-75 mL/min/1.73 m^2, and UACR 200-5000 mg/g, with or without T2D, randomly assigned to receive FARXIGA (10 mg once daily) or placebo for a median follow-up of 2.4 years.[3]

INDICATIONS AND LIMITATIONS OF USE for FARXIGA® (dapagliflozin)

FARXIGA is indicated:

- as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus
- to reduce the risk of hospitalization for heart failure in adults with type 2 diabetes mellitus and either established cardiovascular (CV) disease or multiple CV risk factors
- to reduce the risk of cardiovascular death and hospitalization for heart failure in adults with heart failure (NYHA class II-IV) with reduced ejection fraction
- to reduce the risk of sustained eGFR decline, end-stage kidney disease, cardiovascular death, and hospitalization for heart failure in adults with chronic kidney disease at risk of progression

FARXIGA is not recommended for patients with type 1 diabetes mellitus. It may increase the risk of diabetic ketoacidosis in these patients.

FARXIGA is not recommended for use to improve glycemic control in adults with type 2 diabetes mellitus with an eGFR less than 45 mL/min/1.73 m^2. FARXIGA is likely to be ineffective in this setting based upon its mechanism of action.

FARXIGA is not recommended for the treatment of chronic kidney disease in patients with polycystic kidney disease or patients requiring or with a recent history of immunosuppressive therapy for kidney disease. FARXIGA is not expected to be effective in these populations.

IMPORTANT SAFETY INFORMATION

Contraindications

- Prior serious hypersensitivity reaction to FARXIGA
- Patients on dialysis

Warnings and Precautions

- **Ketoacidosis in Diabetes Mellitus** has been reported in patients with type 1 and type 2 diabetes receiving FARXIGA. In placebo-controlled trials of patients with type 1 diabetes, the risk of ketoacidosis was increased in patients who received SGLT2 inhibitors compared to patients who received placebo. Some cases were fatal. Assess patients who present with signs and symptoms of metabolic acidosis for ketoacidosis, regardless of blood glucose level. If suspected, discontinue FARXIGA, evaluate and treat promptly. Before initiating FARXIGA, consider risk factors for ketoacidosis. Patients on FARXIGA may require monitoring and temporary discontinuation in situations known to predispose to ketoacidosis
- **Volume Depletion:** FARXIGA can cause intravascular volume depletion which may manifest as symptomatic hypotension or acute transient changes in creatinine. Acute kidney injury requiring hospitalization and dialysis has been reported in patients with type 2 diabetes receiving SGLT2 inhibitors, including FARXIGA. Patients with impaired renal function (eGFR less than 60 mL/min/1.73 m^2), elderly patients, or patients on loop diuretics may be at increased risk for volume depletion or hypotension. Before initiating FARXIGA in these patients, assess volume status and renal function. After initiating therapy, monitor for signs and symptoms of hypotension and renal function
- **Urosepsis and Pyelonephritis:** SGLT2 inhibitors increase the risk for urinary tract infections (UTIs) and serious UTIs have been reported with FARXIGA. Evaluate for signs and symptoms of UTIs and treat promptly
- **Hypoglycemia:** FARXIGA can increase the risk of hypoglycemia when coadministered with insulin and insulin secretagogues. Consider lowering the dose of these agents when coadministered with FARXIGA
- **Necrotizing Fasciitis of the Perineum (Fournier's Gangrene):** Rare but serious, life-threatening cases have been reported in patients with diabetes mellitus receiving SGLT2 inhibitors including FARXIGA. Cases have been reported in females and males. Serious outcomes have included hospitalization, surgeries, and death. Assess patients presenting with pain or tenderness, erythema, swelling in the genital or perineal area, along with fever or malaise. If suspected, institute prompt treatment and discontinue FARXIGA
- **Genital Mycotic Infections:** FARXIGA increases the risk of genital mycotic infections, particularly in patients with prior genital mycotic infections. Monitor and treat appropriately

Adverse Reactions

In a pool of 12 placebo-controlled studies, the most common adverse reactions (≥5%) associated with FARXIGA 5 mg, 10 mg, and placebo respectively were female genital mycotic infections (8.4% vs 6.9% vs 1.5%), nasopharyngitis (6.6% vs 6.3% vs 6.2%), and urinary tract infections (5.7% vs 4.3% vs 3.7%).

Use in Specific Populations

- **Pregnancy:** Advise females of potential risk to a fetus especially during the second and third trimesters
- **Lactation:** FARXIGA is not recommended when breastfeeding

DOSING

To improve glycemic control, the recommended starting dose is 5 mg orally once daily. Dose can be increased to 10 mg orally once daily for additional glycemic control.

For all other indications, the recommended dose is 10 mg orally once daily.

Please see Brief Summary of Prescribing Information on adjacent pages.

*You are encouraged to report negative side effects of AstraZeneca prescription drugs to the FDA. Visit **www.FDA.gov/medwatch** or call 1-800-FDA-1088.*

CI=confidence interval; CKD=chronic kidney disease; DAPA-CKD=Dapagliflozin And Prevention of Adverse outcomes in Chronic Kidney Disease; eGFR=estimated glomerular filtration rate; FDA=Food and Drug Administration; HR=hazard ratio; NYHA=New York Heart Association; SGLT2i=sodium-glucose cotransporter 2 inhibitor; RRR=relative risk reduction; T2D=type 2 diabetes; UACR=urine albumin-to-creatinine ratio.

References: 1. FARXIGA® (dapagliflozin) [package insert]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; 2021. **2.** FARXIGA granted Breakthrough Therapy Designation in US for chronic kidney disease [press release]. Published October 2, 2020. Accessed March 17, 2021. https://www.astrazeneca-us.com/media/press-releases/2020/farxiga-granted-breakthrough-therapy-designation-in-us-for-chronic-kidney-disease.html **3.** Heerspink HJL et al. *N Engl J Med.* 2020;383(15):1436-1446.

AstraZeneca

FARXIGA® (dapagliflozin) tablets, for oral use

Initial U.S Approval: 2014

BRIEF SUMMARY of PRESCRIBING INFORMATION.

For complete prescribing information, consult official package insert.

INDICATIONS AND USAGE

FARXIGA (dapagliflozin) is indicated:

- As an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.
- To reduce the risk of hospitalization for heart failure in adults with type 2 diabetes mellitus and either established cardiovascular disease or multiple cardiovascular risk factors.
- To reduce the risk of cardiovascular death and hospitalization for heart failure in adults with heart failure (NYHA class II-IV) with reduced ejection fraction.
- To reduce the risk of sustained eGFR decline, end-stage kidney disease, cardiovascular death, and hospitalization for heart failure in adults with chronic kidney disease at risk of progression.

Limitations of Use

- FARXIGA is not recommended for patients with type 1 diabetes mellitus. It may increase the risk of diabetic ketoacidosis in these patients *[see Warnings and Precautions (5.1) in the full Prescribing Information]*.
- FARXIGA is not recommended for use to improve glycemic control in adults with type 2 diabetes mellitus with an eGFR less than 45 mL/min/1.73 m^2. FARXIGA is likely to be ineffective in this setting based upon its mechanism of action.
- FARXIGA is not recommended for the treatment of chronic kidney disease in patients with polycystic kidney disease or patients requiring or with a recent history of immunosuppressive therapy for kidney disease. FARXIGA is not expected to be effective in these populations.

DOSAGE AND ADMINISTRATION

Prior to Initiation of FARXIGA

Assess renal function prior to initiation of FARXIGA therapy and then as clinically indicated *[see Warnings and Precautions (5.2) in the full Prescribing Information]*.

Assess volume status and, if necessary, correct volume depletion prior to initiation of FARXIGA *[see Warnings and Precautions (5.2) and Use in Specific Populations (8.5, 8.6) in the full Prescribing Information]*.

Recommended Dosage

See Table 1 for dosage recommendations based on estimated glomerular filtration rate (eGFR).

Table 1: Recommended Dosage

eGFR (mL/min/1.73 m^2)	Recommended Dose
eGFR 45 or greater	To improve glycemic control, the recommended starting dose is 5 mg orally once daily. Dose can be increased to 10 mg orally once daily for additional glycemic control*. For all other indications, the recommended starting dose is 10 mg orally once daily.
eGFR 25 to less than 45	10 mg orally once daily*.
eGFR less than 25	Initiation is not recommended, however patients may continue 10 mg orally once daily to reduce the risk of eGFR decline, ESKD, CV death and hHF.
On dialysis	Contraindicated.

* FARXIGA is not recommended for use to improve glycemic control in adults with type 2 diabetes mellitus with an eGFR less than 45 mL/min/1.73 m^2. FARXIGA is likely to be ineffective in this setting based upon its mechanism of action.

hHF: hospitalization for heart failure, CV: Cardiovascular, ESKD: End Stage Kidney Disease.

CONTRAINDICATIONS

- History of a serious hypersensitivity reaction to FARXIGA, such as anaphylactic reactions or angioedema *[see Adverse Reactions (6.1) in the full Prescribing Information]*.
- Patients on dialysis *[see Use in Specific Populations (8.6) in the full Prescribing Information]*.

WARNINGS AND PRECAUTIONS

Ketoacidosis in Patients with Diabetes Mellitus

Reports of ketoacidosis, a serious life-threatening condition requiring urgent hospitalization have been identified in patients with type 1 and type 2 diabetes mellitus receiving sodium-glucose cotransporter 2 (SGLT2) inhibitors, including FARXIGA *[see Adverse Reactions (6.1) in the full Prescribing Information]*. In placebo-controlled trials of patients with type 1 diabetes mellitus, the risk of ketoacidosis was increased in patients who received SGLT2 inhibitors compared to patients who received placebo. Fatal cases of ketoacidosis have been reported in patients taking FARXIGA. FARXIGA is not indicated for the treatment of patients with type 1 diabetes mellitus *[see Indications and Usage (1) in the full Prescribing Information]*.

Patients treated with FARXIGA who present with signs and symptoms consistent with severe metabolic acidosis should be assessed for ketoacidosis regardless of presenting blood glucose levels as ketoacidosis associated with FARXIGA may be present even if blood glucose levels are less than 250 mg/dL. If ketoacidosis is suspected, FARXIGA should be discontinued, the patient should be evaluated, and prompt treatment should be instituted. Treatment of ketoacidosis may require insulin, fluid, and carbohydrate replacement.

In many of the postmarketing reports, and particularly in patients with type 1 diabetes, the presence of ketoacidosis was not immediately recognized, and the institution of treatment was delayed because the presenting blood glucose levels were below those typically expected for diabetic ketoacidosis (often less than 250 mg/dL). Signs and symptoms at presentation were consistent with dehydration and severe metabolic acidosis and included nausea, vomiting, abdominal pain, generalized malaise, and shortness of breath. In some but not all cases, factors predisposing to ketoacidosis, such as insulin dose reduction, acute febrile illness, reduced caloric intake, surgery, pancreatic disorders suggesting insulin deficiency (e.g., type 1 diabetes, history of pancreatitis or pancreatic surgery), and alcohol abuse were identified.

Before initiating FARXIGA, consider factors in the patient history that may predispose to ketoacidosis, including pancreatic insulin deficiency from any cause, caloric restriction, and alcohol abuse.

For patients who undergo scheduled surgery, consider temporarily discontinuing FARXIGA for at least 3 days prior to surgery *[see Clinical Pharmacology (12.2, 12.3) in the full Prescribing Information]*.

Consider monitoring for ketoacidosis and temporarily discontinuing FARXIGA in other clinical situations known to predispose to ketoacidosis (e.g., prolonged fasting due to acute illness or post-surgery). Ensure risk factors for ketoacidosis are resolved prior to restarting FARXIGA. Educate patients on the signs and symptoms of ketoacidosis and instruct patients to discontinue FARXIGA and seek medical attention immediately if signs and symptoms occur.

Volume Depletion

FARXIGA can cause intravascular volume depletion which may sometimes manifest as symptomatic hypotension or acute transient changes in creatinine. There have been post-marketing reports of acute kidney injury, some requiring hospitalization and dialysis, in patients with type 2 diabetes mellitus receiving SGLT2 inhibitors, including FARXIGA. Patients with impaired renal function (eGFR less than 60 mL/min/1.73 m^2), elderly patients, or patients on loop diuretics may be at increased risk for volume depletion or hypotension. Before initiating FARXIGA in patients with one or more of these characteristics, assess volume status and renal function. Monitor for signs and symptoms of hypotension, and renal function after initiating therapy.

Urosepsis and Pyelonephritis

Serious urinary tract infections including urosepsis and pyelonephritis requiring hospitalization have been reported in patients receiving SGLT2 inhibitors, including FARXIGA. Treatment with SGLT2 inhibitors increases the risk for urinary tract infections. Evaluate patients for signs and symptoms of urinary tract infections and treat promptly, if indicated *[see Adverse Reactions (6) in the full Prescribing Information]*.

Hypoglycemia with Concomitant Use with Insulin and Insulin Secretagogues

Insulin and insulin secretagogues are known to cause hypoglycemia. FARXIGA may increase the risk of hypoglycemia when combined with insulin or an insulin secretagogue *[see Adverse Reactions (6.1) in the full Prescribing Information]*. Therefore, a lower dose of insulin or insulin secretagogue may be required to minimize the risk of hypoglycemia when these agents are used in combination with FARXIGA.

Necrotizing Fasciitis of the Perineum (Fournier's Gangrene)

Reports of necrotizing fasciitis of the perineum (Fournier's Gangrene), a rare but serious and life-threatening necrotizing infection requiring urgent surgical intervention, have been identified in postmarketing surveillance in patients with diabetes mellitus receiving SGLT2 inhibitors, including FARXIGA. Cases have been reported in both females and males. Serious outcomes have included hospitalization, multiple surgeries, and death.

Patients treated with FARXIGA presenting with pain or tenderness, erythema, or swelling in the genital or perineal area, along with fever or malaise, should be assessed for necrotizing fasciitis. If suspected, start treatment immediately with broad-spectrum antibiotics and, if necessary, surgical debridement. Discontinue FARXIGA, closely monitor blood glucose levels, and provide appropriate alternative therapy for glycemic control.

Genital Mycotic Infections

FARXIGA increases the risk of genital mycotic infections. Patients with a history of genital mycotic infections were more likely to develop genital mycotic infections *[see Adverse Reactions (6.1) in the full Prescribing Information]*. Monitor and treat appropriately.

ADVERSE REACTIONS

The following important adverse reactions are described below and elsewhere in the labeling:

- Ketoacidosis in Patients with Diabetes Mellitus *[see Warnings and Precautions (5.1) in the full Prescribing Information]*
- Volume Depletion *[see Warnings and Precautions (5.2) in the full Prescribing Information]*
- Urosepsis and Pyelonephritis *[see Warnings and Precautions (5.3) in the full Prescribing Information]*
- Hypoglycemia with Concomitant Use with Insulin and Insulin Secretagogues *[see Warnings and Precautions (5.4) in the full Prescribing Information]*
- Necrotizing Fasciitis of the Perineum (Fournier's Gangrene) *[see Warnings and Precautions (5.5) in the full Prescribing Information]*
- Genital Mycotic Infections *[see Warnings and Precautions (5.6) in the full Prescribing Information]*

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 clinical practice.

FARXIGA has been evaluated in clinical trials in patients with type 2 diabetes mellitus, in patients with heart failure, and in patients with chronic kidney disease. The overall safety profile of FARXIGA was consistent across the studied indications. Severe hypoglycemia and diabetic ketoacidosis (DKA) were observed only in patients with diabetes mellitus.

Clinical Trials in Patients with Type 2 Diabetes Mellitus

Pool of 12 Placebo-Controlled Studies for FARXIGA 5 and 10 mg for Glycemic Control

The data in Table 1 is derived from 12 glycemic control placebo-controlled studies in patients with type 2 diabetes mellitus ranging from 12 to 24 weeks. In 4 studies FARXIGA was used as monotherapy, and in 8 studies FARXIGA was used as add-on to background antidiabetic therapy or as combination therapy with metformin *[see Clinical Studies (14.1) in the full Prescribing Information]*.

These data reflect exposure of 2338 patients to FARXIGA with a mean exposure duration of 21 weeks. Patients received placebo (N=1393), FARXIGA 5 mg (N=1145), or FARXIGA 10 mg (N=1193) once daily. The mean age of the population was 55 years and 2% were older than 75 years of age. Fifty percent (50%) of the population were male; 81% were White, 14% were Asian, and 3% were Black or African American. At baseline, the population had diabetes for an average of 6 years, had a mean hemoglobin A1c (HbA1c) of 8.3%, and 21% had established microvascular complications of diabetes. Baseline renal function was normal or mildly impaired in 92% of patients and moderately impaired in 8% of patients (mean eGFR 86 mL/min/1.73 m^2).

Table 2 shows common adverse reactions associated with the use of FARXIGA. These adverse reactions were not present at baseline, occurred more commonly on FARXIGA than on placebo, and occurred in at least 2% of patients treated with either FARXIGA 5 mg or FARXIGA 10 mg.

Table 2: Adverse Reactions in Placebo-Controlled Studies of Glycemic Control Reported in ≥2% of Patients Treated with FARXIGA

Adverse Reaction	% of Patients		
	Pool of 12 Placebo-Controlled Studies		
	Placebo N=1393	FARXIGA 5 mg N=1145	FARXIGA 10 mg N=1193
Female genital mycotic infections*	1.5	8.4	6.9
Nasopharyngitis	6.2	6.6	6.3
Urinary tract infections†	3.7	5.7	4.3
Back pain	3.2	3.1	4.2
Increased urination‡	1.7	2.9	3.8
Male genital mycotic infections§	0.3	2.8	2.7

Table 2: Adverse Reactions in Placebo-Controlled Studies of Glycemic Control Reported in ≥2% of Patients Treated with FARXIGA (cont'd)

Adverse Reaction	% of Patients		
	Pool of 12 Placebo-Controlled Studies		
	Placebo N=1393	FARXIGA 5 mg N=1145	FARXIGA 10 mg N=1193
Nausea	2.4	2.8	2.5
Influenza	2.3	2.7	2.3
Dyslipidemia	1.5	2.1	2.5
Constipation	1.5	2.2	1.9
Discomfort with urination	0.7	1.6	2.1
Pain in extremity	1.4	2.0	1.7

* Genital mycotic infections include the following adverse reactions, listed in order of frequency reported for females: vulvovaginal mycotic infection, vaginal infection, vulvovaginal candidiasis, vulvovaginitis, genital infection, genital candidiasis, fungal genital infection, vulvitis, genitourinary tract infection, vulval abscess, and vaginitis bacterial. (N for females: Placebo=677, FARXIGA 5 mg=581, FARXIGA 10 mg=598).

† Urinary tract infections include the following adverse reactions, listed in order of frequency reported: urinary tract infection, cystitis, *Escherichia* urinary tract infection, genitourinary tract infection, pyelonephritis, trigonitis, urethritis, kidney infection, and prostatitis.

‡ Increased urination includes the following adverse reactions, listed in order of frequency reported: pollakiuria, polyuria, and urine output increased.

§ Genital mycotic infections include the following adverse reactions, listed in order of frequency reported for males: balanitis, fungal genital infection, balanitis candida, genital candidiasis, genital infection male, penile infection, balanoposthitis, balanoposthitis infective, genital infection, and posthitis. (N for males: Placebo=716, FARXIGA 5 mg=564, FARXIGA 10 mg=595).

Pool of 13 Placebo-Controlled Studies for FARXIGA 10 mg for Glycemic Control

FARXIGA 10 mg was also evaluated in a larger glycemic control placebo-controlled study pool in patients with type 2 diabetes mellitus. This pool combined 13 placebo-controlled studies, including 3 monotherapy studies, 9 add-on to background antidiabetic therapy studies, and an initial combination with metformin study. Across these 13 studies, 2360 patients were treated once daily with FARXIGA 10 mg for a mean duration of exposure of 22 weeks. The mean age of the population was 59 years and 4% were older than 75 years. Fifty-eight percent (58%) of the population were male; 84% were White, 9% were Asian, and 3% were Black or African American. At baseline, the population had diabetes for an average of 9 years, had a mean HbA1c of 8.2%, and 30% had established microvascular disease. Baseline renal function was normal or mildly impaired in 88% of patients and moderately impaired in 11% of patients (mean eGFR 82 mL/min/1.73 m^2).

Volume Depletion

FARXIGA causes an osmotic diuresis, which may lead to a reduction in intravascular volume. Adverse reactions related to volume depletion (including reports of dehydration, hypovolemia, orthostatic hypotension, or hypotension) in patients with type 2 diabetes mellitus for the 12-study and 13-study, short-term, placebo-controlled pools and for the DECLARE study are shown in Table 3 *[see Warnings and Precautions (5.2)]*.

Table 3: Adverse Reactions Related to Volume Depletion* in Clinical Studies in Patients with Type 2 Diabetes Mellitus with FARXIGA

	Pool of 12 Placebo-Controlled Studies			Pool of 13 Placebo-Controlled Studies		DECLARE Study	
	Placebo	FARXIGA 5 mg	FARXIGA 10 mg	Placebo	FARXIGA 10 mg	Placebo	FARXIGA 10 mg
Overall population N (%)	N=1393 5 (0.4%)	N=1145 7 (0.6%)	N=1193 9 (0.8%)	N=2295 17 (0.7%)	N=2360 27 (1.1%)	N=8569 207 (2.4%)	N=8574 213 (2.5%)
Patient Subgroup n (%)							
Patients on loop diuretics	n=55 1 (1.8%)	n=40 0	n=31 3 (9.7%)	n=267 4 (1.5%)	n=236 6 (2.5%)	n=934 57 (6.1%)	n=866 57 (6.6%)
Patients with moderate renal impairment with eGFR ≥30 and <60 mL/min/ 1.73 m^2	n=107 2 (1.9%)	n=107 1 (0.9%)	n=89 1 (1.1%)	n=268 4 (1.5%)	n=265 5 (1.9%)	n=658 30 (4.6%)	n=604 35 (5.8%)
Patients ≥65 years of age	n=276 1 (0.4%)	n=216 1 (0.5%)	n=204 3 (1.5%)	n=711 6 (0.8%)	n=665 11 (1.7%)	n=3950 121 (3.1%)	n=3948 117 (3.0%)

* Volume depletion includes reports of dehydration, hypovolemia, orthostatic hypotension, or hypotension.

Hypoglycemia

The frequency of hypoglycemia by study in patients with type 2 diabetes mellitus *[see Clinical Studies (14.1) in the full Prescribing Information]* is shown in Table 4. Hypoglycemia was more frequent when FARXIGA was added to sulfonylurea or insulin *[see Warnings and Precautions (5.4) in the full Prescribing Information]*.

Table 4: Incidence of Severe Hypoglycemia* and Hypoglycemia with Glucose < 54 mg/dL† in Controlled Glycemic Control Clinical Studies in Patients with Type 2 Diabetes Mellitus

	Placebo/Active Control	FARXIGA 5 mg	FARXIGA 10 mg
Monotherapy (24 weeks)	**N=75**	**N=64**	**N=70**
Severe [n (%)]	0	0	0
Glucose <54 mg/dL [n (%)]	0	0	0
Add-on to Metformin (24 weeks)	**N=137**	**N=137**	**N=135**
Severe [n (%)]	0	0	0
Glucose <54 mg/dL [n (%)]	0	0	0
Add-on to Glimepiride (24 weeks)	**N=146**	**N=145**	**N=151**
Severe [n (%)]	0	0	0
Glucose <54 mg/dL [n (%)]	1 (0.7)	3 (2.1)	5 (3.3)
Add-on to Metformin and a Sulfonylurea (24 Weeks)	**N=109**	**-**	**N=109**
Severe [n (%)]	0	-	0
Glucose <54 mg/dL [n (%)]	3 (2.8)	-	7 (6.4)

Table 4: Incidence of Severe Hypoglycemia* and Hypoglycemia with Glucose < 54 mg/dL† in Controlled Glycemic Control Clinical Studies in Patients with Type 2 Diabetes Mellitus (cont'd)

	Placebo/Active Control	FARXIGA 5 mg	FARXIGA 10 mg
Add-on to Pioglitazone (24 weeks)	**N=139**	**N=141**	**N=140**
Severe [n (%)]	0	0	0
Glucose <54 mg/dL [n (%)]	0	1 (0.7)	0
Add-on to DPP4 inhibitor (24 weeks)	**N=226**	**–**	**N=225**
Severe [n (%)]	0	–	1 (0.4)
Glucose <54 mg/dL [n (%)]	1 (0.4)	–	1 (0.4)
Add-on to Insulin with or without other OADs‡ (24 weeks)	**N=197**	**N=212**	**N=196**
Severe [n (%)]	1 (0.5)	2 (0.9)	2 (1.0)
Glucose <54 mg/dL [n (%)]	43 (21.8)	55 (25.9)	45 (23.0)

* Severe episodes of hypoglycemia were defined as episodes of severe impairment in consciousness or behavior, requiring external (third party) assistance, and with prompt recovery after intervention regardless of glucose level.

† Episodes of hypoglycemia with glucose <54 mg/dL (3 mmol/L) were defined as reported episodes of hypoglycemia meeting the glucose criteria that did not also qualify as a severe episode.

‡ OAD = oral antidiabetic therapy.

In the DECLARE study *[see Clinical Studies (14.2) in the full Prescribing Information]*, severe events of hypoglycemia were reported in 58 (0.7%) out of 8574 patients treated with FARXIGA and 83 (1.0%) out of 8569 patients treated with placebo.

Genital Mycotic Infections

In the glycemic control trials, genital mycotic infections were more frequent with FARXIGA treatment. Genital mycotic infections were reported in 0.9% of patients on placebo, 5.7% on FARXIGA 5 mg, and 4.8% on FARXIGA 10 mg, in the 12-study placebo-controlled pool. Discontinuation from study due to genital infection occurred in 0% of placebo-treated patients and 0.2% of patients treated with FARXIGA 10 mg. Infections were more frequently reported in females than in males (see Table 1). The most frequently reported genital mycotic infections were vulvovaginal mycotic infections in females and balanitis in males. Patients with a history of genital mycotic infections were more likely to have a genital mycotic infection during the study than those with no prior history (10.0%, 23.1%, and 25.0% versus 0.8%, 5.9%, and 5.0% on placebo, FARXIGA 5 mg, and FARXIGA 10 mg, respectively). In the DECLARE study *[see Clinical Studies (14.2) in the full Prescribing Information]*, serious genital mycotic infections were reported in <0.1% of patients treated with FARXIGA and <0.1% of patients treated with placebo. Genital mycotic infections that caused study drug discontinuation were reported in 0.9% of patients treated with FARXIGA and <0.1% of patients treated with placebo.

Hypersensitivity Reactions

Hypersensitivity reactions (e.g., angioedema, urticaria, hypersensitivity) were reported with FARXIGA treatment. In glycemic control studies, serious anaphylactic reactions and severe cutaneous adverse reactions and angioedema were reported in 0.2% of comparator-treated patients and 0.3% of FARXIGA-treated patients. If hypersensitivity reactions occur, discontinue use of FARXIGA; treat per standard of care and monitor until signs and symptoms resolve.

Ketoacidosis in Patients with Diabetes Mellitus

In the DECLARE study *[see Warnings and Precautions (5.1) and Clinical Studies (14.2) in the full Prescribing Information]*, events of diabetic ketoacidosis (DKA) were reported in 27 out of 8574 patients in the FARXIGA-treated group and 12 out of 8569 patients in the placebo group. The events were evenly distributed over the study period.

Laboratory Tests

Increases in Serum Creatinine and Decreases in eGFR

Initiation of SGLT2 inhibitors, including FARXIGA causes a small increase in serum creatinine and decrease in eGFR. These changes in serum creatinine and eGFR generally occur within two weeks of starting therapy and then stabilize regardless of baseline kidney function. Changes that do not fit this pattern should prompt further evaluation to exclude the possibility of acute kidney injury *[see Warnings and Precautions (5.2) in the full Prescribing Information]*. In two studies that included patients with type 2 diabetes mellitus with moderate renal impairment, the acute effect on eGFR reversed after treatment discontinuation, suggesting acute hemodynamic changes may play a role in the renal function changes observed with FARXIGA.

Increase in Hematocrit

In the pool of 13 placebo-controlled studies of glycemic control, increases from baseline in mean hematocrit values were observed in FARXIGA-treated patients starting at Week 1 and continuing up to Week 16, when the maximum mean difference from baseline was observed. At Week 24, the mean changes from baseline in hematocrit were –0.33% in the placebo group and 2.30% in the FARXIGA 10 mg group. By Week 24, hematocrit values >55% were reported in 0.4% of placebo-treated patients and 1.3% of FARXIGA 10 mg-treated patients.

Increase in Low-Density Lipoprotein Cholesterol

In the pool of 13 placebo-controlled studies of glycemic control, changes from baseline in mean lipid values were reported in FARXIGA-treated patients compared to placebo-treated patients. Mean percent changes from baseline at Week 24 were 0.0% versus 2.5% for total cholesterol, and -1.0% versus 2.9% for LDL cholesterol in the placebo and FARXIGA 10 mg groups, respectively. In the DECLARE study *[see Clinical Studies (14.2) in the full Prescribing Information]*, mean changes from baseline after 4 years were 0.4 mg/dL versus -4.1 mg/dL for total cholesterol, and -2.5 mg/dL versus -4.4 mg/dL for LDL cholesterol, in FARXIGA-treated and the placebo groups, respectively.

Decrease in Serum Bicarbonate

In a study of concomitant therapy of FARXIGA 10 mg with exenatide extended-release (on a background of metformin), four patients (1.7%) on concomitant therapy had a serum bicarbonate value of less than or equal to 13 mEq/L compared to one each (0.4%) in the FARXIGA and exenatide-extended release treatment groups *[see Warnings and Precautions (5.1) in the full Prescribing Information]*.

DAPA-HF Heart Failure Study

No new adverse reactions were identified in the DAPA-HF heart failure study.

DAPA-CKD Chronic Kidney Disease Study

No new adverse reactions were identified in the DAPA-CKD study in patients with chronic kidney disease.

Postmarketing Experience

Additional adverse reactions have been identified during postapproval use of FARXIGA in patients with diabetes mellitus. Because these reactions are reported voluntarily from a population of uncertain size, it is generally not possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

- Ketoacidosis
- Acute Kidney Injury
- Urosepsis and Pyelonephritis
- Necrotizing Fasciitis of the Perineum (Fournier's Gangrene)
- Rash

DRUG INTERACTIONS

Positive Urine Glucose Test

Monitoring glycemic control with urine glucose tests is not recommended in patients taking SGLT2 inhibitors as SGLT2 inhibitors increase urinary glucose excretion and will lead to positive urine glucose tests. Use alternative methods to monitor glycemic control.

Interference with 1,5-anhydroglucitol (1,5-AG) Assay

Monitoring glycemic control with 1,5-AG assay is not recommended as measurements of 1,5-AG are unreliable in assessing glycemic control in patients taking SGLT2 inhibitors. Use alternative methods to monitor glycemic control.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

Based on animal data showing adverse renal effects, FARXIGA is not recommended during the second and third trimesters of pregnancy.

Limited data with FARXIGA in pregnant women are not sufficient to determine drug-associated risk for major birth defects or miscarriage. There are risks to the mother and fetus associated with poorly controlled diabetes and untreated heart failure in pregnancy *(see Clinical Considerations)*.

In animal studies, adverse renal pelvic and tubule dilatations, that were not fully reversible, were observed in rats when dapagliflozin was administered during a period of renal development corresponding to the late second and third trimesters of human pregnancy, at all doses tested; the lowest of which provided an exposure 15-times the 10 mg clinical dose *(see Data)*.

The estimated background risk of major birth defects is 6 to 10% in women with pre-gestational diabetes with a HbA1c greater than 7% and has been reported to be as high as 20 to 25% in women with HbA1c greater than 10%. The estimated background risk of miscarriage for the indicated population is unknown. 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.

Clinical Considerations

Disease-associated maternal and/or embryofetal risk

Poorly controlled diabetes in pregnancy increases the maternal risk for diabetic ketoacidosis, preeclampsia, spontaneous abortions, preterm delivery and delivery complications. Poorly controlled diabetes increases the fetal risk for major birth defects, stillbirth, and macrosomia related morbidity.

Data

Animal Data

Dapagliflozin dosed directly to juvenile rats from postnatal day (PND) 21 until PND 90 at doses of 1, 15, or 75 mg/kg/day, increased kidney weights and increased the incidence of renal pelvic and tubular dilatations at all dose levels. Exposure at the lowest dose tested was 15-times the 10 mg clinical dose (based on AUC). The renal pelvic and tubular dilatations observed in juvenile animals did not fully reverse within a 1-month recovery period.

In a prenatal and postnatal development study, dapagliflozin was administered to maternal rats from gestation day 6 through lactation day 21 at doses of 1, 15, or 75 mg/kg/day, and pups were indirectly exposed *in utero* and throughout lactation. Increased incidence or severity of renal pelvic dilatation was observed in 21-day-old pups offspring of treated dams at 75 mg/kg/day (maternal and pup dapagliflozin exposures were 1415-times and 137-times, respectively, the human values at the 10 mg clinical dose, based on AUC). Dose-related reductions in pup body weights were observed at greater or equal to 29-times the 10 mg clinical dose (based on AUC). No adverse effects on developmental endpoints were noted at 1 mg/kg/day (19-times the 10 mg clinical dose, based on AUC). These outcomes occurred with drug exposure during periods of renal development in rats that corresponds to the late second and third trimester of human development.

In embryofetal development studies in rats and rabbits, dapagliflozin was administered throughout organogenesis, corresponding to the first trimester of human pregnancy. In rats, dapagliflozin was neither embryolethal nor teratogenic at doses up to 75 mg/kg/day (1441-times the 10 mg clinical dose, based on AUC). Dose related effects on the rat fetus (structural abnormalities and reduced body weight) occurred only at higher dosages, equal to or greater than 150 mg/kg (more than 2344-times the 10 mg clinical dose, based on AUC), which were associated with maternal toxicity. No developmental toxicities were observed in rabbits at doses up to 180 mg/kg/day (1191-times the 10 mg clinical dose, based on AUC).

Lactation

Risk Summary

There is no information regarding the presence of dapagliflozin in human milk, the effects on the breastfed infant, or the effects on milk production. Dapagliflozin is present in the milk of lactating rats *(see Data)*. However, due to species specific differences in lactation physiology, the clinical relevance of these data are not clear. Since human kidney maturation occurs *in utero* and during the first 2 years of life when lactational exposure may occur, there may be risk to the developing human kidney.

Because of the potential for serious adverse reactions in breastfed infants, advise women that use of FARXIGA is not recommended while breastfeeding.

Data

Dapagliflozin was present in rat milk at a milk/plasma ratio of 0.49, indicating that dapagliflozin and its metabolites are transferred into milk at a concentration that is approximately 50% of that in maternal plasma. Juvenile rats directly exposed to dapagliflozin showed risk to the developing kidney (renal pelvic and tubular dilatations) during maturation.

Pediatric Use

Safety and effectiveness of FARXIGA in pediatric patients under 18 years of age have not been established.

Geriatric Use

No FARXIGA dosage change is recommended based on age.

A total of 1424 (24%) of the 5936 FARXIGA-treated patients were 65 years and older and 207 (3.5%) patients were 75 years and older in a pool of 21 double-blind, controlled, clinical studies assessing the efficacy of FARXIGA in improving glycemic control in type 2 diabetes mellitus. After controlling for level of renal function (eGFR), efficacy was similar for patients under age 65 years and those 65 years and older. In patients ≥65 years of age, a higher proportion of patients treated with FARXIGA for glycemic control had adverse reactions of hypotension *[see Warnings and Precautions (5.2) and Adverse Reactions (6.1) in the full Prescribing Information]*.

In both the DAPA-HF and DAPA-CKD studies, safety and efficacy were similar for patients age 65 years and younger and those older than 65. In the DAPA-HF study, 2714 (57%) out of 4744 patients with HFrEF were older than 65 years. In the DAPA-CKD study, 1818 (42%) out of 4304 patients with CKD were older than 65 years.

Renal Impairment

FARXIGA was evaluated in 4304 patients with chronic kidney disease (eGFR 25 to 75 mL/min/1.73 m^2) in the DAPA-CKD study. FARXIGA was also evaluated in 1926 patients with an eGFR of 30 to 60 mL/min/1.73 m^2 in the DAPA-HF study. The safety profile of FARXIGA across eGFR subgroups in these studies was consistent with the known safety profile *[see Adverse Reactions (6.1) and Clinical Studies (14.3 and 14.4) in the full Prescribing Information]*.

FARXIGA was evaluated in two glycemic control studies that included patients with type 2 diabetes mellitus with moderate renal impairment (an eGFR of 45 to less than 60 mL/min/1.73 m^2 *[see Clinical Studies (14.1) in the full Prescribing Information]*, and an eGFR of 30 to less than 60 mL/min/1.73 m^2, respectively). Patients with diabetes and renal impairment using FARXIGA may be more likely to experience hypotension and may be at higher risk for acute kidney injury secondary to volume depletion. In the study of patients with an eGFR 30 to less than 60 mL/min/1.73 m^2, 13 patients receiving FARXIGA experienced bone fractures compared to none receiving placebo. Use of FARXIGA for glycemic control in patients without established CV disease or CV risk factors is not recommended when eGFR is less than 45 mL/min/1.73 m^2 *[see Dosage and Administration (2.2) in the full Prescribing Information]*.

Efficacy and safety studies with FARXIGA did not enroll patients with an eGFR less than 25 mL/min/1.73 m^2. FARXIGA is contraindicated in patients on dialysis.

Hepatic Impairment

No dose adjustment is recommended for patients with mild, moderate, or severe hepatic impairment. However, the benefit-risk for the use of dapagliflozin in patients with severe hepatic impairment should be individually assessed since the safety and efficacy of dapagliflozin have not been specifically studied in this population *[see Clinical Pharmacology (12.3) in the full Prescribing Information]*.

OVERDOSAGE

There were no reports of overdose during the clinical development program for FARXIGA.

In the event of an overdose, contact the Poison Control Center. It is also reasonable to employ supportive measures as dictated by the patient's clinical status. The removal of dapagliflozin by hemodialysis has not been studied.

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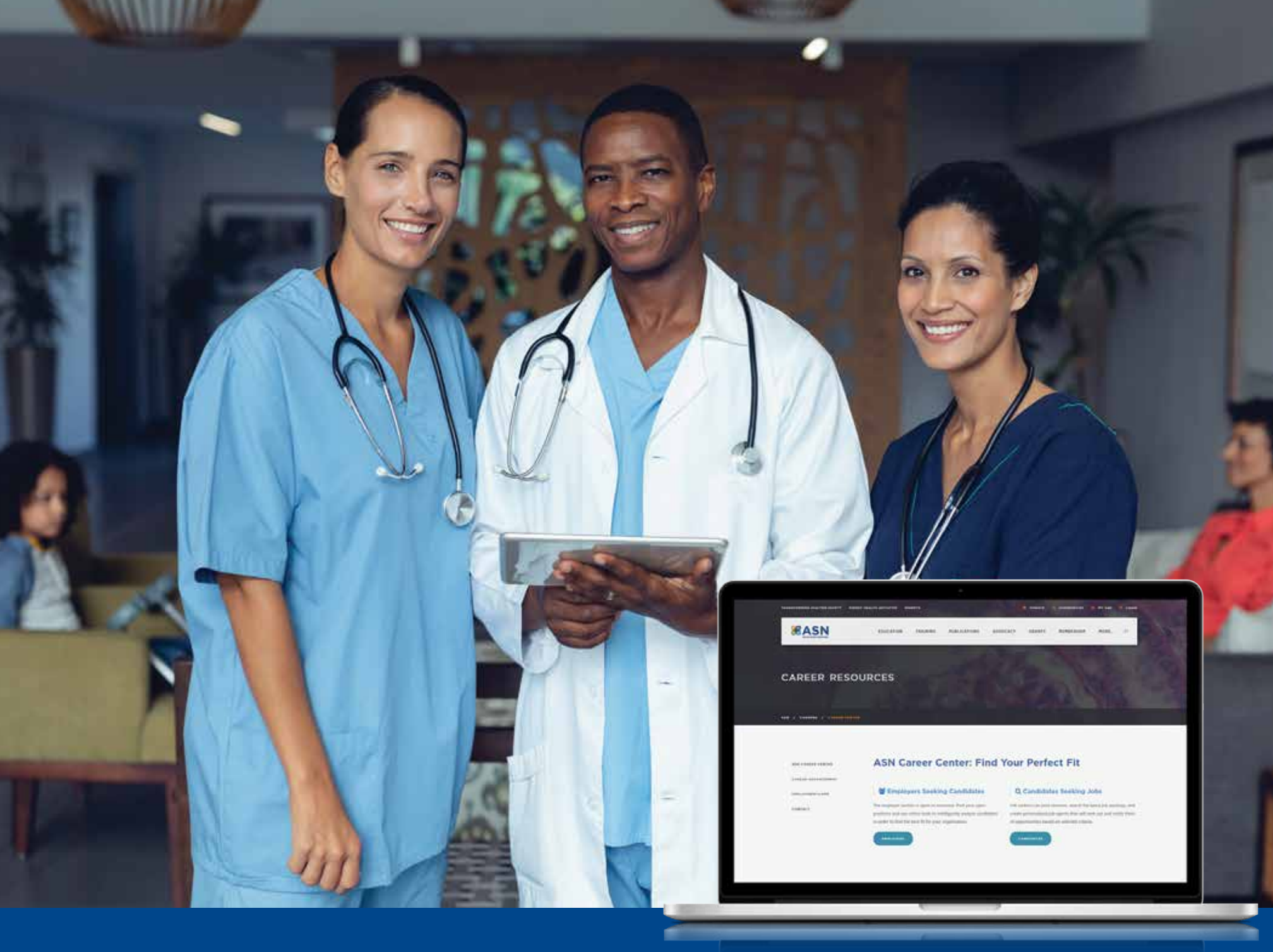

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PRIVATE PRACTICE NEPHROLOGY: THE BALL IS IN OUR COURT

By Katherine Kwon

Much has been written in the past few years about the nephrology workforce crisis. Fellowship positions go unfilled; some recent graduates choose to work as hospitalists instead. However, there are many bright spots on the horizon. Exciting new therapies, such as the sodium-glucose cotransporter-2 (SGLT2) inhibitors, offer the chance to help keep more people from reaching kidney failure. Meanwhile, recent policy advances, especially the Advancing American Kidney Health Executive Order in the United States, will help shift the practice of nephrology toward more comprehensive care of patients living with kidney diseases.

Nephrologists in private practice tend to value their independence and autonomy. In the US healthcare system, however, medicine is a team sport. The majority of US nephrologists are in private practice; it is imperative that their voices be heard in the policy debates. Nephrologists in any practice setting should seek to understand the forces that shape their working world. In this issue of *Kidney News* dedicated to private practice nephrology, we start to examine some of these interplaying forces. The full scope of the nephrology ecosystem is of course beyond one magazine. As you read this issue, I hope you start to think of some parts of your professional world in a different way.

Every nephrologist I know works hard. My belief is that bringing new nephrologists into our profession requires us to also work smart. If there are areas of our practice that need reimagining, we are the ones to do it. Nephrology is a small workforce; this is an opportunity. There are terrific professional nephrology organizations that will help shape the practice environment in the years to come, and each of them welcomes new members. If one of the questions we raise in this month's issue resonates with you, there is no one better to answer it than you. The Editorial Board welcomes ideas for potential articles or even direct submissions on ways we can all make our field better.

Katherine Kwon, MD, FASN, is a partner with Lake Michigan Nephrology in St. Joseph, MI.

PRIVATE PRACTICE TRANSPLANT NEPHROLOGY

ADVANTAGES AND DISADVANTAGES

By Francis L. Weng and Heather Lefkowitz

Over the past 30 years, kidney transplantation has grown greatly, and there are now >200 Centers for Medicare & Medicaid Services (CMS)-approved kidney transplant centers. As a result, many transplant nephrologists are not faculty members at a medical school and do not attend at large teaching centers but instead work in private practice. Almost all private practice nephrologists see some kidney transplant recipients, typically patients who are at least several months posttransplant and relatively stable. Private practice transplant nephrologists, however, also care for transplant recipients during the immediate peri- and posttransplant periods and are on staff at kidney transplant centers.

Private practice transplant nephrology offers many potential rewards. Some transplant nephrologists prefer that private practice focuses on clinical care, without the necessity to perform research, publish scholarly articles, or teach trainees. Private practice usually allows transplant nephrologists to continue practicing general nephrology. Private practice may offer reimbursement opportunities, such as joint ventures with dialysis units, that are unavailable to academic transplant nephrologists. Private practices, by functioning outside the complex structures of academic medicine, may have minimal "red tape" and administrative hassles.

Compared to transplant nephrology at academic medical centers, private practice transplant nephrology also has some disadvantages. Many transplant nephrologists enjoy research, scholarship, and teaching, and these are not as easily possible in private practice. Some transplant nephrologists would prefer to focus solely on transplant medicine. However, such focus requires a larger transplantation volume, and many private practice transplant nephrologists are based at hospitals with lower transplantation volumes. Smaller private practices may lack the infrastructure to fully support the career development of their transplant nephrologists. Private practice transplant nephrologists may be fully employed by their private practices or partly employed or contracted to the hospital and transplant center; these arrangements can be complex. Finally, transplant nephrologists in private practice may find conflicts between the demands of their private practice and the transplant center. For example, the private practice may compete with other nephrology groups that refer patients to the transplant center.

Private practice transplant nephrology is a sometimes-overlooked segment of nephrology that should be considered by trainees. Given the current focus on increasing rates and numbers of kidney transplants, we will likely see a growing need for transplant nephrologists in the private practice setting.

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The authors have worked as private practice transplant nephrologists at different transplant centers and private practices, and Dr. Lefkowitz continues in private practice. The authors have no other disclosures.

Harnessing Electronic Health Records for Population Health Management

By Varsha Danda and Sri Lekha Tummalapalli

Electronic health records (EHRs) have untapped potential for population health management. Population health focuses on the health outcomes of a group of individuals, rather than considering the health of one person at a time (Figure 1) (1). New value-based care models, such as Kidney Care Choices, provide an additional incentive to use EHRs for population health management. Value-based care models tie performance on quality metrics to financial bonuses or penalties and increasingly hold practices at financial risk for total costs of care. If EHR-based tools are effective in improving quality metric performance and preventing unnecessary hospitalizations, they may provide a return on investment.

Three key applications of EHRs for population health management include the following: 1) generating quality reports, 2) tracking care milestones, and 3) ensuring patients are not lost to follow-up. Current EHR systems provide a variety of features to accomplish these goals (Table 1).

Many nephrology practices are partnering with practice management and startup companies to implement EHR-based strategies.

The most commonly used EHR by nephrology practices is Epic Systems. Epic's Reporting Workbench, under the Epic button > Reports > My Reports tab, contains pre-built quality reports, which are also customizable. Clinicians or health systems can also construct chronic kidney disease (CKD) quality dashboards. Epic's SlicerDicer allows clinicians to examine trends in clinical data and stratify by subpopulations. Several institutions, including Cleveland Clinic, Mass General Brigham, Providence St. Joseph Health, and the University of California, Los Angeles (Center for Kidney Disease Research, Education and Hope [CURE-CKD]), have gone further to create CKD registries, which are structured databases of clinical information that can be readily queried. DaVita and Fresenius Medical Care have separately partnered with Epic to create CKD EHR platforms, which combine nephrology-specific workflows with predictive analytics.

Other EHRs have additional population health tools. Allscripts offers an interoperability platform, care coordination software, and transitions of care software. Athenahealth provides helpful features, including >140 pre-built quality reports and automated outreach tools to improve patient engagement.

Many nephrology practices are partnering with practice management and startup companies to implement EHR-based strategies. For example, Global Nephrology Solutions is a practice management platform that uses predictive modeling to identify and coordinate care for potentially high-risk patients. Nephrology Care Alliance is another clinical technology service that connects to EHRs and provides specialized nephrology workflows.

Several key challenges remain. First, publicly available data on the effectiveness of these tools for driving care improvements are still limited. Second, there is often lack of alignment with metrics used for internal quality improvement and those used in national quality programs, such as the Merit-Based Incentive Program. The development of more electronic clinical quality measures (eCQMs) related to CKD could decrease manual data entry requirements, which are burdensome and costly.

In sum, as nephrology practices are shifting their focus onto population health management, EHRs are rising to the challenge with innovative, specialty-focused features that can help identify and bridge health gaps and improve health outcomes as a whole. ■

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Table 1. Population health tools in electronic health records (EHRs)

EHR provider	Population health tools
Epic	Reporting Workbench (My Reports) My Dashboards SlicerDicer
Cerner	HealtheIntent™ population health platform
Allscripts	CareInMotion™ dbMotion™ Solution interoperability platform Care Director care coordination software CarePort™ transitions of care software
Athenahealth	Pre-built quality reports Automated outreach services

EHR functionality varies by local specifications.

Figure 1. Medical and population health models

Medical Model	Population Health Model

• Focus on Individual
• Diagnosis
• Evidence-based Treatment
	• Focus on Population
	• Access to care
	• Allocation of resources
	  • Between groups of patients
	  • Between primary and specialty care
	  • Between healthcare and other sectors of the economy
	• Disease prevention

Demystifying Form 2728

By Adam Weinstein

Although nephrologists complete the "End Stage Renal Disease (ESRD) Medical Evidence Report Medicare Entitlement and/or Patient Registration" form (form 2728) 138,000 times per year, the form is underappreciated and surprisingly important (1). Form 2728 was born in 1973 out of necessity. The form is, primarily, a nephrologist's attestation to the Centers for Medicare & Medicaid Services (CMS) that a patient is eligible to receive the ESRD Medicare benefits, irrespective of age and based solely on his or her diagnosis (2). However, form 2728 is also a critical point of data collection for understanding the population of patients requiring kidney replacement therapy.

Aside from the expected patient demographics, form 2728 collects various diagnostic and care information, for example, primary and secondary diagnoses leading to ESRD status (boxes 14 and 16), aspects of pre-dialysis chronic kidney disease (CKD) care (box 17), and incident laboratory data (box 18) (3). These data, it turns out, are the most impactful.

CMS, the US Renal Data System (USRDS), and, under a CMS contract, the University of Michigan Kidney Epidemiology and Cost Center (UM-KECC) are the prime users of 2728 data. CMS uses the data to administer the ESRD program, for example, determining a patient's first day of dialysis. USRDS uses the data to evaluate and publish patient trends in its annual report. UM-KECC employs 2728 data in a wide variety of metrics to which both medical directors and dialysis facilities are held accountable. It is this last use case that is often underappreciated. For example, UM-KECC uses comorbidity data collected in box 16 for risk-adjusted metrics included in the Quality Incentive Program (QIP), 5-star program, and related dialysis quality metrics (4).

Form 2728 has several limitations of which nephrologists should be aware. First, the list of selectable comorbidities (box 16) and primary causes of renal failure (box 14) are chosen by CMS and are the only choices available. Second, after initial submission, there is only a 5-day window to update a patient's 2728 data (5). Third, CMS has no specific processes to gather feedback for the form. Suggested changes in data elements or processes must go through standard CMS advocacy pathways.

All of this means that the 2728 data may not easily capture the full complexity or intensity of a patient's illness. And the initial data selected persist over the entire duration of a patient's kidney replacement care, irrespective of disease progression. Given this, nephrologists and their care teams have an enormous opportunity to ensure that patients' form 2728 data are comprehensive, timely, and accurate (6, 7). Engaging the right processes and people to create a precise clinical picture of our incident dialysis patients is critical. To be sure, this effort is challenging, but form 2728 is our tool for painting that picture. ■

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Accepting New Patients Undergoing Long-Term Dialysis with a History of Disruptive or Maladaptive Behaviors
Leaving Labels Behind

By Darren C. Schmidt

Nephrology care requires a long-term collaboration among the patient, his or her nephrologist, and the many other essential members of the healthcare team. However, in some situations, circumstances evolve to where it is in the best interest of all parties (including the patient) for a change in provider and/or facility. If an individual has a history of disruptive or maladaptive behaviors, the potential new provider or medical director is confronted with the dilemma of whether to accept the patient (1). There are a number of factors to weigh in making this decision (Table 1), running the gamut from ethical principles and obligations to practical concerns about quality metrics and reimbursement rates. The phrase "problem patient" is pejorative and is to be avoided. When one uses that phrase, often what he or she is referencing is troublesome physician-patient interactions or patient behaviors. The label, problem patient, however, can cause serious damage to an individual and prevent him or her from accessing necessary medical care.

If a patient has a documented history of disruptive or maladaptive behavior(s), it may be helpful to first take inventory of what is occurring with some degree of perspective and emotional detachment (2). Whether functioning as a clinical provider or a medical director, answering some key questions can be helpful in assessing whether to assume care for a patient with this type of history. Who, if anyone, do these behaviors put at risk? Could the behavior be a manifestation of a medical condition (Table 2)? Could these behaviors arise from problematic interactions where both the patient and others involved in his or her care (e.g., the provider, nurses, or dialysis unit staff) are playing a role, and could this dynamic be adjusted for a better outcome? Would the change in environment brought about by the patient joining your practice or dialysis facility potentially lead to the resolution of these issues? Unfortunately, it may not be possible to fully answer these types of questions with the information available at the time a decision needs to be made.

Dialysis facilities should have codes of contact that are shared with patients on admission to the unit and generally at specified intervals thereafter. However, it can be helpful to review these documents with a patient when troublesome behaviors occur. There are some patient behaviors, such as threats or violence toward other patients or healthcare workers, where rigid boundaries must be enforced. The diversity of legal statutes, institutional policies, and cultural practices makes it impossible to offer uniform guidance on how to proceed. Providers are encouraged to consult with their risk managers and other legal resources in specific instances.

In the vast majority of cases, it is in no one's interest, and is particularly unfortunate for the patient, if care devolves into frequent emergency department visits and emergent dialysis. Furthermore, even beyond ethical concerns, medical abandonment can put a provider in legal jeopardy when suitable alternative care has not been found. If the nephrology community has a collaborative approach, where providers and facilities in the area share an understanding that even challenging patients will ultimately need to receive care, then open and honest communication among the healthcare professionals can go a long way to building a foundation for successful transitions of care. ■

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Leaving Labels Behind

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Table 1. Accepting a patient with a history of behavioral issues: Benefits, challenges, and potential solutions

Benefits	Challenges	Solutions
Meeting the ethical obligation to treat those in need of care	Disruption to care for other patients based on problem behavior	Clear expectations for patient and staff behavior
Satisfaction of building relationships with patients	Possible worsened quality metrics	Written code of patient conduct shared with patients
Growing one's practice	Decreased reimbursement based on "poor quality"	Fostering open and non-judgmental communication between patients and healthcare team
Service to the nephrology community	Medico-legal responsibility for the behavior of the patient	Sensitivity to complex social issues affecting the facility and community
	Emotional headaches and stress	Prioritizing mental health issues within in the unit
	Additional staff burden spent on working on behavioral changes	Effective tools for resolving patient grievances

Table 2. Potential medical issues and other causes presenting with behavioral issues

Metabolic problems	Mental health problems	Organic brain problems	Social issues	Other unmet medical needs
Uremia/under-dialysis	Anxiety/depression	Vascular dementia	Substance abuse	Chronic pain
Electrolyte disturbances (e.g., hyponatremia)	Schizophrenia	Alzheimer's disease	Domestic abuse	Hearing impairment
Hypercalcemia	Bipolar disorder	Undiagnosed subdural hematoma	Malnutrition	Occult infection

My Private Practice Journey

By Ojas Mehta

At the start of my second year of fellowship, I started considering what career opportunities were available to me within the vicinity of my fellowship training. I had been in the central Jersey area for many years and had established a strong referral network from colleagues, which I wished to maintain. Once I determined that I did not want to pursue further subspecialty training (i.e., transplant, interventional, etc.), the next decision was academic versus private practice.

My original desire was to join the faculty of my fellowship. Unfortunately, due to budget cuts at the time, there was not enough funding to hire another nephrologist. Fortunately, another opportunity came along in a private practice that seemed to fulfill a lot of what I was looking for.

When evaluating various career opportunities during your general nephrology training, consider what you enjoy and what your long-term career goals are. For me, I enjoyed research, teaching, and case diversity with particular interests in fluids and electrolytes, acid-base, glomerular diseases, and dialysis. Long-term goals included meeting financial targets, teaching, and completing research projects. With this in mind, interests and goals will change over time. As one of my mentors once told me, "I would get bored of my situation about every 10 years, but I was fortunate to find new opportunities to reinvigorate my interest." Now, 10 years after graduating fellowship, I'm finding the same.

What I enjoy about private practice is the autonomy and flexibility. I am able to essentially set and adjust my schedule, train/optimize staff, and decide on what services I prefer to focus (e.g., outpatient, inpatient, dialysis, teaching, publications, etc.). I am also in direct control of the financials and how revenue is allocated and what insurance plans I choose to accept. Additionally, there are no restrictions on participating in external opportunities such as speaking engagements, advisory boards, medical directorships, or joint ventures with dialysis providers.

I am fortunate in that I am affiliated/contracted with a teaching hospital that does not have an academic nephrology division. This allows me to teach students and residents on their clinical and elective rotations, provide didactic lectures, collaborate with others on research and publications, provide services to indigent patients both inpatient and through their affiliated outpatient clinic (thereby giving me exposure to diverse pathology), and be involved in the nephrology teaching curriculum. This, however, may not be the typical situation with all private practices.

Other things to consider about a private practice include the following:

Geography (pathology seen, competition in the area, reimbursements, revenue stream, lifestyle, etc.). For me in particular, there are several competitive groups in the same area, so essentially, I have to build a "brand" of quality, service, and perhaps most important, availability.

Small groups vs. large groups. This will directly influence call schedule (or lifestyle), partnership track along with buy-ins and buy-outs, ability to change things within the practice (e.g., staff recruitment, rounding schedule, etc., since one's "vote" will be diluted with more physicians in the group), and perhaps most important these days, economies of scale (ability to negotiate contracts with insurance providers and dialysis providers and concentrate shared resources such as billing and benefits).

Finally, it appears that there is a major transition in medicine. The days of "mom and pop" practices are slowly ending. Two main trends are emerging:

1) hospital systems contracting with private practices in some capacity and

2) practices converging into one entity and essentially becoming a corporation such as an IPA (independent practice association) or an ACO (accountable care organization). For example, five small nephrology groups in the central New Jersey region may decide to form an IPA under one tax ID.

As we decide our career choices, there are certainly many options to consider. However, just like any other industry, things are evolving and will continue to evolve. Our goals and interests will evolve with them. ■

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Dr. Mehta reports no conflicts of interest.

Strategies for Value-Based Care

By Gurdev Singh, Lauren Ellenburg, and Rajiv Poduval

Value-based care (VBC) is the buzzword in healthcare today, and nephrology is not behind in this venture. The word evokes anxiety and fear in most, as it is usually equated with a push to reduce costs by deploying expensive infrastructure, which comes with significant regulatory burden. What really happens is that the payor (insurance entity) delegates a subset of the population to a risk-bearing entity (RE) that has the skill set and resources to improve the quality of care provided at a lower than historical cost by use of innovative care models and technology. The financial savings (or losses) are then shared by the payor and RE. The patients in the program benefit from better quality and lower out-of-pocket costs. The end result is a win-win-win for all stakeholders.

After a successful 5-year pilot of the End-Stage Renal Disease (ESRD) Seamless Care Organization (ESCO), the Centers for Medicare & Medicaid Innovation (CMMI) launched the next generation of nephrology VBC models—Kidney Care First (KCF) and Comprehensive Kidney Care Contracting (CKCC). Given that the Centers for Medicare & Medicaid Services (CMS) spends $121 billion per year on chronic kidney disease (CKD) with $84 billion going toward non-ESRD, it came as no surprise that these models expanded the population at risk by including CKD stages 4 and 5, correctly recognizing the need for intervention upstream to have a meaningful impact. Some payors are even experimenting with models that include CKD stage 3B.

Patient education and appropriate clinical interventions earlier in the course of disease are expected to slow the progression of CKD. At the same time, CMS recognized the need for the nephrologists to be the driver of these programs, aligning financial incentives. In a major shift from the ESCO pilot where the dialysis organizations created the RE, these new models task the nephrologist to launch the Kidney Contracting Entity (KCE), which mandates the inclusion of a transplant provider but makes the dialysis organization participation optional and by invitation only. In addition, the KCF models make it easier for the nephrologist to participate in a risk-free environment, providing financial incentives linked to quality metrics. The CMMI models are a precursor to an industrywide phenomenon with private payors exploring similar options.

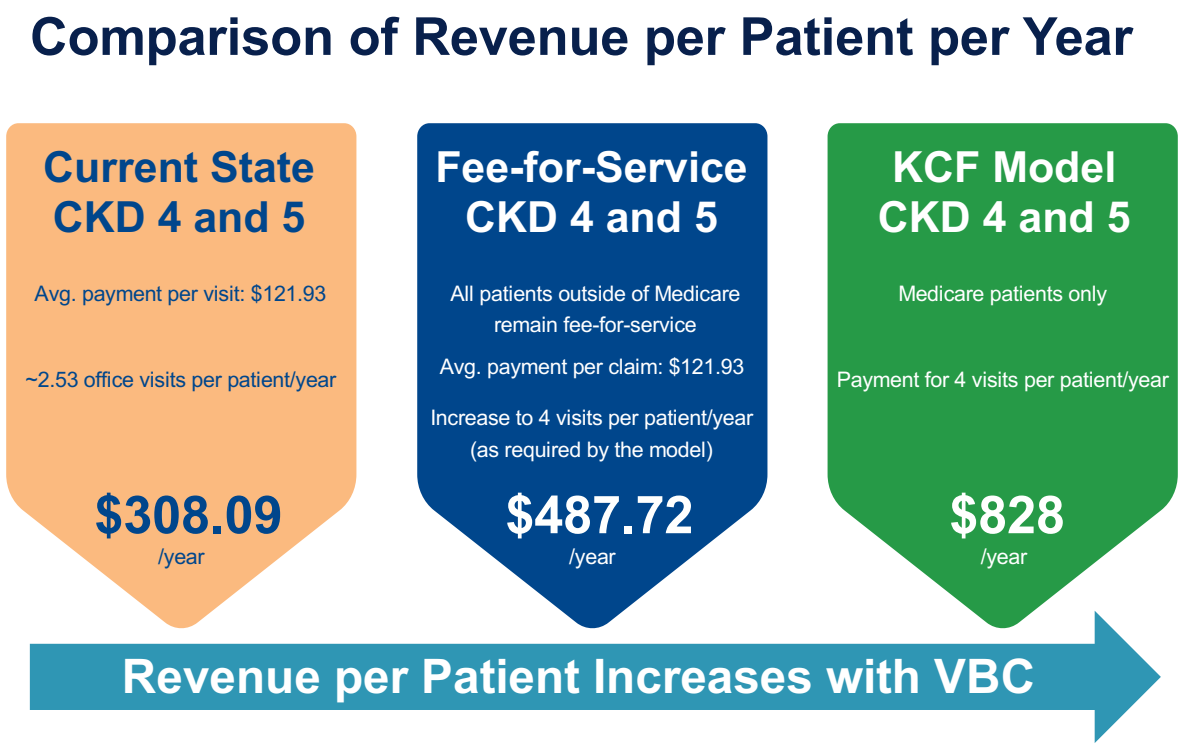
Nephrologists are multidisciplinary team leaders in the dialysis unit and now have the opportunity to lead in VBC models for kidney care. This can be a great opportunity for nephrology practices to meaningfully change how we provide care to our patients. The thought of taking a risk may scare many of us and inhibit our opportunity to lead and in the process not only lose our autonomy and relevance but also the potential financial rewards.

To be successful during this transformation, a private nephrology practice must remain nimble, agile, and devoted to an ideology of enhanced patient outcomes at reduced cost. There are three basic keys to success in this new world.

Alignment and density: Alignment with like-minded nephrologists and physician collaboration becomes integral to the establishment of market density. Market density is important to implement programs that will improve the ability to care for large populations of patients in an efficient manner. CMMI allows for practices to join together in the CKCC model, pooling resources and reaching the required minimum number of patients.

Analytics capabilities: The ability to achieve target outcomes requires leveraging clinical data sets obtained from electronic health records, along with claims data. Analysis, strategic planning, implementation, and tracking become pivotal next steps for successfully managing the population at risk. Choosing a data-analytics partner who can provide this capability is an important step. There are a handful of vendors, mostly new entrants since the launch of the nephrology risk models, that have the knowledge and expertise in the nephrology space. Some focus only on the data, some on the care coordination, or both, whereas others offer a full suite of infrastructure and services, including practice management.

Figure 1. Revenue per patient increases with value-based care



We truly believe that for the first time, nephrologists are in the driver's seat to lead the transformation of kidney care delivery.

Infrastructure: The transition from fee-for-service (FFS) VBC does not require large capital outlay but does need a paradigm shift in how we think about providing care. A multidisciplinary approach with emphasis on patient education and engagement becomes the key to success. A nephrologist-led team of professionals is needed to perform the administrative tasks and implement operational best practices, clinical guidelines, and high-risk programs.

We truly believe that for the first time, nephrologists are in the driver's seat to lead the transformation of kidney care delivery. Although the ESCO focused only on ESRD patients, had high cost outlays, and did not align the financial incentive for the nephrologist, the new models represent a paradigm shift and provide up-front and risk-free financial incentives to the nephrologists who are linked to quality and outcomes. These include an increase in average reimbursement for CKD stages 4 and 5 patients from $400 per year (based on four office visits) to $800 per year (new capitated rate) (Figure 1), a kidney transplant bonus of $15,000 over 3 years, and a 5% alternative payment model (APM) bonus with the Merit-Based Incentive Payment System (MIPS) exemption (Table 1). Moving to the next level, a shared savings model can bring additional financial incentives but comes with a two-sided risk of sharing in losses.

In conclusion, VBC models require us to think differently and provide an opportunity for the nephrologist to be the leader of transformation, but unlike history and prior models, this now represents a true investment in oneself. ■

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Strategies for Value-Based Care

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Table 1. Value-based care alignment

KCC components of reimbursement		
CKD QCP Quarterly capitated payment (QCP) now received automatically with attribution	**ESRD MCP** ESRD payments continue to be reimbursed at traditional FFS	**PD True-Up** $35 per patient per claim for home dialysis
KTB Each transplant completed receives $15,000 over a 3-year period	**5% APM** Participation in Kidney Care Choices (KCC) qualifies as advanced APM, qualifying each practice for an automatic 5% increase on Medicare Part B payments	**Shared savings** 50% shared savings split, comes with risk of shared losses

MCP, monthly capitation payment; PD, peritoneal dialysis; KTB, kidney tuberculosis.

The Predicament of Establishing a Peritoneal Dialysis Program in a Nursing Facility

By Andrew E. Lazar

The case for more PD

According to the United States Renal Data System (USRDS)'s Annual Report for 2020, the number of incident patients with end stage kidney disease (ESKD) in 2018 was 131,636, which was an increase of 2.3% from the year prior (1). Although all-cause mortality increased among patients on dialysis in the first half of 2020 by 29% and 48% for those with a functioning kidney transplant compared with the same 5-week period in 2019 (2), overall mortality in patients with ESKD has trended downward, leading to an increase in prevalent patients on dialysis to a new high of 2042 cases per 1 million people in 2018 (1).

In 2018, there were 14,334 incident patients starting on peritoneal dialysis (PD), up from 10,865 in 2013. We should anticipate that PD prevalence in nursing facilities will increase for the following reasons: the incidence of ESKD in people aged 65–74 years old and 75+ years old reached an all-time high in 2018; PD incidence is on the rise; mortality from PD may be 0.88 for continuous ambulatory PD (CAPD) versus in-center hemodialysis based on the Australia and New Zealand Dialysis and Transplant (ANZDATA) registry (3); ESKD treatment choice (4) models incentivize use of home dialysis modalities; and the cost of PD was $78,159 annually versus $91,795 for in-center hemodialysis, again pushing the Centers for Medicare & Medicaid Services (CMS) to incentivize PD versus in-center hemodialysis (1).

Is consistent, high-quality PD care possible in a nursing facility environment?

In 2018, CMS released its rules on dialysis care in nursing facilities (5). The highlights of these regulations include the necessity for on-site supervision of dialysis by a trained registered nurse (RN) when a nursing home resident is receiving hemodialysis in the nursing facility and by a trained RN or licensed practical nurse (LPN) when PD is provided. In essence, the nursing facility's dialysis program is subject to the conditions for coverage and an updated ESKD core survey process (6).

I had the opportunity to interview some of the key providers of nursing home dialysis care as well as administrators of nursing facilities that have offered on-site PD. Scott Vavrinchik of Affiliated Dialysis (now Dialyze Direct) raised the concern for "keeping staff proficient to a level of standard of care that we are comfortable with," as staff turnover tends to be an issue. Technical failure at a skilled nursing facility may increase peritonitis rates, an issue that should be studied more rigorously but has been reported anecdotally by providers. The space necessity for supplies is an issue at most sites.

From the financial perspective, it may not be feasible to send trained PD staff to do exchanges, necessitating the need for stable and trained staff at the skilled nursing facility to avoid technical failure with subsequent complications. Isaac Lifschutz of Legacy Health Services, a provider of skilled nursing and assisted living services, cited nurse turnover rates as a major issue in providing consistent quality PD care at nursing facilities. According to researchers at the University of California, Los Angeles (UCLA), and Harvard Medical School (7), annual median turnover rates at nursing facilities were 94% in 2017 and in 2018, 141% among RNs.

"There's a very clear negative relationship between quality ratings and turnover," said Ashvin Gandhi, PhD, economics, University of California, Los Angeles, in an interview with *McKnight's Long-Term Care News*. Lifschutz stated that residents, even if alert, may "disrupt their PD catheter, thus contaminating the site," which requires significant oversight. Patients with kidney failure pose a particularly high readmission risk, which is a closely monitored and costly quality measure. Combined, these challenges make on-site PD a formidable challenge for both the nephrologist and nursing facility (Table 1). Indeed, Bellin et al. (9) recently characterized the skilled nursing facility ESKD patient population, suggesting increased mortality with advancing age and better survival with the provision of more frequent hemodialysis.

Nola McMullen of Renew Dialysis, a provider of home hemodialysis services in nursing home and rehab facilities, expressed the importance of maintaining best home dialysis practices for the skilled nursing facility patient while at the home. This should include "a partner helping with PD treatments while in the nursing home if willing." Otherwise, McMullen stated, "The provider (PD program) is obligated to train the nursing home staff." McMullen also said she felt that policies and procedures must be defined for the PD patient in a nursing facility environment to first contemplate whether PD remains the best modality choice and whether urgent-start patients are an option and to ensure that a "rigorous peritonitis prevention program" is in place.

The incidence of patients choosing PD as a preferred modality is continuing to grow. Moreover, the average age of patients who develop kidney failure is also increasing. Thus, the necessity to consider offering PD in the nursing facility is going to become a more pressing one. The challenges include logistics, staffing, and financial constraints that could be overcome with the development of a guideline for best practice and appropriate compensation by payers for both the home dialysis program and the nursing home provider. In essence, appropriate compensation could lead to more

Table 1. Benefits and barriers of PD in a nursing facility

Benefits	Barriers
Improved QOL for patients	Nursing facility staff turnover
Lower transportation costs	Quality-peritonitis risk
Fewer missed meals, medications, and therapies	Space requirements for PD equipment
May lower mortality and hospitalization rate (8)	Inadequate reimbursement
	Need for best practices guideline

QOL, quality of life.

consistent staff, fewer PD technical failures/complications, fewer readmissions, and lower overall cost. ■

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Barriers to Home Dialysis in Private Practice

By Monica Kaul

The use of home dialysis has increased substantially by ~93% over the 10-year period from 2007 to 2017, based on a 2019 report published by the United States Renal Data System (USRDS). Home dialysis and transplants currently account for ~39% of all treatments (~30% transplants, ~7% peritoneal dialysis [PD], and ~2% home hemodialysis [HHD]) (1–3). However, the most recent update to dialysis public policy has set a goal that by 2025, 80% of end-stage kidney disease (ESKD) be treated at home or via transplant. Unless there is a significant increase in kidneys available for transplant, HHD and PD will need to be increased massively to reach these goals.

Advancements in PD treatments have given physicians more confidence in using PD, with increased survival rates and decreased complications. Consequently, large dialysis organizations have increased the number of PD clinics, but most are operating well below maximum census due to low patient census and lack of qualified nurses. This has led to an inefficient use of the workforce where nephrologists are managing patients in sub-optimal office settings where they lack the ability to coordinate with nurses, social workers, and dieticians.

Furthermore, a declining nephrology workforce, along with an acute shortage of nurses and trained home nurses specifically, presents unique challenges to growth of at-home programs. Depending on the area in the United States, another factor that plays a key role is the availability of surgeons trained to put in PD catheters in a successful and timely manner. Finally, for a physician in a busy private practice, the decentralized process of treatment at home versus treatment at a central clinic adds to the burden of optimizing care for patients.

Whereas the public policy framework has laid out the guidelines and rationale to increase home dialysis, numerous obstacles remain. The difficulty for physicians to manage home dialysis for their patients can limit its use in nephrology.

As a community of nephrologists in private practice, we need to embrace these challenges and overcome the obstacles to see how we can better offer and promote home dialysis for our patients. The efficiency of centralized home programs would optimize the use of nursing staff to support surgical development of PD catheter placement, resulting in enhanced workflow for the nephrologist. ■

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Dr. Kaul reports no conflicts of interest.

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Are you a fellow and have a tip or idea you'd like to share with your fellow peers and the broader kidney community?

Send your idea to the *ASN Kidney News* Fellows First column at kidneynews@asn-online.org

Magnesium, the Forgotten Cation

A Skeleton Key Group FOAMed Feature

By Dominique Tomacruz, Sayna Norouzi, and Joel M. Topf

Hello! Welcome to The Skeleton Key Group (SKG) world. We love analyzing and dissecting electrolyte abnormalities. We publish an electrolyte case every month on the Renal Fellow Network. We are honored to be invited to participate in this special *Kidney News* issue as part of a series on free open-access medical education (FOAMed).

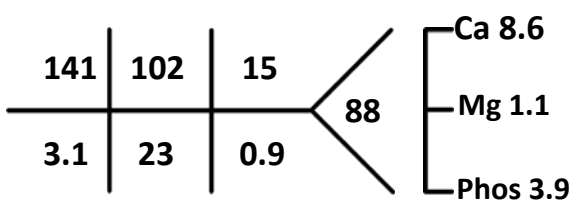
The stem

A 42-year-old woman with a history of hypertension and diabetes mellitus was evaluated for hypokalemia and hypomagnesemia. She was diagnosed with invasive squamous cell carcinoma of the cervix for which she underwent radical hysterectomy and bilateral pelvic lymph node dissection, external beam radiotherapy with brachytherapy, followed by cisplatin and 5-fluorouracil chemotherapy. She reported no nausea, vomiting, or diarrhea.

She was maintained on telmisartan 80 mg daily, amlodipine 5 mg daily, and metformin 500 mg 3 times a day.

Upon physical examination, her blood pressure (BP) was 120/70 mm Hg, heart rate 88/min, and respiratory rate 18/min with no note of difficulty breathing or desaturations. Her upper and lower limbs had a motor power of 5/5 with no sensory deficits. The rest of her physical exam was normal.

The labs



Her most recent glycosylated hemoglobin test was 6.5%. Albumin was normal. Baseline serum creatinine (Cr) during monthly pre-chemotherapy labs ranged from 0.6 to 1.0 mg/dL. This was her first episode of hypomagnesemia and hypokalemia.

Differential diagnoses of hypomagnesemia

The causes of hypomagnesemia can be divided into three distinct buckets (Figure 1).

When trying to distinguish between kidney magnesium (Mg) wasting and extrarenal causes (i.e., skin or intestine) of Mg wasting, it is helpful to assess 24 h urinary Mg excretion or fractional excretion of Mg (FEMg).

More data

Spot urine Mg and Cr along with baseline serum Mg and Cr were obtained.

Urine Mg	3.1 mg/dL
Plasma Mg	1.1 mg/dL
Urine Cr	32.4 mg/dL
Plasma Cr	0.9 mg/dL

The formula for FEMg is as follows:

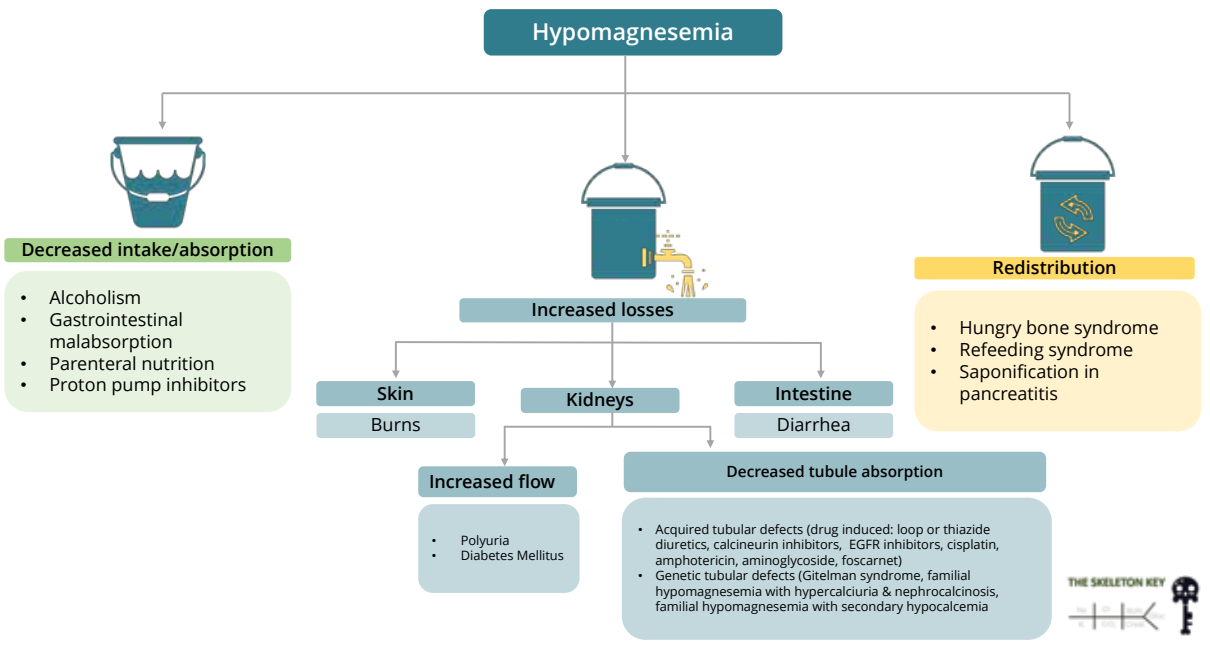
$$\frac{\text{urine Mg x plasma Cr}}{(0.7 \text{ x plasma Mg}) \text{x urine Cr}} \text{ x } 100$$

where 0.7 is used as a correction factor for the plasma Mg concentration to estimate the free, unbound Mg concentration. With the use of this formula, we calculate the FEMg of our patient:

$$\frac{3.1 \text{ x } 0.9}{(0.7 \text{ x } 1.1) \text{ x } 32.4} \; x\; 100 = 0.1118 \; x \; 100 = \; 11.2\%$$

The normal response of the kidney is to conserve Mg in the face of hypomagnesemia. Therefore, a urine Mg excretion rate of >24 mg/day in states of hypomagnesemia is considered abnormal (2). When this is not available, a FEMg >3%–4% in a patient with normal kidney function is indicative of inappropriate kidney Mg wasting (3).

Figure 1. Approach to hypomagnesemia



EGFR, epidermal growth factor receptor. Adapted from *Brenner and Rector's The Kidney* (1).

Her FEMg value of 11.2% points to kidney wasting as the cause of her hypomagnesemia.

The answer

The use of cisplatin in our patient is the most likely cause of hypomagnesemia.

Cisplatin is a cytostatic, platinum compound used in the treatment of several carcinomas, sarcomas, and lymphomas. There are multiple mechanisms by which cisplatin manifests its nephrotoxicity. It can injure the glomerulus, blood vessels, and tubules—causing acute kidney injury and/or tubulopathies manifesting as hypomagnesemia, renal tubular acidosis, isolated proximal tubulopathy, Fanconi syndrome, or rarely, sodium wasting (4).

Cisplatin is freely filtered and actively secreted in the urine via two primary transporters: organic cation transporter 2 (OCT2) and human copper transport protein 1 (Ctr1), present on the basolateral sides of the proximal convoluted tubule and both proximal and distal tubules, respectively (5). Once inside the cell, cisplatin causes DNA damage, cytoplasmic and mitochondrial dysfunction, oxidative stress, inflammation, and apoptosis.

How is Mg reabsorbed in the kidney?

Figure 2 summarizes the distribution of Mg in the body (6).

Mg reabsorption occurs paracellularly in the proximal tubule and thick ascending loop of Henle (TAL). Unlike most solutes, the majority (70%) of filtered Mg is reabsorbed in the TAL. The lumen-positive transepithelial voltage created by the activity of the Na^+-K^+-$2Cl^-$ (NKCC2) cotransporter and renal outer medullary K^+ (ROMK) channels at the apical side, and the kidney-specific Cl^- (ClC-Kb) channel and Na^+/K^+-ATPase on the basolateral side of the TAL create a favorable gradient for paracellular reabsorption through claudins 16 and 19 (5, 7).

The fine tuning of Mg handling in the kidney occurs in the distal convoluted tubule (DCT). Here, Mg is reabsorbed via the transcellular route through the cation channel, transient receptor potential melastatin member 6 (TRPM6) (8). Insulin and epidermal growth factor increase the expression of the TRPM6. Since no significant chemical gradient for Mg exists in this segment, the voltage-gated K channel (Kv1.1) is thought to provide the membrane potential needed for TRPM6 activity and Mg reabsorption in the distal collecting tubule. Its exit pathway in the basolateral side of the DCT is less clear but is thought to be via a Na^+/Mg^{2+} exchanger (Figure 3).

Back to our patient…

Increased intracellular concentrations of cisplatin in the DCT and TAL may activate a number of intracellular injury pathways and cause tubular injury manifesting as hypomagnesemia with or without acute kidney injury (9, 10).

What is the cause of the hypokalemia?

The prevalence of hypokalemia is increased sixfold among patients with cisplatin-induced hypomagnesemia (11). Potassium secretion through the ROMK predominates in the late distal tubular and cortical collecting ducts (CCDs). Intracellular Mg in the TAL, DCT, and CCD regulates the ROMK channel by blocking the channel's pore from the inside, thereby preventing K^+ secretion. In states of hypomagnesemia, this blockage is lost, and potassium is more readily secreted into the lumen causing hypokalemia.

It is also thought that injury to the proximal tubule during cisplatin use may lead to increased delivery of sodium to the distal nephron, which then increases sodium-dependent potassium secretion (11). Impairment of the Mg-dependent Na^+/K^+-ATPase may also contribute to potassium wasting (12).

Management

Management of hypomagnesemia is guided by the severity of symptoms. Most patients are asymptomatic and can tolerate oral supplementation. Electrolyte abnormalities without kidney injury is not a reason to stop cisplatin chemotherapy, especially if the goal is cure from cancer.

Our patient was given Mg oxide 800 mg three times a day as well as potassium chloride 10 mEq twice daily. Electrolytes normalized within 1 week, and supplementation was continued for the duration of cisplatin therapy.

One of the main strategies to prevent cisplatin-induced nephrotoxicity is short-duration, low-volume outpatient hydration a few hours before and after cisplatin administration. There is a lack of consensus on which protocols to use, but usually intravenous (IV) saline incorporated with potassium chloride and Mg sulfate may be used to induce forced diuresis 2–3 h before to 2–3 h after cisplatin administration. This forced diuresis is thought to reduce urinary cisplatin concentrations and proximal tubule transit time, thereby decreasing risk for kidney tubular injury. Electrolyte supplementation is given to avoid diuresis-induced hypokalemia and hypomagnesemia. It has also been suggested that Mg supplementation may reduce kidney tubular damage (13).

Take-home points

- Mg, sometimes called the forgotten ion, is the second-most abundant intracellular cation. It plays an important role in the structure of proteins and enzymatic reactions.
- Cisplatin-induced hypomagnesemia occurs via direct tubular injury in the distal collecting tubule causing impaired Mg absorption and hypokalemia.

Thank you for reading this case. SKG is a team of 57 nephrology enthusiasts who work closely together and publish monthly educational cases. Special shout-out to our fellow editors: Chi Chu and Alex Meraz; our faculty advisors: Kartik Kalra, Sudha Mannemuddu, Michelle Lim, Dhwanil Patel, and Nasim Wiegley; our social media/podcast leaders: Sai Achi, Raad Chowdhury, and Narjes Alamri; and all our team members.

If you liked this case, go to Renal Fellow Network to read more: https://www.renalfellow.org/category/the-skeleton-key-group/ or The Skeleton Key Group webpage: https://www.skeletonkey.group/. ■

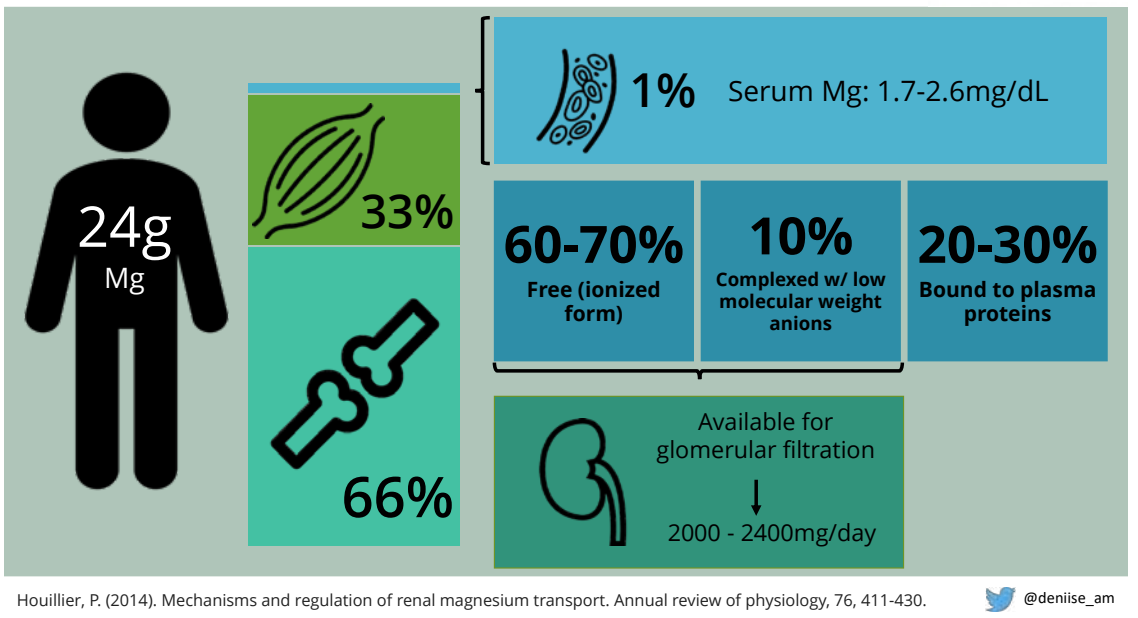
Dominique Tomacruz, MD, is SKG Executive Editor and a Clinical Fellow at Philippine General Hospital, Manila. Sayna Norouzi, MD, is SKG Editor-in-Chief and Assistant Professor of Medicine, Department of Nephrology, Loma Linda University Medical Center, Loma Linda, CA. Joel M. Topf, MD, FACP, is an SKG Faculty Mentor and Assistant Clinical Professor of Medicine, Oakland University William Beaumont School of Medicine, Rochester, MI.

Dr. Tomacruz reports no conflicts of interest. Dr. Norouzi, MD, is Editor-in-Chief of the Skeleton Key Group and Co-Director of the GlomCon virtual fellowship program.

Dr. Topf has an ownership stake in a few DaVita-run dialysis clinics, and his practice, St Clair Nephrology, runs a vascular access center. In the past, he has participated in advisory boards for Cara Therapeutics, AstraZeneca, Bayer, and Tricida. He is the founder and president of NephJC, a 503c organization that supports social media in medical education. NephJC has a history of soliciting

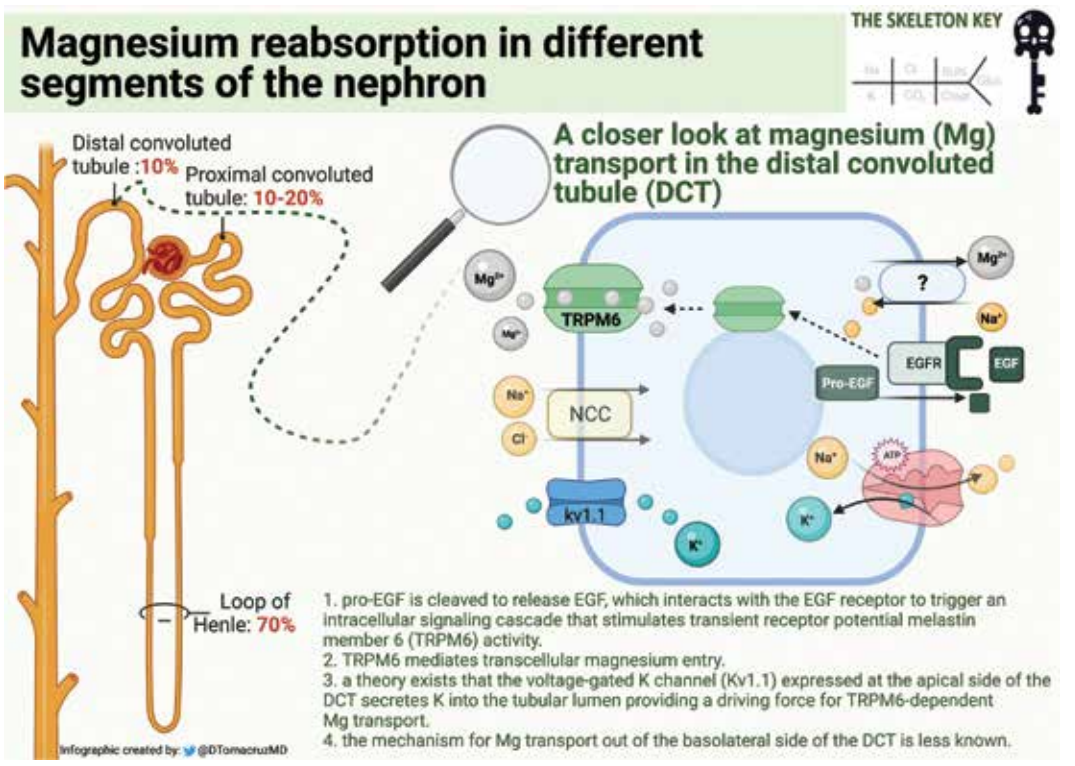
Continued on page 22 ›

Figure 2.

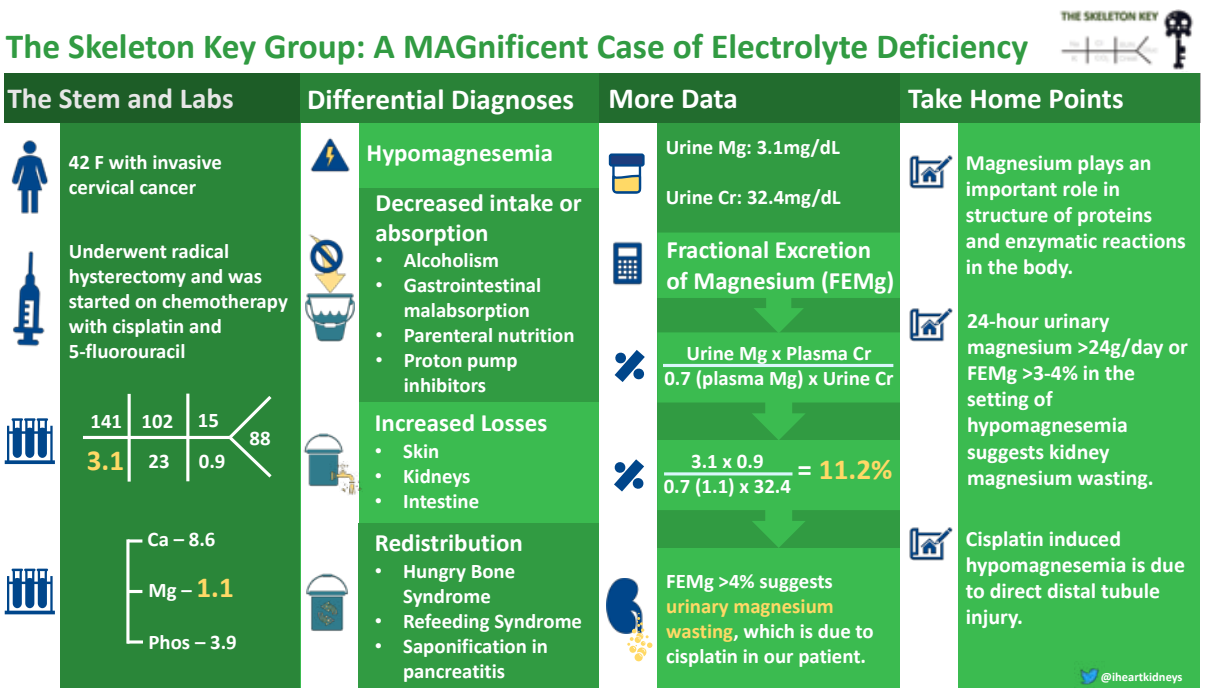


Infographic by Denisse Arellano, MD, Skeleton Key Group member.

Figure 3. Mg reabsorption in different segments of the nephron and a closer look at Mg handling in the DCT



NCC, NaCl cotransporter. Adapted from Zeidel et al. (7).



F, female. Visual abstract by Dhwanil Patel, MD, SKG Faculty Member and Nephrologist, Overlook Medical Center, Summit, NJ.

Magnesium, the Forgotten Cation

Continued from page 21

money from industry and academic supporters, but has not done so since November of 2019.

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A Fellow's Reflections

By Reena Gurung

Late nights and early mornings
Days infused with caffeine and steep learning
Hi, it's renal, what is the reason for calling?
Lytes awry, hematuria, proteinuria, and allograft rejecting
Uremia, hypervolemia, anuria, will you be dialyzing?

Crescents, mesangial, endocapillary cells insane,
Beauties are spikes and pinholes, on the silver stain
ALMS, Euro-Lupus, BLISS-LN, now voclosporin,
Seriously, what else is in the making?

Case conference, journal club, grand round, CPC broadcasting
you name it, we did it, with the virtual platforming
Unlearn and re-learn, then teach and learn,
the entire journey, certainly quite humbling

Through late nights and early mornings
Procedures galore and urine spinning
Through cases common, others rare,
and everything in-between,
past couple of years, nothing short of amazing!

Dr. Gurung earned her MBBS degree from the Kathmandu University School of Medical Sciences in Nepal and completed her Internal Medicine residency at St. Luke's Hospital in St. Louis, MO. She completed her Nephrology Fellowship at Washington University in St. Louis and will join the faculty in the Division of Nephrology in September 2021. Dr. Gurung has a keen interest in glomerular diseases and was a fellow in the inaugural class of the virtual Glomerular Diseases Fellowship at GlomCon (https://edu.glomcon.org/2021-2022-fellowship/2020-2021-fellowship). She wrote this poem to celebrate her and her colleagues' nephrology fellowship graduation.

Index to Advertisers

SARS-CoV-2 Vaccine Acceptability among Patients Treated by Hemodialysis

By Jeffrey Silberzweig

In a *JASN* study, Garcia and colleagues (1) report a survey of patients treated by hemodialysis at 150 facilities in the United States (Figure 1). The 1515 respondents represented 14% of eligible patients. Vaccine hesitancy was reported by 20% with a distribution similar to that of the general population: it was more common among women, people of Black race, Native Americans and Pacific Islanders, as well as younger patients. The most frequently stated reason for vaccine hesitancy was concern about side effects. The most trusted source of information about vaccines was dialysis facility staff, and patients said they were more likely to accept vaccines if they were available in their dialysis facilities.

The study suggests the enormous benefits to be realized from the allocation of vaccines to dialysis facilities (2) on March 25, 2021. According to chief medical officers of US dialysis providers, before the Centers for Disease Control and Prevention approved the network administrator model, and vaccines were rolled out, 25% of patients were vaccinated against SARS-CoV-2; now approximately 70% have been vaccinated. The increase in the proportion of underserved patients vaccinated after the allocation is even more dramatic. Herd immunity may be on the horizon for patients treated by maintenance hemodialysis. ■

Jeffrey Silberzweig, MD, is Chief Medical Officer, The Rogosin Institute, and Associate Professor of Clinical Medicine, Weill Cornell Medicine, New York, NY, and Co-Chair of the American Society of Nephrology COVID-19 Response Team, Emergency Partnership Initiative.

Dr. Silberzweig receives consulting fees from Kaneka Pharma, Bayer, and Alkahest, which are not related to the material presented here.

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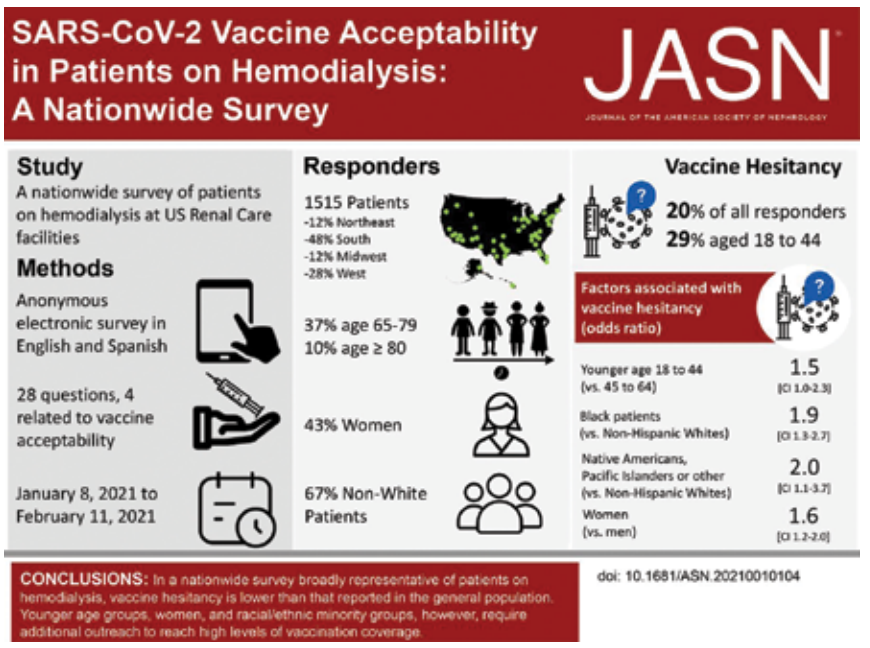
Figure 1. SARS-CoV-2 vaccine acceptability in patients on hemodialysis



Industry Spotlight

Roxadustat Use for CKD-Related Anemia Rejected by FDA Advisory Panel

By Daniel W. Coyne

FibroGen's roxadustat was dreaming of being the first-in-class hypoxia-inducible factor-prolyl hydroxylase inhibitor (HIF-PHI) for treatment of chronic kidney disease (CKD)-related anemia. FibroGen submitted its new drug application to the US Food and Drug Administration (FDA) in December 2019 and suggested roxadustat safety was comparable to placebo and comparable or superior to erythropoiesis-stimulating agents (ESAs) in its global trials.

The dream became a nightmare at the July 15, 2021, FDA Advisory Committee meeting, where a panel of 14 experts overwhelmingly advised against approval of roxadustat for use in anemic non-dialysis or dialysis patients. The FDA is not required to follow the panel's advice.

An April 6, 2021, FibroGen press release presaged trouble at the FDA. The company disclosed that the roxadustat safety data touted since 2019 were wrong, and roxadustat was not superior in any population. Additionally, primary hazard ratios and 95% confidence intervals for major adverse cardiovascular events were moved perilously higher.

Data at the FDA Advisory Committee meeting showed that roxadustat was clearly efficacious for treating anemia, but roxadustat had numerous safety signals including increased thromboses, seizures, major infections, and even higher mortality. Perhaps recognizing that the safety issues were a major problem, FibroGen preemptively proposed that the roxadustat label should recommend a lower hemoglobin target of 10–11 g/dL and a lower roxadustat starting dose than employed in any of the phase 3 trials. The expert panel rejected that those changes would ensure greater safety and opposed approving roxadustat, with votes of 1–13 for non-dialysis CKD and 2–12 for dialysis-dependent CKD.

The next HIF-PHI up for consideration for FDA approval is Otsuka and Akebia's vadadustat, which had significantly higher major adverse cardiovascular events compared to ESAs in the non-dialysis CKD population. ■

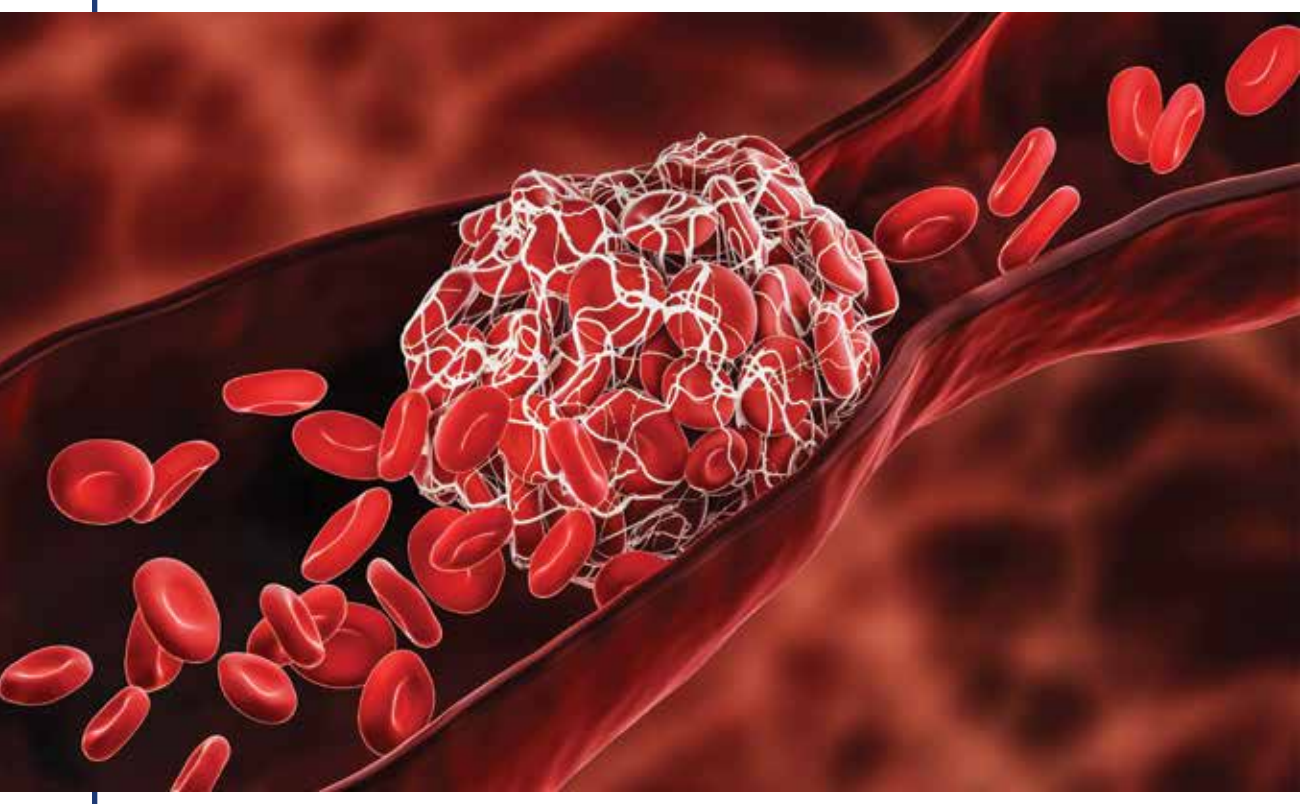
Daniel W. Coyne, MD, is a Professor of Medicine with the Division of Nephrology, Washington University in St. Louis, MO.

Dr. Coyne has been a site investigator for both roxadustat and daprodustat and has been co-author on publications and abstracts for roxadustat. He has been a consultant to the manufacturers of all three HIF-PHIs.

Thrombotic Thrombocytopenic Purpura

International Society on Thrombosis and Haemostasis Guidelines for Diagnosis and Treatment

By Anitha Vijayan



Thrombotic microangiopathy (TMA) is an all-encompassing term that is used to describe an occlusive microvascular disease, manifested by microangiopathic hemolytic anemia (MAHA) and thrombocytopenia (Figure 1). Thrombotic thrombocytopenic purpura (TTP) is a rare TMA that typically presents in adulthood and has a worldwide incidence of 1.5–6 cases per million per year. In the United States, the incidence is 2.99 cases per million per year (1). Although TTP is uncommon, it is a devastating disease with high mortality if left untreated and should be considered a clinical emergency. The classical pentad of clinical manifestations (fever, thrombocytopenia, MAHA, acute kidney injury [AKI], and neurological manifestations) is not present in a majority of the patients, and presence of thrombocytopenia and MAHA alone should be sufficient to consider a diagnosis of TTP. Early diagnosis and treatment are crucial, as untreated TTP has a mortality of >90%. It is important that nephrologists be aware of the manifestations and management of the disease, as kidney complications are common and may lead to chronic kidney disease (2).

The International Society on Thrombosis and Haemostasis (ISTH) has published new clinical practice guidelines for the diagnosis and treatment of TTP. Developed in partnership with McMaster University, the ISTH TTP guidelines are the product of a rigorous, systematic review of evidence by a guideline panel comprised of clinical experts, methodologists, and patient representatives (3, 4). The guidelines can be reviewed in detail on the ISTH website (https://www.isth.org/page/TTPGuidelines).

TTP is caused by severe inherited deficiency of a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13 (ADAMTS13; hereditary or congenital TTP) or due to the presence of antibodies against ADAMTS13 (immune-mediated TTP). ADAMTS13 is responsible for cleaving von Willebrand factor (VWF) multimers, thereby regulating unchecked platelet adhesion and thrombosis in the microvasculature. ADAMTS13 activity of <10% denotes severe disease and confirms the diagnosis of TTP. The PLASMIC clinical score was developed and validated to predict which patients might have an ADAMTS13 activity less than 10% and is now recommended to help with pretest probability and support the diagnosis of TTP (5, 6). The score includes platelet count, hemolysis, presence or absence of malignancy, solid organ or bone marrow transplant, mean corpuscular volume (MCV), international normalized ratio (INR), and serum creatinine (Figure 2). ISTH recommends testing for ADAMTS13 activity for all cases of suspected TTP, but its suggestions for further management are stratified on whether the test is readily available (within 72 h) or available after delay (3–7 days) or whether it is not available at all (3).

The management of TTP involves use of corticosteroids, therapeutic plasma exchange (TPE), rituximab, and/or caplacizumab. Table 1 gives an overview of the ISTH treatment recommendations. Caplacizumab (Cablivi) is an anti-VWF monoclonal antibody, and the US Food and Drug Administration (FDA) approved its use in the United States in February 2019 for treatment of adult patients with acquired TTP. It was approved for use in the European Union (EU) in 2018. In a double-blind randomized controlled trial (RCT), 145 patients were randomized to receive either caplacizumab or placebo, along with TPE. The percentage of patients with a composite outcome of TTP-related death, recurrence of TTP, or thromboembolic event was 74% lower in the treatment group compared to placebo (12% vs. 49%) (7).

It should be noted that a Patient Advisory Panel provided guidance to the committee on its recommendations. Conflicts of interest (COIs) among the committee members for 12 months prior to the initiation date were gathered, and individuals with major COIs were required to abstain from formulating and voting on specific recommendations. The COIs of committee members are noted on the last page of each paper. A majority of recommendations are based on very low certainty evidence, as this is a rare disease with few RCTs. Caplacizumab is extremely expensive ($270,000 per TTP episode) and may not be widely available (8). In cost-effectiveness models, caplacizumab was deemed not cost effective when compared to standard of care (corticosteroids and TPE with or without rituximab) (8). Therefore, recommendations for its use are not generalizable among US medical centers and even less so across the world. The American Society of Nephrology is not providing an endorsement of these guidelines but merely sharing the recommendations for informational and educational purposes. A high index of suspicion, timely and accurate diagnosis, and early treatment with TPE or plasma exchange are crucial in reducing morbidity and mortality from this life-threatening disease. ■

Anitha Vijayan, MD, is Professor of Medicine, Division of Nephrology, Washington University in St. Louis, MO.

Dr. Vijayan reports no disclosures related to the article.

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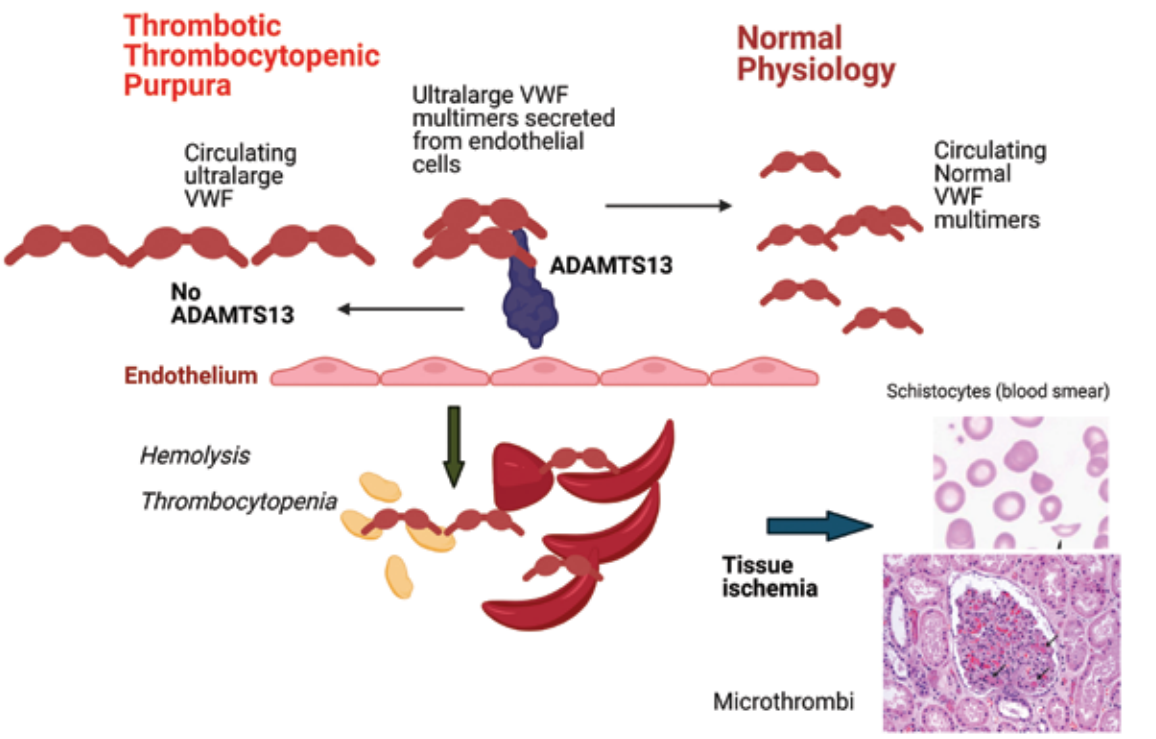
Table 1. ISTH Guidelines for Treatment of TTP

Recommendation 1	iTTP first event	Addition of corticosteroids to TPE alone (strong recommendation in context of low certainty evidence)
Recommendation 2	iTTP first event	Addition of rituximab to corticosteroids and TPE over corticosteroids and TPE alone (conditional recommendation in context of low certainty evidence)
Recommendation 3	iTTP relapse	Addition of corticosteroids to TPE alone (strong recommendation in context of low certainty evidence)
Recommendation 4	iTTP relapse	Addition of rituximab to corticosteroids and TPE over corticosteroids and TPE alone (conditional recommendation in context of low certainty evidence)
Recommendation 5	iTTP – first event or relapse	Panel suggests using caplacizumab over not using caplacizumab (a conditional recommendation in context of moderate certainty evidence).
Recommendation 6	iTTP in remission	For those with low plasma ADAMTS13 activity, panel suggests using rituximab over not using rituximab (a conditional recommendation in the context of low certainty evidence).
Recommendation 7	cTTP in remission	For patients with cTTP who are in remission, the panel suggests either plasma infusion or a watch-and-wait strategy (a conditional recommendation in the context of very low certainty evidence).
Recommendation 8	cTTP in remission	For patients with cTTP who are in remission, the panel suggests against the use of factor VIII (FVIII) concentrate vs. a watch-and-wait strategy (a conditional recommendation in the context of very low certainty evidence).
Recommendation 9	iTTP in pregnancy	For patients with iTTP who are pregnant and have decreased plasma ADAMTS13 activity but with no clinical signs/symptoms, the panel recommends prophylactic treatment over no prophylactic treatment (a strong recommendation in the context of very low certainty evidence).
Recommendation 10A	cTTP in pregnancy	For patients with cTTP who are pregnant, the panel recommends prophylactic treatment over no prophylactic treatment (a strong recommendation in the context of very low certainty evidence).
Recommendation 10B	cTTP in pregnancy	For patients with cTTP who are pregnant, the panel suggests prophylactic treatment with plasma infusion over FVIII products (a conditional recommendation in the context of very low certainty evidence).

TTP, thrombotic thrombocytopenic purpura; iTTP, immune-mediated TTP; cTTP, congenital TTP.

See Zheng et al. (4).

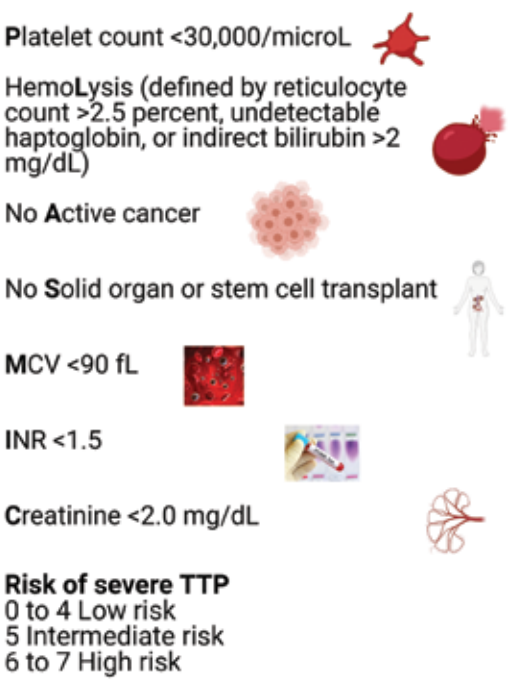
Figure 1. Overview of pathophysiology of thrombotic thrombocytopenic purpura



Thrombotic thrombocytopenic purpura (TTP) is a thrombotic microangiopathy caused by reduced activity (either congenital absence or acquired antibody) of ADAMTS13, which leads to aggregation of platelet-rich micro-thrombi in small vessels. This results in tissue ischemia, primarily manifested in the kidneys and central nervous system.

Figures 1 and 2 created by Kenar Jhaveri, MD, using BioRender®.

Figure 2. PLASMIC score for diagnostic support of thrombotic thrombocytopenic purpura



PLASMIC score, based on platelet count, hemolysis, MCV, INR, serum creatinine, presence or absence of malignancy, and solid organ or stem cell transplant, is a tool to aid in the diagnosis of thrombotic thrombocytopenic purpura (TTP). A high PLASMIC score (6–7) denotes a 96% risk of severe reduction (<10%) of ADAMTS13 activity and high probability for TTP.

Findings

Cycling Exercise During Hemodialysis Reduces Left Ventricular Mass

For hemodialysis (HD) patients, a 6-month progressive exercise intervention leads to significant reductions in left ventricular (LV) mass, according to results from a clinical trial in *Kidney International*.

The CYCLE-HD study included 130 patients receiving HD at three UK centers. In open-label, cluster-randomized fashion, patients were assigned to a structured intradialytic cycling (IDC) intervention or usual care. With the use of specially adapted cycle ergometers, patients in the intervention group performed supervised cycling three times weekly during dialysis sessions, targeting 30 minutes of continuous cycling at a rating of perceived exertion of 12 to 14. Ergometer resistance was adjusted as necessary for exercise progression.

The study was powered to detect a 15-g between-group difference in LV mass, measured with cardiac magnetic resonance (CMR). Myocardial fibrosis, aortic stiffness, physical functioning, quality of life, and ventricular arrhythmias were evaluated as secondary outcomes. One hundred one patients completed the study; the most common reasons for nonadherence were declining participation, feeling unwell, and pain. Intervention patients completed 71.7% of scheduled IDC sessions.

IDC was associated with an 11.1-g reduction in LV mass; the difference remained significant on sensitivity analysis. The data suggested improvement in LV ejection fraction in the IDC group, although the between-group difference was not significant. There was "overwhelming evidence" of reduction in CMR-measured aortic pulse-wave velocity and native T1 times but no change in interdialytic or predialysis blood pressures.

Physical functioning and quality of life were not significantly different between groups. No serious adverse events were attributed to the IDC intervention.

Cardiovascular disease accounts for 42% of deaths in maintenance HD patients. Exercise reduces many important cardiovascular risk factors in patients with end-stage kidney disease.

The CYCLE-HD results suggest that a 6-month program of cycling exercise during dialysis sessions can reduce LV mass in HD patients. The study intervention is "safe, deliverable and well tolerated." The researchers conclude, "IDC improves the cardiovascular health of patients on maintenance hemodialysis" [Graham-Brown MPM, et al. A randomized controlled trial to investigate the effects of intra-dialytic cycling on left ventricular mass. *Kidney Int* 2021; 99:1478–1486. doi: 10.1016/j.kint.2021.02.027]. ■

Mortality from Early Dialysis Withdrawal: Trends and Risk Factors

Early dialysis withdrawal consistently accounts for about one-third of early deaths in the year after dialysis initiation, concludes an Australian study in *Nephrology Dialysis Transplantation*.

The researchers analyzed data on 32,274 patients initiating dialysis in Australia between 2005 and 2018, drawn from the Australian and New Zealand Dialysis and Transplant Registry. Early deaths (within 12 months) from dialysis withdrawal attributed to psychosocial or medical reasons were analyzed, including trends over time and associated risk factors.

Overall, 11% of patients died within 12 months after dialysis initiation. Twenty-two percent of these early deaths were ascribed to early withdrawal due to medical reasons and 14% due to psychosocial reasons. The proportion of deaths from early withdrawal remained unchanged during the study period, with a range from 33% to 38% per year. However, incidence rates of early withdrawal-related mortality decreased from 5.3 per 100 person-years in 2006 to 3.1 per 100 in 2018.

In both categories of early withdrawal, risk factors for early mortality included older age, central venous catheter access, late referral, and cerebrovascular disease. Underweight and high socioeconomic status were risk factors for early psychosocial withdrawal, whereas peripheral vascular disease, chronic lung disease, and cancer were risk factors for early medical withdrawal. Center-level factors were not associated with death related to early withdrawal.

Dialysis withdrawal is a major contributor to the high risk of death in the first year after dialysis initiation. International registry data have suggested upward trends in the proportion of deaths in incident dialysis patients attributed to early withdrawal.

These Australian data show no significant change in the percentage of early deaths from dialysis withdrawal over the past two decades. Early deaths from medical withdrawals exceed those from psychosocial withdrawals.

Similar risk factors apply to both types of early withdrawal-associated mortality. The researchers conclude: "Recognising the patient at-risk of early mortality attributed to dialysis withdrawal may better inform the shared decision-making process, empower patient-focused treatment choices, and facilitate advanced care planning" [Chen JHC, et al. Temporal changes and risk factors of death from early withdrawal within 12 months of dialysis initiation—A cohort study. *Nephrol Dial Transpl*, published online ahead of print June 27, 2021. doi: 10.1093/ndt/gfab207; https://academic.oup.com/ndt/advance-article/doi/10.1093/ndt/gfab207/6310179]. ■

ESRD QIP Penalties Don't Lead to Improvements in Dialysis Center Care

Dialysis centers hit with financial penalties under the Centers for Medicare & Medicaid Services' (CMS) mandatory End-Stage Renal Disease Quality Incentive Program (ESRD QIP) do not show subsequent improvement in quality of care, concludes a study in *Annals of Internal Medicine*.

The study used publicly available Medicare data on 5830 dialysis centers from 2015 to 2018. In 2017, financial penalties (based on 2015 performance) were levied on 1109 centers, representing 19.0% of the total. Regression discontinuity models were used to evaluate the association between penalization and subsequent changes in dialysis center quality, based on data from 2017 and 2018. In addition to the 0 to 100 composite metric, individual factors contributing to the total performance score were analyzed.

Penalized centers were located in ZIP Codes with a higher average percentage of non-White race residents, 36.4% versus 31.2%, and with a lower median income, $49,290 versus $51,686. Chain-affiliated centers accounted for 84.0% of penalized centers versus 93.6% of non-penalized centers. More than one-half (52.2%) of penalized centers were in the South US Census region.

For penalized centers, total performance scores did not improve in subsequent years, with changes of just 0.4 point in 2017 and 0.3 point in 2018. The findings were unchanged by adjustment for dialysis center characteristics or on analysis of centers penalized for the first time in 2017. There were also no improvements in specific components of the total performance score.

The ESRD QIP was designed to address the wide variation in quality of care provided at US outpatient dialysis centers. However, the program has not undergone independent evaluation, and its effects on quality of dialysis care remain unknown.

The study shows little or no improvement in quality of care at dialysis centers receiving financial penalties under the ESRD QIP. The findings are consistent for centers with differing characteristics and across individual quality metrics. The investigators conclude: "These data suggest that CMS may consider changes to the program design as [it continues] to experiment with ways to improve the care of patients with ESRD" [Sheetz KH, et al. Changes in dialysis center quality associated with the End-Stage Renal Disease Quality Incentive Program: An observational study with a regression discontinuity design. *Ann Intern Med*, published online ahead of print June 1, 2021. doi: 10.7326/M20-6662; https://www.acpjournals.org/doi/10.7326/M20-6662]. ■

Plasma KIM-1 Has Prognostic Value in Kidney Disease

Levels of plasma kidney injury molecule-1 (KIM-1) are associated with diagnoses, pathologic findings, and kidney failure risk in patients with a wide range of kidney disease diagnoses, according to a report in the *American Journal of Kidney Diseases*.

The analysis included participants in two prospective, observational cohort studies: 524 patients undergoing clinically indicated native kidney biopsy enrolled in the Boston Kidney Biopsy Cohort (BKBC) and 3800 patients with common types of chronic kidney disease (CKD) from the Chronic Renal Insufficiency Cohort (CRIC) study. Baseline plasma KIM-1 levels were analyzed for association with subsequent kidney failure (defined as initiation of dialysis) and death.

In multivariable analyses of BKBC participants, higher plasma KIM-1 levels were associated with more severe acute tubular injury, tubulointerstitial inflammation, and more severe mesangial expansion. By diagnosis, plasma KIM-1 levels were higher in patients with diabetic nephropathy, glomerulopathies, and tubulointerstitial disease.

In BKBC, during a median follow-up of 5 years, 124

patients progressed to kidney failure, and 85 died. For each doubling of baseline plasma KIM-1, hazard ratio (HR) for kidney failure was 1.19. Plasma KIM-1 was not significantly associated with mortality after multivariate adjustment.

In the CRIC study, higher plasma KIM-1 was associated with non-White race, higher prevalence of diabetes and cardiovascular disease, higher systolic blood pressure, and lower hemoglobin. Plasma KIM-1 was negatively correlated with estimated glomerular filtration rate and positively correlated with urinary albumin-to-creatinine ratio.

At a median follow-up of 11.5 years in CRIC, 1153 patients had progressed to kidney failure, whereas 1356 died. For each doubling of plasma KIM-1, HR for kidney failure was 1.10. In the highest quintile of plasma KIM-1, HR for progression was 1.58. Again, there was no significant association with mortality.

Plasma KIM-1 is a sensitive marker of tubular injury, which may contribute to development or progression of CKD. The new analysis finds that higher plasma KIM-1 is associated with tubulointerstitial and mesangial lesions and is an independent risk factor for progression to kidney failure. The investigators conclude: "Collectively, the findings suggest that plasma KIM-1 may serve as a non-invasive tool to assess histopathologic lesions and has prognostic value across a variety of kidney diseases" [Schmidt IM, et al. Plasma kidney injury molecule 1 in CKD: Findings from the Boston Kidney Biopsy Cohort and CRIC studies. A*m J Kidney Dis*, published online ahead of print June 24, 2021. doi: 10.1053/j.ajkd.2021.05.013; https://www.ajkd.org/article/S0272-6386(21)00694-6/fulltext]. ■

Do Some Diabetes Drugs Reduce the Risk of Severe or Fatal COVID-19?

For patients with COVID-19, two newer classes of antihyperglycemic medications are associated with lower rates of death and other adverse outcomes, according to a study in *Diabetes Care*.

The observational study included 12,466 adult patients with polymerase chain reaction-diagnosed SARS-CoV-2 infection, drawn from the US National COVID Cohort Collective. Included patients had an ambulatory prescription for at least one of three antihyperglycemic medication classes over 24 months before diagnosis: glucagon-like peptide-1 receptor agonist (GLP1-RA), sodium-glucose cotransporter-2 inhibitor (SGLT2i), or dipeptidyl peptidase 4 inhibitor (DPP4i). The patients' mean age was 58.6 years, 53.4% were women, and 62.5% were White race.

Sixty-day mortality and other severe outcomes were compared for patients with premorbid GLP1-RA or SGLT2i use versus DPP4i use. Associations were analyzed with targeted maximum likelihood estimation (TMLE) using a super learner approach, accounting for baseline characteristics.

Patients taking DPP4i drugs were older and had a lower body mass index (BMI) compared to GLP1-RA or SGLT2i users. Patients in the DPP4i group were also more likely to have chronic or end-stage kidney disease, myocardial infarction, congestive heart failure, cancer, dementia, or stroke.

Crude 60-day mortality was 2.06% for patients with premorbid GLP1-RA use and 2.32% for those with SGLT2i use, compared to 5.67% for DPP4i users. Total mortality over the observation period was 2.29%, 2.48%, and 6.18%, respectively. In propensity score-weighted analyses, 60-day mortality was 2.31% in GLP1-RA users versus 4.86% in DPP4i users and 2.70% in SGLT2i users versus 4.74% in DPP4i users. Differences in total mortality also remained significant.

On TMLE analysis, odds ratio (OR) for 60-day mortality was 0.54 for GLP1-RA users versus DPP4i users. Secondary outcome ORs were 0.56 for total mortality, 0.81 for emergency department (ED) visits, 0.73 for hospitalization, and 0.73 for mechanical ventilation. For GLP1-RA versus DPP4i use, ORs were 0.66 for 60-day mortality, 0.63 for total mortality, 0.90 for ED visits, and 0.82 for hospitalization.

Patients with diabetes are at increased risk of death and other adverse outcomes of COVID-19. The newer antihyperglycemic medications GLP1-RA and SGLT2i have been shown to reduce cardiorenal events in high-risk groups. The new study explored the possible impact of these drug classes on COVID-19 outcomes.

The results show lower odds of mortality and other adverse events among COVID-19 patients with premorbid GLP1-RA and SGLT2i use, compared to those prescribed DPP4i medications. The authors note some important limitations of their study, including the older age and higher comorbidity of the DPP4i group. Anti-inflammatory effects of GLP1-RA and SGLT2i drugs might account for the associated improvement in COVID-19 outcomes [Kahkoska AR, et al. Association between glucagon-like peptide 1 receptor agonist and sodium-glucose cotransporter 2 inhibitor use and COVID-19 outcomes. *Diabetes Care* 2021; 44:1564–1572. doi: 10.2337/dc21-0065]. ■

Moral Distress in Nephrology Fellowship Programs

Nephrology fellows experience high rates of moral distress during their fellowship training, according to a survey study in *American Journal of Nephrology*.

An online survey link was sent to the directors of 148 US nephrology fellowship programs, with a request to forward the survey to fellowship trainees. Adapted from a previous questionnaire, the survey focused on workplace scenarios relevant to nephrology training and practice in five domains: dialysis decision-making, futility of care, interdisciplinary communication, perceived powerlessness, and the institutional ethical environment.

Directors reported forwarding the survey to 386 nephrology fellows, of whom 142 responded: a rate of 37%. Ratings of 3 or higher, on a 0-to-4 scale, were considered to denote frequent or moderate to severe moral distress.

Respondents indicated moral distress in a wide range of scenarios involving all five selected domains. Scenarios most frequently rated as causing moderate to severe moral distress involved continuing dialysis in a hopelessly ill patient, 81% of respondents; initiating dialysis in situations perceived as futile, 77%; carrying a high patient census, 75%; and observing other practitioners give unduly optimistic descriptions of the benefits of dialysis, 64%.

Scenarios related to overly optimistic descriptions and futile kidney replacement therapy were cited as occurring often to frequently by more than one-half of respondents, as was following a family's wishes to continue dialysis in an incapacitated patient where the physician believes continued treatment is not in the patient's best interest.

Three-fourths of respondents perceived their fellowship program as stressful. Twenty-seven percent had considered quitting at some point during their fellowship training, including nine percent at the time they completed the survey.

Moral distress is a pervasive problem in healthcare settings. Nephrology fellows may experience uncertainty and constraint-related moral distress in many situations, including decisions about initiating, continuing, or withdrawing or withholding dialysis.

The new survey finds that nephrology fellows commonly experience situations involving moderate to high levels of moral distress. The authors discuss organizational and curricular changes and self-care opportunities to help address and reduce moral distress in fellowship programs [Saeed F, et al. Frequency of severity of moral distress in nephrology fellows: A national survey. *Am J Nephrol*, published online ahead of print June 21, 2021. doi: 10.1159/000516575; https://www.karger.com/Article/Abstract/516575]. ■

Final SPRINT Data Confirm Benefits of Intensive BP Lowering

Final results from the Systolic Blood Pressure Intervention Trial (SPRINT) support an intensive strategy targeting a systolic blood pressure (BP) of less than 120 mm Hg, reports *The New England Journal of Medicine*.

The analysis included patients, aged 50 years or older, with baseline systolic BP of 130 to 8 mm Hg and increased risk for cardiovascular disease, but without diabetes or a history of stroke. Patients were randomly assigned to intensive or standard treatment, with systolic BP targets of less than 120 or 140 mm Hg, respectively. The study was halted early in 2015—at a median follow-up of 3.33 years—due to overwhelming evidence of benefit in the intensive-treatment group. The current report presents final outcomes at a median 3.88 years' follow-up, including data from study close-out visits.

In the initial 2015 report, rates of a primary composite outcome of myocardial infarction, other acute coronary syndromes, stroke, heart failure, or cardiovascular death were 1.77% per year with the intensive-treatment strategy versus 2.40% per year with standard treatment: hazard ratio (HR) 0.73. All-cause mortality was 1.06% versus 1.41% per year: HR 0.75. Intensive treatment was associated with higher rates of some serious adverse events, including hypotension, electrolyte abnormalities, acute kidney injury or kidney failure, and syncope.

On analysis of the combined intervention and postintervention results, rates of both the primary outcome and all-cause mortality were lower with intensive treatment: HR 0.76 and 0.79, respectively. The lower systolic BP target remained associated with lower rates of myocardial infarction and cardiovascular death, although rates of heart failure events no longer differed significantly between groups.

Hypotension, electrolyte abnormalities, and acute kidney injury or kidney failure remained more common in the intensive-treatment group. Most kidney adverse events were solitary, mild, and followed by recovery of kidney function.

The final SPRINT results confirm significant reductions in major adverse cardiovascular events and all-cause mortality with intensive BP-lowering treatment targeting a systolic BP of less than 120 mm Hg. Some adverse events continue to be more frequent in the intensive-therapy group [SPRINT Research Group, et al. Final report of intensive versus standard blood-pressure control. *N Engl J Med* 2021; 384:1921–1930. doi: 10.1056/NEJMoa1901281]. ■

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