Blood Pressure Changes in Young Adulthood Associated with Subsequent Decline in Kidney Function

Studies of hypertension and related complications are conducted most often in populations >40 years of age; studies of outcomes associated with elevated blood pressure in young adulthood have been focused on associations between elevated blood pressure and cardiovascular risks. There are few available data on whether there is an association between exposure to elevated blood pressure early in life and adverse renal outcomes.

Elaine Ku, MD, MAS, and colleagues recently conducted an observational cohort study designed to assess the association between changes in blood pressure between ages 18 and 40 years and subsequent decline in kidney function in later life. The researchers sought to test the hypothesis that there would be an association between higher blood pressure during young adulthood and faster kidney decline. They also hypothesized that the association between changes in blood pressure during young adulthood, even at blood pressures currently not considered to meet the definition for hypertension, and future reduction in kidney function would remain strong. Results were reported in the *American Journal of Kidney Diseases* [2018;72(2):243-250]

The researchers utilized data from the CARDIA (Coronary Artery Risk Development in Young Adulthood) study, a prospective cohort study designed to continue on page

15-Year Decrease in Lower Extremity Amputation Rates of Patients Receiving Dialysis

Approximately 8.5 million individuals in the United States are affected by peripheral artery disease (PAD). The annual incidence of PAD is 2.8% and the prevalence rate is 12.3%. In patients with the most severe forms of PAD, amputation of the lower extremities may be required. Patients with PAD and end-stage renal disease (ESRD) receiving dialysis are at high risk of amputation, due, in part, to the high prevalence of traditional risk factors such as diabetes and...
Indication

Parsabiv™ (etelcalcetide) is indicated for the treatment of secondary hyperparathyroidism (HPT) in adult patients with chronic kidney disease (CKD) on hemodialysis.

Limitations of Use:

Parsabiv™ has not been studied in adult patients with parathyroid carcinoma, primary hyperparathyroidism, or with CKD who are not on hemodialysis and is not recommended for use in these populations.

Important Safety Information

Contraindication: Parsabiv™ is contraindicated in patients with known hypersensitivity to etelcalcetide or any of its excipients. Hypersensitivity reactions, including pruritic rash, urticaria, and face edema, have occurred.

Hypocalcemia: Parsabiv™ lowers serum calcium and can lead to hypocalcemia, sometimes severe. Significant lowering of serum calcium can cause QT interval prolongation and ventricular arrhythmia. Patients with conditions that predispose to QT interval prolongation and ventricular arrhythmia may be at increased risk for QT interval prolongation and ventricular arrhythmias if they develop hypocalcemia due to Parsabiv™. Closely monitor corrected serum calcium and QT interval in patients at risk on Parsabiv™. Significant reductions in corrected serum calcium may lower the threshold for seizures. Patients with a history of seizure disorder may be at increased risk for seizures if they develop hypocalcemia due to Parsabiv™. Monitor corrected serum calcium in patients with seizure disorders on Parsabiv™. Concurrent administration of Parsabiv™ with another oral calcimimetic could result in severe, life-threatening hypocalcemia. Patients switching from cinacalcet to Parsabiv™ should discontinue cinacalcet for at least 7 days prior to initiating Parsabiv™. Closely monitor corrected serum calcium in patients receiving Parsabiv™ and concomitant therapies known to lower serum calcium.

Measure corrected serum calcium prior to initiation of Parsabiv™. Do not initiate in patients if the corrected serum calcium is less than the lower limit of normal. Monitor corrected serum calcium within 1 week after initiation or dose adjustment and every 4 weeks during treatment with Parsabiv™. Measure PTH 4 weeks after initiation or dose adjustment of Parsabiv™. Once the maintenance dose has been established, measure PTH per clinical practice.

Worsening Heart Failure: In Parsabiv™ clinical studies, cases of hypotension, congestive heart failure, and decreased myocardial performance have been reported. Closely monitor patients treated with Parsabiv™ for worsening signs and symptoms of heart failure.

Upper Gastrointestinal Bleeding: In clinical studies, 2 patients treated with Parsabiv™ in 1253 patient years of exposure had upper gastrointestinal (GI) bleeding at the time of death. The exact cause of GI bleeding in these patients is unknown and there were too few cases to determine whether these cases were related to Parsabiv™. Patients with risk factors for upper GI bleeding, such as known gastritis, esophagitis, ulcers or severe vomiting, may be at increased risk for GI bleeding with Parsabiv™. Monitor patients for worsening of common Parsabiv™ GI adverse reactions and for signs and symptoms of GI bleeding and ulcerations during Parsabiv™ therapy.

Adynamic Bone: Adynamic bone may develop if PTH levels are chronically suppressed.

Adverse Reactions: In clinical trials of patients with secondary HPT comparing Parsabiv™ to placebo, the most common adverse reactions were blood calcium decreased (64% vs. 10%), muscle spasms (12% vs. 7%), diarrhea (11% vs. 9%), nausea (11% vs. 6%), vomiting (9% vs. 5%), headache (8% vs. 6%), hypocalcemia (7% vs. 0.2%), and paresthesia (6% vs. 1%).

Please see Brief Summary of full Prescribing Information on adjacent page.

Reference: 1. Parsabiv™ (etelcalcetide) prescribing information, Amgen.
WARNINGS AND PRECAUTIONS

Hypocalcemia
PARSABIV lowers serum calcium [see Adverse Reactions (6.1) in PARSABIV full prescribing information] and can lead to hypocalcemia, sometimes severe. Significant lowering of serum calcium can cause paresthesias, myalgias, muscle spasms, seizures, QT interval prolongation, and ventricular arrhythmia. QT Interval Prolongation and Ventricular Arrhythmia

In the combined placebo-controlled studies, more patients treated with PARSABIV experienced a maximum increase from baseline of greater than 60 msec in the QTcF interval (5% placebo versus 1.2% PARSABIV). In these studies, the incidence of a maximum post-baseline QTcF > 500 msec in the placebo and PARSABIV groups was 1.9% and 4.8%, respectively [see Adverse Reactions (6.1) in PARSABIV full prescribing information]. Patients with congenital long QT syndrome, history of QT interval prolongation, family history of long QT syndrome or sudden cardiac death, and other conditions that predispose to QT interval prolongation and ventricular arrhythmias may be at increased risk for QT interval prolongation and ventricular arrhythmias if they develop hypocalcemia due to PARSABIV. Closely monitor corrected serum calcium and QT interval in patients at risk receiving PARSABIV. Seizures

Significant reductions in corrected serum calcium may lower the threshold for seizures. Patients with a history of seizure disorder may be at increased risk for seizures if they develop hypocalcemia due to PARSABIV. Monitor corrected serum calcium in patients with seizure disorders receiving PARSABIV. Concurrent administration of PARSABIV with another oral calcium-sensing receptor agonist could result in severe, life-threatening hypocalcemia. Patients switching from cinacalcet to PARSABIV should discontinue cinacalcet for at least 7 days prior to initiating PARSABIV [see Dosage and Administration (2.4) in PARSABIV full prescribing information]. Patients with congenital long QT syndrome, history of QT interval prolongation, family history of long QT syndrome or sudden cardiac death, and other conditions that predispose to QT interval prolongation and ventricular arrhythmias may be at increased risk for QT interval prolongation and ventricular arrhythmias if they develop hypocalcemia due to PARSABIV. Closely monitor corrected serum calcium and QT interval in patients at risk receiving PARSABIV. Measure corrected serum calcium prior to initiation of PARSABIV. Do not initiate in patients if the corrected serum calcium is less than the lower limit of normal. Monitor corrected serum calcium within 1 week after initiation or dose adjustment and every 4 weeks during treatment with PARSABIV [see Dosage and Administration (2.4) in PARSABIV full prescribing information]. Educate patients on the symptoms of hypocalcemia, and advise them to contact a healthcare provider if they occur.

If corrected serum calcium falls below the lower limit of normal or symptoms of hypocalcemia develop, start or increase calcium supplementation (including calcium, calcium-containing phosphate binders, and/or vitamin D sterol or increases in dialysate calcium concentration). PARSABIV dose reduction or discontinuation of PARSABIV may be necessary [see Dosage and Administration (2.2.5) in PARSABIV full prescribing information].

Worsening Heart Failure

In clinical studies with PARSABIV, cases of hypotension, congestive heart failure, and decreased myocardial performance have been reported. In clinical studies, heart failure requiring hospitalization occurred in 2% of PARSABIV-treated patients and 1% of placebo-treated patients. Reductions in corrected serum calcium may be associated with congestive heart failure, however, a causal relationship to PARSABIV could not be completely excluded. Closely monitor patients treated with PARSABIV for worsening signs and symptoms of heart failure.

Upper Gastrointestinal Bleeding

In clinical studies, two patients treated with PARSABIV in 1253 patient-years of exposure had upper gastrointestinal (GI) bleeding noted at the time of death while no patient in the control groups in 384 patient-years of exposure had upper GI bleeding noted at the time of death. The exact cause of GI bleeding in these patients is unknown, and there were too few cases to determine whether these cases were related to PARSABIV. Patients with risk factors for upper GI bleeding (such as known gastritis, esophagitis, ulcers, or severe vomiting) may be at increased risk for GI bleeding while receiving PARSABIV treatment. Monitor patients for worsening of common GI adverse reactions of nausea and vomiting associated with PARSABIV [see Adverse Reactions (6.1) in PARSABIV full prescribing information] and for signs and symptoms of GI bleeding and ulcerations during PARSABIV therapy. Promptly evaluate and treat any suspected GI bleeding.

Adynamic Bone

Adynamic bone may develop if PTH levels are chronically suppressed. If PTH levels decrease below the recommended target range, the dose of vitamin D sterol and/or PARSABIV should be reduced or therapy discontinued. After discontinuation, resume therapy at a lower dose to maintain PTH levels in the target range [see Dosage and Administration (2.1) in PARSABIV full prescribing information].

ADVERSE REACTIONS

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

- Hypocalcemia [see Warnings and Precautions (5.1) in PARSABIV full prescribing information]
- Worsening Heart Failure [see Warnings and Precautions (5.2) in PARSABIV full prescribing information]
- Upper Gastrointestinal Bleeding [see Warnings and Precautions (5.3) in PARSABIV full prescribing information]
- Adynamic Bone [see Warnings and Precautions (5.4) in PARSABIV 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 with rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice. The data in Table 2 are derived from two placebo-controlled clinical studies in patients with chronic kidney disease and secondary hyperparathyroidism on hemodialysis. The data reflect exposure of 503 patients to PARSABIV with a mean duration of exposure to PARSABIV of 23.6 weeks. The mean age of patients was approximately 55 years, and 60% of the patients were male. Of the total patients, 67% were Caucasian, 29% were Black or African American, 2.6% were Asian, 1.2% were Native Hawaiian or Other Pacific Islander, and 1.6% were categorized as Other. Table 2 shows common adverse reactions associated with the use of PARSABIV in the pool of placebo-controlled studies. These adverse reactions occurred more commonly on PARSABIV than on placebo and were reported in at least 5% of patients treated with PARSABIV.

Table 2: Adverse Reactions Reported in ≥ 5% of PARSABIV-Treated Patients

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Placebo (N = 513)</th>
<th>PARSABIV (N = 503)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood calcium decreased*</td>
<td>10%</td>
<td>64%</td>
</tr>
<tr>
<td>Muscle spasms</td>
<td>7%</td>
<td>12%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>9%</td>
<td>11%</td>
</tr>
<tr>
<td>Nausea</td>
<td>6%</td>
<td>11%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>5%</td>
<td>9%</td>
</tr>
<tr>
<td>Headache</td>
<td>6%</td>
<td>8%</td>
</tr>
<tr>
<td>Hypocalcemia</td>
<td>0.2%</td>
<td>7%</td>
</tr>
<tr>
<td>Paresthesia*</td>
<td>1%</td>
<td>6%</td>
</tr>
</tbody>
</table>

*Included adverse reactions reported with at least 1% greater incidence in the PARSABIV group compared to the placebo group

*Asymptomatic reductions in calcium below 7.5 mg/dL, or clinically significant asymptomatic reductions in corrected serum calcium between 7.5 and < 8.3 mg/dL (that required medical management)

*Paresthesia includes preferred terms of paresthesia and hyposthesia
Other adverse reactions associated with the use of PARSABIV but reported in < 5% of patients in the PARSABIV group in the two placebo-controlled clinical studies were:

- Hyperkalemia: 3% and 4% for placebo and PARSABIV, respectively.
- Myalgia: 0.2% and 2% for placebo and PARSABIV, respectively.
- Hypophosphatemia: 0.2% and 1% for placebo and PARSABIV, respectively.

Description of Selected Adverse Reactions

Hypocalcemia

In the combined placebo-controlled studies, a higher proportion of patients on PARSABIV developed at least one corrected serum calcium value below 7.0 mg/dL (7.6% PARSABIV, 3.1% placebo), below 7.5 mg/dL (27% PARSABIV, 5.5% placebo), and below 8.3 mg/dL (19% PARSABIV, 18% placebo). In the combined placebo-controlled studies, 1% of patients in the PARSABIV group and 0% of patients in the placebo group discontinued treatment due to an adverse reaction attributed to a low corrected serum calcium.

Hypophosphatemia

In the combined placebo-controlled studies, 19% of patients treated with PARSABIV and 8.2% of patients treated with placebo had at least one measured phosphorus level below the lower normal limit (i.e., 2.2 mg/dL).

QTc Interval Prolongation Secondary to Hypocalcemia

In the combined placebo-controlled studies, more patients treated with PARSABIV experienced QTcF interval prolongation with a maximum increase from baseline of greater than 10 ms (in the QTcF interval 0% placebo versus 1.2% PARSABIV). The patient incidence of maximum post-baseline prolongation QTcF > 500 msec in the placebo and PARSABIV groups was 1.9% and 4.8%, respectively.

Hypersensitivity

In the combined placebo-controlled studies, the subject incidence of adverse reactions potentially related to hypersensitivity was 4.4% in the PARSABIV group and 3.7% in the placebo group. Hypersensitivity reactions in the PARSABIV group were pruritic rash, urticaria, and face edema.

Immunogenicity

As with all peptide therapeutics, there is potential for immunogenicity. The detection of anti-drug binding antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody positivity in an assay may be influenced by several factors, including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to etelcalcetide with the incidence of antibodies to other products may be misleading.

In clinical studies, 7.1% (71 out of 995) of patients with secondary hyperparathyroidism treated with PARSABIV for up to 6 months tested positive for binding anti-etelcalcetide antibodies. Fifty-seven out of 71 (80%) had pre-existing binding anti-etelcalcetide antibodies. Fifty-seven out of 71 had pre-existing binding anti-etelcalcetide antibodies. Fifty-seven out of 71 had pre-existing binding anti-etelcalcetide antibodies. Fifty-seven out of 71 had pre-existing binding anti-etelcalcetide antibodies. Fifty-seven out of 71 had pre-existing binding anti-etelcalcetide antibodies. Fifty-seven out of 71 had pre-existing binding anti-etelcalcetide antibodies. Fifty-seven out of 71 had pre-existing binding anti-etelcalcetide antibodies. Fifty-seven out of 71 had pre-existing binding anti-etelcalcetide antibodies. Fifty-seven out of 71 had pre-existing binding anti-etelcalcetide antibodies. Fifty-seven out of 71 had pre-existing binding anti-etelcalcetide antibodies. Fifty-seven out of 71 had pre-existing binding anti-etelcalcetide antibodies. Fifty-seven out of 71 had pre-existing binding anti-etelcalcetide antibodies. Fifty-seven out of 71 had pre-existing binding anti-etelcalcetide antibodies. Fifty-seven out of 71 had pre-existing binding anti-etelcalcetide antibodies. Fifty-seven out of 71 had pre-existing binding anti-etelcalcetide antibodies. Fifty-seven out of 71 had pre-existing binding anti-etelcalcetide antibodies. Fifty-seven out of 71 had pre-existing binding anti-etelcalcetide antibodies. Fifty-seven out of 71 had pre-existing binding anti-etelcalcetide antibodies. Fifty-seven out of 71 had pre-existing binding anti-etelcalcetide antibodies. Fifty-seven out of 71 had pre-existing binding anti-etelcalcetide antibodies. Fifty-seven out of 71 had pre-existing binding anti-etelcalcetide antibodies. Fifty-seven out of 71 had pre-existing binding anti-etelcalcetide antibodies. Fifty-seven out of 71 had pre-existing binding anti-etelcalcetide antibodies. Fifty-seven out of 71 had pre-existing binding anti-etelcalcetide antibodies. Fifty-seven out of 71 had pre-existing binding anti-etelcalcetide antibodies. Fifty-seven out of 71 had pre-existing binding anti-etelcalcetide antibodies. Fifty-seven out of 71 had pre-existing binding anti-etelcalcetide antibodies. Fifty-seven out of 71 had pre-existing binding anti-etelcalcetide antibodies. Fifty-seven out of 71 had pre-existing binding anti-etelcalcetide antibodies. Fifty-seven out of 71 had pre-existing binding anti-etelcalcetide antibodies. Fifty-seven out of 71 had pre-existing binding anti-etelcalcetide antibodies. Fifty-seven out of 71 had pre-existing binding anti-etelcalcetide antibodies. Fifty-seven out of 71 had pre-existing binding anti-etelcalcetide antibodies. Fifty-seven out of 71 had pre-existing binding anti-etelcalcetide antibodies. Fifty-seven out of 71 had pre-existing binding anti-etelcalcetide antibodies. Fifty-seven out of 71 had pre-existing binding anti-etelcalcetide antibodies. Fifty-seven out of 71 had pre-existing binding anti-etelcalcetide antibodies. Fifty-seven out of 71 had pre-existing binding anti-etelcalcetide antibodies. Fifty-seven out of 71 had pre-existing binding anti-etelcalcetide antibodies. Fifty-seven out of 71 had pre-existing binding anti-etelcalcetide antibodies. Fifty-seven out of 71 had pre-existing binding anti-etelcalcetide antibodies. Fifty-seven out of 71 had pre-existing binding anti-etelcalcetide antibodies. Fifty-seven out of 71 had pre-existing binding anti-etelcalcetide antibodies. Fifty-seven out of 71 had pre-existing binding anti-etelcalcetide antibodies. Fifty-seven out of 71 had pre-existing binding anti-etelcalcetide antibodies. Fifty-seven out of 71 had pre-existing binding anti-etelcalcetide antibodies. Fifty-seven out of 71 had pre-existing binding anti-etelcalcetide antibodies. Fifty-seven out of 71 had pre-existing binding anti-etelcalcetide antibodies. Fifty-seven out of 71 had pre-existing binding anti-etelcalcetide antibodies. Fifty-seven out of 71 had pre-existing binding anti-etelcalcetide antibodies. Fifty-seven out of 71 had pre-existing binding anti-etelcalcetide antibodies. Fifty-seven out of 71 had pre-existing binding anti-etelcalcetide antibodies. Fifty-seven out of 71 had pre-existing binding anti-etelcalcetide antibodies. Fifty-seven out of 71 had pre-existing binding anti-etelcalcetide antibodies. Fifty-seven out of 71 had pre-existing binding anti-etelcalcetide antibodies. Fifty-seven out of 71 had pre-existing binding anti-etelcalcetide antibodies. Fifty-seven out of 71 had pr...
Becoming Precise in Diagnosing Acute Kidney Injury

From the time that I trained in nephrology more than 30 years ago, I have been teaching students and fellows the importance of framing the differential diagnosis of acute kidney injury (AKI) along anatomical lines: prerenal, renal, and postrenal, and contextualizing based on the presence or absence of oliguria and on the tempo of the disease process. In the past decade, however, the definition and classification of AKI has moved toward using serum creatinine-based criteria, such as the Risk, Injury, Failure, Loss and End-Stage Kidney Disease (RIFLE), The Acute Kidney Injury Network (AKIN), and Kidney Disease Improving Global Outcomes (KDIGO) guidelines. Are these criteria relevant clinically?

In an interesting Comment in the Lancet, Jonathan Barasch and colleagues point to several limitations of a creatinine-based approach. They point out: “The uniform application of serum creatinine ‘stages’ in lieu of a primary etiologic or anatomic diagnosis, (i) provides inadequate quantitative assessment of excretory dysfunction, and (ii) obfuscates the important distinctions among fundamentally different etiologies that raise serum creatinine and motivate personalized therapy.” They further make the point that “AKI stages’ not only poorly describe the extent of defective excretory function, but they are often at variance with kidney pathology and physiology.”

In reply to the Barasch Lancet article, Kellum and Lamiere rebut what they call nostalgia “for a time when acute renal dysfunction was evaluated according to the classification of prerenal, intrarenal, and postrenal causes,” pointing out that several forms of AKI include intrarenal and extra-renal etiologies, for example sepsis, cardiac surgery, liver disease, and trauma. This seems to sidestep the issue. As nephrologists we have long appreciated that some forms of AKI have overlapping prerenal and intrarenal causes. We can handle this moderate degree of complexity but the question is: Does it justify abandoning a long-established framework to the diagnosis and management of AKI? Barasch and colleagues think not.

Kellum and Lamiere also point out that the KDIGO guidelines do not substitute for the importance of clinical judgment. Of course, most nephrologists understand this. But the point that Barasch and colleagues make is that a stage-based approach to AKI is intrinsically flawed because it is based on using serum creatinine as a biomarker. The limitations of serum creatinine are well known. Rather, Barasch et al. point to emerging advances in kidney transcriptomics and urinary proteomics that overlie on etiologic and anatomic diagnoses will be more clinically valuable than a stage based approach.

Pickering et al. and Lamiere have pointed out that RIFLE, AKIN, and KDIGO have key differences that might create confusion and the possibility of AKI misclassification. Indeed, RIFLE defines AKI by a change from baseline in the serum creatinine or estimated glomerular filtration rate (eGFR), and incorporates urine output over a specified time period. In contrast, AKIN defines AKI based on the RIFLE criteria but incorporates an absolute change in serum creatinine of ≥0.3 mg/dL but without eGFR criteria, and includes 48 hours as a time constraint. On the other hand, the KDIGO guidelines retain the AKIN staging criteria but allow a time frame of 7 days for a 50% increase in serum creatinine.

The door seems to be opening to a much more personalized genetic and proteomic approach. This would be most welcome, since our current ways of managing AKI remain rather rudimentary.

So the bottom line for me is that I will continue to teach fellows and students at the Brigham and Women’s Hospital where I practice to frame AKI both anatomically and etiologically. I will make them aware of the importance of the KDIGO guidelines and encourage them to apply them where relevant.

REFERENCES
hypertension and ESRD-related risk factors including chronic inflammation and uremia. Dialysis initiation is also an independent risk factor for amputation.

A recent analysis of data from the general Medicare population found a 45% decrease in rates of lower extremity amputation from 1996 to 2011. Possible explanations for the decrease in rates include better screening for PAD and improved vascular care, particularly for patients with diabetes. There are few data available on whether there had been a similar improvement in rates of lower extremity amputation in patients with ESRD who receive dialysis.

Douglas Franz, MD, MPH, and colleagues utilized the national ESRD registry to examine the rates of lower extremity amputation from 2000 to 2014 for patients with ESRD receiving dialysis. The researchers sought to determine whether the rates were associated with patient characteristics or comorbidities. Regional differences in amputation practices and 1-year mortality rates following lower extremity amputation were also assessed. Results were reported online in JAMA Internal Medicine [doi:10.1001/jamainternmed.2018.2436].

The retrospective study utilized records from the US Renal Data System for all patients initiating hemodialysis or peritoneal dialysis between January 1, 1996, and October 1, 2004 (n=3,700,902). Due to the accrual of prevalent patients with time, the size of each annual cohort increased progressively, as did dialysis vintage. Exclusion criteria were age <18 years or >110 years at incident ESRD, Centers for Medicare & Medicaid Services form 2728 missing or filed >45 days following dialysis initiation, or missing data on race or sex. Patients who recovered kidney function within 365 days of dialysis initiation were also excluded.

The primary outcome of interest was the number of lower extremity amputations per 100 patient-years for each cohort year, identified using International Classification of Diseases, Ninth Edition procedure codes and Current Procedure Terminology, 4th Revision codes. Amputations were classified as major (above- or below-knee) or minor (below-ankle). Only the highest-level amputation per patient per calendar year was included. A secondary outcome was 1-year mortality following lower extremity amputation (applied only to those patients in each annual cohort who underwent amputation in 2000 through 2013).

In each annual cohort, there were fewer women (47.5% in 2000, 46.2% in 2005, 44.9% in 2010, and 44.0% in 2014), more than half of the participants were white (58.1% in 2000, 56.9% in 2005, 56.9% in 2010, and 56.7% in 2014), and a relatively small proportion were employed (13.9% in 2000, 15.1% in 2005, 16.1% in 2010, and 16.5% in 2014). Over time, the proportion of patients with diabetes and hypertension increased, and the proportion of patients with coronary artery disease and recognized PAD decreased.

From 2000 to 2014, the adjusted rate of all lower extremity amputations decreased, from 5.42 per 100 person-years (95% confidence interval [CI] 5.28-5.6) to 2.66 per 100 person-years (95% CI, 2.59-2.72). The relative decrease over that time period was 51.0%. The adjusted rate of above-knee amputations decreased by 65.0% and the adjusted rate of below-knee amputations decreased by 58.5%; the adjusted rate of below-ankle amputations decreased by 25.9% during the period 2000 to 2014.

During the study period, the adjusted rate of any lower extremity revascularization procedure decreased from 1.63 per person-years (95% CI, 1.55-1.71) in 2000 to 1.28 per person-years (95% CI, 1.24-1.33) in 2014, a decrease of 21.5%. The adjusted rates of surgical bypass decreased by 56.4% (95% CI, 52.5%-60.0%); the adjusted rate of endovascular revascularization increased by 37.0% (95% CI, 25.8%-49.7%) during the study period.

The adjusted amputation rate for patients with diabetes decreased from 8.65 per 100 person-years (95% CI, 8.41-8.88) in 2000 to 4.09 per 100 person-years (95% CI, 3.99-4.19) in 2014, a decrease of 52.8%. The adjusted amputation rate for patients without diabetes also decreased during that time period, from 1.43 per 100 person-years (95% CI, 1.31-1.54) to 0.74 per 100 person-years (95% CI, 0.69-0.79). The amputation rate decreased more quickly for patients with diabetes compared with patients without diabetes (P<.001 for interaction). However, the rates of amputation in patients with diabetes remained >5 times as high as those without diabetes during the study period.

Patients without diabetes or hypertension had lower adjusted rates of amputation compared with that of the overall cohort: 1.03 per 100 person-years (95% CI, 0.78-1.27) in 2000 and 0.50 100 person-years (95% CI, 0.57-0.63) in 2014, a decrease of 51.1%.

In age-based analyses, adjusted amputation rates per 100 person-years were similar in 2000 for patients <65 years of age (5.38; 95% CI, 5.18-5.57) compared with patients ≥65 years of age (5.25; 95% CI, 5.06-5.45). Over time, however, the adjusted rates of amputation decreased less rapidly for patients <65 years of age than for patients ≥65 years of age: in 2014, amputation rates were 2.92 (95% CI, 2.83-3.00) per 100 person-years versus 2.25 (95% CI, 2.16-2.35) per 100 person-years, respectively (P=.005 for interaction).

Adjusted rates for men were higher than for women in 2000; the rates for both men and women decreased similarly with time (P=.06 for interaction). Among all hospital referral regions, the rates of lower extremity amputation generally decreased during the study period; however, regional variability in rates of amputation persisted with time, despite adjustment for differences in patient demographics or comorbid conditions.

During the study period, the adjusted 1-year mortality rates following lower extremity amputation in the study population decreased by 17% (95% CI, 14%-20%); from 52.2% (95% CI, 50.9%-53.4%) in 2000 to 43.6% (95% CI, 42.5%-44.8%) in 2013. Study limitations cited by the authors included the inability to determine laterality of amputation from billing claims, depending on the Medical Evidence Report to determine comorbid conditions, and limiting the analysis to patients with ESRD with Medicare Parts A and B as primary coverage.

In conclusion, the researchers said, “Although rates of lower extremity amputations among US patients with ESRD who receive dialysis decreased by 51% during a recent 15-year period, mortality rates remained high, with nearly half of patients dying within a year after lower extremity amputation. Our results highlight the need for more research on ways to prevent lower extremity amputation in this extremely high-risk population.”
integrated electronic medical record cohort (Geisinger Health System), accounting for time-dependent eGFR stage, and for potential confounding from variables, including concomitant insulin use. They then sought to replicate the findings in a separate nationwide cohort derived from 350 private health systems.

In both cohorts, the researchers compared risk of acidosis during metformin use with the risk during alternative management of diabetes mellitus to test the hypothesis that acidosis would be more common among metformin users within categories of eGFR. Results were reported in JAMA Internal Medicine [2018;178(7):903-910].

The Geisinger cohort included 75,413 patients with diabetes, with time-dependent assessment of eGFR stage from January 2004 until January 2007. The primary outcome of interest was hospitalization with acidosis, using International Classification of Diseases, Ninth Revision, Clinical Modification code 276.2. Mean age in the Geisinger cohort was 60.4 years, 51% were female, and mean body mass index was 34.1. At the time of enrollment, 14,662 patients had an eGFR <60 mL/min/1.73 m² and 1765 had an eGFR <30 mL/min/1.73 m². Median duration of follow-up was 5.7 years and the median number of creatinine measurements per year was 2.1; the number of measurements increased with lower eGFR.

At study enrollment, 45% of patients were taking metformin (n=34,095); 13,781 of the remaining patients were subsequently prescribed metformin during follow-up. Median duration of metformin use was 2.8 years. There were 2335 hospitalizations with acidosis over 470,114 person-years of follow-up; 737 events occurred over 188,578 person-years of metformin use and 1598 occurred over 281,536 person-years of no metformin use. Only 29 of these events had an acidosis code in the primary position.

Overall, the adjusted hazard ratio of acidosis during metformin use compared with nonuse was 0.98 (95% confidence interval, 0.89-1.08). At lower eGFR, the risk of acidosis was higher (P<.01 for interaction). Overall, the adjusted hazard ratio (HR) of acidosis during metformin use compared with nonuse was 0.98 (95% confidence interval [CI], 0.89-1.08). At lower eGFR, the risk of acidosis was higher (P<.01 for interaction). The risk associated with metformin use was not statistically significant at eGFR >90 mL/min/1.73 m² (adjusted HR, 0.88; 95% CI, 0.73-1.05); eGFR 60 to 89 mL/min/1.73 m² (adjusted HR, 0.87; 95% CI, 0.75-1.02); eGFR 45 to 59 mL/min/1.73 m² (adjusted HR, 1.16; 95% CI, 0.95-1.41), and eGFR 30 to 44 mL/min/1.73 m² (adjusted HR, 1.09; 95% CI, 0.83-1.44). At eGFR <30 mL/min/1.73 m², there was an increased risk of acidosis associated with metformin use (adjusted HR, 2.07; 95% CI, 1.33-3.22). Following adjustment for other time-dependent medication use, the results were similar.

In the MarketScan database (replication cohort), there were 67,578 new metformin users and 14,439 new sulfonylurea users from 2010 to 2015. Compared with the sulfonylurea users, the metformin users were slightly younger and more likely to be female. Median follow-up was 12.0 months in the metformin group and 11.5 months in the sulfonylurea group.

The number of acidosis events in the metformin group was 238; in the sulfonylurea group the number was 94. The incidence rate of acidosis in the metformin group was 2.7 events per 1000 person-years; in the sulfonylurea group, the incidence rate was 5.0 events per 1000 person-years.

In both groups, lower eGFR was a risk factor for acidosis. Overall, the risk associated with metformin use was slightly lower than with sulfonylurea (adjusted HR, 0.75; 95% CI, 0.58-0.97) and was not increased in patients with eGFR 45 to 59 mL/min/1.73 m² and eGFR 30 to 44 mL/min/1.73 m² (adjusted HR, 0.83; 95% CI, 0.42-1.62 and 0.86; 95% CI, 0.37-2.01, respectively). There was a higher but not statistically significant risk in patients with eGFR <30 mL/min/1.73 m² (adjusted HR, 1.83; 95% CI, 0.57-5.88).

There were some limitations to the study, including the possibility of residual confounding due to the observational design, the use of a diagnostic code that was not specific for lactic acidosis, the inability to differentiate whether a change in eGFR stage occurred due to progression of CKD or an acute kidney injury, and the possibility of limited generalizability of the results due to the majority of Geisinger Health System population being white.

In conclusion, the researchers said, “Metformin use was not associated with incident acidosis in patients with eGFR 30 to 60 mL/min/1.73 m² in two large and diverse cohorts, but there was increased risk at eGFR <30 mL/min/1.73 m². Our results support cautious use of metformin in patients with type 2 diabetes mellitus and eGFR of at least 30 mL/min/1.73 m².”

**Proteinuria Is a Marker of Uncontrolled Hypertension**


**Proteinuria Is a Marker of Uncontrolled Hypertension**

Researchers conducted a study in two large cohorts of patients with type 2 diabetes and mild to moderate chronic kidney disease (CKD) to examine the relationship between metformin therapy and the incidence of acidosis in that patient population. **Takeaway Points**

- Data regarding the safety of metformin in patients with type 2 diabetes mellitus and mild to moderate chronic kidney disease (CKD) are inconclusive.
- Researchers conducted a study in two large cohorts of patients with type 2 diabetes and mild to moderate CKD designed to examine the relationship between metformin therapy and the incidence of acidosis in that patient population.
- Results of the study support cautious use of metformin in patients with type 2 diabetes, an estimated glomerular filtration rate of at least 30 mL/min/1.73 m².

- **Proteinuria Is a Marker of Uncontrolled Hypertension**

  - Proteinuria is a marker for cardiovascular disease. Identification of patients with proteinuria allows for early treatment to decrease the cardiovascular risk. Michael P. Carson, MD, and colleagues conducted a retrospective chart review designed to identify hospitalized patients with proteinuria, examine the prevalence of concurrent use of medications known to decrease the level of proteinuria, and determine the number of patients placed on anti-proteinuric medications. Results of the analysis were reported during a poster session at the NKF 2018 Spring Clinical Meetings in a poster titled Prevalence of Proteinuria in Hospitalized Patients: A Marker of Uncontrolled Hypertension. The analysis cohort included patients admitted to the Jersey Shore University Medical Center, Neptune, New Jersey, during the period 2010-2015. Available data included demographics, medical history, and laboratory values, including urinalysis. The researchers also identified appropriate medications, including antihypertensives known to mitigate proteinuria. A total of 201 charts were reviewed of those patients, 121 had urinalysis results. Forty-one of those patients (33%) had proteinuria on the first urinalysis; 14 of those patients had a second urinalysis performed, nine subsequently had no proteinuria. Of the 41 patients with proteinuria, 21 patients were on one blood pressure medication, six were on two medications, and 14 were not taking any blood pressure medications (two of those patients had blood pressure medications initiated during the index admission).

  - Mean systolic blood pressure and diastolic blood pressure among those with proteinuria >3 (n=7) were higher than among those with proteinuria ≤3 (n=13) and higher than the total cohort (n=201). Proteinuria was found in 35% (n=70) of patients diagnosed with chronic hypertension compared with 5% of patients without chronic hypertension. Blood pressure control was inadequate in 53% of patients with chronic hypertension.

  - Proteinuria is prevalent, more severe in those with chronic hypertension, and only 47% of inpatients with chronic hypertension had proper blood pressure control. Our findings suggest that detection of proteinuria on admission presents an opportunity to identify patients eligible for quality improvement projects regarding optimization of chronic hypertension,” the researchers concluded.
Blood Pressure Changes
continued from page 1

The analysis included data on 3429 participants. At the time of enrollment in CARDIA, mean age was 25 years, approximately half were white and women, and very few had comorbid conditions such as diabetes or use of antihypertensive medications. At year 10, approximately 6% had diabetes and 3% were being treated with antihypertensive medications. Mean follow-up in the CARDIA study was 19.4 years.

An analysis of the distribution of change in blood pressure (determined from best linear unbiased predictions in linear mixed models) between year 0 and year 10 found clinically significant declines in systolic blood pressure (defined as >5 mm Hg decline over 5 years) in very few participants.

To examine model assumptions and understand the relative contribution of one-time blood pressures versus change in blood pressure to subsequent changes in estimated glomerular filtration rate based on serum cystatin C (eGFR$_{\text{cys}}$), the researchers cross-tabulated changes in eGFRs across nine categories, defined by tertiles of change in blood pressure and tertiles of year-10 blood pressure. Following stratification by year-10 blood pressure, there was as association between qualitatively higher systolic blood pressure and diastolic blood pressure slope tertiles and a more rapid decline in eGFR$_{\text{cys}}$ (there was some overlap in confidence intervals [CIs], however).

Following adjustment for comorbid conditions and systolic blood pressure at year 10, there was an association between every 10-mm Hg higher level of systolic blood pressure and diastolic blood pressure in year 10 and a change in estimated glomerular filtration rate of –0.09 and –0.07 mL/min/1.73 m$^2$, respectively.

The association between diastolic blood pressure slope and decline in kidney function, even after accounting for 10-year diastolic blood pressure. When one-time measurement of observed blood pressure slopes to vary over time in a time-dependent manner, findings regarding the associations between blood pressure slope and subsequent kidney function were similar to those of the primary analysis for systolic blood pressure. The association between diastolic blood pressure slope and decline in subsequent kidney function was no longer significant after accounting for 10-year diastolic blood pressure. When one-time measurement of observed blood pressure was used as an independent predictor (year-10 systolic blood pressure and diastolic blood pressure), there was a statistically significant association between the blood pressures and decline in kidney function.

Every 10-mm Hg increase in diastolic blood pressure per 5-year period was associated with a statistically significant annual decline in eGFR$_{\text{cys}}$ (−0.80 [95% CI, −1.21 to −0.40] mL/min/1.73 m$^2$ per year). Every 10-mm Hg increase in diastolic blood pressure per 5-year period was associated with a statistically significant annual decline in eGFR$_{\text{cys}}$ (−0.80 [95% CI, −1.21 to −0.40] mL/min/1.73 m$^2$ per year). The association between change in systolic blood pressure between years 0 and 10 and subsequent decline in kidney function remained statistically significant in this model, even following adjustment for year-10 systolic blood pressure. The effect size was not substantially altered after further adjustment for albuminuria at year 10.

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To evaluate the association between blood pressure slope and subsequent changes in estimated glomerular filtration rate based on serum cystatin C (eGFR$_{\text{cys}}$), the researchers cross-tabulated changes in eGFRs across nine categories, defined by tertiles of change in blood pressure and tertiles of year-10 blood pressure. Following stratification by year-10 blood pressure, there was as association between qualitatively higher systolic blood pressure and diastolic blood pressure slope tertiles and a more rapid decline in eGFR$_{\text{cys}}$ (there was some overlap in confidence intervals [CIs], however).

“”In conclusion, our results suggest that increasing blood pressures over a 10-year time span in young adulthood are significantly associated with early kidney function decline in individuals without decreased kidney function or clinical hypertension at baseline. Close monitoring of changes in blood pressure over time during early adulthood may help identify individuals at higher risk for subsequent renal complications. Young adults who have continued increases in their blood pressures over time, even in the absence of clinical hyperpertension, may warrant screening for kidney disease,” the researchers said.

Every 10-mm Hg increase in diastolic blood pressure per 5-year period was associated with a statistically significant annual decline in eGFR$_{\text{cys}}$ (−0.80 [95% CI, −1.21 to −0.40] mL/min/1.73 m$^2$ per year). Every 10-mm Hg increase in diastolic blood pressure per 5-year period was associated with a statistically significant annual decline in eGFR$_{\text{cys}}$ (−0.80 [95% CI, −1.21 to −0.40] mL/min/1.73 m$^2$ per year).
INDICATION
Velphoro® (sucroferric oxyhydroxide) is a phosphate binder indicated for the control of serum phosphorus levels in patients with chronic kidney disease on dialysis.

IMPORTANT SAFETY INFORMATION
• Velphoro must be administered with meals. Velphoro tablets must be chewed and not swallowed whole. To aid with chewing and swallowing, the tablets may be crushed.
• Patients with peritonitis during peritoneal dialysis, significant gastric or hepatic disorders, following major gastrointestinal (GI) surgery, or with a history of hemochromatosis or other diseases with iron accumulation have not been included in clinical studies with Velphoro. Monitor effect and iron homeostasis in such patients.
• In a parallel design, fixed-dose study of 6 weeks duration, the most common adverse drug reactions to Velphoro chewable tablets in hemodialysis patients included discolored feces (12%) and diarrhea (6%).

Velphoro can be administered concomitantly with oral calcitriol, ciprofloxacin, digoxin, enalapril, furosemide, HMG-CoA reductase inhibitors, hydrochlorothiazide, losartan, metoprolol, nifedipine, omeprazole, quinidine and warfarin. Take doxycycline at least 1 hour before Velphoro. Velphoro should not be prescribed with oral levothyrinone.

Please see Brief Summary on adjacent page or visit www.Velphoro.com for full Prescribing Information.

A retrospective analysis of pharmacy data assessed the real-world effectiveness of Velphoro in 1,029 adult in-center hemodialysis patients who were switched to Velphoro during routine care. The study compared the proportion of patients with phosphorus levels ≤5.5 mg/dL and the mean prescribed phosphate binder pills/day at baseline (3 months prior to Velphoro) and during Velphoro follow-up (6 months after switch to Velphoro, n=424). This was a noninterventional analysis and did not impact prescriptions or prescribing patterns.1

VELPHORO®
(sucroferric oxyhydroxide) chewable tablets

INDICATIONS AND USAGE
Velphoro (sucroferric oxyhydroxide) is a phosphate binder indicated for the control of serum phosphorus levels in patients with chronic kidney disease on dialysis.

DOSEAGE AND ADMINISTRATION
Velphoro tablets must be chewed and not swallowed whole. To aid with chewing and swallowing, the tablets may be crushed. The recommended starting dose of Velphoro is 3 tablets (1,500 mg) per day, administered as 1 tablet (500 mg) 3 times daily with meals. Adjust by 1 tablet per day as needed until an acceptable serum phosphorus level is reached, with regular monitoring afterwards. Titrate as often as weekly.

DOSEAGE FORMS AND STRENGTHS
Velphoro (sucroferric oxyhydroxide) chewable tablets 500 mg.

CONTRAINDICATIONS
None.

WARNINGS AND PRECAUTIONS
Patients with peritonitis during peritoneal dialysis, significant gastric or hepatic disorders, following major gastrointestinal surgery, or with a history of hemochromatosis or other diseases with iron accumulation have not been included in clinical studies with Velphoro. Monitor effect and iron homeostasis in such patients.

ADVERSE REACTIONS
In a parallel design, fixed-dose study of 6 weeks duration, the most common adverse drug reactions to Velphoro chewable tablets in hemodialysis patients included discolored feces (12%) and diarrhea (6%). The following adverse reactions were identified during post approval use of Velphoro, and were reported voluntarily from a population of uncertain size.

Gastrointestinal Disorders: tooth discoloration
Skin and Subcutaneous Tissue Disorder: rash

To report SUSPECTED ADVERSE REACTIONS, contact Fresenius Medical Care North America at 1-800-323-5188 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS
Velphoro can be administered concomitantly with oral calcitriol, ciprofloxacin, digoxin, enalapril, furosemide, HMG-CoA reductase inhibitors, hydrochlorthiazide, losartan, metoprolol, nifedipine, omeprazole, quinidine and warfarin.

Take doxycycline at least 1 hour before Velphoro.

Velphoro should not be prescribed with oral levothyroxine.

USE IN SPECIFIC POPULATIONS
Pregnancy

Labor and Delivery

No Velphoro treatment-related effects on labor and delivery were seen in animal studies with doses up to 16 times the maximum recommended clinical dose on a body weight basis. The effects of Velphoro on labor and delivery in humans are not known.

Nursing Mothers

Since the absorption of iron from Velphoro is minimal, excretion of Velphoro in breast milk is unlikely.

Pediatric Use

The safety and efficacy of Velphoro have not been established in pediatric patients.

Geriatric Use

Of the total number of subjects in two active-controlled clinical studies of Velphoro (N=835), 29.7% (n=248) were 65 and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects.

OVERDOSAGE

There are no reports of overdosage with Velphoro in patients. Since the absorption of iron from Velphoro is low, the risk of systemic iron toxicity is low. Hypophosphatemia should be treated by standard clinical practice.

Velphoro has been studied in doses up to 3,000 mg per day.

HOW SUPPLIED/STORAGE AND HANDLING

Velphoro are chewable tablets supplied as brown, circular, bi-planar tablets, embossed with "PA 500" on 1 side. Each tablet of Velphoro contains 500 mg iron as sucroferric oxyhydroxide. Velphoro tablets are packaged as follows:

NDC 49230-645-51 Bottle of 90 chewable tablets

Storage

Store in the original package and keep the bottle tightly closed in order to protect from moisture. Store at 25°C (77°F) with excursions permitted to 15 to 30°C (59 to 86°F).

PATIENT COUNSELING INFORMATION

Inform patients that Velphoro tablets must be chewed and not swallowed whole. To aid with chewing and swallowing, the tablets may be crushed [see Dosage and Administration]. Velphoro should be taken with meals.

Instruct patients on concomitant medications that should be dosed apart from Velphoro [see Drug Interactions].

Inform patients that Velphoro can cause discolored (black) stool.

Inform patients that Velphoro can stain teeth.

Inform patients to report any rash to their healthcare professional.

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FRESENIUS MEDICAL CARE
Breaking Down the Kidney Care Industrial Complex: Putting Kidney Disease Patients at the Center of Proactive Care

Chronic kidney disease (CKD) affects 30 million adults in the United States—almost 11% of the population. Yet kidney disease patients are at the mercy of a system that is inadequate to care for them—from lack of, or haphazard, diagnosis and little preventative care to the financial incentives that result in patients getting churned through the for-profit industrial complex of kidney care.

Patients deserve better, and therefore a complete overhaul is required. Now is the time for healthcare providers and payers to come together, putting patients first by adopting a multidisciplinary approach that ensures they receive the care most suited to their needs.

Inadequate Care Under Today’s System
As a clinician, teacher and researcher, I’ve seen the struggles that patients with kidney disease endure, and the frustrations that my fellow nephrologists feel trying to help them manage their health.

The current situation is untenable. Rather than focusing on prevention of kidney disease through education and screenings for high-risk individuals, diagnosis remains hit or miss and many people do not realize they have kidney disease until it’s too late.

Other factors contribute to the current state of healthcare for CKD patients. There is no national systematic screening process. And even if tests are done, providers may not properly interpret the results. Often patients do not know they have kidney disease until they’re in the emergency department in urgent need of dialysis. Compounding this, many patients starting dialysis have never seen a nephrologist. Care is fragmented; primary care physicians (PCPs) receive little support, nephrologists are overwhelmed and not supported to focus on prevention, home therapies are underutilized, and many patients still think in-center dialysis is their only hope. Often alternatives to dialysis are not considered or discussed.

This tragic situation often becomes a profitable endeavor for large for-profit dialysis clinics, at the expense of patients and payers. Patients who are black, Hispanic, Asian, Native American, or of a lower socioeconomic status face even worse outcomes and have lower rates of transplants. The rates of pre-emptive transplant in the United States remains too low. It’s no surprise that the economic model around which this ecosystem has formed rewards providers for moving patients into dialysis, rather than preventing or slowing the progression to CKD and end-stage renal disease (ESRD).

The current situation for kidney disease patients is so absurd and contrary to common sense that John Oliver was inspired to point out how broken the system is in a lengthy segment on his show Last Week Tonight more than a year ago.

Proactive, Multidisciplinary Approach Needed
To ensure kidney disease patients get the best care, we need to move away from today’s reactive approach—where catastrophic events are the most common way patients are recognized by the system—to a more proactive model.

Ideally, the healthcare system should focus on prevention of kidney disease. Clinicians should be empowered with the resources they need to educate and screen for kidney disease in those at highest risk, such as individuals with diabetes and/or high blood pressure or those who take certain medications.

Once diagnosed, patients should receive evidence-based care that is handled by multidisciplinary teams, including a nephrologist and a PCP, who will support them on their journey as CKD progresses and ensure that they, and their families, are prepared for, and confident to handle, life changes that may come throughout that journey.

Social support, including peer mentors and mental health and wellness, should be key components of programs to help patients navigate a very complex system. Patients also need an infrastructure that can support them along their entire journey, from their home life to their interactions with the medical system. Electronic health records should be used for early identification of those at risk. And, those who have advanced kidney disease should be empowered to understand how each new medication, life event, dietary change, or hospitalization can influence their disease progression. Care should be easily organized and accessible, so that any provider can readily understand where patients are in the course of their kidney disease. Additionally, patients must understand that they have options. Risk for kidney disease, or a CKD diagnosis, does not automatically mean that a patient will need to spend hours a day, several days a week, at an outpatient dialysis center. With the right information and care team, patients and their families can make educated decisions about their care, including the opportunity for in-home dialysis, conservative care without dialysis when appropriate, or a pre-emptive transplant.

Most importantly, the economic model for kidney care must change. Providers should be incentivized to prevent or slow the progression of CKD and end-stage renal disease—not rewarded for moving patients immediately into outpatient dialysis.

To ensure patients receive the care they need and deserve, we can no longer be content with the status quo. It is time that healthcare providers and payers embrace a new, proactive model that puts patients first. By taking this approach, the healthcare community will see how costs can ultimately be reduced while vastly improving care and patient outcomes.
Children with chronic kidney disease (CKD), including end-stage renal disease (ESRD), are at risk for weight loss. Results of prior cross-sectional studies in adults have suggested that weight loss begins to occur at an estimated glomerular filtration rate (eGFR) of 40 mL/min/1.73 m². However, there are few available data for longitudinal assessments of the timing or degree of weight loss in children with CKD.

Elaine Ku, MD, MAS, and colleagues conducted an observational cohort study to examine the trajectory of weight change as kidney function declines, using data from the CKiD (CKD in Children) Study. CKiD, an observational cohort study, was conducted in North America in children and adolescents with CKD followed up longitudinally since 2005. The current analysis tested the hypothesis that the “weight trajectory would not be linear with the progression of CKD and that weight loss would primarily occur after the onset of the advanced stages of CKD (stage ≥4).” The researchers also sought to determine the characteristics of participants in CKiD who lost significant weight with advancing CKD and whether there was an association with weight changes and a higher risk for ESRD. Results of the analysis were reported in the American Journal of Kidney Diseases [2018;71(5):648-656].

Mean age of CKiD participants was 10.8 years and 63% were boys. The trajectory analysis included 854 participants who had available data on body mass index (BMI) and serum creatinine from an average of 3.8 visits per participant. Mean longitudinal follow-up was 3.4 years.

Before eGFRₖ of 35 mL/min/1.73 m², there was an association between every 10–mL/min/1.73 m² decline in eGFRₖ and a mean decline in BMI z score of 0.008 (95% confidence interval [CI], –0.01 to 0.02). After eGFRₖ decreased to <35 mL/min/1.73 m², there was an association between every 10-mL/min/1.73 m² further decline in eGFRₖ and a mean decrease in BMI z score of 0.13 (95% CI, 0.09-0.17).

There were no significant changes in results after adjusting for demographic characteristics, cause of CKD, and proteinuria: a decline in BMI z score of 0.14 (95% CI, 0.10-0.18) was noted with every 10-mL/min/1.73 m² decrease in eGFRₖ after eGFRₖ decreased to <35 mL/min/1.73 m², and there was an association between every 10-mL/min/1.73 m² further decline in eGFRₖ and a mean decrease in BMI z score of 0.13 (95% CI, 0.09-0.17).

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Among participants with significant weight loss (decline in BMI z score >0.2 per year) following a decrease in eGFR to <35 mL/min/1.73 m², the odds of ESRD were 3.28 (95% CI, 1.53-7.05) times greater compared with participants with stable BMI z scores (BMI z score change per year of 0-0.1).

There were two deaths and 130 cases of ESRD among the 268 children and adolescents who had at least two BMI and serum creatinine measurements after eGFR decreased to <35 mL/min/1.73 m². During 2.7 years of follow-up, approximately 25% of participants had significant weight loss; those with significant weight loss were more likely to have a glomerular cause of CKD. Those who gained weight were most likely to have lower BMI z scores at the visit when eGFR first decreased to <35 mL/min/1.73 m². There were no associations between the prevalence of poor appetite by self-report and weight change categories.

Of the subset of participants with two or more BMI measurements after eGFR decreased to <35 mL/min/1.73 m², there was a graded association between degree of weight loss and the odds of ESRD;
results were similar in both unadjusted and adjusted analyses. There was also an association between weight gain and higher odds of ESRD; those findings did not reach statistical significance, however.

There was an interaction between significant weight loss and BMI z score starting at the time eGFR \(_r\) first decreased to <35 mL/min/1.73 m\(^2\) \((P=0.04)\). The adjusted odds of ESRD among participants with BMI z scores >0.3 \((n=122)\) when eGFR \(_r\) first decreased to <35 mL/min/1.73 m\(^2\) were 5.8 \((95\% \text{ CI}, 1.61-21.0)\) times higher among those who had significant weight loss compared with the reference group. Conversely, among those with BMI z scores ≤0.3 \((n=125)\), the odds of ESRD when eGFR \(_r\), first decreased to <35 mL/min/1.73 m\(^2\), was no statistically significant difference from that of participants who maintained weight \((\text{odds ratio, 0.86; 95\% CI, 0.18-4.00})\).

There were some limitations to the study, including the likely underestimation of the degree of nonedematous weight loss that occurred, and the limited number of longitudinal measurements of inflammatory markers such as C-reactive protein and cholesterol to include in the analyses. There may also be limitations in the ability for BMI measurements to distinguish between adiposity versus fluid weight. Finally, the observational nature of the study makes it difficult to rule out the possibility of residual confounding.

"In conclusion, significant weight loss appears to occur primarily after eGFR decreases to <35 mL/min/1.73 m\(^2\) in children and adolescents with CKD during longitudinal follow-up. The development of significant weight loss in children and adolescents with CKD was associated with higher risk for ESRD. Careful attention to nutritional parameters starting in CKD stage 3 may be warranted, with earlier and more frequent assessments than currently recommended. Further research is needed to determine reasons behind the association between weight loss and risk for ESRD in children and adolescents," the researchers said.

**Center-Level Characteristics and Variations in Peritoneal Dialysis Outcomes**

One of the most common reasons for discontinuation of peritoneal dialysis therapy is peritonitis. A significant proportion of patients receiving peritoneal dialysis who develop peritonitis experience serious adverse outcomes, including hospitalization, relapse or recurrent peritonitis, removal of the peritoneal dialysis catheter, permanent transfer to hemodialysis therapy, and/or death.

Studies have documented marked variation in peritonitis rates and technique survival across peritoneal dialysis centers. In addition, there is an association between a substantial proportion of this variation and center-level characteristics. There are few data related to center variation in peritoneal dialysis-related outcomes of peritonitis and the relative contributions of center and patient effect.

Hay Htay, MBBS, MRCP, and colleagues recently conducted a retrospective cohort study designed to examine the associations of key peritonitis outcomes with center-level characteristics after adjustment for patient-level characteristics. A secondary aim was to assess changes in peritonitis outcomes over time. The researchers reported results of the study in the *American Journal of Kidney Diseases* [2018;71;(6):814-821].

The primary outcome of interest was cure with antibiotic therapy alone, defined as an episode not complicated by relapse or recurrent peritonitis. Secondary outcomes were peritonitis-related catheter removal, transfer to hemodialysis therapy for ≤30 days, relapse or recurrent peritonitis, hospitalization, and mortality. Multilevel mixed logistic regression was used to analyze outcomes.

The study population included all incident peritoneal dialysis patients in Australia who developed peritonitis form January 1, 2004, through December 31, 2014, utilizing deidentified data from the Australia and New Zealand Dialysis and Transplant Registry (ANZDATA). Patient-level characteristics examined were age at peritoneal dialysis therapy initiation, sex, race, body mass index (BMI), smoking status, primary kidney disease, comorbid conditions (diabetes, chronic lung disease, and cardiovascular disease), late referral to nephrology care, modality of initial renal replacement therapy, initial peritoneal dialysis modality, and socioeconomic position.

During the study period, 9452 episodes of peritoneal dialysis-related peritonitis occurred in 4624 incident peritoneal patients. Of those patients, 167 were excluded from the analysis, resulting in 9100 episodes of peritonitis in 4428 patients from 51 centers in the final analysis.

Among the final cohort, 59% \((n=2591)\) were male; mean age was 59.6 years; 72% \((n=3191)\) were white; mean BMI was 27.3 kg/m\(^2\); 45% \((n=2015)\) were nonsmokers; 45% \((n=1993)\) had diabetes mellitus, 48% \((n=2144)\) had cardiovascular disease, 15% \((n=664)\) had chronic lung disease; primary kidney disease cause was glomerulonephritis in 25% \((n=1120)\), diabetes mellitus in 35% \((n=1565)\), hypertension in 14% \((n=626)\), polycystic kidney disease in 6% \((n=239)\), and other causes in 20% \((n=878)\); 21% \((n=921)\) had late nephrology referral; 79% \((n=3358)\) had continuous ambulatory peritoneal dialysis as initial peritoneal dialysis modality; 14% \((n=616)\) had peritoneal dialysis as initial renal replacement therapy; and the mean IRSAD (Index of Relative Socioeconomic Advantage and Disadvantage) score was 974.

Of the 9100 peritonitis episodes included in the analyses, 69% \((n=6285)\) were cured by antibiotic therapy alone. Rates of peritonitis cure for individual centers varied between 38% and 86%. Independent and significant center-level characteristics associated with achievement of cure were a higher proportion of dialysis patients treated with peritoneal dialysis \((>29\%)\) peritoneal dialysis patients; adjusted odds ratio \((OR), 1.21; 95\% \text{ confidence interval (CI),} 1.04-1.40\) and a higher proportion of peritonitis episodes receiving complete empirical antibiotic cover \((OR, 1.22; 95\% \text{ CI,} 1.06-1.42)\). There were no other center-level characteristics significantly associated with peritonitis cure, including center size, transplantation center status, automated peritoneal dialysis exposure, peritoneal
equilibration test performance at initiation of peritoneal dialysis therapy, icodextrin exposure, proportion of culture-negative peritonitis, and proportion of patients co-prescribed antifungal prophylaxis with antibiotic treatment.

Patient-level characteristics significantly associated with higher odds of cure with antibiotic therapy were younger age (OR, 0.96; 95% CI, 0.93-1.00) and low-risk causative organisms (OR, 0.96; 95% CI, 0.93-1.00). Following adjustment for all patient-level characteristics, variation in the odds of cure with antibiotic therapy across centers was increased by 9%, but reduced by 66% after adjustment for center-level characteristics, compared with the model adjusted for causative organisms only.

Of the 9100 peritonitis episodes, 1739 required removal of the peritoneal dialysis catheter. Rates of catheter removal at individual centers varied from 12% to 50%. In centers with higher proportions of dialysis patients treated with peritoneal dialysis (>29%), odds of peritonitis-related catheter removal were lower (OR, 0.78; 95% CI, 0.62-0.97). There were no significant associations between center-level characteristics and catheter removal.

There was an association between episodes of peritonitis with organisms categorized as high and moderate risk for catheter removal and higher odds of catheter removal compared with peritonitis episodes from organisms categorized as low risk (OR, 9.64; 95% CI, 8.34-11.1 and OR, 2.63; 95% CI, 2.29-3.02, respectively). Following adjustment for all patient-level characteristics, variation in the odds of catheter removal across centers was increased by 6%, but reduced by 42% following adjustment for center-level characteristics, compared with the model adjusted for causative organisms only.

There were 1667 peritonitis episodes that culminated in patients transferring to hemodialysis therapy for 230 days. Transfer rates for individual centers varied between 10% and 50%. Centers with higher proportions of patients receiving peritoneal dialysis had lower odds of transfer to hemodialysis therapy (OR, 0.78; 95% CI, 0.62-0.97). Of the 9100 peritonitis episodes, 12% (n=1126) resulted in relapse or recurrence, with variation between centers between 0% and 23%. Centers with higher (>29% peritoneal dialysis patients; OR, 0.68; 95% CI, 0.48-0.98) and lower proportions of patients receiving peritoneal dialysis (<18% patients receiving peritoneal dialysis; OR, 0.68; 95% CI, 0.51-0.90) had lower risks for relapsed/recurrent peritonitis compared with centers with an average proportion of peritoneal dialysis patients. Smoking status was the only patient-level characteristic significantly associated with the odds of relapsed or recurrent peritonitis.

Nine percent of the patients (n=406/4428) had peritonitis-related mortality. Individual center rates varied between 0% and 25%; there were no significant associations between center-level characteristics and the odds of peritonitis-related mortality. Patient-level characteristics that were significantly and independently associated with peritonitis-related mortality were older age, presence of diabetes mellitus, presence of chronic lung disease, lower socioeconomic status, and causative organism.

Hospital admission was required in 68% of peritonitis episodes (n=6222), with individual center rates varying between 37% and 100%. Lower proportion of peritonitis patients was the main center-level characteristic associated with higher odds of hospital admission. Patient-level characteristics associated with higher odds of hospital admission were lower socioeconomic status and moderate- or high-risk causative organism.

Finally, compared with an earlier study period (2004-2009), the contemporary period (2010-2014) was significantly associated with higher odds of peritonitis cure with antibiotic therapy (OR, 1.17; 95% CI, 1.04-1.30) and lower odds of relapsed or recurrent peritonitis (OR, 0.66; 95% CI, 0.55-0.80).

Limitations to the study cited by the authors included the retrospective design and the limited depth of data available in the ANZDATA database.

“These results suggest that center effects contribute substantially to the appreciable variation in peritoneal dialysis peritonitis outcomes that exist across peritoneal dialysis centers within Australia,” the researchers said.
Developing and Validating New Models to Estimate Lean Body Mass in Patients with CKD

Protein-energy wasting (PEW), a condition associated with adverse outcomes due to cardiac comorbidity and inflammation, is a common complication in patients with CKD. Patients undergoing dialysis experience PEW most often, but PEW is also seen in non–dialysis-dependent CKD patients. As renal function declines, protein catabolism can be gradually aggravated via various complex mechanisms and may become apparent in nutritional indices such as somatic and visceral protein storage.

Reduced lean body mass (LBM) is a key index for somatic protein deficit and is a predictor of high mortality in CKD patients not on dialysis. Accurately measuring LBM during routine care can identify PEW, allowing for initiation of intervention, particularly in patients with CKD stage 3 to 5.

However, according to Xue Tian, MD, and colleagues, measurements for LBM are not routinely conducted due to the lack of accurate and simple measurement techniques. The gold-standard (tracer dilution) and reference (dual energy x-ray absorptiometry [DEXA]) techniques are laborious, invasive, and not suitable for routine care. Currently, there are no LBM estimation methods that are simple, practical, and reliable.

Recent studies in patients receiving hemodialysis have demonstrated similarity between LBM as measured by DEXA and LBM estimated using hand-grip strength and mid-arm muscle circumference measurements. Dr. Tian et al. developed and validated two new equations for estimating LBM in patients on peritoneal dialysis based on hand-grip strength and mid-arm muscle circumference. The equations have good precision and accuracy and small bias; they also demonstrate improved performance over creatinine kinetics and anthropometry methods.

Equations for estimating LBM in patients with non–dialysis-dependent CKD are also needed. The researchers conducted a study to develop equations for that patient population (patients with CKD stage 5 to S), based on mid-arm muscle circumference and hand-grip strength. The equations were validated using comparisons to LBM measured by DEXA as the reference method. Study results were reported in the *Journal of Renal Nutrition* [2018;28(3):156-164].

The researchers recruited 300 patients with stage 5 to S non–dialysis-dependent CKD who were divided into two groups: 150 in the development group and 150 in the validation group. There were no differences between the two groups in demographic data, distribution of CKD, stage, and comorbidity (*P*>.05). With the exception of mean hemoglobin, laboratory measurements were also similar between groups (*P*>.05) (mean hemoglobin was higher in the validation group).

Mid-arm muscle circumference was significantly higher in the validation group compared with patients in the development group (*P*<.001). However, LBM, determined using DEXA, hand-grip strength for two sides, and dietary protein and energy intake, was comparable between the groups. There were no significant differences in body composition, including extracellular water, total body water, or the ratio of extracellular to total body water, between the groups.

Using the development dataset, the researchers constructed two equations for LBM estimation: LBM-H, based on hand-grip strength (defined as the dominant hand-grip strength), and LBM-M, based on mid-arm muscle circumference. Potential variables for the regression equations from age, sex, height, and weight were selected via performance of stepwise procedures. In Spearman correlation analyses, LBM-DEXA was correlated significantly with sex, height, weight, hand-grip strength (*r*=0.72), and mid-muscle arm circumference (*r*=0.66; all *P*<.001). There were no correlations between LBM-DEXA and serum albumin or daily protein intake. Two multiple regression equations were established using hand-grip strength or mid-arm muscle circumference in combination with the selected demographic variables of sex, height, and weight. The R-square values were 0.900 for LBM-H and 0.894 for LBM-M.

The two formulas were applied to the validation group and compared with measurements made utilizing LBM-DEXA. Estimated LBM values using LBM-H and LBM-M were numerically close to those measured with DEXA (44.6 kg) and significantly correlated with them (*P*<.001 for both). There was significant correlation with hand-grip strength and mid-arm muscle circumference with values estimated using the equations and values measured using LBM-DEXA (*P*<.001 for all). There was no significant correlation with serum creatinine, daily protein, and energy intake (as observed in the development dataset). LBM-H and LBM-M, but not LBM-DEXA, were also significantly correlated with serum albumin.

In further assessment of the performances of the new equations, still using LBM-DEXA as the reference method, the LBM was slightly overestimated with both the LBM-H and LBM-M formula. The analyses were repeated in mutually exclusive strata to compare the performance of the equations in varying ranges of LBM. Analyses were conducted in strata of higher and lower than the LBM-DEXA median of 44.6 kg; at CKD stage 3 and CKD stages 4 and S; and higher and lower than the ratio of extracellular to total body water. The observed biases were consistent across all the groups (*P*<.001-0.05).

Generally, the interquartile range differences with both equations were small (3.92-5.32 kg) and were independent of the values of LBM-DEXA, the ratio of extracellular to total body water, and CKD stage, indicating the preciseness of the two new equations.

Limitations to the study cited by the authors included developing the prediction model in single-center non-dialyzed CKD patients, possibly limiting the generalizability of the findings, and including only clinically stable patients in the cohort.

“In summary, two new models for predicting LBM using hand-grip strength and mid-arm muscle circumference were developed and then validated in a relatively large sample of non-dialyzed CKD patients. Results of the validation indicated that the equations can provide reliable and accurate estimates of LBM in non-dialyzed CKD patients in clinical practice. Further studies are needed to validate the models in a larger study population, and longitudinal studies are required to evaluate the suitability of the formulae for detecting changes in LBM in response to the intervention,” the researchers concluded.
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eGFR‡ levels can remain steady over many years, but enlarging cysts continue to increase kidney volume, damaging renal tissue.2,3

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*Autosomal recessive polycystic kidney disease.
†Autosomal dominant polycystic kidney disease.
‡Estimated glomerular filtration rate.

Mineral Handling in Hemodialysis Patients

There is an association between chronic kidney disease (CKD) and an increased risk of cardiovascular morbidity and mortality. In patients with CKD, increased circulating concentrations of phosphate and fibroblast growth factor-23 (FGF23) are highly predictive of cardiovascular disease.

In order to maintain long-term calcium and phosphate balance, in healthy individuals an ingested mineral load is acutely buffered by a rapidly exchangeable calcium phosphate pool in the bone and excess minerals are disposed of via renal excretion. In patients with CKD with glomerular filtration rate >30 mL/min/1.73 m², phosphate balance is maintained by increased secretion of parathyroid hormone (PTH) and FGF23.

In patients with severe CKD, GFR < 30 mL/min/1.73 m², there are no compensatory mechanisms sufficient to maintain phosphate balance, and patients are characterized by increased plasma phosphate despite often very high concentrations of PTH and FGF23. In addition, plasma calcium may be low due to high plasma phosphate and low 1,25-dihydroxyvitamin D (1,25(OH)D).

Following meal intake in patients with end-stage renal disease (ESRD), the ingested calcium and phosphate cannot be effectively eliminated by the renal route, making it necessary to neutralize the excess calcium and phosphate via other mechanisms. However, there are few available data regarding the way patients on hemodialysis adapt to a mineral load following meal intake.

Mark Richard, MD, PhD, and colleagues recently conducted a controlled intervention study designed to examine the acute handling of a mineral load in hemodialysis patients compared with a cohort of individually matched controls. The researchers reported results in the Journal of Renal Nutrition [2018;28(3):175-182].

The study matched 12 nondiabetic hemodialysis patients with 12 healthy controls, based on sex, age, height, and weight. The study was conducted between January and June 2012. Eligible patients were > 18 years of age, on stable hemodialysis for at least 3 months, and had well-functioning arteriovenous fistulas with a recirculation < 5%. Exclusion criteria were diabetes mellitus, body mass index < 18.5 or > 35.0 kg/m², malnutrition (defined as Subjective Global Assessment score C), active malignant disease, immunosuppressive treatment (including glucocorticoid treatment), evidence of an ongoing inflammatory disease, or pregnancy. Eligible diagnoses were chronic glomerulonephritis (n=4), chronic renal failure of unknown origin (n=4), autosomal dominant polycystic kidney disease (n=2), scleroderma progressive diffusa (n=1), and granulomatosis with polyangiitis (n=1).

The intervention consisted of blood samples taken for the 9 hours after a weight-adjusted standardized meal; the samples were tested for ionized calcium, phosphate, PTH, and FGF23. The fractional excretion of calcium and phosphate was also measured in the control group. Participants in the patient group were not allowed to take phosphate binders 24 hours prior to the experiment; the intervention was performed on a non-hemodialysis day.

At baseline, compared with controls, participants in the patient group had significantly higher fasting concentrations of circulating phosphate, PTH, and FGF23. Serum FGF23 concentrations were 217-fold times higher in the hemodialysis patients than in the control group (P<.001).

There were no significant differences in postprandial changes in plasma ionized calcium between the hemodialysis patient and the control group; further, there were no significant deviations in concentrations from baseline at any point in the hemodialysis patients or controls.

There were statistically significant differences in plasma phosphate between controls and the hemodialysis patients (P=.03). In the hemodialysis patients, there was a decrease shortly below baseline at 60 to 120 minutes after the meal by maximum 10% (P<.001); among the controls, there were no significant deviations from baseline. In subgroup analysis among the hemodialysis patients, changes in plasma phosphate did not differ based on treatment status with calcium-containing phosphate binders, sevelamer, lanthanum, cinacalcet, or vitamin D analogs.

There were no significant differences between the two groups in post-meal changes in PTH. PHT increased above baseline at 240 minutes in the hemodialysis group and remained above baseline to the end of the study, with a peak at 300 minutes of 11% above baseline. In the control group, PTH decreased shortly below baseline at 60 minutes by 15%, and then increased above baseline at 300 to 360 minutes by a maximum 11%.

There were significant differences in post-prandial FGF23 between the hemodialysis group and controls (P<.001). There were no significant deviations in FGF23 from baseline in the hemodialysis patients (P=.09); in the control group, FGF23 concentrations decreased below baseline at 120 minutes and continued to decline with nadir values at the end of the study at 16% below baseline (P<.001).

Among the healthy controls, there was significant increase in the fractional excretion of calcium, with an excretion rate above baseline from 60 minutes to the end of the study, with peak excretion at 120 minutes of 153% above baseline values (P<.001). The controls also demonstrated an increase in the fractional excretion of phosphate immediately after the meal, remaining above baseline to the end of the study. The increase was more modest compared with calcium, showing a late peak at 360 minutes of 58% above baseline.

There were some limitations to the study cited by the authors, including estimating rather than directly measuring the mineral contents in the meals.

“In conclusion, the postprandial mineral handling is severely impaired in hemodialysis patients who lack the ability to excrete excess minerals in the urine. Since hemodialysis patients cannot excrete calcium and phosphate in the urine, the formation of calcium-phosphate complexes may be extensive and enhance soft tissue and vascular calcification. In the healthy subjects, PTH seemed to play a role in the acute adaption to a phosphate load, whereas FGF23 did not. In hemodialysis patients, the apparent normal circadian rhythm of FGF23 seemed to be disrupted, and it is unknown if FGF23 is still modifiable by dietary interventions,” the researchers said. 

TAKEAWAY POINTS

- In patients on maintenance hemodialysis, excess calcium and phosphate must be neutralised by mechanisms other than excretion in the urine.
- Researchers conducted a controlled intervention study to assess the acute handling of a mineral load in hemodialysis patients compared with healthy controls.
- In the hemodialysis patients the mineral load induced a decrease in plasma phosphate, ionized calcium remained unchanged and PTH increased.
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Iron status should be determined on pre-dialysis blood samples. Post dialysis serum iron parameters may overestimate serum iron and transferrin saturation.

Adverse Reactions
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Approximately one-third of older adults in Europe are classified as malnourished upon admission to the hospital. Many patients also have chronic kidney disease (CKD), making nutritional problems more complex compared with those without CKD. Protein-energy wasting (PEW) is defined as inadequate nutrient intake, in combination with other factors including inflammation, acidosis, and endocrine disorders that lead to increased net breakdown of protein or fat.

Protein-Energy Wasting
More Prevalent in Women
and Increases with Age

The prevalence of PEW is well described in patients initiating or receiving maintenance dialysis; however, there are few data available on the prevalence and risk factors for PEW among nondialysis-dependent patients with CKD. Further, existing studies do not focus on the most vulnerable elderly patients and the majority were single-center studies.

Researchers in Sweden conducted a prospective observational cohort study designed to examine the prevalence and risk factors for PEW determined by the seven-point Subjective Global Assessment (SGA) tool. In addition, the researchers sought to describe the association between PEW and obesity in relation to patients’ baseline characteristics. Study results were reported in the Journal of Renal Nutrition [2018; 28(3):165-174].

The analysis included a total of 1334 patients. Median age was 76 years, and 65.5% were male. Median estimated glomerular filtration rate was 18.2 mL/min/1.73 m² (interquartile range, 14.8-21.4). Most of the patients had normal nutritional status by SGA score (SGA 6-7), 26% were moderately malnourished (SGA 3-5), and 1% had severe malnutrition (SGA 1-2). In SGA scales, 20.8% (n=278) of the patients had experienced recent weight loss, 23.4% (n=312) had inadequate food intake and/or gastrointestinal symptoms, 28.1% (n=375) had signs of subcutaneous fat loss, and 33.8% (n=451) had signs of muscle wasting.

In general, a muscle wasting score ≤5 on a SGA subscale was more prevalent than an overall SGA score ≤5. The prevalence of both PEW and muscle wasting was greater in the oldest patients (36% in those ≥80 years of age). Nearly 60% of patients with a diagnosis of depression or dementia were diagnosed with PEW.

There was no influence of the comorbidity burden based on the Charlson comorbidity index on the risk of PEW; however, late referral, defined as <1 year prior to inclusion, had a borderline statistically significant association with PEW. The strongest association with PEW was seen in a history of psychiatric disease such as depression or dementia: OR, 3.72; 95% CI, 2.33-5.95. The risk of PEW also increased with the presence of other comorbid conditions such as chronic pulmonary disease, cerebrovascular disease, heart failure, peripheral artery disease, and cancer; these associations did not reach statistical significance, however. BMI confounded the relationship between diabetes and PEW and had no association in the adjusted model.

Overall, the study cohort was overweight, with a mean BMI of 28.4 kg/m² and mean waist circumference of 105.8 cm in men and 100.3 cm in women. Based on World Health Organization standards, 34% of patients (n=438) were obese, 37% (n=469) were overweight, and 9% (n=110) were underweight (BMI <22 kg/m², according to European Society of Clinical Nutrition and Metabolism recommendations). Women were more often obese and underweight than men, and patients >80 years of age were more often underweight and less often obese.

Limitations to the study cited by the authors included the possibility that the generalizability of results may be limited by the manner in which patients were recruited.

In summary, the researchers said, “This European, multicenter study reports that the prevalence of PEW is 26% in older adults with CKD (stage 4-5) not on dialysis. Patients especially at risk are elderly (>80 years), women, and those with psychiatric disease. Protein wasting was common (25%) among the obese; ie, obese sarcopenia. We conclude that it is very important to detect early signs of PEW in older adults with CKD, and further research is needed to study interventions directed specifically toward the elderly.”
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TAKE-IT Intervention Improves Medication Adherence in Children and Young Adults

Pediatric kidney transplant recipients face a high-risk period during adolescence and young adulthood. Rates of graft failure increase from approximately 11 years of age and are higher in patients between 17 and 24 years of age than in any other age group. One factor contributing to the high graft failure rates in this age group may be poor adherence to immunosuppressive therapy, which is a key factor limiting survival of renal allografts in any age group.

Most poor adherence is unintentional; forgetting and poor organization and planning were the barriers to adherence most often cited by young kidney transplant recipients. The ability to manage medications may also be affected by neurocognitive dysfunction, particularly disturbances in executive function and memory associated with pediatric chronic kidney disease.

In 2008, the National Institutes of Health called for randomized trials promoting interventions for adolescent and young adult kidney transplant recipients. The TAKE-IT (Teen Adherence in Kidney Transplant Effectiveness of Intervention Trial) intervention was developed to address modifiable barriers to adherence in that patient population. The intervention utilized an approach that was individually tailored and included a combination of electronic monitoring and feedback, problem-solving skills, goal setting, and adherence support using text message dose reminders. The intervention showed promise in prior studies and has been reinforced with systematic reviews.

Bethany J. Foster, MD, and colleagues recently conducted a prospective, unblinded parallel-arm randomized trial to examine the efficacy of a novel multicomponent adherence-promoting intervention, compared with an attention control condition, in improving medication adherence in adolescent and young adult kidney transplant recipients. The researchers sought to test the hypothesis that adherence would be significantly better with the TAKE-IT intervention compared with a control group. Results were reported in the American Journal of Kidney Diseases [2018;72(1):30-41].

The intervention in TAKE-IT was designed to improve implementation of the prescribed medication regimen, defined as “the extent to which a patient’s actual dosing corresponds to the prescribed dosing regimen.” The trial was conducted at eight pediatric transplant centers in Canada and the United States from February 2012 to May 2016.

The study population included prevalent kidney-only transplant recipients 11 to 24 years of age who were ≥3 months post-transplant, expected follow-up was 15 months. Exclusion criteria were impending graft failure, severe neurocognitive disabilities, lack of electronic pillbox connectivity, use of liquid immunosuppressive medications, having a sibling participating in another adherence-promoting intervention study, or the inability to communicate comfortably in English (or French, Montreal site only).

During a 3-month run-up period, adherence was electronically monitored in all participants; the run-up period was followed by a 12-month intervention. Participants in the TAKE-IT arm could opt to receive text message, e-mail, and/or visual cue dose reminders; they also met with a coach at 3-month intervals to review adherence data from the previous 3 months. Barriers identified as important by the participant were addressed using “Action-Focused Problem Solving” techniques. Participants in the control group met with coaches at 3-month intervals but did not receive feedback on adherence data.

The primary outcomes of interest were electronically measured “taking” adherence, defined as the proportion of prescribed doses of immunosuppressive medications taken, and “timing” adherence, defined as the proportion of doses of immunosuppression medication taken between 1 hour before and 2 hours after the prescribed time of administration, on each day of observation. Secondary outcomes included the standard deviation of tacrolimus trough concentrations, self-reported adherence, acute rejection, and graft failure.

Of the 388 patients screened, 277 met eligibility criteria. Of those, 172 were enrolled between February 3, 2012, and February 1, 2015. The final cohort included 169 participants, 81 in the intervention arm and 88 in the control arm. The two groups were similar in baseline characteristics, although not perfectly balanced. Median age in the intervention arm was 15.5 years and 57% were male; in the control arm, median age was 15.8 years and 61% were male.

Preintervention results of the adolescent and parent versions of the Medication Barriers Survey were similar between the two groups as well. Compared with controls, patients in the intervention arm spent more time with the coach.

In the intervention group, taking adherence improved immediately after the first intervention visit and remained fairly stable thereafter, compared with the control group where there was no change in taking adherence. During the intervention period, taking adherence was 100% in 78% of days for the intervention arm and 68% for the control arm. Among patients in the intervention arm, the likelihood of better taking adherence was significantly greater than in the control arm (odds ratio [OR], 1.66; 95% confidence interval [CI], 1.15-2.39; P=.006).

Immediately following the first intervention visit, timing adherence also improved in the intervention group. Timing adherence was 100% on 73% of days in the intervention arm and 100% on 61% of days in the control arm. The odds of higher timing adherence scores were significantly higher in the intervention arm compared with the control arm (OR, 1.74; 95% CI, 1.21-2.50; P=.003).

In reweighted analyses and after supplementing electronic adherence data with patients’ adherence logs and adjusting for confounders, the results were unchanged.

In analyses of secondary outcomes, there was no difference between the two groups in the standard deviation of tacrolimus trough concentrations. Taking and timing adherence were both high on self-report and did not differ between the groups. There were no graft failures in the overall cohort. There was a nonstatistically significant difference between the groups in acute rejection rates; the rates were numerically...
lower in the intervention group than in the control group. There was no difference in annualized change in estimated glomerular filtration rate during the intervention interval by group. With the exception of cytomegalovirus infection that was higher in the intervention group, there were no differences in rates of adverse events between the groups.

Limitations cited by the authors included the possibility of attention bias due to the longer duration of visits for intervention patients compared with controls, the inability to power the study to access the outcomes of numbers of graft failures and acute rejections, and the possibility that the findings may not be generalizable due to the relatively small proportion of participants who were black (13% in the control arm and 11% in the intervention arm).

In conclusion, the researchers said, “The multicomponent TAKE-IT intervention resulted in significantly better medication adherence than the control condition. Better medication adherence may result in improved graft outcomes, but this will need to be demonstrated in larger studies.”

### Incidence of Post-Transplant De Novo Heart Failure Deceased from 1998 to 2010

Compared with other modes of renal replacement therapy, kidney transplantation offers improved survival and quality of life. However, life expectancy among kidney transplant recipients is lower than that in the general population. Cardiovascular disease is one factor that contributes to the increased rates of mortality in the transplant population; heart failure, myocardial infarction, and stroke occur frequently in the first 3 years post-transplantation. In the first and second years following kidney transplantation, heart failure is the most common primary cardiovascular diagnosis for hospitalized kidney transplant recipients. There is an association between posttransplantation diagnosis of heart failure and reduced graft and patient survival.

Studies conducted among the general population have demonstrated a decrease in the incidence of heart failure during the past two decades. There are few data available in whether a similar trend exists in the kidney transplantation population. Colin R. Lenihan, MB BCh, BAO, PhD, and colleagues conducted a retrospective observational cohort study designed to examine secular trends in the incidence of de novo heart failure following kidney transplantation and the associated mortality between 1998 and 2010. Results of the study were reported in the American Journal of Kidney Diseases [2018;72(2):223-233].

Study participants were adult patients in the US Renal Data System who underwent their first kidney transplantation in the United States between 1998 and 2010. Eligible patients had at least 6 months of continuous Medicare parts A and B coverage prior to transplantation and no prior evidence for a diagnosis of heart failure prior to transplantation.

The outcomes of interest were de novo post-transplantation heart failure defined using diagnosis codes from the International Classification of Diseases, Ninth Revision, and mortality following de novo heart failure diagnosis post-transplantation. Cox proportional hazards analysis was used to examine secular trends in de novo post-kidney transplantation heart failure.

A total of 48,771 patients met eligibility criteria. Between 1998 and 2010, there were increases in age at transplantation, body mass index (BMI), and dialysis vintage in the study population. There were also increases in the prevalence of comorbid conditions at baseline, including diabetes mellitus, coronary artery disease, peripheral arterial disease, and hypertension during the study period.

Of the 48,771 patients, 7269 developed de novo heart failure within the first three years after kidney transplantation. Median time to diagnosis was 0.76 years. Following adjustment for all available demographic data, comorbid conditions, and transplantation characteristics, the risk for developing de novo heart failure in the first 3 years following kidney transplantation was 31% lower for patients who underwent the procedure in 2010 compared with those who underwent transplantation in 1998 (hazard ratio, 0.69; 95% confidence interval, 0.60-0.79).

Results were similar in sensitivity analyses that (1) treated death and graft failure as competing risks, (2) treated death and graft failure as censoring events, (3) treated death as a competing risk and excluded graft failure from the analysis, and (4) treated death as a censoring event and excluded graft failure. In analyses limited to the subgroup of patients who were diagnosed with de novo heart failure, graft failure occurring prior to heart failure diagnosis, defined as post-transplantation return to dialysis or retransplantation, was included as an additional baseline value. There was no temporal trend in the probability of death following a diagnosis of de novo heart failure within 3 years of kidney transplantation during the study period.

When the analyses were limited to complete cases only, results were similar. In a parallel analysis that required 1 year of Medicare parts A and B coverage prior to transplantation (n=47,054), and identification of pre-existing heart failure was limited to medical claims in the year prior to the procedure, the secular trend in de novo post-transplantation heart failure was nearly identical to that of the main analysis.

The relative impact of each individual covariate was assessed using one-at-a-time analysis. The most consistent confounders across the study period for the outcome of de novo post-kidney transplantation heart failure were recipient age, recipient sex, BMI, graft failure, and dialysis vintage. For the outcome of mortality, the most consistent confounders were recipient age, recipient sex, and transplant vintage.

There were some limitations to the study cited by the authors, including the potential for residual confounding from either incorrectly ascertained or unavailable confounders, and including only Medicare beneficiaries in the study population.

“In conclusion, the adjusted incidence of de novo post-kidney transplantation heart failure has declined significantly in the kidney transplantation population in 1998 to 2010. Further studies are required to identify factors contributing to this positive trend,” the researchers said.

### TAKEAWAY POINTS

- Recipients of kidney transplantation have lower life expectancy than the general population. However, there are few data available in whether a similar trend exists in the kidney transplantation population.
- Compared with other modes of renal replacement therapy, kidney transplantation offers improved survival and quality of life. However, life expectancy among kidney transplant recipients is lower than that in the general population. Cardiovascular disease is one factor that contributes to the increased rates of mortality in the transplant population; heart failure, myocardial infarction, and stroke occur frequently in the first 3 years post-transplantation.
- Studies conducted among the general population have demonstrated a decrease in the incidence of heart failure during the past two decades. There are few data available in whether a similar trend exists in the kidney transplantation population.
- Colin R. Lenihan, MB BCh, BAO, PhD, and colleagues conducted a retrospective observational cohort study designed to examine secular trends in the incidence of de novo heart failure following kidney transplantation and the associated mortality between 1998 and 2010. Results of the study were reported in the American Journal of Kidney Diseases [2018;72(2):223-233].
- Study participants were adult patients in the US Renal Data System who underwent their first kidney transplantation in the United States between 1998 and 2010. Eligible patients had at least 6 months of continuous Medicare parts A and B coverage prior to transplantation and no prior evidence for a diagnosis of heart failure prior to transplantation.
- The outcomes of interest were de novo post-transplantation heart failure defined using diagnosis codes from the International Classification of Diseases, Ninth Revision, and mortality following de novo heart failure diagnosis post-transplantation. Cox proportional hazards analysis was used to examine secular trends in de novo post-kidney transplantation heart failure.
- A total of 48,771 patients met eligibility criteria. Between 1998 and 2010, there were increases in age at transplantation, body mass index (BMI), and dialysis vintage in the study population. There were also increases in the prevalence of comorbid conditions at baseline, including diabetes mellitus, coronary artery disease, peripheral arterial disease, and hypertension during the study period.
- Of the 48,771 patients, 7269 developed de novo heart failure within the first three years after kidney transplantation. Median time to diagnosis was 0.76 years. Following adjustment for all available demographic data, comorbid conditions, and transplantation characteristics, the risk for developing de novo heart failure in the first 3 years following kidney transplantation was 31% lower for patients who underwent the procedure in 2010 compared with those who underwent transplantation in 1998 (hazard ratio, 0.69; 95% confidence interval, 0.60-0.79).
- Results were similar in sensitivity analyses that (1) treated death and graft failure as competing risks, (2) treated death and graft failure as censoring events, (3) treated death as a competing risk and excluded graft failure from the analysis, and (4) treated death as a censoring event and excluded graft failure. In analyses limited to the subgroup of patients who were diagnosed with de novo heart failure, graft failure occurring prior to heart failure diagnosis, defined as post-transplantation return to dialysis or retransplantation, was included as an additional baseline value. There was no temporal trend in the probability of death following a diagnosis of de novo heart failure within 3 years of kidney transplantation during the study period.
- When the analyses were limited to complete cases only, results were similar. In a parallel analysis that required 1 year of Medicare parts A and B coverage prior to transplantation (n=47,054), and identification of pre-existing heart failure was limited to medical claims in the year prior to the procedure, the secular trend in de novo post-transplantation heart failure was nearly identical to that of the main analysis.
- The relative impact of each individual covariate was assessed using one-at-a-time analysis. The most consistent confounders across the study period for the outcome of de novo post-kidney transplantation heart failure were recipient age, recipient sex, BMI, graft failure, and dialysis vintage. For the outcome of mortality, the most consistent confounders were recipient age, recipient sex, and transplant vintage.
- There were some limitations to the study cited by the authors, including the potential for residual confounding from either incorrectly ascertained or unavailable confounders, and including only Medicare beneficiaries in the study population.
- “In conclusion, the adjusted incidence of de novo post-kidney transplantation heart failure has declined significantly in the kidney transplantation population in 1998 to 2010. Further studies are required to identify factors contributing to this positive trend,” the researchers said.
Fresenius Awards $100,000 Grant to ANNA in Celebration of Nephrology Nurses Week

In recognition of the 50th anniversary year of the American Nephrology Nurses Association (ANNA) and in honor of Nephrology Nurses Week, September 9-15, Fresenius Medical Care North America awarded a $100,000 grant to ANNA. According to a press release from Fresenius Medical Care North America, the award will be used to “fund an ongoing scholarship program, help increase awareness of the profession, and strengthen engagement with nurses dedicated to caring for patients with chronic kidney disease.”

Franklin Maddux, MD, FACP, chief medical officer and executive vice president for clinical and scientific affairs at Fresenius Medical Care North America, said, “Nephrology nurses provide compassionate, individualized care every day to people living with kidney disease. Nephrology nurses forge deep connections with patients to help them thrive during their dialysis journey, and we are committed to providing the support nurses need to deliver superior patient care every day.”

Lynda Ball, MSN, RN, CNN, president of ANNA, said, “We appreciate this partnership and generous grant from Fresenius Medical Care North America to benefit nephrology nurses who want to continue their nursing education and to support our efforts to reach new nurses about the career opportunities available in nephrology.”

All members of ANNA are eligible for the scholarship. The deadline to apply for scholarships through this grant is March 15, 2019. Winners will be announced in April 2019. For more information, visit annanurse.org/fresenius-scholarships.

Frenova Renal Research Adds Fifth Practice to Site Management Organization

Frenova Renal Research, a division of Fresenius Medical Care North America, has announced the addition of a fifth clinical research site to its Site Management Organization (SMO). The new site is in Baton Rouge, Louisiana. According to a press release, Frenova Renal Research is the “world’s only contract clinical research services provider dedicated exclusively to renal research.”

The Baton Rouge site will bring 6000 patients with chronic kidney disease and 1500 patients with end-stage renal disease in the care of the practice. Three new principal investigators and 10 sub-investigators will be added to the SMO, increasing the ability to quickly enroll patients in renal clinical trials.

Michael W. Roppolo, MD, of Renal Associates of Baton Rouge, LLC, will head the new site. All operational trial activities will be overseen by Frenova, including training and management of Frenova clinical research staff working at the site. Research site protocol adherence, data quality site payment, regulatory obligations to the FDA and Institutional Review Board, drug accountability, and site performance will also be managed by Frenova.

“It is a privilege to be part of Frenova’s growing Site Management Organization, Dr. Roppolo said. “Frenova SMO and the FIRST Up® [Frenova Rapid Start Up] network are improving the health outcomes and quality of life for patients through important clinical research. By allowing Frenova to direct the clinical research staff and trial operations, we can enroll more patients into studies and ultimately help patients by introducing new advances and treatments to the market.”

Kurt Mussina, vice president and general manager, Frenova Renal Research, added, “This important collaboration will bring more patients into our network who are eligible for renal-specific clinical studies, enabling us to support the increasing number of clinical trials seeking to improve the lives of people with renal disease.”

RenalGuard® Reaches Patient Milestone in Europe

In a late-August press release, RenalGuard Solutions™, Inc., announced the treatment of 20,000 patients with RenalGuard® for the prevention of contrast-induced nephropathy, a form of acute kidney injury (AKI) affecting 10% to 20% of patients undergoing imaging procedures that utilize toxic contrast dyes. RenalGuard Solutions is a medical device company that focuses on fluid management technologies for the cardiac and vascular markets.

RenalGuard is currently being used in Europe and in countries that recognize the CE mark. The device manages real-time fluid balance in conjunction with interventional procedures that involve contrast media in at-risk patients undergoing cardiovascu lar imaging procedures. Results of recent studies suggest that RenalGuard protects patients from AKI following catheterization procedures compared with standard of care.

Jim Dillon, chief executive officer at RenalGuard Solutions, said, “We are very pleased by the positive response in the medical community in Europe towards the use of RenalGuard in high-risk patients undergoing cardiovascular procedures. This is a huge milestone for the product, the company, and our patients.”

RenalGuard therapy was demonstrated at the Transcatheter Cardiovascular Therapeutics meeting in San Diego, California, in September.

Novel Kidney Assay May Guide Sepsis Treatment

In preliminary research, an assay from BioMérieux has been shown to detect acute kidney injury (AKI) due to sepsis earlier than the current standard of care. The assay combines the NephroCheck AKI test with a procalcitonin test that may enable physicians to alter treatment before irreversible kidney damage occurs.

The research, presented in a talk sponsored by BioMérieux at the American Association of Clinical Chemistry meeting in August, was conducted by Eric Gluck, MD, a critical care physician at Swedish Covenant Hospital in Chicago. In a press release, Dr. Gluck noted that the standard of care has been to use serum creatinine level as a marker of kidney injury. However, Dr. Gluck said that by the time that particular marker is evident, “the kidney is 80% destroyed. There was nothing you could do at that point in time, so you sort of waited through that storm and hoped that the kidney would regain function eventually if the patient survived.”

NephroCheck measures two proteins present in urine and can indicate whether a patient’s kidney is under stress. Dr. Gluck and colleagues identified 227 patients who had positive procalcitonin tests; of those patients, ~40% had severe sepsis and were further tested using NephroCheck. Of those, 85% had positive values, indicating impending renal failure.

The researchers saw a 30% decrease in the need for dialysis in the patients whose NephroCheck test led to kidney-sparing changes in sepsis treatment. In addition, there was an association between kidney stress in sepsis, indicated by positive procalcitonin and Neph roCheck test results, and a 60% increase in mortality, from 25% with sepsis along to ~35% with sepsis and kidney damage.

Cricket Health Announces Series A Funding Round

In a press release in early September, Cricket Health announced that it closed a Series A funding round of $24 million. Cricket Health is a technology-enabled provider of integrated kidney care. New investors include Oak HC/FT as well as Cigna Corporation, LifeForce Capital, iSeed Ventures, Liquid 2 Ventures, Halle Tecco, and Sami Inkinen. Returning investors include First Round Capital, Box Group, Nexus Ventures, Seven Peaks Ventures, Aberdare Management, and LinkedIn CEO Jeff Weiner.

Arvind Rajan, Cricket Health CEO, said, “Our mission at Cricket is to reduce the burden of kidney disease and put patients back in control of their lives with care that is cost-effective, keeps them healthy, and gives them hope for the future. This funding
News Briefs

will help us provide better care to millions of Americans facing kidney disease.”

The Series A funding will be used to help Cricket Health expand its programs and its clinical footprint, including the ongoing development of care management for patients with end-stage renal disease to delay the need for dialysis, and the creation of new home dialysis and in-center programs.

Nancy Brown, a partner at Oak HC/FT, said, “Cricket Health has the approach, technology, and leadership to transform [the kidney care] industry, improve the quality of care, and bring down costs. We are excited to support their innovation and growth.”

Outset Medical Announces Financing for Tablo® System

Outset Medical has announced it raised $132 million in a Series D equity financing. According to a press release from Outset Medical, the round was led by new investor Mubadala Investment Company, an investment company in Abu Dhabi. Also participating in the equity round were the venture capital arm of Baxter International, Fidelity Management and Research Company, Partner Fund Management LP, Perceptive Advisors, funds advised by T. Rowe Price Associates, Inc., and Warburg Pincus.

Outset Medical will use the financing to increase production capabilities and accelerate commercial expansion of its Tablo® Hemodialysis System in acute and chronic care markets in the United States. Tablo is designed to reduce the cost and complexity of dialysis, expanding how, when, and where dialysis can be provided.

Camilla Macapili Languille, senior vice president of Pharma & Medtech at Mubadala, said, “Our investment in Outset Medical represents an exciting opportunity for Mubadala, as it is aligned with our goal of improving people’s lives while meeting a major global market need. We selected Outset Medical as our first US private medtech investment because of Tablo’s ability to significantly improve global dialysis care and address one of the biggest areas of worldwide healthcare spend with very disruptive and innovative technology.”

Outset Medical designed Tablo to “transform [the] large, but stagnant, dialysis landscape,” the press release said. Tablo delivers real-time water purification and dialysis fluid production integrated in a single, compact system.

Leslie Trigg, chief executive officer at Outset Medical, said, “Tablo offers patients and healthcare providers a new option for more flexible and convenient dialysis treatment, improving the dialysis experience while at the same time reducing overall dialysis spend. We are grateful to our investors for the opportunity to significantly impact the future of dialysis care.”

The Tablo system is CE-marked and FDA-cleared for use in acute and chronic care settings. The company is currently conducting a clinical trial to expand the labeled indication of Tablo to include home use.

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ClearGuard® HD Caps are the first and only device cleared for sale in the US that kills infection-causing bacteria inside a long-term hemodialysis catheter hub. New and now available, ClearGuard HD caps are used in place of a standard cap.

Multiple large, prospective, randomized, multicenter trials demonstrated the superiority of ClearGuard HD caps in reducing bloodstream infections vs. commonly used caps.

ClearGuard® HD Caps are the first and only device cleared for sale in the US that kills infection-causing bacteria inside a long-term hemodialysis catheter hub. New and now available, ClearGuard HD caps are used in place of a standard cap.

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info@pursuitvascular.com
www.clearguardhd.com

2018-08 ML-0017 Rev A


The ClearGuard HD Antimicrobial Barrier Cap has been shown to be effective at reducing microbial colonization in hemodialysis catheter hubs and to reduce the incidence of CLABSI in hemodialysis patients with catheters. See the Instructions for Use for full indications. Rx Only.
Abstract Roundup

**ACUTE KIDNEY INJURY**

Liver Transplant Outcomes Worsen with AKI

*Journal of Intensive Care Medicine*
doi.org/10.1177/0885066618790558

Both prior to and following liver transplant, the development of acute kidney injury (AKI) in the setting of liver disease is a significant event. AKI may be the cause of worse outcomes or may merely be associated with worse outcomes; the occurrence of renal failure affects prognosis as well as diagnosis and therapeutics. According to Jeffrey DallaVolpe, MD, MPH, and colleagues, there are some etiologies that are correctable, including hypovolemia, nephrotoxic medications, and acute tubular necrosis. In the period following liver transplantation, AKI is associated with graft failure and overall worse outcomes. “Prompt recognition, workup, and intervention can significantly impact outcomes and survival both before and after liver transplant,” the researchers said.

**CHRONIC KIDNEY DISEASE**

Estimating Glomerular Filtration Rate: Beyond Creatinine and Cystatin C

*Current Opinion in Nephrology and Hypertension* doi:10.1097/MNH.0000000000000444

Reduced glomerular filtration rate (GFR) is associated with increased risk for numerous adverse outcomes. Equations used to estimate GFR use serum concentrations of creatinine and cystatin C to facilitate the assessment of kidney function. However, according to Dominik Steubl, MD, and Lesley A. Inker, MD, MS, current equations are less than optimal in some clinical settings. The researchers prepared a review that focused on approaches to improve the estimation of GFR.

In populations where creatinine or cystatin C measurements are inaccurate, low molecular weight proteins such as b-trace-protein and b-2 microglobulin, as well as newly discovered metabolites, have shown promise as filtration markers. Drs. Steubl and Inker hypothesized that the combination of multiple novel markers, either alone or in combination with creatinine, cystatin C, or demographics, may improve estimation of GFR.

They added, “Current GFR estimating equations are an essential part of routine clinical practice but have limitations. The use of multiple markers combined in a single equation appears to be the most promising approach. Future research is required to validate proposed equations in diverse populations.”

Survival Improved with Dialysis Initiation at Higher Levels of Kidney Function

*Journal of the American Society of Nephrology* 2018;29(8):2169-2177

Patient selection and optimal timing of initiation of dialysis among older adults with chronic kidney disease are not well defined. Manjula Kurella Tamura, MD, and colleagues conduct-

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**IMPORTANT SAFETY INFORMATION**

**CONTRAINDICATION:** AURYXIA® (feric citrate) is contraindicated in patients with iron overload syndromes.

**WARNINGS AND PRECAUTIONS:**

- **Iron Overload:** Monitor ferritin and transferrin saturation (TSAT). Patients may require a reduction in dose or discontinuation of concomitant intravenous (IV) iron.
- **Risk of Overdosage in Children Due to Accidental Ingestion:** Accidental ingestion and resulting overdose of iron-containing products is a leading cause of fatal poisoning in children under 6 years of age. Advise patients to keep AURYXIA out of the reach of children.

**PREGNANCY AND LACTATION:** Overdosing of iron in pregnant women may carry a risk for spontaneous abortion, gestational diabetes and fetal malformation. Rat studies have shown the transfer of iron into milk. There is possible infant exposure when AURYXIA is taken by a nursing woman.

**ADVERSE REACTIONS:** In clinical trials, likely adverse reactions occurring in >5% of patients treated with AURYXIA were discoloration of feces, diarrhea, constipation, nausea, vomiting, cough, abdominal pain and hyperkalemia.

To report suspected adverse reactions, contact Keryx Biopharmaceuticals at 1-844-445-3799

**FOR MORE INFORMATION, VISIT AURYXIA.COM**

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ed a study to examine the association between dialysis versus medical management and survival at varying ages and levels of kidney function. Data from a nationally representative 20% sample of US veterans with estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m² between 2005 and 2010 were utilized for the analysis; follow-up continued through 2012. The study population included 73,349 individuals. An extended Cox model was used to determine associations among the time-varying exposures, age, and provision of dialysis with survival. Over a mean follow-up of 3.4 years, 15.5% of patients initiated dialysis and 52% died. There was variation by age in the eGFR at which dialysis, compared with medical management,
Auryxia© (feric citrate) tablets
AURYXIA® (feric citrate) tablets for oral use containing 210 mg of feric iron equivalent to 1 g AURYXIA® for oral use.

INDICATION AND USAGE
AURYXIA is indicated for the treatment of iron deficiency anemia in adult patients with chronic kidney disease not on dialysis.

CONTRAINDICATIONS
AURYXIA is contraindicated in patients with iron overload syndrome (e.g., hereditary hemochromatosis).

WARNINGS AND PRECAUTIONS
Iron Overload: Iron absorption from AURYXIA may lead to excessive elevations in iron stores. Increased serum ferritin and transferrin saturation (TSAT) levels were observed in clinical trials. In a 56-week safety and efficacy trial evaluating the control of serum phosphate levels in patients with chronic kidney disease on dialysis in which concomitant use of intravenous iron was permitted, 6% of patients treated with AURYXIA had a ferritin level >1500 ng/mL, as compared with 13% of patients treated with active control. Assess iron parameters (e.g., serum ferritin and TSAT) prior to initiating AURYXIA, and monitor iron parameters while on therapy. Patients receiving intravenous iron may require a reduction in dose or discontinuation of intravenous iron therapy.

Risk of Overdose in Children Due to Accidental Ingestion: Accidental ingestion and resulting overdose of non-containing products is a leading cause of fatal poisoning in children under 6 years of age. Advise patients of the risks to children and to keep AURYXIA out of the reach of children.

ADVERSE REACTIONS
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 adverse reaction rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Iron Deficiency Anemia in Chronic Kidney Disease Not on Dialysis
Across two trials, 190 unique patients with chronic kidney disease (CKD-NDD) were treated with AURYXIA. This included a study of 117 patients treated with AURYXIA and 116 patients treated with placebo in a 16-week, randomized, double-blind trial and a study of 75 patients treated with AURYXIA and 73 treated with placebo in a 12-week randomized double-blind period. Dosage regimens in these trials ranged from 210 mg to 2,520 mg of feric iron per day, equivalent to 1 to 12 tablets of AURYXIA.

Adverse reactions reported in at least 5% of patients treated with AURYXIA in these trials are listed in Table 1.

Table 1: Adverse Reactions Reported in Two Clinical Trials in at least 5% of patients receiving AURYXIA

<table>
<thead>
<tr>
<th>Body System</th>
<th>Adverse Reaction</th>
<th>AURYXIA % (N=190)</th>
<th>Placebo % (N=188)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any Adverse Reaction</td>
<td>75</td>
<td>62</td>
<td></td>
</tr>
<tr>
<td>Metabolism and Nutrition Disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperkalemia</td>
<td>5</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal Disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>21</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>Constipation</td>
<td>18</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>10</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Abdominal Pain</td>
<td>5</td>
<td>2</td>
<td></td>
</tr>
</tbody>
</table>

During the 16-week, placebo-control trial, 12 patients (10%) on AURYXIA discontinued study drug because of an adverse reaction, as compared to 10 patients (8%) in the placebo control arm. Diarrhea was the most common adverse reaction leading to discontinuation of AURYXIA (2.4%).

DRUG INTERACTIONS
Orally administered doxycycline has to be taken at least 1 hour before AURYXIA. Orally administered cephradine should be taken at least 2 hours before or after AURYXIA. Oral drugs that can be administered concomitantly with AURYXIA are: amiodarone, aspirin, atorvastatin, calcitrol, ciclosporin, digoxin, diltiazem, doxazosin, enalapril, fluvastatin, glibenclamide, levofloxacain, losartan, metoprolol, pravastatin, propranolol, steglatin, and warfarin.

Oral medications not listed above

There are no empirical data on avoiding drug interactions between AURYXIA and most concomitant oral drugs. For oral medications where a reduction in the bioavailability of that medication would have a clinically significant effect on its safety or efficacy, consider separation of the timing of the administration of the two drugs. The duration of separation depends upon the absorption characteristics of the medication concomitantly administered, such as the time to reach peak systemic levels and whether the drug is an immediate release or an extended release product. Consider monitoring clinical responses or blood levels of concomitant medications that have a narrow therapeutic range.

USE IN SPECIFIC POPULATIONS

Pregnancy: Risk Summary
There are no available data on AURYXIA use in pregnant women to inform a drug-associated risk of major birth defects and miscarriage. Animal reproduction studies have not been conducted using AURYXIA. Skeletal and encephalic malformation was observed in neonatal mice when ferric gluconate was administered intraperitoneally to gravid dams on gestation days 7-9. However, oral administration of other ferric or ferrous compounds to gravid CD1 mice and Wistar-rats caused no fetal malformation. An overdose of iron in pregnant women may carry a risk for spontaneous abortion, gestational diabetes and fetal malformation.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. Advise pregnant women to avoid AURYXIA use in pregnancy and to stop therapy at the time of a positive pregnancy test if AURYXIA use is not essential.

The estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies are 2 to 4% and 15% to 20% respectively.

Clinical Considerations
The effect of AURYXIA on the absorption of vitamins and other nutrients has not been studied in pregnant women. Requirements for vitamins and other nutrients are increased in pregnancy.

Lactation: Risk Summary
There are no human data regarding the effect of AURYXIA in human milk, the effects on the breastfed child, or the effects on milk production. Data from rat studies have shown the transfer of iron into milk by disalyn metal transport protein (DMT-1) and ferropontin-1 (FPN-1). Hence, there is a possibility of infant exposure when AURYXIA is administered to a nursing woman. The development and health benefits of breastfeeding should be considered along with the mother’s clinical need for AURYXIA and any potential adverse effects on the breastfed child from AURYXIA or from the underlying maternal condition.

Pediatric Use: Safety and efficacy of AURYXIA have not been established in pediatric patients.

Geriatric Use: Clinical studies of AURYXIA included 292 subjects aged 65 years and older (104 subjects aged 75 years and older). Overall, the clinical study experience has not identified any obvious differences in responses between the elderly and younger patients in the tolerability or efficacy of AURYXIA.

OVERDOSAGE
No data are available regarding overdose of AURYXIA in patients. In patients with chronic kidney disease, the maximum dose studied was 2,520 mg ferric iron (12 tablets of AURYXIA) per day. Iron absorption from AURYXIA may lead to excessive elevations in iron stores, especially when concomitant intravenous iron is used.

In clinical trials, one case of elevated iron in the liver as confirmed by biopsy was observed in a patient on dialysis administered 4 g iron and AURYXIA.

PATIENT COUNSELING INFORMATION

Dosing Recommendations: Instruct patients to take AURYXIA as directed with meals and to avoid their prescribed diet. Instruct patients on concomitant medications that should be dosed apart from AURYXIA. Advise patients not to chew or crush AURYXIA because tablets may cause discoloration of mouth and teeth.

Adverse Reactions: Advise patients that AURYXIA may cause dark (black) stools, but this staining of the stool is considered normal with oral ingestion by a child. Discoloration of mouth and teeth.

AURYXIA may cause diarrhea, nausea, constipation, vomiting, hyperkalemia, abdominal pain, and cough. Advise patients to report severe or persistent gastrointestinal symptoms to their physician.

Advisement: Advise patients to keep this product out of the reach of children and to seek immediate medical attention in case of accidental ingestion by a child.

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Abstract Roundup
continued from page 27

was associated with lower mortality (P <0.01). For those aged <65, 65-74, 85-84, and 85 years, dialysis was associated with lower mortality for those with eGFR not exceeding 6 to 9, 6, 9 to 12, and 9 to 12 mL/min/1.73 m², respectively.

There was an association between dialysis initiation at eGFR <6 mL/min/1.73 m² and a higher median life expectancy of 26, 25, and 19 months for patients aged 65, 75, and 85 years, respectively. When dialysis was initiated at eGFR <9.12 mL/min/1.73 m², the estimated difference in median life expectancy was <1 year in this patient population.

“Provision of dialysis at higher levels of kidney function may extend survival for some older patients,” the researchers said.

DIALYSIS
Use of Phosphate-Binders Lowers Risk of Infection-Related Mortality
Scientific Reports doi:10.1038/s41598-018-2957-0

Treatment with phosphate binders in patients on hemodialysis allows for increased protein intake, thus helping patients maintain good nutritional status. The risk of infection-related death is increased in patients with protein-energy-malnutrition. There are few data available on the association between phosphate binder use and the relative risks of infection-related death. Shunsuke Yamada, MD, PhD, and colleagues conducted an analysis of data from 2925 patients registered to the Q-Cohort Study. During the 4-year follow-up period, 106 patients died of infection-related causes and 492 patients died of any cause. The incidence of infection-related death was significantly lower in patients with phosphate-binder use compared with those without phosphate-binder use (hazard ratio for infection-related mortality, 0.63; 95% confidence interval, 0.40-0.99). Following application of four different propensity score-based analyses, the results remained significant. Use of phosphate-binders was also associated with lower risk of all-cause mortality.

According to the researchers, “Further studies including randomized controlled clinical trials and observation studies analyzed by an instrumental variable model will provide more robust evidences for the associations observed in our study.”

Burnt-Out Diabetes Phenomenon In Patients on Peritoneal Dialysis
Diabetes Research and Clinical Practice. doi.org/10.1016/j.diabres.2018.07.026

A phenomenon known as burnt-out diabetes is defined as spontaneous improvement in glycemic control, resulting in normal levels of hemoglobin A1c (HbA1c). It is thought that glycated albumin may be a better indicator of glycemic control than HbA1c in hemodialysis patients; this has not been studied in patients receiving peritoneal dialysis.
Masanori Abe, MD, PhD, and colleagues conducted a study involving patients on peritoneal dialysis with available data on HbA1c level and antidiabetes therapy. The study had two cohorts: (1) those with HbA1c measurements alone and (2) subsequently those with both HbA1c and glycated albumin measurements. The burn-out diabetes phenomenon was assessed in both cohorts.

There were 1296 patients in the HbA1c cohort; when burn-out diabetes was defined as HbA1c <6.0% without treatment, it was found in 269 patients (20.8%). When 413 patients were added subsequently to the second cohort, burn-out diabetes was found in 73 patients (17.7%). When burn-out diabetes was defined as HbA1c <6.0% and glycated albumin <16.0% without treatment, burn-out diabetes was observed in 45 patients (10.9%).

In summary the researchers said, “Although the burn-out diabetes phenomenon was present in 17.7% of patients with diabetes on peritoneal dialysis based on HbA1c, the rate was significantly decreased to 10.9% when taking glycated albumin into account.”

**Vitamin D Lowers Risk of Infection in Dialysis Patients**

Patients with end-stage renal disease (ESRD) receiving maintenance dialysis are at increased risk for infections, some of which can be fatal. There have been conflicting results from recent studies examining the association between infection and vitamin D status or use of vitamin D; data on the association in patients undergoing long-term dialysis are limited.

Guobin Su, MD, and colleagues conducted a systematic review and meta-analysis on vitamin D deficiency and treatment versus the risk of infection in that patient population. PubMed, Web of Science, Cochrane Library, Embase, and three Chinese databases were searched from inception until December 2017.

Search criteria were for interventional controlled trials (randomized and non-randomized), cohort studies, and case-control studies on levels of serum 25-hydroxyvitamin D (25(OH)D), or use of vitamin D (supplemental nutritional vitamin D or vitamin D receptor activator [VDRA]); and infection in long-term dialysis patients. Infection included any infection, infection-required hospitalization, infection-related death, or composite. The meta-analysis examined the relative risk (RR) of infection and level of 25(OH)D or use of vitamin D.

The search revealed 2440 reports. Of those, 17 studies met inclusion criteria; all were of moderate quality. Six cohort studies examined serum concentrations of 25(OH)D and 11 (2 randomized controlled trials and nine observational studies) assessed the use of vitamin D.

In individuals with high or normal levels of 25(OH)D, the risk of composite infection was 39% lower compared with those with low levels (RR, 0.61; 95% confidence interval [CI], 0.41-0.9). The pooled adjusted risk for composite infection was 41% lower in those who used vitamin D compared with those who did not use vitamin D (RR, 0.59; 95% CI, 0.43-0.81).

In conclusion, the researchers said, “High or normal serum levels of 25(OH)D and the use of vitamin D, particularly VDRA, were each associated with a lower risk of composite infection in long-term dialysis patients.”

**Hemodialysis versus Conservative Medical Management for Elderly Patients with ESRD**

Jeffrey Perl, MD, and colleagues recently conducted a study to estimate the prevalence and incidence of end-stage renal disease requiring maintenance dialysis (ESRD-D) among immigrants in Ontario, Canada. Using administrative health and immigration datasets, the researchers categorized adults residing in Ontario in 2014 as long-term Canadian residents or immigrants. ESRD-D prevalence among those adults was determined and age-adjusted prevalence ratios (PRs) comparing immigrants to long-term residents were calculated. Among individuals who immigrated to Ontario between 1990 and 2012, age-adjusted incidence of ESRD-D was calculated by world region and country of birth; immigrants from Western nations were the referent group.

Of 1,902,394 immigrants, 0.09% (n=1700) presented with ESRD-D; among 8,860,283 long-term residents, 0.10% (n=8909) did so. Following adjustment for age, the prevalence of ESRD-D was higher among immigrants from sub-Saharan Africa (PR, 2.17; 95% confidence interval [CI], 1.84-2.57), Latin America and the Caribbean (PR, 2.11; 95% CI, 1.90-2.34), South Asia (PR, 1.45; 95% CI, 1.32-1.59) and East Asia and the Pacific (PR, 1.34; 95% CI, 1.22-1.46).

The highest age-adjusted ESRD-D PRs relative to long-term residents were seen in immigrants from Somalia (PR, 4.18; 95% CI, 3.11-5.61), Trinidad and Tobago (PR, 2.88; 95% CI, 2.23-3.73), Jamaica (PR, 2.88; 95% CI, 2.40-3.44), Sudan (PR, 2.84; 95% CI, 1.53-5.27), and Guyana (PR, 2.69; 95% CI, 2.19-3.29). Immigrants from those countries also had higher incidence of age-adjusted ESRD-D compared with immigrants from Western nations.

In conclusion, the researchers said, “Among immigrants in Canada, those from sub-Saharan Africa and the Caribbean have the highest ESRD-D risk. Tailored kidney-protective interventions should be developed for these susceptible populations.”
MS’s Patients Over Paperwork (POP) initiative signals welcome relief from decades of increasingly oppressive documentation requirements. While the proposed changes to evaluation and management services (E&M) coding levels have grabbed headlines due to concerns about possible reduced reimbursement, there is great value in allowing providers to focus more on patient care and less on documentation.

For years providers have complained about the hoops they must jump through to be properly reimbursed for their services. Providers spend an inordinate amount of time documenting their services to satisfy payer and government agency regulatory requirements. The steady increase in the amount of required documentation has come at the same time reimbursement for services has declined.

The creation of electronic health records (EHRs) allowed providers to capture, organize, and manipulate data in ways not possible before, but many providers still report it takes them longer to document a visit in an EHR than on paper. EHR companies provided documentation and coding tools to help providers shorten the amount of time spent on documentation, but the temptation to improperly use shortcuts, e.g., cutting and pasting, have resulted in multitudes of providers being denied reimbursement for services genuinely rendered.

Medicare contractors and EHR companies have created coding assist tools to help providers code properly. However, when using these tools it is surprisingly easy for a Level 4 visit to be coded as a Level 2 because the provider forgot to include a seemingly small item in their visit record. When two providers perform the same service and one is paid at a Level 4 and the other at a Level 2 simply because one did not think to check a single box out of many choices, something is wrong with the system. Simplifying E&M coding to two levels, one for the most basic services and one for everything else, makes a lot of sense to me. The documentation requirements for the higher of the two levels are dramatically reduced from what they are currently.

Reduced documentation requirements would benefit providers in several important ways. First, the excessive amount of time currently required to completely document each patient encounter would be greatly reduced. Second, much less coding and documentation training and retraining would be required. Third, fewer providers would face losing their reimbursement due to technicalities. Fourth, providers would spend less time and money on audits and appeals. In short, providers would spend less time on documentation and administration and more time focused on patient care.

Regarding the potential drop in reimbursement for some providers, the big question is whether lower costs associated with reduced documentation would offset a potential drop. In addition to looking at actual dollars saved, providers should consider how their individual time and quality of life would be affected. Also, if less time were spent on documentation, would there be time to see additional patients, thus generating additional reimbursement not possible under the current requirements?

In visiting with renal providers, a number have expressed great frustration with current coding and documentation requirements. Many face increasing pressure from payers who target nephrologists as coding too high compared with other providers, even other nephrologists. Payers may demand extensive supporting documentation for past visits. Depending on what payers find when they review the documentation, they may recoup money previously paid for all or part of the provider’s services.

The pressure applied by payers to bill with lower coding levels has frightened a number of nephrologists into coding at more “safe” levels, such as a Level 3, even though they believe their documentation supports a higher level. When nephrologists pursue this safe course, it lends credence to the payers notifying other nephrologists that their coding levels are higher than other nephrologists. Providers with higher coding levels draw the attention of payers and these providers, even if they are coding correctly, are required to spend a considerable amount of time and labor submitting documentation to support their coding. Reimbursement can be delayed or recouped and some providers determine it is not worth the fight so they begin coding at lower levels. The proposal to reduce the number of E&M levels to two would likely curtail or possibly eliminate this problem with payers. That, in and of itself, would be worth a lot.

Rick Collins is the director of business development for Sceptre Management Solutions, LLC, a company specializing in billing for outpatient ESRD facilities, nephrology practices, and vascular access. Your questions are welcome and he can be reached at rcollins@sceptremanagement.com or 801.775.8010.
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The PRISMAFLEX System is one of the best tools we’ve used in our ICU. And with Baxter’s support, we can do so much for our patients now that we’ve implemented our Super User Program and CRRT Task Force.”

Juan Carlos Aycinena, MD

Dr. Aycinena dedicated himself to becoming a nephrologist because he wanted to be able to offer hope to the sickest patients. In the past 4 years that he has been using the PRISMAFLEX System, he feels like his team has been able to do so much more for those patients, especially since implementing a CRRT Task Force. Including Baxter on that Task Force was an important decision and just one example of how we are always striving to partner with our customers. Baxter is committed to supporting Dr. Aycinena and his team as they continue to optimize their CRRT program.

Watch Dr. Aycinena’s story at renalacute.com/stories

The PRISMAFLEX Control Unit is intended for:
Continuous Renal Replacement Therapy (CRRT) for patients weighing 20 kilograms or more with acute renal failure and/or fluid overload.
Therapeutic Plasma Exchange (TPE) therapy for patients weighing 20 kilograms or more with diseases where fluid removal of plasma components is indicated.

Rx Only. For safe and proper use of this device, refer to the Operator’s Manual.