Outcomes of Left Ventricular Assist Device Placement in Patients with ESRD

For patients with advanced heart failure, left ventricular assist devices (LVADs) are used as a bridge to heart transplant as well as destination therapy to prolong survival and improve quality of life. In results of the REMATCH (Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure) trial, compared with medical therapy alone, survival was improved with placement of an LVAD. The US FDA approved the use of LVADs as destination therapy for patients with advanced heart failure in 2008, creating a pathway for expansion of the use of these devices.

In patients with end-stage renal disease (ESRD), the prevalence of heart failure is ~40%; 37% of patients with ESRD die from heart failure. There are few data available on outcomes among recipients of LVADs with kidney disease; those studies that have been conducted focused on patients with early stages of kidney disease, including those not receiving maintenance dialysis and on patients with acute kidney injury (AKI); patients with ESRD have not been well represented in these trials.

Nisha Bansal, MD, and colleagues recently conducted a trial designed to compare national trends in the utilization and outcomes following LVAD placement among patients with ESRD with those in patients without ESRD. Results were reported online.

AKI and Increased Risk of Heart Failure in Hospitalized US Veterans

The incidence of acute kidney injury (AKI) in the US population is increasing. AKI is associated with poor long-term outcomes such as the development of chronic kidney disease (CKD) and death. There may also be an association between AKI and subsequent atherosclerotic cardiovascular disease.

Patients with CKD commonly develop heart failure as a manifestation of cardiovascular disease; in patients with CKD, the risk for heart failure is 3-fold greater than in patients without CKD. The mechanisms that link kidney disease and heart failure may also exist or become accelerated in the setting of AKI.

According to Misha Bansal, MD, and colleagues, it is unclear whether there is an association between AKI and subsequent incident heart failure. The researchers

Incident Atrial Fibrillation Increases Risk of Adverse Events in Patients with Decreased eGFR

Chronic kidney disease (CKD), a common medical problem with a high disease burden, is associated with increased risk for hospitalization, adverse cardiovascular outcomes, and death. The increased risks for adverse cardiovascular outcomes include an increase in the risk for atrial fibrillation (AF). Worldwide, AF affects approximately 33 million people and is the most common arrhythmia. The incidence of AF continues to increase, negatively affecting quality of life and creating increases in healthcare costs.

The development of cardioembolic stroke is common among patients with AF, and there are evidence-based guidelines in use for therapeutic interventions among patients with no CKD. AF is also associated with increased risk for other cardiovascular outcomes including congestive heart failure (CHF) and myocardial infarction (MI); AF is also associated with the development of CKD.

Earlier studies of AF have focused on patients with end-stage kidney disease (ESRD), a population with an increased incidence of AF and the associated risk for adverse outcomes. David Massicotte-Azarniouch, MD, and colleagues
Parsabiv™ —
the control of calcimimetic delivery you’ve always wanted,
the sustained lowering of sHPT lab values your patients deserve

Parsabiv™ gives you the ability to control calcimimetic administration at the end of hemodialysis. Lower and maintain PTH, phosphate, and corrected calcium levels with the first and only IV calcimimetic. With Parsabiv™, calcimimetic control of delivery is in your hands.

Not an actual Parsabiv™ vial.
The displayed vial is for illustrative purposes only.

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.

IV = intravenous; sHPT = secondary hyperparathyroidism; PTH = parathyroid hormone.

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

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Visit ParsabivHCP.com for more information.
Please see package insert for full prescribing information.

INDICATIONS AND USAGE
PARSABIV 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 chronic kidney disease who are not on hemodialysis and is not recommended for use in these populations.

CONTRAINDICATIONS
Hypersensitivity
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 with PARSABIV (see Adverse Reactions (6.1) in PARSABIV full prescribing information).

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). 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 steroid or increases in dialysate calcium concentration). PARSABIV dose reduction or discontinuation of PARSABIV may be necessary (see Dosage and Administration (2.2.6) in PARSABIV full prescribing information).

Worsening Heart Failure
In clinical studies with PARSABIV cases of hypertension, 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 steroid 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, 26% 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>

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

Asymptomatic reductions in corrected serum calcium between 7.5 and < 8.3 mg/dL (that required medical management)

• 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 hypesthesia
Pregnancy

Risk Summary

There are no available data on the use of PARSABIV in pregnant women. In animal reproduction studies, effects were seen at doses associated with maternal toxicity that included hypocalcemia. In a pre- and post-natal study in rats administered etelcalcetide during organogenesis through delivery and weaning, there was a slight increase in perinatal pup mortality, delay in parturition, and transient effects on pup growth at exposures 1.6 times the human exposure for the clinical dose of 15 mg three times per week. There was no effect on sexual maturation, neurobehavioral, or reproductive function in the rat offspring. In embryo-fetal studies, when rats and rabbits were administered etelcalcetide during organogenesis, reduced fetal growth was observed at exposures 2.7 and 7 fold clinical exposures, respectively, there was reduced fetal growth associated with maternal toxicities of hypocalcemia, tremoring, and reductions in body weight and food consumption. In a pre- and post-natal development study in Sprague-Dawley rats administered etelcalcetide at 0.75, 1.5, and 3 mg/kg/day by the intravenous route (gestation day 7 to lactation day 20), there was a slight increase in perinatal pup mortality, delay in parturition, and transient reductions in post-natal growth at 3 mg/kg/day (representing 1.8-fold human exposures at the clinical dose of 15 mg three times per week based on AUC), associated with maternal toxicities of hypocalcemia, tremoring, and reductions in body weight and food consumption. There were no effects on sexual maturation, neurobehavioral, or reproductive function at up to 3 mg/kg/day, representing exposures up to 1.8-fold human exposure based on AUC.

Lactation

Risk Summary

There are no data regarding the presence of PARSABIV in human milk or effects on the breastfed infant or on milk production. Studies in rats showed [14C]-etelcalcetide was present in the milk at concentrations similar to plasma. Because of the potential for PARSABIV to cause adverse effects in breastfed infants including hypocalcemia, advise women that use of PARSABIV is not recommended while breastfeeding.

Data

Animal Data

There were no effects on embryo-fetal development in Sprague-Dawley rats when etelcalcetide was dosed at 0.75, 1.5, and 3 mg/kg/day by the intravenous route during organogenesis (pre-mating to gestation day 17) at exposures up to 1.8 times human exposures at the clinical dose of 15 mg three times per week based on AUC. No effects on embryo-fetal development were observed in New Zealand White rabbits at doses of etelcalcetide of 0.375, 0.75, and 1.5 mg/kg/day by the intravenous route (gestation day 7 to 19), representing up to 4.3 times human exposures based on AUC. In separate studies at higher doses of 4.5 mg/kg in rats (gestation days 6 to 17) and 2.25 mg/kg in rabbits (gestation days 7 to 20), representing 2.7 and 7 fold clinical exposures, respectively, there was reduced fetal growth associated with maternal toxicities of hypocalcemia, tremoring, and reductions in body weight and food consumption. In a pre- and post-natal development study in Sprague-Dawley rats administered etelcalcetide at 0.75, 1.5, and 3 mg/kg/day by the intravenous route (gestation day 7 to lactation day 20), there was a slight increase in perinatal pup mortality, delay in parturition, and transient reductions in post-natal growth at 3 mg/kg/day (representing 1.8-fold human exposures at the clinical dose of 15 mg three times per week based on AUC), associated with maternal toxicities of hypocalcemia, tremoring, and reductions in body weight and food consumption. There were no effects on sexual maturation, neurobehavioral, or reproductive function at up to 3 mg/kg/day, representing exposures up to 1.8-fold human exposure based on AUC.

OVERDOSAGE

There is no clinical experience with PARSABIV overdose. Overdose of PARSABIV may lead to hypocalcemia with or without clinical symptoms and may require treatment. Although PARSABIV is cleared by dialysis, hemodialysis has not been studied as a treatment for PARSABIV overdose. In the event of overdose, corrected serum calcium should be checked and patients should be monitored for symptoms of hypocalcemia, and appropriate measures should be taken (see Warnings and Precautions (5.1) in PARSABIV full prescribing information).
Ironically, the request from the editorial staff for 250 to 500 words coincides with day five of our electronic records being disabled. We have been informed that a “ransomware attack” has forced our service provider to block access to our digital records in the name of privacy and security. Unable to get medication lists, labs, and radiologic data, I have been forced to look my patients in the eye when I take their history and actually show empathy rather than a pathologic obsession with completing the chart.

Obvious challenges aside, I have found it refreshing to get back to the basic tasks of being a physician. Simply, to provide concerned and compassionate care for my patients. I have found that a similar ethos applies to the weekly evaluation of our ESRD population. Required to see the dialysis patients weekly in order to maximize reimbursement, it is often difficult to discuss the same health issues repeatedly. I sometimes find that a discussion about sports, politics, or family issues is much more rewarding for myself and the patient, rather than repeated admonitions about the risks associated with hyperphosphatemia.

I have surveyed my patients on numerous occasions and most of them are of the false assumption that electronic records are immediately transferred to their other care providers once I have signed out of the encounter. They have been led to believe that digitalization of patient visits was established to improve quality rather than limit reimbursement. I am sure they would be equally surprised to understand that, for the most part, the only discernible and useful parts of an encounter is that which is free texted or dictated. This is particularly striking with the required four monthly dialysis visits when I am completely unable to follow an established patient narrative because the electronic record is indecipherable.

I won’t appeal to you to spend more time connecting with your patients. I am painfully aware that we would all like nothing more. It continues to be our main reason for going to work every day and unfortunately has become more and more difficult given our constraints. I do ask that we use our limited time more constructively so that while we are imparting our vast experience, we also understand that our patients are more than a dry weight, crit line, or maturing AV access. When I spend the next three nights trying to recreate the records that I manually scribed rather than watching the Flyers game, I will be grateful for computer viruses.
The study cohort included 6,390,410 adult patient hospitalizations in 116 Veterans Affairs hospitals from January 1, 2002, through December 31, 2013. To allow for 2 years of data collection prior to the index hospitalization to define baseline covariates and allow 2 years of follow-up time following the index hospitalization, the current analysis included 4,970,665 patients ≥18 years of age with qualifying hospitalizations after January 1, 2004, through December 31, 2011.

Overall, the associations of AKI with risk for incident heart failure were consistent across subgroups by age, race, diabetes, coronary artery disease, and baseline eGFR category.

The primary exposure was the first AKI event during the index hospitalization. AKI was determined using creatinine laboratory value data and dialysis procedure codes collected during the index hospitalization. The primary predictor of AKI at any stage was defined based on the Kidney Disease: Improving Global Outcomes creatinine-based staging criteria. Incident heart failure was defined as either (1) hospitalization occurring after the index hospitalization with the appropriate validated primary or secondary International Classification of Diseases-Ninth Revision (ICD-9) codes or (2) two or more outpatient visits occurring after the index hospitalization with the heart failure ICD-9 codes (the second visit was then assigned the heart failure date for the analysis).

Following application of inclusion and exclusion criteria, 1,210,145 patients were eligible for the study. Median age was 62 years, 5% were women, 19% were African-American, and median estimated glomerular filtration rate (eGFR) was 76 mL/min/1.73 m². Patients who developed AKI were more likely to be older, be African-American, use either diuretics or renin angiotensin aldosterone system inhibitors prior to admission, have diabetes, have hypertension, and have sepsis during the index hospitalization. Among 300,868 (80%) matched patients with and without AKI, groups were well matched by year of admission, demographics, preadmission comorbid conditions, and medication use, and characteristics of the index hospitalization. Of 150,434 patients with AKI, 83% had stage 1, 11% had stage 2, and 6% had stage 3.

Within a median follow-up of 1.7 years, 4.7% of the matched cohort had incident heart failure after the index hospitalization. The overall heart failure incidence rate was 27.8 per 1000 person years (95% confidence interval [CI], 19.3-39.9). Patients who developed heart failure were more likely to be older, be white, and have proteinuria and lower eGFRs prior to the index hospitalization, diabetes and hypertension, and acute coronary syndrome during the index hospitalization. The incidence rate of heart failure was higher in patients with AKI compared with those without AKI: 30.8 (95% CI, 21.08-43.5) versus 24.9 (95% CI, 16.9-36.5) per 1000 person-years, respectively.

The cumulative incidence of heart failure was higher among patients with AKI. Following multivariable adjustment in the matched cohort, there was an association between a prior hospitalization for AKI and a 23% greater risk for incident heart failure within 2 years (hazard ratio [HR], 1.23; 95% CI, 1.19-1.27). To account for the matched nature of the data, the researchers repeated this analysis in sensitivity analyses, conducting a stratified cause-specific hazard model; the association of AKI and risk for incident heart failure was similar to that of the primary analysis (HR, 1.27; 95% CI, 1.23-1.32).

Compared with patients who had no AKI during the index hospitalization, risks for developing incident heart failure among patients with AKI stages 2 or 3 were similar to those of patients with AKI stage 1 (HR, 1.19; 95% CI, 1.12-1.28 and HR, 1.23; 95% CI, 1.19-1.28, respectively). Patients with AKI stage 2 or 3 had higher rates of death after discharge than patients with AKI stage 1 (incidence rate, 157.8 [95% CI, 136.5-181.7] versus 124.5 [95% CI, 105.4-146.4] per 1000 person-years, respectively).

Overall, the associations of AKI with risk for incident heart failure were consistent across subgroups by age, race, diabetes, coronary artery disease, and baseline eGFR category.

The researchers cited a few limitations to the study, including the matched study design that created the possibility that the matches differ from the overall population; the inability to perform adjudication of heart failure events of interest due to the use of validated ICD-9 codes to identify heart failure; and including only US veterans in the study, possibly limiting the generalizability of the findings.

The researchers said in conclusion, “In a large cohort of hospitalized US veterans, AKI was associated with the development of incident heart failure. These findings were consistent among important patient subgroups. These data contribute to the growing body of literature that has demonstrated that AKI is associated with significant long-term comorbidity. Future studies to identify underlying mechanisms and modifiable risk factors for heart failure in AKI survivors are needed.”
Our data show that patients with pre-existing end-stage renal disease (ESRD) at the time of LVAD placement have a very poor prognosis, with most surviving for less than 3 weeks. This information may be critical to support shared decision making around treatments for advanced heart failure for patients with ESRD.

—Nisha Bansal, MD, MAS

**TAKEAWAY POINTS**
- Researchers conducted a study to assess outcomes associated with placement of left ventricular assist devices in patients with and without end-stage renal disease (ESRD).
- During median follow-up of 272 days, 81.9% of patients with ESRD died compared with 36.4% of those in the non-ESRD cohort.
- Median time to death among patients with ESRD was 16 days, compared with 2125 days for patients without ESRD.

**Kidney Week**

**Gender-Related Differences in Hypoglycemia with Glucose-Lowering Treatment**

New Orleans—Treatment recommendations for lowering glucose vary by chronic kidney disease (CKD) stage. Despite possible differences in efficacy, there are no differences in treatment recommendations by gender, raising the possibility of differences in glucose control and hypoglycemia by gender.

In a French study conducted by Marie Metzger, MD, and colleagues, 3013 patients with CKD stages 3 to 5 were recruited, of those 645 men and 288 women were treated with glucose lowering drugs. Uncontrolled glucose was defined by hemoglobin A1c (HbA1c) ≥7%. Hypoglycemia was defined by self-report. Dr. Metzger reported study results during a poster session at Kidney Week 2017 in a paper titled "Impact of Gender on the Patterns of Glucose-Lowering Treatment and Hypoglycemia in Patients with Type 2 Diabetes and Advanced CKD. The French CKD-REIN Study."

Fifty-five percent of men were treated with insulin, 65% of women were treated with insulin; insulin treatment was more common in patients with later stages of CKD. At lower CKD stages, fewer women than men were treated with insulin. Overall, 31% were treated with insulin only, 28% were treated with a combination regimen of insulin and another drug, and 42% were treated with non-insulin glucose lowering drugs.

The prevalence of uncontrolled glucose was 57%. In a multivariable model, there were associations between insulin treatment and longer duration of diabetes and higher body mass index (BMI). There were no associations between insulin treatment and gender, age, estimated glomerular filtration rate (eGFR).

Fifty percent of men and 59% of women reported hypoglycemia; there was no relationship between hypoglycemia and eGFR or HbA1c. Following adjustment for age, sex, BMI, and duration of diabetes, reports of hypoglycemia were more frequent among people treated with insulin.

In summary, the researchers said, "In people with diabetes and CKD, HbA1c, CKD stage, and reported hypoglycemia were not associated. However, glucose lowering treatment and hypoglycemia, but not glucose control, were gender dependent; this seems to be related to insulin treatment which may need to be adapted to avoid hypoglycemia, especially in women."

Incident Atrial Fibrillation Increases Risk
continued from page 1
recently conducted a population-based retrospective cohort study in Ontario, Canada to examine the association between AF and cardiovascular outcomes (CHF and MI), ESRD, and all-cause mortality in patients with a decrease in estimated glomerular filtration rate (eGFR). The researchers also sought to determine whether different categories of eGFR would influence those associations and to test the hypothesis that AF would be associated with higher risk for adverse events in patients with low eGFR and the risk would vary by eGFR level. Results were reported in the American Journal of Kidney Diseases [2018;71(2):191-199].

Using linked databases to ascertain patient characteristics, the researchers identified patients with at least one outpatient eGFR obtained from April 1, 2006, to March 31, 2015, and then looked forward 12 months for first evidence of AF. Only patients with eGFRs <90 mL/min/1.73 m² were included. The index date for each patient was the first eligible incident AF diagnosis. A random index date for patients who did not develop AF during the 12-month index period was assigned based on the distribution of index dates. Exclusion criteria included <18 years of age, any history of kidney transplantation, evidence of dialysis, or evidence of CHF or AF 5 years prior to the patient’s index date.

Estimated glomerular filtration rate was calculated using the CKD Epidemiology Collaboration creatinine equation and was categorized as 60 to <90, 30 to <60, and <30 mL/min/1.73 m². Incident clinically identified AF was defined by a single International Classification of Diseases or billing code on first diagnosis during hospitalization, during a visit to the emergency department, or during an ambulatory office visit. Patients were followed up forward in time until receipt of dialysis, kidney transplantation, all-cause mortality, CHF, MI, or end of the study follow-up period (March 31, 2015).

During total follow-up time of 795,131 person-years, the incidence of all study outcomes was higher among patients in the AF group; this was pronounced during the first 6 months following the AF diagnosis.

Using propensity scores, eGFRs, and index dates, the final study cohort matched 93,414 individuals with CKD with AF to 93,414 individuals with CKD without AF. Prior to matching, patients with AF were older, had more comorbid conditions (diabetes, hypertension, stroke, and cardiovascular disease), and had greater use of healthcare (hospitalizations, visits to the emergency department, and physician visits) compared with participants without AF. Following matching, the two groups were balanced for all measured covariates with no detected statistically significant differences. During total follow-up time of 795,131 person-years, the incidence of all study outcomes was higher among patients in the AF group; this was pronounced during the first 6 months following the AF diagnosis. The incidence of AF, CHF, MI, and mortality (<.001); the highest risk remained among those with eGFRs of 60 to <90 mL/min/1.73 m². The researchers cited some limitations to the study, including the observational design of the study that may have allowed residual confounding; the lack of data for medication use and treatments for AF; the use of a single outpatient serum creatinine value to define reduced eGFR with no inclusion of albuminuria; and exclusion of patients with a history of AF and CHF.

The researchers summarized by saying, “Patients with reduced eGFRs have a high incidence of AF and the development of AF is a risk factor for adverse events. A diagnosis of AF is associated with 11.6-, 4.8-, and 2.6-fold higher risks for CHF, MI, ESRD, and all-cause mortality, respectively, in the short term, and this attenuated but persisted in the long term compared with those without AF. Given the high burden of disease of patients with AF and reduced eGFRs, future areas of research should examine the mechanisms by which AF leads to adverse events and possible therapeutic means of prevention.”

Kidney Week
Continuation of Loop Diuretics Beneficial in First Year after Dialysis Initiation
New Orleans—Patients with non-dialysis dependent chronic kidney disease are often managed with use of loop diuretics. Upon initiation of hemodialysis, loop diuretics are often discontinued, despite potential benefits of augmented urine output. Researchers, led by Steven M. Brunelli, MD recently conducted an analysis designed to examine the association between the early decision to continue versus discontinue loop diuretics at start of dialysis and clinical outcomes during the first year following dialysis initiation.

Results of the analysis were reported during a poster session at Kidney Week 2017. The poster was titled Association of Continuation of Loop Diuretics at Hemodialysis Initiation with Clinical Outcomes. The analysis included all patients who initiated in-center hemodialysis at a large dialysis organization from 2007 to 2013. Eligible patients were covered by Medicare parts A and D who had an active supply of loop diuretics at the start of dialysis (n=11,297). Exposure status was determined based on whether the prescription for loop diuretics was refilled following initiation of dialysis or within 30 days of depletion of prior supply. Follow-up on an intention-to-treat basis continued for up to 12 months. Outcomes of interest were death, hospitalization, or intradialytic hypotension (IDH). Of the 11,297 patients, 5,219 refilled a prescription for loop diuretics and 6,078 did not. Following adjustments for case mix and clinical differences, compared with discontinuation of loop diuretics, there was an association between continuation of loop diuretics and lower rate of hospitalization (P=0.001) and IDH (P=0.001), and a lower death rate (did not reach statistical significance).

In conclusion, the researchers said, “Among incident hemodialysis patients, continuation of loop diuretics in the immediate post-transition period was associated with lower rate of hospitalization and IDH over the first year of dialysis. The practice of discontinuing loop diuretics should be re-evaluated.” The researchers said.


Funding for this poster was provided by DaVita, Inc.
Mar Cor Purification is the largest supplier and service provider of hemodialysis water systems and associated components in North America. Mar Cor offers hemodialysis providers a turn-key solution that is designed to make sure critical water needs are being served in compliance with applicable regulations. All of our systems meet F.D.A, requirements and AAMI standards.
Insulin Sensitivity and Risk for Hyperfiltration in Youth with Type 2 Diabetes Mellitus

The leading cause of end-stage renal disease (ESRD) is diabetic kidney disease. Among children and adolescents with type 2 diabetes mellitus (T2DM), early diabetic kidney disease, including hyperfiltration and increased excretion of albumin, is common; progression occurs at "an alarming rate," according to Peter Bjornstad, MD, and colleagues. In a small cohort of 46 adolescents with T2DM, the prevalence of hyperfiltration was 24% and of increased albumin excretion, 34%.

Dr. Bjornstad et al. previously reported longitudinal data from the TODAY (Treatment Options for Type 2 Diabetes in Adolescents and Youth) study. The results demonstrated that the prevalence of increased excretion of albumin increased from 6.3% at baseline to 16.6% by the end of the study. The data were reported after only 3.9 years of follow-up; further, there were no laboratory data available to assess hyperfiltration.

Children and adolescents diagnosed with T2DM appear to have a particularly high risk for progression to diabetic kidney disease; the risk is significantly greater than that in youth with type 1 diabetes or in adults diagnosed with T2DM with similar duration of disease. Hyperfiltration is an early indicator of diabetic kidney disease and often precedes increased excretion of albumin and decline in kidney function, making identification of clinical phenotypes associated with hyperfiltration and predictive of diabetic kidney disease a key factor in improving outcomes in adolescents with T2DM.

In adults with and without T2DM, reduction in insulin sensitivity has been associated with the development of future kidney disease. The mechanisms underlying the association between reduced insulin sensitivity and diabetic kidney disease are unclear; however, experimental evidence indicates that the energy profile of T2DM cannot accommodate the renal hypermetabolism of diabetic kidney disease. In a small cross-sectional cohort of adolescents with T2DM, associations between insulin resistance and hyperfiltration have been reported; however, data in larger cohorts are lacking. In addition, there are few data available on the role of hyperfiltration in adolescents with T2DM.

In a recent issue of the American Journal of Kidney Diseases [2018;71(1):65-74], Dr. Bjornstad and colleagues added to their previous work by describing the prevalence and incidence of hyperfiltration in the TODAY study cohort at baseline and over 5 years; data on albumin excretion out to 5 years is also reported. The researchers also sought to examine the longitudinal relationship between estimated insulin sensitivity and renal outcomes during the 5 years of the study to test the hypothesis that there would be an association between lower estimated insulin sensitivity in adolescents with T2DM and diabetic kidney disease, reflected by increased risk for hyperfiltration and increased albumin excretion.

The current analysis included 532 participants; 63.9% (n=340) were female, mean age was 13.9 years, mean duration of diabetes was 7.9 months, 33.6% (n=179) were black non-Hispanic, 43.0% (n=229) were Hispanic, 20.1% (n=107) were white non-

Survival with Intensive Home Hemodialysis Similar to Deceased Donor Kidney Transplantation

New Orleans—For patients with end-stage renal disease (ESRD), the treatment of choice is kidney transplantation; however, there is a shortage of available kidney donors. Results of a previous study in Canada suggested that intensive home hemodialysis had similar survival rates to that of recipients of deceased donor kidney transplantation. Angie G. Nishio-Luca, MD, and colleagues conducted a study in the same region in the United States to compare survival in a large cohort of patients treated with intensive home hemodialysis with recipients of kidney transplantation. Dr. Nishio-Luca reported study results during a poster session at Kidney Week 2017 in a poster titled "Intensive Home Hemodialysis Survival is Comparable to Deceased Donor Kidney Transplantation."

The cohort included all consecutive adult patients in the same region in Virginia who received a first kidney transplant or initiated intensive home hemodialysis between October 1997 and June 2014. Data on kidney transplantation were obtained from the Scientific Registry of Transplant Recipients; data on intensive home hemodialysis patients were obtained from Lynchburg Nephrology Physicians practice in Lynchburg, Virginia.

Exclusion criteria were recipients of en-bloc kidneys, multi-organ transplants, and subsequent kidney transplantation, as well as patients receiving other home dialysis therapies, in-center hemodialysis, or home hemodialysis of >20 hours per week or <4 sessions per week. Overall survival among different modalities was estimated using the Kaplan-Meier method. Intensive home hemodialysis versus living donor transplantation and intensive home hemodialysis versus deceased donor transplant. Multivariate Cox proportional hazard regression was used to estimated adjusted hazard ratios [HRs]. Following application of inclusion and exclusion criteria, the cohort included 3097 kidney transplant recipients and 116 intensive home hemodialysis patients. Baseline characteristics were similar in the two groups: females, 40.5% in the transplant group versus 41.4% in the dialysis group; 48.9% African Americans in the transplant group versus 50.9% in the dialysis group; and 36.5% with diabetes in the transplant group versus 37.1% in the transplant group. Patients in the intensive home hemodialysis group were more likely to be obese and have a history of malignancy than those in the transplantation group.

Patients in the living donor transplantation group had the highest patient survival. At 5 years, survival probability in the intensive home hemodialysis group was 79% [95% confidence interval (CI), 0.68-1.62; P=.837].

In conclusion, the researchers said, “In this study, survival of intensive home hemodialysis patients was not statistically different from deceased donor kidney transplantation, suggesting intensive home hemodialysis could be a reasonable alternative to deceased donor kidney transplantation.”

Alert System Reduces Odds of Overlooked AKI Events among Hospitalized Patients

Decline in kidney function and increased risk for mortality are closely associated with acute kidney injury (AKI). To date, there is no universal treatment for AKI, although several therapeutic and preventive interventions have been developed. It is widely accepted that early detection of AKI events is key to improving outcomes; the importance of nephrologist care is also well known in this patient population.

AKI is primarily defined by criteria based on serum creatinine (Scr). There have been efforts to develop an efficient surveillance system for AKI (AKI alert); however, negative results were reported from a published randomized trial of AKI alerts. Other studies have demonstrated promising preliminary outcomes, but have carried several limitations to the system.

Researchers in South Korea, led by Sehoon Park, MD, reported results of an AKI alert system implemented in their hospital in 2014 [American Journal of Kidney Diseases; 2018;71(1):9-19]. In the system reported on, the attending clinicians could easily generate automatic direct consultation with the nephrology division. The current report assessed the impact of the system using comparisons of outcomes of patients with AKI events prior to and following implementation of the alert system.

The study was conducted at a tertiary referral hospital in Korea with >1000 general admission beds. The AKI alert system was launched on June 1, 2014. There were no other major changes in activities related to AKI or in laboratory procedures related to AKI.

The study cohort included index admission cases of adult patients who had mean...
The primary outcomes of interest were overlooked AKI events (defined as not measuring the follow-up creatinine), and the consultation pattern of clinicians.

The researchers cited some limitations to the study, including (1) the study design and lack of randomization, (2) the inability of the AKI alert system to report AKI events in real time, (3) the lack of criteria for baseline Scr concentrations, (4) the possibility of selection bias because the alert group was admitted to the hospital for longer periods and had worse baseline characteristics, and (5) the possibility that the results may not be transferable to other hospitals, depending on size and location.

“In conclusion, our EMR-based AKI alert system altered the behavior of clinicians, increased the involvement of specialists, and improved AKI outcomes. Therefore, adoption of an AKI alert system linked to early nephrology intervention could be considered in hospitals to improve patient prognosis,” the researchers said.

### Kidney Week

**Statin Therapy Reduces Occurrence of AKI after Angiography**

New Orleans—The diagnosis and treatment of cardiovascular diseases is often complicated by the presence of acute kidney injury (AKI). Previous studies have demonstrated a significant decrease in the occurrence of AKI when patients were treated with statin therapy prior to coronary angiography and/or intervention; however, the association between pretreatment statin therapy and the occurrence of AKI in patients with peripheral artery disease is unknown. Researchers in Japan conducted a retrospective analysis to examine the association between statin therapy and the occurrence of AKI in patients with peripheral artery disease.

Daisuke Kanai, MD, reported results of the analysis during a poster session at Kidney Week 2017. The poster was titled Association Between Statin Therapy and Occurrence of AKI in Patients with Peripheral Artery Diseases.

The researchers utilized data from the endovascular treatment database at Nishiwaki Municipal Hospital, Nishiwaki, Japan, to identify angiography and/or intervention performed for peripheral artery disease between November 1, 2011, and March 2016 (n=337 patients). Of those, 69 patients with chronic kidney disease receiving hemodialysis and 13 lacking sufficient data were excluded. The remaining 295 patients were divided into two groups: those who did not receive statin therapy (control group, n=157) and those who did receive statin therapy (statin group, n=138) for at least one month prior to admission. AKI was defined by absolute increase in serum creatinine of ≥0.5 mg/dL or a relative increase of ≥25% measured 1 week following the procedure. Prior to the procedure, the two groups were similar in sex, serum creatinine level, amount of contrast medium, use of renin angiotensin system inhibitors, smoking, and blood pressure.

The incidence of AKI was significantly lower in the statin group compared with the control group (5% vs 16%, P<.05). In multivariate analyses adjusted for age, BMI, diabetes mellitus, LDL-C, serum creatinine, and statin therapy, statin therapy was significantly correlated with the lower occurrence of AKI (P<.05).

In conclusion, the researchers said, “The results of our study suggested that statin therapy may prevent the occurrence of AKI after angiography and/or intervention for peripheral artery disease.”

Risk of VTE Increases with Albuminuria in Patients with Normal eGFRs

There is an increase in the risk of venous thromboembolism (VTE) in patients with chronic kidney disease (CKD) with elevated albuminuria or with low estimated glomerular filtration rate (eGFR). However, according to David Mascotte-Azariniouch, MD, and colleagues, it is unclear whether the increased risk of VTE associated with albuminuria differs by level of kidney function.

Noting that clarifying the individual and combined contributions of albuminuria and kidney function would be of use in accurately determining the risk of VTE and identifying appropriate prophylactic therapies for patients at risk, the researchers utilized a large population-based database to examine the association of VTE events in patients by albuminuria and eGFR. Results were reported in the American Journal of Kidney Diseases [2017;70(6):826-833].

The final analytic cohort included 694,956 adults in Ontario, Canada, from 2002 to 2012. Patients were stratified according to albumin-creatinine ratio (ACR). Those with higher urine ACRs were older, more likely to be male, and had lower eGFRs. They also had lower income status and more comorbid conditions (diabetes mellitus, hypertension, stroke, hemorrhage, cardiac disease, chronic obstructive pulmonary disease, and liver disease). Further, VTE-specific risk factors, including recent surgery, remote/active cancer, and lower-extremity fracture, were all more common in patients with higher ACRs. Utilization of healthcare (determined by visits to the emergency department and family or general physician visits) were higher in that patient population, as well.

In total, there were 15,180 VTE events during the study period. The proportion of VTEs increased with heavier albuminuria: ACR <30 mg/g: 2.0%; ACR 30 to 300 mg/g: 2.9%; ACR >300 mg/g: 3.1%. There were 248 VTE events in patients with eGFR 15 to 29 mL/min/1.73 m². Median time to VTE event was 3.7 years; median time to VTE or death was 3.7 years. Median times to death, end-stage renal disease, or end of study were 5.3, 4.2, and 6.4 years, respectively.

When examined as continuous variables, in fully adjusted models that included an ACR x eGFR interaction term (P<.001) for both ACR and eGFR, ACR and eGFR were independently associated with VTE. The subdistribution hazard ratio (HR) increased 0.1% per 1-mg/g greater urine ACR. The subdistribution HR decreased 0.4% per 1-mL/min/1.73 m² in greater eGFR. The interaction for ACR x eGFR was highly significant (P<.0001); ACR was an effect modifier on the association of eGFR and VTE.

The researchers examined whether the VTE risk was consistent in ACR categories across categories of eGFR. With higher albuminuria there was a steeper risk in the adjusted subdistribution HR for VTE with eGFR of 120 mL/min/1.73 m² compared with eGFR of 30 mL/min/1.73 m². The subdistribution HR at eGFR of 120 mL/min/1.73 m² and ACR of 500 mg/g was 2.05 (95% CI, 1.74-2.41), whereas at eGFR of 30 mL/min/1.73 m² and ACR of 500 mg/g, the subdistribution HR was 1.42 (95% CI, 1.24-1.62). There was no substantial change in the risk for VTE with a higher ACR at eGFR of 30 mL/min/1.73 m² (ACR of 0 mg/g: subdistribution HR, 1.26; 95% CI, 1.20-1.33; ACR of 500 mg/g: subdistribution HR, 1.42 (95% CI, 1.24-1.62).

The researchers cited some limitations to the findings, including the observational design of the study that limits the establishment of causality, the inability to specifically examine the cause for declines in kidney function or albuminuria, sensitivity of only 75%, determining eGFR and ACR based on clinical indication rather than population-level screening, and lack of information on medication use in the study population.

“In conclusion, CKD, defined as reduced eGFR and/or albuminuria, is a significant independent risk factor for the development of VTE. The albuminuria-associated risk for VTE changes depending on level of eGFR. In patients with normal kidney function, higher ACR is associated with much larger increase in risk for VTE compared with patients with reduced kidney function. Given the high prevalence, morbidity, and mortality of both CKD and VTE, developing prevention strategies for VTE events in at-risk patients through the use of evidence-based screening tools could decrease the incidence and population-level impact of VTE,” the researchers said.
A Review of Use of Phosphate Binders among US Dialysis Patients

In 2015, Medicare paid more than $1.5 billion for phosphate binders for patients on dialysis in the United States and for patients with chronic kidney disease (CKD). Previous analyses have shown that phosphate binders are the most commonly used medications for treatment of CKD-mineral and bone disorder (MBD). The analyses also demonstrated a faster increase in Part D costs for CKD-MBD medications (phosphate binders, vitamin D analogues, and cinacalcet) for patients on dialysis from 2007 to 2010 than costs for all Part D medications (36% vs 22%). The increases occurred despite relatively stable use within medication classes. For 2014, phosphate binders represented 37% of all Medicare Part D expenditures for dialysis patients.

In a policy forum perspective article in the American Journal of Kidney Diseases [2018;71(2):246-253], Wendy L. St Peter, PharmD, Lori D. Wazny, PharmD, and Eric D. Weinhandl, PhD, MS, provided an update on trends in phosphate-binder use, calcium and phosphorous values, and costs for dialysis patients covered by Medicare. The authors utilized primary data to evaluate the trends and then reviewed the literature on the effectiveness and cost-effectiveness of phosphate binders in that patient population.

**USE, COSTS, AND EFFECTIVENESS**

From 2008 to 2013, the number of patients on dialysis who were dispensed at least one Part-D covered phosphate binder increased 29% (from 204,208 to 263,404); corresponding percentages of phosphate binder users were stable at approximately 76%. Over time, there was as shift in use of specific phosphate binders. There was a decrease in use of calcium acetate from 38% to 34%; no change in use of non-calcium containing phosphate binders; an increase in use of sevelamer carbonate; and a decrease in use of sevelamer hydrochloride (by 2013, only 7% of dialysis patients were dispensed sevelamer hydrochloride). Part D does not cover calcium carbonate; it is not included in the analyses.

There was a 118% increase in annual Medicare costs for phosphate binders between 2008 and 2013 (an increase of $486 million). Of the total cost in 2013, sevelamer carbonate and sevelamer hydrochloride together accounted for $741 million (83% of phosphate binder costs covered by Part D for Medicare beneficiaries on dialysis). For the same time period (2008-2013), total costs per user-year for phosphate binders increased from $2221 to $3716 (a 67% cumulative increase, or a 10.8% compound annual growth rate). Total costs per user-year for all other drugs covered by Part D cumulatively increased by 21% during that same time period.

**PHOSPHATE BINDER REGULATION**

The percentages of Medicare Part D beneficiaries using phosphate binders was steady from 2008 through 2013. However, there was an increase in patient prevalence, accounting for the increase in Medicare costs for phosphate binders. It does not account for the increased costs of phosphate binders outpacing costs related to all other Part D-covered drugs for dialysis patients during the same time period.

Phosphate binders are approved by the US FDA for control of serum phosphorous concentrations in dialysis patients and/or patients with CKD. Despite the increased costs, the researchers note, there has not been improvement in control.

**CONCLUSIONS**

There are few available data from randomized clinical trials demonstrating that: (1) lower compared with higher phosphorous concentration of (2) therapy with any phosphate binder reduces hard clinical endpoints compared with placebo or another phosphate binder. The authors suggest that the FDA “should consider requiring adequately powered placebo-controlled blinded trials of sufficient duration to evaluate clinical outcomes and not simply phosphorous concentration reduction... Because no clinical trials of phosphate binders have been powered adequately to assess cardiovascular outcomes, the FDA should consider convening an advisory committee to determine whether cardiovascular risk should be addressed during the drug development stage for new phosphate binders.

“Given that Medicare is the main payer for phosphate binders for US dialysis patients and the skyrocketing Medicare costs, the Centers for Medicare & Medicaid Services should have a vested interest in answering the question of whether maintaining lower versus higher phosphorous concentrations improves hard clinical outcomes, and if so, whether particular phosphate binders are superior to placebo or other binders in improving these outcomes. A validated method for assessing adherence is essential to understanding effects on outcomes. Trials should be consistently designed and conducted so that future meta-analyses and valid cost-effectiveness analyses will be possible. This is the only way to know if we are getting enough bang for our collective buck for phosphate binders in dialysis patients,” they concluded.

There was a 118% increase in annual Medicare costs for phosphate binders between 2008 and 2013 (an increase of $486 million).
**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 levothyroxine.

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; binders included sevelamer carbonate, calcium acetate, and lanthanum carbonate) 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.*

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.

DOSE 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.

DOSE FORMS AND STRENGTHS
Velphoro (sucroferric oxyhydroxide) chewable tablet 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, hydrochlorothiazide, losartan, metoprolol, nifedipine, omeprazole, quinidine and warfarin.

Take doxycycline at least 1 hour before Velphoro.

VELPHORO chewable tablets must be chewed and not swallowed whole. To aid with chewing and swallowing, the tablets may be crushed.

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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Impact of Pre-Transplant Vascular Disease on Long-Term Outcomes after Transplantation

Vascular disease is associated with an increased risk of death among dialysis patients on the transplant waiting list. Among candidates for transplantation on the deceased donor waiting list, the annual rate of vascular-related deaths is >8%; the rate increases with cumulative time on dialysis therapy. Even with the modest survival benefit of transplantation for patients with vascular disease, vascular-disease–related death remains a significant impediment to improvement in long-term outcomes associated with transplantation. In Australia and New Zealand, cardiovascular disease (CVD) and other vascular diseases are associated with >30% of deaths in patients with a functioning transplant; similar mortality rates are observed worldwide.

Short-term outcomes for transplant recipients have improved with advances in kidney transplantation, but there are few data on long-term outcomes among patients with comorbid vascular conditions. Wai H. Lim, MD, and colleagues recently conducted a population cohort study designed to examine the association of vascular disease prior to transplantation with graft and patient survival following transplantation. The study also evaluated whether diabetes status modified that association. Results were reported in the American Journal of Kidney Diseases [2018;71(1):102-111].

The researchers utilized data from the Australia and New Zealand Dialysis and Transplant Registry to identify primary adult deceased donor kidney transplant patients ≥18 years of age for 1990 to 2012. Exclusion criteria included receipt of multiple organ transplants and transplants prior to the index date.

The primary clinical outcome of interest was all-cause mortality. Secondary outcomes were overall transplant loss, death-censored transplant loss, death with a functioning transplant, and cause-specific mortality (CVD, infection mortality, cancer, and other vascular disease–related mortality). Other vascular disease–related mortality was defined as death from cerebrovascular or peripheral vascular disease (PVD)–related comorbid conditions, pulmonary embolus, bowel infection, and ruptured aortic aneurysm.

The total cohort included 7128 transplant recipients. Of those, 84.3% (n=6011) had no recorded vascular disease at the time of transplantation; 12.0% (n=854) had vascular disease at one site, and 3.7% (n=263) had vascular disease at two or more sites. Mean age of patients with no vascular disease, vascular disease at one site, and vascular disease at two or more sites was 46.7, 54.4, and 56.9 years, respectively. Median follow-up was 7.3 years (58,120 patient-years).

Patients with vascular disease were more likely to have diabetes (P.<001). CVD was the most prevalent type of vascular disease (67.9%; n=759), followed by PVD (38.5%, n=430), and cerebrovascular disease (21.4%, n=239). P.<001. Over successive transplantation eras, the proportion of recipients with any vascular disease increased.

In conclusion, the researchers said, “We demonstrated that graft and patient survival rate of spousal donor kidney transplantation was not inferior to living related donor transplantation, despite their immunologic risk. Moreover, we found that longer marriage duration after transplantation was a novel protective factor for biopsy proven acute rejection-free survival rate. Not only immunologic similarity but also habitual similarity between donor and recipient may influence graft outcome after kidney transplantation.”

Donor and Recipient Views on Anonymity Policies in Kidney Donation

In Spain and in the Netherlands, anonymity is maintained for kidney donation from live donors in nondirected (specified) and paired exchange (specified indirect) donation. The anonymity is required both prior to and following kidney donation for nondirected and paired exchange proceedings. In other countries, including the United Kingdom and the United States, there is no requirement of anonymity for those procedures, or the policy is one of conditional anonymity, allowing for donor-recipient pairs to meet after a period of time if both parties agree.

The anonymity policy is based on the rationale that it will protect donors and recipients against potential risks. To date, there is little empirical evidence informing the debate surrounding the issue of anonymity in kidney donation. Dorthe Slaats, MSc, and colleagues conducted an exploratory, multivcenter, retrospective, mixed-methods, survey study designed to examine the experiences, preferences, and attitudes of donors and recipients regarding anonymity.

The study included an investigation into differences between donors and recipients who participated in varying transplantation programs such as nondirected transplantations and paired procedures; nondirected donors elected to donate in a strictly anonymous manner, while paired exchange donors originally intended to donate to their known recipient. The study also examined differences in attitudes and experiences between participants from Sweden and the Netherlands, and whether elapsed time from the surgery had an influence on feelings regarding anonymity. Study results were reported in the *American Journal of Kidney Diseases* [2018;71(1):S2-S64].

The survey was administered to recipients and donors who received or donated a kidney anonymously (nondirected or...
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Kidney Week

New Orleans—Doomer kidney graft survival is associated with advanced donor age, recipient age, and donor-recipient size mismatch. However, there are few available data on the interaction among these variables. Researchers in Canada conducted a retrospective cohort study designed to examine those interactions. Fanny Lepétryre, MD, reported results of the study during a poster session at Kidney Week 2017 in a poster titled The Effect of Donor-Recipient Size Mismatch on Graft Survival Is Modified by Kidney Transplant Recipient and Donor Age. The study utilized data from the Scientific Registry of Transplant Recipients on all first deceased kidney transplantation performed between January 1, 2000, and January 1, 2015, on adults ≥18 years of age. The association between donor-recipient body surface area ratio (0.9 vs. 0.9) and overall graft survival was assessed using multivariable Cox proportional hazards models. Overall graft survival was defined as death with function, return to dialysis, or retransplantation. The researchers examined the interaction between body surface area ratio and recipient age (≥54 vs. ≥54 years of age) and donor age (≥60 vs. ≥60 years of age), as well as the three-way interaction term of body surface area ratio by recipient age and donor age. Over a median follow-up of 4.8 years. 33.3% of 118,101 patients (n=39,310) experienced graft loss. The three-way donor-recipient body surface area ratio by donor age by recipient age interaction was statistically significant (P=0.02).

More recipients than donors would have liked to meet the other party before (P=0.002) and after (P=0.006) surgery. Seven percent of donors indicated they would have liked to meet the other party before and 22% after surgery; 15% of recipients would have liked to have met the donor before the surgery and 31% after. Significantly more recipients than donors wanted to meet the other party. If the other party indicated a willingness to meet, a greater percentage of participants said they would be open for a meeting (donors, 58%; recipients, 60%). There was no relationship between willingness to meet the other party and time since surgery and the other party being willing to meet. There was agreement between donors and recipients on meeting both before and after surgery if both parties agreed.

Significantly more recipients than donors wanted to meet the other party.

Donors agreed significantly more with the principle of anonymity both before and after surgery compared with recipients. Both donors and recipients thought it should be permissible to meet before and after surgery if both parties agreed. When asked about the pros and cons of anonymity, 51% of all participants reported both advantages and disadvantages; 29% reported only advantages; 3% reported only disadvantages; and 17% left the answer blank or responded “don’t know.” Emotional and relational considerations included self-protection versus curiosity: participants feared that breaking anonymity might damage their image of the anonymous donor or recipient, but there was also a degree of curiosity about the other party and outcomes of the procedure.

Another benefit was seen in anonymity preventing an obligation to enter into a relationship, negating the need to deal with the potentially uncomfortable issue of gratitude, and preventing dealing with varying expectations of the relationship. Conversely, others felt that anonymity created a barrier to the chance to express feelings, share experiences, and gratitude. Anonymity was seen as a way to ensure fairness of allocations based on medical considerations, leaving the decision making up to physicians. Further, particularly among non-directed donors, anonymity was considered a path to ensuring altruism and unconditionality.

There were some limitations to the study, including the relatively low response rate of recipients that may have limited the generalizability of the findings, and the possibility of recall bias due to the time lag between transplantation and collection of data. In summary, the researchers said, “Most participants in this study were satisfied with anonymity. However, most participants view an unduly strict policy on anonymity as unnecessary if the donor and recipient want to meet. When considering the anonymity policy, recipients’ and donors’ perspectives should be taken into account. We recommend that anonymity before and after the transplantation should be the norm. However, if all parties independently agree to a nonanonymous procedure, this should be considered. We recommend re-assessing the current policy of absolute anonymity in consideration of these findings. By increasing understanding of the reasons behind the attitudes for and against anonymity, this study may also help to improve education and decision making.”

New Orleans—Poorer kidney graft survival is associated with advanced donor age, recipient age, and donor-recipient size mismatch. However, there are few available data on the interaction among these variables. Researchers in Canada conducted a retrospective cohort study designed to examine those interactions. Fanny Lepétryre, MD, reported results of the study during a poster session at Kidney Week 2017 in a poster titled The Effect of Donor-Recipient Size Mismatch on Graft Survival Is Modified by Kidney Transplant Recipient and Donor Age. The study utilized data from the Scientific Registry of Transplant Recipients on all first deceased kidney transplantation performed between January 1, 2000, and January 1, 2015, on adults ≥18 years of age.

The association between donor-recipient body surface area ratio (0.9 vs. 0.9) and overall graft survival was assessed using multivariable Cox proportional hazards models. Overall graft survival was defined as death with function, return to dialysis, or retransplantation. The researchers examined the interaction between body surface area ratio and recipient age (≥54 vs. ≥54 years of age) and donor age (≥60 vs. ≥60 years of age), as well as the three-way interaction term of body surface area ratio by recipient age and donor age. Over a median follow-up of 4.8 years. 33.3% of 118,101 patients (n=39,310) experienced graft loss. The three-way donor-recipient body surface area ratio by donor age by recipient age interaction was statistically significant (P=0.02).

Among transplant recipients ≥54 years of age, there was an association between a donor-recipient body surface area ratio ≤0.9 and a higher risk of graft failure when donors were ≥60 years of age [hazard ratio (HR) 1.11; 95% confidence interval (CI) 1.07-1.14]. When the donor was ≥60 years of age, there was no association between donor-re- cipient body surface area ratio ≤0.9 and graft survival (HR 0.92; 95% CI 0.81-1.04). In transplant recipients ≥54 years of age, there was a significant association between donor-recipient body surface area ratio ≤0.9 and graft failure, re- gardless of donor age [HRs, 1.07; 95% CI 1.03-1.10 for donors ≥60 years of age and 1.09; 95% CI 1.02-1.16 for donors ≥60 years of age].

“We find donor-recipient size mismatch to have a small but significant impact on graft survival in all but younger recipients of older deceased donors. We hypothesize that in the latter group, the adverse impact of donor age super- sodes the effect of donor-recipient size mismatch, and a size mismatch should not be considered as adversely affect- ing graft survival in this patient popula- tion,” the researchers said.

Fresenius Kidney Care 5-Diamond Patient Safety Program Ratings Announced

Fresenius Kidney Care, the dialysis division of Fresenius Medical Care North America announced results for the 2017 5-Diamond Patient Safety Program. The program includes nine end-stage renal disease networks in the United States and is designed to aid dialysis facilities in improving the patient experience by building a culture of patient safety.

According to a press release from Fresenius Kidney Care, the company maintained its 5-Diamond status at 99% of its participating facilities in its second year in the program, while increasing enrollment from 2385 clinics in 2016 to 2417 in 2017. The %Diamond program included 18 patient-safety education modules. In the first year of program participation, each dialysis facility is required to complete five modules, followed by three modules each consecutive year, to be recognized and to maintain status as a 5-Diamond Patient Safety Facility.

Ron Rodgers, executive vice president, Fresenius Medical Care North America and president, Fresenius Kidney Care, said, “As a leading dialysis provider, Fresenius Kidney Care is dedicated to ensuring the safety of our patients and employees. This second-year achievement demonstrates our unwavering commitment to our culture of patient safety in each and every clinic.”

The greatest improvement year-over-year was seen in the Inpatient Services unit at Fresenius Kidney Care, with a 32% increase in the number of programs that achieved 5-Diamond status in 2017. The unit provides acute-care management for those living with ESRD.

“Employee education is an integral part of our focus on providing the highest quality of care to patients,” Mr. Rodgers said. “We pride ourselves in employing people who continue to learn with each advancement in our field and demonstrate their commitment to exceeding safety expectations.”

Fresenius Kidney Care will continue participating in the 5-Diamond Safety Program “as part of its commitment to delivering an exceptional patient experience,” according to the press release.

Diagnosed Prevalent Cases of CKD Projected to Increase by 2026

GlobalData, a data and analytics company, has released a report estimating the growth of the burden of chronic kidney disease (CKD) over the next decade. In a press release, Qaisrah Khalid, healthcare analysis at GlobalData, said, “In the seven major markets, GlobalData epidemiologists forecast that the diagnosed prevalent cases of CKD stages 1-4 will grow by 9.9% over the forecast period [2016-2026] at an annual growth rate of 0.99%, from just under 25.78 million cases in 2016 to just under 28.33 million cases in 2026.”

In 2016, with just under 5.56 million cases, the United States accounted for 21.56% of the diagnosed prevalent cases of CKD among the seven major markets. In the five European Union markets, there were nearly 17.19 million cases (66.68% of the diagnosed prevalent cases), followed by Japan with approximately 3.05 million cases (11.77% of the diagnosed prevalent cases).

Of the seven major markets, the United Kingdom is expected to account for the highest number of diagnosed prevalent cases at the end of the decade, increasing from 13,397,021 in 2016 to 14,035,651 in 2026. The epidemiology analysis conducted by GlobalData found that the United Kingdom has a higher rate of diagnosis for CKD stages 1 and 2 compared with the other markets.

Major Meetings 2018

National Kidney Foundation Spring Clinical Meetings 2018
April 10-14, 2018 | Austin, Texas
www.kidney.org/professionals/news/meetings

American Nephrology Nurses Association 2018 National Symposium
April 15-18, 2018 | Las Vegas, Nevada
http://bit.ly/2m3ivxK

American Transplant Congress 2018
June 2-6, 2018 | Seattle, Washington
www.atcmeeting.org

American Society of Nephrology Kidney Week 2018
October 23-28, 2018 | San Diego, California
Abstract Roundup

Recurrent AKI Episodes Associated with Relevant Complications

Kidney Blood Pressure Research. https://doi.org/10.1598/0048734

Following a first incidence of acute kidney injury (AKI) related to hospitalization, patients often experience recurrent AKI; however, there are few data available regarding the prognosis of recurrent episodes of AKI in the development of chronic kidney disease (CKD), cardiovascular events, and mortality. Eva Rodriguez, MD, PhD, and colleagues recently conducted a retrospective study among patients admitted to a single center from 2000 to 2010.

There were 359 patients who survived a hospital-related AKI episode; of those, 250 new episodes were seen in 122 patients. The study identified variables that were independently associated with new episodes, including type 2 diabetes mellitus (odds ratio [OR], 1.2; 95% confidence interval [CI], 1.2-3.8; P =.001), ischemic heart disease (OR, 1.9; 95% CI, 1.1-3.6; P =.012), and serum creatinine level at first AKI event >2.6 mg/dL (OR, 1.2; 95% CI, 1.03-1.42; P =.02).

Patients with recurrent AKI were more likely to develop CKD during 4 years of follow-up (hazard ratio [HR], 2.2; 95% CI, 1.09-4.3; P =.003). Development of CKD occurred during the first 6 months following the initial AKI event in 44% of patients who developed CKD. Patients with recurrent AKI also experienced cardiovascular events compared with those with only one AKI episode (47.2% vs 24%; P =.001). At 4 years, mortality was higher in the subgroup with several AKI episodes compared with patients with only one AKI episode (HR, 4.5; 95% CI, 2.7-7.5; P =.001).

In conclusion, the researchers said, “Episodes of recurrent AKI have a high potential to be associated with relevant complications such as cardiovascular events, mortality, and CKD development.”

AKI Risk Factor for Post-Procedural Bleeding in Patients with Decompensated Cirrhosis

Liver International. doi:10.1111/liv.13712

In decompensated cirrhosis patients undergoing low-risk invasive procedures, bleeding can be life threatening or can lead to other complications. Despite abnormal coagulation parameters, the rate of procedure-related bleeding is low in unstratified cohorts of hospitalized patients with cirrhosis. Researchers, led by Adelina Hung, MD, recently conducted a retrospective chart review designed to identify patients with uncomplicated cirrhosis at high risk of developing bleeding related to low-risk procedures with the aim of assessing the value of preprocedure transfusions. The study cohort included hospitalized patients with cirrhosis who developed post-paracentesis hemoperitoneum (PPH), confirmed by computed tomography (CT) scan, from January 2012 to August 2016. The cohort was compared with patients who were hospitalized during the same period in
whom PPH was suspected but ruled out by CT scan. The chart review sought to determine the specifics of the adverse event, patient characteristics, and risk factors for bleeding. Following multivariate analysis, the only independent predictor of PPH was acute kidney injury prior to paracentesis (odds ratio, 4.3; 95% confidence interval, 1.3-13.5; P=.01). The association persisted regardless of Model of End-Stage Liver Disease score, large volume paracentesis, sepsis, platelets, international normalized ratio, and hemoglobin levels.

“Infection/sepsis is generally considered predictive of bleeding in cirrhosis. Our study suggests that AKI, and not sepsis, is the most important predictor of postprocedure bleeding in AURYXIA is the only oral iron tablet approved by the FDA for the treatment of iron deficiency anemia specifically in adult patients with CKD not on dialysis

• Proven effective in patients who were previously intolerant of or had an inadequate therapeutic response to traditional oral iron supplements
• Patients in the Phase III pivotal trial achieved results without the use of ESAs or IV iron
• 52% of patients achieved the primary endpoint of a hemoglobin increase of ≥1.0 g/dL by Week 16
• 18 ± 1% increase in mean TSAT at Week 16 from baseline
• Discontinuation rates due to adverse reactions were similar between AURYXIA and placebo (10% vs 9%)
• Convenient mealtime dosing
• Each tablet contains 210 mg of elemental iron

Please see Brief Summary including patient counseling information on following page

IMPORTANT SAFETY INFORMATION

CONTRAINDICATION: AURYXIA® (ferric 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 discolored 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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patients with decompensated cirrhosis. Although end-stage renal disease is a known cause of bleeding in non-cirrhotic patients, there are new studies establishing AKI as a risk factor for post-procedure bleeding in cirrhosis. Future studies investigating blood product transfusion needs in cirrhosis prior to procedures should carefully look at AKI,” the researchers said.

**Iron Deficiency Anemia in Chronic Kidney Disease Not on Dialysis**

Auryxia (ferric citrate) tablets

AU RYXIA® (ferric citrate) tablets for oral use containing 210 mg of ferric iron equivalent to 1 g AURYXIA for oral use.

**INDICATIONS AND USAGE**

AURYXIA is indicated for the control of serum phosphorous levels in adult patients with chronic kidney disease on dialysis. 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 syndromes (e.g., hemochromatosis).

**WARNINGS AND PRECAUTIONS**

Iron Overload: Iron absorption from AURYXIA may lead to excessive elevations in iron stores. Increases in 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, 55 (19%) of patients treated with AURYXIA had a ferritin level >1500 ng/mL as compared with 13 (9%) 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 iron-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.

Hyperphosphatemia in Chronic Kidney Disease on Dialysis

A total of 289 patients were treated with AURYXIA and 149 patients were treated with active control (sevelamer carbonate and/or calcium acetate) during the 52-week, randomized, open-label, active control safety and efficacy trial evaluating the control of serum phosphate levels in patients with chronic kidney disease not on dialysis. Across two trials, 190 unique patients with CKD-NDD were treated with AURYXIA. This included a study of 117 patients treated with AURYXIA and 73 treated with placebo in a 12-week, randomized, double-blind period 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 ferric iron per day, equivalent to 1 to 12 tablets of AURYXIA.

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

**DRUG INTERACTIONS**

Orally administered doxycycline has to be taken at least 1 hour before AURYXIA. Orally administered ciprofloxacin should be taken at least 2 hours before or after AURYXIA. Oral drugs that can be administered concomitantly with AURYXIA are: amiodipine, aspirin, atorvastatin, atorvastatin, calcitriol, clopidogrel, digoxin, diltiazem, doxercalciferol, enalapril, fluvasatin, glimespiride, levofloxacin, losartan, metoprolol, pravastatin, prasugrel, statins, and warfarin.

Oral medications not listed above by biopsy was reported in a patient on dialysis administered IV iron and was not reported in any patients treated with AURYXIA. Skeletal and encephalic malformation was observed in neonatal mice and Wistar-rats caused no fetal malformation.

**USE IN SPECIFIC POPULATIONS**

**Pregnancy:**

There are no available 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.

**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>All Reactions</td>
<td>Any Adverse Reaction</td>
<td>75</td>
<td>62</td>
</tr>
<tr>
<td></td>
<td>Metabolism and Nutrition Disorders</td>
<td>20</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>Hyperkalemia</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Gastrointestinal Disorders</td>
<td>20</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>Discolored feces</td>
<td>10</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Constipation</td>
<td>10</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Nausea</td>
<td>5</td>
<td>2</td>
</tr>
</tbody>
</table>

During the 16-week, placebo-control trial, 12 patients (10%) on AURYXIA continued study drug because of an adverse reaction, as compared to 10 patients (9%) in the placebo control arm. Diarrhea was the most common adverse reaction leading to discontinuation of AURYXIA (2%).

Hyperkalemia: Serum potassium levels were increased in some patients treated with AURYXIA. The potential for increasing serum potassium levels with AURYXIA may be exacerbated by concomitant use of drugs that can increase serum potassium levels, as discussed in Drug Interactions and Precautions.

Adverse reactions reported in more than 5% of patients treated with AURYXIA included: abdominal pain, diarrhea, nausea, vomiting, and abnormal stools.

**Clinical Considerations**

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

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.
leagues recently conducted an analysis to determine the risk of clinically significant (stage 4 and higher) chronic kidney disease (CKD) in patients treated for kidney cancer in the Veterans Health Administration from 2001 to 2013. The overall incidence of stage 4 or higher CKD after radical (n=9,759) or partial nephrectomy (n=4,370) in patients with preoperative estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m² was 7.9%. Median time after surgery to stage 4 or higher CKD was 5 months, after which few patients progressed.

Compared with radical nephrectomy, partial nephrectomy was associated with a significantly lower relative risk of incident stage 4 or higher CKD in propensity score-matched cohorts (hazard ratio [HR], 0.34; 95% confidence interval [CI], 0.26-0.43). There was also an association between partial nephrectomy and a significantly lower relative risk of incidental CKD stage 3b or higher (HR, 0.15; 95% CI, 0.11-0.19 vs radical nephrectomy) in a parallel analysis comparing patients undergoing partial nephrectomy with patients with normal or near-normal preoperative kidney function (eGFR ≥ 60 mL/min/1.73 m²) in propensity score-matched cohorts. Competing risk regression models yielded consistent results. The risk of mortality was also reduced in patients treated with partial nephrectomy (HR, 0.58; 95% CI, 0.49-0.62) compared with radical nephrectomy.

In conclusion, the researchers noted, “Compared with radical nephrectomy, partial nephrectomy was associated with a marked reduction in the incidence of clinically significant CKD and with enhanced survival. Postoperative decline in kidney function occurred mainly in the first year and appeared stable over time.”

**Risk of Incident CKD and Progression to ESRD Increases with Air Pollution Levels**

*Journal of the American Society of Nephrology. 2018; 29(1):218-230*

The association between elevated levels of fine particulate matter <2.5 µm in aerodynamic diameter (PM₉.₅) and increased risks of cardiovascular outcomes and mortality are well documented, but there are few data regarding the risk of chronic kidney disease (CKD) and end-stage kidney disease (ESRD). Utilizing the Environmental Protection Agency and Department of Veterans Affairs databases to create an observational cohort of US veterans (n=2,482,737), Benjamin Bowe, MD, and colleagues used survival models to assess the association between concentrations of PM₉.₅ and the risk of incident estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m², incident CKD, decline in eGFR ≥30%, and ESRD. Median follow-up was 8.52 years.

At baseline, county-level exposure was defined as the annual average PM₉.₅ concentrations in 2004, and separately as time-varying where it was updated annually and as cohort participants moved. In analyses of baseline exposure (median, 11.8 µg/m³), there was an assoc-

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**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 divalent metal transporter-1 (DMT-1) and ferroportin-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:** The 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 ferrous 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 reported in a patient on dialysis administered IV iron and AURYXIA.

**PATIENT COUNSELING INFORMATION**

**Dosing Recommendations:** Instruct patients to take AURYXIA as directed with meals and adhere to their prescribed diets. 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 discolored (dark) stools, but this staining of the stool is considered normal with oral medications containing iron. AURYXIA may cause diarrhea, nausea, constipation, vomiting, hyperkalemia, abdominal pain, and cough. Advise patients to report severe or persistent gastrointestinal symptoms to their physician.

**Accidental Ingestion:** 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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association between a 10-μg/m² increase in PM$_{2.5}$ concentration and increased risk of eGFR <60 mL/min/1.73 m² (hazard ratio [HR], 1.21; 95% confidence interval [CI], 1.14-1.29), and ESRD (HR, 1.27; 95% CI, 1.17-1.38), decline in eGFR >50% (HR, 1.28; 95% CI, 1.18-1.39), and ESRD (HR, 1.26; 95% CI, 1.17-1.35). In time-varying analyses, there were similar associations between a 10-μg/m² increase in PM$_{2.5}$ concentration and increased risk of eGFR <60 mL/min/1.73 m², CKD, decline in eGFR >30%, and ESRD. Data from the National Aeronautics and Space Administration satellite yielded similar results. “Our findings demonstrate a significant association between exposure to PM$_{2.5}$ and risk of incident CKD, eGFR decline, and ESRD,” the researchers said.

“Our findings demonstrate a significant association between exposure to PM$_{2.5}$ and risk of incident CKD, eGFR decline, and ESRD,” the researchers said.

**DIALYSIS**

**Intensive Blood Pressure Management in Hemodialysis Patients**

*Journal of the American Society of Nephrology. 2018;29(1):307-316*

The optimal blood pressure target for patients receiving hemodialysis is unknown. Dana Miskulin, MD, and colleagues recently conducted a preliminary trial to determine the feasibility and safety and to shape the design of a full-scale trial. A secondary objective was to assess changes in left ventricular mass.

The preliminary trial randomized 126 hypertensive patients on dialysis to either a standardized predialysis systolic blood pressure of 110-140 mmHg (intensive arm) or 155-065 mmHg (standard arm). Median follow-up was 365 days.

There was no change in the 2-week moving average systolic blood pressure in the standard arm during the intervention period; at 4.5 months in the intensive arm, systolic blood pressure decreased from baseline 160 mmHg to 143 mmHg. From months 4 to 12, the mean separation in systolic blood pressure between arms was 12.9 mmHg.

There were four deaths in the intensive arm and one death in the standard arm. For the intensive arm versus the standard arm, the incidence rate ratio for major adverse cardiovascular events was 1.18 (95% confidence interval [CI], 0.40-3.38), for hospitalization 1.61 (95% CI, 0.87-2.97), and for vascular access thrombosis 3.09 (95% CI, 0.96-8.78). Median changes in left ventricular mass were similar in the two groups (–0.84 g in the intensive group and 1.4 g in the standard group).

“Although we identified a possible safety signal, the small size and short duration of the trial prevent definitive conclusions. Considering the high risk for major adverse cardiovascular events in patients receiving hemodialysis, a full-scale trial is needed to assess potential benefits of intensive hypertension control in this population,” the researchers said.

**TRANSPLANTATION**

**Telehealth Reduces Time and Costs Related to Pretransplant Evaluation**

*Transplantation. 2018;102(2):279-283*


Patients were 92.6% white and 70.6% were males. Over the 30-year period, the initial length of hospital stay post-transplant declined 37% (P <.01). From era 1 to era 2, the 10-year death-censored graft survival improved from 60% to 80% (P =.04). There was no significant change across the eras in incidence of acute rejection, graft thrombosis, cytomegalovirus, or urine leaks. The frequency of diagnosis of Epstein-Barr virus increased from era 2 to era 3 (P <.01). Compared with eras 1 and 3, incidence of post-transplant lymphoproliferative disorder increased in era 2 (P =.03).

The researchers said, “Infants deserve earlier consideration for kidney transplant.” Length of initial hospital stay and patient and graft survival rates after kidney transplantation have improved in infants since 1984.”
Losing Money by “Saving” Money

It is a saying I have never forgotten. “For a company to make a profit, you can cut costs or bring in more money. I prefer to bring in more money.”

These words were spoken by the owner of a small company that was struggling to make ends meet. Over the years, I have found this statement to be more profound than I ever imagined.

I am amazed at the number of healthcare providers who try to save money by cutting costs on that which can most improve their financial situation: billing properly for the services they provide. Common pitfalls include hiring the cheapest billers they can find; hiring fewer billers than they need; and trusting their electronic medical record (EMR) to capture all billing information completely and correctly.

One of the first physician practices I looked at was a model for problems that I would find repeated in many other offices and healthcare institutions in subsequent years. This six-physician practice had hired one biller, who was assisted at times by the practice manager. If the receptionist was out, the biller was asked to fill in for her by answering calls and helping patients who came into the office. The doctors paid these three individuals significant wages and benefits so they did not want to hire any more billers.

In reviewing their billing processes, I found they were 90 days behind in billing procedures that had been performed. Because they were so far behind in filing claims for those procedures, they had no time to follow up on claims that had been denied. Thus, their accounts receivable was very large for a practice of their size.

If they had hired one additional biller, this person could have brought in as much as five times the amount of her wages and benefits. Thus, by trying to save money on wages and benefits, it was costing the doctors much, much more by not adding an additional person. In addition to losing out on a lot of reimbursement, they were also vulnerable to audits that could have resulted in them having to refund significant amounts from previously paid claims.

Another area where providers lose money is relying too heavily on their EMR to capture billing information. Normally, the data within the EMR is transmitted to its billing module or other billing software. In some cases, the billing module/software has an automated process for generating claims, retrieving payment data, and posting payments. The more automated the process, the less expensive it is for this type of billing services. However, the cost savings can be minimal compared to the loss of reimbursement due to missed charges and incomplete documentation.

For example, a problem with automation is that customers of EMR companies sometimes demand modifications to their software that cause incorrect or missing data. To accommodate their clients, the EMR companies make the changes without them or the client realizing the change will result in missing or incorrect billing data which results in lower reimbursement.

Also, as the claims payment posting process becomes more automated, EMRs/billing software may automatically post write-offs assigned by the insurance company that are incorrect. While the EMR or software may show there is no balance due on a claim, there may be procedures that should have been paid.

Checking the status of unpaid claims, following up promptly on rejected or improperly paid claims, and filing appeals as needed are also critical parts of the billing cycle. These processes are becoming more automated and, while automation may resolve simple issues, EMRs/billing software are normally unable to deal with problems that require personal involvement and critical thinking.

Another issue that cannot be automated is explaining to a payer how to correctly pay a renal claim. Our staff members are prepared with copies of regulations, examples, and prior experiences with payers in order to help them understand how the claim should be paid after it was processed incorrectly.

Some software can be programmed to file appeals automatically, but appeals are usually not the best way to fight denied claims. EMR processes cannot conduct the thorough investigations needed to be done by people to get to the real problems that caused a claim to deny.

EMR vendors are quick to point out that checks are built into their systems that look for incorrect or missing data in order to prevent errors. However, what happens when an EMR vendor inadvertently programs their software in a way that results in missed reimbursement opportunities? What about lower revenues that come from a software update that causes an unexpected error in another part of the software? While an efficient EMR can be a valuable time-saving tool, none are infallible. To be fair, no biller is infallible. However, a trained billing staff working with an efficient EMR make a dynamic team that can result in maximized revenues and minimized errors. The additional reimbursement providers can receive make it well worth the relatively small cost to have experienced billers actively monitoring the claims and payment information generated by the EMR.

Rick Collins is the director of business development and Sarah Tolson is the director of operations for Sceptre Management Solutions, Inc., a company specializing in billing for outpatient ESRD facilities, nephrology practices, and vascular access. Your questions are welcome and they can be reached at 801.775.8010, rcollins@sceptremanagement.com, stolson@sceptremanagement.com or via Sceptre’s website, www.sceptremanagement.com.
The Only Iron Replacement Therapy That Maintains Hemoglobin

Triferic® is an innovative iron therapy that effectively treats the iron loss and anemia that hemodialysis patients suffer from.

Increases Healthy Red Blood Cells
Hemoglobin enables red blood cells to carry oxygen to all parts of the body, providing energy.

Gives Iron When and Where Patients Need it
Triferic® enters the blood via dialysate and donates its iron immediately to transferrin, making red blood cells and maintaining hemoglobin.

Proven Safety Profile
No iron trapped in the liver and no increase in ferritin, inflammation, toxicity or infections. No anaphylaxis. Decrease in blood transfusions.1

The Only FDA Approved Drug Indicated to Replace Iron and Maintain Hemoglobin in Adult CKD-HD Patients

To schedule a web-enabled presentation on the benefits that Triferic® can provide to your patients email us at trifericpres@rockwellmed.com or call 800.449.3353

IMPORTANT SAFETY INFORMATION
Warnings and Precautions
Serious hypersensitivity reactions, including anaphylactic-type reactions, some of which have been lifethreatening and fatal, have been reported in patients receiving parenteral iron products. Patients may present with shock, clinically significant hypotension, loss of consciousness, and/or collapse. Monitor patients for signs and symptoms of hypersensitivity during and after hemodialysis until clinically stable. Personnel and therapies should be immediately available for the treatment of serious hypersensitivity reactions. Hypersensitivity reactions have been reported in 1 (0.3%) of 292 patients receiving Triferic® in two randomized clinical trials. Iron status should be determined on pre-dialysis blood samples. Post dialysis serum iron parameters may overestimate serum iron and transferrin saturation.

Adverse Reactions
The most common adverse reactions (>3% and at least 1% greater than placebo) in controlled clinical studies include: headache, peripheral edema, asthenia, AV fistula thrombosis, urinary tract infection, AV fistula site hemorrhage, pyrexia, fatigue, procedural hypotension, muscle spasms, pain in extremity, back pain, and dyspnea.

For full Safety and Prescribing Information please visit www.triferic.com.

1 In Clinical Trials vs. Placebo. Triferic® [Package Insert], Rockwell Medical, Wixom, MI, September 2015.

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