AKI and Risk of Chronic Kidney Disease Common after Heart Transplantation in Children

Children with congenital heart disease who undergo heart transplantation commonly experience acute kidney injury (AKI) following the procedure; rates of AKI as high as 61% have been reported. AKI after heart transplantation has been associated with poor long-term kidney outcomes.

In the population of children, adolescents, and young adults, risk factors for AKI have been identified, including preoperative kidney function, younger age, cyanotic heart lesions, and longer cardiopulmonary bypass times. AKI is associated with prolonged need for inotropic support and mechanical ventilation, longer hospital length of stay, increased healthcare costs, and greater in-hospital mortality.

The relationship between heart transplantation and long-term kidney function is not well known. Seth A. Hollander, MD, and colleagues recently conducted a retrospective cohort study designed to examine the incidence of AKI, recovery from AKI, and subsequent development of chronic kidney disease (CKD). The researchers sought to test the hypothesis that AKI and CKD were common following heart transplantation and that there would be an association between AKI and sub-

Incremental Hemodialysis Schedule Preserves Residual Kidney Function

Regardless of a patient’s residual kidney function (RFK), maintenance hemodialysis is most often prescribed three times a week. RFK in end-stage renal disease patients is critical in dialysis adequacy, quality of life, and survival. There is an association between endogenous clearance conferred by RFK and greater survival compared with dialysis clearance per se. Further, at a certain RFK level, higher dialysis dose may not influence clinical outcomes in patients receiving either hemodialysis or peritoneal dialysis.

Results from previous studies have been conflicting in terms of the clinical benefits of higher dialysis dose or frequency, either of which may accelerate decline in RFK. Incremental hemodialysis regimens (initiation of dialysis therapy at a lower frequency) were initially suggested based on urea kinetic models in the late 1990s. In 2006, the National Kidney Foundation–Kidney Disease Outcomes Quality Initiative (NKF-KDOQI) suggested a twice weekly schedule of dialysis for patients

Hemodiafiltration Associated with Better Survival versus Standard Hemodialysis

In the late 2000s, data from the observational Dialysis Outcomes and Practice Patterns Study (DOPPS) and from a small randomized controlled study of hemodiafiltration, provided evidence of improved survival with hemodiafiltration (HDF). HDF combines diffusion and convection to improve removal of uremic toxins in the middle-molecule range. At that time, the percentage of hemodialysis patients treated with HDF was low.

The findings from DOPPS had possible confounding by indication, and subsequent randomized controlled trials reported different conclusions about the effects of HDF on survival. The most consistent finding was the association of high (but not low) convention volume and improved survival. However, this finding was based on secondary subgroup analyses.

Lucile Mercadal, MD, PhD, and colleagues recently conducted a study utilizing
Uncontrolled secondary hyperparathyroidism (SHPT) leads to bone disease, vascular calcification, and cardiovascular disease. A common challenge when treating SHPT in patients with stage 3 or 4 chronic kidney disease (CKD) is raising serum total 25-hydroxyvitamin D to adequate levels as well as achieving and sustaining clinically meaningful suppression of intact parathyroid hormone (iPTH) without causing an undesirable increase in serum calcium and phosphorus.


Can SHPT progression be disrupted? STOP CHASING SHPT
START STOPPING IT.

Uncontrolled secondary hyperparathyroidism (SHPT) leads to bone disease, vascular calcification, and cardiovascular disease.¹ A common challenge when treating SHPT in patients with stage 3 or 4 chronic kidney disease (CKD) is raising serum total 25-hydroxyvitamin D to adequate levels as well as achieving and sustaining clinically meaningful suppression of intact parathyroid hormone (iPTH) without causing an undesirable increase in serum calcium and phosphorus.²⁻⁵

Can SHPT progression be disrupted?

CKD Prevalence Rises Dramatically in African Americans

There are approximately 20 million Americans with chronic kidney disease (CKD) and approximately 400,000 patients on dialysis. Commensurate with this is the cost of treating kidney disease—approximately one in every five Medicare dollars is spent on CKD and ESRD (nearly $50 billion).

A paper published in the *Annals of Internal Medicine*¹ and data from the United States Renal Data System (USRDS)² present some welcome news. The Centers for Disease Control and Prevention (CDC) Surveillance System, utilizing the National Health and Nutrition Examination Survey (NHANES), reports that the overall prevalence of CKD stage 3 and 4 has plateaued at around 7% of the US population³. Mirroring this, the 2014 USRDS report reveals that the number of newly reported ESRD cases has plateaued or declined slightly since a monotonous year-by-year rise from 1980 through 2010. Similarly, the prevalence of ESRD in the United States decreased from 386 to 353 per million in the time period 2003 to 2012.

The *Annals* paper by Daniel Murphy, MD, and colleagues¹ assessed the prevalence of CKD every 2 years from 1999 to 2012. They report that the 6.9% prevalence has remained essentially stable from 2003 to 2012. However, the prevalence of CKD in African Americans over the same period has seen a dramatic increase.

The increase in CKD prevalence among African Americans is striking: 3.7% to 6.2%. If the plateauing in CKD prevalence for Americans reflects better management of CKD progression and tighter diabetes control, then the dramatic increase in African Americans is quite worrying.

One possibility is a widening economic disparity between African Americans and white American counterparts. According to the 2014 US Census Bureau American Community Survey (ACS study)⁴, 27% of all African American men, women, and children live below the poverty level, compared with just 11% of all Americans. Since 2000, the percentage of black families that meet the poverty criteria increased from 19.3% to 22.9%. This economic disparity could mean lower access to medications, potentially fewer doctors’ appointments, and a lower likelihood of eating a healthier diet.

Looking at data about health insurance among African Americans, approximately 21%, or 1 in 5, nonelderly African Americans have health insurance compared with 13% of white American counterparts⁵. Philethea Duckett and Samantha Artiga, writing for the Kaiser Commission on Medicaid and the Uninsured⁶ point out that this represents a health insurance disparity that, in large part, seems to reflect African Americans’ inability to access employer-sponsored insurance or to afford private coverage on the individual market due to low incomes.

While the CDC and USRDS data represent good news for Americans as a whole, this isn’t time to celebrate. Much work needs to be done among African Americans. The problem of CKD among African Americans is growing at a time when their ability to manage the financial hardships that result from CKD is increasingly challenging. The human cost is huge, and the effect on families cannot be underestimated.

As well, in the long run, since kidney disease is so costly, it makes sense, simply from a macro-economic perspective, to intensify our focus on preventing kidney disease, especially among African Americans.

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Incremental Hemodialysis Schedule
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with “substantial residual renal urea clearance,” defined as ≥10 mL/min/1.73 m². According to Yoshitsugu Ohi, MD, PhD, and colleagues, “given that estimated glomerular filtration rate is ≥10 mL/min/1.73 m² upon initiation of maintenance dialysis in up to 45% of patients in the United States,” RKF may be preserved with use of an incremental regimen of hemodialysis; other clinical and economic advantages may also be seen with such a schedule of therapy.

The researchers recently conducted a longitudinal cohort study to test the hypothesis that there is an association with a less frequent schedule at hemodialysis therapy initiation and greater preservation of RKF with no compromise in survival among patients with substantial RKF. They reported results in the American Journal of Kidney Diseases [2016;68(2):256-265].

The study predictor was incremental versus conventional hemodialysis regimens. Incremental hemodialysis was defined as routine twice weekly for ≥6 consecutive weeks during the first 91 days upon transition to dialysis, and conventional dialysis regimen was defined as three times a week treatments. The primary outcomes of interest were changes in renal urea clearance and urine volume during 1 year after the first quarter and survival after the first year.

A total of 69,811 incident in-center hemodialysis patients survived their first year of dialysis. The prevalences of the twice-weekly schedule in the first four patient quarters were 0.9% (n=647), 1.4% (n=963), 16% (n=1114), and 1.7% (n=1173), respectively. Following removal of patients who received either fewer than two treatments per week or more than three treatments per week, there were 63,368 patients who received either twice-weekly or thrice-weekly treatments. Of those, 23,645 had reassured urea clearance at baseline (defined as the first patient-quarter or first 91 days of dialysis, or months 1-3); those patients who received either twice-weekly or thrice-weekly treatments had higher baseline renal urea clearance and urine volume during 1 year after the first quarter and survival after the first year.

In patients with inadequate baseline renal urea clearance, defined as <3.0 mL/min/1.73 m²; hazard ratio [HR], 1.61; 95% CI, 1.07-2.44), incremental regimens were associated with higher risk of mortality. Conversely, in patients with higher baseline renal urea clearance, there was no association with increased mortality risk (HR, 0.99; 95% CI, 0.76-1.28).

The primary outcomes of interest were changes in renal urea clearance and urine volume during 1 year after the first quarter and survival after the first year.

Across higher increments of renal urea clearance and lower increments of weekly interdialytic weight gain, there was a significant trend toward better survival in patients in the incremental hemodialysis group (P for trend, =.05 and =.03, respectively). There was not a significant trend observed in urine volume categories (P for trend, =.2).

Study limitations cited by the authors included the possibility of confounding by indication (physicians may be less likely to prescribe twice-weekly hemodialysis to patients with lower RKF or higher comorbid condition burden), and including patients who survived at least 1 year following initiation of hemodialysis, which might have introduced survivor bias.

“In conclusion, in our select cohort of incident hemodialysis patients with measured RKF, the incremental hemodialysis regimen that starts with a twice-weekly schedule on transition to dialysis therapy is associated with greater preservation of RKF in the first 15 months and may be safely implemented among incident hemodialysis patients with substantial RKF. However, it was associated with high mortality in patients with less RKF after the first year. Periodic evaluation of RKF may be useful to individualize hemodialysis treatment. Further studies, especially randomized controlled trials, are needed to identify patients who would most benefit from the incremental regimen by evaluating its impact on RKF preservation, survival, and other relevant outcomes, including cost-effectiveness, and patient-centered outcomes, before implementing incremental regimen protocols in practice,” the researchers said.
Acute Kidney Injury
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The primary independent variable was AKI within the first 7 days after transplantation, determined according to the Kidney Disease: Improving Global Outcomes criteria (increase in serum creatinine ≥1.5 times the baseline measurement within the 7 days). The outcomes of interest were recovery from AKI at 3 months, determined as estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m² for ≥3 months.

The review included all pediatric patients (≤20 years of age) who underwent orthotopic heart transplantation at a pediatric hospital in Stanford, California, from September 1, 2007, to November 20, 2013. There were 95 pediatric heart transplantations during the study period; of those, 88 were included in the analysis. Of the seven excluded patients, three underwent combined liver-heart transplantation, two underwent retransplantation, and two had ventricular assist devices placed intraoperatively.

Mean age at transplantation was 6.3 years; 44% (n=39) were female, 57% (n=50) had the transplant for cardiomyopathy, and 43% (n=38) had the transplant for failed palliation of congenital heart disease. Thirty-two patients were bridged to transplantation with a ventricular assist device; median duration of ventricular assist device support was 71 days.

Nine patients required extracorporeal membrane oxygenation pretransplantation; eight of those were transitioned to ventricular assist device support. One patient underwent transplantation directly from extracorporeal membrane oxygenation.

Time from listing to transplantation was a median 69 days. Median donor ischemic time was 208 minutes. Length of stay in the intensive care unit was a median 18 days. Twenty-nine patients received angiotensin-converting enzyme inhibition with enalapril within the first 7 days postsurgery.

AKI was diagnosed in 72% of patients (n=63/88) in the first 7 days after transplantation. Forty-three percent had AKI stage 1, 38% stage 2, and 19% stage 3. CKD was more common in patients with AKI had moderate to severe disease. None of the patients received renal replacement therapy. Among patients with AKI, mean serum creatinine level peaked on postoperative day 2; among those without AKI, serum creatinine level peaked on postoperative day 1, followed by a downward trend in both groups.

At 3 months postsurgery, recovery from AKI was seen in 39 of the 63 patients. Renal function was less common in patients with moderate to severe AKI (50% recovery for stages 2 and 3 vs 78% recovery for stage 1; P=.04). There was no association between age, race, cause of heart failure, pretransplantation ventricular assist device use, listing status at time of transplantation, days on the wait list, or transplant ischemic time and the subsequent development of AKI.

The analyses examined the presence of CKD at 6 months and again at 12 months. Six months after transplantation, 4% (n=3/82) had CKD. There was no difference in CKD incidence between the group with AKI and the group without AKI (5% vs 0%; P=.6). CKD was more common in patients who did not recover from their AKI event (14% vs 0%; P=.04)

At 12 months, 5% of patients (n=4/76) had CKD. CKD was more common in patients who had not recovered kidney function after AKI (18% vs 0%; P=.03). There was an association between moderate to severe AKI and a lower rate of kidney function recovery; there was no association between moderate to severe AKI and CKD at 6 or 12 months.

Limitations cited by the researchers included the retrospective design and the single-center nature of the study, as well as the relatively small sample size and the need to rely on eGFRs rather than direct measurement of GFR.

“Nevertheless, the present study demonstrates that AKI and CKD are common after heart transplantation in children, adolescents, and young adults. Nonrecovery from AKI is common, especially in patients who have more severe AKI events. Additionally, nonrecovery from AKI following transplantation is a significant risk factor for the subsequent development of CKD. Finally, the present study underscores the importance of using both standard AKI and CKD definitions in such studies; using standard criteria on larger scales will improve our ability to understand risk factors for both AKI and CKD in the heart transplantation population,” the researchers said.

“Acute kidney injury (AKI) following pediatric cardiac surgery occurs commonly and is increasingly recognized as a predictor for poor outcomes. In children undergoing heart transplantation, AKI may still occur, however, the restoration of normal cardiac function allows for renal recovery beyond that of traditional cardiac surgery. In our study we found that both AKI and AKI recovery occurred frequently after transplant, and that failure to recover from AKI in the early post-operative period predicted chronic kidney disease in the first post-transplant year, highlighting the importance of renal protective measures in children undergoing heart transplantation.”

—Seth Hollander, MD
Help your new-to-dialysis patients succeed with Velphoro

Start with high potency. Stay with long-term control. *1

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.

*1 A 52-week, open-label, active-controlled, phase 3 study evaluated the safety and efficacy of Velphoro in lowering serum phosphorus levels in patients (N=1,054) with chronic kidney disease on hemodialysis or peritoneal dialysis.

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.

DOSAGE AND ADMINISTRATION
Velphoro tablets must be chewed and not swallowed whole. To aid with chewing and swallowing, 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.

DOSAGE 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%).

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 should not be prescribed with oral levothyroxine.

USE IN SPECIFIC POPULATIONS
Pregnancy
Pregnancy Category B: Reproduction studies have been performed in rats and rabbits at doses up to 16 times the maximum recommended clinical dose on a body weight basis. The effects of Velphoro on labor and delivery in humans are not known.

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

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

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

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

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

HOW SUPPLIED/STORAGE AND HANDLING
Velphoro are chewable tablets supplied as brown, circular, bi-planar tablets, embossed with “PA 500” on 1 side. Each tablet of Velphoro contains 500 mg iron as sucroferric oxyhydroxide. Velphoro tablets are packaged as follows:

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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.

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data from the French Renal Epidemiology and Information Network to further investigate survival with HDF. To take indication bias into account, the researchers analyzed HDF as both a patient- and facility-level predictor. The analyses were conducted by patient subgroups (sex and various clinical outcomes including serum albumin status) to identify patients who might benefit most from HDF. The researchers also separately compared outcomes of patients treated with standard hemodialysis and online HDF in the dialysis facilities that offered both treatment modalities.

Analysis results were reported in the American Journal of Kidney Diseases [2016;68(2):247-255]. The data analyzed represented patients who initiated hemodialysis therapy from January 1, 2008, through December 31, 2011, who continued therapy for >3 months. Follow-up continued through the end of 2012. The outcomes of interest were all-cause and cardiovascular mortality, using Cox models to estimate hazard ratios (HRs) of HDF as time-dependent covariate at the patient level, with age as time scale and fully adjusted for comorbid conditions and laboratory data at baseline, catheter use, and facility type as time-dependent covariates.

The proportion of patients treated by HDF grew substantially during the study period. Likewise, the percentage of patients treated by HDF at each facility tended to increase over time. A total of 28,407 patients were included in the analysis. Of those, 22,881 were never treated by HDF and 5526 were treated exclusively with HDF, those with therapy. Following exclusion of patients who spent 63% of their dialysis vintage on HDF. Patients in the HDF group had more cardiovascular comorbid conditions and less mobility. With the exception of a slightly higher estimated glomerular filtration rate in the JDG group, laboratory data at initiation of dialysis therapy was similar for both groups. Those never treated by HDF had a higher crude rate of kidney transplantation.

There was an association between HDF use and a significant reduction in all-cause and cardiovascular mortality in Cox proportional hazards model analysis following adjustment for sex and age as the time-scale model. Following full adjustment, the hazard ratio (HR) for all-cause mortality associated with HDF was 0.84 (95% confidence interval [CI], 0.77-0.91); for cardiovascular mortality, the HR associated with HDF was 0.73 (95% CI, 0.61-0.88). HRs were constant with age according to Schoenfeld residual testing. HRs for all-cause and cardiovascular mortality of patients treated exclusively by HDF (n=2254), compared with those for patients never treated by HDF (n=22,881) were 0.77 (95% CI, 0.67-0.87) and 0.66 (95% CI, 0.50-0.86), respectively. Patients treated by standard hemodialysis in facilities that also provided HDF had no survival advantage over those treated with standard hemodialysis in facilities that did not offer HDF (HR, 1.02; 95% CI, 0.95-1.09).

In the total cohort, facility-level predictor analyses showed a significant reduction in all-cause and cardiovascular mortality compared to HDF. The researchers also separately analyzed the benefit of HDF in different facility settings, including high-volume and low-volume facilities. The benefit was more pronounced in high-volume facilities, where HDF was used more frequently.

The analysis of the French Renal Epidemiology and Information Network (REIN) registry evidenced a survival benefit of HDF over HD, both in individual and practice based analyses to treat the indication bias. The analyses were conducted without adjustment for the convection volume not monitored at the registry level and the benefit was significant in the whole cohort of persons treated with HDF. Persons dialyzed in HDF centers but in HD had no survival benefit. Combined with the practice level analysis, one can conclude that the water conditions are not the main reason for the HDF survival benefit.”

— Lucile Mercadal, MD, PhD

“Dialysis monitors especially equipped to perform high efficiency hemodiafiltration with high permeability membranes now currently reach a convection volume higher than 20 liters. In real life conditions, the analysis of the French Renal Epidemiology and Information network (REIN) registry evidenced a survival benefit of HDF over HD, both in individual and practice based analyses to treat the indication bias. The analyses were conducted without adjustment for the convection volume not monitored at the registry level and the benefit was significant in the whole cohort of persons treated with HDF. Persons dialyzed in HDF centers but in HD had no survival benefit. Combined with the practice level analysis, one can conclude that the water conditions are not the main reason for the HDF survival benefit.”

TAKEAWAY POINTS

- Data on the effects of high-convention-volume hemodiafiltration (HDF) on mortality compared with standard hemodialysis have been inconsistent. Researchers in France conducted an observational study to examine trends in the use of HDF and its relationship with mortality.
- The primary outcome of interest was all-cause and cardiovascular mortality, using Cox models to estimate hazard ratios of HDF as a time-dependent covariate at both patient- and facility-level.
- In analyses of patient- or facility-level predictors, treatment by HDF was associated with better all-cause and cardiovascular survival.
Acute Kidney Injury Occurs Often after Major Surgery

Acute kidney injury is a common postoperative complication; approximately one third of cases of AKI acquired in the hospital setting occur postoperatively. Observational evidence shows an association of AKI with adverse outcomes, including progression to chronic kidney disease and end-stage renal disease (ESRD), as well as death. There are few preventive or therapeutic interventions that are effective in AKI; strategies and therapeutics are currently in development, but their efficacy needs to be tested with randomized clinical trials. The few previous trials of AKI prevention have focused on AKI following cardiac surgery. There are limited data on outcomes after AKI following other types of major surgery. Morgan E. Grams, MD, PhD, and colleagues conducted an observational cohort study designed to determine the frequency of, risk factors for, and outcomes following postoperative AKI after major cardiac, general, ear, nose and throat (ENT), thoracic, vascular, urologic, and orthopedic surgeries.

The trial assigned baseline creatinine level as the mean outpatient creatinine value in the year before surgery. Additional trial outcomes included risk factors for postoperative AKI and outcomes of postoperative AKI; outcomes were assessed overall and based on type of surgery. Trial results were reported in the American Journal of Kidney Diseases [2016;67(6):872-880].

The researchers utilized data from national Veterans Affairs Corporate Data Warehouse LabChem files on all patients with estimated glomerular filtration rates (eGFR) ≥60 mL/min/1.73 m², measured between October 1, 2004, and September 30, 2006. Follow-up continued until September 15, 2011. There were 161,185 patients who underwent an eligible major surgery during the study period. Of those, mean age was 64 years, 96.3% were men, and 16.9% were African American. In the year prior to surgery, average blood pressure was 133/76 mm Hg, average body mass index (BMI) was 29 kg/m², mean eGFR was 80 mL/min/1.73 m², and 12.0% of the study population had eGFRs <60 mL/min/1.73 m².

The most common type of surgery was general (27.7%), followed by orthopedic (20.8%), vascular (16.5%), and cardiac (13.8%). Patients who underwent ENT, general, or orthopedic surgery tended to be slightly younger (61, 63, and 63 years, respectively); those undergoing cardiac surgery were 65 years of age and those undergoing vascular surgery were 66 years of age. Baseline eGFR <60 mL/min/1.73 m² was seen most often in patients undergoing cardiac surgery (13.1%), orthopedic surgery (12.4%), and vascular surgery (13.2%). In all, 19,025 (11.8%) cases of major surgery involved postoperative AKI. Of those, 76.1% were stage 1 AKI, 14.6% were stage 2, 7.1% were stage 3 without renal replacement therapy (RRT), and 2.2% were stage 3 AKI with RRT.

The highest rates of postoperative AKI occurred with cardiac surgery (18.7%), followed by general surgery (13.2%), and thoracic surgery (12.0%). Procedures performed later in the hospital stay had higher risk for AKI compared with those performed during the first 5 days of admission (5-14 days after admission, RR, 1.33; 95% CI, 1.287-1.38; 15-30 days after admission, RR, 1.58; 95% CI, 1.46-1.71).

The most consistent risk factors for AKI in the overall population were older age, male sex, African American race, and higher BMI in univariate, demographic-adjusted, and fully adjusted models. There was a non-linear association of eGFR and AKI; both lower (<90 mL/min/1.73 m²) and higher (≥90 mL/min/1.73 m²) levels of eGFR conferred higher risk of AKI. Liver disease was strongly associated with postoperative AKI (RR, 1.71; 95% CI, 1.56-1.87). In analyses of outcomes of postoperative AKI, patients with postoperative AKI had longer hospital lengths of stay (15.8 days vs 8.6 days), higher rates of 30-day readmission (21% vs 13%), higher inpatient mortality (8.2% vs 1.1%), and higher 1-year ESRD continued until September 15, 2011.

Study limitations cited by the authors included reliance on laboratory data obtained as part of routine clinical care to establish baseline kidney function and AKI and a lack of information about urine output. Further, the cohort included mostly men, possible limiting the generalizability of the findings.

“In summary, AKI is common after both cardiac and noncardiac major surgery with similar risk factor and adverse outcome associations across surgery types. These findings provide important information that can inform future research in the development of AKI prevention strategies, particularly within clinical trials in the perioperative setting,” the researchers said.
Patients with end-stage renal disease (ESRD) requiring renal replacement therapy (RRT) have approximately one-third the life expectancy as that of the general population: a patient 67 years of age with ESRD has a life expectancy of 4.6 years compared with 15.5 years in the general population.

The fastest growing sector of the population on dialysis is among patients more than 75 years of age. A 77-year-old dialysis patient has a life expectancy of 3.3 years compared with 9.1 years in the general population. The Renal Physicians Association has issued clinical practice guidelines to assist physicians in addressing advance care planning with elderly dialysis patients.

However, according to Osama W. Amro, MD, MS, and colleagues, there are few evidence-based recommendations evaluating strategies for discussing advance care planning with patients with limited life expectancy and their families. Patients with ESRD who receive RRT are usually treated in an integrated multidisciplinary setting, making a structured approach to discussing goals of care to be implemented in dialysis centers a potentially effective strategy to educate certain patients regarding end-of-life care.

Dr. Amro et al. sought to develop a practical, widely available, and comprehensive model with an emphasis on patient choice and values. They described the project in the American Journal of Kidney Diseases (2016;68(1):103-109). The outcome of interest was change in MOLST completion rate and identification of preferences for limits on life-sustaining treatment.

There were 201 ESRD patients on hemodialysis enrolled at two outpatient facilities; mean age was 66 years, 35% were white. All staff nephrologists (n=9) at the two facilities participated. Eighty-eight percent (n=8) of the physicians had been practicing for more than 10 years.

When the nephrologists were asked the “surprise” question (Would I be surprised if this patient died in the next year?), they answered “no” to 50 (25%) of the 201 enrolled patients. Those 50 patients, projected to have a shorter life expectancy, tended to be older and had a higher prevalence of comorbid conditions (coronary artery disease, heart failure, cerebrovascular disease, dementia, peripheral vascular disease, amputation, and active cancer). Only nine of the 50 patients (18%) with a physician-predicted shorter life expectancy had a written do not resuscitate (DNR) physician order in their medical record prior to the planned intervention. Of the 50 identified patients, 48 and/or their family members participated in the dedicated encounter (one patient declined to participate and one healthcare proxy could not be reached).

Following the dedicated encounter, an additional 12 patients opted for a DNR order, making a total of 21 of the 50 patients (42%) with a DNR order (P=.001). Of the additional 12 patients, two had previously discussed their preferences for limitations on life-sustaining treatment, but the information had not been communicated to their nephrologist.

Prior to the dedicated encounter, 10% of patients completed a MOLST form; following the dedicated encounter, the proportion increased to 90%. A re-evaluation at 6 months of patients not receiving the intervention showed no significant change in completion of the MOLST form.

Vital status was ascertained for all 201 patients. At the 12-month follow-up point, 19% (n=39) had died. Patients with physician-predicted lower life expectancy had a cumulative lower 12-month survival rate compared with those with a longer predicted life expectancy: 58% vs 92% (P<.001). These data supported the prognostic validity of the surprise question for targeting advance care planning efforts.

The authors cited some limitations to the project: there are no data on the patient experience and comfort with the encounter, no control group for comparison, and the sample size was too small to consider the impact of cultural or religious beliefs. In addition, the success of the approach in this project is highly dependent on the communication skills of the clinician.

In summary, the authors said, “Nephrologist-facilitated advance care planning targeting hemodialysis patients with limited life expectancy led to significant changes in documented patient preferences for cardiopulmonary resuscitation and limits on life-sustaining treatment. These changes demonstrate the benefit of advance care planning with dialysis patients and likely reflect better understanding of end-of-life treatment options.”

TAKEAWAY POINTS

- Patients with end-stage renal disease requiring renal replacement therapy have approximately one-third the life expectancy of that of the general population.
- This quality improvement project sought to develop a method to increase patient autonomy and informed decision-making in advance care planning and end-of-life care.
- The project demonstrated the impact of a dedicated encounter to address advance care planning in a cohort of hemodialysis patients with physician-predicted limited life expectancy.
Aspirin Use Not Associated with CVD Risk Reduction in Transplant Recipients

The most common cause of morbidity and mortality in patients with chronic kidney disease (CKD) is cardiovascular disease (CVD). The optimal therapy for patients with kidney failure is kidney transplantation; there were more than 16,000 kidney transplantsations performed in the United States in 2015. CVD is the leading cause of death among individuals living with a functioning transplant.

Recommendations from the American Heart Association and the American College of Cardiology call for the use of aspirin for secondary prevention of CVD in all patients unless contraindicated. Aspirin use is also recommended for primary prevention of CVD in those at high risk, including patients with diabetic elevated CVD risk and women with end-stage renal disease.

According to Taimur Dad, MD, and colleagues, there are few data on the role of aspirin to prevent CVD in kidney transplant recipients. The FAVORIT (Folic Acid for Vascular Outcome Reduction in Transplantation) trial was a multicenter, randomized, double-blind, controlled trial aimed at determining whether vitamin B supplementation reduced the risk for atherosclerotic CVD outcomes in stable kidney transplant recipients.

Dr. Dad et al. recently conducted a post hoc cohort analysis of data from FAVORIT to assess whether aspirin reduces the risk for CVD, death, and kidney failure outcomes in patients with a functioning kidney transplant. They reported results of the analysis in the American Journal of Kidney Diseases [2016;68(2): 277-286].

The study participants were prevalent adult kidney transplant recipients with hyperhomocysteinemia and stable kidney function from the United States, Canada, and Brazil, with no known history of CVD. The analysis predictor was aspirin use; aspirin users were matched to nonusers using propensity score.

The outcomes of interest were incident CVD events, kidney failure, all-cause mortality, a composite of CVD events or mortality, and a composite of kidney failure or mortality.

ABSTRACT

Delays in Requests for PLD Status Affect Time to Transplantation

Individuals in need of a kidney transplant who are prior living donors (PLDs) receive high priority on the Organ Procurement and Transplantation Network (OPTN) kidney waiting list. However, program delays in adding PLDs to the list, setting their status to active, and submitting requests for PLD priority may affect timely access to transplantation.

Jennifer L. Wainright, PhD, and colleagues conducted a study utilizing data from the OPTN and the Centers for Medicare & Medicaid Services to examine the timing of listing of PLDs on the waitlist, activation on the waitlist, and requests for PLD priority in relation to the listing date. The researchers reported study results online in the Clinical Journal of the American Society of Nephrology [2016 Sept 2. pii:CJN.01360216. Epub ahead of print].

Between January 1, 2010, and July 31, 2015, there were 210 PLDs (221 registrations) added to the OPTN kidney waiting list.

As of September 4, 2015, of the 210 PLDs added to the waiting list, 167 had received deceased donor transplants, six received living donor transplants, two died, five were too ill to undergo transplantation, and 29 were still waiting for a transplant. The median waiting time from being added to the list and deceased donor transplant was 98 days.

Of the 221 PLD registrations, 40.7% (n=90) were listed prior to receiving renal replacement therapy; 68.3% were in inactive status for <90 days, 17.6% were in inactive status for 90 to 365 days, 8.6% were in inactive status for 1 to 2 years, and 5.4% were in inactive status for >2 years.

The median time of PLDs in active status prior to receiving PLD priority was 2 days. PLD priority was granted to 67.4% of PLDs within 7 days following activation, 15.4% waited 8 to 30 days, 8.1% waited 1 to 3 months, 4.1% waited 3 to 12 months, and 5.0% waited >1 year after activation for PLD priority.

Following receipt of PLD status, most received a transplant quickly. Median time in active status with PLD priority prior to deceased donor transplant was 23 days.

In conclusion, the researchers said, “Fewer than half of listed PLDs were listed before starting dialysis. Most listed PLDs are immediately set to active status and receive PLD priority quickly, but a substantial number spend time in active status without PLD priority or a large amount of time in inactive status, which affects access to timely transplants.”
WARNINGS AND PRECAUTIONS
Serious hypersensitivity reactions, including anaphylactic-type reactions, some of which have been life-threatening and fatal, have been reported in patients receiving Injectafer. 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 Injectafer administration for at least 30 minutes and until clinically stable following completion of the infusion. Only administer Injectafer when personnel and therapies are immediately available for the treatment of serious hypersensitivity reactions.

In clinical trials, serious anaphylactic/anaphylactoid reactions were reported in 0.1% (2/1775) of subjects receiving Injectafer. Other serious or severe adverse reactions potentially associated with hypersensitivity which included, but were not limited to, pruritus, rash, urticaria, wheezing, or hypotension were reported in 1.5% (26/1775) of these subjects.

In clinical studies, hypertension was reported in 3.8% (67/1775) of subjects. Transient elevations in systolic blood pressure, sometimes occurring with facial flushing, dizziness, or nausea were observed in 6% (106/1775) of subjects. These elevations generally occurred immediately after dosing and resolved within 30 minutes. Monitor patients for signs and symptoms of hypertension following each Injectafer administration.

In the 24 hours following administration of Injectafer, laboratory assays may overestimate serum iron and transferrin bound iron by also measuring the iron in Injectafer.

ADVERSE REACTIONS
In two randomized clinical studies, a total of 1775 patients were exposed to Injectafer, 15 mg/kg of body weight, up to a single maximum dose of 750 mg of iron on two occasions, separated by at least 7 days, up to a cumulative dose of 1500 mg of iron. Adverse reactions reported by ≥2% of Injectafer-treated patients were nausea (7.2%); hypertension (3.8%); flushing/hot flush (3.6%); blood phosphorus decrease (2.1%); and dizziness (2.0%).

The following serious adverse reactions have been most commonly reported from the post-marketing spontaneous reports: urticaria, dyspnea, pruritus, tachycardia, erythema, pyrexia, chest discomfort, chills, angioedema, back pain, arthralgia, and syncope.

To report adverse events, please contact American Regent at 1-800-734-9236. You may also contact the FDA at www.fda.gov/medwatch or 1-800-FDA-1088.

Please see Brief Summary on the following page.

For more information, please visit Injectafer.com
BRIEF SUMMARY OF PRESCRIBING INFORMATION

INJECTAFER® (ferric carboxymaltose injection)

INDICATIONS AND USAGE: Injectaferr (ferric carboxymaltose injection) is an iron replacement product indicated for the treatment of iron deficiency anemia in adult patients.

• who have intolerance to oral iron or who have had unsatisfactory response to oral iron,
• who have non-dialysis-dependent chronic kidney disease.

DOSAGE AND ADMINISTRATION: For patients weighing 50 kg (110 lb) or more: Give Injectaferr in two doses separated by at least 7 days. Give each dose as 750 mg for a total cumulative dose not to exceed 1500 mg of iron per course.

For patients weighing less than 50 kg (110 lb): Give Injectaferr in two doses separated by at least 7 days. Give each dose as 15 mg/kg body weight for a total cumulative dose not to exceed 1500 mg of iron per course.

Injectaferr treatment may be repeated if iron deficiency anemia recurs.

Administer Injectaferr intravenously, either as an undiluted slow intravenous push or by infusion. When administering as a slow intravenous push, give at the rate of approximately 100 mg (2 mL) per minute. When administered via infusion, dilute up to 750 mg of iron in no more than 250 mL of sterile 0.9% sodium chloride injection, USP, such that the concentration of the infusion is not less than 2 mg of iron per mL and administer over at least 15 minutes.

Inspect parenteral drug products visually for the absence of particulate matter and discoloration prior to administration. The product contains no preservatives. Injectaferr is a single-use vial.

Avoid extravasation of Injectaferr since brown discoloration of the extravasation site may be long lasting. Monitor for extravasation. If extravasation occurs, discontinue the Injectaferr administration at that site.

DOSAGE FORMS AND STRENGTHS: Single-use vials containing 50 mg elemental iron per mL in the following presentation: 750 mg iron / 15 mL.

CONTRAINDICATIONS: Hypersensitivity to Injectaferr or any of its inactive components.

WARNINGS AND PRECAUTIONS: Hypersensitivity Reactions: Serious hypersensitivity reactions, including anaphylactic-type reactions, some of which have been life-threatening and fatal, have been reported in patients receiving Injectaferr. 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 Injectaferr administration for at least 30 minutes. Avoid extravasation of Injectaferr since brown discoloration of the extravasation site may be long lasting. Monitor for extravasation. If extravasation occurs, discontinue the Injectaferr administration at that site.

WARNINGS AND PRECAUTIONS: Hypersensitivity Reactions: Serious hypersensitivity reactions, including anaphylactic-type reactions, some of which have been life-threatening and fatal, have been reported in patients receiving Injectaferr. 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 Injectaferr administration for at least 30 minutes.

Other serious or severe adverse reactions potentially associated with hypersensitivity which included, but not limited to, pruritus, rash, urticaria, wheezing, or hypotension were reported in 1.5% (26/1735) of these subjects.

Hypertension: In clinical trials, hypertension was reported in 3.8% (67/1,775) of subjects in clinical trials 1 and 2. Transient elevations in systolic blood pressure, sometimes occurring with facial flushing, dizziness, or nausea were observed in 6% (106/1,775) of subjects in these two clinical trials. These elevations generally occurred immediately after dosing and resolved within 30 minutes. Monitor patients for signs and symptoms of hypertension following each Injectaferr administration.

Laboratory Test Alterations: In the 24 hours following administration of Injectaferr, laboratory assays may overestimate serum iron and transferrin bound iron by also measuring the iron in Injectaferr.

ADVERSE REACTIONS: Adverse Reactions in Clinical Trials: Because clinical trials are conducted under widely varying conditions, the adverse reaction rates observed cannot be directly compared to rates in other clinical trials and may not reflect the rates observed in clinical practice.

In two randomized clinical studies, a total of 1,775 patients were exposed to Injectaferr 15 mg/kg body weight up to a maximum single dose of 750 mg of iron on two occasions separated by at least 7 days up to a cumulative dose of 1500 mg of iron.

Adverse reactions reported by ≥ 1% of treated patients are shown in the following table.

Table 1. Adverse reactions reported in ≥ 1% of Study Patients in Clinical Trials 1 and 2

<table>
<thead>
<tr>
<th>Term</th>
<th>Injectaferr (N=1,775)</th>
<th>Placebo Comparator* (N=1,781)</th>
<th>Oral iron (N=215)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>7.2</td>
<td>1.8</td>
<td>1.2</td>
</tr>
<tr>
<td>Hypertension</td>
<td>3.8</td>
<td>1.9</td>
<td>0.4</td>
</tr>
<tr>
<td>Facial flushing</td>
<td>2.6</td>
<td>0.2</td>
<td>0.0</td>
</tr>
<tr>
<td>Blood Phosphorus Decrease</td>
<td>2.1</td>
<td>0.1</td>
<td>0.0</td>
</tr>
<tr>
<td>Dizziness</td>
<td>2.0</td>
<td>1.2</td>
<td>0.0</td>
</tr>
<tr>
<td>Nerveting</td>
<td>1.7</td>
<td>0.5</td>
<td>0.4</td>
</tr>
<tr>
<td>Injection Site Discoloration</td>
<td>1.4</td>
<td>0.3</td>
<td>0.0</td>
</tr>
<tr>
<td>Headache</td>
<td>1.2</td>
<td>0.9</td>
<td>0.0</td>
</tr>
<tr>
<td>Alkaline Phosphatase Increase</td>
<td>1.1</td>
<td>0.2</td>
<td>0.0</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>1.1</td>
<td>2.1</td>
<td>0.0</td>
</tr>
<tr>
<td>Hypertension</td>
<td>0.8</td>
<td>0.9</td>
<td>0.0</td>
</tr>
<tr>
<td>Constipation</td>
<td>0.5</td>
<td>0.9</td>
<td>1.2</td>
</tr>
</tbody>
</table>

*Includes oral iron and all formulations of iron other than Injectaferr

Other adverse reactions reported by ≥ 0.5% of treated patients include abdominal pain, diarrhea, gamma glutamyl transpeptidase increase, injection site pain/irritation, rash, parasthesia, sneezing.

Transient decreases in laboratory blood phosphorus levels (< 2 mg/dL) have been observed in 27% (440/1638) of patients in clinical trials.

Adverse Reactions from Post-marketing Experience: The following serious adverse reactions have been most commonly reported from the post-marketing spontaneous reports with Injectaferr: arthralgia, dyspnea, pruritus, tachycardia, erythema, pyrexia, chest discomfort, chills, angioedema, back pain, arthralgia, and syncope. One case of hypophosphatemic osteomalacia was reported in a subject who received 500 mg of Injectaferr every 2 weeks for a total of 16 weeks. Partial recovery followed discontinuation of Injectaferr.

DRUG INTERACTIONS: Formal drug interaction studies have not been performed with Injectaferr.

USE IN SPECIFIC POPULATIONS:

Pregnancy: Pregnancy Category C. Adequate and well controlled studies in pregnant women have not been conducted. Injectaferr should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: A study to determine iron concentrations in breast milk after administration of Injectaferr (n=11) or oral ferrous sulfate (n=14) was conducted in 25 lactating women with postpartum iron deficiency anemia. Mean breast milk iron levels were higher in lactating women receiving Injectaferr than in lactating women receiving oral ferrous sulfate.

Pediatric Use: Safety and effectiveness has not been established in pediatric patients.

Geriatric Use: Of the 1775 subjects in clinical studies of Injectaferr, 50% were 65 years and over, while 25% were 75 years and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

OVERDOSAGE: Excessive dosages of Injectaferr may lead to accumulation of iron in storage sites potentially leading to hemosiderosis. A patient who received Injectaferr 10,000 mg over 6 months developed hemosiderosis with multiple joint disorder, walking disability and anemia. Hypophosphatemic osteomalacia was reported in a patient who received Injectaferr 4000 mg over 6 months. Partial recovery followed discontinuation of Injectaferr.

CLINICAL STUDIES: The safety and efficacy of Injectaferr for treatment of iron deficiency anemia were evaluated in two randomized, open-label, controlled clinical trials (Trial 1 and Trial 2). In these two trials, Injectaferr was administered at dose of 15 mg/kg body weight up to a maximum single dose of 750 mg of iron on two occasions separated by at least 7 days up to a cumulative dose of 1500 mg of iron.

PATIENT COUNSELING INFORMATION:

• Question patients regarding any prior history of reactions to parenteral iron products.
• Advise patients of the risks associated with Injectaferr.
• Advise patients to report any signs and symptoms of hypersensitivity that may develop during and following Injectaferr administration, such as rash, itching, dizziness, lightheadedness, swelling and breathing problems.

Injectaferr is manufactured under license from Yfle (International) Inc, Switzerland.

This is not the all risk information for Injectaferr. Please see www.injectafer.com for Full Prescribing Information.
High Ultrafiltration Rates Are Associated with Increased Mortality

The Dialysis Outcomes Quality Initiative (DOQI) was launched in 1995 by the National Kidney Foundation (NKF) with the aim of improving outcomes for patients with end-stage renal disease (ESRD) receiving maintenance dialysis. The initiative resulted in the publication of clinical practice guidelines in 1997 that addressed dialysis treatment adequacy.

Since 1997, there have been two updates to the guidelines; however, according to Holly Kramer, MD, MPH, and colleagues, there are unanswered clinical questions. The researchers published a special report on the controversy surrounding thresholds for ultrafiltration rates (UFRs) in maintenance hemodialysis online in the American Journal of Kidney Diseases [doi:10.1055/j.ajkd.2016.06.010].

During the past 10 years, high hemodialysis UFRs have been seen as an important and modifiable risk factor for morbidity and mortality in patients receiving maintenance hemodialysis. However, there have been no clinical trials assessing clinical outcome associated with a given UFR limitation.

The Kidney Care Quality Alliance (KCQA) and the Centers for Medicare & Medicaid Services (CMS) have developed measures that address UFR in hemodialysis patients. The KCQA development process utilized a modified Delphi survey of stakeholders in the dialysis community and identified volume management as the area of greatest need of attention. The KCQA and CMS measures differ slightly; the KCQA measure was included in the 2016 End-State Renal Disease Quality Incentive Program proposed rule. The CMS did not include a UFR reporting or performance measure in the 2016 Final Rule.

The current report reviewed the history of dialysis treatment time, and discussed the controversies surrounding the possible inclusion of UFR as a measure of clinical performance. The authors also named research areas where clinical evidence is needed to inform clinical decision-making regarding UFR limitations.

The UFR is a function of the total fluid removal and the time spent removing that fluid, adjusted for patient weight; it is determined by the predialysis weight and the desired postdialysis weight. Ultrafiltration removes volume from the vascular space. The ability of fluid from the interstitial space to refill the vascular space is necessary to maintain effective circulating volume; the refill varies from patient to patient. If the fluid is removed too quickly, patients may experience symptomatic intradialytic hypotension and or cramping, potentially causing the patient to terminate the dialysis session early. Treatment for intradialytic hypotension may include isotonic or hypertonic saline solution, which then impeded the ability to reach the prescribed ultrafiltration goal and postdialysis dry weight. Higher rates of hospitalization and mortality are associated with recurrent episodes of hypotension.

The first NKF-DOQI (Hemodialysis and Peritoneal Dialysis Adequacy and Vascular Access, 1997), included a discussion of the debate of hemodialysis time versus adequacy. The initial guideline established the need for measuring the dose of dialysis in all long-term dialysis patients; however, there was no consensus regarding the minimum time for a dialysis treatment session.

In the guideline on dialysis adequacy released in 2006, the NKF-DOQI suggested a minimum of 3 hours of treatment time per session or 9 hours per week for patients with low (<2 mL/min) residual kidney function. The guideline also acknowledged that there were no clinical data supporting a minimum standard for session length.

Conversely, the European Best Practices Guidelines for Hemodialysis (2002) stated that the standard minimum hemodialysis dose should be delivered as three 4-hour sessions per week, and session length and/or frequency should be extended in patients with hemodynamic instability. B-level evidence was used to support the statement.

In a secondary analysis of data from the Hemodialysis Study (HEMO), the risk for cardiovascular and all-cause mortality increased sharply with UFRs between 10 and 14 mL/kg/h, compared with UFRs <10 mL/kg/h.

TAKEAWAY POINTS

- Cardiovascular disease (CVD) is among the leading causes of death in kidney transplant recipients. It is known that aspirin use aids in the secondary prevention of CVD in the general population, but there are few data on its effect on kidney transplant recipients.

- An analysis of data from the FAVORIT trial examined whether there was an association between reported aspirin use in participants with no history of CVD and a reduction in CVD events, kidney failure, or all-cause mortality.

- There was no association between aspirin use and reduced risk for incident CVD, all-cause mortality, or kidney failure in stable kidney transplant patients with no history of CVD.
Participants in the HEMO Study were stratified into three UFR groups: ≤10, 10 to 13, and >13 mL/kg/h. The highest UFR group had a higher percentage of participants with heart failure compared with the other groups. Heart failure at baseline modified the association between UFR and mortality: there was an association between UFRs of 10 to 13 mL/kg/h and increased all-cause mortality in patients with heart failure. However, there was no association between UFRs of 10 to 13 mL/kg/h and mortality in patients without heart failure.

The 2010 CMS Technical Expert Panel that was working to establish metrics for the ESRD Quality Improvement Program (QIP) explored volume management measures as a potential metric of dialysis quality. However, efforts to include fluid management metrics in the QIP were not successful amid concerns that the proposed measure could be easily manipulated.

The 2015 NKF-KDOQI guideline for dialysis adequacy emphasized a need to go beyond the standard measures of dialysis adequacy to determine whether dialysis was meeting the needs of an individual patient. The guideline supported earlier recommendations for a 3-hour minimum session length for patients with residual kidney function <2 mL/min/h, without specifying a UFR limit.

Implementing UFR limits will necessitate increased efforts for patients, clinicians, and staff, with an emphasis on reducing intradialytic weight gain (IDWG) in patients with high UFRs. Limiting fluid intake to <1 L/d regarding body weight is a common practice for controlling IDWG, although restricting sodium intake may be more effective.

When strategies for mitigating high IDWG are not successful, hemodialysis treatment time needs to be extended to liberalization of fluid intake. Only 12.2% were willing to add a fourth treatment per week and 13.5% were willing to accept nocturnal dialysis.

There is a trial underway to determine whether extending dialysis time affects outcomes and quality of life (Cluster-Randomized, Pragmatic Trial of Hemodialysis Session Duration; clinicaltrials.gov, study number NCT02019225). The study is designed to evaluate whether a minimum session length of 4.25 hours three times a week compared with usual care is associated with lower mortality, fewer hospitalizations, and improved health-related quality of life.

“Since, the unique payment structure for dialysis treatment in the United States has led to shorter dialysis session lengths requiring high UFRs in patients with large IDWGs. High UFRs are associated with increased mortality and limiting UFRs has been proposed as a way to improve patient outcomes. If not properly implemented, it is also possible that a policy establishing a UFR limit could increase the risk for unintended consequences... For many patients, increasing hemodialysis session length or adding additional sessions will be required to avoid high UFRs, an unpalatable prospect for many patients. Currently, few studies have examined the effectiveness of behavioral modification programs, and dialysate concentrations to minimize IDWG... More studies are also needed to identify accurate and reliable methods to determine the extracellular volume status of a patient receiving maintenance hemodialysis and how these measures can be implemented into practice to optimize patient quality of life and overall survival. Identifying these gaps in knowledge may greatly improve the care of patients receiving maintenance hemodialysis and will help delineate the clinical implications of a UFR limitation as a clinical performance measure,” the authors concluded.

**Blood Volume Management Compared with Routine Clinical Assessment**

Philadelphia—Managing fluid is an important part of hemodialysis treatment. Poor outcomes have been associated with both over- and underestimation of dry weight: current standard of care estimates the dry weight based on clinical examination, a subjective process that is prone to errors.

Blood volume monitoring (BVM) has been proposed as a tool that can be used to improve fluid management in patients receiving hemodialysis. Wael F. Hussein, MD, and colleagues conducted a cross-sectional observational study designed to determine the fluid status of hemodialysis patients using BVM compared with routine standard care. They reported study results during a poster session and Kidney Week 2014 in a poster titled Blood Volume Monitoring During Hemodialysis Identifies Fluid Overload Not Recognized by Clinical Assessment.

The study included randomly selected patients from five Satellite Healthcare dialysis centers between February and May 2014. Eligible patients were adults receiving in-center maintenance hemodialysis three times a week. Fluid status was assessed using BVM; that measurement was compared with clinical criteria (dry weight achievement or nurse assessment).

BVM was performed once on the second or third treatment of the week using Crit-Line®III; dry weight achievement was defined using post-dialysis weight >0.5 above the prescribed dry weight were considered wet; nurse assessment was defined as asking the dialysis nurse “Does the patient still have excess fluid?” at the end of the treatment. Crit-Line uses optical technology to monitor residual blood volume during dialysis. The failure to drop blood volume below -5.0% during ultrafiltration time was considered an indication of fluid excess (Crit-line-Wet). Ultrafiltration is switched to the minimum for the last 10 minutes of the dialysis session. Re-fill from the extracorporeal compartment causes an upstroke in the curve. A change in blood volume of >1.5% was considered an indication of fluid excess (Critline-Wet).

Crit-Line demonstrated that 43% (n=73) of the 169 patients in the analysis had excess fluids. All 169 patients were assessed using BVM and dry weight achievement; 164 were assessed using nurse clinical evaluation. Of the patients who achieved dry weight, 40% (n=54) were Critline-Wet. Of the patients with no fluid excess by nurse evaluation, 40% (n=40) were Critline-Wet. The findings between dry weight achievement and Crit-Line measurement did not agree, nor did those between Crit-Line and the clinical assessment.

In summary, the researchers said, “A substantial proportion of patients undergoing routine hemodialysis are found to have inadequate fluid removal identified by BVM but undetected by routine clinical assessment. Crit-Line provides useful data to improve fluid management in the majority of hemodialysis patients. However, algorithms combining Crit-Line data and clinical assessment for both hemodynamically stable and unstable patients need to be developed to optimize fluid management in hemodialysis patients.”

Inside, you will find:

✓ Important news, views, and events in the world of nephrology
✓ Interviews with key opinion leaders
✓ Insights into clinical data and how it impacts your practice
✓ Highlights and news from Kidney Week and more
Analysis of Secondary Data on Patiromer

Results of a pre-specified exploratory analysis of data from the phase 3 OPAL-HK trial of Veltassa® (patiromer) for oral suspension were reported online in Kidney International. Results of the newly published analysis demonstrated that patients taking patiromer had significant decreases in systolic and diastolic blood pressure and reduced levels of aldosterone in the blood.

In a press release from Relypsa, Inc., the makers of patiromer, Matthew R. Weir, MD, lead investigator of the OPAL-HK trial and lead author of the Kidney International paper, said, “High aldosterone levels can be problematic for patients as they are associated with worsening of cardiovascular and kidney disease and are associated with increased in blood pressure. This analysis suggests that patiromer’s potassium lowering effects may be associated with reductions in blood pressure and aldosterone production. These findings could be important for people with chronic kidney disease (CKD) and are worth evaluating further.”

The OPAL-HK trial included 243 patients with CKD with hyperkalemia, defined as blood potassium levels ≥5.1 to <6.5 mEq/L. The main results of the study were previously reported in the New England Journal of Medicine.

Dendritic Cells Play Key Role in Organ Rejection

In a study reported recently in Nature Communications, researchers found that targeting certain donor cells lowered the risk of organ rejection in mice that underwent kidney and heart transplants.

In an article on Medical News Today, Fadi Lakkis, MD, co-author of the study, said, “The success of organ transplantation has reached a plateau over the past 10 or 20 years, with a significant proportion of patients still losing their grafts to rejection despite immunosuppressive treatment. New methods to tackle rejection are needed, and this discovery is another step toward finding a solution.”

The researchers found that dendritic cells play a key role in driving rejection of transplanted organs by activated T cells that have already entered the transplanted organ. The findings suggest that elimination of transplant-infiltrating dendritic cells would reduce proliferation and survival of T cells within the graft, thus prolonging transplant survival.

“The next step would be to devise methods to specifically target dendritic cells within transplanted organs,” Dr. Lakkis added. “Such methods carry the promise of preventing or interrupting rejection without compromising the patient’s overall immune defenses.”

TOURMALINE Study Meets Primary End Point

In late August, Relypsa, Inc., makers of Veltassa® (patiromer) announced topline results from a new phase 4 study demonstrating that the efficacy of patiromer in lowering blood pressure remains consistent with and without being taken with food. The TOURMALINE study was designed to test the efficacy and safety of patiromer for oral suspension given with and without food for the treatment of hyperkalemia.

The TOURMALINE study evaluated 114 patients in the United States with blood potassium levels ≥5.1 to <6/5 mEq/L. Patients were randomized to receive patiromer at a starting dose of 8.4 g/day, either with or without food. The primary end point was a comparison of the proportion of patients with either week 3 or week 4 serum potassium in the target range (3.8 to 5.9 mEq/L).

In a press release from Relypsa, Lance Berman, MD, chief medical officer, said, “In clinical studies supporting its approval, Veltassa was administered with food and its prescribing information requires Veltassa to be given with food. We’re pleased that this study showed a similar efficacy and safety profile whether Veltassa was taken with or without food and will discuss these results with the FDA.”

Chief Medical Officer’s Thoughts on CMS Proposed Rule

Brigitte Schiller, MD, chief medical officer at Satellite Healthcare, has issued the following statement on the recent Centers for Medicare & Medicaid Services Proposed Rule for changes to the end-stage renal disease (ESRD) payment system. Satellite Healthcare is a not-for-profit dialysis provider currently caring for nearly 200 patients undergoing more frequent home dialysis therapy.

Dr. Schiller said, “As a physician who had worked as a referring nephrologist in the United States and who now oversees quality care at Satellite Healthcare, I am writing to urge you to reconsider the Proposed Rule regarding the capitation of prescription allowances for more frequent dialysis, and leave the decision-making in the hands of nephrologists.

“Home hemodialysis therapy allows [patients] to live a life as normal as possible with ESRD, the full life we always envisioned when introducing dialysis to every ESRD patient in the United States.

“The Proposed Rule will put up an additional barrier for patients to have access to a modality which truly enables them to live the life they were meant to live.”

Results from DUET Study of Drug to Treat FSGS Positive

Retrophin, Inc., announced positive topline results from the phase 2 DUET
study of sparsentan for the treatment of focal segmental glomerulosclerosis (FSGS), a rare kidney disorder that has no approved pharmacologic treatment. According to a press release from Retrophin, maker of sparsentan, the study achieved statistical significance in the primary efficacy end point for the overall sparsentan group; there was a greater than two-fold reduction of proteinuria compared with irbesartan following the 8-week, double-blind treatment period.

Retrophin’s chief executive officer, Stephen Aselage, said, “We are very pleased with the robust topline results from DUET, which suggest sparsentan could be a significant advancement in the treatment of FSGS. FSGS patients today face poor outcomes with limited medical options; we look forward to working with the FDA to find the most expeditious path forward that would deliver the first approved pharmacologic treatment for the FSGS community.”

In the study, the mean reduction of proteinuria from baseline after 8 weeks of treatment for all patients treated with 200, 400, and 800 mg/day of sparsentan (n=64) was 44.8%, compared with a mean reduction of proteinuria for all patients receiving 300 mg/day of irbesartan (n=32) of 18.5% (P=.006).

The topline results suggest that sparsentan was generally safe and well tolerated. In 2015, the US FDA and European Commission each granted sparsentan orphan drug designation for the treatment of FSGS.

### Home Dialyzors United 2016 Award Winners

Home Dialyzors United has announced recipients of its 2016 awards. The Chris Blagg Award, presented to honor the spirit of innovation in dialysis, is awarded to Shuvo Roy, PhD, and colleagues, who invented the artificial kidney. Kay Deck, vice president of home therapies and clinical services at Satellite Healthcare, will receive the Trailblazer Award, honoring Satellite’s efforts in fostering knowledge about home dialysis and access to home treatment. Finally, the Rich Berkowitz Memorial Award, given to an individual who has demonstrated exceptional leadership in patient education, is presented to Mark Neumann of Nephrology & News Issues for his work championing home dialysis and patients and their families.
ACUTE KIDNEY INJURY

Results from the Acute Renal Failure Trial Network Study

In trials of more intensive versus less intensive renal replacement therapy (RRT), there have been adverse effects associated with more intensive RRT that account for the absence of observed benefit. Finnian R. Mc Causland, MD, and colleagues recently conducted a study aimed at defining the association of more intensive RRT with changes in urine output as a marker of worsening residual renal function in critically ill patients with acute kidney injury (AKI).

In the Acute Renal Failure Trial Network Study (n=1124), randomized patients with AKI requiring initiation of RRT to more intensive therapy (defined as hemodialysis or sustained low-efficiency dialysis six times per week or continuous venovenous hemodi-
alfiltration at 35 mL/kg per hour) or to less intensive therapy (defined as hemodialysis or sustained low-efficiency dialysis three times a week or continuous venovenous hemodi-
alfiltration at 20 mL/kg per hour).

Mean age of participants was 60 years, 72% were men, and 30% were diabetic. In adjusted models, among patients who survived ≥7 days, mean urine output was, on average, 31.7 mL/d higher for those in the less intensive group than in patients in the more intensive group (P=.01). More intensive RRT was associated with 29% greater unadjusted risk of decline in urine output of ≥50% (hazard ratio, 1.29; 95% confidence interval, 1.10-1.51).

“More intensive versus less intensive RRT is associated with a greater reduction in urine output during the first 7 days of therapy, and a greater risk of developing a decline in urine output in ≥50 in critically ill patients with severe AKI,” the researchers said.

DIALYSIS

Priming with Heparin and Albumin in Patients At-Risk for Bleeding
Hemodialysis International. doi:10.1111/hdi.12472

Among patients with a risk for bleeding, prior to or following surgery or brain hem-orrhage for example, intermittent hemodial-
ysis may be necessary. In such cases, inter-
mittent hemodialysis needs to be modified to limit the conventional anticoagulation used to avoid clotting of the extracorporeal circuit (ECC). Malin Skagerlin and colleagues recently conducted a retrospective data study to determine whether priming using a heparin and albumin (HA) mixture could minimize the exposure to heparin.

Data from 1995 to 2013 were collected from 1408 acute dialysis treatment protocols that included 321 patients. The researchers compared intermittent hemodialysis patients who were at increased risk for bleeding and were treated with standard anticoagulation (Group-S; n=883) with those at increased risk for bleeding (Group-HA, n=221). The ECC in Group-HA was primed with a solution of unfractioned heparin (UFH) (5000 Units/L) and albumin (1 g/L) in saline that was discarded after priming.

Among patients with AKI requiring initiation of RRT to more intensive therapy (defined as hemodialysis or sustained low-efficiency dialysis six times per week or continuous venovenous hemodi-
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Mean age in Group-S was 61.6 years, dialysis time was 197 minutes, and total dose of intravenous anticoagulant per intermittent hemodialysis was a median 5000 Units. In Group-HA, mean age was 62.2 years, dialysis time was 190 minutes, and total dose of intravenous anticoagulant per intermittent dialysis was a median 1200 Units (P=0.01 for comparisons). There were 24 patients who were treated without any additional heparin.

Clotting that resulted in interrupted dialysis was similar in both groups (0.8%, Group-SD vs 1.0% for Group-HA; P=0.8). Neither group reported any secondary bleeding.

In conclusion, the researchers said, "HA priming minimized the risk of clotting and enabled acute intermittent hemodialysis in vulnerable patients without increased bleeding, thus allowing completion of intermittent hemodialysis to the same extent as for standard hemodialysis."

**Abstract Roundup**

**GERIATRIC NEPHROLOGY**

**Geriatric Impairments in Patients Initiating Dialysis**

*Clinical Journal of the American Society of Nephrology. 2016;11:1245-1259*

As the general population ages, patients initiating dialysis therapy are increasingly likely to have geriatric impairments and a significant comorbidity burden. According to Ismay N. van Loon, and colleagues, it is unclear whether assessment of those geriatric impairments would aid in the decision-making process of dialysis initiation.

The researchers conducted a systematic Medline and Embase search to identify studies that examined the association between risk of mortality or hospitalization and one or more geriatric impairments at the start of dialysis therapy. Impairments of interest included cognitive function, mood, performance status or (instrumental) activities of daily living, mobility (including falls), social environment, or nutritional status.

Of the potential studies, 27 that assessed one or more geriatric impairments with respect to prognosis were identified. In most of the studies, cognitive impairment and functional outcomes at dialysis initiation were related to increased mortality. However, not all studies applied systematic assessment tools, potentially missing relevant impairment.

In conclusion, the researchers said, "Geriatric impairment across multiple domains at dialysis initiation is related to poor outcome. However, information in the elderly is sparse, and a systematic approach of multiple domains with respect to poor outcome has not been performed. Because a geriatric assessment has proved useful in predicting outcome in other medical fields, its potential role in the ESRD population should be the subject of future research."

**Use of Antihypertensive Medications During Transition from CKD to ESRD**

*Clinical Journal of the American Society of Nephrology. 2016;11:1401-1412*

There are few data on the pattern of antihypertensive medication use during the transition from chronic kidney disease (CKD) to end-stage renal disease (ESRD). Tara I. Chang, MD, MS, FASN, and colleagues recently conducted a study to examine use of antihypertensive medication from the four quarters prior to and eight quarters following incident ESRD treated with maintenance dialysis.

Using data from the US Renal Data System, the researchers identified patients with Medicare and low-income subsidy ≥67 years of age who initiated dialysis therapy between January 2008 and December 2010. They determined the incidence of acute kidney injury and hyperkalemia during each quarter on the basis of having at least one claim for the condition.

As patients near ESRD, the number of antihypertensive drugs used increased, peaking at an average of 3.4 in the quarter immediately before initiation of dialysis. Two years later, use had declined to 2.2 medications. Use of angiotensin-converting enzyme inhibitors (ACEIs) and/or angiotensin II receptor blockers (ARBs) was stable (~40%), even among patients with coronary disease and systolic heart failure. There was no correlation between use of ACEIs or ARBs and AKI or hyperkalemia.

Initiation of dialysis was associated with a 40% lower adjusted level of diuretic use; diuretic use continued to decline after ESRD. Prior to ESRD, three-and four-drug combinations that included a diuretic were most common. Following ESRD, the most common medication regimens were one- and two-drug beta-blocker or calcium-channel blocker-based combinations.

"The use of antihypertensive medications, particularly ACEIs/ARBs and diuretics, may be suboptimal during the transition from CKD to ESRD, especially in patients with coronary disease or systolic heart failure. Future studies are needed to identify strategies to increase the appropriate use of antihypertensive medications during this critical transition period," the researchers said.

**PEDIATRIC NEPHROLOGY**

**First AVF Cannulation in Children on Hemodialysis**

*Pediatric Nephrology. 2016; 31:1647*

Arteriovenous fistulas (AVFs) are the preferred access for hemodialysis. Veronika Alnäs-Sperling, MD, and colleagues recently conducted a retrospective cohort study to assess the influence of first cannulation of AVFs on primary and secondary patency rates in children on hemodialysis.

The study included 42 pediatric patients (median age, 14 years; range, 7-17 years). At the time of surgical AVF creation, 21 patients (end-stage renal disease) were on hemodialysis via central venous catheter or peritoneal catheter; 21 were preemptive with initiation of hemodialysis expected within a few weeks. The same surgeon performed all the AVF procedures between February 1993 and May 2014.

Primary failure was defined as the inability to use the AVF even once due to absent maturation or occlusion within 4 weeks after creation. Primary patency was defined as the interval from time of access placement to any intervention designed to maintain or reestablish patency, to access thrombosis, or the time of measurement of patency. Secondary patency was defined as the total lifespan from creation to access abandonment, end of follow-up, or loss.

In six of 42 AVFs (all radiocephalic fistulas), primary failure was observed within 10 days after cannulation. Excluding primary failure, primary patency/secondary patency rates at 1, 3, 6, 12, 18, and 24 months were 100/100, 91/99, 86/98, 76/95, 55/85, and 44/77%, respectively.

When first cannulation was performed within the first 30 days after creation, there was a significant decrease in primary patency compared with the first cannulation performed after 30 days (P=.004). There was no significant difference in the outcome of primary or secondary patency between the first cannulation within the first 45 days after creation and that after 45 days.

In conclusion, the researchers said, “These findings suggest that cannulation of AVF within 30 days after surgical creation reduces primary patency, while secondary patency may be influenced less by time until cannulation. We also found no significant differences in primary patency after maturing periods >45 days.”
**ICD-10 FLEXIBILITY ENDS**

There was a lot of hoopla and fear accompanied by the implementation of ICD-10 a year ago. Thanks to the “flexibility” of coding implemented by Medicare, most providers experienced few problems related to claims payment under ICD-10.

October first was another significant date in the implementation of ICD-10 coding, but there has been little in the way of warning or media coverage. Last year, CMS stated that as long as ICD-10 codes were in the same family of codes they would not deny claims. Family is defined as the first three digits of the ICD-10 code. Beginning October 1, CMS expects as much specificity as possible and could begin to deny claims that processed smoothly previously. ICD-10 codes can stretch to seven characters in length in order to provide specificity not previously possible under prior diagnosis code sets. Codes ending in 9 may undergo particular scrutiny as they indicate a certain condition is unspecified.

Medicare is not the only payer that allowed flexibility with ICD-10 codes last year. Several large commercial payers followed the Medicare policy and have allowed claims to process without specificity. However, these payers will also require as much specificity as possible, beginning with claims filed for dates of service on or after October 1. It is also possible that Medicaid claims will be affected in some states. Medicare Advantage plans and Medicaid Managed Care plans processed by commercial payers could also be affected.

As was the case last year, providers would be wise to set aside funds or have funds available in the event they experience a significant delay in claim payments beginning in October. However, if your billing staff was able to resolve issues with commercial payers this past year who did not allow flexibility with ICD-10 coding, the number of delays and claim denials should be minimal.

**COST REPORT AUDITS**

Each year Medicare reviews dialysis facility cost reports in order to adjust numerical values and verify that the provider’s bad debts meet Medicare’s criteria for allowable bad debts. In addition to these standard reviews, Medicare is currently conducting comprehensive audits of end-stage renal disease (ESRD) cost reports, according to statements in the 2017 ESRD PPS Proposed Rule.

Medicare states they expect the audits to result in “greater uniformity in reporting methods and, in turn, heightened data quality in future years.” In last month’s column, I mentioned that one of the difficulties Medicare has with using cost report data to determine true costs is the wide variance in reporting by facilities. An example they used to illustrate their difficulty was the amount of nursing time required for home training. Many facilities reported an hour or two, but in at least one case a facility reported 50 hours. While I cannot speak definitively about this because I am not involved in these audits, I am guessing that the facility that reported 50 hours is likely to be contacted by a Medicare auditor for clarification.

In addition to increased consistency in cost report reporting, Medicare is also considering significant changes to the cost report itself. New fields and revised worksheets will likely be a result of the current audits along with Medicare’s desire to have greater detail and specificity.

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**BURDENSOME COINSURANCES**

Medicare ESRD patients are assessed a 20% coinsurance each month, which normally results in fees of around $500 to $1200. Patients who do not qualify for Medicaid as a secondary payer are supposed to pay the monthly coinsurance out of their own pockets or obtain a secondary policy, which normally costs several hundred dollars per month, often as much as the cost of the coinsurance they are trying to cover. Commercial plans also can generate large annual deductibles and monthly coinsurance amounts.

New fields and revised worksheets will likely be a result of the current audits along with Medicare’s desire to have greater detail and specificity.

Surely there is a better way to help these patients cover their coinsurances and deductibles and have providers reimbursed at a reasonable amount. Most ESRD patients pay little, if anything, to the dialysis provider for their assigned coinsurances and deductibles. Medicare's Allowed Amount under the Bundle is approximately at or slightly above cost for most dialysis providers. Because Medicare only pays 80% of their Allowed Amount, dialysis facilities treating Medicare patients with no secondary coverage are supposed to pay the monthly coinsurance out of their own pockets or obtain a secondary policy. Patients who do not qualify for Medicaid as a secondary payer are supposed to pay the monthly coinsurance out of their own pockets or obtain a secondary policy, which normally costs several hundred dollars per month, often as much as the cost of the coinsurance they are trying to cover. Commercial plans also can generate large annual deductibles and monthly coinsurance amounts.

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**Rick Collins** is the chief operating officer of Sceptre Management Solutions, Inc., a company specializing in billing for outpatient ESRD facilities, nephrology practices, and vascular access. Your questions are welcome and he can be reached at rcollins@sceptremanagement.com or 801.775.8010.
TRIFERIC® (ferric pyrophosphate citrate) solution, for addition to bicarbonate concentrate

BRIEF SUMMARY OF FULL PRESCRIBING INFORMATION

INDICATIONS AND USAGE: Triferic is indicated for the replacement of iron to maintain hemoglobin in adult patients with hemodialysis-dependent chronic kidney disease (HDD-CKD).

LIMITATION OF USE. Triferic is not intended for use in patients receiving peritoneal dialysis. Triferic has not been studied in patients receiving home hemodialysis.

CONTRAINDICATIONS: None

WARNINGS AND PRECAUTIONS: Hypersensitivity Reactions. Serious hypersensitivity reactions, including anaphylactic-type reactions, some of which have been life-threatening 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 [see Adverse Reactions]. Hypersensitivity reactions have been reported in 1 (0.3%) of 292 patients receiving Triferic in two randomized clinical trials.

Iron Laboratory Testing. 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 following adverse reactions are described below and elsewhere in the labeling: Hypersensitivity Reactions [see Warnings and Precautions].

Clinical Trials Experience. Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug may not reflect the rates observed in practice. In two randomized, placebo-controlled clinical trials, a total of 292 patients were administered Triferic for periods of up to 1 year [see Clinical Studies in the Full Prescribing Information]. The mean total exposure in the randomized treatment period was 5 months. A total of 296 patients received placebo treatment for a similar time period. In the two studies, 64% were male and 54% were Caucasian. The median age of patients was 60 years (range, 20 to 89 years). Adverse events occurring in 3% or greater of patients treated with Triferic in the randomized clinical trials are listed in Table 1.

Table 1: Adverse Reactions Reported in Two Clinical Trials in at Least 3% of Patients Receiving Triferic and at an Incidence at least 1% Greater than Placebo

<table>
<thead>
<tr>
<th>System organ class</th>
<th>Preferred term</th>
<th>Triferic N=292 n (%)</th>
<th>Placebo N=296 n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients with at least one adverse reaction</td>
<td>229 (78.4)</td>
<td>223 (75.3)</td>
<td></td>
</tr>
<tr>
<td>General Disorders and Administration Site Conditions</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>20 (6.8)</td>
<td>11 (3.7)</td>
<td></td>
</tr>
<tr>
<td>Pyrexia</td>
<td>13 (4.5)</td>
<td>9 (3.0)</td>
<td></td>
</tr>
<tr>
<td>Asthenia</td>
<td>12 (4.1)</td>
<td>9 (3.0)</td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>11 (3.8)</td>
<td>6 (2.0)</td>
<td></td>
</tr>
<tr>
<td>Infections and Infestations</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>13 (4.5)</td>
<td>4 (1.4)</td>
<td></td>
</tr>
<tr>
<td>Injury, Poisoning, and Procedural Complications</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Procedural hypotension</td>
<td>63 (21.6)</td>
<td>57 (19.3)</td>
<td></td>
</tr>
<tr>
<td>Arteriovenous fistula thrombosis</td>
<td>10 (3.4)</td>
<td>6 (2.0)</td>
<td></td>
</tr>
<tr>
<td>Arteriovenous fistula site hemorrhage</td>
<td>10 (3.4)</td>
<td>5 (1.7)</td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal and Connective Tissue Disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Muscle spasms</td>
<td>28 (9.6)</td>
<td>24 (8.1)</td>
<td></td>
</tr>
<tr>
<td>Pain in extremity</td>
<td>20 (6.8)</td>
<td>17 (5.7)</td>
<td></td>
</tr>
<tr>
<td>Back pain</td>
<td>13 (4.5)</td>
<td>10 (3.4)</td>
<td></td>
</tr>
<tr>
<td>Nervous System Disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>27 (9.2)</td>
<td>16 (5.4)</td>
<td></td>
</tr>
<tr>
<td>Respiratory, Thoracic and Mediastinal Disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dyspnea</td>
<td>17 (5.8)</td>
<td>13 (4.4)</td>
<td></td>
</tr>
</tbody>
</table>

Adverse Reactions Leading to Treatment Discontinuation. In clinical trials, adverse reactions leading to treatment discontinuation included headache, asthenia, dizziness, constipation, nausea, hypersensitivity reactions, intradialytic hypotension, pruritus, and pyrexia. Adverse reactions reported in the treatment extension period were similar to those observed in the randomized clinical studies.

USE IN SPECIFIC POPULATIONS: Pregnancy. Pregnancy Category C. Risk Summary: There are no adequate and well-controlled studies of Triferic in pregnant women. In pregnant rats and rabbits, ferric pyrophosphate citrate caused developmental toxicity at maternally toxic dose levels that were higher than the maximum theoretical amount of iron transferred to patients from Triferic. The incidence of major malformations in human pregnancies has not been established for Triferic. However, all pregnancies regardless of exposure to any drug have a background rate of 2 to 4% for major malformations, and 15 to 20% for pregnancy loss. Use Triferic during pregnancy only if the potential benefit justifies the potential risk to the fetus. Animal Data: In a fertility and early embryonic development study in female rats, the maternally toxic ferric pyrophosphate citrate dose of 40 mg/kg administered three times per week by intravenous (IV) infusion was not toxic to the developing embryo. In embryo-fetal developmental toxicity studies, ferric pyrophosphate citrate was administered during the period of organogenesis as a one-hour IV infusion to pregnant rats and rabbits. No maternal or developmental toxicity was observed at doses up to 30 mg/kg/day in rats and 20 mg/kg/day in rabbits. Maternally toxic doses affected embryo-fetal development, resulting in post-implantation loss due to early resorptions, abnormal placentae, decreased fetal body weight and fetal head and vertebral malformations at 90 mg/kg/day in rats and vertebral malformations at 40 mg/kg/day in rabbits. A pre-and post-natal development study was conducted in pregnant rats with intravenous doses of ferric pyrophosphate citrate up to 90 mg/kg/day. The maternally toxic dose of 90 mg/kg/day resulted in reductions in the number of live offspring and lower offspring body weights. There were no adverse effects on survival of offspring at doses up to 30 mg/kg/day, or on behavior, sexual maturation or reproductive parameters of offspring at any dose level. Nursing Mothers. It is not known if ferric pyrophosphate citrate is present in human milk. Because many drugs are excreted in human milk and because of the potential for adverse events in nursing infants, a decision should be made whether to discontinue nursing or to avoid Triferic, taking into account the importance of iron to the mother and the known benefits of nursing. Pediatric Use. Safety and effectiveness have not been established in pediatric patients. Geriatric Use. In controlled clinical trials, 99 (28.6%) patients ≥ 65 years of age were treated with Triferic. No overall differences in safety and efficacy were observed between older and younger patients in these trials [see Clinical Studies in the Full Prescribing Information].

OVERDOSAGE: No data are available regarding overdosage of Triferic in humans.

NONCLINICAL TOXICOLOGY: Carcinogenesis, Mutagenesis, Impairment of Fertility. Studies examining the carcinogenic potential of ferric pyrophosphate citrate have not been conducted. Ferric pyrophosphate citrate was clastogenic in the in vitro chromosomal aberration assay in CHO cells in the presence of metabolic activation. Ferric pyrophosphate citrate was not mutagenic in the in vitro bacterial reverse mutation (Ames) test or clastogenic in the in vitro chromosomal aberration assay in CHO cells in the absence of metabolic activation. Ferric pyrophosphate citrate is not mutagenic in the in vivo mouse micronucleus assay. In a combined male and female fertility study in rats, ferric pyrophosphate citrate was administered intravenously over one hour three times per week at doses of up to 40 mg/kg. No adverse effects on fertility or reproduction were noted.

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IMPORTANT SAFETY INFORMATION

Warnings and Precautions
Serious hypersensitivity reactions, including anaphylactic-type reactions, some of which have been life-threatening 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: procedural hypotension (21.6%), muscle spasms (9.6%), headache (9.2%), pain in extremity (6.8%), peripheral edema (6.8%), dyspnea (5.8%), back pain (4.5%), pyrexia (4.5%), urinary tract infection (4.5%), asthenia (4.1%), fatigue (3.8%), arteriovenous (AV) fistula thrombosis (3.4%), and AV fistula site hemorrhage (3.4%).

References:
1. Rockwell Medical, Inc. Data on File. Independent Market Research Study Conducted in August 2015 with 103 U.S. Based Nephrologists – Based upon efficacy, safety, most appealing aspect, contrast to IV iron and choice between Triferic and IV iron.