Volume Overload and Survival in Patients on Peritoneal Dialysis

Patients on peritoneal dialysis receive individualized dialysis prescription by combining various techniques (automated versus manual), dialysis solutions (tonicity, biocompatibility, type of osmotic agent), and number and duration of dwells. The goal is to optimize maintenance of residual kidney function, preserve the peritoneal membrane, and control uremic symptoms, volume, and nutritional status, all designed to prolong technique and patient survival.

In patients receiving renal replacement therapy, elevated systolic blood pressure and volume overload are associated with a higher risk of mortality. Both factors occur equally in patients in hemodialysis and peritoneal dialysis. In a large cohort of patients on hemodialysis, baseline and cumulative volume overload over 1 year, assessed by bioimpedance spectroscopy, was associated with mortality, independent of baseline blood pressure.

Among prevalent peritoneal dialysis patients, volume overload is frequent and associated with mortality. Until the start of the international multicenter study Initiative for Patient Outcomes in Dialysis-Peritoneal Dialysis (IPOD-PD), there were few data on incident patients on peritoneal dialysis. Researchers sought to correlate expression of specific metabolites with simultaneously measured eGFR and ht-TKV.

Postdialysis Hypokalemia and All-cause Mortality in Patients on Hemodialysis

Among patients on hemodialysis, the mortality rate is 13.6 per 100 person-years, higher than in the general population. Sudden cardiac death is the leading cause of death in patients on hemodialysis, caused primarily by hyperkalemia, making serum potassium of particular interest in the management of dialysis patients. Serum potassium levels during dialysis are determined on the basis of the predialysis potassium level, making assessment of predialysis potassium a possible aid in the prevention of sudden cardiac death associated with hyperkalemia.

Anxiety Associated with Mortality and Hospitalization in Patients on Dialysis

Patients with end-stage renal disease on maintenance dialysis have a high prevalence of mood disorders, most commonly depressive and anxiety disorders. When using a cutoff value in self-report questionnaires, the prevalence for anxiety symptoms ranges from 39% to 53%, and for depressive symptoms, the range is from 37% to 42%. These symptoms have an impact on a patient's quality of life and may be associated with adverse medical outcomes.

A previous study among non-dialysis-dependent patients with chronic kidney disease showed a significant association between anxiety symptoms and mortality. Robbert W. Schouten, MSc, and colleagues recently conducted a study designed to examine the association between anxiety symptoms and mortality in a population of patients on dialysis. The researchers also sought to assess the association between anxiety and 1-year hospitalization rate and length of stay. For comparison purposes, the researchers also examined the association between depressive symptoms and adverse clinical outcomes. Results of the study were reported in the American Journal of Kidney Diseases [2019;74(2):158-166].

The study utilized data from DIVERS (Depression Related Factors and Outcomes in Dialysis Patients with Various Ethnicities and Races Study). DIVERS is an observational prospective cohort study conducted in The Netherlands from 10 dialysis centers between June 2012 and October 2016.
Updated KDIGO guidelines recommend limiting the use of calcium-based binders...

SWITCHING TO VELPHORO CAN MAKE A WORLD OF DIFFERENCE

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 chewable tablets must be administered with meals. Velphoro should be chewed or crushed. Do not swallow whole.
- 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 (8%).
- Velphoro can be administered concomitantly with oral calcitriol, ciprofloxacin, digoxin, enalapril, furosemide, HMG-CoA reductase inhibitors, hydrochlorothiazide, losartan, metoprolol, nifedipine, omeprazole, quinidine and warfarin. For oral medications where a reduction of bioavailability would be clinically significant consider separating the timing of administration. Consider monitoring clinical responses or blood levels of the concomitant medications.

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

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

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

DOSEAGE 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.

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

CONTRAINDICATIONS
None.

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

ADVERSE REACTIONS
In a parallel design, fixed-dose study of 6 weeks duration, the most common adverse drug reactions to Velphoro chewable tablets in hemodialysis patients included discolored feces (12%) and diarrhea (6%).

The following adverse reactions were identified during post approval use of Velphoro and were reported voluntarily from a population of uncertain size.

Gastrointestinal Disorders: tooth discoloration
Skin and Subcutaneous Tissue Disorder: rash
To report SUSPECTED ADVERSE REACTIONS, contact Fresenius Medical Care North America at 1-800-323-5188 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

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

Take acetylsalicylic acid, cephalexin and doxycycline at least 1 hour before Velphoro.
Take levothyroxine at least 4 hours before Velphoro.
For oral medications not listed above where a reduction of bioavailability would be clinically significant consider separation of the timing of administration. Consider monitoring clinical responses or blood levels of the concomitant medication.

USE IN SPECIFIC POPULATIONS
Pregnancy
Pregnancy Category B: Reproduction studies have been performed in rats and rabbits at doses up to 16 and 4 times, respectively, the human maximum recommended clinical dose on a body weight basis, and have not revealed evidence of impaired fertility or harm to the fetus due to Velphoro. However, Velphoro at a dose up to 16 times the maximum clinical dose was associated with an increase in post-implantation loss in pregnant rats. Animal reproduction studies are not always predictive of human response. There are no adequate and well-controlled studies in pregnant women.

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

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

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

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

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

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

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

Velphoro tablets are packaged as follows:
NDC 49230-645-51 Bottle of 90 chewable tablets

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

PATIENT COUNSELING INFORMATION
Inform patients that Velphoro tablets should be chewed or crushed. Do not swallow whole [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, but this discoloration of the stool is considered normal with oral medications containing iron.

Inform patients that Velphoro can stain teeth.

Inform patients to report any rash to their healthcare professional.

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Dialysis Moonshot Revisited: Options for the Elderly

In a previous editorial, I made the case for the federal government funding a Dialysis Moonshot initiative, set up similarly to the Obama administration’s Cancer Moonshot that was spearheaded by Vice President Joe Biden.

In occasional articles, I intend to cover areas of dialysis care where research is very limited and the impact of research on patient lives could be substantial. One specific area that could be funded is research examining the benefit of initiating dialysis versus maximal conservative therapy in the very elderly (defined as age ≥75 years). Outcomes could include health-related quality of life (QoL) and mortality.

The number of dialysis patients older than 75 is growing rapidly. However, outcomes among these patients are very poor. USRDS data from 2018 report that among those 75 years and older, expected remaining lifetime in years is 3.3 for men and 3.6 years for women on dialysis, compared with 7.6 and 8.3 years for men and women in the general population, respectively.1

Indeed, life span on dialysis steeply declines for both men and women after the age of 60, and mortality is nearly doubled for those >75 years of age (195 and 188 vs 364 and 339 deaths per 1000 patient years respectively).1

Berger and Hedayati, in a paper in a 2012 CJASN, discuss the challenges with renal replacement in the elderly. Factors that influence higher mortality include increased frailty, falls, and functional/cognitive impairment. Jennifer S. Scherer and Markus Bitzer writing in Kidney News Online3 discuss the limitations of current guidelines with respect to dialysis care among the elderly. They are “disease oriented and with a one-size-fits-all-approach that pays little attention to QoL.” The authors state that there is no right answer for an elderly patient: “A time-limited trial begins with the identification of patient-specific goals, often relevant to QoL and geriatric syndromes, with planned re-evaluations to assess the patient’s perceptions of the benefits and burdens of dialysis. This continuous dialogue also allows for a fluid transition into advance care planning. Advance care planning with dialysis patients can promote the use of hospice, a benefit often underused in this population. In the general population advance care planning is associated with fewer intensive procedures at the end of life, death at the location of choice, increased patient satisfaction, and increased use of hospice.”

In a recent longitudinal comparison of older patients beginning dialysis versus enrolling in maximum conservative therapy, the GOLD (Older Patients Starting Dialysis) study, van Loon and colleagues4 reported four key findings: (1) patients starting dialysis compared with patients choosing conservative care had similar overall QoL, (2) over time, QoL in the dialysis group remained stable versus a small decline of QoL observed in the conservative group; (3) hospitalization was significantly higher among dialysis patients compared with conservative patients, despite conservative patients being older; and (4) survival at 12-months in patients over 80 years old was not significantly longer in patients initiating dialysis compared with maximum conservative care patients.

There are currently major gaps in understanding what should be the optimal care of elderly patients with kidney failure. Data suggest that lifespan is limited regardless of whether these patients are treated with dialysis or maximal conservative therapy. A sensible approach might be to focus on quality of life. Figuring this out could be a goal of a Dialysis Moonshot!

REFERENCES
A total of 687 patients were included in the cohort. The cohort included prevalent (n=433; 64%) and incident dialysis patients (n=240; 36%). Median dialysis vintage among the prevalent patients was 13 months. Overall, mean age was 65 years, 62% were men, and 48% were immigrants. Maximum follow-up was 4 years; median follow-up was 3.1 years. Twenty-five percent of the participants (n=173) died during follow-up.

Both anxiety and depressive symptoms had a dose response: there was an association between higher burden of symptoms and higher risk for all-cause mortality.

There were differences between the group with high anxiety symptoms and the group with low anxiety in immigrant status, prevalence of diabetes, depressive symptoms, and Mental Component Summary score on the 12-Item Short Form Health Survey (SF-12), a health-related quality of life questionnaire. There were no significant differences in social characteristics, vascular access, treatment modality, residual diuresis, and SF-12 Physical Component Summary score.

In predefined cutoff scores, 22% of patients had anxiety and 42% had depressive symptoms. Eighteen percent of patients had comorbid depressive and anxiety symptoms. The majority of patients with anxiety had depressive scores above the cutoff value. In the anxiety group, 27% of patients reported severe depressive symptoms. Measurements of anxiety and depression were taken after 6 months. In mixed-model analyses, there were no changes in Beck Anxiety Inventory (BAI) and Beck Depression Inventory (BDI) scores between the 6-month time points.

There was an association between anxiety and all-cause mortality. A 1-point greater BAI score was associated with a 5.1% greater risk for mortality [hazard ratio (HR), 1.051; 95% confidence interval (CI), 1.016-1.088; P=.004]. The same trend was seen for depressive symptoms: each 1-point greater BDI score was associated with a 4.3% greater risk for all-cause mortality (HR, 1.043; 95% CI, 1.004-1.083; P=.03).

There were only minor changes in the HR when the model included confounders, including a large number of medical co-morbid conditions. Results were similar in additional analyses using predefined cutoff values and the severity index of anxiety and depressive symptoms. Both anxiety and depressive symptoms had a dose response: there was an association between higher burden of symptoms and higher risk for all-cause mortality.

In both univariable and multivariable models, there were significant associations between anxiety and depressive symptoms and the number of hospitalizations and length of stay. A 1-point increase in either BAI or BDI score was associated with 1.8% greater 1-year hospitalization rate. Fifty-two percent of patients had at least one hospitalization during the first year of follow-up, and 16% had three or more hospitalizations in the first year of follow-up. Median hospital length of stay was 6 days.

Limitations to the findings included the overlap between depression and anxiety; the use of self-reported anxiety and depressive symptoms rather than a Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition diagnosis; and missing data that may have impacted the generalizability of the findings.

“Anxiety symptoms are highly prevalent and independently associated with increased risk for mortality, hospital admission rate, and hospital length of stay,” the researchers said. “This study provides clinicians and researchers with an indication of the clinical significance of anxiety in dialysis patients. Future studies should take anxiety symptoms into account when investigating mental health in dialysis patients. More research is needed to identify effective treatments for anxiety symptoms and provide the clinicians with the evidence for practical guidelines.”

**TAKEAWAY POINTS**

- Patients on dialysis often experience symptoms of anxiety and/or depression leading to adverse clinical outcomes.
- In a prospective cohort study in The Netherlands, there was an association between a 1-point greater increase in Beck Anxiety Inventory score and a 5.1% greater risk for all-cause mortality.
- Anxiety was also associated with an increase in hospitalization rate and length of stay. Anxiety symptoms had a clear dose-response relationship with mortality.
However, according to researchers in Japan, led by Tsuyoshi Ohnishi, PhD, the effects of hypokalemia may be underestimated. Dialysate usually has lower potassium concentration than serum, causing serum potassium levels to drop significantly following dialysis; 45% of patients present with postdialysis hypokalemia (<3.5 mEq/L).

The researchers conducted a cohort study to test the hypothesis that postdialysis potassium is a clinically important factor associated with mortality. The study was designed to examine the relationship between postdialysis potassium and all-cause mortality. The study utilized data from the Dialysis Outcomes and Practice Patterns Study in Japan (J-DOPPS). Results of the study were reported in the Clinical Journal of the American Society of Nephrology [2019;14(6):873-881].

The observational period began at study enrollment and ended at death, kidney transplant, loss to follow-up, or the end of the study, whichever came first. The primary outcome of interest was all-cause death during the observational period.

Patients were stratified into one of four groups based on baseline postdialysis potassium levels: (1) low group, potassium <3.0 mEq/L; (2) medium-low group, potassium 3.0 to <3.5 mEq/L; (3) medium-high group, 3.5 to <4.0 mEq/L; and (4) high group, potassium ≥4.0 mEq/L. The time course of each group over the observation period was determined using Kaplan-Meier curves.

Study participants had been treated at 61 facilities. Of 4675 potentially eligible participants, 117 were excluded due to short dialysis duration and 591 were excluded due to lack of baseline postdialysis potassium level measurement. The total number of eligible participants was 3967: 1929 were in J-DOPPS phase 4 (2009-2012) and 2038 were in J-DOPPS phase 5 (2012-2015).

Of the total cohort, 64% were men (n=2552) and 36% were women (n=1415), median age was 65 years, and median dialysis vintage was 3.9 years. There were 374 patients in the low group, 1752 in the medium-low group, 1427 in the medium-high group, and 414 in the high group. Patients in the low group tended to be elderly and frail, with high average age, low body mass index, low albumin level, high C-reactive protein level, and low normalized protein catabolic ratio. Patients in the low group also had the highest prevalence of chronic heart failure, cancer, psychiatric disorders, and cerebrovascular disease.

Overall, >30% of patients were treated with angiotensin II receptor blockers; there was no specific trend for any medication in any group. Ninety-six percent (3804/3967) were treated with dialysate potassium of 2.0 to <2.5 mEq/L, a trend that was consistent in all four groups. Only 21 participants were treated with low (<2.0 mEq/L) or high (>2.5 mEq/L) dialysate potassium. During the median observational period of 2.6 years, 14% of participants died (n=552/3967): 96 in the low postdialysis potassium group, 220 in the medium-low group, 179 in the medium-high group, and 57 in the high postdialysis group. The incidence rates were 11.2, 6.0, 6.2, and 7.4 per 100 person-year, respectively; the overall incidence rate was 6.7 per 100 person-years. The most common causes of death were sudden death and infectious disease.

In analyses using postdialysis potassium as a categorical variable, there was a significant association between postdialysis hypokalemia (<3.0 mEq/L) and mortality in unadjusted analysis (hazard ratio [HR], 1.84; 95% confidence interval [CI], 1.44-2.34; P<.01). Following adjustment for baseline confounders of patient demographic characteristics, comorbidities, and medications, the HR of postdialysis hypokalemia was 1.41 (95% CI, 0.97-2.00; P=.07). In a model that included adjustment for baseline confounders plus time-varying laboratory variables without predialysis potassium, the HR of postdialysis hypokalemia was 1.44 (95% CI, 1.14-1.82; P<.01). In a third model, following further adjustment for time-varying potassium, the HR of postdialysis hypokalemia was 1.10 (95% CI, 0.84-1.44; P=.49). There was no association between medium-high and high postdialysis potassium and mortality in either model.

In patients with predialysis hypokalemia only, the HR was 1.40 (95% CI, 1.02-1.91; P=.04). In patients with both pre- and postdialysis hypokalemia, the HR was 1.72 (95% CI, 1.35-2.19; P<.01). The P value for interaction among combination categories was <.01.

In citing limitations to the study, the authors included the inability to establish causality due to the observational design; the findings possibly not including residual confounding factors such as malnutrition and inflammation; the uncertainty of the generalizability of the findings to patients treated with dialysis for extremely long or short periods; the possibility that treatment quality in each facility may have confounded the results; and measuring postdialysis potassium levels only once during each dialysis session.

“In conclusion, postdialysis hypokalemia was associated with mortality, but the association was not independent of predialysis potassium. Having both pre- and postdialysis hypokalemia was associated with the highest mortality,” the researchers said.
current strategies used to reduce volume overload include the risk of adverse side effects, such as faster degradation of the peritoneal membrane by the use of hypertonic exchanges or faster decline of residual kidney function when volume depletion follows.

At all time points, volume overload was higher in men than in women and higher in participants with versus without diabetes.

The IPOD-PD study investigated volume status in a population of incident patients on peritoneal dialysis to relate patient characteristics and practice patterns over a long-term follow-up to volume status and patient-relevant outcomes. Results of the study were reported by Wim Van Biesen, MD, PhD, and colleagues in the Clinical Journal of the American Society of Nephrology (2019;14[June]:882-893).

The study recruited consecutive incident participants on peritoneal dialysis from included centers between January 2011 and December 2012; participant follow-up continued until December 2015, and lasted a minimum of 3 and a maximum of 5 years.

A total of 1092 participants were recruited in 138 centers from 28 countries. Of the participants recruited from Asia Pacific, all but two were recruited in South Korea. Following application of exclusion criteria, the final analysis consisted of 1054 participants from Western Europe (n=715), Eastern Europe and Middle East (n=80), Asia Pacific (n=129), and Latin America (n=130). Thirty-six percent of participants were enrolling at the start of peritoneal dialysis; however, the majority showed either moderate (33%) or severe (24%) volume overload, with some differences between regions.

At the start of the study, 77% of the participants were treated with continuous ambulatory peritoneal dialysis; in all regions, during the first 3 years on dialysis, the proportion of automated peritoneal dialysis increased to 54%. The majority of participants (73%) were prescribed biocompatible solutions (defined as peritoneal dialysis solutions prepared in two-chamber bags); different regions differed somewhat in proportion of patients prescribed biocompatible solutions. At baseline, 31% of the entire cohort were prescribed hypertonic peritoneal dialysis solutions, defined as at least one exchange with a dextrose concentration >1.5%. At month 36, the percentage had increased to 51%. At baseline, hypertonic solutions were prescribed to 54% and 28% of volume-overloaded and non-volume-overloaded participants, respectively. At month 36, the percentages were 50% and 53%. There were substantial differences between regions in use of hypertonic solutions.

At three years, the cumulative study dropout rate was 74%. The primary causes of dropout were transfer to hemodialysis (23%) and transplantation (22%). Dropout for any reason was lowest in the Asia Pacific region: at 3 years, 60% of participants were still on peritoneal dialysis, compared with 26%, 23%, and 16% in Western Europe, Eastern Europe and Middle East, and Latin America, respectively.

Prior to the start of peritoneal dialysis treatment, mean volume overload was 1.9 L, with a reduction to 1.2 L during the first year. At years 2 and 3, volume overload remained relatively stable at 1.4 L both years. At all time points, volume overload was higher in men than in women and in participants with versus without diabetes. In all groups, the course of relative volume overload showed a slight and similar decrease. After 3 years of follow-up, the mean relative volume overload in the remaining cohort was lower than at baseline in participants from all regions with the exception of those from Latin America, where the mean volume overload increased.

Prior to the start of peritoneal dialysis, 57% of participants had a relative volume overload of >7%. After 1, 2, and 3 years of follow-up, the proportion decreased to 48%, 49%, and 53%, respectively. At all time points, relative fluid retention (<–7%) was found in 3% to 8% of participants. On average, mean relative volume increased in the first year in participants with volume depletion at baseline; among participants with volume overload at baseline a decreasing trend in mean relative volume was seen in the first year. Follow-up observations indicated that both groups (with and without volume depletion) tended toward enoolmation.

After controlling for change to hemodialysis and transplantation, in a competing risk model on time to death, the variables volume overload (defined as >17.3% of the 75th percentile of relative volume overload at month 1 in the study), age, cardiovascular disease, liver disease, and diabetes were used. The subdistributional hazard ratio for participants with volume overload was 1.59 compared with participants without volume overload (95% confidence interval, 1.08-2.33; P=.02).

The observational design of the study was cited by the researchers as a limitation to the findings, as was the possible limiting of the generalizability of the observations.

The researchers said, “In conclusion, our study found that substantial volume overload was present in this incident cohort of patients on peritoneal dialysis, with men and patients with diabetes being more affected. Volume overload was associated with mortality. The study revealed different treatment practices across centers and regions. Despite not using hypertonic exchanges, automated peritoneal dialysis, or polyglucose, the best technique survival was noted in Asia Pacific.”

**Cancer Incidence Higher in Patients with CKD**

In patients receiving renal replacement therapy, via either hemodialysis or peritoneal dialysis, elevated systolic blood pressure and volume overload are associated with increased risk for mortality.

Currently, there is conflicting evidence regarding the role of volume status in patients on peritoneal dialysis and related to patient outcomes.

**TAKEAWAY POINTS**

- In patients receiving renal replacement therapy, via either hemodialysis or peritoneal dialysis, elevated systolic blood pressure and volume overload are associated with increased risk for mortality.
- Researchers conducted a prospective cohort study to follow-up volume status in patients on peritoneal dialysis and related those data to patient outcomes.
- In the large cohort with varying treatment practices across centers and regions, a large proportion of patients had volume overload at initiation of dialysis. Over time there was improvement in volume overload; there was an association between the improvement and survival.

Survival Probability in Patients Receiving Maintenance Dialysis versus Patients with Cancer

The burdens of end-stage renal disease (ESRD) may not be fully understood by the general public. In 2010, more than 2 million patients worldwide were being treated for ESRD with maintenance dialysis; the number is expected to increase to 5.4 million by 2030. The mortality rate among dialysis patients is high; approximately 55% of patients die within 5 years of dialysis initiation. The poor prognosis seems to be poorly understood, even among patients in the hemodialysis population; >90% overestimate their 5-year survival probability.

Noting that cancer is a well-known disease in the general population, Kyla L. Naylor, PhD, and colleagues conducted a population-based cohort study designed to compare the survival of patients on maintenance dialysis with that of patients with common cancers to enhance the understanding of the burdens of ESRD. Subanalyses included survival probability presented by age, trends in survival probability over time, and the hazard ratio (HR) of mortality adjusting for clinical characteristics. The primary outcome of interest was all-cause mortality.

The researchers reported results of the study in the American Journal of Kidney Diseases [2019;73(6):765-776].

The study utilized data from linked administrative healthcare databases from Ontario, Canada, held at the ICES (Institute for Clinical Evaluation Sciences). Data from six linked databases were included. Patients initiating maintenance hemodialysis therapy were identified via the Canadian Organ Replacement Registry. Cancer patients were identified via the Ontario Cancer Registry. Data from the Registered Persons Database that captures demographic data and vital status for all Ontarians, the Canadian Institute for Health Information Discharge Abstract Database, the National Ambulatory Care Reporting System, and the Ontario Health Insurance Plan were also used in the study.

The maintenance dialysis subcohort included incident hemodialysis and peritoneal dialysis patients from January 1, 1997, to December 31, 2015. Exclusion criteria were <18 years of age or >105 years of age at time of dialysis therapy initiation, history of any cancer other than nonmelanoma skin cancer, previous receipt of an organ transplant (including kidney), or evidence of maintenance dialysis therapy >180 days prior to cohort entry. The index date for the maintenance dialysis subcohort was the date of maintenance dialysis therapy initiation.

Individuals in the cancer subcohort were diagnosed with cancer between January 1, 1997, to December 31, 2015. Included cancers were colorectal, lung, pancreas, breast (women) and prostate (men). Exclusion criteria were age <18 years or >105 years at cancer diagnosis, history of cancer other than nonmelanoma skin cancer, and previous evidence of chronic kidney disease (dialysis and kidney transplantation). The index date for the cancer subcohort was the date of cancer diagnosis.

The final study cohort included 33,500 maintenance dialysis patients (women, n=13,587 [40.6%] and men, n=19,913 [59.4%]) and 532,452 patients with cancer (women, n=256,938 [48.3%] and men, n=275,514 [51.7%]). For women, median age at initiation of dialysis therapy was 66 years and median age at diagnosis of cancer was 65 years. For men, median age at dialysis initiation was 65 years and median age at time of cancer diagnosis was 68 years.

Compared with cancer patients, patients on maintenance dialysis had a higher proportion of patients in the lowest income quintile (quintile 1). Dialysis patients had generally more comorbid conditions than patients in the cancer subcohort.

During a maximum of 20.3 years, in dialysis patients, total follow-up was 167,059 person years; in the cancer subcohort, total follow-up was 3,191,753 person-years. A total of 20,790 patients in the dialysis subcohort and 272,782 patients in the cancer subcohort died during the follow-up period.

Median survival in female dialysis patients was 5.0 years; in women with breast, lung, colorectal, and pancreatic cancer, median survival was 19.4, 0.8, 7.5, and 0.4 years, respectively (log rank P <.001). In men in the dialysis subcohort, median survival was 5.1 years; in men with prostate, lung, colorectal, and pancreatic cancer, median survival was 15.6, 0.6, 6.9, and 0.4 years, respectively (log rank P <.001).

In unadjusted analysis in women, dialysis had a worse 5-year survival probability (49.8%; 95% confidence interval [CI], 48.8%-50.7%) compared with breast (82.1%; 95% CI, 81.9%-82.4%) and colorectal (56.8%; 95% CI, 56.3%-57.2%) cancer. Women on maintenance dialysis had better 5-year survival probability than women with lung (19.7%; 95% CI, 19.4%-20.1%) and pancreatic cancer (9.4%; 95% CI, 8.9%-10.0%). In men, 5-year survival was worse in dialysis (50.8%; 95% CI, 50.1%-51.6%) compared with prostate (83.3%; 95% CI, 83.1%-83.5%) and colorectal (56.1%; 95% CI, 55.7%-56.5%) cancer; 5-year survival among dialysis patients was better than in men with lung (14.0%; 95% CI, 13.7%-14.3%) and pancreatic (9.1%; 95% CI, 8.5%-9.7%) cancer. Rates were similar in analyses of 1- and 10-year survival probabilities. In both men and women, colorectal cancer had a lower 1-year survival probability compared with dialysis patients. Following adjustments for clinical characteristics, results were also similar for lung and pancreatic cancer in both men and women; dialysis patients had a higher rate of death at 24 years after diagnosis. Women and men 270 years of age with incident kidney failure treated with maintenance dialysis had unadjusted 10-year survival probabilities that were comparable to pancreatic and lung cancer.

The researchers cited some limitations to the study, including the possibility that the results are not generalizable to other countries and races; lack of data on cancer stage; and the possibility of unmeasured confounding.

The researchers said, “Mortality is high in the maintenance dialysis population, with mortality being particularly high in the elderly dialysis population (aged ≥70 years). Many dialysis patients experienced a higher probability of death compared with several common cancers. The results of this study highlight the urgent need to fund, develop, and test interventions to improve survival in maintenance dialysis patients and include such patients in trials for other conditions (e.g., coronary heart disease). Furthermore, rates highlight the need for advance care planning and can be used to facilitate this planning in elderly patients beginning treatment with maintenance dialysis.”

Researchers in Canada conducted a study to compare survival of patients on maintenance dialysis with that of patients with common cancers. In women, patients on maintenance dialysis had worse unadjusted 5-year survival than breast and colorectal cancer but better survival than patients with lung and pancreatic cancer. In men, unadjusted 5-year survival was worse in patients on dialysis compared with prostate and colorectal cancer but better than in patients with lung and pancreatic cancer.
Protein Loss in PD Patients Underestimated in Current Equations

The risk of losing muscle mass is elevated in patients with chronic kidney disease (CKD) due, in part, to episodes of metabolic acidosis during disease progression, low-protein diets aiming to slow CKD progression, bone and mineral disorders, and background inflammation. Current clinical guidelines call for regular assessment of dietary protein intake; nutritional targets are designed to reduce muscle breakdown and loss.

If a patient with CKD is not losing muscle mass, they are assumed to be in neutral protein balance. A useful laboratory measure of neutral protein balance is the difference between protein (i.e., nitrogen) intake and nitrogen losses. Traditionally, the protein equivalent of nitrogen appearance (PNA) has been estimated from combined urinary and peritoneal urea losses, and it is assumed that urea represents a constant proportion of total nitrogen excreted.

However, according to Surachet Vongsanim, MD, and colleagues, depending on fluctuating acid-base balance, nitrogen excretion switches between urea and ammonia, creating the possibility that a relative increase in the proportion of nitrogen excreted as ammonia may be undetected. The result would be a false-positive nitrogen balance possibly masking concomitant muscle protein loss.

At present, there are three equations used in clinical practice to estimate PNA. Dr. Vongsanim et al. sought to determine whether there were differences in those equations in determining PNA. The researchers measured the excretion of nitrogen in urine and peritoneal dialysate effluent in the form of either urea or total nitrogen. In each equation, the intercept and slope of the relationship between urea and total nitrogen, including other nitrogen losses (e.g., ammonia, protein), that are ~55% of total nitrogen loss.

The regression equation derived from previous studies is used as a basis in each of the three equations to convert urea nitrogen into total nitrogen. In each equation, the intercept and slope of the relationship between urea and total nitrogen, including other nitrogen losses in the dialysate (an inflation factor), differed.

The researchers compared total nitrogen lost in the spent dialysates and the urea nitrogen equivalent adjusted by the individual inflation factor. There was a positive correlation with total nitrogen losses for all three equations (r=0.74; P<0.001).

There were significant differences in the difference between measured –4.1 total nitrogen and that estimated by each of the three equations: measured loss was 27.7 g per day versus Bergström, 16.5 g per day; Randerson, 16.4 g per day; and Blumenkrantz, 12.9 g per day (P<0.001).

The researchers said, “Our findings demonstrate that at higher protein losses, the currently used predictive equations underestimate the amount lost. It is important to compensate the iatrogenic protein loss by recommending the appropriate intake of dietary protein to patients, in an attempt to minimize muscle wasting. This discrepancy may have arisen because of the characteristics of newer peritoneal prescriptions and change in patient demographics. We propose a new equation: PNA g/day = 0.31 × (urea loss mmol) + 7.17, which will require prospective validation in additional studies.”

There are many factors that influence this loss, such as the type of dialysis, the presence of infections, and the patient’s diet. The study suggests that current equations may be underestimating protein loss, leading to inadequate protein intake for patients.

**Takeaway Points**
- Patients with chronic kidney disease receiving peritoneal dialysis are at increased risk for muscle wasting. Current guidelines call for assessment of dietary intake via calculating protein equivalent of nitrogen appearance (PNA) to ensure sufficient protein intake.
- Researchers conducted a cross-sectional observational cohort study to re-evaluate the three equations currently used to estimate PNA by comparing measured peritoneal nitrogen losses with the estimates as determined by the equations.
- Analysis revealed that at higher protein losses, each of the three equations underestimated protein loss.
Hypotensive Events in Patients Receiving Meals during Hemodialysis

End-stage renal disease (ESRD) poses a major public health concern in the United States; the standard treatment for ESRD is hemodialysis. Patients receiving maintenance hemodialysis have dietary needs and restrictions, including requirements for increased protein (1.2 g/kg/day) and energy (30-35 kcal/kg/day) intake and restricted intake of phosphorus, sodium, potassium, and/or fluid.

The restrictions add to the difficulty of meeting the protein and energy requirements; other impediments may include postdialysis fatigue, nausea and vomiting, poor appetite, dysgeusia, lack of dietary information, and lack of access to food. The estimated average protein and energy intake of patients receiving hemodialysis is below current recommendations and patients in that population are commonly diagnosed with protein-energy wasting (PEW). Previous studies have also found that energy and protein intake is significantly lower on dialysis treatment days. PEW is known to be associated with poor outcomes, including diminished quality of life and increased mortality rate.

Providing nutrition through food or supplements during hemodialysis sessions has gained support and interest recently. However, despite studies demonstrating potential benefits to quality of life and clinical outcomes, eating during hemodialysis is commonly prohibited or discouraged in dialysis centers in the United States. The practice is discouraged primarily due to various perceived risks, including concern over increased intradialytic postprandial hypotension.

Noting that there are very few data regarding the practice of providing nutrition during hemodialysis, Mun Sun Choi, MS, and colleagues recently conducted a pilot study to examine the effect of high-protein meals provided during dialysis. The primary outcome of interest was the effect on the frequency of symptomatic hypotensive events; secondary outcomes were related to nutritional status, quality of life, and acceptability of meals during dialysis. Results of the study were reported in the Journal of Renal Nutrition [2019;29(2):102-111].

The study intervention was a meal given approximately 1 hour following the start of the dialysis session. A research dietitian designed the meal options, which had consistent nutrient content; patients could choose their meal based on personal preferences. The main items were tuna bowtie salad, chicken salad plate, beef wrap with potato salad, chicken breast sandwich, turkey salad, chicken salad sandwich, vegan bowtie salad, and chicken lettuce salad. Beginning the Wednesday of the first week of the intervention, patients in the intervention group received lunch during their dialysis session; center staff recorded the time of the meal delivery and the return, along with a subjective assessment of the amount of food consumed (0%, 10%, 25%, 50%, 75%, 90%, and 100%).

A total of nine patients in each group (intervention and nonintervention [control]) completed the study and were included in the data analysis. The two arms were similar in baseline characteristics, with the exception of those in the intervention arm being older and having evidence of lower protein intake. The meals were generally well tolerated; one patient in the intervention arm vomited during a meal due to illness and one reported nausea and vomiting prior to three separate dialysis sessions, resulting in decline of meals twice. One patient vomited during a meal reportedly due to the consistency of the food.

Among the patients in the intervention group, there were 19 symptomatic hypotension events in five patients over 25 dialysis sessions in the prestudy period and 19 symptomatic hypotension events in six patients over 25 dialysis sessions per patient during the study period. There was no difference in median overall survival from metastatic diagnosis for those with brain metastases compared with those without brain metastases (26.4 months vs 27.8 months; P = .305). When analyzed according to IMDC risk factors, the results were similar.

In conclusion, the researchers said, “Overall survival from the diagnosis of metastatic RCC did not significantly differ with or without brain metastases in a cohort treated with modern systemic and CNS-directed therapies regardless of the timing of brain metastases diagnosis or presence of IMDC risk factors.”

statistical significance in the difference in symptomatic hypotension event frequency from prestudy to during study period in the intervention group. There were also no statistically significant differences in frequency of hypotension events in the control group. There was no effect on nutritional status.

Of the total cohort of 18 patients, 17 completed the End-of-Study Questionnaire (eight in the intervention arm and nine in the control arm). Overall, patients in both arms had positive attitudes regarding receiving nutritious meals during dialysis; there were no differences in responses between the two groups. In response to the question “how easy do you feel it is for you to eat nutritionally or follow a renal diet?” only 35% of the total cohort responded with “somewhat easy” or “very easy.” When asked “how interested would you be in receiving nutritious meals during dialysis?” 71% responded with “somewhat interested” or “very interested.”

The pilot/feasibility design of the study was cited by the authors as a limitation to the findings. Other limitations cited were the small sample size, the nonrandomization of the two arms, and the uneven distribution between the arms of the baseline characteristics of the patients.

In summary, the researchers said, “These pilot data suggest that meals during hemodialysis do not increase the frequency of symptomatic hypotension events. In addition, patients generally had positive attitudes toward receiving meals and such meals could help educate patients about appropriate food selection. However, changes in nutritional status indicators were not observed. Larger, longer-term, randomized-controlled studies with patients selected for hypoalbuminemia at baseline are needed to confirm these results along with effects on nutritional and clinical outcomes in patients undergoing hemodialysis. Nevertheless, our data do not support the current practice of restricting eating meals during hemodialysis. Our conclusions are in agreement with the new consensus statement on eating during hemodialysis from the International Society of Renal Nutrition and Metabolism.”

TAKEAWAY POINTS
- Patients on maintenance hemodialysis are required to increase protein and energy intake and restrict phosphorus, sodium, potassium and/or fluid intake.
- Researchers conducted a pilot study to examine the effect of high-protein meals provided during dialysis sessions.
- The primary outcome of interest was the frequency of symptomatic hypotension events; secondary outcomes were nutritional status, quality of life, and acceptability of meals during dialysis.
- There was no statistically significant difference in the change in the frequency of symptomatic hypotension events between the two groups (intervention vs. control) from prestudy to during study. There was no effect on nutritional status between the arms; both groups reported positive attitudes toward receiving meals during dialysis.

Patients on maintenance hemodialysis are required to increase protein and energy intake and restrict phosphorus, sodium, potassium and/or fluid intake. Researchers conducted a pilot study to examine the effect of high-protein meals provided during dialysis sessions. The primary outcome of interest was the frequency of symptomatic hypotension events; secondary outcomes were nutritional status, quality of life, and acceptability of meals during dialysis.

C hronic periodontitis is a local inflammatory condition that affects the tooth-supporting tissues. There is an association between periodontitis and higher levels of locally produced proinflammatory markers, contributing to low-grade systemic inflammation. It is possible that periodontitis contributes to decline in kidney function because: (1) periodontitis contributes to overall systemic inflammatory burden, possibly triggering kidney function decline; and (2) periodontal bacteria and related products can be found in the bloodstream, possibly damaging the kidney epithelium.

There are limited data on the relationship between chronic periodontitis and kidney function. Christin Wangerin, DDS, and colleagues recently conducted a population-based cohort study designed to examine the association between current and cumulative periodontal disease status with kidney function. Results of the study were reported in the *American Journal of Kidney Diseases* [2019;73(4):S13-S24].

The researchers utilized 11-year follow-up data from the population-based prospective Study of Health in Pomerania (SHIP). Glomerular filtration rate estimated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) creatinine-cystatin C equation (eGFR<sub>cre-cys</sub>) and urinary albumin-creatinine ratio (UACR) were used to assess kidney function. Periodontal disease was
assessed via analysis of five exposure variables to evaluate the consistency of the potential exposure-outcome effects using continuous rather than categorical variables.

Baseline SHIP data were available on 2297 participants, and 11-year follow-up data were available on 1512 participants. Eligible participants for the current analysis were 20 to 59 years of age. The outcomes of interest were eGFR<sub>cr-cys</sub> and moderately increased albuminuria, defined as UACR >30 mg/g.

Periodontal disease is characterized by current (pocket probing depth [PPD]) and cumulative (clinical attachment level [CAL]) characteristics. For the current analysis, the researchers evaluated variables quantifying disease severity (mean value) and extent (percentage of diseased sites) on the participant level, using both PPD and CAL measures. The analysis also evaluated total PPD to quantify current exposure to periodontal inflammation and account for the reduction in inflammatory exposure due to tooth loss.

The initial hypothesis that periodontitis might be associated with decreased eGFR was not supported by these results.

At baseline, mean age of participants included in the eGFR<sub>cr-cys</sub> analyses was 40 years, 47% of participants were men, 20% were highly educated, and 39% were current smokers. There were significant differences across categories of total PPD in covariate levels; low education, current smoking status, and high consumption of alcohol were seen more often in periodontally diseased individuals (highest category).

Those with periodontal disease also were more likely to have known diabetes mellitus, dyslipidemia, and hypertension than those with lower PPD levels. The remaining variables were significantly greater across greater categories of total PPD. In addition, across categories of total PPD, average eGFR<sub>cr-cys</sub> at baseline and follow-up decreased from 121.8 to 115.2 and from 105.0 to 101.8 mL/min/1.73 m<sup>2</sup>, respectively. Median UACR at baseline and at follow-up increased from 6.6 to 7.8 mg/g and from 7.6 to 9.1 mg/g, respectively, across categories of total PPD.

In linear and logistic mixed models, comprehensive modeling of various exposure and outcome variables did not reveal consistent statistically significant associations. In eGFR<sub>cr-cys</sub> models, effect estimates for periodontal variables were consistently nonsignificant. In UACR (long-transformed) models, there were significant associations between mean PPD, mean interproximal CLA, and percentage of...
Median urinary albumin-creatinine ratio at baseline and at follow-up increased from 6.6 to 7.8 mg/g and from 7.6 to 9.1 mg/g, respectively, across categories of total pocket probing depth.

sites with interproximal CAL ≥3 mm and UACR. Those with higher levels of periodontitis measures had greater worsening of UACR over time. There were no significant associations with any of the periodontitis variables when moderately increased albuminuria (UACR ≥30 mg/g) was used as the outcome.

In mixed models, evaluation of eGFRcr-cys as the outcome yielded significant hits for total PPD (ß=0.222 for highest versus reference category) and percentage of sites with interproximal CAL ≥3 mm. However, because effect estimates had implausible directions such that higher levels of periodontitis variables were associated with less pronounced decreases in eGFRcr-cys, the initial hypothesis that periodontitis might be associated with decreased eGFR was not supported by these results.

There were several study limitations cited by the authors, including the partial recording protocol of periodontal status that may have led to underestimation of severity of periodontal disease; basing changes in eGFR and albuminuria on only two measurements; assessing UACR using a spot urine sample; excluding individuals mainly due to missing confounder (only baseline) or outcome data (baseline and follow-up); and incomplete data on gum treatment during follow-up.

“In summary, mixed models failed to indicate consistent associations of periodontitis with decreased kidney function in a general population examined over 11 years. Thus, our results do not support the hypothesis that periodontitis might be a risk factor for decreased kidney failure,” the researchers said.

Researchers conducted a population-based cohort study to determine whether chronic periodontitis is associated with subsequent decreases in kidney function.

Baseline and 11-year follow-up data from the study of Health in Pomerania were used in the study. outcomes were glomerular filtration rate, estimated from serum creatinine and serum cystatin C, and increases in albuminuria.

The results do not support the hypothesis that periodontitis is an important risk factor for chronic kidney disease.
Association of Plasma Metabolites and Lipids with Kidney Function in Early ADPKD

A
tosomal dominant polycystic kid-
ney disease (ADPKD), characterized
by gradual enlargement of numer-
cous cysts in the kidneys over decades,
affects one in 1000 individuals. The disease
process begins before loss of estimated glo-
merular filtration rate (eGFR) occurs. The
most common genetic cause of ADPKD are
mutations in polycystin 1 (PKD1, ~75%); the
second most common are mutations in polycystin 2 (PKD2, ~15%). A third
causative gene, GANAB, has recently been identified in ADPKD (0.3%) and autosomal
dominant polycystic liver disease. When
GANAB is mutated and PKD1 maturation is
blocked, 5% to 10% of patients have no de-
tectable mutation following DNA sequenc-
ing of their PKD1 and PKD2 genes.

Depending on which gene is mutated and the strength of the mutation, the course of
ADPKD is variable. Environmental factors
such as dietary sodium intake and smoking
exposure also contribute to the variability of
disease progression and severity. With
the recognition that ADPKD is, at least in part, a
metabolic disease based on the discovery that
glucose, histidine, glutamine, and arginine
metabolic pathways are reprogrammed, there
is an opportunity to study such pathways to
develop new therapies for this disease.

The Consortium for Radiologic Imaging
Studies of Polycystic Kidney Disease study
established height corrected total kidney volume
(ht-TKV) as an accurate and reliable
measure of renal cyst burden; it is also a
specific plasma metabolite that is useful for future studies designed to predict
disease progression and severity. With the
strength of the mutation, the course of
ADPKD is variable. Environmental factors
such as dietary sodium intake and smoking
exposure also contribute to the variability of
disease progression and severity. With
the recognition that ADPKD is, at least in part, a
metabolic disease based on the discovery that
glucose, histidine, glutamine, and arginine
metabolic pathways are reprogrammed, there
is an opportunity to study such pathways to
develop new therapies for this disease.

To assess for systematic shifts among the
samples, the researchers investigated re-
producibility and time-dependent variation
using the repeated measurements for the 35
technical replicates for metabolomics and
the 36 technical replicates for lipidomics.

Following accounting for covariates, 20
metabolites were significantly correlated with eGFR at a P value of .05. Of those, there was
significant correlation between 12 metabo-
lines and eGFR at a q-value <.05. All the four metabolites were among the 12 previously identified as signifi-
cant at FDR q-value <.05 without controlling for
ht-TKV. In analyses of ht-TVK while con-
trolling for eGFR as a covariate, only taurine
was significant at FDR q-value <.05. The researchers performed further analy-

There was significant correlation between
12 metabolites and eGFR at FDR q-value <.05.

Data from a HALT-A subset of 277 white
participants who had known mutations in
either the PKD1 or PKD2 genes were
analyzed. To identify individual metabo-
lites whose intensities are significantly correlated with eGFR and ht-TKV, associa-
tion analyses were performed using linear
regression with each metabolite signal level
as the primary predictor variable and base-
line eGFR and ht-TKV as the continuous
outcomes of interest, while adjusting for co-

Twelve metabolites were significantly correlated with eGFR and two triglycerides
significantly correlated with baseline ht-TKV.

Identification of metabolic derangements in
early ADPKD may aid in prediction of
disease outcome and ultimately lead to new
therapeutic paradigms for this patient
population.

Utilizing plasma from the baseline visit
of participants in the randomized HALT-
A clinical trial following cessation of all
antihypertensive medications for at least
2 weeks, Kyounghi Kim, PhD, and col-
leagues recently sought to correlate expres-
sion of specific metabolites with simultane-
ously measured eGFR and ht-TKV. Results
were reported online in *BMC Nephrology*

In conclusion, the researchers said, “This
study identifies metabolic derangements in
early ADPKD which may be prognostic
for ADPKD progression. Such data will be
useful for future studies designed to predict
outcome of disease based on such early
metabolic changes and will likely lead to
new therapeutic paradigms for a disease
with quite limited therapeutic options.”

TAKEAWAY POINTS
- Researchers tested the hypothesis that specific plasma metabolites would correlate
with known predictors of disease progression [estimated glomerular filtration rate (eGFR)]
and height corrected total kidney volume (ht-TKV) in patients with autosomal
dominant polycystic kidney disease (ADPKD) in early stages of the disease.
- Twelve metabolites were significantly correlated with eGFR and two triglycerides
significantly correlated with baseline ht-TKV.
- Identification of metabolic derangements in early ADPKD may aid in prediction of
disease outcome and ultimately lead to new therapeutic paradigms for this patient
population.
HCV Status and Kidney Transplantation Outcomes

In the general population in the United States, the prevalence of hepatitis C virus (HCV) is 1%; the prevalence among patients on hemodialysis ranges between 3% and 14%. Current US practice guidelines call for screening of all dialysis patients for HCV infection by testing for anti-HCV antibody and, more recently, HCV RNA to confirm chronic infection.

For many patients with kidney failure, transplantation is the ideal therapy. However, there are few data available on outcomes among HCV-seropositive dialysis patients because HCV serostatus for wait-listed patients is not included in national registry data (i.e., the Organ Procurement and Transplantation Network [OPTN] and the US Renal Data System).

Deidre Sawinski, MD, and colleagues recently conducted a retrospective cohort study designed to examine the association between HCV serostatus and dialysis survival and kidney transplantation. The researchers also sought to determine whether kidney transplantation offered a survival benefit versus remaining on the waitlist among HCV-seropositive patients. Finally, the study assessed the impact of transplantation with an HCV-seropositive donor kidney on survival compared with waiting for a kidney from an HCV-negative donor. Results of the study were reported in the American Journal of Kidney Diseases [2019;73(6):815-826].

The study cohort included adults ≥18 years of age who were incident and prevalent patients receiving outpatient dialysis therapy between January 1, 2004, and December 31, 2014, at facilities in the United States managed by a large national dialysis provider (DaVita). Exclusion criteria were patients with indeterminate HCV serostatus and/or HIV infection. Using five different identifiers, clinical data from DaVita were linked to data from the OPTN: Social Security number, date of birth, first name, last name, and sex.

The primary exposure was HCV antibody status; results of assessment were reported as positive, negative, or indeterminate. The primary outcomes of interest were (1) mortality on dialysis therapy; (2) wait-listing for kidney transplantation; (3) kidney transplantation; and (4) estimated survival benefit from kidney transplantation versus remaining on the transplant waitlist. Secondary outcomes included removal from the waitlist. A total of 442,171 adult maintenance dialysis patients had a defined HCV serostatus; of those, 410,547 were HCV seronegative and 31,624 were HCV seropositive. Patients in the seropositive group were younger (median age, 56 vs 64 years; P<.001), more likely to be male (65.9% vs 54.4%; P<.001), and more likely to be African American (54% vs 29.1%; P<.001) than patients in the HCV seronegative group. Patients who were HCV seropositive were twice as likely to have Medicaid as their primary insurance (7.4% vs 3.3%; P<.001) than those in the HCV seronegative group.

The majority of the cohort received in-center hemodialysis; the most common vascular access was central venous catheter. In the HCV-seropositive group, median serum albumin and platelet count values were lower than in the HCV-seronegative group; the differences were not clinically significant.

There was an association between HCV seropositivity and increased risk for death on dialysis therapy (adjusted hazard ratio [aHR], 1.09; 95% confidence interval [CI], 1.07-1.11). Median follow-up was 652 days. In secondary analyses limited to hemodialysis patients or including the Fibrosis-4 index, results were similar. The most commonly reported causes of death were cardiovascular disease (33% HCV-seropositive vs 35.8% HCV-seronegative) and infection (8.5% HCV-seropositive vs 7.7% HCV-seronegative). In the HCV-seropositive cohort, patient death was attributed to liver disease in 3.3% of the cohort versus 0.6% in the seronegative patients (P<.001).

Following application of exclusion criteria, the researchers analyzed 410,804 patients regarding wait-listing (29,263 HCV-seropositive and 381,541 HCV-seronegative). In the seropositive cohort, median time to wait-listing was 354 days compared with 478 days in the seronegative cohort (P<.001). There was an association between HCV seropositivity and a lower likelihood of wait-listing for kidney transplant (aHR, 0.67; 95% CI, 0.61-0.74). The association remained consistent in models accounting for death as a competing risk for wait-listing and in secondary analyses.

A total of 51,625 patients were wait-listed for a kidney transplant. Of those, 16,490 seronegative and 1117 seropositive patients underwent transplantation. There was no significant difference between the groups in overall time to transplantation (507 days for HCV seronegative vs 433 days for HCV seropositive, P=6). However, the time to transplantation was significantly shorter for recipients of HCV-seropositive kidneys (251 days; P<.002).

In both unadjusted and adjusted analyses, there was no significant association between patient HCV seropositivity and rate of transplantation (aHR, 1.11; 95% CI, 0.97-1.28).

Compared with remaining on the waitlist, there was an association between kidney transplantation and decreased risk for death among the HCV-seropositive patients; this benefit was achieved by 9 months following transplantation. By year 3, the adjusted hazard ratio of death associated with transplantation compared with remaining on the waitlist was 0.42 (95% CI, 0.27-0.63). Of the 1117 seropositive recipients, 394 received kidneys from HCV-seropositive donors; survival benefit with transplantation was independent of donor HCV serostatus (aHR for death at 3 years, 0.42 [95% CI, 0.25-0.72] for kidneys from HCV-seronegative donors versus 0.52 [95% CI, 0.30-0.93] for kidneys from HCV-seropositive donors.

Study limitations cited by the authors included lack of data for HCV viral loads and incomplete data on severity of liver disease.

“In conclusion, this study provides important and comprehensive insights into outcomes for HCV-seropositive patients with end-stage renal disease on the spectrum from maintenance dialysis therapy through kidney transplantation. HCV-seropositive patients are younger yet experience a slightly higher adjusted rate of death on dialysis therapy. They have diminished access to the transplant waiting list, but those who undergo transplantation rapidly achieve a significant survival benefit. The survival benefit from kidney transplantation among HCV-seropositive patients suggests that removing barriers to wait-listing for this patient group should be a priority for providers. The benefit in accepting an HCV-infected organ over waiting for an HCV-negative one should encourage patients to carefully consider post-transplantation HCV treatment,” the researchers said.

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**The time to transplantation was significantly shorter for recipients of HCV-seropositive kidneys [251 days; P<.002].**

**Takeaway Points**

- In the United States, among patients with chronic kidney disease, the prevalence of hepatitis C virus infection is substantially higher than in the general population. Researchers conducted a retrospective cohort study to examine dialysis survival and transplantation outcomes in patients with CKD who were HCV seropositive.
- There was an association between HCV seropositivity and a small elevation in the rate of death and a substantially lower rate of entry onto the kidney transplant waitlist.
- Compared with remaining on the waitlist, receiving an HCV-seropositive donor kidney provided a survival advantage at the 2-year post-transplantation time point.
Treatment for c-aABMR May Improve Long-Term Allograft Survival

The introduction of calcineurin inhibition (CNI), and induction therapy with T cell depleting agents has significantly improved short-term outcomes of kidney transplantation; however, improvement in long-term renal allograft survival remains a considerable clinical challenge. Recent studies have suggested that chronic-active antibody mediated rejection (c-aABMR) is one of the major barriers for long-term renal allograft survival. Advanced c-aABMR often presents as progressive loss of allograft function and progressive proteinuria and hypertension. Most patients diagnosed with c-aABMR develop allograft failure within 2 years. Based on favorable results, in the past decade a renal transplant center in The Netherlands (Erasmus Medical Center, Department of Nephrology & Transplantation, Rotterdam) began treating patients with c-aABMR with a single course of intravenous immunoglobulin (IVIG) therapy and pulse intravenous methylprednisolone (MP). Kaasia A. Sablik, MD, and colleagues recently conducted a retrospective analysis to examine the efficacy of that treatment in patients with c-aABMR. Results of the analysis were reported online in BMC Nephrology [doi.org/10.1186/s12882-019-1385-z].

Inclusion criteria were biopsy proven c-aABMR, treatment with three doses of 1 g intravenous MP over a 3-day period combined with a single dose of IVIG (1g/kg body weight), sufficient data on allograft function, and no further treatment. All biopsies were for cause and were evaluated at the time of biopsy by an experienced renal pathologist based on the then current Banff classification. Of the 167 patients potentially eligible for inclusion, 69 met inclusion criteria. In addition, the researchers identified a historical patient group (n=27) who did not receive any additional treatment on diagnosis of c-aABMR. Most of the patients in the historical group were diagnosed prior to 2008 when the local treatment guideline for c-aABMR was adopted.

Among the 69 patients analyzed, average age was 53 years, and 75% received a living donor kidney transplant. The maintenance immunosuppressive regimen consisted of double immunosuppression with a combination of tacrolimus and mycophenolate mofetil. Forty-six percent of the patients used steroids.

Time to biopsy from time of transplantation was a median of 6.3 years; median estimated glomerular filtration rate (eGFR) was 34 mL/min/1.73 m², and median proteinuria was 230 mg/mmol at the time of renal biopsy. There were no deaths in the first year of follow-up. Among the 69 patients treated with IVIG-MP, renal allograft function declined from an average eGFR of 44 mL/min/1.73 m² at 1 year prior to therapy to 34 mL/min/1.73 m² at time to treatment. Allograft function further declined to 28 mL/min/1.73 m² the year after treatment. The calculated average decline in eGFR of 6.3 mL/min/1.73 m² in the year after IVIG-MP treatment was significantly less than the average decline of 9.8 mL/min/1.73 m² in the year prior to treatment (multilevel analysis, P<.001).

One year after treatment, 43 of the 69 patients (62%) had an eGFR of at least 25% above the projected eGFR and were categorized as responders. There were two frequent patterns of response: (1) significant slowing of progressive eGFR loss and (2) stabilization of renal function after treatment. Improvement of eGFR within the year after treatment was not usually seen. Decline in allograft function among the responders as a group was from 43 mL/min/1.73 m² 1 year prior to treatment to 33 mL/min/1.73 m² at time of treatment (eGFR decline: 10.3 mL/min/1.73 m²). After IVIG-MP treatment, the calculated average decline in eGFR was 2.0 mL/min/1.73 m².

In the untreated historic group, the average decline in eGFR was 11.3 mL/min/1.73 m² prior to the diagnosis of c-aABMR and 9.7 mL/min/1.73 m² following the diagnosis. There was no significant change in graft function. Three patients in the treatment group (non-responders) had relentless progression of disease to graft failure and returned to dialysis within the first year after IVIG-MP administration. Responders had significantly improved graft survival; mean survival was 5.9 years versus 3.1 years for non-responders (P=.003).

At 1, 3, and 5 years following diagnosis of c-aABMR, graft survival among responders was 100%, 75%, and 59%, respectively, compared with 89%, 57%, and 20% for the non-responders. Graft survival among the untreated patients was similar to that of the non-responders (74%, 38%, and 33%, respectively). Of all clinical variables, the only significant difference between responders and non-responders was age of donor. Responders had, on average, slightly older donors compared with non-responders (53 vs 47 years; P=.046). Responders more often had a living donor compared with non-responders, a difference that did not reach statistical significance (81% vs 65%; P=.14).

An analysis of data of 41 patients on the effects of treatment on proteinuria was conducted (the remaining 28 patients had insufficient data for the analysis). There was, on average, an association between IVIG-MP treatment and a decrease in proteinuria level the first year after treatment administration. Initially, proteinuria increased in the 41 patients from 75 mg/mmol 1 year before treatment to 229 mg/mmol at time of treatment. In the year after treatment with IVIG-MP, proteinuria decreased from 229 mg/mmol to 190 mg/mmol.

There were some limitations to the study, according to the authors. The retrospective design allowed for unknown bias due to selection of patients with a for-cause biopsy; the design also excluded the possibility of a uniform schedule of maintenance immunosuppression. In conclusion, the researchers said, “Immunosuppressive therapy with IVIG-MP may significantly slow eGFR loss in a substantial proportion of patients with c-aABMR, leading to improved graft survival. As c-aABMR is now recognized as a major cause of long-term renal allograft loss, the efficacy of IVIG-MP treatment is an important and hopeful finding.”

**TAKEAWAY POINTS**

- Long-term kidney allograft loss is associated with chronic-active antibody mediated rejection [c-aABMR]. Researchers conducted a retrospective analysis to examine the efficacy of that treatment in patients with c-aABMR.
- Sixty-nine patients at a center in the Netherlands were treated with IVIG-MP (IVIG-MP) after 1 year of treatment. 43 patients were considered responders, showing slowing of deterioration of graft function.
- There was also a significant improvement in proteinuria upon treatment.
AMA Grants CPT-PLA Code for KidneyIntelX™

The American Medical Association (AMA) has granted a CPT® (Current Procedural Terminology) Proprietary Laboratory Analyses (PLA) Code for KidneyIntelX™, the lead product from RenalytixAI. The new code, 0105U, has been approved and published by the AMA CPT Editorial Panel, effective October 1, 2019.

According to a press release from RenalytixAI, a payment rate for the new code will be established for Medicare patients through the 2019 Clinical Lab Fee Schedule Annual Public Meeting process. RenalytixAI will provide comments and a recommendation on the appropriate basis for establishing a national Medicare price for this new PCT code.

Michael J. Donavan, PhD, MD, chief medical officer at RenalytixAI, said, “This is an important step as we prepare for KidneyIntelX's scaled rollout in the United States. A CPT code is instrumental in obtaining insurance coverage and reimbursement, and will increase access to KidneyIntelX testing results for patients with chronic kidney disease.”

CPT terminology is the most widely accepted medical nomenclature in the United States. PLA codes, recently added to the CPT Code set, are alpha-numeric CPT codes with a corresponding descriptor for labs or manufacturers who want to identify their test more specifically.

KidneyIntelX is designed to improve identification and clinical management of patients with type 2 diabetes and rapidly progressing kidney disease. KidneyIntelX utilizes machine learning algorithms to assess a combination of predictive blood-based biomarkers, including sTNFR1, sTNFR2, and KIM1, and features from a patient’s electronic health record, according to the press release.

Fresenius Invests in BioIntelliSense

In a recent press release, Fresenius Medical Care North America announced a major investment in BioIntelliSense, a Denver-based company that is developing a medical grade data services platform for continuous health monitoring, predictive analytics, and algorithmic clinical insights. According to a press release from Fresenius, the investment was completed through the Fresenius Medical Care Ventures division that invests in early stage companies that develop products, technologies, and therapies that will result in significant value for patients and the healthcare system.

Bill Valle, CEO of Fresenius Medical Care North America, said, “We are committed to helping more people living with chronic kidney disease through earlier interventions and are proud to invest in a company that is leading innovation in remote health sensors and services that we believe will help us accelerate change, further improve quality care, and slow progression of chronic kidney disease. We made this strategic investment in BioIntelliSense to enable our medical staff to more efficiently and effectively continuously monitor patients, facilitating precise and timely interventions and reducing cost to the system. We are pleased that the Centers for Medicare & Medicaid Services recognizes the benefit to patients and has provided separate reimbursement to fairly compensate for the cost of the devices and physician interpretation of the captured data and analytics.”

Founder and CEO of BioIntelliSense, James Mault, MD, said, “We are at the inception of a remarkable new era in healthcare that will employ novel sensor technologies to capture remote patient data and generate cost-effective clinical intelligence. Chronic kidney disease patients have complex health challenges and BioIntelliSense is both honored and excited to work closely with Fresenius Medical Care North America in developing scalable health monitoring solutions that might benefit this important patient population.”

RenalytixAI Names Thomas McLain to Leadership Team

RenalytixAI has announced the appointment of Thomas McLain as president and chief commercial officer. According to a press release from RenalytixAI, Mr. McLain will be responsible for heading the commercial program for KidneyIntelX™, focusing on establishing national and international clinical adoption and reimbursement. RenalytixAI develops artificial intelligence-enabled diagnostics for kidney disease.

Most recently, Mr. McLain led business and commercial strategy for the Exosome Diagnostics’ ExosomeDx® Prostate (Intelliscore) test, a liquid biopsy diagnostic for identifying men at increased risk for aggressive or high grade prostate cancer. Mr. McLain has been recognized as a leading voice for progressive diagnostic reimbursement strategy, including innovative collaborations and programs with private insurance groups to encourage collection of outcome and health economic data leading to accelerated clinical adoption and positive coverage determinations.

James McCullough, chief executive officer at RenalytixAI, said, “I am honored to welcome Tom to the RenalytixAI leadership team. Tom’s deep understanding of diagnostic product commercialization, healthcare markets, and reimbursement will be a great asset to our company.”

continued on page 18
AI and Estimations of GFR
Ultrasound imaging of the kidney is considered optimal in clinical practice due to its safety, convenience, and affordability. However, according to Chin-Chi Kuo, MD, PhD, and colleagues in Taiwan, the high subjective variability in image acquisition and interpretation makes incorporating experience-based prediction into standardized practice difficult. The researchers developed an artificial intelligence (AI) noninvasive tool to predict kidney function using estimated glomerular filtration rates (eGFR) based on serum creatinine concentrations.

The researchers tested the algorithm in a large registry-based cohort of patients with CKD. Results were reported online in Nature Partner Journals/Digital Medicine [npj Digital Medicine, volume 2, Article number:29 (2019)].

For classification of eGFR with a threshold of 60 mL/min/1.73 m², the model achieved an overall accuracy of 85.6%, which was higher than that of experienced nephrologists. The area under the receiving operating characteristic curve was 0.904. Attained specificity was up to 92.1%, indicating the effectiveness of the deep learning algorithm for assessing CKD using ultrasound images. However, the sensitivity was only moderate (~60.7%).

The relationship between artificial intelligence (AI) and estimates of eGFR based on serum creatinine was strong, indicated by a Pearson correlation coefficient of 0.741.

In summary, the researchers said, “Our model is the first fundamental step toward realizing the potential of transforming kidney ultrasound imaging into an effective, real-time, distant screening tool. AI-GFR estimation offers the possibility of noninvasive assessment of kidney function, a key goal of AI-powered functional automation in clinical practice.”

Positive Top-Line Results from CONFIRM Study
In late August, Mallinckrodt announced positive top-line results from the phase 3 CONFIRM study designed to evaluate the efficacy and safety of terlipressin in a cohort of 300 adults with hepatorenal syndrome type 1 (HRS-1). According to a press release from Mallinckrodt, the study met the primary end point of verified HRS-1 reversal, defined as (1) improvement in renal function; (2) avoidance of dialysis; and (3) short-term survival. Data will be presented at an upcoming medical meeting.

IMPORTANT SAFETY INFORMATION
CONTRAINDICATION: AURYXIA® (ferric citrate) is contraindicated in patients with iron overload syndromes.

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

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

ADVERSE REACTIONS: The most common adverse reactions reported with AURYXIA in clinical trials were:
- Iron Deficiency Anemia in CKD Not on Dialysis: Discolored feces (22%), diarrhea (21%), constipation (18%), nausea (10%), abdominal pain (5%) and hyperkalemia (5%)

To report suspected adverse reactions, contact Akebia Therapeutics at 1-844-445-3799.

FOR MORE INFORMATION, VISIT AURYXIA.COM
There are no approved drug therapies for HRS-1 currently in the United States or Canada; HRS-1 is estimated to affect 30,000 to 40,000 patients in the United States annually. Mallinckrodt plans to submit a New Drug Application to the US FDA in early 2020.

Lead investigator Arun Sanyal, MD, said, “The initial results from the phase 3 CONFIRM study are very encouraging in that they demonstrate terlipressin reversed the course of HRS-1 as measured by improvement in renal function, avoidance of dialysis, and short-term survival. The study met nearly all of the pre-specified secondary end points. HRS-1 is a life-threatening disease that is extremely difficult to treat. We anticipate the complete results will continue to help inform the effectiveness and safety profile of terlipressin in the patient population with urgent unmet medical needs.”

For the treatment of iron deficiency anemia in adult patients with chronic kidney disease (CKD) not on dialysis

**Designed to be different**

AURYXIA is the only oral iron tablet approved by the FDA for the treatment of iron deficiency anemia specifically in adult patients with CKD not on dialysis

- Proven effective in patients who were previously intolerant of or had an inadequate therapeutic response to traditional oral iron supplements
- Patients in the Phase III pivotal trial achieved results without the use of ESAs or IV iron
- 52% of patients achieved the primary endpoint of a hemoglobin increase of ≥1.0 g/dL at any time point by Week 16
- Mean TSAT increased from 20.2% at baseline to 35.6% at Week 161,2
- Discontinuation rates due to adverse reactions were similar between AURYXIA and placebo (10% vs 9%)
- Convenient mealtime dosing
- Each tablet contains 210 mg of elemental iron
- Patients with commercial insurance can pay as little as $0 per fill of AURYXIA

ESAs=erythropoiesis stimulating agents.


Please see Brief Summary including patient counseling information on following page
Barbara Murphy, MD, the lead investigator for the two studies, said, “In transplant, the inability to accurately identify rejection before any clinical signs appear has a significant impact on therapeutic manage- ment and long-term viability of the transplanted kidney. These study results demonstrate that non-invasive measurements may be used to stratify patients immunologically so that immunosuppressive therapy can be tailored to the individual patient needs.”

RenalytixAI plans to initiate larger scale clinical validation of the Fractal Serial Dx for diagnosis of sub-clinical acute (or underlying) rejection as early as the last part of 2019, with formal launch as a laboratory developed test through its New York City clinical laboratory expected in 2020.

Otsuka Announces Resources for Physicians and Patients

Otsuka America Pharmaceutical, Inc., has launched two websites for patients and physicians seeking resources and information on polycystic kidney disease (PKD). PKDNetwork.org is sourced by nephrology experts and is aimed at physicians treating patients with PKD, including autosomal dominant PKD (ADPKD). The site includes announcements of educational events and other resources for clinicians, as well as a PKD disease progression simulator intended to enhance physician-patient conversations regarding disease prognosis and symptoms. PKDinfo.com is a patient-focused website that houses information on ADPKD including disease management, seeking help from physicians, and other professional resources for patients and caregivers.

**News Briefs**

FractaDx kidney transplant diagnostic portfolio. RenalytixAI is a developer of artificial intelligence to advance clinical diagnostics for kidney disease.

According to a press release from RenalytixAI, the results demonstrate a blood test can diagnose kidney rejection before clinical signs of kidney damage and may be use to tailor immunosuppressive therapy. The post-transplant diagnostic, FractaDx ACR, is the second of the candidate test from the FractaDx portfolio licensed by RenalytixAI from the Ichan School of Medicine at Mount Sinai, New York, New York.

### USE IN SPECIFIC POPULATIONS

**Pregnancy:**

> There are no available data on AURYXIA use in pregnant women to inform a drug-associated risk of major birth defects and miscarriage. Animal reproduction studies have not been conducted using AURYXIA. Skeletal and epimorphic malformation was observed in neonatal mice when fenofibrate was administered intraperitoneally to gravid dams on gestation days 7.5. However, oral administration of other fenofibrate compounds to gravid CD1-mice and Wistar rats caused no fetal malformation.

An overdose of iron in pregnant women may carry a risk for spontaneous abortion, gestational diabetes and fetal malformation.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. Adverse outcomes in pregnancy occur regardless of the health of the mother or the use of medications. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies are 2% to 4% and 15% to 20% respectively.

### Clinical Considerations

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

**Lactation:**

There are no data available regarding the effect of AURYXIA in human milk, the effects on the breastfeeding child, or the effects on milk production. Data from rat studies have shown the transfer of iron into milk by divalent metal transport 1 (DMT1) and ferroporin-1 (FPN-1). Hence, there is a possibility of infant exposure when AURYXIA is administered to a nursing woman. The development and health benefits of breastfeeding should be considered along with the mother’s clinical need for AURYXIA and any potential adverse effects on the breastfed child from AURYXIA or from the underlying maternal condition.

**Gestational Use:**

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

**OVERDOSAGE**

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

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

**PATIENT COUNSELING INFORMATION**

**Dosing Recommendations:**

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

**Adverse Reactions:**

Advise patients that AURYXIA may cause discolored (dark) stools, but this staining of the stool is considered normal with oral medications containing iron.

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

**Accidental Ingestion:**

Advise patients to keep this product out of the reach of children.

Assess iron parameters (e.g., serum ferritin and TSAT) prior to initiating AURYXIA and monitor iron parameters while on therapy. Patients receiving intravenous iron may require a reduction in dose or discontinuation of intravenous iron therapy.

Risk of Overdose in Children Due to Accidental Ingestion:

Accidental ingestion and resulting overdose of iron-containing products is a leading cause of fatal poisoning in children under 6 years of age. Advise parents of the risks to children and to keep AURYXIA out of the reach of children.

ADVERSE REACTIONS

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the general population. AURYXIA is contraindicated in patients with iron overload syndromes (e.g., hemochromatosis).

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

<table>
<thead>
<tr>
<th>Body System</th>
<th>Adverse Reaction</th>
<th>AURYXIA % (N=190)</th>
<th>Placebo % (N=185)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any Adverse Reaction</td>
<td>75</td>
<td>62</td>
<td></td>
</tr>
<tr>
<td>Metabolic and Nutrition Disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>5</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal Disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>22</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Constipation</td>
<td>18</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>10</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Abdominal Pain</td>
<td>5</td>
<td>2</td>
<td></td>
</tr>
</tbody>
</table>

During the 16-week, placebo-control trial, 12 patients (10%) on AURYXIA discontinued the study drug because of an adverse reaction, as compared to 10 patients (11%) on the placebo. Discontinuation of the drug was the most common adverse reaction leading to discontinuation of AURYXIA (2.6%).

**DRUG INTERACTIONS**

Orally administered dioxynitric acid has been taken at least 1 hour before AURYXIA. Oral administration of ciprofloxacin should be taken at least 2 hours before or after AURYXIA. Oral drugs that can be administered concomitantly with AURYXIA are: amlodipine, aspirin, atorvastatin, amlodipine, clopidogrel, digoxin, diltiazem, doxercalciferol, enalapril, fluvastatin, glimepiride, lovastatin, losartan, metoprolol, pravastatin, propranolol, sitagliptin, and warfarin.

Oral medications not listed above

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

**Effects of Acute Kidney Injury on Urinary Protein Excretion**
Journal of the American Society of Nephrology. 2019;30(7):1271-1281

There are few available data on the potential effects of acute kidney injury (AKI) on proteinuria, despite the fact that proteinuria is a strong risk factor for future loss of renal function. Researchers, led by Chi-yuan Hsu, MD, MS, conducted an analysis of data from the ASSESS-AKI (Assessment, Serial Evaluation, and Subsequent Sequelae of AKI) study, and from a subset of participants in the CRIC (Chronic Renal Insufficiency Cohort) study recruited from Kaiser Permanente Northern California. Both prospective cohort studies included annual assessment of urine protein-to-creatinine ratio, estimated glomerular filtration rate (eGFR), blood pressure, and medication use.

For hospitalized patients, an episode of AKI was defined using inpatient serum creatinine measurement taken as part of clinical care (peak/nadir inpatient serum creatinine ≥1.5 mg/dL). The analysis included mixed effects regression to examine change in log-transformed urine protein-to-creatinine ratio after AKI, controlling for time-updated covariates.

Among the 2048 eligible participants, baseline median eGFR was 62.9 mL/min/1.73 m² and median urine protein-to-creatinine ratio was 0.12 g/g. During 9271 person-years of follow-up, 324 participants experienced at least one episode of hospitalized AKI. Of first AKI episodes, 50.3% were Kidney Disease Improving Global Outcomes stage 1, 23.8% were stage 2, and 25.9% were stage 3. There was an independent association between an episode of hospitalized AKI and a 9% increase in the urine protein-to-creatinine ratio in multivariable analysis.

In conclusion, the researchers said, “Our analysis of data from two prospective cohort studies found that hospitalization for an AKI episode was independently associated with subsequent worsening of proteinuria.”

Yusuke Sakaguchi, MD, PhD, and colleagues recently conducted a 2-year, open-label, randomized controlled trial designed to examine the efficacy of magnesium oxide and/or the oral carbon adsorbent AST-120 for slowing progression of CAC in patients with CKD. Eligible patients had stage 3-4 CKD with risk factors for CAC (diabetes mellitus, history of cardiovascular disease, high low-density lipoprotein cholesterol, or smoking). Patients were randomly assigned in a two-by-two factorial design to either an magnesium oxide group or a control group, and to an AST-120 group or a control group. The primary outcome of interest was percentage change in CAC score.

Following results of an interim analysis with the first 125 enrolled participants, the study was prematurely terminated. At the time of study termination, 96 of the 125 enrolled patients had completed the study. The interim analysis demonstrated that the median change in CAC score was significantly smaller for magnesium oxide versus control (11.3% vs 39.5%). In addition, the proportion of patients with an annualized percentage change in CAC score of ≥15% was significantly smaller for the magnesium oxide group than for the control group (23.9% vs 62.0%). However, magnesium oxide did not suppress the progression of thoracic aorta calcification. The dropout rate was higher in the magnesium oxide group than in the control group (27% vs 17%); participants dropped out primarily due to diarrhea.

There was no significant difference in percentage in CAC score between the AST-120 group and the control group. “Magnesium oxide, but not AST-120, appears to be effective in slowing CAC progression. Larger-scale trials are warranted to confirm these findings,” the researchers said.

DAPT Duration in Patients with CKD and Drug-Eluting Stents

It is not known whether prolonged dual antiplatelet therapy (DAPT) is more protective in patients with chronic kidney disease (CKD) and drug-eluting stents compared with shorter duration of DAPT. Thomas A. Mavranakas, MD, MSc, FRCP, FASN, and colleagues conducted a literature search and meta-analysis to examine whether there is an association between shorter DAPT in patients with drug-eluting stents and CKD and lower mortality or major adverse cardiovascular events compared with longer duration of DAPT.

Randomized trials were identified using a Medline literature search; the trials compared varying DAPT duration strategies; eligible trials included patients with CKD. The primary outcome of included trials was a composite of all-cause mortality, myocardial infarction, stroke, or stent thrombosis (definite or probable). The secondary outcome was major bleeding. A random-effects model was used to estimate the risk ratio (RR).

The meta-analysis included five randomized trials representing 1902 patients with CKD. Short DAPT, defined as ≥6 months, was associated with a similar incidence of the primary outcome, compared with 12-month DAPT in patients with CKD (48 vs 50 events; RR, 0.93; 95% confidence interval [CI], 0.64-1.36; P=.72). There was also an association between 12-month DAPT and a similar incidence of the primary outcome compared with extended DAPT, defined as ≥30 months, in the CKD subgroup (35 vs 35 events; RR, 1.04; 95% CI, 0.67-1.62; P=.87).

Numerically lower rates of major bleeding events were detected with shorter versus 12-month DAPT (9 vs 13 events; RR, 0.69; 95% CI, 0.30-1.60; P=.39) and 12-month versus extended DAPT (9 vs 12 events; RR, 0.83; 95% CI, 0.35-1.93; P=.66) in the patients with CKD.

In conclusion, the researchers said, “Short DAPT does not appear to be inferior to longer DAPT in patients with CKD and drug-eluting stents. Because of imprecision in estimates (few events and wide confidence intervals), no definite conclusions can be drawn with respect to stent thrombosis.”

CHRONIC KIDNEY DISEASE

**Magnesium Oxide Slows Progression of Coronary Artery Calcification**

Development of strategies for the management of coronary artery calcification (CAC) in patients with chronic kidney disease (CKD) remains clinically challenging. Results of experimental studies have suggested that magnesium inhibits vascular calcification and that uricemic toxin indoxyl sulfate aggravates it.

DIABETES

**Hyperfiltration and Long-term Outcomes in Diabetic Kidney Disease**

Researchers have hypothesized that glomerular hyperfiltration is a contributing factor to the development of diabetic kidney disease (DKD). Mark E. Molitch, MD, and colleagues conducted an analysis of glomerular filtration rate (GFR) follow-up data on patients with type 1 diabetes who were undergoing 123I-iothalamate clearance on entry into the Diabetes Control and Complications Trial (DCCT)/Epidemiology of Diabetes Interventions and Complications Study.

The study cohort included patients with...
type 1 diabetes who underwent an 125I-iothalamate clearance (iGFR) at DCCT baseline. The association between the baseline hyperfiltration status and subsequent risk of reaching an estimated GFR <60 mL/min/1.73 m² was calculated using Cox proportional hazards models.

Of the 446 eligible participants, 24% (n=106) had hyperfiltration at baseline. Hyperfiltration was defined as iGFR levels ≥140 mL/min/1.73 m²; secondary thresholds were 130 or 150 mL/min/1.73 m².

Median follow-up was 28 years. During that time, 53 participants developed an eGFR <60 mL/min/1.73 m². Among the participants with hyperfiltration at baseline, the cumulative incidence of eGFR <60 mL/min/1.73 m² at 28 years of follow-up was 11.0%, compared with 12.8% among participants with baseline GFR <140 mL/min/1.73 m².

In an unadjusted Cox proportional model, there was no significant association between hyperfiltration and subsequent risk of developing eGFR <60 mL/min/1.73 m² (hazard ratio [HR], 0.83; 95% confidence interval [CI], 0.43-1.62); the association did not reach statistical significance in the adjusted model (HR, 0.77; 95% CI, 0.38-1.59). Findings were similar upon application of alternate thresholds to define hyperfiltration (130 or 150 mL/min/1.73 m²).

In summary, the researchers said, “Early hyperfiltration in patients with type 1 diabetes was not associated with a higher long-term risk of decreased GFR. Although glomerular hypertension may be a mechanism of kidney injury in DKD, higher total GFR does not appear to be a risk factor for advanced CKD.”

DIALYSIS

High Risk CKD-MBD Phenotypes Identified
Nephrology Dialysis Transplantation. 2019;34(4):682-691

Due primarily to difficulties in defining high-risk phenotypes based on serum biomarkers, clinical management of chronic kidney disease-mineral bone disorder (CKD-MBD) remains challenging. Luca Neri, MD, PhD, and colleagues recently conducted a 5-year follow-up study in a large, multinational cohort of chronic dialysis patients to examine the prevalence and outcomes of 27 mutually exclusive CKD-MBD phenotypes.

In this historical cohort study, all hemodialysis patients registered in EvClID® (European Clinical Database) on July 1, 2011, across 28 countries in Europe, the Middle East and Africa (EMEA), and South America were enrolled. The researchers created the 27 phenotypes based on combinations of serum parathyroid hormone (PTH), phosphorus, and calcium 6-month averages (L, low; T, target; H, high). Outcome risk score-adjusted proportional hazard regression was used to test the association between CKD-MBD phenotypes and the 5-year risks of mortality and hospitalization.

A total of 35,721 patients were eligible for the analysis. CKD-MBD control was generally poorer in Eastern European and South American countries when compared with Western European countries (prevalence ratio, 0.79; P<.001). Overall, there were 15,795 deaths (126.7 deaths per 1000 person-years; 95% confidence interval [CI], 124.7-128.7); 18,014 patients had at least one hospitalization (203.9 hospitalization events per 1000 person-years; 95% CI, 201.0-206.9); and the incidence of the composite end point was 280.0 events per 1000 person-years (95% CI, 276.6-283.5).

In the fully adjusted model, the relative mortality risk ranged from hazard ratio (HR) 1.07 (PTH/calcium/phosphorus: TLT) to HR, 1.59 (PTH/calcium, phosphorus: LTL); the relative composite end point risk ranged from HR, 1.07 (PTH/calcium/phosphorus: TLT) to HR, 1.36 (PTH/calcium/phosphorus: LTL).

In summary, the researchers said, “We identified several CKD-MBD phenotypes associated with reduced hospitalization-free survival and increased mortality. Ranking of relative risk estimates or excess events concurs in informing healthcare priority setting.”

Dialysate Cooling AmelioratesDecline in Residual Renal Function
Survival in patients with end-stage renal disease is associated with residual renal function (RRF); however, RRF declines following initiation of dialysis. Prior studies demonstrated that dialysate cooling reduced hemodialysis-induced circulatory stress and protected the brain and heart from ischemic injury. It is not known whether renal perfusion is affected by hemodialysis-induced circulatory stress and if it can be ameliorated with dialysate cooling to reduce RRF loss.

Raanan Margars, MSc, and colleagues utilized renal computed tomography perfusion imaging to scan 29 patients undergoing continuous dialysis under standard (36.5°C dialysate temperature) conditions; an additional 15 patients were scanned under both standard and cooled (35.0°C) conditions. Imaging was performed immediately before, 3 hours into, and 15 minutes after hemodialysis sessions.

Renal perfusion decreased 18.4% during standard hemodialysis (P<.005) and correlated with myocardial injury (r=−0.33; P<.05). In the sessions with dialysate cooling, patients experienced a 10.6% decline in perfusion; the difference was not statistically different from the decline with standard hemodialysis. Ten of the 15 patients showed improved or no effect on myocardial stunning.

“This study shows an acute decrease in renal perfusion during hemodialysis, a first step toward pathophysiology characterization of hemodialysis-mediated RRF decline. Dialysate cooling ameliorated this decline but this effect did not reach statistical significance. Further study is needed to explore the potential of dialysate cooling as a therapeutic approach to slow RRF decline,” the researchers said.

PRETRANSPLANTATION

Pre-transplant anti-HLA Antibodies and Graft Survival
Nephrology Dialysis Transplantation. 2019;34(6):1056-1063

There is an association between pre-transplant donor-specific anti-human leucocyte antigen (HLA) antibodies and impaired kidney graft survival. However, the clinical significance of non-donor-specific anti-HLA antibodies (nDSAs) is uncertain. Laura A. Michielsen, PhD, and colleagues conducted a paired kidney graft study to compare the clinical relevance of DSAs and nDSAs.

The post hoc paired kidney graft analysis was conducted as part of a Dutch multicenter study evaluating all transplantation between 1995 and 2005 with available pre-transplant serum samples. A Luminex single-antigen bead assay was used to detect anti-HLA antibodies.

There were 3237 eligible deceased donor transplantations; of those, 115 recipient pairs receiving a kidney from the same donor with one recipient being DSA positive and the other without anti-HLA antibodies were identified. Ten-year death-censored graft survival was significantly lower in patients with pre-transplant DSAs (55% vs 82%; P=0.001).

Of 192 pairs with one recipient as nDSA positive (against Class I and/or II) and the other without anti-HLA antibodies, there was no significant difference in graft survival between the two groups (74% vs 77%; P=.79). In patients with both nDSAs Class I and II, there was a trend toward a lower graft survival (58%; P=0.06).

In a small group of 42 recipient pairs, 10-year graft survival in recipients was 49% versus 68% in recipients with nDSAs (P=.11).

In conclusion, the authors said, “This paired kidney analysis confirms that the presence of pre-transplant DSAs in deceased donor transplantations is a risk marker for graft loss, whereas nDSAs in general are not associated with a lower graft survival. Subgroup analysis indicated that only in broadly sensitized patients with nDSAs against Class I and II, nDSAs may be a risk marker for graft loss in the long-term.”
Monthly Capitation Payment Breakdown

In recent months, I’ve received an influx of questions from readers about the Medicare Monthly Capitation Payment (MCP). Many of these questions are related to the increasing utilization of physician assistants (PAs) and nurse practitioners (NPs), in addition to questions about CMS regulation changes at the beginning of the year that allow free-standing dialysis facilities and patient homes to be acceptable originating sites for end-stage renal disease (ESRD)-related telehealth services. In this issue, we will explore these areas as well as the MCP fundamentals.

WHAT IS THE MCP?
A Monthly Capitation Payment (MCP) is a payment made to physicians for most dialysis-related physician services furnished to Medicare ESRD patients on a monthly basis. Medicare reimbursement for an in-center ESRD patient who receives four visits is the same as the reimbursement for supervising a patient that dialyzes at home. Reimbursement of the MCP for in-center patients that receive three or fewer visits can vary depending on the number of visits provided during the calendar month. Reimbursement also varies based on the age of the ESRD patient.

WHAT SERVICES ARE INCLUDED IN THE MCP AND WHAT PHYSICIAN SERVICES CAN BE BILLED SEPARATELY FROM THE MCP?
The Medicare claims processing manual states that the MCP is reported once per month for services performed in an outpatient setting that are related to the patient’s ESRD. These outpatient services include assessment of diet and nutrition needs, appropriate mode of dialysis, access type, transplant qualification, dialysis prescription, anemia management, bone and mineral metabolism, hypertension, review of dialysis adequacy, physical assessments, interpretation of various tests, coordination of care with other medical professionals, and any other ESRD-related outpatient service as outlined in CMS Pub. 100-04, Ch 8.

Services excluded from MCP include interpretation of tests that have a professional component (electrocardiograms, 24-hour blood pressure monitor, biopsies, etc.), surgical services such as dialysis catheter placement or repair, thrombectomy of clotted cannula or bone marrow biopsy, patient training for home dialysis, covered physician services furnished to hospital inpatients, and non-renal related physician’s services—as long as they are not incidental to services furnished during a dialysis session or office visit necessitated by the renal condition.

CAN TELEHEALTH VISITS REPLACE SOME OF THE FACE-TO-FACE VISITS IN THE MCP?
Effective the first of this year, CMS recognizes free-standing dialysis facilities and patient homes as eligible originating sites for telehealth services. This policy change has the potential to greatly benefit home dialysis patients and nephrologists. After a patient’s first three months on home dialysis, Medicare allows for a monthly comprehensive telehealth visit twice per quarter. Some considerations for the use of telehealth in a nephrology practice include the availability of internet connectivity in the patient’s home, ability to clearly visualize the patient’s access, and whether there are options to help the patient with sight or hearing impairments as well as equipment to capture the patient’s vital signs remotely.

WHO SHOULD BILL FOR THE MCP IN A NEPHROLOGY PRACTICE WHERE NPS AND PAs PROVIDE SOME OF THE MONTHLY VISITS FOR A PATIENT?
Medicare allows some flexibility to physicians and nonphysician practitioners providing care to ESRD patients. Physicians, clinical nurse specialists, nurse practitioners, and physicians’ assistants are acceptable provider types to provide face-to-face visits. The MCP physician may use other practitioners or physicians to provide visits during the month without being present as long as the other practitioner is a partner, employee of the same group practice, or employee of the MCP physician.

The billing physician, according to the Medicare claims processing manual, should be the physician who provides the complete assessment, establishes the patient’s plan of care, and provides ongoing management. In the event the practitioner that performs the complete assessment and establishes the plan of care is a nonphysician practitioner, the MCP service should be billed under the PIN of the non-physician practitioner.

Sarah Tolson is the director of operations for Sceptre Management Solutions, Inc., a company specializing in billing for outpatient ESRD facilities, nephrology practices, and vascular access. Your questions are welcome and she can be reached at stolson@sceptremanagement.com, 801.775.8010, or via Sceptre’s website www.sceptremanagement.com.
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