Frailty in Dialysis Patients and Increased Hospitalization and Mortality

According to the United States Renal Data System, 44.5% of patients with end-stage renal disease (ESRD) who receive maintenance dialysis are ≥65 years of age. In addition, the prevalence of ESRD patients on dialysis is increasing rapidly among older age groups. In a nationwide ESRD patient registry in Korea, the mean age of these patients increased from 55.2 years in 2005 to 60.3 years in 2014. The proportion of people with ESRD ≥65 years of age increased from 28.0% to 40.7% during the same time period.

Chronic kidney disease (CKD) accelerates the aging process at the cell, tissue, and organ level due to energy wasting, various uremic toxins, inflammation, and oxidative stress. The effects of chronological and pathological aging help explain why the frailty phenotype is more common among patients with CKD compared with the general population with no impairment of kidney function.

Researchers in Korea, led by So-Young Lee, MD, PhD, recently conducted a prospective study designed to examine the clinical implications of frailty in patients with CKD receiving maintenance hemodialysis and chronic peritoneal dialysis. Results were reported in the Journal of Renal Nutrition [2017;27(2):106-112].

Better HRQoL with Frequent Hemodialysis versus Conventional Hemodialysis

In the effort to make healthcare and health policies more patient-centered, awareness of the ways a treatment affects patient-reported outcomes has gained importance. Among patients with end-stage renal disease (ESRD), health-related quality of life (HRQoL) is of great importance, and information regarding how choice of dialysis modality will affect their HRQoL is a high priority for patients.

Worldwide, more than two million individuals receive conventional hemodialysis three sessions per week. Small studies have found that more frequent hemodialysis, defined as five or six sessions per week, results in greater weekly solute and fluid removal and may be associated with improved HRQoL.

Amit X. Garg, MD, and colleagues recently extended the findings of two previous clinical trials to estimate the effects of frequent versus conventional hemodialysis on additional measures of HRQoL. The researchers reported results of the current study in Kidney International [2017;91(3):746-754].

The two trials involved in this analysis were the Daily Trial and the Nocturnal Trial. In the Daily Trial, 245 patients were randomly assigned to receive frequent risk of chronic kidney disease with use of PPIs without intervening AKI

According to the National Health and Nutrition Examination Survey, 7.8% of adults in the United States had a prescription proton pump inhibitor (PPI) in the previous 30 days. Studies have shown an association between use of PPIs and an increase in risk for adverse health outcomes, including acute kidney injury (AKI), incident chronic kidney disease (CKD), progression of CKD, and end-stage renal disease (ESRD).

AKI is a significant risk factor for the development and progression of CKD and ESRD. Studies demonstrating the association of PPI use with AKI have postulated that the association is mediated by the occurrence of intervening AKI. However, there are few data on whether CKD associated with PPI use is mediated by the occurrence of intervening AKI or via other pathways. It is not known whether there is an association between the use of PPIs and untoward long-term kidney outcomes, includ-
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Proton Pump Inhibitors and the Risk of CKD

Proton pump inhibitors (PPIs) are one of the most common classes of prescribed drugs worldwide. Indications include the treatment of acid reflux and peptic ulcer disease. Concerns regarding over-utilization of PPIs have been raised; however, extensive use continues. In the United States, even excluding over-the-counter sales, there are estimated to be more than 170 million PPI prescriptions each year.

Generally, the literature points to PPIs being well tolerated. However, achlorhydria, hypergastrinemia, acute interstitial nephritis, and acute kidney injury (AKI) have been cited as potential problems with acute and chronic PPI use. Retrospective studies have also raised concerns about an association between PPIs and bone fracture, a higher rate of enteric infections, such as from Campylobacter, Salmonella, Shigella, and Listeria as well as Clostridium difficile-associated diarrhea (CDAD), and community-acquired pneumonia.

Lazarus and colleagues were the first to raise the alarm about the association between PPI use and chronic kidney disease (CKD). They utilized a prospective population-based cohort, the Atherosclerosis Risk in Communities (ARIC) study, to evaluate whether PPI use was associated with CKD. Incident CKD was defined by International Classification of Diseases (ICD) code at discharge. Lazarus et al reported an increased risk of CKD with PPI utilization (adjusted hazard ratio [HR], 1.35; 95% confidence interval [CI], 1.17–1.55) that persisted even when different ways of adjusting for confounding were applied. The finding also persisted when they studied a different cohort (the Geisinger replication cohort) using the same methodologic approach. A dose effect was also detected—a higher risk of PPI-associated CKD was observed with twice-daily versus single-daily dosing of PPI. Observational data such as this have limitations of course. These include residual confounding and the low sensitivity of ICD codes to define kidney disease. Still, the conclusion that there was a 20% to 30% higher risk of CKD associated with PPI use is very concerning, especially given how extensively PPIs are used (and misused).

The Lazarus study received considerable attention in early 2016, both in the lay press and the scientific literature.

In October 2016, publishing in the Journal of the American Society of Nephrology, Xie and colleagues reinforced the Lazarus findings by using a combination of several US Department of Veterans Affairs (VA) databases to ascertain the 5-year risk of CKD between PPI versus H2 antagonist users. They reported a 28% higher risk of incident CKD and a higher risk of both doubling in serum creatinine and the incidence of end-stage renal disease. The risk of CKD was also higher depending on the length of exposure.

Xie and colleagues have more recently refined our understanding of this issue by excluding patients with AKI. This is important because PPI exposure has been reported for unclear reasons to cause AKI, even after excluding PPI-induced acute interstitial nephritis as the cause for AKI. Thus, defining whether PPI use is associated with CKD independent of AKI is important. If AKI is not in the causal pathway for CKD, then clinicians need to beware because chronic PPI use may cause CKD without any warning signs over the long-term.

Very recently publishing in Kidney International, Xie and colleagues again utilized the VA databases, but now in their survival models censored cohort participants at the time of AKI occurrence. Thus, they excluded intervening AKI in their analysis. Nevertheless, the risk of CKD from exposure to PPI as compared to H2 blockers was approximately 20% and statistically significant (HR, 1.26; 95% CI, 1.20–1.33). These results supported an independent effect of PPI exposure on the risk of CKD.

Researchers reported a 28% higher risk of incident CKD and a higher risk of both doubling in serum creatinine and the incidence of end-stage renal disease. The risk of CKD was also higher depending on the length of exposure.

So, what is the bottom line here?

Observational data support a robust association between PPI use and the incidence of CKD even when there is no intervening episode of AKI. Although this conclusion is based on observational data that are open to a number of biases, and causality is not proven, the data should make physicians pause. It seems reasonable to reconsider how, and for how long, PPIs are utilized in treating patients. Using H2 blockers as an alternative should be considered. Prescribing a lower single daily PPI dose, and treating for short periods makes sense, as does checking kidney function regularly.

REFERENCES
Better HRQoL
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(six times per week) or conventional (three times per week) in-center hemodialysis. In the Nocturnal Trial, 87 patients were randomly assigned to receive frequent nocturnal (six times per week) or conventional (three times per week) home hemodialysis. Baseline characteristics of patients assigned to frequent versus conventional hemodialysis were similar in both trials.

Prior to randomization, all patients were on conventional hemodialysis, with an average feeling temperature score of 70 to 75 (a visual analog scale from 0 to 100 where 100 is perfect health), an average general health score of 40 to 47 (a scale from 0 to 100 where 100 is perfect health), and an average dialysis session recovery time to 2 to 3 hours.

DAILY TRIAL
At baseline, the mean score in the feeling thermometer was 74 in patients assigned to frequent hemodialysis and 71 in those assigned to conventional hemodialysis. Over the first 4 months of follow-up, patients in the frequent hemodialysis group demonstrated a significant improvement in their feeling thermometer, compared with patients in the conventional hemodialysis group whose score remained similar (change of 5.6 vs −0.5 from baseline, respectively). At 12 months after randomization, the trends remained (5.8 vs −0.6 from baseline, respectively). Over 1 year, there was a significant 6.4-point between-treatment group difference in score (95% confidence interval [CI], 1.8–11.1).

The baseline general health scale score was 47 in patients in the frequent hemodialysis group and 44 in the conventional hemodialysis group. Over the first 4 months of follow-up, patients in the frequent group had a significant improvement in their general health score; the score remained similar to baseline in patients in the conventional group (change of 6.5 vs −1.6 from baseline, respectively); the trends persisted to 12 months after randomization. There was a significant 9.7-point between-treatment group difference in the change in score over 1 year (95% CI, 4.7–14.7).

Between baseline and 12 months of follow-up, the median time to recover from a dialysis session decreased from 150 minutes to 60 minutes in the frequent hemodialysis group; in the conventional group, median dialysis recovery time remained similar (from 120 minutes to 180 minutes). At baseline, a recovery time of ≥60 minutes was observed in 58% of patients in the frequent hemodialysis group and in 79% of patients in the conventional hemodialysis group. At 1 year after randomization, the percentages were 43% and 63%, respectively.

At 4 months and 12 months of follow-up, there was no consistent statistical difference between the frequent hemodialysis and conventional hemodialysis groups in the change in the health utilities index, or in its eight attributes.

NOCTURNAL TRIAL
At baseline, the mean feeling thermometer score was 74 in the frequent hemodialysis group and 78 in the conventional hemodialysis group. Over the first 4 months of follow-up, patients in the frequent hemodialysis group had an improvement in their feeling thermometer scores; the score remained similar in the conventional group (change of 3.7 vs −0.4 from baseline, respectively). At 12 months after randomization, the change persisted; however, the between-group difference in the change in score by 1 year was not statistically significant (8.0; 95% CI, −0.5 to 16.1).

In the frequent group, the baseline score on the general health scale was 40; the score was 45 at baseline in the conventional group. By 12 months, patients in the frequent group demonstrated a greater improvement in the general health scale score compared with patients in the conventional group (change of 8.0 vs 1.5 from baseline, respectively). The between-group difference in change in score was not statistically significant at 1 year (6.6; 95% CI, −1.5 to 16.1).

In the frequent hemodialysis group, the median time to recovery from a dialysis session decreased from 180 minutes at baseline to 30 minutes at 12 months of follow-up. In the conventional hemodialysis group, median recovery time changed from 180 minutes to 120 minutes. At baseline, a recovery time of ≥60 minutes was seen in 58% of patients in the frequent group and 63% of those in the conventional group. At 1 year after randomization, the percentages were 24% and 59%, respectively.

In the health utilities index, there was no consistent statistical difference between the two groups in change in score over 4 and 12 months of follow-up, or its eight attributes.

“In this analysis of two randomized controlled trials, we found patients recovered on average approximately 1 hour earlier from frequent compared with conventional hemodialysis. This was true whether the dialysis was received in a hemodialysis center or at home. Patients who received frequent hemodialysis in a dialysis center also scored better on several other health-related quality of life measures compared with patients who received conventional hemodialysis. Although there was more time spent on dialysis with frequent compared with conventional hemodialysis each week, patients reported a sizeable reduction in the total weekly time to recover after their dialysis sessions. In other words, while in these trials patients received more hours of hemodialysis, they experienced more hours during which they felt more normal and less washed out.”

—Amit X. Garg, MD

There were some limitations to the analyses cited by the researchers, including the possibility that responses to the questionnaires completed by the patients assigned to the frequent hemodialysis group may have been influenced by enthusiasm for the novel therapy, and the patients who agreed to be randomized into each trial had a higher HRQoL than those who provided consent but were not randomized, creating the possibility that the results of the analyses may not be generalizable to the entire hemodialysis population.

“In conclusion, as compared with conventional thrice-weekly hemodialysis, frequent in-center hemodialysis and frequent home-based nocturnal hemodialysis both reduce the time it takes to recover from a hemodialysis session. Frequent in-center hemodialysis also yielded statistically significant and clinically important changes in general measures of HRQoL,” the researchers said.
Frailty in Dialysis Patients
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Study participants were recruited from 27 dialysis centers in South Korea from July 2012 to December 2012. Follow-up continued until December 31, 2104. Frailty was defined using components identical or similar to those used in the Dialysis Morbidity and Mortality Study Wave 2. Study participants were asked questions related to the frailty components of slowness, weakness, exhaustion, shrinking, and physical inactivity using the RAND 36 Item Short Form (SF-36).

Participants were also asked questions on the Physical Function Scale of the SF-36, consisting of ten items related to physical activities usually performed on a typical day. Limitations of each activity were classified into three categories: (1) limited a lot; (2) limited a little; or (3) not limited at all. A total of 1658 patients met eligibility criteria, including 1285 receiving maintenance hemodialysis and 403 receiving chronic peritoneal dialysis. Mean age of the participants was 55.9 years, 25.6% were ≥65 years of age, 35.7% were male, and 39.4% had diabetes. Mean time on dialysis was 5.2 years, and 19.1% of the participants were observed with disability.

Of the 1658 participants, 34.8% (n=577) met the study definition of frail and 45.7% (n=757) met the study definition of prefrail. The prevalence of frailty increased as the patients became older and the prevalence of prefrailty decreased as the patients became older.

There were significant associations between frailty and female sex, older age, higher body mass index (BMI), unemployed status, lower educational level, disability, and comorbidities such as diabetes mellitus, as well as cardiovascular, and cerebrovascular disease. There were no significant associations between frailty and dialysis modality or dialysis duration.

Following adjustment for age, sex, unemployment, disability, BMI, education level, dialysis modality, comorbidity, hemoglobin, phosphorous, serum albumin, potassium, total iron binding capacity, intact parathyroid hormone, blood urea nitrogen, and creatinine, associations with frailty and age, comorbid conditions, disability, unemployment, higher BMI, and lower education level remained.

Of the total study cohort, 37.0% (n=608) were hospitalized at least once during follow-up of 30.0 months, 87 died, and 66 underwent kidney transplantation. For the nonfrail participants, the hospitalization rate was 24.4%, compared with 33.0% for prefrail participants, and 48.4% for frail participants (P <.001). Causes of hospitalization included infectious diseases (29.3%), cardiovascular disease (12.0%), gastrointestinal bleeding (11.4%), cerebrovascular disease (4.0%), and others.

In univariate analysis, prefrail and frail patients were 1.4 and 2.4 times more likely to be hospitalized over the 30-month follow-up period, respectively. Further, the proportion of patients with two or more hospitalizations was significantly higher among the frail patients (25.3%) compared with nonfrail (9.6%) and prefrail (12.5%) patients (P <.001). The association of frailty with hospitalization remained after adjustment for age, sex, comorbidities, dialysis modality, disability, serum albumin, and creatinine (adjusted hazard ratio [HR], 1.80; 95% confidence interval [CI], 1.38-2.36). Following the adjustments, there was no association between prefrailty and hospitalization. During the study period, mortality rates were 3.1% for nonfrail participants, 3.2% for prefrail participants, and 9.2% for frail patients (P <.001). Infection-related disease, cardiovascular disease, and cerebrovascular disease were the most common causes of death (24.1%, 23.0%, and 12.6%, respectively). In univariate analysis, frail patients were three times more likely to die during the 30-month follow-up period compared with nonfrail and prefrail patients (HR, 3.05; 95% CI, 1.55-6.00). Following adjustment for multiple other risk factors, the significant relationship remained (HR, 2.97; 95% CI, 1.11-5.02). There were no significant associations between mortality and prefrailty or multivariate analyses.

Limitations to the study cited by the authors included using self-reported constructs to define frailty rather than a physical-performance-based definition, and the lack of significant clinical implications of prefrailty in the population of patients with CKD.

“Departmental analysis, frailty is an independent risk factor for mortality, and patients with prefrailty are at heightened risk for hospitalization.” The researchers noted.

In univariate analysis, prefrail and frail patients were 1.4 and 2.4 times more likely to be hospitalized over the 30-month follow-up period, respectively. Further, the proportion of patients with two or more hospitalizations was significantly higher among the frail patients (25.3%) compared with nonfrail (9.6%) and prefrail (12.5%) patients (P <.001). The association of frailty with hospitalization remained after adjustment for age, sex, comorbidities, dialysis modality, disability, serum albumin, and creatinine (adjusted hazard ratio [HR], 1.80; 95% confidence interval [CI], 1.38-2.36). Following the adjustments, there was no association between prefrailty and hospitalization. During the study period, mortality rates were 3.1% for nonfrail participants, 3.2% for prefrail participants, and 9.2% for frail patients (P <.001). Infection-related disease, cardiovascular disease, and cerebrovascular disease were the most common causes of death (24.1%, 23.0%, and 12.6%, respectively). In univariate analysis, frail patients were three times more likely to die during the 30-month follow-up period compared with nonfrail and prefrail patients (HR, 3.05; 95% CI, 1.55-6.00). Following adjustment for multiple other risk factors, the significant relationship remained (HR, 2.97; 95% CI, 1.11-5.02). There were no significant associations between mortality and prefrailty or multivariate analyses.

Limitations to the study cited by the authors included using self-reported constructs to define frailty rather than a physical-performance-based definition, and the lack of significant clinical implications of prefrailty in the population of patients with CKD.

“The findings show a high prevalence of frailty in ambulatory chronic dialysis patients without a recent admission history. The frail phenotype is significantly associated with hospitalization and mortality. Therefore, we should pay more attention to the frailty status of patients, even those who appear to be in good condition, to improve their morbidity and mortality,” the researchers said.

### Dietary Counseling Improves Compliance with CKD Dietary Restrictions

**Chicago**—In patients with chronic kidney disease (CKD), a key element of multidisciplinary care is dietary restriction. However, according to researchers, there are few data on barriers to adherence to dietary regimens important in CKD care.

Maya K. Rao, MD, and colleagues recently conducted a cross-sectional study among English and Spanish speaking patients with stage 4 and 5 CKD. The researchers reported study results during a poster session at Kidney Week 2016 in a poster titled Barriers to Dietary Adherence in Chronic Kidney Disease.

Study participants completed a five-part analysis designed to evaluate possible barriers to dietary adherence: (1) Short Assessment of Health Literacy (SAHL) screen; (2) Newest Vital Sign (NVS), a numeracy screen; (3) a survey evaluating barriers to adherence; (4) a food frequency questionnaire, and (5) a knowledge assessment of foods high in potassium and phosphorus.

Of the 52 patients in the study, 71% (n=37) had limited health literacy and numeracy. Limited health literacy was defined as a SAHL score of <8; limited numeracy was defined as an NVS score of ≤3.

Compared with patients without limited health literacy and numeracy, those 37 patients were more likely to be older (P =.006), Hispanic (P =.014), have lower educational level (P =.003), and be primarily Spanish speaking (P =.009).

Most patients (81%) reported receiving dietary counseling. Patients who received dietary counseling were more likely than those not receiving dietary counseling to report changing their diet following CKD diagnosis (P =.024) and had improved compliance with kidney dietary restrictions (P =.002).

There were no differences in dietary intake of sodium, potassium, phosphorus, and protein between patients with and without limited literacy and numeracy, or patients who did and did not receive dietary counseling. Overall, the mean number of correct answers in identifying the four high potassium and four high phosphorus foods were 2.4 and 1.5, respectively. Those numbers did not differ among patients with and without limited literacy and numeracy, or between patients with and without dietary counseling.

In conclusion, the researchers summarized, “Limited health literacy and numeracy is common among patients with CKD 4 and 5 but there was no difference in dietary intake of restricted nutrients, or knowledge of restricted foods in subjects with and without limited literacy and numeracy. Dietary counseling did not result in better knowledge of restricted foods or differences in intake of restricted nutrients. Methods to improve the efficacy of dietary counseling need to be explored further.”

The researchers utilized the VA databases to establish a national cohort of new users of acid suppression therapy (PPI or histamine H2 receptor antagonists [H2 blockers]) with no kidney disease at baseline (defined as estimated glomerular filtration rate [eGFR] >60 mL/min/1.73 m²). Follow-up continued for 5 years.

The cohort included 144,032 new users of acid suppression therapy; of those, 18,436 were new users of H2 blockers and 125,956 were new users of PPIs. There were 118,793 cohort participants with no AKI during the time in the cohort (from time 0 at cohort entry until the end of follow-up or ESRD or death); of those, 16,101 were new users of H2 blockers and 102,692 were new users of PPIs. New users of PPIs and H2 blockers had similar demographic characteristics; PPI users were more likely to have diabetes, chronic lung disease, hyperlipidemia, cardiovascular disease, and gastrointestinal conditions.

Over a median follow-up of 5 years, in the study cohort, compared with users of H2 blockers, incident users of PPIs had a significantly increased risk of an eGFR <60 mL/min/1.73 m² (hazard ratio [HR], 1.19; 95% confidence interval [CI], 1.15-1.24), incident CKD (HR, 1.26; 95% CI, 1.20-1.33), an eGFR decline >30% (HR, 1.22; 95% CI, 1.16-1.28), and ESRD or a decline in eGFR >50% (HR, 1.30; 95% CI, 1.15-1.48).

In models that excluded participants with AKI either before chronic renal outcomes, during the time of the cohort, or before cohort entry, results were consistent. PPI users had an increased risk of eGFR <60 mL/min/1.73 m² (HR, 1.17; 95% CI, 1.12-1.22), incident CKD (HR, 1.23; 95% CI, 1.16-1.30), decrease in eGFR >50% (HR, 1.19; 95% CI, 1.13-1.26), and ESRD or decrease >50 in eGFR (HR, 1.21; 95% CI, 1.04-1.40).

Mediation analyses demonstrated that the proportion of PPI effect mediated by AKI was 44.7% for an incident eGFR <60 mL/min/1.73 m², 45.47% for incident CKD, 46.00% for an eGFR decrease >30.0%, and 46.72% for ESRD or a >50.0% decrease in eGFR.

Limitations cited by the authors included the cohort consisting of mostly older white male US veterans, possibly limiting the generalizability of the findings; lack of data on the volume of daily urine output; inability to account for AKI that was not clinically detected; and the possibility that some participants in the cohort might have acquired PPIs without having a prescription.

The researchers said, “In sum, our results show a significant association of PPI use and the risk of CKD and progression to ESRD among PPI users is not significant as a sole risk mitigation strategy. Exercising vigilance in PPI use, even in the absence of AKI, and careful attention to kidney function in PPI users may be a reasonable approach.”

## Risk of Chronic Kidney Disease

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CRIC Study Analysis: No Significant Racial/Ethnic Differences in Risk for Cardiovascular Outcomes

The risks for cardiovascular disease, cardiovascular mortality, and all-cause mortality are all increased in the presence of chronic kidney disease (CKD), yet reasons for the high burden of cardiovascular disease among patients with CKD are unclear. Patients with CKD experience a high prevalence of traditional and nontraditional cardiovascular risk factors that likely play a key role in the pathogenesis of cardiovascular disease in this patient population.

It is well established that the risk for cardiovascular events and death among non-Hispanic blacks and Hispanics with end-stage renal disease receiving dialysis is lower than among non-Hispanic whites. However, data regarding racial/ethnic disparities in patients with CKD not dependent on dialysis are inconclusive.

Data from NHANES (National Health and Nutrition Examination Survey) show that black/African Americans with CKD >65 years of age are more likely to die than white individuals. Conversely, a 2011 study that utilized data from KEEP (Kidney Early Evaluation Program) found no difference in mortality between African Americans and whites. Kaiser Permanente Northern California has reported data suggesting that Hispanics with CKD have reduced all-cause and cardiovascular mortality compared with non-Hispanic whites.

CRIC (Chronic Renal Insufficiency Cohort), a prospective cohort study, provides comprehensive longitudinal clinical and demographic data that provide insight into potential racial-ethnic variations in cardiovascular outcomes in patients with reduced kidney function. James P. Lash, MD, and colleagues recently conducted an analysis of CRIC data to compare the risk for atherosclerotic cardiovascular events and heart failure among three major racial/ethnic groups (non-Hispanic white, non-Hispanic black, and Hispanic). They reported results in the American Journal of Kidney Diseases [2016;68(4):545-553].

CRIC and Hispanic CRIC are ongoing prospective observational studies of risk factors for CKD progression and cardiovascular disease. Inclusion criteria were age 21 to 74 years and mild to moderate CKD, defined as estimated glomerular filtration rate (eGFR) from 20 to 70 mL/min/1.73 m². CRIC included 170 Hispanics and 3289 non-Hispanics from seven clinical centers in the United States; recruitment occurred from May 2003 through March 2007. Hispanic CRIC included 327 Hispanics recruited at the University of Illinois at Chicago and the Chicago metropolitan area from October 2005 through June 2008.

The current analyses include 3785 participants who self-reported race/ethnicity as non-Hispanic white, white, or non-Hispanic black. Primary outcomes of interest were atherosclerotic cardiovascular events (myocardial infarction, stroke, or peripheral artery disease), heart failure, and two composite outcomes (atherosclerotic event or death from any cause and heart failure or death from any cause).

Mean age of the participants was 58 years, 45% were women, 1638 (43%) were non-Hispanic white, 1650 (44%) were non-Hispanic black, and 497 (13%) were Hispanic. Among the Hispanics, nine participants identified themselves as black. Overall, 48% had diabetes, mean eGFR was 45 mL/

App Aids in Patient Training for Self-Care In Center or At Home

Chicago—It is important to provide education for dialysis patients regarding their therapy options, and maintenance of kidney function and health. Previous studies have demonstrated that educated patients make better choices and are more adherent to their therapy. However, training is labor intensive and requires hours of staff time; those constraints have led to clinic staff in providing patient education that may increase the burden on clinic staff in providing training and reduce the training time for patients. The app has 10 modules, each with comprehensive quiz. Each of the quizzes must be completed before moving on to the next module.

Sixteen patients from four dialysis units recently participated in a trial of the app. The time each patient spent on each module was recorded in the app’s proprietary algorithm; that data was subsequently analyzed. In addition, the patients completed a survey about their experience with the app. Of the 16 patient surveys, 94% (n=15) reported that the app was easy to understand. Twelve of the patients (75%) said the app provided information that would increase their interest in becoming more involved in their dialysis therapy. When asked about the format, 88% said it was easy to follow; in response to questions about the content of the app, 81% reported they were surprised at how much they learned. Finally, the average time spent on the app to complete the training modules and quizzes was 3 hours and 19 minutes.

In conclusion, the researchers said, “A new tablet-based app developed for the Tablo™ Hemodialysis System provides approachable patient education that may increase patient interest in self-care and reduce the amount of training time to reach competency needed for self-care whether at home or in-center.”

and Hispanics, 1.74 per 100 person-years. Compared with non-Hispanic whites, non-Hispanic blacks were more likely to have a history of heart failure and stroke and be current smokers. Compared with non-Hispanic whites, Hispanic participants were younger and less likely to have a history of myocardial infarction/vascularization, be current smokers, and receive nephrology care.

Hispanics were less likely to be on aspirin or antiplatelet therapy compared with non-Hispanic whites or blacks. Non-Hispanic blacks were more likely than non-Hispanic whites to be receiving an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker; they were less likely to be receiving beta-blockers and statins.

Median follow-up was 6.6 years. During that time, there were 506 atherosclerotic events, 551 heart failure events, 692 deaths, 999 atherosclerotic events or deaths, and 1010 heart failure events or deaths. The aggregate retention by racial/ethnic group for this analytic cohort was 89.1% non-Hispanic white, 87.2% non-Hispanic black, and 89.2% Hispanic.

Following adjustment, rates for atherosclerotic events were similar among the three groups: non-Hispanic whites, 1.83 per 100 person-years; non-Hispanic blacks, 2.25 per 100 person-years; and Hispanics, 1.74 per 100 person-years.

Compared with non-Hispanic whites and Hispanics, heart failure rates were higher in non-Hispanic blacks (1.64 and 1.76 vs 2.43 per 100 person-years, respectively). Following adjustment for clinical center, in Cox models, non-Hispanic blacks were at higher risk for heart failure events compared with non-Hispanic whites and Hispanics (hazard ratio [HR], 1.59; 95% confidence interval [CI], 1.29-1.95). Following adjustment for socioeconomic factors and nephrology care, this association remained significant; it was no longer significant following adjustment for baseline eGFR and proteinuria. The risk for heart failure events for Hispanics was similar to that of non-Hispanic whites.

Rates of all-cause deaths were similar in all three groups: non-Hispanic whites, 2.06 per 100 person-years; non-Hispanic blacks, 2.46 per 100 person-years; and Hispanics, 1.84 per 100 person-years. Corresponding rates of the composite atherosclerotic event or death outcome were 3.45, 4.33, and 3.22 per 100 person-years, respectively. The corresponding rates of the composite of heart failure or death outcome were 3.24, 4.42, and 3.14 per 100 person-years, respectively.

Following adjustment for clinical center, there were no significant differences in risk for the composite outcome of atherosclerotic event or death between non-Hispanic blacks and whites. However, following further adjustment for cardiovascular risk factors, medications, and markers of mineral metabolism, non-Hispanic blacks had a 17% lower adjusted rate of the composite outcome (HR, 0.83; CI, 0.69-0.99) than non-Hispanic whites. There was no significant association with Hispanic ethnicity.

The researchers cited some limitations to the analysis, including the Hispanic participants being largely recruited from a single center, and the study being underpowered to evaluate the association between Hispanic ethnicity and mortality.

“In conclusion, we found that there were no significant racial/ethnic differences in risk for atherosclerotic or heart failure outcomes in this cohort of individuals with CKD. In addition, we found that in adjusted models, non-Hispanic blacks had lower risk for the composite of atherosclerotic event or death compared with non-Hispanic whites. Future work is needed to better understand reasons underlying racial/ethnic variation in death in CKD,” the researchers said.

**TAKEAWAY POINTS**

- Data on possible racial/ethnic variation in cardiovascular outcomes in individuals with chronic kidney disease not dependent on dialysis are limited.
- Using data from the CRIC (Chronic Renal Insufficiency Cohort) and Hispanic CRIC studies, researchers conducted an analysis to compare the risk for atherosclerotic cardiovascular events and heart failure among non-Hispanic whites, non-Hispanic blacks, and Hispanics.

In this cohort, there were no significant racial/ethnic differences in the risk for atherosclerotic or heart failure outcomes. In adjusted models, non-Hispanic blacks had lower risk for the composite of atherosclerotic event or death than non-Hispanic whites.

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**Chronic Kidney Disease**

**Glycemic Control Levels and Infections in Hemodialysis Patients with Diabetes Mellitus**

**Chicago**—There are few data on the associations between glycemic control and infections requiring hospitalization or fatal infections in hemodialysis patients with diabetes mellitus. Using data from the US Renal Data System and from electronic health records from a large dialysis provider in the United States, Jinnie J. Rhee, MD, and colleagues recently conducted a study to examine such associations. They reported their findings during a poster session at Kidney Week 2016 in a poster titled Associations between Glycemic Control and Infections among US Hemodialysis Patients with Diabetes Mellitus. The records were merged at the patient level. Socioeconomic status was determined using area-level US census data.

The analysis included Medicare beneficiaries with diabetes mellitus >18 years of age who initiated in-center maintenance hemodialysis treatment from 2006 to 2011 with >90-day survival. The exposure was time-averaged hemoglobin A1c (HbA1c); quarterly mean HbA1c levels were categorized as <6.5% (reference), 6.5% to <7.5%, 7.5% to <8.5%, and ≥8.5%.

The primary outcomes were hospitalizations for infection and fatal infections. The researchers identified infection-related hospitalizations from Medicare claims. End-Stage Renal Disease Notification (Centers for Medicare & Medicaid Services CMS-2746) was used to identify death from infectious cause. Cox proportional hazards models were used to estimate multivariable-adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) for the associations between time-averaged HbA1c category and these infectious events, adjusting for demographics, updated comorbidities from claims, and time-averaged vital signs and laboratory results.

There were 16,387 patients who met inclusion and criteria. Among those patients, there were 6885 hospitalizations related to infection and 887 deaths linked to infection. Compared with patients whose HbA1c was <6.5%, HRs for infection-related hospitalizations were 0.99 (95% CI, 0.93-1.06), 1.03 (95% CI, 0.95-1.13), and 1.12 (95% CI, 1.02-1.22) for patients whose HbA1c was 6.5% to <7.5%, 7.5% to <8.5%, and ≥8.5%, respectively (P for trend=0.2). Corresponding HRs for deaths from infection were 0.88 (95% CI, 0.70-1.10), 0.82 (95% CI, 0.61-1.09), and 0.74 (95% CI, 0.52-1.04) for patients with HbA1c <6.5%, ≥7.5% to <8.5%, and ≥8.5%, respectively, compared with those with HbA1c <6.5% (P for trend=0.8).

The researchers summarized by saying, “While time-averaged HbA1c was not clearly associated with the risk of infection-related mortality, there was a significant trend toward higher rates of infection-related hospitalizations with increasing HbA1c levels.”

Patients with Elevated C-Reactive Protein at Increased Risk for ESRD

O

f adults with self-reported diabetes in the United States, 40% are affected by chronic kidney disease (CKD). For CKD patients, diabetes is a major risk factor for progression of CKD; it is the leading cause of end-stage renal disease (ESRD), associated with approximately 50,000 new cases in 2012 alone.

In patients with and without a history of cardiovascular events and in patients with CKD, elevated concentrations of C-reactive protein, a biomarker seen in the presence of inflammation, are associated with the development of future cardiovascular events. In turn, CKD is a risk factor for cardiovascular disease; the most common causes of death in patients with CKD and diabetes are cardiovascular events.

Previous studies of the role of chronic inflammation in progression of both diabetes and CKD have resulted in conflicting evidence regarding the association of C-reactive protein level with decline in kidney function (defined as changes in serum creatinine or estimated glomerular filtration rate); some studies have reported a significant association whereas others have not.

Finnian R. Mc Causland, MBCh, MMSc, MRCP, and colleagues recently conducted a post hoc analysis of data from the TREAT (Trial to Reduce Cardiovascular Events with Aranesp Therapy) to test the hypothesis that patients with higher baseline concentrations of C-reactive protein would be at increased risk for the development of ESRD and death or ESRD. They reported results in the American Journal of Kidney Diseases [2016;68(6):873-881].

There were 4038 participants with type 2 diabetes mellitus, CKD, and anemia in the primary cohort. Of those, 57% were women, mean age was 67 years, 64% were white, and 52.3% had a baseline concentration of C-reactive protein at or below the lower limit of detection (≤3.0 mg/L). Of the remaining individuals in the cohort, 23.6% (n=953) had a mildly elevated C-reactive protein level (3.0 to ≤6.9 kg/L), and 24.1% (n=973) had a moderately to markedly elevated level (≥6.9 mg/L).

Those with higher levels of C-reactive protein were more likely to be younger and female; have a history of acute kidney injury; be a current or former smoker; and have higher concentrations of low-density lipoprotein cholesterol and ferritin. Participants with higher levels of C-reactive protein were also more likely to use insulin and have higher body mass index and glycated hemoglobin levels, but less likely to have retinopathy or be taking a statin or an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker.

Serum creatinine concentration was statistically higher and eGFR was statistically lower in patients in the higher C-reactive protein categories; however, absolute differences were very small and unlikely to be of clinical importance.

Median follow-up was 2.2 years. During that time, 668 adjudicated ESRD events were recorded. In unadjusted analyses, compared with patients with C-reactive protein levels ≤3.0 mg/L, those in the mildly elevated group had a 21% greater risk for developing ESRD (hazard ratio [HR], 1.21; 95% confidence interval [CI], 1.02-1.46; P=0.04); those in the moderate/markedly elevated group had 37% greater risk (HR, 1.37; 95% CI, 1.34-1.64; P<0.001). In fully adjusted models, compared with those with C-reactive protein levels ≤3.0 mg/L, those with moderate/markedly elevated levels had 32% greater risk for developing ESRD (HR, 1.32; 95% CI, 1.07-1.63; P=0.01).

Results were similar when time-varying coefficients were added to the model, and similar trends were seen when subgroup analyses of individuals with baseline C-reactive protein levels >3.0 ng/mL (n=1926) were performed.

Regarding doubling of serum creatinine level and a composite of ESRD or doubling of serum creatinine level, during a median follow-up of 2.1 years, 428 individuals experiencing doubling of serum creatinine level. There was no significant association of elevated categories of baseline C-reactive protein with the risk of developing doubling of serum creatinine level or the development of the composite of ESRD or serum creatinine doubling.

Compared with individuals with baseline C-reactive protein levels ≤3.0 mg/L, those with levels ≥6.9 mg/L had a higher adjusted risk for ESRD (HR, 1.32; 95% CI, 1.07-1.63) and the composite outcome of death of ESRD (HR, 1.41; 95% CI, 1.21-1.64).

The researchers cited a few limitations to the study, including the use of standard sensitivity measurements of C-reactive protein with a lower limit of measurement of 3.0 mg/L, restricting the ability to examine C-reactive protein level as a continuous variable; having only one baseline measurement of C-reactive protein; and including patients with type 2 diabetes mellitus, anemia, and CKD, possibly limiting the generalizability to patients without that comorbid disease pattern.

In conclusion, the researchers said, “We found that higher baseline C-reactive protein level was associated with greater risk for developing ESRD and the composite of ESRD or death in patients with the triad of type 2 diabetes mellitus, CKD, and anemia. When reviewing a patient with these comorbid conditions, the presence of an elevated C-reactive protein level may prompt the clinician to explore for potentially modifiable sources of inflammation, such as infection. Whether interventions that lower C-reactive protein levels will result in a reduced risk for ESRD is unknown, but may provide opportunities for future research.”
Cell Cycle Arrest Biomarkers Predict Risk of AKI

Acute kidney injury (AKI) occurs in as many as 20% of hospitalized patients; AKI is associated with high morbidity and mortality. A key component of management of patients with AKI is limiting further renal damage when injury occurs. Early diagnosis and recognition of AKI can attenuate ongoing injury. In patients with underlying chronic conditions, it can be challenging to identify AKI, partly due to the fact that biomarkers often perform poorly in that patient population.

Researchers led by Michael Heung, MD, MS, recently pooled data from two trials of critically ill patients at risk for AKI. The two multicenter trials (Sapphire and Topaz) were designed to validate urinary tissue inhibitor of metalloproteinases-2 (TIMP-2) and insulin-like growth factor-binding protein 7 (IGFBP7), markers associated with cell cycle arrest, for risk stratification for moderate-to-severe AKI.

The current secondary analysis was conducted to assess the impact of comorbidities (chronic kidney disease [CKD], congestive heart failure, diabetes mellitus) on the performance characteristics of cell cycle arrest markers in the prediction of moderate-to-severe AKI. Results of the analysis were reported in Nephrology Dialysis Transplantation [2016;31(10):1633-1640].

The Sapphire trial enrolled 744 critically ill patients >21 years of age who were at risk for developing AKI. The Topaz study included 420 critically ill adult patients with similar inclusion and exclusion criteria to the Sapphire study. Inclusion criteria were evidence of pulmonary or cardiovascular dysfunction and not yet meeting criteria for moderate-to-severe AKI (Kidney Disease Improving Global Outcomes [KDIGO] Stage 2 or 3). Patients were recruited within 24 hours of enrollment serum creatinine level and non-renal Sequential Organ Failure Assessment (SOFA) score of 0.85-0.97. The relative risk for AKI with a TIMP2/IGFBP7 value above the previously validated cutoff of 0.3 was 2.4 (95% CI, 1.6-4.0). Of the 326 patients with diabetes, TIMP2/IGFBP7 was significantly higher in patients who developed AKI compared with those who did not develop AKI (1.5 vs 0.3, P <0.001); these values were consistent across a variety of comorbid conditions and remained statistically different between AKI and non-AKI patients.

In all, 97 patients had CKD. Of those, the area under the curve (AUC) for TIMP2/IGFBP7 prediction of moderate-to-severe AKI was 0.91 (95% confidence interval [CI], 0.85-0.97). The relative risk for AKI with a TIMP2/IGFBP7 value above the previously validated cutoff of 0.3 was 2.4 (95% CI, 1.6-4.0). Of the 326 patients with diabetes, TIMP2/IGFBP7 testing yielded an AUC of 0.83 (95% CI, 0.77-0.89), and a value of >0.3 was associated with a relative risk for moderate-to-severe AKI of 12.8 (95% CI, 4.1-40.1).

Among patients with no AKI or stage 1 AKI (n=992), 59% were men, mean age was 62 years, median body mass index (BMI) was 27 kg/m², 80% were white, and 13% were black. Of those with AKI stage 2 or 3 (n=139), 53% were men, mean age was 65 years, median BMI was 31 kg/m², 81% were white, and 12% were black.

In the overall cohort, median TIMP-2 and IGFBP7 was significantly higher in patients who developed AKI compared with those who did not develop AKI (1.5 vs 0.3, P <0.001); these values were consistent across a variety of comorbid conditions and remained statistically different between AKI and non-AKI patients.

Of the 1164 patients recruited for the two trials, 21 were excluded from the Sapphire study and 12 were excluded from Topaz. Patients characteristics in the two trials were similar. The final cohort consisted of 1131 patients; of those, 12.2% (n=139) developed moderate-to-severe AKI. For purposes of the current analysis, AKI refers to KDIGO Stage 2 or 3 AKI and no AKI refers to either no AKI or Stage 1 AKI.

A greater proportion of patients who developed AKI had pre-existing diabetes and hypertension than the patients without pre-existing diabetes. The percentage of patients with underlying CKD was similar between the AKI groups; median enrollment serum creatinine was higher in patients who developed AKI.

Of the 326 patients with diabetes, TIMP2/IGFBP7 testing yielded an AUC of 0.83 (95% CI, 0.77-0.89), and a value of >0.3 was associated with a relative risk for moderate-to-severe AKI of 12.8 (95% CI, 4.1-40.1).

Researchers conducted an analysis of data from two studies of critically ill patients that validated the novel biomarker panel of urinary tissue inhibitor of metalloproteinases-2 and insulin-like growth factor-binding protein 7. Results of the analysis suggested that there was no significant impairment in the performance of cell cycle arrest biomarkers related to the presence of chronic comorbid conditions.
No Differences in Measured GFR Between Blacks and Whites

Ethnic and minority groups in the United States shoulder a disproportionate burden of chronic kidney failure; incidence rates for treatment of kidney failure by dialysis and transplantation are approximately three times higher in older blacks compared with whites. There are no conclusive data on the cause of the higher incidence of kidney failure in blacks compared with whites; however, community-based population samples suggest possible associations with racial differences in glomerular filtration rate (GFR) and albuminuria. Investigation of that hypothesis requires studies of measured GFR (mGFR) in cohorts that include whites and blacks who are not selected because of the presence or absence of kidney disease.

Lesley A. Inker, MD, MS, and colleagues utilized data from the Multi-Ethnic Study of Atherosclerosis (MESA) to conduct an ancillary study, MESA-Kidney, comparing mGFR and albuminuria in a sample of older black and white individuals from a community-based cohort. The study also aimed to assess sex and age associations, and compare mGFR with and without indexing to body surface area to determine whether potential sex and race differences are due to differences in body size. Study results were reported in the *American Journal of Kidney Diseases* [2016;68(5):743-751].

A total of 746 MESA participants completed visit 3, 4, or 5 at Johns Hopkins University, of whom 674 were approached to participate in MESA-Kidney. Of those, 26 met exclusion criteria; of the remaining 648, 307 provided consent to enrollment in MESA-Kidney. Of those, 294 had complete data and were included in the analysis.

The difference between blacks and whites in mean GFRs not indexed for body surface area was larger in magnitude, but remained nonsignificant.

Mean age of the participants was 71 years, 47% were black, 48% were women, 25% had diabetes, 64% had hypertension, and 5% had a history of cardiovascular disease; there were some significant differences between blacks versus whites or men versus women. Mean body surface area was 1.94 m² and mean body mass index was 29.7 kg/m².

Most, but not all, measurements of body size were greater in blacks than in whites and in men compared with women; there was a larger difference between men and women than between blacks and whites. In the overall cohort, mean GFR was 73 mL/min/1.73 m² when indexed to body surface area and 82 mL/min/1.73 m² without indexing to body surface area. Median albumin-creatinine ratio (ACR) was 10.0 mg/g.

On average, GFR was 1.02 (95% confidence interval [CI], 0.79-1.24) mL/min/1.73 m² lower per year older, without significant differences between blacks and whites (P = .8) or men and women (P = .3). There was wide variation, however, in GFRs at any age. Among participants 66 to 70 years of age, median GFR was 72 mL/min/1.73 m² but ranged from 39 to 109 mL/min/1.73 m²; among those 76 to 80 years of age, median GFR was 68 mL/min/1.73 m² but ranged from 16 to 103 mL/min/1.73 m². GFR not indexed for body surface area was 1.27 (95% CI, 0.96-1.58) mL/min/1.73 m² lower per year; there were no significant differences between race and sex groups, also with wide variation at any age.

Compared with whites, GFR indexed for body surface area was not significantly higher in blacks (mean difference, 2.94 [95% CI, –1.37 to 7.26] mL/min/1.73 m²; P = .2); this relationship did not change following adjustment for age and sex. The difference between blacks and whites in mean GFRs not indexed for body surface area was larger in magnitude, but remained nonsignificant.

Mean GFR indexed for body surface area was lower in women than in men (mean difference, –9.34 [95% CI, –13.53 to –5.15] mL/min/1.73 m²; P < .001). The difference remained significant following adjustment for demographics, clinical characteristics, and other measures of body size. When GFR was not indexed for body surface area, differences between men and women were substantially greater (mean difference, –21.39 [95% CI, –26.75 to –16.03] mL/min/1.73 m²; P < .001). Attenuation was greatest with adjustment for body surface area and height.

Urine ACR was higher at older age; difference in ACR was 3.2% (95% CI, 1.5%-4.8%) higher per year of age and larger in men than women (P = .03), but not in blacks versus whites. There was wide variation in ACR at any age: for participants 66 to 70 years of age, median ACR was 11 mg/g, with a range of 3 to 533 mg/g; for participants 76 to 80 years of age, median ACR was 14 mg/g, with a range of 2 to 3429 mg/g.

Limitations to the analysis cited by the authors included the cohort of seniors being by definition survivors who were healthy enough to participate, limiting the generalizability of the findings; the small sample size; and the cohort being drawn from one city.

In summary, the researchers said, “In this first community-based population study of blacks and whites with mGFR, we found no difference in mGFRs between blacks and whites. These findings suggest that other factors must account for the higher incidence rate of kidney failure in older blacks versus whites. The findings of higher GFRs in men than women may be due to differences in body size, which may not be adequately accounted for by indexing for body surface area.”
Help your new-to-dialysis patients succeed with Velphoro

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

INDICATION
Velphoro® [sucroferric oxyhydroxide] is a phosphate binder indicated for the control of serum phosphorus levels in patients with chronic kidney disease on dialysis.

IMPORTANT SAFETY INFORMATION
• Velphoro must be administered with meals. Velphoro tablets must be chewed and not swallowed whole. To aid with chewing and swallowing, the tablets may be crushed.
• Patients with peritonitis during peritoneal dialysis, significant gastric or hepatic disorders, following major gastrointestinal (GI) surgery, or with a history of hemochromatosis or other diseases with iron accumulation have not been included in clinical studies with Velphoro. Monitor effect and iron homeostasis in such patients.
• In a parallel design, fixed-dose study of 6 weeks duration, the most common adverse drug reactions to Velphoro chewable tablets in hemodialysis patients included discolored feces (12%) and diarrhea (6%).
• Velphoro can be administered concomitantly with oral calcitriol, ciprofloxacin, digoxin, enalapril, furosemide, HMG CoA reductase inhibitors, hydrochlorothiazide, losartan, metoprolol, nifedipine, omeprazole, quinidine and warfarin. Take doxycycline at least 1 hour before Velphoro. Velphoro should not be prescribed with oral levothyroxine.

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

*Clinical results of individual patients from long-term trial.

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TO DOWNLOAD $0 CO-PAY SAVINGS CARDS
AND OTHER RESOURCES.

† A 52-week, open-label, active-controlled, phase 3 study evaluated the safety and efficacy of Velphoro in lowering serum phosphorus levels in patients (N=1,454) with chronic kidney disease on hemodialysis or peritoneal dialysis.

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

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

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

CONTRAINDICATIONS
None.

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

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

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

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

Take doxycycline at least 1 hour before Velphoro.

Velphoro should not be prescribed with oral levethroxyline.

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
Store in the original package and keep the bottle tightly closed in order to protect from moisture.

Store at 25°C (77°F) with excursions permitted to 15 to 30°C (59 to 86°F).

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

Velphoro should be taken with meals.

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

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

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Fresenius Medical Care North America
920 Winter Street
Waltham, MA 02451

US Patent Nos. 6174442 and pending, comparable and/or related patents.
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DASH Diet May Offer Protection Against Kidney Disease

**Multiple clinical guidelines recommend the DASH (Dietary Approaches to Stop Hypertension) diet for the promotion of good health and prevention of disease. DASH includes a dietary pattern high in fruits, vegetables, and dairy products that are low in fat. Reducing sodium intake further lowers blood pressure and reduces the risk for hypertension, type 2 diabetes, cardiovascular disease, stroke, and mortality.**

A standard approach for the prevention of kidney disease includes treatment of cardiovascular risk factors such as hypertension and diabetes. However, according to Casey M. Rebholz, PhD, MS, MPH, and colleagues, there are few data on the efficacy of a dietary approach for the prevention of kidney disease. Current clinical guidelines on kidney disease prevention rely on dietary restriction of protein and sodium, albeit with weak supporting evidence.

Previous studies have shown a significant association between the DASH diet and kidney function reduction in older white women. Dr. Rebholz et al. recently conducted a study designed to examine the longitudinal relationship between adherence to a DASH-style diet with sodium reduction and subsequent risk for kidney disease in a diverse general population of African American and white men and women.

The researchers reported study results in the American Journal of Kidney Diseases [2016;68(6):853-861]. Data from the ARIC (Atherosclerosis Risk in Communities) study were prospectively analyzed. The ARIC study included 15,792 middle-aged (45-64 years) predominantly African American and white men and women. Following application of exclusion criteria, the sample size of the current analysis was 14,882 individuals. Baseline characteristics of the included individuals were similar to those of the total ARIC study population.

The excluded participants (n=910) were more likely to be African American and overweight or obese, more likely to have diabetes and hypertension, and less likely to have a high school education. By definition, the excluded individuals had worse kidney function at baseline.

Participants were stratified according to DASH diet score: higher scores signify that the participant's dietary pattern more closely matches a DASH-style diet. Participants in the lowest tertile of DASH diet score were younger, more likely to be male and African American, and less likely to have completed high school compared with other participants. The lowest tertile group also had lower physical activity, were more likely to smoke, and had a higher percentage of being overweight or obese. Participants with higher DASH diet scores were associated with lower systolic blood pressure and higher prevalence of diabetes. Estimated glomerular filtration rates (eGFRs) at baseline were statistically but not clinically different across the tertiles of DASH diet score.

During a median follow-up of 23 years, there were 3720 cases of kidney disease. Following adjustments (for age, sex, race-center, level of education, smoking status, physical activity, total caloric intake, baseline eGFR, overweight/obese status, diabetes, hypertension, systolic blood pressure, and use of angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers), participants in the lowest tertile of DASH diet score were 1.16 times more likely to develop kidney disease than those in the highest tertile of DASH diet score (P for trend across tertiles <.001).

Using a secondary DASH diet index that incorporates nutrients rather than food items, there was also an association between DASH diet score and kidney disease risk. Using indices modified to exclude dietary intake of sodium from the score, similar patterns were seen. In a sensitivity analysis utilizing only eGFR for the outcome definition, there were 2030 cases of kidney disease (55% of a total of 3720 cases) and effect estimates were stronger than for those with the primary method for ascertaining causes of kidney disease.

In an analysis based on the individual components of the DASH diet score, there were significant associations between higher consumption of red meat and processed meat and increased risk for kidney disease. Higher intake of nuts and legumes and low-fat dairy was associated with lower risk for kidney disease. Analysis using the secondary DASH diet score found a statistically significant association between higher intake of magnesium and calcium and reduced risk for kidney disease; higher dietary intake of protein was associated with higher risk for kidney disease.

The researchers cited some limitations to the study, including utilizing self-report to assess dietary intake, which is prone to reporting bias; other possible sources of measurement error; residual confounding; and the lack of data for albuminuria, which is strongly associated with decline in kidney function. The researchers concluded by saying, “Consumption of a DASH-style diet was associated with a lower risk for kidney disease independent of demographic characteristics, caloric intake, socioeconomic status, lifestyle factors, comorbid conditions, antihypertensive medication use, and baseline kidney function in this general population sample of African American and white men and women. The DASH diet, designed for blood pressure reduction and now widely recommended for reducing the risk for cardiovascular disease and other chronic diseases, may also protect against kidney disease.”

**Takeaway Points**

- Researchers report on the findings of a prospective cohort study aimed at examining the longitudinal relationship between consumption of a DASH-style diet with sodium reduction and subsequent risk for kidney disease in a diverse population of African American and white men and women.
- Participants were stratified into three groups according to DASH diet score: those in the lowest tertile were 16% more likely to develop kidney disease than those in the highest tertile.
- Analyses based on individual components of the DASH diet demonstrated that high intake of red and processed meat were associated with increased risk of kidney disease, and high intakes of nuts, legumes, and low-fat dairy products were associated with decreased risk of kidney disease.
Outcomes in Transplant Recipients Treated with RAS Blockade Agents

In 2013, there were more than 100,000 cases of end-stage renal disease (ESRD) in the United States and the prevalence is increasing by 21,000 each year, making ESRD a major public health problem. The optimal renal replacement therapy is kidney transplantation; however, long-term outcomes are less than optimal, with 10-year transplant rates of 45% for recipients of deceased donor kidneys. Proteinuria and reduced glomerular filtration rate (GFR) are common in recipients of kidney transplant, and both are risk factors for transplant loss and mortality.

Studies in the general population have shown that renin-angiotensin system (RAS) blockade reduces proteinuria and blood pressure, and decreases the risk for ESRD and mortality in diabetic and nondiabetic populations. Studies conducted in the kidney transplant population have had conflicting results of RAS blockade: some studies have shown increases in transplant and patient survival in patients using RAS blockade agents compared with nonusers, while others have found no difference in transplant and patient survival in users versus nonusers.

In 2007, Swapnil Hiremath, MD, et al. conducted a systematic review of 21 randomized trials of RAS blockade in kidney transplant recipients. Results of that analysis found that blood pressure and proteinuria were both reduced with RAS blockade, but were accompanied by a reduction in GFR. A 2009 Cochrane review confirmed those findings. Dr. Hiremath and colleagues recently conducted a systematic review and meta-analysis of randomized controlled trials involving RAS blockade in kidney transplant recipients; the review focused on transplant and patient survival. The researchers reported results of the current analysis in the American Journal of Kidney Diseases [2017;69(1):78-86]. The review utilized MEDLINE (1966 to November 2013), Embase (1980 to November 2015), and the Cochrane Library (third quarter 2015), in combination with a PubMed search for recent nonindexed citations. Selection criteria were randomized controlled trials evaluating the use of angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) in recipients of kidney transplantation. Eligible studies had follow-up of ≥1 year and reported clinical outcomes of interest (patient survival; transplant failure, defined as return to dialysis therapy or repeat transplantation; or doubling of serum creatinine level).

The updated literature search identified 890 nonduplicate citations. Following application of study selection criteria, the researchers reviewed 52 articles in full text. Of those, 44 were excluded (17 had follow-up of <1 year, 15 did not report an outcome of interest, and 12 were not randomized trials). The eight eligible trials involved 1502 kidney transplant recipients.

Median sample size was 142 (range, 47-502); five trials used an ACE inhibitor (Lisinopril, 3; and Ramipril, 2) as the study intervention and three trials used an ARB (telmisartan, losartan, and candesartan). Five of the eight trials used a placebo control, two compared to standard care defined as any treatment other than RAS blockade, and one used nifedipine as a comparison. Median follow-up was 1.5 years (range, 1-10 years). Three of the trials were industry funded, three were funded from peer-reviewed institutional grants, one trial reported no funding, and one did not report a funding source.

Across the eight trials, average age was approximately 50 years; most trials included a mix of living and deceased donor transplants (with the exception of one that included only recipients of deceased donor transplants). In two trials, time from transplantation to randomization was relatively early (3 days and 58 days). Of the other six trials, time from transplantation to randomization ranged from 1.3 to 10.4 years. At baseline, kidney function was comparable, with the exception of one trial that explicitly included recipients with chronic allograft nephropathy.

Among the 1502 transplant recipients in the eight trials, there were 71 deaths. In pooled analyses, there was no mortality difference between patients treated with an ACE inhibitor or ARB and controls (summary risk ratio [RR], 0.96; 95% confidence interval [CI], 0.62-1.1; P=.9). The eight trials reported a total of 72 transplant failures (one trial did not have any transplant failures). Pooled analyses did not show any difference between patients treated with an ACE inhibitor or ARB and controls with respect to risk for transplant loss (summary RR, 0.76; 95% CI, 0.48-1.18; P=.5). Sixty patients of 1068 from five trials had doubling of serum creatinine level; pooled analyses did not reveal any difference between patients treated with an ACE inhibitor or ARB for this outcome (summary RR, 0.84; 95% CI, 0.51-1.39; P=.5).

There were no significant differences between the subgroups of interest (ACE inhibitor or ARB as intervention, follow-up of 1 year or follow-up >1 year, and proteinuria at baseline). In analyses of adverse events, the risk for hyperkalemia was significantly higher in patients treated with an ACE inhibitor or ARB (summary RR, 2.44; 95% CI, 1.53-3.90; P=.001).

There was no statistical heterogeneity in any of the pooled analyses. Limitations to the analysis cited by the researchers included the small number of studies that met inclusion criteria, the lack of data on baseline proteinuria in two of the studies, limiting the analysis to randomized trials only, and the possibility of publication bias.

“In conclusion, this analysis neither supports nor refutes the hypothesis that RAS blockade improves clinical outcomes in kidney transplant recipients. A trial with more than 10,000 patients would be needed to definitively answer whether RAS blockade reduces transplant loss in this population. In the meantime, clinicians should weigh the risks and benefits of using these medications with their patients on a case-by-case basis,” the researchers said.
Kidney transplantation is associated with better patient outcomes and lower costs than dialysis; however, only <3% of patients with end-stage renal disease (ESRD) receive a kidney transplant before initiation of dialysis therapy and <30% of prevalent patients with ESRD have a functioning transplant.

At present, there are no pay-for-performance indicators related to transplantation in the Centers for Medicare & Medicaid Services (CMS) ESRD Quality Incentive Program (QIP). A CMS technical panel recently developed and proposed performance measures intended to increase access to transplantation among dialysis patients. One possible indicator is referral of patients for kidney transplantation evaluation by the dialysis facility, but it is unclear whether referral is associated with existing dialysis facility quality indicators.

Laura C. Plantinga, PhD, and colleagues recently conducted a cross-sectional study designed to examine whether the percentage of patients referred from a dialysis facility was associated with other existing indicators of quality of care at the facility level. The researchers also sought to determine whether individual patient likelihood of being referred was related to quality of care at the treating dialysis facility. Study results were reported in the American Journal of Kidney Diseases [2017;69(2):257-265].

The researchers utilized data for all referrals for evaluation for kidney transplantation to all three adult transplantation centers in Georgia in 2005 to 2012. Referral data were sent from each center directly to ESRD Network 6, the data coordinating center for the study. The referral data were linked to US Renal Data System (USRDS) data from January 1, 2005, through September 30, 2012. The USRDS includes data for all patients with ESRD treated in the United States.

Data from the Dialysis Facility Report (DFR) included facility-reported data for all publicly reported measures and are available for 2008 to 2011. Patients who were treated at transplantation-only or Veterans Affairs dialysis facilities and those who received ESRD therapy for <90 days are excluded from the aggregate measures in the DFR data set.

Following merger of USRDS and Georgia referral data, 15,279 patients 18 to 69 years of age who initiated dialysis therapy at one of 308 Georgia facilities from January 1, 2005, through September 30, 2011, were identified. After application of exclusion criteria, 12,926 patients and 241 facilities were included in the primary analysis.

Among the 241 facilities, the median within-facility cumulative percentage of patients referred for kidney transplantation within 1 year of initiation of dialysis therapy was 25.4%. In comparisons of high versus low referral, those with high referral were more likely to be for profit and have higher standardized transplantation ratios and percentages of patients on the transplant waitlist. Further, percentages of patients with fistulas were higher, and percentages of dialysis patients with only a catheter for access after 90 days were lower at the higher-referral facilities.

In an analysis of the association between facility-level referral and high, intermediate, and low facility-level performance on quality indicators, there was no significant association between predialysis quality-of-care indicators and referral. There was also no association between the percentage of incident patients being informed of transplantation options at initiation of dialysis therapy and facility-level referral. There was an association between higher facility-level referral and better performance with respect to standardized transplantation ratio (high, 30.7%; intermediate, 25.1%; and low, 19.2%; P < .001). There was no association between higher referral and better performance on other concurrent facility indicators of quality of care, including those capturing mortality, morbidity, prevention, and management of anemia.

In fully adjusted multilevel mixed models, the odds of being referred within 1 year of dialysis among patients who had nephrology care prior to progressing to ESRD or those who had a permanent access used at initiation of dialysis therapy were approximately one-third higher than among those who did not receive nephrology care prior to ESRD or who did not have permanent access at time of dialysis initiation.

Patients who received information regarding transplantation options within the first 45 days of initiation of dialysis therapy had 63% higher odds of being referred within 1 year of dialysis initiation compared with patients who did not receive information.

Among the 241 facilities, the median within-facility cumulative percentage of patients referred for kidney transplantation within 1 year of initiation of dialysis therapy was 25.4%.

**TAKEAWAY POINTS**

- A Centers for Medicare & Medicaid Services technical panel recently developed and proposed performance measures intended to increase access to transplantation among dialysis patients. Referral of patients for kidney transplantation evaluation by the dialysis facility is one possible indicator.

- In a recent cross-sectional study utilizing data from dialysis facilities in Georgia, researchers examined whether there is an association between referral for transplantation and existing dialysis facility quality indicators.

- There was a positive (but not entirely correspondent) association between quality indicators related to kidney transplantation and higher percentages of patients referred for transplantation evaluation.

In summary, the researchers said, ‘In general, we found that patient-level indicators related to quality of care received by a patient before dialysis therapy initiation were associated with higher patient likelihood of referral, but with the exception of other measures of access to kidney transplantation, most other facility-level indicators of quality of care were not associated with transplantation referral.’ These results, although preliminary and geographically limited, could generate testable hypotheses about how transplantation referral of dialysis patients relates to delivery of quality care at dialysis facilities. Furthermore, the results could inform current efforts underway to develop and adopt quality measures related to access to kidney transplantation.”

Nephrology Times | April 2017
News Briefs

Bipartisan Bill to Protect Living Organ Donors Introduced

In early March, Representative Jerrold Nadler (D-NY) and Representative Jaime Herrera Beutler (R-WA) introduced the Living Donor Protection Act of 2017. The bill is intended to protect the rights of living organ donors, according to a press release from Mr. Nadler’s office.

The act includes three mechanisms to protect donors: (1) prohibition of life, disability, and long-term care insurance companies from denying or limiting coverage and from charging higher premiums for living organ donors; (2) clarification that living organ donors may use Family and Medical Leave Act time to recover from the surgeries and procedures involved in the donation; and (3) direction to the US Department of Health and Human Services to update their materials on live organ donation to reflect the new protections and encourage individuals to donate an organ.

The bipartisan bill has the support of groups that advocate on behalf of organ transplantation, including the American Society of Transplant Surgeons, the American Society of Transplantation, the National Kidney Foundation, the American Society of Nephrology, Waitlist Zero, and the Renal Physicians Association.

Presentations on Triferic® at Dialysis Conference

Rockwell Medical presented a poster and two oral presentations on Triferic® at the Annual Dialysis Conference, March 11-14, in Long Beach, California, according to a press release.

Pretransplant Duration of Dialysis Risk Factor for Post-Transplant Mortality

Chicago—There are few data available on the effects of pre-transplant dialysis modality or duration of pre-transplant dialysis on clinical outcomes following kidney transplantation. Researchers in Korea, led by Hyunjeong Cho, MD, recently conducted an analysis of data from the Korean Health Insurance Review & Assessment Service. The data were compiled from records of 35,422 adults who initiated hemodialysis and peritoneal dialysis from 2005 to 2008, the researchers analyzed clinical outcomes in 1563 kidney transplant recipients of those 35,422 patients.

Analysis results were reported during a poster session at Kidney Week 2016 in a poster titled Effect of Pre-Transplant Dialysis Modality and Duration on Recipient’s Outcome: A National Population-Based Cohort Study Between 2005 and 2008 in Korea. Median follow-up was 6.9 years after transplantation. During the follow-up period, 6.8% (n=106) of patients died and 1.8% (n=28) experienced major adverse cardiovascular events. In multivariable-adjusted Cox proportional hazard model analysis, there was no association between pretransplant dialysis modality and an increased risk of mortality. There was also no association between pretransplant dialysis modality and an increased risk of major adverse cardiovascular events. There was no association between pretransplant dialysis duration and development of major adverse cardiovascular events. In comparisons of the group with duration >10.8 months prior to transplantation and the group with duration <10.6 months prior to transplantation, the hazard ratio for mortality was 1.66 (95% confidence interval, 1.11-2.47) in the overall study population. Analyses of patients in the hemodialysis and peritoneal dialysis groups also found duration of pre-transplant dialysis was an independent risk factor for mortality.

In conclusion, the researchers said, “The duration of dialysis before kidney transplantation was independently associated with mortality, regardless of the dialysis modality in this national population-based cohort study. Pre-transplant dialysis duration could be a useful marker in predicting mortality in kidney transplant recipients.”


from the company. Triferic is Rockwell’s late-stage investigational iron-replacement drug to treat iron deficiency in patients who chronic kidney disease receiving hemodialysis. It is the only FDA-approved therapy indicated to replace iron and maintain hemoglobin in that patient population.

The poster, presented by lead author Ajay Gupta, MD, was titled Ferric Pyrophosphate Citrate (Triferic): One Month Intraperitoneal Toxicology and Toxicokinetic Study. The poster was presented on Sunday, March 12 and again on Monday, March 13. Raymond Pratt, MD, Sarah Grimberg, and Ajay Gupta, MD, made the first of two oral presentations on Monday, March 13. Pharmacokinetics of Triferic Administered IV and Via Dialysate. Later that day, Dr. Pratt, Dr. Gupta, Mark Bush, PhD, and Scott Brantley, PhD, presented a session titled Pharmacokinetics (PK) of Triferic Administered IV to Healthy Volunteers: Modeling Diurnal Iron and Additivity of Triferic Iron.

The conference is an international gathering of practitioners and researchers who meet to discuss current developments in dialysis. Sessions are designed for health professionals involved in established dialysis programs, as well as those working in new and emerging programs.
join DaVita Kidney Care as vice president of medical affairs, within the office of the chief medical officer. Dr. Nissenson said, “Dr. Weinstein's extensive background in healthcare policy and regulation, as well as his wide-spread knowledge in IT, brings unparalleled expertise to DaVita. This unique combination will allow Dr. Weinstein to work directly with clinical IT while closely supporting DaVita's physician electronic health record team.”

**ANNA Issues Call for Abstracts**

The American Nephrology Nurses Association has issued a call for abstracts and proposals for the 2018 National Symposium. The meeting will be held April 15-18, 2018, at the Westgate Las Vegas Resort, Las Vegas, Nevada.

Proposals are requested for 60 to 75 minute presentations; abstracts are requested for 15-minute verbal poster presentations. The submission deadline for proposals is June 19, 2017; the deadline for abstracts is October 30, 2017. Proposal and abstract submission forms are available here: http://bit.ly/2m2xAFs

**ASN Offers Board Preparation Course**

The American Society of Nephology (ASN) is offering an interactive course for preparation for the ABIM (American Board of Internal Medicine) Nephrology Board certification and recertification examinations. The ASN Board Review Course & Update is structured and scheduled to maximize participants' readiness for the examination.

The course provides a comprehensive update for practicing nephrologists. Each topic section is patterned after the ABIM nephrology examination blueprint. Key knowledge is reinforced with lectures, interactive case discussions, and panel Q&A sessions. The course includes complimentary access to all lectures online following the course and up to 61.75 CME credits and MOC points.


**David Domzalski Named to Rockwell Medical Board**

Rockwell Medical has announced that David Domzalski has been nominated to join the company's board of directors. Mr. Domzalski's nomination is to replace Ken Holt, whose term is expiring.

In a press release in March, Robert L. Chioini, founder, chairman, and CEO of Rockwell Medical, said, “David has a proven track record at a senior level in the pharmaceutical industry. He has extensive experience in building commercial organizations and launching products, which will be helpful as we commercialize Triferic® globally.”

Mr. Domzalski said, “I am excited to join the Rockwell Medical board of directors at this exciting time for the company. I look forward to working with the executive team and the board and contributing to the successful launches of their drug products into the global marketplace.”

Mr. Domzalski is the president of the US subsidiary of Foamix Pharmaceuticals, Inc. He has a record of achievement in new product launches and life-cycle management across multiple therapeutic classes, according to the Rockwell press release.

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**Upcoming Major Meetings**

**National Kidney Foundation Spring Clinical Meetings 2017**

April 18-22, 2017

Orlando, Florida

[www.kidney.org/spring-clinical](http://www.kidney.org/spring-clinical)

**ISN World Congress of Nephrology 2017**

April 21-25, 2017

Mexico City, Mexico

[www.wcn2017.org](http://www.wcn2017.org)

**American Transplant Congress**

April 29-May 3, 2017

Chicago, Illinois

[www.atcmeeting.org](http://www.atcmeeting.org)

**American Society of Nephology Kidney Week 2017**

October 31-November 5, 2017

New Orleans, Louisiana

[www.asn-online.org/education/kidneyweek/archives/future.aspx](http://www.asn-online.org/education/kidneyweek/archives/future.aspx)
Abstract Roundup

ACUTE KIDNEY INJURY
Algorithm Assists RRT Initiation Timing Decision Making
Severe acute kidney injury (AKI) that requires renal replacement therapy is associated with a >40% in-hospital mortality rate. There are no standardized recommendations related to clinical decision making regarding initiation of renal replacement therapy for patients with AKI in the medical intensive care unit (ICU).

Malika L. Mendi, MD, and colleagues conducted a 13-month prospective cohort study from November 2013 to December 2014 in a medical ICU involving implementation of an AKI Standardized Clinical Assessment and Management Plan. The plan is an algorithm designed to aid decision making for clinicians treating patients with AKI.

Patients whose clinicians adhered to the plan’s recommendation to start RRT had lower in-hospital mortality and 60-day mortality compared with patients whose clinicians did not adhere to the plan’s recommendations (42% vs 63% and 46% vs 68%, respectively; compared with patients whose clinicians treating patients with AKI. Following analysis of the six studies included in the review, there was no improvement in risk of mortality or reduction in use of renal replacement therapy with use of e-alerts (odds ratio, 1.05; 95% confidence interval [CI], 0.84-1.31 and 1.20, 95% CI, 0.91-1.57, respectively). Isolated studies reported improvement in selected care processes.

The researchers said, “In the available studies, e-alerts for AKI do not improve survival or reduce renal replacement therapy utilization. The impact of e-alerts on processes of care was variable. Additional research is needed to understand those aspects of e-alerts that are most likely to improve processes and outcomes.”

CARDIOVASCULAR OUTCOMES
Changes in GFR after Initiation of Renin-Angiotensin System Blockade
Kidney International. 2017;91(3):683-690
Acute decreases in glomerular filtration rate (GFR) may be associated with initiation of blockade of the renin-angiotensin system. However, according to Catherine M. Class, MB, MSc, and colleagues, the prognostic significance of this is unknown. The researchers conducted a post hoc analysis of patients with, or at risk for, vascular disease in two randomized controlled trials.

In 9340 patients new to renin-angiotensin blockade, there was a fall in GFR of 11.5% at 2 weeks after initiating renin-angiotensin blockade in 16% of the patients (n=1480), with persistence at 8 weeks in 7% (n=760). Acute increases and decreases in GFR after initiation of renin-angiotensin blockade were associated with tendencies to increased risk of cardiovascular outcomes; which occurred in 1280 patients, and microalbuminuria, which occurred in 864 patients. The tendencies were primarily statistically nonsignificant.

The researchers said, “Thus, both increases and decreases in GFR on initiation of renin-angiotensin system blockade are common, and may be weakly associated with increased risk of cardiovascular and renal outcomes. Changes do not predict increased benefit from therapy.”

CHRONIC KIDNEY DISEASE
Emergency Department Use among Patients with CKD
Patients with chronic kidney disease (CKD) have high healthcare resource use, but there are few data on visits to emergency departments (ED) among this patient population and on the proportion of encounters specifically related to CKD care. Paul E. Ronksley, MD, and colleagues recently conducted a study in Canada to calculate adjusted rates of overall ED use as well as rates of potentially preventable ED encounters.

Following adjustment, rates of overall ED use were highest among patients with more advanced CKD; 5.8% of all ED visits were related to CKD-specific, ambulatory care-sensitive conditions. Approximately 3% of those CKD-related visits resulted in hospital admission. For patients with CKD categories G3A, G3B, and G4, heart failure accounted for >80% of all potentially preventable ED events. For patients on dialysis, hyperkalemia accounted for 48% of all ED visits related to CKD-specific ambulatory care-sensitive conditions.

“Emergency department use is high among patients with CKD, although only a small proportion of these encounters is for potentially preventable CKD-related care. Strategies to reduce emergency department use among patients with CKD will, therefore, need to target conditions other than CKD-specific ambulatory care-sensitive conditions,” the researchers said.

Early Low-Dose ESAs and CKD Progression
Nephrology Dialysis Transplantation. 2017;32(2):279-287
There are few data on whether early intervention with low-dose erythropoiesis-stimulating agents (ESAs) in patients without anemia can delay progression of chronic kidney disease (CKD). Danilo Fliser, MD, and colleagues recently conducted a single-blind, 24-month trial among adults with estimated glomerular filtration rate (eGFR) 30 to 59 mL/min/1.73 m² and type 2 diabetes mellitus or previous kidney transplantation. Trial participants were randomized to receive low-dose continuous erythropoiesis receptor activator (CERA; n=115) or placebo (n=120). The study’s primary end point was annual change in eGFR.

At baseline, mean eGFR was 40.7 mL/min/1.73 m² in the CERA group and 39.8 mL/min/1.73 m² in the placebo group. At the final visit, the mean eGFRs were 39.0 mL/min/1.73 m² and 39.7 mL/min/1.73 m², respectively. Median annual reduction in eGFR was 0.5 mL/min/1.73 m² with CERA versus 0.4 mL/min/1.73 m² with placebo. There were no significant differences in annual change in eGFR between groups in the subpopulations with type 2 diabetes or kidney transplant.

In conclusion, the researchers said, “Patients with moderate CKD and type 2 diabetes or previous kidney transplantation showed stable renal function that was unaffected by administration of low-dose ESA. In addition, there was no clinically meaningful effect of 2-year low-dose ESA treatment on albuminuria, an important surrogate marker of kidney injury.”
DIALYSIS
Phosphate-Containing Drugs Contribute to Low Adherence in Dietary Phosphate Limit
doi:10.1053/j.jrn.2016.09.007

Hyperphosphatemia, associated with all-cause mortality in patients on hemodialysis, is managed by restricting intake of dietary phosphate. However, adherence rates are poor among many patients, particularly among those prescribed medications containing phosphate salts. Seana M. L. Nelson, MSc, MD, and colleagues conducted a cross-sectional study to quantify the burden of phosphate from prescription medication in patients on hemodialysis.

The researchers reviewed 1744 drug formulations of 124 different medications; of those, 185 contained a phosphate salt. Central nervous system (CNS) medications accounted for 65% of the phosphate-containing medications, followed by cardiovascular (CVD) medications, accounting for 24%. Thirty percent of the study participants were taking at least one phosphate-containing medication; median phosphate burden from prescription medications was 111 mg per day.

In conclusion, the researchers said, “Knowledge about the phosphate content of commonly prescribed drugs within different classes should influence prescribing patterns. Particular consideration of which formulation of CVD and CNS drugs contain phosphate should be applied when prescribing. Phosphate-containing medications can meaningfully contribute to the daily phosphate load in hemodialysis patients; however, this burden will differ based on local dispensing patterns.”

Vitamin K Antagonists Risk Factor for Lower Limb Ulcers
Therapeutic Apheresis and Dialysis.
doi:10.1177/1744-99712507

Patients on dialysis may experience peripheral arterial disease; vitamin K antagonists promote metastatic calcifications, which are the primary determinants of vascular damage. Andrea De Mauri, MD, and colleagues recently conducted a retrospective study to assess the role of vitamin K antagonists in the development of lower limb ulcers in dialyzed patients.

A total of 316 dialyzed patients were enrolled in the study. Mean age was 68 years, 65% were male, 32% had diabetes, and 43% had ischemic heart disease. Follow-up continued for 56 months.

Sixty patients were on vitamin K antagonist therapy. Those 60 patients were older, had a higher prevalence of heart disease, and were at greater risk for death. The patients in the vitamin K antagonist group developed more ulcers and underwent more lower-limb amputations compared with the other patients in the cohort. Independent risk factors for foot lesions were peripheral artery disease, vitamin K antagonists, and diabetes. Vitamin K antagonists were also an independent risk factor for death.

“Vitamin K antagonists are a potent independent risk factor for the development of the uremic foot syndrome and death,” the researchers said.

TRANSPLANTATION
HIV-Infected Waitlist Candidates Less Likely to Receive Living Donor Kidney Transplantation
Clinical Journal of the American Society of Nephrology. doi: 10.2215/CJN.07460716

Jayne E. Locke, MD, and colleagues recently conducted analysis of data from the Scientific Registry of Transplant Recipients linked to Intercontinental Marketing Statistics pharmacy fills (January 1, 2001, to October 1, 2012) to identify and examine kidney transplantation candidates with HIV (HIV+: n=1636) and without HIV (HIV-; n=72,297). HIV+ patients were identified as having filled one or more antiretroviral medications unique to HIV treatment.

Waiting list candidates who were HIV+ were more often young (<50 years of age; 62.7% vs 57.6%; P=.001), more often men (75.2% vs 59.3%; P=.001), more often black (73.6% vs 27.9%; P=.001), had longer dialysis duration (2.5 years vs 0.8 years; P=.001), were more often infected with hepatitis C virus (9.0% vs 3.9%; P=.001), and were less likely to remain active on the waiting list (37.7% vs 49.4%; P=.001), compared with those who were HIV-. The likelihood of living donor kidney transplantation was 47% lower among those who were HIV+ (adjusted hazard ratio, 0.53; P=.001).

“Our findings highlight the need for additional study to better understand disparities in access to kidney transplantation, particularly living donor kidney transplantation, among HIV+ kidney waitlist candidates,” the researchers said.

L-Carnitine to Protect Against Delayed Graft Function
doi:10.1053/j.jrn.2016.11.002

Delayed graft function (DGF) following deceased donor kidney transplantation has significant adverse effects on graft outcomes. A major cause of DGF is ischemia-reperfusion injury during transplantation, which causes a decrease in tissue concentrations of carnitine. Atefeh Jafari, PharmD, and colleagues in Iran recently conducted a pilot study to examine the possible protective effect of L-carnitine against DGF.

The trial included 56 patients undergoing their first kidney transplantation who were randomized to L-carnitine or placebo groups. The intervention group received three divided doses of 3 g of L-carnitine each day for four consecutive days, beginning the day prior to kidney transplantation.

There was no difference in incidence of DGF between the two groups: 18.51% in the L-carnitine group versus 23.8% in the placebo group (P=.68). Within 3 months following kidney transplantation, total allograft failure occurred in six patients in the placebo group and one in the L-carnitine group (P=.05).

The researchers said, “This study showed no protective effects of oral L-carnitine supplementation against DGF occurrence in participants; however, 3-month graft loss was lower in the L-carnitine supplemented group.”

Time-Weighted Variability of Tacrolimus Blood Level and Graft Survival
Nephrology Dialysis Transplantation.
2017.32(2):393-399

There are few data on the effect of variability of tacrolimus blood levels during the early post-transplantation period. Benaya Rozen-Zvi, MD, and colleagues conducted a retrospective cohort study to examine the association between time-weighted variability in the early post-transplantation period and graft survival. The study included all patients undergoing kidney transplantation at the Rabin Medical Center, Petah Tikva, Israel, between January 1, 2000, and September 29, 2013, who were treated with tacrolimus (n=803).

The researchers defined time-weighted coefficient of variability (TWCV) as time-weighted standard deviation divided by the mean drug level. The primary outcome of patient and graft survival was calculated with univariate and multivariate Cox proportional hazard model.

There was an association between the high tertile of TWCV of tacrolimus blood levels and reduced graft survival in univariate and multivariate analyses (hazard ratio [HR], 1.69; 95% confidence interval [CI], 1.14-2.52; P=.01 and HR, 1.74, 95% CI, 1.14-2.63; P=.01, respectively). There was significant association with the interaction between high TWCV and exposure to inadequately low drug levels and reduced survival (P=.004).

There was no significant association between TWCV and high drug blood levels.

“The combination of high TWCV and exposure to low drug levels might identify high-risk patients in the early post-transplantation period,” the researchers said.
AKI Billing and Reimbursement Update

While it is exciting that dialysis clinics can now receive reimbursement for treatments provided to acute kidney injury (AKI) patients, there are still a number of unknowns where reimbursement is concerned.

The final rule and related change requests indicate that Medicare will pay the base rate adjusted by the wage index. End-stage renal disease (ESRD) dialysis treatments paid under the bundle are adjusted by several factors, including the patient’s height and weight. As no such adjustment will occur for an AKI treatment, is it necessary to report the patient’s height and weight?

Another area not addressed by the Centers for Medicare & Medicaid (CMS) in the final rule or the change requests related to AKI treatments is erythropoietin stimulating agent (ESA) billing for non-ESRD patients. Epoetin and darbepoetin alfa each have two codes, one for ESRD use and a second code for non-ESRD use. Many billers are familiar with the coding requirements surrounding ESAs for ESRD patients, but the codes required for non-ESRD patients may have different local or national coverage determinations or diagnostic coding requirements.

In the final rule, CMS wrote that services considered renal dialysis services for an ESRD patient are also considered renal dialysis services for a patient with an AKI. Thus, no separate payment would be made for renal dialysis drugs, biologics, laboratory services, and supplies that are included in the ESRD PPS base rate. [CMS Publication 100-02, Transmittal 1725, Change Request 9598.]

However, in reviewing the Medicare remittance advice for our first AKI claims paid this year, some medications and labs were paid in addition to the ESRD PPS amount. We are unable to determine if the Medicare contractor paid the claims correctly or if modifications are needed to its claim processing system. If you have not already done so, review your AKI explanation of benefits closely. You should contact your Medicare contractor with questions. I invite you to share your AKI claims and payment issues with me so I can share appropriate information with readers. Your name and your facility’s name and contact information will be kept confidential.

WHEN THE PAYER WON’T PAY

Payers can be difficult to work with. In my time as a medical biller, I’ve been placed on hold for hours, hung up on, misinformed, and mislead by representatives from various payers.

The reasons for problems vary, but the bottom line is that if you as a provider rendered covered services to a patient and billed those services according to the payer’s requirements, you should be reimbursed. Most payers have some type of dispute resolution process to follow. These processes usually involve your claim being reviewed by a special department to determine whether a payment should have been made. Some insurance companies assign provider representatives to the providers in their network. Provider representatives typically function as an advocate for the provider with other departments within the insurance company. Even after exhausting all available resources within the payer, you still may be denied fair reimbursement. Fortunately, there are entities that providers can turn to for assistance or to report the insurance company in question.

For example, Medicare Administrative Contractors (MACs) and, to some extent, companies that offer Medicare Advantage Plans must follow guidelines put in place by CMS. Your CMS regional office may be able to facilitate a resolution to a problem with either the MAC or Medicare Advantage Plan. Contact information for the CMS regional offices can be found here: www.cms.gov/About-CMS/Agency-Information/RegionalOffices/index.html?redirect=/RegionalOffices/. Commercial insurance companies have to follow the rules of the state in which they operate. Most states have a Department of Insurance or similar entity that offer a mechanism for providers to file complaints. The provider complaint sites for California, Texas, New York, and Florida can be found here:

- California Department of Insurance: www.insurance.ca.gov/0500-about-us/
- Texas Department of Insurance: www.tdi.texas.gov/hprovider/index.html
- NY Department of Insurance: www.dfs.ny.gov/consumer/filoacomplaint.htm
- Florida Department of Insurance: www.dfs.ny.gov/consumer/filoacomplaint.htm

Recently, the state of Illinois created a portal for healthcare providers to report problems with Medicaid Managed Care plans. This portal can be found at www.illinois.gov/hfs/MedicalProviders/cc/Pages/ManagedCareComplaints.aspx.

Sarah Tolson is the director of training 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.
Inside, you will find:

✓ Important news, views, and events in the world of nephrology
✓ Interviews with key opinion leaders
✓ Insights into clinical data and how it impacts your practice
✓ Highlights and news from Kidney Week and more
When stability is critical, every piece counts.

CRRT built for the ICU

When you choose Baxter for your CRRT program, you’re not only choosing industry-leading CRRT technology, you are also selecting a partner dedicated to ensuring your clinical success in treating AKI patients. Our commitment to you starts with an individualized program customized to your facility’s needs and complete support every step of the way:

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