Predicting Long-Term Outcomes in Immunoglobulin A Nephropathy

Worldwide, immunoglobulin A (IgA) nephropathy (IgAN) is one of the most common types of primary glomerulonephritis; in Asian regions, IgA accounts for ~45.3% of cases of primary glomerulonephritis. Clinical presentation of IgAN varies widely, from isolated hematuria to rapid progression to kidney failure. Patients may also present with a variety of histologic lesions, from mild mesangial hypercellularity to crescentic glomerulonephritis and diffuse sclerosis. Recent long-term studies have found that the prognosis for IgAN is poor; 30% to 40% of patients develop end-stage renal disease (ESRD) within 10 to 25 years of initial diagnosis.

Previous studies have identified multiple risk factors affecting the prognosis of IgAN, including baseline urinary protein excretion >1 g per day, hypertension, decreased glomerular filtration rate (GFR), hyperuricemia, male sex, and scores indicating severe pathology. Prediction of IgAN prognosis has been achieved via a variety of scoring systems that are, according to researchers in China, limited by small derivation sample sizes, varying pathologic scoring standards, inclusion of relatively few variables, and poor clinical applicability.

The researchers, led by Tingyu Chen, MD, and Xiang Li, PhD, recently conducted a multicenter retrospective cohort study designed to identify a more accurate scoring system for predicting long-term outcomes in IgAN patients.

Sodium Zirconium Cyclosilicate for Management of Predialysis Hyperkalemia

Renal potassium excretion is severely reduced in patients with end-stage renal disease (ESRD), requiring hemodialysis or peritoneal dialysis to maintain normal serum potassium levels. However, despite receiving dialysis, many patients experience persistent predialysis hyperkalemia, a condition that is potentially life-threatening and associated with cardiac arrhythmias and death. There is an association between a serum potassium concentration of ≥5.6 mmol/L and increased risk of all-cause and cardiac death. In addition, the unadjusted survival rates for patients with hyperkalemia are significantly lower than those for patients with normal serum potassium levels.

Sodium zirconium cyclosilicate (SZC) is a novel potassium binder approved by the U.S. Food and Drug Administration for the management of hyperkalemia in patients with ESRD for whom conventional dietary and potassium-lowering medications have been ineffective. SZC works by promoting the excretion of potassium in the urine, thereby lowering serum potassium levels.

Barbara Ruggiero, MD, and Matias Trillini, MD, and colleagues conducted a phase 2, prospective, randomized, controlled, open-label, crossover study to evaluate the safety and efficacy of SZC in patients with dialysis-accessimal hyperkalemia. The study included 48 patients who were randomized to receive either placebo or SZC for 8 weeks each in a crossover design. The primary endpoint was the change in serum potassium levels from baseline to week 8.

Results showed that SZC significantly reduced serum potassium levels compared to placebo, with a mean decrease of 0.4 mmol/L in the active treatment group versus a mean increase of 0.1 mmol/L in the placebo group. The treatment was well tolerated, with no significant adverse events reported.

Sevelamer Carbonate Effects on Patients with CKD and Proteinuria

Although chronic kidney disease (CKD) has reached epidemic proportions worldwide, the factors associated with progression of the disease are not completely understood. The best predictor of decline in glomerular filtration rate (GFR) in the long term is proteinuria. Interventions designed to achieve remission of proteinuria, i.e., optimal renin-angiotensin system (RAS) blockade, slow progressive loss of kidney function in patients with chronic proteinuria nephropathies. However, in patients with residual proteinuria despite RAS inhibition and achievement of target blood pressure, there remains a substantial risk of progression of CKD.

Recent studies have suggested an association between hyperphosphatemia and increased risk for CKD progression as well as reduction in the antiproteinuric effects of RAS blockers. It is not known whether lowering serum phosphate levels results in a reduction in proteinuria and/or a slowing of CKD progression. Further, there are no available data on the effect of phosphate binders on proteinuria and/or CKD progression. Sevelamer carbonate, a calcium-free binder, is commonly used to safely and efficiently reduce levels of serum phosphate in patients with CKD.

Barbara Ruggiero, MD, and Matias Trillini, MD, and colleagues conducted a phase 2, prospective, randomized, controlled, open-label, crossover study to...
Updated KDIGO guidelines recommend limiting the use of calcium-based binders...

SWITCHING TO VELPHORO
CAN MAKE A WORLD OF DIFFERENCE

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

IMPORTANT SAFETY INFORMATION
- Velphoro chewable tablets must be administered with meals. Velphoro should be chewed or crushed. Do not swallow whole.
- Patients with peritonitis during peritoneal dialysis, significant gastric or hepatic disorders, following major gastrointestinal (GI) surgery, or with a history of hemochromatosis or other diseases with iron accumulation have not been included in clinical studies with Velphoro. Monitor effect and iron homeostasis in such patients.
- In a parallel design, fixed-dose study of 6 weeks duration, the most common adverse drug reactions to Velphoro chewable tablets in hemodialysis patients included discolored feces (12%) and diarrhea (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. For oral medications where a reduction of bioavailability would be clinically significant consider separating the timing of administration. Consider monitoring clinical responses or blood levels of the concomitant medications.

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

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

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

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

The recommended starting dose of Velphoro is 3 tablets (1,500 mg) per day, administered as 1 tablet (500 mg) 3 times daily with meals. Adjust by 1 tablet per day as needed until an acceptable serum phosphorus level is reached, with regular monitoring afterwards. Titrate as often as weekly.

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

CONTRAINDICATIONS
None.

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

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

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

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

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

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

Velphoro can be administered concomitantly with oral calcitriol, inhibitors, hydrochlorothiazide, losartan, metoprolol, nifedipine, omeprazole, quinidine and warfarin.

Velphoro can be administered concomitantly with oral calcitriol, inhibitors, hydrochlorothiazide, losartan, metoprolol, nifedipine, omeprazole, quinidine and warfarin.

Velphoro should be taken with meals.

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

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

NDC 49230-645-51 Bottle of 90 chewable tablets

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

PATIENT COUNSELING INFORMATION
Inform patients that Velphoro tablets should be chewed or crushed. Do not swallow whole [see Dosage and Administration]. Velphoro should be taken with meals.

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

Inform patients that Velphoro can cause discolored (black) stool, but this discoloration of the stool is considered normal with oral medications containing iron.

Inform patients that Velphoro can stain teeth.

Inform patients to report any rash to their healthcare professional.

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From the Chair

Remove the Medicare Restriction for Hospice Care for Dialysis Patients

Nearly one-half of patients >75 years of age who initiate dialysis are dead within 6 months (almost one-half are dead within 1 month of initiation). These patients have a terminal illness. Among those who survive, withdrawal from dialysis occurs in only about 30%, and many patients suffer on dialysis with failure to thrive, problems with activities of daily living, and multiple comorbidities.1

Eric Cassel, MD, in his landmark contribution published almost 30 years ago in the New England Journal of Medicine2 wrote that suffering may occur both during the course of a disease and from the treatment of the disease. In the case of elderly dialysis patients, suffering occurs before and after dialysis is initiated.

Says Cassel: “Patients sometimes report suffering when one does not expect it, or do not report suffering when one does expect it…a person can suffer enormously at the distress of another, especially a loved one.”

One strategy to help patients and families manage end-of-life is to offer them hospice care. Some think that hospice care is only about keeping patients comfortable with pain relief. While pain control is important, hospice care provides home visits by the care team, including a physician, nurse, medical social worker, home-health aide, and chaplain/spiritual adviser. Hospice care allows access to special services, such as physical and occupational therapy, and dietary counseling; hospice also helps with modifying the home through installation of equipment to enhance mobility and prevent falls.

Patients who discontinued dialysis received hospice care three times more frequently than those who continued with dialysis (58% vs 18%).

In a cross-sectional study of more than 770,000 Medicare beneficiaries, only 20% of maintenance hemodialysis patients enroll in hospice and for just a few days. This is about 50% less than the general population. The under-utilization of hospice care may be because Medicare restricts coverage for hospice care until the patient discontinues disease-modifying treatment such as dialysis, and when the patient is declared by their treating physician to have fewer than 6 months to live.

With an elderly dialysis patient, treatment with dialysis is neither curative nor disease-modifying; rather it is more in the realm of supportive therapy. In addition, compared with younger patients, the mortality of elderly dialysis patients is very high—more than half die within 6 months.

The Veterans Administration (VA), one of the largest health systems in the United States, spends hundreds of billions of dollars of taxpayers money. Unlike Medicare, the VA pays for hospice care for dialysis patients regardless of the patient withdrawing or continuing dialysis.

In a recent VA study of the effect of hospice care in dialysis patients4, Richards et al. looked at quality of care survey data among patients who withdrew versus those who continued dialysis. They reported that withdrawal from dialysis was associated with a higher quality of care perceived by family members. Patients who discontinued dialysis received hospice care three times more frequently than those who continued with dialysis (58% vs 18%). Family members rated the quality of care 20% higher when hospice care was provided.

In an accompanying editorial5 to the Richards paper, Tate and Matlock raise the issue of what it means to have a “good death” using a social justice framework. In their reckoning, little consideration is given to allowing patients to define what a good death means to them. Medicare restrictions prevent dialysis patients to opt for hospice. Rather, the choice confronting elderly patients—if presented this choice—is of discontinuing with hospice and then dying, or continuing with dialysis and suffering without hospice. A Faustian bargain, indeed.

In the Richards study, patients who stopped dialysis were less likely to be black or live in the South Atlantic region. Tate and Matlock make a social justice argument for providing all patients choice: “Clinicians must inform patients of their options and respect their decisions, and we must ensure that those options are available to them.”

My take on this is that Medicare should remove the restriction to hospice care for elderly dialysis patients. The largest public health system in the US provides no such limitation. Its difficult enough surviving as an elderly dialysis patient, but patients ought to be offered hospice as well as other services to make life more bearable.

REFERENCES


Sodium Zirconium Cyclosilicate
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Researchers reported results of the phase 3b DIALIZE study that examined sodium zirconium cyclosilicate (SZC) in the management of hyperkalemia in patients with end-stage renal disease on maintenance hemodialysis. Patients were randomized to receive SZC (n=97) or placebo (n=99). The primary end point was the proportion of patients during the 4-week stable dose evaluation period who maintained predialysis serum potassium level of 4.0-5.5 mmol/L during at least three of four hemodialysis treatments. The safety profile of SZC observed in patients managed by he-

hazard ratio between different serum potassium categories is U-shaped; the best survival is in patients with serum potassium concentrations of 4.6 to 5.6 mmol/L.

Patients with ESRD receiving hemodialysis require additional strategies for the management of hyperkalemia. Options for treatment include potassium binding resins such as sodium polystyrene sulfonate (SPS), patiromer, and sodium zirconium cyclosilicate (SZC; AstraZeneca AB, Södertälje, Sweden).

SZC is an orally administered, insoluble, nonabsorbed, inorganic crystalline compound that selectively captures potassium ions in exchange for hydrogen and sodium ions in the gastrointestinal lumen. The free concentration of serum potassium is reduced and fecal excretion of potassium is increased, resolving hyperkalemia. SZC is approved in Europe and the United States for the treatment of hyperkalemia in adults.

Steven Fishbane, MD, and colleagues reported results of the phase 3b DIALIZE study (NCT03303521) that sought to examine the safety and efficacy of SZC in stable patients with ESRD who were being managed by adequate hemodialysis. The study results were reported in the Journal of the American Society of Nephrology [2019;30(9):1723-1733].

The study randomized adults with ESRD who were receiving hemodialysis three times a week and had predialysis hyperkalemia to receive placebo or SZC 5 g once daily on nondialysis day and titrated toward maintaining normokalemia over 4 weeks, in increments of 5 g to a maximum of 15 g.

The primary efficacy end point of interest was the proportion of patients during the 4-week stable-dose evaluation period who maintained predialysis serum potassium of 4.0 to 5.0 mmol/L during at least three of four hemodialysis treatments after the long interdialytic interval. The secondary efficacy end point was the proportion of patients who required any urgent rescue intervention to reduce serum potassium in the setting of severe hyperkalemia (>6.0 mmol/L). Safety outcomes of interest were assessment of adverse events (AEs), laboratory parameters/vital signs, electrocardiogram, and interdialytic weight gain.

Of the 443 patients screened, 247 were excluded, primarily for not meeting inclusion criteria. A total of 97 patients were randomized to the SZC group and 96 were randomized to the placebo group. With the exception of one patient in the SZC group, all patients received treatment. A total of 188 patients (95.9%) completed the study; rates of study completion were balanced between the two groups (SZC, 92/97, 94.8%; placebo, 96/99, 97.0%).

Of the total study cohort, 58.7% were men, mean age was 58.1 years, and mean weight was 71.0 kg. Fifty-two percent were white, 33.7% were Asian, and 9.7% were black or African American. With the exception of a small difference in age distribution, patient characteristics were balanced between the groups; patients in the SZC group were younger compared with the placebo group (mean age=55.7 vs 60.4 years, respectively). Dialysis adequacy parameters were comparable between the two groups.

Following the dose titration period, 37%, 43%, and 19% of patients in the SZC group received SZC 5, 10, and 15 g, respectively, and 8%, 8%, and 83% of the placebo group received 5, 10, and 15 g, respectively. The mean rate of patient compliance was high during the overall treatment period (98.7%), and was balanced between the groups (SZC, 98.9%; placebo, 98.4%). The mean rate of patient compliance with treatment during the evaluation period was also high (99.0%) and balanced between the groups (SZC, 98.6%; placebo, 99.4%).

In the primary efficacy outcome, the proportion of patients during the 4-week stable dose evaluation period who maintained predialysis serum potassium of 4.0-5.5 mmol/L during at least three of four hemodialysis treatments, there was a significantly higher proportion of responders in the SZC group than in the placebo group: 41.2% (n=40/97) versus 1.0% (n=1/99); odds ratio [OR], 68.8; 95% confidence interval [CI], 10.9-2810.9; P<.001). Results of sensitivity analysis were consistent with those of the primary analysis: there was a higher proportion of responders in the SZC group than in the placebo group (42.3% [n=41/97] vs 2.0% [n=2/99]; OR, 35.3; 95% CI, 8.5-309.5; P<.001).

Analysis of the secondary efficacy outcome, the need for rescue therapy, found comparable and low proportions of patients in the SZC group and the placebo group needed rescue therapy to reduce serum potassium level during the overall treatment period: SZC, 2.1% (n=2/97); placebo, 5.1% (n=5/99).

Forty patients (41.7%) in the SZC group had an AE compared with 46 patients (46.5%) in the placebo group. Most AEs were mild or moderate; the most common were gastrointestinal disorders (19 in the SZC group and 17 in the placebo group). Twelve patients in the SZC group reported infections; nine in the placebo group reported infections. Serious AEs occurred in 7.3% of the SZC group and 8.1% of the placebo group. Angina pectoris was the most common serious AE in the SZC group (2.1%; n=2). The most common serious AEs in the placebo group were hyperkalemia requiring rescue therapy (3.0%; n=3) and fluid overload (2.0%, n=2). All serious AEs were considered non-study related by the investigator. Interdialytic weight gain was comparable between the two groups.

Possible study limitations included the relatively short duration; additional studies are needed to determine the long-term efficacy and safety of SZC in patients receiving chronic hemodialysis. In addition, while treatment compliance was high, the findings may not be generalizable to all patients in a real world setting.

The researchers said, “In conclusion, in the phase 3b DIALIZE study, SZC was effective in reducing serum potassium levels in patients on hemodialysis. The safety profile of SZC observed in patients managed by hemodialysis was similar to that known in the nondialysis population and raised no new concerns. The results indicate that SZC is an option for the management of hyperkalemia in this setting.”

This study was supported by AstraZeneca.
Sevelamer Carbonate Effects
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With the exception of a nonclinically relevant increase in alkaline phosphatase levels during the sevelamer versus without sevelamer treatment (64 vs 68 IU/L pre- vs post-sevelamer; P<.02), there were no major safety signals.

Fifty-three participants were recruited from two Italian centers between November 2013 and December 2014. Patients meeting inclusion criteria who were on maximal tolerated doses of ramipril and irbesartan were initially stratified according to serum phosphate level ≤4 or ≥4 mg/dL. Each group was then randomly assigned to one of two treatment sequences: (1) 3 months of treatment with sevelamer carbonate, 1600 mg, three times per day during meals, followed by a 1-month washout, and 3 months without sevelamer; or (2) 3 months without sevelamer, followed by a 1-month washout, and 3 months of treatment with sevelamer carbonate, 1600 mg, three times daily.

The primary outcome of interest was 24-hour proteinuria (per-protocol efficacy analyses n=49); secondary outcomes were measured GFR, office blood pressure, serum lipid levels, levels of inflammation and bone metabolism biomarkers, urinary electrolyte levels, and arterial stiffness.

At the time of randomization, 41 patients were receiving dual RAS blockade with ramipril and irbesartan, but 12 remained on single RAS inhibition with ramipril (n=7, except one taking benazepril) or irbesartan (n=5, except one taking valsartan).

In the intention-to-treat analysis, there was no observed difference in change in 24-hour proteinuria between the two periods with sevelamer or without sevelamer. When the high- or low-serum phosphate strata were considered separately, the findings were similar; findings were also similar when analyses were restricted to the first treatment period.

Treatment with sevelamer did not affect office systolic blood pressure. Office diastolic blood pressure increased with sevelamer treatment; however, the change did not significantly differ in the comparison of sevelamer versus without sevelamer.

During sevelamer treatment, 24-hour urinary phosphate excretion decreased; it did not decrease during the without sevelamer period, and there were statistically significant differences in changes in urinary phosphate excretion between treatment periods. However, there were no changes in serum phosphate levels during both treatment periods. Sevelamer reduced C-reactive protein (CRP), glycated hemoglobin (HbA1c), and total and low-density lipoprotein (LDL) cholesterol levels, and increased high-density lipoprotein (HDL) cholesterol levels without affecting levels of office blood pressure, measured GFR, fibroblast growth factor 23, klotho, intact parathyroid hormone, serum vitamin D, or other urinary electrolytes.

With the exception of a nonclinically relevant increase in alkaline phosphatase levels during the sevelamer versus without sevelamer treatment (64 vs 68 IU/L pre- vs post-sevelamer; P<.02), there were no major safety signals. Most adverse events were nonserious. Patient withdrawal was related to an incident of colon cancer and three nonserious adverse events; all were considered unlikely to be related to sevelamer treatment. There were three other serious adverse events likely related to sevelamer. Nine events in seven patients were possibly treatment-related adverse events; one was constipation and one was hypophosphatemia that recovered following discontinuation of sevelamer.

Limitations to the findings cited by the authors included the short treatment duration, the possibility that the study was underpowered, and lower pretreatment urinary phosphate excretion decreased; it did not decrease during the without sevelamer period, and there were statistically significant differences in changes in urinary phosphate excretion between treatment periods. However, there were no changes in serum phosphate levels during both treatment periods. Sevelamer reduced C-reactive protein (CRP), glycated hemo-

TAKEAWAY POINTS
- There is an association between hyperphosphatemia and increased risk for progression of chronic kidney disease (CKD) and reduced antiproteinuric effects of renin-angiotensin system (RAS) blockers.
- Researchers in Italy conducted a phase 2, open-label, crossover trial to examine whether the phosphate binder sevelamer carbonate enhanced the antiproteinuric effect of RAS-inhibitors in patients with CKD.
- Three-month treatment with sevelamer did not reduce proteinuria in patients with CKD on maximal RAS blockade. Sevelamer did ameliorate inflammation and dyslipidemia in patients with CKD.
to use machine learning to build a prognostic prediction and risk stratification system (Nanjing IgAN Risk Stratification System) that combines clinical and pathologic variables to assist physicians in predicting kidney prognosis quickly and accurately. The system was described in the American Journal of Kidney Diseases [2019;74(3):300-309].

The study utilized data from 2047 patients with IgAN and long-term follow-up. Inclusion criteria were ≥18 years of age, follow-up >12 months, estimated GFR (eGFR) ≥30 mL/min/1.73 m², proteinuria with protein excretion ≥0.5 g per day, and a biopsy specimen with ≥8 total glomeruli on periodic acid-Schiff staining. Patients who progressed to ESRD or had a 50% reduction in eGFR within the first 12 months of follow-up were also included. Exclusion criteria were secondary causes of mesangial IgA deposits such as IgA vasculitis and autoimmune disorders, or comorbid conditions such as diabetes mellitus or Alport syndrome.

The data were retrieved consecutively from the Nanjing Glomerulonephritis Registry between January 2006 and June 2009 (derivation cohort). Multicenter data were retrieved from 18 renal centers between January 1997 and June 2010 (validation cohort). Follow-up data were updated to August 2017.

Two risk models were constructed: a prediction model using eXtreme Gradient Boosting (XGBoost), which would require a computer for accurate risk prediction, and a simpler restricted variable scoring scale model (SSM) derived by stepwise Cox regression for risk stratification.

In the derivation and validation cohorts with complete medical records, median follow-up was 7.9 and 7.8 years, respectively. Most patients in the two cohorts were treated with renin-angiotensin system blockade, resulting in good blood pressure control during follow-up. The 5- and 10-year kidney survival rates were 96.8% and 92%, respectively, in the derivation cohort; the rates in the validation cohort for score 0 though 4 points were 83.8% and 76.4%, respectively. The XGBoost model, trained on 36 variables, had a C statistic of 0.89 (95% CI, 0.87-0.94) for the validation cohort while using a confidence interval (CI), 0.87-0.94) for the derivation cohort. Most patients in the two cohorts were treated with renin-angiotensin system blockade, resulting in good blood pressure control during follow-up. The 5- and 10-year kidney survival rates were 96.8% and 92%, respectively, in the derivation cohort; the rates in the validation cohort were 83.8% and 76.4%, respectively.

The XGBoost model, trained on 36 variables, had a C statistic of 0.89 (95% confidence interval [CI], 0.87-0.94) for the derivation cohort and 0.84 (95% CI, 0.80-0.88) for the validation cohort while using the 10 most important variables measured by XGBoost importance score as input (TABLE 1). Among the machine learning models and traditional regression models, the XGBoost model achieved the best prediction performance.

The SSM model was constructed using three variables (tubular/interstitial fibrosis, global sclerosis, and urine protein excretion). Scores corresponding to these variables were added together to obtain the patient’s risk score (TABLE 2).

Using the SSM risk score, the 5-year risks for the combined event in the validation cohort for score 0 though 4 points were 2.7%, 4.8%, 16.4%, 30.8%, and 72.4%, respectively. The low-risk group (SSM risk score 0-1 point) included the majority of patients with IgAN in the derivation (69.8%; 713/1022) and validation (66.0%; 677/1025) cohorts.

In both cohorts, using the Kaplan-Meier method, the survival curve without a combined event during follow-up was significantly better (P <.001) in the absence of T1, T2, global sclerosis >25%, and urine protein excretion >1 g/day. The SSM successfully stratified the patients (P <.001).

The researchers cited some limitations to the study: the cohort is not from a prospective therapeutic trial, and the therapeutic interventions were variable; the prediction model was developed using data from a Chinese population, possibly limiting the generalizability of the findings to other ethnic groups.

In conclusion, the researchers said, “We established and externally validated the Nanjing IgAN Risk Stratification System including an accurate XGBoost prediction and a simplified SSM for risk stratification, both of which show promising performance and have better prediction power than the absolute renal risk. The Nanjing IgAN Risk Stratification System is accessible online with consideration of both model prediction performance and interpretation. The Nanjing IgAN Risk Stratification System could be easily implemented in clinical practice for physicians and patients to stratify risk and predict kidney prognosis quickly and accurately, thereby serving as a more favorable tool to strengthen individualized treatment and management in patients with IgAN.”

**TAKEAWAY POINTS**

- Researchers in China developed and validated a system to aid in predicting long-term outcomes and stratifying risk in patients with Immunoglobulin A nephropathy (IgAN).
- Two risk models were developed: (1) a prediction model using extreme Gradient Boosting (XGBoost) that requires a computer for accurate risk prediction, and (2) a simpler restricted variable scoring scale model (SSM) derived by stepwise Cox regression for risk stratification.
- The two models, both of which showed promising performance and better prediction power than the absolute renal risk, resulted in the Nanjing IgAN Risk Stratification System.
The American Society of Nephrology held its annual meeting, Kidney Week 2019, November 5 through 9 at the Walter E. Washington Convention Center in Washington, DC. The meeting welcomed more than 13,000 kidney professionals from around the world to share and discuss the latest findings in kidney health research and attend educational sessions on advances in the care of patients with kidney and related disorders.
Nutritional Predictors of All-Cause Mortality in Hemodialysis Patients

Washington, DC—Patients with end-stage renal disease require close monitoring of nutrition. However, in patients on hemodialysis, obtaining adequate nutritional status while avoiding fluid overload, hyperphosphatemia, and hyperkalemia is difficult. Researchers in Korea, led by Eunjin Bae, MD, PhD, conducted a retrospective cohort study to examine the clinical significance of serum albumin and other nutritional markers in patients on maintenance hemodialysis. Results of the study were reported during a poster session at Kidney Week 2019 in a poster titled Clinical Significance of Nutritional Predictors in Prevalent Hemodialysis Patients.

The cohort included patients who received hemodialysis for more than 3 months from 2016 to March 2019. The patients who died within 30 days were excluded. The study examined the factors associated with all-cause mortality and major adverse cardiovascular events, as well as factors related to sarcopenia (defined as skeletal muscle mass index ≤10.75 kg/m² [men] or ≤6.75 kg/m² [women]).

The total cohort included 284 patients; of those, 63.7% were men, mean age was 64.2 years, and mean body mass index (BMI) was 22.7 kg/m². The most common underlying diseases were hypertension and diabetes. Median follow-up was 16.7 months. During follow-up, 39 patients (13.7%) experienced a major cardiovascular adverse event and 35 patients (12.3%) died.

Results of multivariate Cox analyses demonstrated significant associations between all-cause mortality and lower albumin, higher C-reactive protein level, and history of cardiovascular disease. There was a significant positive correlation between skeletal muscle mass index and BMI, serum phosphorus, blood urea nitrogen, creatinine, and uric acid level. In the total cohort, skeletal muscle mass index was not predictive of all-cause mortality; however, in the subgroup with diabetes, skeletal muscle mass index did significantly predict all-cause mortality.

In logistic regression analyses, there were significant associations between older age, lower BMI, diabetes, male sex, and sarcopenia. There were also significant associations between major cardiovascular adverse events and higher serum calcium, phosphorus level, history of cardiovascular disease, and cerebrovascular accident.

In conclusion, the researchers said, “In prevalent hemodialysis patients, nutrition, inflammation, and previous cardiovascular disease are the major risk factors for all-cause mortality. Skeletal muscle mass index might be an important predictor for all-cause mortality in diabetes patients. In patients with a history of cardiovascular disease or cerebrovascular accident, management of serum calcium and phosphorus is a particularly important aspect of major cardiovascular adverse events.”


Patient Reactions to Genetic Testing for ADTKD

Washington, DC—Reactions to a diagnosis of autosomal dominant tubulointerstitial kidney disease (ADTKD) due to UMOD and MUC17 mutations in asymptomatic patients are unknown. Researchers in the United States and Czechia, led by Anthony J. Bleyer, MD at Wake Forest University School of Medicine, Winston-Salem, North Carolina, developed a cross-sectional survey regarding quality of life and genetic testing for individuals who had undergone genetic testing from families with known ADTKD. Results of the survey were presented during a poster session at Kidney Week 2019 in a poster titled Quality of Life in Patients with Autosomal Dominant Tubulointerstitial Kidney Disease.

Of 622 individuals provided the survey, 286 completed it. Of those, 21% (n=61) were genetically unaffected; 52% (n=145) had stage 1, 2 chronic kidney disease (CKD), 18% (n=55) had stage 3 CKD, 14% (n=41) had stage 4 pre-dialysis CKD, 7% (n=20) were receiving dialysis, and 16% (n=47) were on/TP kidney transplantation.

Fifty-five respondents thought they had normal kidney function at the time of testing and were found to have ADTKD. 93% of those individuals (n=51) were happy the testing was performed. 5% (n=3) were neutral, and 2% (n=1) was neutral/unhappy of the affected individuals. 23% (n=163) said ADTKD has a “substantial effect and I think about it daily.” Twenty-six percent (n=47) think about ADTKD weekly. 26% (n=48) think about it monthly, and 26% (n=48) think about it less than monthly.

Mean PROMIS® Patient-Reported Outcomes Measurement Information System anxiety scores were similar between affected and unaffected individuals and with the general population. Forty-one percent of affected individuals experienced depression compared with 23% of unaffected individuals [P=0.01]. In conclusion, the researchers said, “Genetic testing of presymptomatic patients for ADTKD is reasonable when requested. This study provides reassurance regarding the impact on quality of life of the increased use of genetic testing to diagnose kidney disease. ADTKD has a significant impact on quality of life with depression, not anxiety, being more prevalent in affected individuals.”


S2C Improves Potassium Balance in Hyperkalemic Dialysis Patients

Washington, DC—Despite hemodialysis, patients with end-stage renal disease frequently experience predialysis hyperkalemia. The DIALIZE trial (NCT03303521), a phase 3b, randomized, double-blind, placebo-controlled trial, investigated the effect of sodium zirconium cyclosilicate (S2C) on predialysis serum potassium after the long interdialytic interval in dialysis patients with hyperkalemia.

Steven Fishbane, MD, and colleagues conducted a post hoc analysis of data from DIALIZE to further examine the effect of S2C in hyperkalemic hemodialysis patients. Results were reported at Kidney Week 2019 in a presentation titled Sodium Zirconium Cyclosilicate (S2C) Improves Potassium Balance in Hyperkalemic Hemodialysis Patients. Results from the Phase 3b, Randomized, Placebo-Controlled DIALIZE Study.

The DIALIZE trial included a total of 196 patients. Mean age was 58.1 years. The patients were randomized 1:1 to receive placebo (n=99) or S2C (n=97) 5 mg once daily starting dose on nondialysis days for 8 weeks: a 4-week S2C dose- titration phase (maximum, 15 g) to achieve target predialysis serum potassium 4.0 to 5.0 mmol/L, and a 4-week stable-dose evaluation phase (S2C, 5, 10, or 15 g).

Post hoc analyses of DIALIZE data included assessment of the number of visits where patients had serum potassium 4.5-5.0 mmol/L, and 3.5-5.5 mmol/L, as well as the maximum serum potassium during the evaluation phase. Cross tabulation of categorized change in potassium gradient from baseline to end of the evaluation phase was also assessed. The change in potassium gradient was defined as the difference between the predialysis serum potassium and dialysate potassium.

Rapid lowering of serum potassium is permitted with a high serum potassium to dialysate potassium gradient at the start of hemodialysis. However, there can be an association between rapid serum potassium lowering and an increased risk of adverse events, such as cardiac arrhythmias and hospitalization.

There was an association between S2C and more patients achieving serum potassium 4.0 to 5.0 mmol/L and being maintained as serum potassium 3.5 to 5.5 mmol/L versus placebo for one, two, three, and four visits. During the evaluation period, 56 patients in the placebo group had severe predialysis hyperkalemia (defined as serum potassium ≥6.0 mmol/L) compared with only 14 in the S2C group.

In the S2C group there was a shift in potassium gradient toward values below the reported higher risk threshold of 3 mmol/L. 10% of patients (n=13/118) moved from gradient 4.5 to 2.3 mmol/L and 56.5% (n=65/118) moved from 3.4 to 2.3 mmol/L.

In conclusion, the researchers said, “These findings suggest that treatment with S2C improves potassium balance in hyperkalemic hemodialysis patients. Results from the phase 3b, randomized, placebo-controlled DIALIZE study. Abstract of a presentation at the American Society of Nephrology Kidney Week 2019 (Abstract SA-P0601), November 9, 2019. Washington, DC.”

Clinical Variables and Timing of RRT Initiation for AKI Patients

Washington, DC—There is no clear consensus on the optimal timing of initiation of dialysis in critically ill patients with acute kidney injury (AKI). Current practice focuses on analyzing survival outcome with arbitrary definitions of early or late start. However, there are few data available on the competing effects of other variables, including clinical comorbidities, dialysis indication, or acuity of illness.

Anirban Ganguli, MD, and colleagues at Medstar Washington Hospital Center, Washington, DC, conducted an analysis of new adult patients with AKI initiated on renal replacement therapy (RRT) while in the intensive care unit (ICU) from January 1, 2010, through December 31, 2015. The researchers sought to identify clinical variables associated with survival to hospital discharge. Analysis results were reported during a poster session at Kidney Week 2019 in a poster titled Impact of Clinical Variables at Dialysis Initiation for AKI in the ICU on In-Hospital Mortality.

A total of 235 patients initiated RRT in medical and surgical ICUs; of those, mean age was 61.8 years, 60% were male, and 47% were African-American. Charlson Comorbidity Score (CCS) was 5.5 and acuity scores were 29.6 [APACHE-II [Acute Physiology and Chronic Health Evaluation II]] and 12.0 [SOFA (Sequential Organ Failure Assessment)] at start of dialysis. Continuous RRT was the most common RRT modality (67.2%). In logistic regression models, there was an independent association between survival and low serum lactate, low SOFA scores, elevated serum creatinine at initiation of RRT, and hyperkalemia. There was no association between survival and CCS and time from KDIGO (Kidney Disease Improving Global Outcomes) stage 3 AKI to dialysis initiation (as a surrogate for timing). There was an inverse correlation of serum lactate at initiation with survival beyond 48 hours. Stratifying patients by SOFA scores at initiation of RRT (≤10, low risk; >10, high risk) identified the severity of volume overload or hyperkalemia (low-risk group) and RRT modality type or serum lactate (high-risk group), as being associated with survival. Receiver-operator characteristics of biochemical variables at initiation of dialysis demonstrated that only serum lactate had a moderate c-statistic of 0.8759 in discriminating survivors from nonsurvivors.

“Data from critically ill AKI patients initiated on RRT in the ICU primarily showed acuity of illness at the start of RRT affecting survival. Since time from KDIGO stage 3 AKI to dialysis initiation was not associated with survival, the validity of definitions such as ‘early’ or ‘late’ RRT initiation remains uncertain. Triaging clinical decision based on acuity scores may optimize clinical outcomes. Finally, the absence of any association between hospital survival and comorbid scores has great implications for prognostication and palliative care,” the researchers said.


Defibrillator Use in Dialysis Patients: National Cardiovascular Data Registry Report

Washington, DC—Researchers, led by Patrick H. Pun, MD, conducted a retrospective analysis to evaluate trends and the use and in-hospital outcomes of subcutaneous implantable cardioverter defibrillators (S-ICD) compared with transvenous ICDs (TV-ICD) in dialysis patients in the United States. Results of the analysis were reported at a presentation at Kidney Week 2019 in a presentation titled Trends in Use of In-Hospital Outcomes of Subcutaneous Implantable Cardioverter Defibrillators in Dialysis Patients: A Report from the National Cardiovascular Data Registry.

The analysis included data on 22,136 implants in dialysis patients reported to the National Cardiovascular Data Registry (NCDR) Registry between 2012 and 2018. The first analysis examined the utilization and patient and procedure characteristics of dialysis patients who received S-ICD: a secondary analysis used inverse probability weighted estimators to identify trends in adoption of S-ICD as a proportion of all ICD implants and compare in-hospital outcomes (death, complications) among DS-ICD and TV-ICD recipients.

Of the total of 22,136 implants during the study period, 13,871 (62.3%) were S-ICD. Among eligible first-time ICD dialysis recipients, there was a yearly increase in the proportion of S-ICDs, from 10.3% in 2012 to 64.5% in 2018. Recipients of S-ICDs were more likely to be black than recipients of TV-ICD implants (42.6% vs. 34.3%) and undergo implantation in teaching hospitals (62.8% vs. 54.2%). In the secondary analysis of 3,327 patients, recipients receiving S-ICDs had a higher rate of in-hospital cardiac arrest compared with patients receiving TV-ICDs (15.2% vs. 0.36%; P < .001). Patients receiving S-ICDs also had higher rates of in-hospital complications (2.4% vs. 1.48%; P < .08) and length of hospitalization (1.17 vs. 1.24 days; P < .08).

In summary, the researchers said, “There has been a steady increase in the utilization of S-ICD among dialysis patients in the United States. The increased risk of in-hospital cardiac arrest in S-ICD recipients could have been due to residual confounding and selection bias, but randomized clinical trials are needed to definitively compare the outcomes of TV-ICD with S-ICDs in dialysis patients.”


Timing of Renal Replacement Therapy Initiation in the ICU

Washington, DC—Increased morbidity and mortality are both associated with acute kidney injury in critically ill patients. The optimal timing of renal replacement therapy (RRT) is unclear and there are no guidelines to aid physicians in decision-making regarding timing of RRT. Mohamed A. Kalet, MD, and colleagues conducted a systematic review and meta-analysis to analyze and synthesize available evidence to guide clinical decisions for critically ill patients suffering from acute renal failure (ARF). Results were reported during a poster session at Kidney Week 2018 in a poster titled Timing of Initiation of Renal Replacement Therapy in Critically Ill Patients with AKI: A Systematic Review and Meta-Analysis.

Results of a literature search and meta-analysis of randomized controlled trials that included mortality, and length of stay in the hospital and in the intensive care unit yielded 13 trials that were included in the analysis. The pooled estimates did not show a difference in mortality between early RRT initiation and late RRT. Early versus late RRT initiation, early initiation was associated with a decrease in length of stay in the ICU [mean difference, 1.52 days; 95% CI, 0.61-2.43; P = .001] and in hospital stay [mean difference, 6.26 days; 95% CI, 4.97-7.56; P < .001]. There was an association between early RRT initiation and decreased hyperkalemia [OR, 0.57; 95% CI, 0.34-0.97; P = .04] and respiratory complications [OR, 0.87; 95% CI, 0.77-0.97; P = .03].

‘Early initiation of RRT in AKI in critically ill patients does not seem to alter mortality or the dependence on long-term dialysis. However, it does shorten the ICU and hospital length of stay and is associated with decreased hyperkalemia and respiratory complications,’ the researchers said.

Chronic Kidney Disease Surveillance Using State-Level Medicaid Data

Washington, DC—Medicaid is a source of health insurance for low-income individuals, including children. There are variations in Medicaid coverage by state. Researchers, led by Zubin J. Modi, MD, conducted an analysis to examine the feasibility of using Medicaid data at the state level to provide surveillance of chronic kidney disease (CKD) in a disadvantaged, low-income, and younger population in the United States.

The researchers reported results of the analyses during a poster session at Kidney Week 2019 in a poster titled State-Level Kidney Disease Surveillance Using Medicaid Data in Michigan and California.

The analysis utilized data from the 2012 Medicaid Analytic Extract for Michigan and California. Inclusion criteria were 4 months of Medicaid eligibility and one or more Medicaid claims. International Classification of Diseases, Clinical Modifications diagnosis codes for CKD for two outpatient or one inpatient claim were used to define CKD. Descriptive analyses were conducted for children <22 years of age and adults ≥22 years of age.

The Michigan study population included 1,700,044 individuals. Of those, 58.9% (n=989,834) were children. In California, the study population was 7,457,920 individuals, of whom 49% (n=3,661,569) were children. In Michigan, CKD was diagnosed in 9160 of the children (0.9%) and 26,580 adults (3.7%). In California, CKD was diagnosed in 26,090 children (0.7%) and in 71,183 adults (3.0%).

The prevalence of diagnosed CKD differed geographically. Patients in Michigan with CKD had higher proportions of diabetes and hypertension than those without CKD: diabetes, children 3.9% with CKD versus 0.7% without CKD, adults, 43.1% versus 11.7%, hypertension, children, 7.6% versus 0.6%, adults, 62.4% versus 17.2%. In California, the proportions were: diabetes, children 2.2% with CKD versus 0.4% without CKD, adults, 40.6% versus 7.9%, hypertension, children, 6.6% versus 0.2%, adults, 47.7% versus 11.1%.

In both states, use of the emergency department was higher among patients with CKD compared with those without CKD. Michigan children with CKD 59.4% versus 40.5% without CKD, adults, 65.9% versus 40.9%, California children 49.8% versus 28.2% adults, 41.6% versus 21.4%.

In conclusion, the researchers said, “We demonstrate the feasibility of utilizing Medicaid data from two states for CKD surveillance efforts. There is substantial geographic variation of diagnosed CKD in both Michigan and California with higher prevalence mostly in urban areas. Children and adults with CKD had a higher prevalence of comorbidities and emergency department use compared with those without CKD. This work serves as a foundation for future analyses of other state and longitudinal data to guide upstream disease prevention and management for a young and socioeconomically disadvantaged population.”


Changes in ECG in Acute versus Chronic Hyperkalemia

Washington, DC—Hyperkalemia resulting from kidney failure is associated with life-threatening arrhythmias. Joshua Powell, MD, and colleagues conducted a study to test the hypothesis that patients with chronic hyperkalemia from end-stage renal disease (ESRD) have fewer electrocardiography (EGG) changes and less arrhythmias than patients with acute hyperkalemia from acute kidney injury. Results of the study were reported in an oral presentation at Kidney Week 2019 in a presentation titled Electrocardiographic Manifestations of Acute vs Chronic Hyperkalemia.

The researchers reviewed 256 adult admissions from the Oakland University William Beaumont School of Medicine, Royal Oak, Michigan, with primary or secondary diagnoses of hyperkalemia in patients with chronic hyperkalemia from ESRD, and patients with acute hyperkalemia without ESRD. The study measured the overall incidence of ECG changes, and assessed differences between the two groups using unpaired t-tests, chi-square tests, and multivariate analysis logistic regression.

Changes in ECG due to hyperkalemia were seen in 32% of encounters. There was no difference in ECG change incidence between patients with chronic hyperkalemia and those with acute hyperkalemia. However, in univariate analysis, the risk of ECG changes was increased with increased patient age (69.9 vs 61.7 years; P = 0.003), increased serum potassium (7.05 vs 6.8; P = 0.0434), and history of ischemic heart disease (P = 0.03). In multivariate analysis, there was an independent association between higher endogenous serum calcium levels and less T-wave peaking (odds ratio 0.68; 95% CI). In conclusion, the researchers said, “This study demonstrated no difference in ECG changes between acute and chronic hyperkalemic groups, thus did not support the hypothesis that clinical arrhythmias are less prevalent with chronic hyperkalemia. As expected, increasing age, increasing potassium levels, and prior ischemic heart disease predisposed patients to ECG changes. Although pharmacologic calcium is known to protect against hyperkalemic arrhythmias, this study is unique in finding less T-wave peaking with higher endogenous serum calcium levels, implying that higher nonpharmacologic calcium serum levels may be protective against arrhythmias.”


Converting PCR to ACR to Develop CKD Risk Equations

Washington, DC—Staging of chronic kidney disease (CKD) commonly relies on the urine albumin-creatinine ratio (ACR), used in equations to predict the risk of adverse clinical outcomes. However, according to Keichii Sumida, MD, MPH, PhD, FASN, and colleagues, many trial cohorts and health systems prefer to measure urine protein-creatinine ratio (PCR) rather than ACR. Because these assays measure different components of protein, there are few available data on how levels of PCR may be converted to ACR.

To develop an equation for conversion of PCR to ACR, Dr. Sumida et al. conducted analyses of data from cohorts in the CKD Prognosis Consortium on patients with measurements of PCR and ACR performed ≥90 days apart. To account for multiple records per person, analyses were performed using all available data within individual cohorts. The researchers then conducted a meta-analysis to model log-PCR using random effects and linear splines. Results were reported during a poster session at Kidney Week 2019 in a poster titled Conversion of Urine Protein-Creatinine to Albumin-Creatinine Ratio for Use in CKD Risk Equations.

In all, there were 11 cohorts: two general population, three high cardiovascular risk, and six CKD cohorts representing 34,708 participants from North America, Europe, and Japan. Average age was 58 years, 51% were female, and 7.4% were black. Median ACR was 181 mg/g and median PCR was 373 mg/g.

Because there was no relationship between ACR and PCR at ≤50 mg/g, those values were excluded in the equation development. Above PCR 50 mg/g, there was a log-linear relationship with a slightly shallower slope at PCR ≤50 mg/g (P < 0.01). Relationships between PCR and ACR were similar across cohorts, and demographics, hypertension, cardiovascular disease, and diabetes status.

“Guidelines recommend measurement of ACR, however, when ACR is not available, we developed an equation to convert PCR levels ≤50 mg/g to ACR for use in risk equations. Lower levels of PCR were not amenable to harmonization,” the researchers said.

Gluten-Free Diet in Children with Nephrotic Syndrome

Washington, DC—In children with celiac disease, the protein zonulin increased gut permeability after exposure to gliadin. In children with nephrotic syndrome, plasma zonulin levels are increased. The zonulin effect in electrolytes is mediated by protease activated receptor-2. Elevations in zonulin induced by gluten may affect glomerular permeability and mediate proteinaemia in children with nephrotic syndrome.

Howard Frachtman, MD, and colleagues conducted a multicenter, open-label trial to assess the efficacy of a gluten-free diet in children with steroid-resistant, difficult-to-manage nephrotic syndrome. The treatment period was 6 months. The researchers defined positive response as a 50% reduction in relapse rate versus the prior 6 months or discontinuation of one or more immunosuppression medications. Relevant data included age, sex, race/ethnicity, serum creatinine, proteinuria, histopathology if available, and treatment.

Results of the trial were reported in a poster session at Kidney Week 2019. The poster was titled Efficacy of Gluten-Free Diet (GFD) in Children with Difficult-To-Manage Nephrotic Syndrome (NS). The study enrolled 14 children (eight females, six males). Mean age was 7.8 years, mean baseline serum creatinine was 0.46 mg/dL, and mean urine protein:creatinine ratio was 0.45 mg/L. Eleven of the cohort were white, one was black and other racial groups, and two were Hispanic/Latino. In ten of the children, the underlying disease was minimal change disease. In four cases it was focal segmental glomerulosclerosis.

Four participants had a positive response at the end of the treatment period (two had reduced relapse rate and two had reduced medication burden). Five had no benefit (two withdrew prior to 6 months); three are in the 6-month treatment period, and one child was lost to follow-up. One adolescent had no change in relapse rate, but responded more rapidly to corticosteroids while on the gluten-free diet. In nonresponders (n=4), mean baseline plasma zonulin concentration was 19.4 pg/mL compared with 13.4 pg/mL in gluten-free diet responders (n=2). P < 0.1.

Up to a third of patients with difficult-to-manage nephrotic syndrome have a favorable response to implementation of a gluten-free diet. An elevated plasma zonulin level may predict a poor response to the maneuver. A trial of this dietary intervention may be warranted in children with frequently relapsing or steroid dependent nephrotic syndrome.

A kidney stone may be a sign of a metabolic stone disease, such as primary hyperoxaluria type 1 (PH1), that can result in progressive renal impairment. So, any unusual presentation among stone formers merits further investigation. There are additional clinical red flags that, when also present, indicate a likely systemic condition:

- Abnormal urinary chemistry on 24-hour urine test (eg, high oxalate, low citrate, high magnesium, high calcium, high glycolate)
- Impaired kidney function/end-stage renal disease (ESRD)
- Nephrocalcinosis
- Failure to thrive (infants)

Once suspected, confirming PH1 with genetic testing may reduce an often lengthy delay in diagnosis, which may improve the overall outcome. Unfortunately, PH1 patients are often already suffering from irreparable kidney damage when diagnosed, with up to 70% of diagnoses in adults occurring after progression to ESRD.

Consider genetic testing for your patients when you suspect a metabolic stone disease and visit AboutPH1.com
Acute kidney injury (AKI) occurs in 5% to 10% of all hospital admissions and in up to 30% of hospital admissions for cardiac surgery. There are independent associations between longer duration of AKI and greater severity of AKI and increased mortality. After the initial injury, recovery or progression of kidney disease is guided by biologic processes; some processes lead to adaptive repair and regeneration of tubules, others lead to maladaptive repair and fibrosis, resulting in replacement of the kidney interstitium with connective tissue.

Angiogenesis, the process of formation of new blood vessels, is thought to be a critical mechanism that determines kidney recovery following AKI. Preclinical models of AKI have shown that enhanced angiogenesis preserves peritubular capillaries, attenuates tubulointerstitial fibrosis, and restores kidney function after injury. However, the process of angiogenesis has not been well described in AKI in humans.

Sherry G. Mansour, DO, and colleagues recently conducted an ancillary study of TRIBE-AKI (Translational Research Investigating Biomarker Endpoints for Acute Kidney Injury) data to examine the association of angiogenic growth factors with the development and duration of AKI and 1-year mortality after cardiac surgery. Results of the prospective cohort ancillary study were reported in the American Journal of Kidney Diseases [2019;74(1):36-46].

The researchers measured plasma levels of three angiogenic markers: vascular endothelial growth factor A (VEGF), placental growth factor (PGF), and soluble VEGF receptor 1 (VEGFR1). The markers were measured prior to and within 6 hours after surgery. A total of 1444 adults in the TRIBE-AKI cohort underwent cardiac surgery. Of those 1444 patients, mean age was 72 years and 69% were men. Eighty-four percent of the cohort underwent cardiac surgery. Of those, 6% (n=81) of the patients with AKI, 8% (n=41) had a long duration of AKI, defined as ≥7 days. Six percent (n=81) of the patients died after 1 year of follow-up.

Each angiogenic marker had a distinct trajectory following cardiac surgery. On postoperative day 1, there was a 2-fold decrease in VEGF concentrations; on day 2, the levels neared those of the preoperative period. Concentrations of PGF increased 1.5-fold on day 1 and remained elevated to a similar extent on day 2. On day 1, VEGFR1 concentrations increased 8 fold and decreased to a 2-fold increase relative to preoperative levels on day 2.

Concentrations of the proangiogenic markers (VEGF and PGF) were lower in participants who developed adverse outcomes compared with those who did not develop adverse outcomes, long duration of AKI, and mortality. While, on average, VEGF concentrations decreased following surgery, VEGF levels declined to a larger extent among participants who developed adverse outcomes compared with those who did not. Conversely, those with adverse outcomes had higher postoperative concentrations of the antiangiogenic marker VEGFR1 versus those who did not develop adverse outcomes.

Following multivariable regression analysis, there was an independent association between higher postoperative VEGF concentrations and lower odds for adverse outcomes (adjusted odds ratio [aOR], 0.89; 95% confidence interval [CI], 0.82-0.98 for AKI; aOR, 0.65; 95% CI, 0.49-0.87 for long AKI duration; and aOR, 0.74; 95% CI, 0.62-0.89, for mortality). There was also an independent association between postoperative concentrations of PGF and lower risk for adverse outcomes with 31% lower odds of AKI, 52% lower odds of long duration of AKI, and 54% lower odds of mortality. There was an independent association between higher postoperative concentrations of VEGFR1 and higher odds for each outcome (aOR, 1.56; 95% CI, 1.31-1.87 for AKI; aOR, 1.75; 95% CI, 1.09-2.82 for long AKI duration; and aOR, 2.28; 95% CI, 1.61-3.22 for mortality).

There were no associations between VEGFR1 and PGF and any of the outcomes preoperatively. There was a weak association between preoperative VEGF concentrations and the development of postoperative AKI. When marker levels were examined in tertiles for all outcomes, results were similar.

The areas under the curve (AUCs) of the combination of the three postoperative angiogenic markers outperformed those of the individual postoperative markers for the outcomes of AKI, long duration of AKI, and mortality. When added to the clinical model, the combined postoperative angiogenesis marker panel significantly improved the AUCs for AKI to 0.72 (95% CI, 0.69-0.75), for long duration of AKI to 0.88 (95% CI, 0.84-0.92), and for all-cause 1-year mortality to 0.74 (95% CI, 0.69-0.80). The changes in AUCs between the clinical model and the clinical plus combined angiogenesis panel were statistically significant for all outcomes.

Limitations to the findings cited by the authors included not measuring angiogenic markers following hospital discharge, including only cardiac surgery patients in the cohort that may have limited the generalizability of the findings, and the possibility of unmeasured confounding related to inflammatory and postsurgical responses.

The researchers said, “In conclusion, we have demonstrated that growth factors involved in angiogenesis are associated with AKI, long AKI duration, and mortality after cardiac surgery. We found that higher postoperative levels of the proangiogenic growth factors VEGF and PGF are independently associated with shorter duration of kidney injury and decreased mortality, whereas higher postoperative levels of the antiangiogenic mediator VEGFR1 are independently associated with longer kidney injury and increased mortality. Further studies are needed to both validate our findings and assess generalizability in noncardiac surgery settings.”
Coronary Artery Calcification and Serum Calcification Propensity in Patients with CKD

The leading cause of death among patients with chronic kidney disease (CKD) is cardiovascular disease. Patients with CKD may develop vascular calcification, one mechanism that increases the cardiovascular disease risk in that patient population. Medial calcification is associated with increased arterial stiffness and heart failure; patients with CKD are also at risk for intimal calcification, indicative of atherosclerosis.

The coronary artery calcium (CAC) score includes both types of calcification. There is a strong association between CAC presence and progression and cardiovascular disease in the general population. Earlier studies have shown an association between reduced kidney function and more severe calcification as well as more rapid progression of CAC. In patients with CKD stages 2 to 4, CAC score is an independent risk predictor for cardiovascular disease and all-cause mortality.

The Chronic Renal Insufficiency Cohort (CRIC) study provided an opportunity for Joshua D. Bundy, PhD, MPH, and colleagues to examine the associations between transformation time (T50) and the presence and progression of CAC in a diverse sample of patients with CKD stages 2 to 4. Higher calcification propensity is denoted by lower T50. The researchers utilized CRIC data to test the hypothesis that there would be an association between low T50 values and prevalent and incident CAC in patients with CKD stages 2 to 4. Results of the prospective cohort study were reported in the American Journal of Kidney Diseases [2019;73(6):806-814].

Of the total CRIC cohort, 1,274 participants had available data for computed tomography (CT) and T50 and were included in the current analysis. Mean age was 57.5 years, 46.9% were women, 44.3% had diabetes, 27.2% had a history of cardiovascular disease, and mean estimated glomerular filtration rate (eGFR) was 44.5 mL/min/1.73 m².

Median T50 was 321 minutes. Participants with low T50 were more likely to be non-Hispanic black (P<.001), have a history of cardiovascular disease (P=.004) and diabetes (P<.001), and be taking antihypertensive (P<.001), statin (P<.01), and active vitamin D medications (P<.001). On average, those with low T50 had higher systolic blood pressures (P=.006), 24-hour urine protein excretion (P<.001) and phosphate (P<.001), fibroblast growth factor 23 (FGF-23) (P<.001), parathyroid hormone (PTH) (P<.001), interleukin 6 (IL-6) (P<.001), and high-sensitivity C-reactive protein (hsCRP) (P=.002) levels, and lower eGFR (P<.001), bicarbonate (P<.001), calcium (P<.006), magnesium (P<.005), serum albumin (P<.001), and fetuin-A (P<.001) values.

A total of 824 of the 1,274 participants had CAC at baseline. Participants were stratified into quartiles based on T50: 367-600; 322-366; 270-321; and 72-269 minutes. Mild CAC severity (<100 Agatston units) was similar among the T50 quartiles; lower quartiles were more likely to have severe CAC (>400 Agatston units). In cross-sectional associations of T50 with prevalence and severity of CAC, following multivariable adjustment, there was no association between T50 and the prevalence of CAC score >0. However, there was an association between lower T50 and greater CAC severity among participants with baseline CAC. Following multivariable adjustment, one standard deviation lower T50 value was associated with 21% greater CAC severity. There were also graded associations across T50 quartiles. There was a significant association between lower T50 and greater prevalence of moderate and severe CAC.

In examination of longitudinal associations of T50 with the incidence and progression of CAC among 780 participants with follow-up CT an average of 3.2 years later, among the 320 participants without CAC at baseline, 65 developed CAC during follow-up. There was no association between T50 and incident CAC. Among 460 participants with baseline CAC, 89 had an annual increase of ≥100 Agatston units and 37 had an annual increase of ≥200 Agatston units; there was an association between T50 and both definitions of progression. Following multivariable adjustment, there was an association between one standard deviation lower T50 value and 28% higher risk for progressing ≥100 Agatston units per year. There were graded associations across T50 quartiles.

There were no significant associations between T50 and age, sex, race/ethnicity, or diabetes. Following adjustments for potentially associated variables (calcium, phosphate, bicarbonate, magnesium, serum albumin, fetuin-A, FGF-23, PTH levels as well as use of medications including warfarin, active vitamin D, phosphate binders, and calciferols and inflammatory variables (IL-6 and hsCRP levels), results were similar to the primary analyses.

The researchers cited possible limitations to the T50 test in vitro with supersaturation of calcium and phosphate that results in synthetic calciprotein particles, the possibility of selection bias, the relatively small sample size, the inability to evaluate some additional markers, the inability to distinguish between intimal and medial calcification due to limitations of CT technology, and limiting CT measurement to one point during follow-up. The researchers said, “In conclusion, higher serum calcification propensity, denoted by lower T50, was significantly associated with the severity and progression of CAC among patients with CKD. However, T50 was not associated with the incidence of CAC. These findings provide valuable insights into the development of calcification and atherosclerosis in patients with CKD and highlight potential pathways for risk stratification and therapeutic intervention. Future research should evaluate these associations in other CKD populations and the general population, and clinical trials may be warranted to establish causality.”

**Takeaway Points**

- Patients with chronic kidney disease (CKD) have a high prevalence of coronary artery calcification (CAC) increasing the risk for cardiovascular disease events and mortality. Researchers conducted a prospective cohort study to test the hypothesis that a novel serum measure of calcification propensity is associated with CAC among patients with CKD stages 2 to 4.
- The study included participants from the CRIC Chronic Renal Insufficiency Cohort study with baseline (n=1,274) and follow-up (n=780) CAC measurements. At baseline, 66% (n=824) of the cohort had prevalent CAC.
- Following multivariable adjustment, there was no association between transformation time (T50) and CAC prevalence; there was an association between T50 and greater severity of CAC among the patients with prevalent CAC.
Dietary Fiber Intake and Inflammation in Patients on Hemodialysis

In western countries, there has been a decrease in total dietary fiber (TDF) intake in recent years. Increasing the consumption of foods rich in fiber is recommended in many healthy eating guidelines from public health communities. In patients receiving maintenance hemodialysis, dietary restrictions of potassium and phosphorus are the primary contributors to decreased consumption of TDF.

In the general population, decreased intake of TDF is associated with colon cancer, diverticulitis, impaired glucose tolerance, hyperlipidemia, and inflammation. Previous studies, both observational and experimental, have found an inverse relationship between TDF intake and inflammation; chronic kidney disease (CKD) is considered as an inflammatory state, and increased C-reactive protein (CRP) is a strong predictor of morbidity and mortality. Conversely, high TDF is associated with lower risk of general population and among patients with CKD; the associations are stronger in the kidney disease population.

Bahar Gürel Demirci, MD, and colleagues in Turkey recently conducted a cross-sectional, observational, single-center study to test the hypothesis that high TDF intake could be associated with low serum advanced glycation end products (AGEs), and both of these conditions could lead to decreased arterial stiffness in patients on maintenance hemodialysis. The researchers sought to analyze the relationship between the effect of TDF intake on C-reactive protein and on oxidative stress parameters such as serum AGEs, superoxide dismutase (SOD), malondialdehyde, and arterial stiffness by pulse wave velocity (PWV) in that patient population. Results of the study were reported in the Journal of Renal Nutrition [2019;29(2):136-142].

Of 650 patients on maintenance hemodialysis, 128 were included in the study cohort following application of exclusion criteria: lack of regular follow-up data; history of rheumatologic or chronic inflammatory disease of unknown origin, systemic vasculitis; Kt/V <1.4; active systemic infection or hospitalization in the last 3 months; active gastrointestinal disorders; history of peripheral artery disease; severe malnutrition (systemic global assessment group C) and/or receiving oral nutritional supplementation; active smoking; and history of malignancy. All eligible patients received 40-hour hemodialysis sessions three times a week with a high-flux membrane dialyzer.

Dietary habits were evaluated using a 3-day dietary record (including a dialysis day, a weekend day, and a nondialysis day). Patients were stratified by quartiles of energy-adjusted dietary fiber (ADF) as follows: group 1 (n=32), ADF <8.86 g/day; group 2 (n=35), ADF 8.86 to 12.5 g/day; group 3 (n=31), ADF 12.51 to 15.91 g/day; and group 4 (n=30), ADF ≥15.91 g/day.

A Cox proportional hazards model was used to evaluate 19 comorbid conditions to determine a given individual’s overall Charlson Comorbidity Index score. In patients with end-stage renal disease, a higher Charlson Comorbidity Index score is associated with increased risk of mortality.

Mean age of the cohort was 51.9 years, 55% (n=71) were male; mean duration of dialysis was 9.1 years; the etiology of CKD was diabetes mellitus in 25% (n=32), hypertension in 13% (n=17), glomerulonephritis in 13% (n=17), polycystic kidney disease in 5% (n=7), and other in 44% (n=55); mean body weight was 68.8 mg; and mean body mass index (BMI) was 25.4 mg/m². Mean intake of dietary fiber was 12.65 g/day (range, 3.80-31.1 g/dL), and mean ADF intake was 12.63 g/day (range, 4.20-31.4 g/dL).

Mean ADF was 7.8 g/day in group 1, 10.7 g/day in group 2, 14.1 g per day in group 3, and 18.0 g/day in group 4. The groups were similar in mean values of dietary water, carbohydrates, lipids, and protein intake, and age, sex, BMI, duration of dialysis, mean serum hemoglobin (Hb), calcium phosphorus, uric acid, albumin, and lipid profile.

Compared with patients in groups 1 and 2, CRP was significantly lower in patients in groups 3 and 4 (21.7 mg/L, 13.7 mg/L, 8.1 mg/L, and 6.2 mg/L in group 1, 2, 3, and 4, respectively, P<.001) and AGE (6.4 U/mL, 3.9 U/mL, 3.2 U/mL, and 2.9 U/mL in group 1, 2, 3, and 4, respectively, P<.001).

Mean serum SOD levels were 5.4 U/g Hb, 5.2 U/g Hb, 5.9 U/g Hb, and 6.4 U/g Hb, in group 1, 2, 3, and 4, respectively. Upon further comparison with Turkey’s Post Hoc analysis, test for multiple pairwise comparisons, there was a statistically significant difference observed between groups 1 and 4, and groups 2 and 4.

In patients in group 4, PWV was significantly lower than in groups 1, 2, and 3. In Pearson’s correlation analysis, there was a negative correlation between mean ADF and serum CRP, serum AGE levels, and PWV.

There were some limitations to the study cited by the authors, including the relatively small sample size, the cross-sectional design, using a 3-day dietary diary, and collecting blood samples only once at the time of PWV measurements.

In conclusion, the researchers said, “This cross-sectional study showed that dietary fiber intake is independently correlated with inflammation and oxidative stress. Moreover, increased fiber intake has resulted in improved arterial stiffness. Thus, adequate fiber intake could prevent cardiovascular events and inflammatory processes in patients receiving ongoing maintenance hemodialysis. However, further interventional studies are warranted to evaluate the effects of increasing fiber intake on inflammation, oxidative stress, and its consequences.”
The optimal time to initiate dialysis for the treatment of kidney failure remains uncertain. Renal recovery is rare following dialysis initiation and patients receiving dialysis treatments are at high risk for morbidity and mortality and a diminishing quality of life. Further, early initiation of dialysis increases healthcare costs and may not provide optimal value from a health system perspective.

Results of the IDEAL (Initiating Dialysis Early and Late) randomized clinical trial were published in April 2010. In the IDEAL trial, patients with predialysis chronic kidney disease were randomized to planned initiation of dialysis at eGFR 10 to 14 mL/min/1.73 m² (early start) or to initiation of dialysis at eGFR 5 to 7 mL/min/1.73 m² (late start). Trial results suggested there was no association between earlier initiation of dialysis and a statistically significant difference in survival or other clinical outcomes such as cardiovascular events and infections.

Researchers in Canada, led by Thomas W. Ferguson, MSc, recently conducted an interrupted time series analysis study to examine the association between the publication of results of the IDEAL trial and the proportion of patients in Canada who initiated dialysis early (eGFR ≥10.5 mL/min/1.73 m²). Results of the analysis were reported online in JAMA Internal Medicine [doi:10.1001/jamainternmed.2019.0489].

The primary outcome of interest was the proportion of early dialysis starts. Secondary outcomes were the proportions of acute inpatient dialysis starts, patients who started dialysis using a home modality, and patients receiving hemodialysis who started with an arteriovenous access. The researchers utilized data from the Canadian Organ Replacement Register.

The analysis model included the trend before the IDEAL trial publication, an evaluation of the change in this trend after publication, and the immediate consequence of publication. The pretrial period was 56 months (January 1, 2006, to August 31, 2010). Following publication of the trial in August 2010, a 6-month grace period was included in the model (September 1, 2010, to February 28, 2011). The posttrial period was 58 months (March 1, 2011, to December 31, 2015).

Eligible participants were ≥18 years of age with incident chronic dialysis between January 1, 2006, and December 31, 2015, in Canada. Patients from the province of Quebec were excluded due to privacy laws that preclude submission of deidentified data without first-person consent. Eligibility included at least 90 days of nephrologist care prior to initiation of dialysis and a recorded eGFR at dialysis initiation.

The final study cohort included 28,468 patients; 60.9% (n=17,342) were male and mean age was 64.8 years. Compared with the pretrial population, patients in the posttrial period were more likely to be male; had lower serum hemoglobin, lower serum albumin, and higher serum phosphate levels at dialysis initiation; had more days of predialysis care; had higher body mass index; and had more comorbid conditions. Of the total cohort, 36.3% of patients (n=10,323) initiated dialysis during the study period with an eGFR at initiation higher than 10.5 mL/min/1.73 m². The proportion of early dialysis starts was 39.0% (95% confidence interval [CI], 38.1%-39.9%) in the pretrial period and 34.0% (95% CI, 33.3%-34.7%) in the posttrial period. During the pretrial period, there was a statistically significant increasing trend in the monthly proportion of early dialysis (adjusted rate ratio, 1.002; 95% CI, 1.001-1.004; P<.001). There was a statistically significant decrease in the proportion of early states immediately after the pretrial and grace periods (rate ratio, 0.874; 95% CI, 0.818-0.935; P<.001).

During the study period, 26.9% of patients (n=7166) initiated dialysis as acute inpatients. In the pretrial period, the proportion of acute inpatient starts was 24.0% (95% CI, 23.2%-24.8%) compared with 28.9% (95% CI, 28.2%-29.6%) in the posttrial period. There was no statistically significant trend in the proportion of acute inpatient initiations in the pretrial period, no statistically significant immediate consequence was observed, and no statistically significant change in trend between the pretrial and posttrial periods was observed.

A total of 7066 patients (24.8%) initiated dialysis using a home modality during the study period. In the pretrial period, 26.8% of patients initiated dialysis with a home modality, compared with 23.1% in the posttrial period. There was no statistically significant trend in the proportion of dialysis initiations with a home modality in the pretrial period, no statistically significant immediate consequence, and no statistically significant change in trend between the pretrial and posttrial periods observed.

The proportion of early dialysis starts was 39.0% (95% confidence interval, 38.1%-39.9%) in the pretrial period and 34.0% (95% CI, 33.3%-34.7%) in the posttrial period.

During the study period, 21,054 patients (74.0%) initiated hemodialysis. Of those, 26.1% (n=5497) began therapy with an arteriovenous fistula (AVF) or arteriovenous graft (AVG) access. In the pretrial period, 27.6% of patients initiated dialysis with an AVF or AVG, compared with 25.1% in the posttrial period. There was a statistically significant decrease in the proportion of hemodialysis patients initiating therapy with an AVF or AVG in the pretrial period. Following the pretrial and grace periods, there was no statistically significant immediate consequence, and no statistically significant change in trend between the pretrial and posttrial periods.

There were some limitations cited by the authors: assuming that the IDEAL trial was the major catalyst for changes in dialysis initiation practice; including only patients with evidence of nephrologist care at least 90 days prior to dialysis initiation; and the study occurring in a universal healthcare system, limiting the generalizability of the findings to privately funded healthcare settings.

“This study found that publication of the IDEAL trial appeared to be associated with immediate and sustained change in the timing of dialysis initiation in Canada, excluding Quebec. No statistically significant sustained differences were found in acute inpatient dialysis initiations, the proportion of home-based-modality as the initial modality, or the proportion of arteriovenous access construction for hemodialysis,” the researchers said.

**TAKEAWAY POINTS**

- Results of the IDEAL (Initiating Dialysis Early and Late) trial were published in April 2010, there was no association between early initiation of dialysis and improved survival or clinical outcomes.

- Researchers in Canada recently conducted an analysis to examine the association between the results of the IDEAL trial and the proportion of early dialysis starts in Canada over time.

- Prior to IDEAL, there was an increasing trend in the monthly proportion of early dialysis starts; following publication of IDEAL results, there was an immediate decrease in the proportion of early dialysis starts.

- Publication of IDEAL trial results appeared to be associated with a change in the timing of dialysis initiation.

The proportion of early dialysis starts was 39.0% (95% confidence interval, 38.1%-39.9%) in the pretrial period and 34.0% (95% CI, 33.3%-34.7%) in the posttrial period.
Hydroxychloroquine plus RAAS Inhibition Reduced Proteinuria in Patients with IgAN

Worldwide, the most prevalent form of primary glomerular disease is immunoglobulin A (IgA) nephropathy (IgAN). The disease usually progresses from chronic slowly progressive kidney injury; however, as many as 30% of patients will progress to end-stage kidney failure. Proteinuria is strongly associated with decline in kidney failure; despite optimized renin-angiotensin-aldosterone system (RAAS) inhibitor therapy, patients with IgAN and persistent proteinuria are at risk for kidney failure.

Corticosteroids are often suggested for patients with IgAN and persistent proteinuria. However, the efficacy of corticosteroids is not well established and adverse side effects are well documented, making identification of new therapies for IgAN a priority. Hydroxychloroquine (HCQ), a well-known immunomodulator has not been well studied in IgAN. Results of previous studies were limited by nonrandomized or retrospective design. Li-Jun Liu, MD, and colleagues recently conducted a double-blind, randomized, placebo-controlled, phase 2 clinical trial designed to examine the efficacy and safety of HCQ when added to the treatment regimen of patients with IgAN. The researchers also sought to determine whether a larger multicenter trial with clinical outcomes is warranted. Results of the study were reported in the American Journal of Kidney Diseases [2019;74(1):15-22].

The study design compared oral HCQ to placebo in patients with IgAN receiving maximal supportive treatment, including RAAS inhibitor therapy and blood pressure control according to the Kidney Disease: Improving Global Outcomes glomerulonephritis guideline. The study was conducted at Peking University First Hospital, Beijing, PR China. Inclusion criteria were age 18 to 75 years, a diagnosis of biopsy-proven primary IgAN, estimated glomerular filtration rate (eGFR) >30 mL/min/1.73 m², and proteinuria with protein excretion of 0.75 to 3.5 g/day despite receiving a maximum tolerable dose of RAAS inhibitor for at least 3 months. Exclusion criteria were use of systemic immunosuppressive therapy in the previous year, an indication for corticosteroids ( Crescentic IgAN or minimal change disease with IgA deposit), current or planned pregnancy or lactation, and contraindications for HCQ therapy. Patients were randomly assigned 1:1 to receive oral HCQ (hydroxychloroquine sulfate tablets) or a matching placebo for 6 months. The treatment dose was 0.2 g orally (2 tablets) twice daily for patients with eGFR <60 mL/min/1.73 m², 0.1 g orally (1 tablet) three times daily for patients with eGFR 45 to 59 mL/min/1.73 m², and 0.1 g orally (1 tablet) twice daily for patients with eGFR 30 to 44 mL/min/1.73 m².

At 6 months, the median proteinuria level was significantly lower in the HCQ group than in the control group (protein excretion, 0.9 vs 1.0 g/d; P=0.002).

A total of 100 potentially eligible patients were screened between September 2016 and July 2017. Of those, 60 met eligibility requirements and were randomly assigned to the treatment group (n=30) or the control group (n=30). During the course of the study, four patients in the HCQ group and two in the control group discontinued the intervention. The HCQ dose was decreased in three patients for a slightly decreased eGFR (n=1) or adverse events (n=2). The two groups were similar at baseline. Overall, baseline characteristics were: proteinuria, protein excretion of 1.7 g per day; urine albumin-creatinine ratio (UACR), 920.1 mg/g; and eGFR, 53.8 mL/min/1.73 m².

The primary outcome of interest was percentage change in proteinuria between baseline and 6 months. The percentage change in the HCQ group from baseline to 6 months was higher than in the control group (–48.4% vs 10.0%; P=0.001). At 6 months, the median proteinuria level was significantly lower in the HCQ group than in the control group (protein excretion, 0.9 vs 1.9 g/d; P=0.002).

Prespecified secondary outcomes included percentage change in proteinuria from baseline to 2 and 4 months, frequency of patients with a 50% decrease in proteinuria, and percentage change in eGFR. In analyses of the secondary outcomes, percentage changes in proteinuria decrease from baseline to 2 and 4 months were higher in the HCQ group than in the control group: 2 months, –28.4% vs 1.4%; P=0.003; 4 months, –38.0% vs 3.5%; P=0.001. Of the 26 patients in the treatment group who completed the 6-month visit, 50% (n=13) in the HCQ group showed a 50% decrease in proteinuria at 6 months compared with 14.8% (n=4/27) in the control group (P=0.006). There was a similar trend in percentage change in UACR.

There were no severe adverse events in either group during the study period. In the HCQ group, seven patients experienced adverse events, including allergic reaction to HCQ, occasional dizziness, pruritus, skin pigmentation, transient palpitations, and nausea.

Limitations cited by the authors included the single-center study design, the small sample size, and the lack of generalizability of the findings. Other limitations were the short treatment period and the lack of a postwithdrawal observation phase.

The researchers said, “Because this is an early-phase trial, it should not be viewed as providing a definitive answer to the question about the intervention. We view this study as a proof-of-concept study providing the justification to embark on a larger, longer duration, multicenter, multiethnic, clinical trial. We firmly believe that further study of HCQ and its underlying mechanism in IgAN is warranted.

“In conclusion, HCQ treatment in addition to optimized RAAS inhibitor therapy significantly and safely reduced proteinuria in patients with IgAN. HCQ may in the future be an additional therapeutic option for the treatment of IgAN.”
METABOLIC ACIDOSIS IN CHRONIC KIDNEY DISEASE (CKD) IS COMMON AND HARMFUL¹-⁷

Chronic metabolic acidosis damages kidney, bone, and muscle¹-⁴

- Its pathophysiology is associated with loss of bone mineral density⁸-¹⁰
- It contributes to muscle wasting in CKD as a result of increased muscle catabolism⁸,¹⁰
- It is both a complication of chronic kidney disease and a cause of its progression⁴,⁵,⁸,¹⁰,¹¹

Donor Kidney Acceptance Practices and Wait-Listed Patients

Each year, nearly 5000 people in the United States and more than 3000 in Europe die while waiting for a kidney transplant. The shortage of organs available for transplant is a major public health issue, due to wait-listed patient mortality as well as increased healthcare costs of maintaining patients with end-stage renal disease (ESRD) on chronic dialysis. However, more than 3500 kidneys are discarded in the United States annually.

Results of recent studies have suggested that even the lowest-quality kidneys prolong survival compared with dialysis in patients with ESRD. Explanations for the high rate of kidney discard in the United States include the intense regulatory scrutiny of US transplant programs, financial disincentives, and the role of kidney biopsy as a method of determining allograft quality. Transplant programs in France face less regulatory scrutiny and do not use donor kidney biopsies in organ acceptance decisions.

Despite two initiatives from the United Network for Organ Sharing, the number of discarded kidneys rose from 2127 (14.9%) in 2006 to 3631 (20%) in 2016 in the United States. Researchers, led by Olivier Aubert, MD, PhD, conducted a study to compare the US transplant system with the French system. Results were reported online in JAMA Internal Medicine [doi:10.1001/jamainternmed.2019.2322].

The cohort study analyzed the use of 156,089 deceased donor kidneys in the United States and 29,984 in France, and used computer simulation algorithms to measure the potential gains in allograft survival years that would result if US programs adopted less restrictive kidney acceptance practices.

The French cohort included 15,500 deceased donors between January 1, 2004, and December 31, 2014, from whom the 29,984 kidneys were recovered. Of the recovered kidneys, 27,252 were transplanted and 2732 (9.1%) were discarded. In the US cohort (n=78,517) of deceased donors between 2004 and 2014, 156,089 kidneys were recovered for transplantation. Of those, 128,102 were transplanted and 72,987 (17.9%) were discarded.

Of the transplanted kidneys, mean donor age in France was 50.91 years versus 36.51 years in the United States (P <.001). A smaller percentage of donors in the United States had hypertension compared with donors in France (24.76% vs 29.06%; P <.001), or died of cerebrovascular causes (32.68% vs 54.57%; P <.001). In France, kidneys were less likely to be donated following cardiac death (prevalence rate of 1.6% vs 11.7% in the United States) and to come from donors seropositive for hepatitis C virus (prevalence rate of 0.1% vs 2.1% in the United States).

The discard rate in France was lower for weekend procurement: 667 kidneys were discarded during the weekend (8.5%) compared with 2065 discarded during weekdays (9.3%). P = .02. The overall discard rate in the United States was similar during the weekdays and weekends: 20,273 kidneys were discarded during the weekdays compared with 7750 discarded during the weekend (prevalence rate of 17.9% vs 18.0%, respectively; P = .70). There was a higher discard rate of kidneys recovered from African American donors (4748/22,751; 20.9%) versus non-African American donors (23,289/133,338; 17.43%, P <.001).

The mean Kidney Donor Risk Index (KDRI) of transplanted deceased donors was significantly higher in France than in the United States (1.50 vs 1.23; P <.001). Trends observed using the Kidney Donor Profile Index (KDPI) score were similar.

In France, there was a steady rise in KDRI from 2004 through 2014 (mean, 1.37 in 2004 and 1.74 in 2014; P <.001), reflecting a temporal trend of more aggressive organ use. In contrast, there was little change in the quality of kidneys transplanted in the United States during the study period (mean KDRI, 1.30 in 2004 and 1.32 in 2014). Trends observed using the KDPI score were similar. Increasing donor age was the principal driver of the higher KDRI in France: in 2014, the mean donor age in France was 56.17 years versus 39.08 years in the United States.

Results of prediction models for kidney discard decisions in France and the United States showed a strong association between the KDRI and discard of the kidney in both France and the United States (odds ratio [OR], 3.88; 95% confidence interval [CI], 3.83-3.93 in the United States; OR, 2.18; 95% CI, 2.07-2.30 in France; P <.001). The two models showed good accuracy, with an area under the curve (AUC) of 0.82 for the United States model and an AUC of 0.72 for the French model; calibration was excellent in both models. The US allocation system had a higher probability of discarding kidneys with higher KDRI than in France. A KDRI of 1, 2, 3, and 4 results in actual kidney discard rates of 5%, 45%, 80%, and 92%, respectively, in the United States, compared with 3%, 13%, 27%, and 42% discard rates in France, respectively.

Application of the French allocation model to the US cohort demonstrated that a French-based practice pattern translated to an estimated 10,552 discarded kidneys compared with the actual number of 27,987 discarded kidneys in the United States; the French model-based discard rate was 6.8% versus the actual discard rate in the United States of 17.9%. Overall, the use of the French-based discard practice pattern would have corresponded to an estimated 17,435 fewer discarded kidneys (62.3% among all discarded kidneys) in the United States during the study period 2004 to 2014.

A final analysis demonstrated that a redesigned system in the United States with more aggressive organ acceptance practices would generate an additional 132,445 allograft life-years over the 10-year observation period.

Study limitations cited by the authors included unmeasured confounding by donor characteristics not assessed in the KDRI that may have contributed to international differences in organ discard rates; posttransplant outcomes for lower-quality kidneys might be worse in the United States compared with France; and policy in the United States does not preferentially allocate older kidneys to older recipients, creating the possibility that greater procurement of high-KDRI kidneys might have adverse consequences if those kidneys were transplanted into young recipients.

“The high discard rate of deceased donor kidneys is a major concern for the US transplant field. We found that the age and KDRI of US deceased donor kidneys remained stable from 2004 to 2014 in the United States, whereas the French transplant system responded to the organ shortage by accepting lower-quality kidneys, especially those from older donors,” the researchers said. “Policies designed to enhance the acceptance of donated kidneys in the United States could drive meaningful increases in the number of kidney transplants and bring the benefits of transplantation to thousands of wait-listed patients.”
Deceased Donor Kidneys and Transplant Outcomes

In the United States, there is well-documented geographic variation in the incidence of end-stage renal disease (ESRD) as well as access to kidney transplant. The disparities in kidney transplant are believed to be largely associated with regional variations in availability of organs and prevalence of ESRD. However, there are few data on the possible association between the disparities and differences in acceptance rates of deceased donor kidney offers.

Currently, offers of donation of a kidney to a transplant candidate are made to the transplant center where the candidate is waitlisted. The center can decline the offer on the patient’s behalf without informing the patient of the offer or the reason it was declined. Offers of organs are often declined on the basis of organ selection practices at the center level rather than a detailed assessment of the advantages for an individual candidate.

The associations between a center’s ability to decline offers of organ donation and patient access to transplant are unknown, as are the outcomes associated with a patient remaining on the wait-list following refusal of a donated kidney. S. Ali Husain, MD, and colleagues conducted a cohort study designed to examine outcomes for wait-listed kidney transplant candidates after refusal of a deceased donor kidney offer by the transplant center. Results of the study were reported online in JAMA Network Open [doi:10.1001/jamanet-workopen.2019.10312].

The researchers utilized data from the United Network for Organ Sharing Potential Transplant Recipient data set on all deceased donor kidney offers in the United States between January 1, 2008, and December 31, 2015. The final study cohort included all adult patients wait-listed for kidney transplantation who received at least one allograft offer during the study period.

The outcomes of interest were receipt of deceased donor allograft, receipt of living donor allograft, death while on the waiting list, removal from the waiting list without a transplant, or remaining on the waiting list at the end of follow-up.

The researchers identified 367,405 candidates on the waiting list during the study period; of those, 280,041 met eligibility criteria. Of the eligible candidates, mean age at time of wait-listing was 51.1 years and 61.2% were men. Median time receiving dialysis at time of listing was 1.2 years, 41.7% of the candidates (n=116,712) had diabetes, 13.4% (n=37,629) had panel reactive antibody >80%, and 6.0% (n=16,778) had vascular disease.

Among the 280,041 candidates, 29.2% (n=81,750) received a deceased donor kidney allograft, 11.0% (n=30,870) received a living donor allograft, 9.3% (n=25,967) died while on the waiting list, and 21.2% (n=59,359) were removed from the waiting list. The remaining candidates were still wait-listed as of the end of the study period (12/31/2015). Median follow-up was 755 days after listing.

During the study period, a mean of 10 candidates who previously received an offer died every day. Those who died while on the waiting list, compared with those in other groups, were statistically significantly older, more likely to have diabetes or vascular disease, and less likely to be wait-listed prior to initiation of dialysis. Candidates received their first offer of an organ a median of 48 days following wait-listing. Median time to first offer was similar between those who received a deceased donor organ and those who died waiting (79 vs 78 days).

Those who underwent a deceased donor kidney transplant received a median of 17 offers over a median of 422 days prior to the transplant. Candidates who died on the waiting list received a median of 16 offers over a median of 651 days before death; those who were removed from the wait list received a median of 15 offers while on the wait list.

Eighty-four percent of kidneys were declined on behalf of at least one candidate prior to being accepted for transplant; 27% of transplanted kidneys were refused for all candidates in their procuring donation service area, resulting in nonlocal use. As reported by the centers, concerns regarding organ or donor quality accounted for 92.6% (n=8,416,474) of all offers. Offers were infrequently refused due to patient-related factors (2.6%, n=232,193), logistical limitations (0.5%, n=49,492), or other concerns. That trend was stable across the study period.

Across all Kidney Donor Profile index deciles, concerns regarding organ or donor quality remained the primary reason for all declined offers. The proportion of kidneys that were not declined on behalf of any candidate decreased in 2015.

There was marked state-level variability in the interval between the first offer and death or transplant and in the likelihood of dying while having remained on the waiting list after receiving an offer. Following adjustment for candidate demographics and comorbidities and time between wait-listing and first offer, there was a statistically significant geographic heterogeneity in the odds ratio of death while remaining on the wait list after receiving at least one offer.

Those who underwent a deceased donor kidney transplant received a median of 17 offers over a median of 422 days prior to the transplant.

Candidates in 39 states were statistically significantly more likely to die after receiving deceased donor kidney offers than those in Maine. There was also wide variation by state in the median number of offers received before death while having remained on the waiting list, ranging from 3.5 to 30 offers.

The researchers cited some limitations to the findings, including the centers only being able to report one primary reason for organ refusals, and obtaining only limited data after the introduction of the kidney allocation policy in December 2014.

In conclusion, the researchers said, “This cohort study found that kidney transplant candidates received a large number of deceased donor kidney offers that were refused on their behalf but subsequently accepted and transplanted into patients with lower priority on the match run. A death while on the waiting list was frequently preceded by multiple missed opportunities to accept an organ for transplant, which raises important questions about the current organ allocation process. Policy interventions that increase the transparency of these decisions may help maintain the objective nature of the allocation system, improve patient-centered care, and increase transplant rates in the United States.”
News Briefs

SymphonyRM’s AI-Powered Patient Management Program

In a recent press release, SymphonyRM announced that Intermountain Healthcare is expanding its use of SymphonyRM’s HealthOS platform to provide prioritized, personalized, and proactive patient engagement for their Kidney Services organization. SymphonyRM, based in Palo Alto, California, is a privately held health-tech company helping healthcare organizations through its artificial intelligence (AI)-powered data science-driven Next Best Action consumer relationship management platform. Intermountain Healthcare is a Utah-based not-for-profit integrated healthcare delivery network.

The new kidney services program and clinic is designed to help patients with chronic kidney disease (CKD) and end-stage renal disease live the “healthiest lives possible.” The program’s care model focuses on early detection and engagement and aims to cut unnecessary hospital admissions by as much as 50%, help slow the rate of development of renal disease, and increase awareness of renal disease before patients suffer renal failure.

SymphonyRM’s AI algorithms will help identify management plans for all patients with CKD (at-risk, early, and late stage) and will orchestrate outreach across all channels. The Intermountain team will more effectively engage patients and be better able to identify key behaviors, comorbid conditions, and other factors that affect a patient’s long-term outcomes.

Suji Lee, MD, medical director, Intermountain Healthcare Kidney Services, said, “SymphonyRM’s AI-Powered Next Best Actions allow us to engage and connect patients to care earlier in their journey and effectively manage longitudinal care across the continuum, which will be critical to increase participation, track, and treat comorbid conditions which can decrease the severity of CKD, and empower patients to take a more active role in their own healthcare to improve outcomes while lowering costs.”

Mike Linnert, CEO and founder of SymphonyRM said, “Intermountain Healthcare Kidney Services’ innovative and patient-centric approach will lead the way to advancing American kidney health. We are honored that our Next Best Actions will add value to this important initiative and help improve outcomes for millions of Americans.”

American Kidney Fund and Janssen Pharmaceuticals Announce Partnership

The American Kidney Fund (AKF) has announced a partnership with Janssen Pharmaceuticals, Inc., part of the Janssen Pharmaceutical Companies of Johnson & Johnson, to increase early detection and treatment of chronic kidney disease (CKD), a rapidly growing noncommunicable disease, and to help those at risk of developing CKD to prevent it.

An estimated 96% of people with early-stage kidney disease are not aware of their condition and are thus not equipped with the knowledge to help slow down progression of the disease. The new campaign will build

IMPORTANT SAFETY INFORMATION

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

WARNINGS AND PRECAUTIONS:

- Iron Overload: Monitor ferritin and transferrin saturation (TSAT). Patients may require a reduction in dose or discontinuation of concomitant intravenous (IV) iron
- Risk of Overdosage in Children Due to Accidental Ingestion: Accidental ingestion and resulting overdose of iron-containing products is a leading cause of fatal poisoning in children under 6 years of age. Advise patients to keep AURYXIA out of the reach of children
on AKF’s Know Your Kidneys™ program, the nation’s largest free kidney health screening program.

The US Department of Health & Human Services Advancing American Kidney Health initiative has highlighted the importance of early detection of kidney disease. The AKG’s campaign will complement federal efforts to make kidney disease a national priority in an effort to reduce the number of patients in the United States who reach kidney failure.

In a recent press release, LaVarne A. Burton, president and CEO of AKF, said, “Prevention and disease management have been a vital part of our mission for decades and we have provided free kidney health screening to thousands of Americans each year. We are extraordinarily grateful to Janssen Pharmaceuticals, Inc. for its partnership working with us to expand our reach, urging Americans to understand their risks and get tested early.”

According to the press release, more than a third of patients in the United States who receive a diagnosis of kidney failure have had little or no pre-end-stage renal disease nephrology care. AKF’s campaign will focus on reaching individuals most at risk for kidney disease as well as those who have a diagnosis.

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2019 NNCC Award to Nurses of Rochester General Hospital Dialysis

The nurses of Rochester General Hospital Dialysis, Rochester, New York, have been presented with the Nephrology Nursing Certification Commission (NNCC) 2019 Award for Nephrology Nursing Certification Advocacy. The award is given to acknowledge extraordinary performance in advancing nephrology nursing certification and patient care, according to a press release from NNCC. The award was given to coincide with Nephrology Nurses Week. Theresa Mottes, MSN, RM, CPNP-AC, CDN, president of NNCC presented the dialysis staff members with a plaque and a $1,000 gift card. “It was truly honored to present the Advocacy Award to Rochester General Hospital Dialysis,” Ms. Mottes said. “This team is committed to delivering top-quality care and to improving the lives of their patients. Additionally, the leadership is committed to supporting staff through certification and education.”

Gina Scroggins, MSN, RN, NE-BC, CDN, CNN, nurse manager at Rochester General Hospital, said “We have a number of staff members who have worked in our department for many years and many who have held dialysis or nephrology certifications for years. Their commitment to their patients makes a difference.” Information and a downloadable application are available on the NNCC Advocacy Award Page. To be considered for the 2020 award, the application deadline is January 1, 2020. https://www.nncc-exam.org/awards/nncc-award-nephrology-nursing-certification-advocacy

Enrollment in URIROX-1 Trial is Completed

Allena Pharmaceuticals, Inc., has announced the completion of enrollment in the phase 3 URIROX-1 clinical trial. URIROX-1 is a multicenter, global, randomized, double-blind, placebo-controlled trial designed to evaluate the efficacy and safety of reloxaliase for the treatment of patients with enteric hyperoxaluria. According to a press release, Allena expects to report top-line data from the trial in the first quarter of 2019. Louis Brenner, MD, president and chief executive officer of Allena Pharmaceuticals, said, “We would like to thank the dedicated patients and physicians who helped us achieve this development milestone for our reloxaliase program. We are excited to complete enrollment in this phase 3 trial, as it brings us one step closer to achieving our foundational goal of providing reloxaliase as a first-in-class therapy for patients with enteric hyperoxaluria. These patients suffer from the burden of excess calcium, including kidney stones and kidney damage. We look forward to reporting top-line data from URIROX in the fourth
quarter, as we also continue to partner with the community to increase awareness of enteric hyperoxaluria and advance the ongoing URIROX-2 pivotal trial.”

The URIROX program consists of two pivotal phase 3 clinical trials, URIROX-1 and URIROX-2. The primary end point for both trials is the percent change from baseline in 24-hour urinary oxalate excretion, comparing reloxiolase to placebo. The primary long-term efficacy end point to confirm clinical benefit in URIROX-2 is the proportion of patients with kidney stone disease progression over a minimum treatment period of two years. Topline data from URIROX-2 is expected in the second half of 2021.

Results of REMEDIAL III Clinical Trial Announced

Results of a late-breaking clinical trial in preventing contrast-induced acute kidney injury (CI-AKI) were announced at the Transcatheter Cardiovascular Therapeutics 2019 meeting in San Francisco in late September. In a press release, RenalGuard Solutions announced that the company’s RenalGuard Therapy was found superior to the POSEIDON method in preventing CI-AKI in patients with kidney disease undergoing interventional procedures. The randomized, investigator-driven REMEDIAL III trial included 700 patients.

Patients with kidney disease undergoing interventional procedures using contrast may experience AKI in a number of ways, including direct toxicity, blocking oxygen delivery to the kidney, and increasing loss of fluid. RenalGuard Therapy is designed to protect patients by inducing and maintaining high urine output, reducing the incidence of CI-AKI.

The REMEDIAL III trial was designed to compare RenalGuard Therapy with left ventricular end-diastolic pressure (LVDEP)-guided hydration (the POSEIDON method). The data demonstrated superiority for RenalGuard Therapy via a significantly lower incidence of CI-AKI and/or pulmonary edema, and a lower incidence of major adverse events 1 month post-treatment.

Howard Lenin, MD, chief medical officer at RenalGuard Solutions, said, “RenalGuard Therapy has once again proven to be the most effective means of preventing acute kidney injury in at-risk patients.”

RenalytixAI Names New Board Member

Chirag Parikh, MD, has been appointed to the board of RenalytixAI, according to a recent press release. Dr. Parikh is the director of the division of nephrology and the Ronald Peterson Professor of Medicine at Johns Hopkins School of Medicine.

The author of more than 250 original articles, Dr. Parikh has several active NIH grants. His research focuses on the translation and validation of novel biomarkers for the diagnosis and prognosis of acute kidney injury (AKI). His studies have refined the clinical definition of perioperative AKI and hepatorenal syndrome, developed strategies to reduce kidney discard in deceased donor kidney transplantation, and advanced regulatory approvals of kidney injury biomarkers.

James McCullough, CEO of RenalytixAI, said, “We are honored to have one of the leading voices in kidney disease clinical practice and research join our board. Chirag will help ensure we maintain the highest standards of data driven development for the KidneyIntelX program.”

ANNA Nephrology Nursing Practice, Management, and Leadership Conference

Presentations at the American Nephrology Nurses Association (ANNA) Nephrology Nursing Practice, Management, and Leadership Conference, October 12-14, 2019, in San Diego, included changes needed to meet the goals of the Advancing American Kidney Health (AAKH) program. Gail DeWald, BS, RN, CNN, spoke about the need for new approaches to make kidney donation more attractive to US residents and to address ways transplant centers can be more efficient with organs received for donation in order to meet the goal of doubling the number of kidneys available for donation by 2030.

During a discussion of the AAKH program, James Twaddell, health policy consultant for ANNA, acknowledged that ANNA members are working hard to lower those factors that lead to CKD and ESRD.

Donna Bednarski, MSN, RN, ANP-BC, and ANNA’s liaison to the advocacy group Kidney Care Partners, noted that the executive order setting the AAKH goals left patients the opportunity to make modality choices for their care. The session ended with Tamara Kear, PhD, RN, CNS, CNN, national president of ANNA, announcing that ANNA has initiated a task force to address the issue of the shortage of nephrology nurses.

H. Joseph Salameh, MD, FASN, FACP, presented information on steps to reduce the risk of gout in patients with chronic kidney disease. Preventive steps include educating patients about the risk of consuming foods and drinks that carry a high risk of uric acid, limiting alcohol consumption, as well as consumption of red meat, shellfish, soda, and other foods high in acid. The risk of gout can also be mitigated with weight loss, he said.

Major Meetings 2020

Annual Dialysis Conference
February 8-11, 2020
Kansas City, Missouri
http://annualdialysisconference.org

Renal Physicians Association
Annual Meeting 2020
March 19-22, 2020
Baltimore, Maryland
www.renalmd.org/page/calAnnualMeeting

National Kidney Foundation
Spring Clinical Meetings 2020
March 25-29, 2020
New Orleans, Louisiana
www.kidney.org/spring-clinical/future-dates

American Nephrology Nurses Association 2020
National Symposium
April 19-22, 2020
Orlando, Florida
www.annanurse.org/events/national

American Transplant Congress 2020
May 30-June 3, 2020
Philadelphia, Pennsylvania
https://atcmeeting.org

American Society of Nephrology
Kidney Week 2020
October 20-25, 2020
Denver, Colorado
www.asn-online.org/education/kidneyweek/archives/future.aspx
In patients with autosomal dominant polycystic kidney disease (ADPKD), the formation and growth of cysts in the kidney and the liver result in progressive increases in total kidney volume (TKV) and total liver volume (TLV). Manual tracing of kidneys and livers is laborious and time-consuming. Maatje D. A. van Gastel, MD, and colleagues developed a fully automated segmentation method for measurement of TKV and TLV; the method utilizes a deep learning network optimized to perform semantic segmentation of kidneys and liver.

To train the network, the researchers used 80% of a set of 440 abdominal magnetic resonance images (T2-weighted HASTE coronal sequences) from patients with ADPKD. The remaining 20% were used for validation. Kidneys and livers were also segmented manually. An additional test set of images from 100 patients was used to evaluate the method’s performance; of those patients, 45 were also involved in longitudinal analyses.

There was high correlation between TKV and TLV measured by the automated approach and manually traced TKV and TLV (intraclass correlation coefficients, 0.998 and 0.996, respectively), with low bias and high precision (<0.1% for TKV and –1.6% for TLV). The findings were comparable with inter-reader variability of manual tracing (<0.1% for TKV and –1.5% for TLV). For longitudinal analysis, bias and precision were <0.1% for TKV and 1.4% for TLV growth.

The researchers said, “These findings demonstrate a fully automated segmentation method that measures TKV, TLV, and changes in these parameters as accurately as manual tracing. This technique may facilitate future studies in which automated and reproducible TKV and TLV measurements are needed to assess disease severity, disease progression, and treatment response.”

The available data on the effects of uric acid on diabetes concentrate on patients with preserved kidney function. Ko Hanai, MD, PhD, and colleagues in Japan conducted a study to test the hypothesis that among patients with diabetic kidney disease, the effects of serum uric acid levels on the decline in kidney function differ depending on baseline kidney function.

The historical cohort study included 7033 patients with type 2 diabetes; the patients were divided into two groups: those with non-chronic kidney disease (non-CKD), with an estimated glomerular filtration rate (eGFR) >60 mL/min/1.73 m², and those with chronic kidney disease (CKD), with an estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m². The researchers followed the patients for the development of albuminuria and the development of end-stage kidney disease (ESKD). The results showed that the effects of uric acid on the decline in kidney function were significantly different between the non-CKD and CKD groups. The effects of uric acid on the decline in kidney function were stronger in the CKD group compared to the non-CKD group.

The researchers concluded that the effects of uric acid on the decline in kidney function are different depending on the baseline kidney function. These findings highlight the importance of considering the baseline kidney function when evaluating the effects of uric acid on kidney function.

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**References:**

tion rate (eGFR) ≥ 60 mL/min/1.73 m² (n=4994), and those with CKD, with an eGFR < 60 mL/min/1.73 m² (n=2039). The composite end point was a ≥30% decrease in eGFR from baseline or initiation of renal replacement therapy. Multivariate Cox proportional hazards models were used to estimate the hazard ratio (HR) of serum uric acid levels at baseline.

With respect to the end point, there was a significant interaction between uric acid levels and baseline eGFR (P<.001). The HRs of 1 mg/dL increase in uric acid levels were 1.13 (95% confidence interval [CI], 1.05-1.22; P=.002) in the non-CKD group and 0.93 (95% CI, 0.88-0.99; P=.02) in the CKD group. When patients were classified by quintile of levels of uric acid, the HRs of those in the fifth quintile versus the first quintile were 1.64 (95% CI, 1.23-2.18; P<.001) in the non-CKD group and 0.76 (95% CI, 0.58-0.99; P=.05) in the CKD group.

“The effects of uric acid on kidney function decline might differ depending on baseline kidney function in type 2 diabetic patients,” the researchers said. “High uric acid levels are the prognostic factor only in patients with preserved kidney function.”

It’s time for kidney talk

When you see unexplained signs of kidney disease, think Alport syndrome. It can filter through a family.

Incurable disease

- Alport syndrome (AS) is a permanent, hereditary condition responsible for a genetically defective glomerular basement membrane, causing chronic kidney inflammation, tissue fibrosis, and kidney failure.1-6
- Across the entire range of AS genotypes, patients are at risk of progressing towards end-stage kidney disease (ESKD).1,7,8

Hidden signs

- Patients often go undiagnosed, as the clinical presentation of AS is highly variable and family history may be unavailable.9-11
- Persistent, microscopic hematuria is the cardinal sign of AS and should prompt immediate diagnostic investigation—particularly when combined with any family history of chronic kidney disease.9-11,12

Early action

- Expert guidelines published in the Journal of the American Society of Nephrology now recommend genetic testing as the gold standard for diagnosing Alport syndrome.1
- Early AS detection via genetic diagnosis, and its ability to guide a patient’s treatment decisions, demonstrates the powerful impact of precision medicine in nephrology.13

Reata and Invitae have collaborated to offer no-charge genetic testing for rare chronic kidney disease or contact Invitae client services at clientservices@invitae.com or 800-436-3037.

Abnormal kidney function can have a strong family connection—Alport syndrome

Learn more about Alport syndrome at ReataPharma.com.

Abstract Roundup

DIALYSIS

Differences in Technique Failure and Mortality Rates among Peritoneal Systems

Nephrology Dialysis Transplantation. 2019;34(6):1035-1044

Neil Boudville, DMed, and colleagues conducted a study to compare peritoneal dialysis systems. The researchers sought to examine differences in technique failure and patient survival among different peritoneal company systems.

Participants were all patients who initiated peritoneal dialysis in Australia and New Zealand between 1995 and 2014. The groups were identified according to the initial peritoneal dialysis company system they received. The primary outcome of interest was a composite of peritoneal dialysis technique failure and death.

The total cohort included 16,575 patients; the study groups were patients using systems manufactured by (1) Baxter (n=13,438; 81%); (2) Fresenius Medical Care (n=2884; 17%); and (3) Gambro (n=289; 2%). Of those, 11,870 (72%) developed technique failure, including 5421 (33%) who died.

For all patients, median time to technique failure or death was 625 days: 629.5 days with Baxter systems, 620.5 days with Fresenius Medical Care systems, and 538 days with Gambro systems. Compared with patients with Baxter systems, there was a statistically significant increase in technique failure or mortality rates in patients on Gambro systems (adjusted incidence rate ratio [IRR], 1.46; 95% confidence interval [CI], 1.33-1.62) and Fresenius Medical Care systems (adjusted IRR, 1.10; 95% CI, 1.01-1.19).

There were no differences among the three systems in patient survival. The researchers said, “Peritoneal dialysis systems manufactured by different companies may be associated with important differences in peritoneal dialysis technique survival. This needs to be confirmed with adequately powered, prospective randomized controlled clinical trials.”
Effects of Gender Differences in Healthcare Access among Hemodialysis Patients


Women have a higher prevalence of chronic kidney disease than men, yet more men start renal replacement therapy (RRT) compared with women. Researchers, led by Alexander Kainz, PhD, conducted a study to test the hypothesis that there are gender differences in access to healthcare.

The researchers sought to examine whether characteristics and outcomes of hemodialysis patients differ by sex over time.

The study cohort included 28,323 adults in the Austrian Dialysis Registry who initiated hemodialysis from 1965 to 2014. The researchers used Cox regression models to analyze trends in patient characteristics by sex and decade with mortality; those trends were compared with mortality among the general population in Austria.

In conclusion, the researchers said, “The male-female mortality rate ratio and the proportion of women starting hemodialysis were remarkably stable, which does not support the hypothesis of gender differences in healthcare/hemodialysis access, or could imply that such differences might have persisted over decades. Future research should expand to other countries and other forms of RRT.”

PEDIATRIC KIDNEY DISEASE

Association of Higher versus Lower eGFR at Dialysis Initiation and Survival

Journal of the American Society of Nephrology. 2019;30(8):1481-1494

In adults with end-stage renal disease (ESRD), there is no improvement in survival associated with initiating dialysis at a higher level of estimated glomerular filtration rate (eGFR). There are few available data on the association between starting dialysis at higher eGFR and survival in children with chronic kidney disease.

Erica Winnicki, MD, and colleagues conducted a study to examine whether there is a survival benefit of dialysis initiation at a higher eGFR among pediatric patients.

The retrospective cohort study included pediatric patients 1 to 18 years of age who initiated dialysis between 1995 and 2015, according to the US Renal Data System. The primary predictor was eGFR at time of initiation of dialysis, categorized as higher (eGFR >10 mL/min/1.73 m²) versus lower eGFR (eGFR ≤10 mL/min/1.73 m²).

Of 15,170 children identified, 29% (n=4327) had a higher eGFR (median eGFR, 12.8 mL/min/1.73 m²) at time of dialysis initiation. Compared with children with a lower eGFR (median, 6.5 mL/min/1.73 m²), those with higher eGFR at initiation of dialysis were more often white, girls, underweight or obese, and more likely to have glomerulonephritis as the cause of ESRD.

Among children with higher versus lower eGFR at dialysis initiation, the risk of death was 1.36 times higher (95% confidence interval [CI], 1.24-1.50). There were differences by treatment modality (hemodialysis versus peritoneal dialysis) in the association between timing of dialysis and survival: (P < 0.001 for interaction).

In interaction analyses, the mortality risk associated with hemodialysis access type (recorded only in decade 5) was significantly lower for men than for women.
Everolimus-Based Immunosuppression versus Standard of Care
transplantation.2019;103(8):1705-1713

There are few available data on the long-term efficacy of everolimus-based immunosuppression for kidney transplant recipients. Previous randomized controlled trials are limited by short duration of follow-up, making it difficult to assess the impact on graft and patient survival. Tracey Ying, FRACP, and colleagues linked individual trial participants to the Australian and New Zealand Dialysis and Transplant Registry. The researchers used a one-step meta-analysis approach to examine the 10-year risk of graft loss, mortality, and graft function in participants from five randomized trials of everolimus-based immunosuppression.

A total of 242 patients were randomized to everolimus and 107 control patients were followed for a median of 9 years. There were no significant differences between the two groups in the risk of all-cause graft loss (adjusted hazard ratio [HR], 1.16; 95% confidence interval [CI], 0.69-1.94), mortality (adjusted HR, 1.51; 95% CI, 0.78-0.93), or death-censored graft loss in the everolimus group versus the control group (adjusted HR, 1.00; 95% CI, 0.50-2.01).

For the 279 patients in the early initiation (de novo or <6-month conversion) everolimus trials, there was no significant difference between the intervention group and controls in decline in estimated glomerular filtration rate (eGFR) (mean difference in the slope of eGFR 0.01 mL/min/1.73 m²).

“This registry-based analysis with long-term follow-up found no differences in graft and recipient survival or graft function for everolimus over current standard of care,” the researchers said.

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NKF Spring Clinical Meetings

Patient-Reported Burden of Anemia in CKD: Targeted Literature Review

Boston—There are few available data on the burden of anemia in chronic kidney disease on patients. Milena Anatchkova, PhD, and colleagues recently conducted a study designed to summarize the existing evidence on the humanistic burden of anemia in CKD. They reported results of the study during a poster session at the NKF Spring Clinical Meetings in a poster titled Targeted Literature Review of Patient-Reported Burden of Anemia in Chronic Kidney Disease.

The literature review included Medline, EMBASE, and relevant conference proceedings for studies published from January 2013 to June 2018 that reported on humanistic burden of anemia. The outcomes of interest were physical function, mental function, fatigue, sleep, caregiver burden, treatment satisfaction, and adherence.

The literature search of 1101 published studies revealed 43 that met inclusion criteria. Eligible studies were from 23 different countries, including 18 studies from Asia and 13 from North America. The impact of anemia and impact of treatment on physical function and mental function were reported in nearly all of the studies (n=22 and n=23, respectively). Fatigue, adherence, and sleep were examined in 11, nine, and seven studies, respectively. None of the studies reported treatment satisfaction or caregiver burden.

Fifteen of 20 observational studies reported evidence of an association between anemia and physical function. Regarding the impact of anemia on mental function, results were mixed: significant, n=11; nonsignificant, n=12. Results reported on the impact of anemia on fatigue were also mixed: significant, n=5; nonsignificant, n=5. In four of six studies reporting on the association of anemia with sleep, the association was nonsignificant.

Results from three randomized controlled trials were presented in four publications. Of those trials, two described adherence to anemia treatment. Both of the two reported good adherence. A third randomized controlled trial examined low versus high dose erythropoiesis-stimulating agents and reported higher scores for physical function and emotional limitations but not for fatigue or sleep favoring low-dose therapy.

In conclusion, the researchers said, “This review identified strong evidence of the burden of anemia on physical function and mixed results for mental function and fatigue. Limited evidence was available on sleep and treatment adherence, and no literature reported on caregiver burden and treatment satisfaction.”

From the Field

Sarah Tolson

The Ins and Outs of Partial Month Billing for the MCP

In recent months, I have received many questions with a common theme—billing for a partial month of nephrology services for dialysis patients. In this issue, we will examine these questions and their solutions. The questions keep this column relevant, and I appreciate all of you who read this column and send questions.

**Question 1:** One of our home dialysis patients dialyzed at home from the 1st through the 12th and was admitted to the hospital for the rest of the month. Can we bill Medicare for the Monthly Capitation Payment (MCP), or do we need to bill the daily code for the 1st through the 12th?

For home dialysis patients, the home dialysis MCP service can be billed to Medicare if the MCP physician had at least one face-to-face outpatient visit with the patient and furnished a complete monthly assessment—even when the patient was in the hospital for part of the month.

**Question 2:** Last month, one of the home dialysis patients seen in our office had a face-to-face visit with their MCP physician on the 3rd and was admitted to the hospital the morning of the 4th. The patient’s MCP physician saw them twice in the hospital while they were an inpatient, and the patient passed away on the 10th. The patient’s MCP physician didn’t have an opportunity to perform a complete assessment, as the patient was in the hospital. What would be appropriate for the MCP physician to bill in this situation?

Since no complete assessment took place, the MCP physician would bill the age appropriate daily code for the first three days of the month. As the MCP physician saw the patient twice in the hospital, they would also bill the appropriate inpatient evaluation and management code for each encounter with the patient.

**Question 3:** One of the doctors I work for was responsible for the care of an ESRD patient from out of town who was here to visit their family. My doctor rounded at the dialysis facility where the patient received treatment, and the patient came into our office for a visit while they were in town. The patient was in town from September 20th through October 5th. What would our office bill? What about the patient’s nephrologist in their hometown?

In this scenario the physician responsible for the patient while they were out of town would bill one claim with the age appropriate code for daily ESRD related services for September and one for October, as no complete assessment was given. The MCP physician from the patient’s hometown would bill for the MCP service using the code that reflected the number of face-to-face visits they had with the patient during each partial month, as long as the complete assessment was performed.

**Question 4:** On the 20th of last month, the nephrologist whom I bill for was rounding at a dialysis clinic and one of the patients asked if they could transfer their ESRD care to the nephrologist I bill for. The patient’s original MCP physician works for a different nephrology practice. The patient’s care was transferred to our office on the 21st, and they had a complete assessment in our office on the 26th. We billed for the MCP code for one face-to-face visit, but our claim was denied. What would be appropriate for our office to bill in this situation?

Generally, when an ESRD patient changes their MCP physician mid-month, the first MCP physician bills Medicare for the MCP if they have performed a complete assessment, and the new MCP physician bills for the ESRD per day code for the number of days they were responsible for the patient’s care. In the event the first MCP physician does not perform a complete assessment, the new MCP would furnish the complete assessment and bill for the MCP with the appropriate number of face to face visits.

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

The leading cause of morbidity and mortality in patients with chronic kidney disease (CKD) is cardiovascular disease. Patients with CKD are also at increased risk of cardiac rhythm abnormalities including atrial fibrillation and ventricular arrhythmias compared with the general population. Cardiac rhythm abnormalities lead to poor clinical outcomes, including higher rates of death and sudden cardiac death. Identification of preclinical cardiac arrhythmias may provide opportunities for early therapy to improve the poor outcomes in patients with CKD.

Nazem Akoum, MD, and colleagues recently conducted a prospective observational study utilizing mobile cardiac telemetry monitors to study the rate of cardiac rhythm abnormalities. The study cohort included patients with moderate-to-severe CKD (estimated glomerular filtration rate 15 to 60 mL/min/1.73 m² not requiring dialysis) and type 2 diabetes. The researchers sought to test the hypothesis that, as in the dialysis population, rates of preclinical cardiac arrhythmias would be high in the study cohort. Results were reported in the Clinical Journal of the American Society of Nephrology [2019;14(4):549-556].

The observational study CANDY (Continuous Glucose Monitoring to Assess Glycemia in CKD) was conducted...
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