Vascular Disease Contributes to Cognitive Decline in Patients with Kidney Disease

By Bridget M. Kuehn

Chicago—Underlying vascular disease likely explains the high risk of cognitive impairment in patients with kidney disease, according to study results presented at Kidney Week 2016 in November.

Although it is well known that patients with kidney disease are at high risk of cognitive decline, the relationship between the two conditions is unclear, wrote lead author Daniel Weiner, MD, an associate professor of medicine at Tufts University School of Medicine in Boston. To better understand this connection and probe the potential role of vascular disease in these conditions, Weiner and his colleagues analyzed baseline data from a substudy of the Systolic Blood Pressure Intervention (SPRINT) study called SPRINT-MIND.

The SPRINT-MIND study enrolled 9361 participants, including more than 2700 who in addition to kidney disease-related testing completed an extensive battery of cognitive tests and 637 who underwent brain imaging. When Weiner and his colleagues adjusted baseline study data for certain demographic and clinical characteristics, they found that having a higher albumin-to-creatine ratio (ACR) in the urine was associated with worse performance on tests of overall cognitive function, executive function, memory, and attention. In fact, the cognitive effect of each doubling of ACR was comparable to the effect of 6 to 14 months of aging.

Lower estimated glomerular filtration rates (eGFR) also were associated with worse performance on tests of overall cognition and memory. Among patients who underwent brain imaging, higher ACRs were associated with abnormalities in the brain’s white matter, but lower eGFRs were not linked to such brain changes.

“The findings cement the association between kidney damage and cognitive dysfunction,” Weiner said.

Basic Science Helps Decode the AKI to CKD Transition

Until recently, nephrologists may have underestimated the risks that acute kidney injury (AKI) poses to long-term kidney health. But a raft of clinical and epidemiological studies has shown that AKI greatly increases the risk of chronic kidney disease (CKD), end stage renal disease, and death (Coca SG, et al. Kidney Int 2012; 81:442–448).

“There has been a dramatic shift in our understanding of potential patient outcomes following AKI,” said David P. Basile, PhD, associate professor of medicine at Indiana University in Indianapolis, during a symposium at Kidney Week 2016.

A growing understanding of the molecular mechanisms underlying the continuum between AKI and CKD is helping nephrologists better understand why some patients with AKI never fully recover. The discoveries may one day help identify patients with AKI at risk of CKD and lead to kidney-protective AKI interventions.

Capillary loss

A rat model of what was thought to be “reversible AKI” first led Basile and his colleagues to discover permanent vascular damage that could lead to CKD. The rats undergo an ischemia reperfusion injury, and closer study revealed that not all the rats return to normal (Basile D, et al. Am J Physiol 2001; 281:F887–899).
functioning, suggesting that albumin in the urine and changes in brain structure are likely both representations of the same vascular process, just in different organs," said Weiner in a press release. "This manifests with worse brain function, particularly in domains linked to cerebrovascular disease."

The fact that the results came from a large study of a nationally representative population of patients with kidney disease suggests the results may be relevant to "tens of millions of US adults," said Weiner. "It's a great study to take advantage of to look at these relationships," said Anne Murray, MD, MSc, professor of medicine and geriatrics at the Hennepin County Medical Center's Berman Center for Clinical Research in Minneapolis.

The results confirm previous studies that show vascular disease contributes to cognitive decline in patients with chronic kidney disease, Murray said. She noted evidence that the brain and kidneys share many common anatomical and vasoregulatory features; they are low resistance end organs exposed to high-volume blood flow, which may make them especially vulnerable to microvascular damage (Bugnicourt JM, et al. J Am Soc Nephrol 2013; 24:353–363).

"The results also highlight that memory is impaired to a greater extent than executive function, in contrast to some other studies," said Murray. She noted, however, that this result is consistent with results from the Brain in Kidney Disease Study (BRINK) (Murray AM, et al. Am J Kidney Dis 2016; 67:593–600).

One of the study's strengths is that it looked at both ACR and eGFR, which showed that multiple mechanisms are likely involved, Murray said. One limitation is that the mean eGFR was high and the mean ACR was low in this patient population. Only a small percentage of patients had eGFRs below 30, a point at which the risk of cognitive impairment is high, and memory loss becomes more predominant, Murray explained.

"So, it's difficult to interpret the 'dose' effect of lower ranges of eGFR and higher ACR on each outcome," she said.

In the meantime, it is important for clinicians to be aware that patients with eGFRs below 45, especially those with eGFRs below 30, and even somewhat elevated ACRs may be experiencing cognitive decline, Murray said.

"Clinicians should suspect significant cognitive impairment and manage their care accordingly," she said. For example, the patient may not be able to be compliant with their medications so physicians might suggest having a caregiver or family member supervise medication administration. If there are decisions that need to be made regarding access, placement, dialysis initiation, or being placed on the transplant list those discussions should be held with family members present in case the patient's judgment is impaired," she stressed. This is particularly important for patients starting dialysis who are likely to experience further cognitive declines after 3-6 months of dialysis, she noted.

"Cognitive Function and Kidney Disease: Baseline Data from the SPRINT Trial" (Abstract 744)
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A Look into the Future

In my last column I looked back at nephrology in 1966, the year ASN was founded, and marveled at the advances made in the past 50 years. In this column I’ve described my thoughts of what will be roles and activities of the nephrologist of the future, and the way in which kidney professionals will transform that future.

A Look into the Future

There will be an increasing reliance on “big data” to inform our understanding of underlying mechanisms of kidney pathophysiology, and we will have new and more precise tools to analyze the data so that we can break down barriers between basic and clinical research and between disciplines.

• Precision medicine initiatives will provide a better understanding of the interactions of genetic and environmental factors in kidney diseases and will help in the design of more focused clinical trials and more targeted therapies.

• “Telehealth” will no longer be separated from “health.”

• Transplant waiting lists will shrink as the number of suitable kidneys for transplant, though improved allocation strategies and utilization of, telehealth, which can help to provide access to health care for patients in remote or underserved areas.

• We must work to overcome the current problem of insufficient organs for our potential transplant patients. Although improved allocation strategies may incrementally increase the number of suitable kidneys for transplant, ultimately transplant medicine will be transformed by technology, and in the future new technologies, either xenotransplantation or stem cell based technologies, will give all potential kidney transplant patients the chance to receive a functioning organ.

• Nephrology, with its focus on the holistic care of our patients and mastery of all aspects of nephrology, is well suited to lead advances in care, and will help in the design of more focused clinical trials and more targeted therapies.

• It is imperative that nephrologists propell transformative change to assure that the profession will remain vibrant.

• Nephrologists may be uniquely suited to apply their skills, talents, and interests to propel transformative change to assure that the profession will remain vibrant.

• Nephrologists have always excelled at data interpretation.

• Having access to large datasets about human kidney disease will allow more focused preclinical studies by MDs and PhDs, and better integration with, and design of, meaningful clinical studies.

• It is imperative that nephrologists work in concert with all health care agencies, providers, and government agencies to decrease disparities in access to care for our kidney patients both in this country and around the world. One concrete step that we can take is to continue to advocate strongly for increased funding for, and utilization of, telehealth, which can help to provide access to health care for patients in remote or underserved areas.

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• Nephrology, with its focus on the holistic care of our patients and mastery of the complex data involved in their care, is well suited to lead advances in care that alter the lives of all patients, not just those with kidney diseases. We must ensure that all kidney professionals are trained and ready to take on this challenge to shape dramatic and positive changes in the future of medicine and science.

ASN President’s Column

By Raymond C. Harris, MD, FASN

Nephrologists Transforming the Landscape

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Dialysis Outcomes Unchanged after ‘Bundling’ and ESA Label Changes

Five years after the shift to a “bundled” reimbursement system and revised drug labeling for erythrocyte-stimulating agents (ESAs), overall outcomes are no worse—and some outcomes have improved—for hemodialysis patients covered by fee-for-service Medicare, reports a study in *JAMA Internal Medicine*.

The retrospective analysis included data on nearly 70,000 incident hemodialysis patients, 66 years or older, who were enrolled in Medicare parts A, B, or D for at least 12 months before starting dialysis. One cohort initiated hemodialysis before the transition to a bundled comprehensive payment system and ESA labeling changes (2008–09); the other cohort started dialysis after these changes (2011–13).

Differences in outcomes were compared between groups, including major adverse cardiovascular events (MACEs), hospitalization for congestive heart failure, venous thromboembolism, and red blood cell transfusions.

The two cohorts had similar baseline characteristics. There was no difference in the overall risk of MACEs, death, congestive heart failure hospitalizations, or venous thromboembolism. The postpolicy cohort had a significant reduction in stroke, hazard ratio (HR) 0.77.

Use of ESAs decreased after the policy and labeling changes, while the rate of blood transfusions increased: HR 1.09. Subgroup analyses showed significant reductions in MACEs and all-cause mortality.
Adjuvant Sunitinib Improves Survival in High-Risk RCC

Adjuvant treatment with the oral antiangiogenic drug sunitinib increases disease-free survival but increases toxicity in patients with metastatic renal cell carcinoma (RCC) at high risk of recurrence, reports a trial in The New England Journal of Medicine.

The randomized, international, phase 3 trial included 615 patients with locoregional, high-risk clear-cell RCC who had undergone nephrectomy. Intervention patients received sunitinib, 50 mg/d, on a 4-weeks-on, 2-weeks-off schedule. Treatment continued for up to 1 year; controls received placebo. Disease-free survival was compared between groups, along with secondary outcomes.

Sunitinib was associated with significant improvement in disease-free survival: 6.8 months versus 4.7 months in the control group (HR 0.75; 95% CI 0.61 to 0.93; P=0.01).

The findings help to answer concerns that the change to bundled payments and the ESA drug labeling changes might adversely affect clinical outcomes for hemodialysis patients. The results show no overall change in MACEs after these changes, but a significant reduction in stroke. The changes are associated with a decrease in monthly ESA dose and a modest increase in blood transfusions. Black patients showed significant reductions in MACEs and overall mortality (Wang C, et al. Association between changes in CMS reimbursement policy and drug labels for erythropoietin-stimulating agents with outcomes for older patients undergoing hemodialysis covered by fee-for-service Medicare. JAMA Intern Med Published online October 24, 2016. doi:10.1001/jamainternmed.2016.6520).

For the control of serum phosphorus levels in patients with chronic kidney disease on dialysis

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CLINICALLY PROVEN TO MANAGE HYPERPHOSPHATEMIA1-6

• Proven control of serum phosphorus to 4.88 mg/dL at Week 56 (within KDOQI guidelines)8
• Demonstrated safety and tolerability profile over 52 weeks
• A starting dose of 6 tablets a day (2 tablets with each meal) with a maximum dose of 12 tablets a day

References:
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Continued from page 7

High-Risk RCC

versus 5.6 years, hazard ratio 0.76. Overall survival could not be assessed at the time of data cutoff; about 20% of patients had died in the general population. Sunitinib was associated with increased toxicity, including higher rates of grade 3 and 4 adverse events and adverse events requiring dose reductions, interruptions, or discontinuations. The overall rate of serious adverse events was 21.9% with sunitinib and 17.1% with placebo, with no toxicity-related deaths. Previous studies have established that sunitinib, a vascular endothelial growth factor pathway inhibitor, is an effective treatment for metastatic RCC. Two studies show that adjuvant sunitinib can increase survival in patients with locoregional, high-risk clear-cell RCC. Sunitinib is associated with increased toxicity, leading to moderate declines in quality of life during active treatment [Ravandi A, et al. Adjuvant sunitinib in high-risk clear-cell carcinoma].

Findings

Angioplasty and Stenting for Renal Stenosis: Evidence Still Limited

Available evidence shows no consistent benefit of percutaneous angioplasty with stent replacement over medical therapy for patients with atherosclerotic renal artery stenosis (ARAS), concludes an updated systematic review in the Annals of Internal Medicine. A comprehensive literature review identified 83 studies providing evidence on the benefits and harms of PTFAs versus medical therapy for ARAS. Thirty-three studies were newly identified since a 2007 review. The review was funded and followed a standard protocol by the Agency for Healthcare Research and Quality.

The review identified 15 comparative studies including a total of 4006 patients. Of these, 7 were randomized controlled trials (RCTs) including 2178 patients, most enrolled in two large trials (AS-TRAL and CORAL). Five of the RCTs reported similar blood pressure control with ARAS versus medical therapy. None found significant differences in kidney function, mortality, need for renal replacement therapy (RRT), cardiovascular events, or pulmonary edema.

There were 8 nonrandomized comparative studies including 1828 patients. The findings were variable, especially in terms of kidney function and blood pressure. Most of the studies reported no differences in mortality, RRT, or cardiovascular events.

There were few procedure-related adverse events, no deaths, and no medication-related adverse events. Two RCTs reported no patient factors affecting clinical outcomes with either PTFAs or medical treatment. Some relevant patient characteristics were reported in single-group studies, but these were inconsistent. Some case reports suggested clinical benefits of PTFAs in patients with acute decompensation.

The updated review does not find strong evidence that PTFAs is superior to medical therapy alone for most patients with ARAS. Some observational studies suggest improvements in kidney function or blood pressure for certain groups of “high-risk” patients. The researchers write, “Future studies should focus on patients who are putatively most likely to benefit from PTFAs, namely those with proven hemodynamically significant ARAS or those who have signs of compensation” [Raman G, et al. Comparative effectiveness of management strategies for renal artery stenosis: an updated systematic review. Ann Intern Med 2016; 165:635–649].

BRIEF SUMMARY

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

INDICATIONS AND USAGE

AURYXIA® is a phosphite binder indicated for the control of serum phosphorus levels in patients with chronic kidney disease on dialysis.

CONTRAINDICATIONS

AURYXIA® is contraindicated in patients with iron overload syndromes (e.g., hemochromatosis).

WARNINGS AND PRECAUTIONS

Iron Overload: AURYXIA® and IV iron may lead to excessive elevations in iron stores. Increases in serum ferritin and transferrin saturation (TSAT) levels were observed in clinical trials. In a 54-week, safety and efficacy trial in which concomitant use of AURYXIA and IV iron was permitted, 55 (17%) of patients treated with AURYXIA had a ferritin level >1500 ng/mL, as compared with 13 (9%) of patients treated with active control.

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

Adverse Events:

Patients with Gastrointestinal Bleeding or Inflammation: Patients with inflammatory bowel disease or active, symptomatic gastrointestinal bleeding were excluded from clinical trials. Safety has not been established in these populations.

ADVERSE REACTIONS

Because AURYXIA® is administered under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to adverse reaction rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Adverse reactions to a drug are most readily ascertained by comparison with placebo, but there is little placebo-controlled experience with AURYXIA®, so this section describes adverse events with AURYXIA®, some of which may be disease-related, rather than treatment-related.

A total of 289 patients were treated with AURYXIA® and 149 patients were treated with active control (sevelamer carbonate and/or calcium acetate) during the 52-week, randomized, open-label, active control phase of a trial in patients on dialysis. A total of 322 patients were treated with AURYXIA® for up to 28 days in three short-term trials. Across these trials, 557 unique patients were treated with AURYXIA®, dosage regimens in these trials ranged from 210 mg to 2,520 mg of ferric iron per day, equivalent to 1 to 12 tablets of AURYXIA®. In these trials, adverse events reported for AURYXIA® were similar to those reported for the active control group.

Adverse events reported in more than 5% of patients treated with AURYXIA® in these trials included diarrhea (21%), nausea (11%), constipation (8%), vomiting (7%), and cough (6%).

During the 52-week active-control period, 60 patients (21%) on AURYXIA® discontinued the drug because of an adverse event, as compared to 21 patients (14%) in the active control arm.

Patients who were previously intolerant to any of the active control treatments (calcium carbonate and sevelamer carbonate) were not eligible to enroll in the study. Gastrointestinal adverse reactions were the most common reason for discontinuing AURYXIA® (14%) due to AURYXIA® is associated with discoloration (dark stools) related to the iron content, but this staining is not clinically relevant and does not affect laboratory tests for occult bleeding, which detect hemate rather than non-heme iron in the stool.

PATIENT COUNSELING INFORMATION

Dosing Recommendations: Inform patients to take AURYXIA® as directed with meals and adhere to their prescribed diets. Instruct patients on concomitant medications that should be dosed apart from AURYXIA®.

Advise patients that AURYXIA® may cause discoloration (dark stools), but this staining of the stool is considered normal with oral medications containing iron. AURYXIA® may cause diarrhea, nausea, constipation and vomiting.

Advise patients to report severe or persistent gastrointestinal symptoms to their physician.

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ASN News

ASN Aligns Bylaws with New Strategic Plan

Endorsing a more diverse, inclusive, and global society, 93% of ASN Active Members recently approved the first revision of the society’s bylaws since 2006.

In addition to making several “technical corrections” to ensure that the bylaws comply with the new Washington, DC, business organizations code § 29 401.02(24), the revised bylaws help ASN move toward accomplishing its new strategic plan. The new ASN Strategic Plan required two additional changes to the bylaws.

The revised bylaws (available on ASN’s website) change the structure of the ASN Council (the society’s governing body). The new Council structure offers several different opportunities for service. This change is intended to encourage members who are interested in contributing to the Council (but who are not interested in serving as president) to participate. Importantly, the term of service has been reduced from a seven-year to a four-year commitment.

The first change to the bylaws increases the number of ASN Councilors from eight to nine. Four of the nine councilors are elected at-large members who serve staggered four-year terms. At-large councilors are limited to one term, although they are eligible to run for and, if elected, serve one term as an officer or appointed treasurer.

Four of the nine councilors will serve as elected officers. The progression of those elected to Council as officers is Year 1 (secretary), Year 2 (president-elect), Year 3 (president), and Year 4 (past president). Elected officers cannot serve a second term, and are not eligible to serve as at-large councilors or treasurer after completing their term as officers.

Following tradition, the Council will appoint a ninth member as treasurer, who serves one non-renewable four-year term, is eligible to serve as an at-large councilor or officer, and could have previously served as an at-large councilor but not as an officer.

As of this change, active members now have three pathways to become ASN Councilors:

- Serve as an at-large councilor for four years.
- Serve as an officer for four years.
- Be appointed by the ASN Council to serve as ASN Treasurer for four years.

Voting rights

The second change to the ASN bylaws concerns voting rights. Previously, only ASN Active Members (MDs, PhDs, or equivalent who live in North or Central America) had the right to vote. Based on ASN membership data for 2015, less than 50% of the society’s members had the right to vote. As a result of the recent election, ASN Corresponding Members (MDs, PhDs, or equivalent who live outside North or Central America) now have the right to vote (Table 1).

Table 1

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<th>Number</th>
<th>Percentage of total membership</th>
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Many societies that are similar to ASN in mission, focus, and culture have already extended the right to vote to physicians and scientists across the world. ASN now joins these organizations in expanding voting rights.

ASN continues to work with its leadership, contributors from the ASN Communities, as well as kidney health professionals throughout the world, to collect feedback, continue to improve, and maintain its status as a dynamic organization that provides a structure and services to help its members lead the fight against kidney diseases. In 2017, ASN will continue to focus on accomplishing its new strategic plan (http://www.asn-online.org/about/).

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Quality Payment Program: What You Need to Know

By David White

With Kidney Week 2016 in review and the end of the year rapidly approaching, one New Year’s treat is already waiting for everyone. It arrived January 1, 2017, as scheduled. The New Year heralds the beginning of the new Quality Payment Program (QPP) that was created by the Medicare Access and CHIP Reauthorization Act (MACRA).

Congress passed MACRA in 2015 with large bipartisan vote margins in both the Senate and House of Representatives. There is widespread consensus that while parts of the program may have to be adjusted if the Affordable Care Act is repealed or modified, the new Medicare reimbursement program will proceed largely intact.

American Society of Nephrology (ASN) President Raymond C. Harris, MD, FASN, spoke eloquently about the future of nephrology in his Kidney Week President’s Address as ASN marked its 50th anniversary. With the future in mind, Dr. Harris emphasizes that “the move to a quality-driven Medicare payment system and get started.”

Responding to concerns raised by ASN and other peer societies regarding the short timeline to prepare for the new program, Medicare determined that 2017 will be a transition year. As such, the Quality Payment Program in 2017 will have reduced reporting requirements and lower scoring thresholds to allow clinicians the opportunity to adjust to the new reimbursement system. Here’s what everyone needs to know.

Who participates in the Quality Payment Program?
You participate in the Quality Payment Program if you bill Medicare Part B more than $30,000 per year and provide care for more than 100 Medicare patients per year, and are one of the following clinicians:
• Physician
• Physician assistant
• Nurse practitioner
• Clinical nurse specialist
• Certified registered nurse anesthetist

However, if 2017 is your first year participating in Medicare, you will not be required to participate in MIPS.

There are two paths to participation in the Quality Payment Program.
• Merit-Based Incentive Program (MIPS)
• Advanced Alternative Payment Models (APMs)

What is MIPS?
This program replaces three Medicare reporting programs: Meaningful Use (MU), the Physician Quality Reporting System (PQRS), and the Value-Based Payment Modifier (VM). Physicians and practices that participated in the old reporting programs will find that much of MIPS is familiar.

MIPS has four performance categories:
• Quality—Replaces Physician Quality Reporting System (PQRS)
• Cost—Replaces Value Modifier; will not be counted until the 2018 performance year
• Improvement Activity—New category
• Advancing Care Information—Replaces Meaningful Use

What does “Pick Your Own Pace” mean?
Since 2017 is a transition year, you have flexibility in reporting and may select the number of measures and timeframe you report. These four options will enable you to avoid a negative payment adjustment, and in certain cases offer the potential for a positive adjustment, in 2019:
• Test the Quality Payment Program by submitting some data,
• Participate for part of the 2017 calendar year,
• Participate for the full 2017 calendar year, or
• Participate in an Advanced APM in 2017.

Physicians and practices that do not participate at all in 2017 will receive a 4% negative payment adjustment. For more information, visit ASN’s Quality Payment Program resource page and CMS’ updated Quality Payment Program website.

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Telehealth services for home dialysis patients and care for patients with acute kidney injury (AKI) will get a boost from changes to the Physician Fee Schedule and the End-Stage Renal Disease (ERSD) Prospective Payment System (PPS) announced by the Centers for Medicare & Medicaid Services (CMS) in October and November.

The changes, which go into effect in 2017, are part of an ongoing effort by the agency to improve care quality while lowering costs by changing the way care is delivered and clinicians are paid, according to the agency. The changes expand access to outpatient dialysis for patients with acute kidney injury (AKI), encourage telehealth consultations for home dialysis education and advanced care planning, and will allow patients to choose having their nephrologist lead their care.

The new Physicians Fee Schedule will let patients designate their nephrologist as their primary care provider. This allows them to avoid additional visits to a primary care physician on top of coming to a dialysis center three times a week or doing daily home dialysis, said Rajnish Mehrotra, MD, MS, a professor at the University of Washington and nephrology section chief at Harborview Medical Center in Seattle.

“It will be better for patients,” Mehrotra said. “Even nephrologists sometimes lose sight of the enormous burden that the treatment of ERSD places on patients.”

It may also allow nephrologists more time to provide high quality care. For example, Mehrotra noted managing high blood pressure or diabetes requires time for patient education and a good relationship between the patient and the health care team.

It also lays the groundwork for the development of new payment models that will reward nephrologists for coordinating the care of their patients.

“Clearly, this is an area that needs further exploration in demonstration projects, but it seems to be a reasonable first step in recognizing the care that many nephrology practices are already providing,” said Daniel Weiner, MD, MS, associate professor of medicine at Tufts University in Boston.

Acute kidney injury
Perhaps the biggest change for nephrologists is that patients with AKI will now be able to receive dialysis from outpatient centers that serve patients with ERSD. Previously, patients with AKI had to receive dialysis through a hospital, which could be far from home, explained Mehrotra.

“Now, they can go to the dialysis unit in their community,” Mehrotra said.

They also will no longer miss out on the specialized chronic disease care, including social work and dietary advice, that ERSD centers provide, Weiner said.

Services that are needed for patients with AKI, including drugs and lab tests, that are not currently covered as part of the ERSD bundle will be reimbursed by CMS. Weiner stated, however, that there are still some questions about how tests and interventions included in the bundle will be reimbursed. For example, he noted that he would more frequently check kidney function labs, urine clearance, and electrolytes in patients with AKI than in patients with ERSD.

There are also questions about when patients who don’t recover from AKI should be designated as having ERSD.

Overall, the changes are an improvement, Weiner said.

“There remains a lot of work to be done here, including review of payment adequacy, clinical monitoring, and clinical outcomes,” he said. “Hopefully, this year’s PPS rule will be the first step in an iterative process that will mature over time.”

Telemedicine
The rules also boost reimbursement for telehealth services for patients with chronic kidney disease.

Payments for home dialysis training were doubled to $95.60 under the ERSD program. The Physician Fee Schedule also extended coverage for telehealth services for patients receiving dialysis at home and for advanced care planning. Such services avoid unnecessary patient trips to a facility and may increase the likelihood of patients getting care, Mehrotra noted. They also afford patients more privacy than might be possible at a dialysis center for delicate discussions about sensitive issues like end-of-life care, he said.

“Many patients select home dialysis due to logistic considerations that make visiting centers challenging,” said Weiner. “A lot more work is needed to explore how to best incorporate telehealth into dialysis and other nephrology care, but this expanded coverage is a necessary first step.”

New CMS Payment Changes Boost AKI Care, Telehealth

By Bridget M. Kuehn

December 2016 | ASN Kidney News | 11
A New Direction in SHPT

Rayaldee® is the first and only extended-release prohormone of the active form of vitamin D₃ that raises 25-hydroxyvitamin D and lowers iPTH levels.

**Indication and Limitations of Use**
Rayaldee® (calcifediol) extended-release 30 mcg capsules is indicated for the treatment of secondary hyperparathyroidism in adults with stage 3 or 4 chronic kidney disease and serum total 25-hydroxyvitamin D levels less than 30 ng/mL. Rayaldee is not indicated in patients with stage 5 chronic kidney disease or end-stage renal disease on dialysis.

**Important Safety Information**
Hypercalcemia: Excessive administration of vitamin D compounds, including Rayaldee, can cause hypercalcemia and hypercalciuria. Severe hypercalcemia due to substantial overdosage of vitamin D and its metabolites may require emergency attention. Patients should be informed about the symptoms of elevated calcium. • Digitalis toxicity: Potentiated by hypercalcemia of any cause. Monitor serum calcium and signs and symptoms of digitalis toxicity more frequently when...
Rayaldee® (calcifediol) extended-release 30 mcg capsules is indicated for the treatment of secondary hyperparathyroidism in adults with stage 3 or 4 chronic kidney disease and serum total 25-hydroxyvitamin D levels less than 30 ng/mL. Rayaldee is not indicated in patients with stage 5 chronic kidney disease or end-stage renal disease on dialysis.

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• Digitalis toxicity: Potentiated by hypercalcemia of any cause. Monitor serum calcium and signs and symptoms of digitalis toxicity more frequently when initiating or adjusting the dose of Rayaldee.

• Adynamic Bone Disease: Monitor for abnormally low levels of intact PTH levels when using Rayaldee, and adjust dose if needed.

• The most common adverse reactions (≥3% and more frequent than placebo) were anemia, nasopharyngitis, increased blood creatinine, dyspnea, cough, congestive heart failure and constipation.

• Care should be taken while dosing Rayaldee with cytochrome P450 inhibitors, thiazides, cholestyramine or drugs stimulating microsomal hydroxylation due to the potential for drug interactions.

• Serum calcium should be below 9.8 mg/dL before initiating treatment.

• Monitor serum calcium, phosphorus, 25-hydroxyvitamin D and intact parathyroid hormone (iPTH) 3 months after starting therapy or changing dose.

A New Direction in SHPT

Rayaldee® is the first and only extended-release prohormone of the active form of vitamin D3 that raises 25-hydroxyvitamin D and lowers iPTH levels.

Please see Brief Summary of Prescribing Information on following page, and Full Prescribing Information at RAYALDEE.com.
Patients with acute kidney injury (AKI) seen in the emergency department are at increased risk of chronic kidney disease (CKD) and death within 5 years, reports a study from France.

The prospective cohort study included 616 patients admitted to the emergency department of a Portuguese tertiary hospital and followed up for a median of 5 years. Of these, 130 met criteria for AKI. Another 159 had transient azotemia and 15 had stable CKD; the remaining 312 had normal kidney function. Risks of CKD and mortality associated with community-acquired AKI were assessed, along with the added predictive value of plasma biomarkers measured in the emergency department.


Increased CKD Risk after Community-Acquired AKI

INDICATIONS AND USAGE:
RAYALDEE® is a vitamin D3 analog indicated for the treatment of secondary hyperparathyroidism in patients with stage 5 chronic kidney disease or in patients with end-stage renal disease on dialysis. RAYALDEE is not indicated for the treatment of asymptomatic hyperparathyroidism in patients with stage 1 to 4 chronic kidney disease or in patients with a less severe but more common condition.

CONTRAINDICATIONS:
None.

WARNINGS AND PRECAUTIONS:
Hypervitaminosis D: Hypervitaminosis D can occur with oral doses as low as 10 000 IU of vitamin D per day. Symptoms of hypervitaminosis D may include nausea, vomiting, constipation, increased thirst, increased urination, and weight loss.

Adynamic bone disease with subsequent increased risk of fractures may develop if toxic levels of vitamin D are present. Symptoms of vitamin D toxicity include weakness, fatigue, paresthesias, or muscle weakness.

Increased risk of fractures may develop if vitamin D toxicity is present. Symptoms of vitamin D toxicity include weakness, fatigue, paresthesias, or muscle weakness.

Lactation:
Calcifediol is excreted in human milk. Caution should be exercised when RAYALDEE is administered to a nursing woman.

OVERDOSAGE:
Overdosage of RAYALDEE can cause hypercalciuria, hypercalcemia, and associated renal toxicity. The treatment of acute accidental overdosage with RAYALDEE should consist of general supportive measures, with administration of fluids at a rate to maintain urine output. Serum calcium concentrations should be closely monitored if a patient initiates or discontinues therapy with phenobarbital or rifampin.

No specific antidotes have been established [see Indications and Usage].

DIAGNOSIS AND TREATMENT IN AMALGAMATED POPULATIONS

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RAYALDEE is not indicated for the treatment of asymptomatic hyperparathyroidism in patients with stage 1 to 4 chronic kidney disease or in patients with a less severe but more common condition.

1. The new study shows a fivefold increased predictive ability for both markers: HR 5.7; and death, HR 1.9. In a model predicting both markers, patients with AKI were at significantly increased risk of chronic kidney disease or death: CKD: HR 2.4. 
2. Criticalillness patients who survive an episode of AKI have a known increase in the risk of progression to CKD. Less is known about the risk of CKD or death associated with community-acquired AKI, a less severe but more common condition.

The new study shows a fivefold increase in the risk of stage 3 CKD among patients with community-acquired AKI, compared to emergency department patients with normal renal function. The AKI patients also show a modest but significant increase in mortality risk. The researchers conclude: “Our findings highlight the importance of follow-up of patients with community-acquired acute kidney injury, for potential early initiation of renal protective strategies” [Soto K, et al. The risk of chronic kidney disease and mortality are increased after community-acquired acute kidney injury. Kidney Int 2016; 90:1090–1099].

Compared to cyclosporine, belatacept-based immunosuppression improves long-term outcomes in extended criteria donor (ECD) kidney recipients, reports a study in the American Journal of Transplantation.

The researchers present 7-year follow-up data on 543 kidney recipients from the “Belatacept Evaluation of Nephroprotection and Efficacy as First-Line Immunosuppression Trial—Extended Criteria Donors” (BENEFIT-EXT) study. Patients were assigned to primary immunosuppression with a more-intensive or less-intensive belatacept regimen, or to a cyclosporine regimen. Patient and graft survival and estimated glomerular filtration rate (eGFR) were assessed at 7 years follow-up.

With both the more- and less-intensive belatacept regimens, time to death or graft loss was similar to that with cyclosporine. At 7 years, mean estimated eGFR was 53.9 mL/min/1.73 m² with more-intensive belatacept and 54.2 with less-intensive belatacept, compared to 55.3 with cyclosporine. Patients receiving less-intensive belatacept were less likely to meet a composite endpoint of death, graft loss, or eGFR of 20 mL/ min/1.73 m² or less: hazard ratio 0.706.

Acute rejection rates and safety outcomes were similar across regional. The belatacept groups had lower rates of de novo donor-specific antibodies.

Belatacept might have advantages for ECD transplant recipients, who may be more vulnerable to nephrotoxicity from calcineurin inhibitors. As in the 5-year results, ECD kidney recipients receiving belatacept show improvement in eGFR through 7 years’ follow-up. Risks of death and graft loss were similar with belatacept versus cyclosporine, as are safety outcomes [Durbach A, et al. Long-term outcomes in belatacept-versus cyclosporine-treated recipients of extended criteria donor kidneys: final results from BENEFIT-EXT, a phase III randomized study. Am J Transpl 2016; 16:3192–3201].

Belatacept Improves Long-Term Renal Function after ECD Kidney Transplant
Smoking Counteracts the Benefit of Medications for Kidney Disease

Smoking has been linked to worsening kidney disease, according to a study presented at Kidney Week 2016.

Lowering systolic blood pressure to 120 mmHg or less was found to reduce deaths by 27% compared to standard blood pressure control after an average follow-up of 3.26 years in the Systolic Blood Pressure Intervention Trial (SPRINT). The SPRINT trial enrolled 9361 adults age 50 or older at high risk of cardiovascular disease. Participants were randomized to either intensive blood pressure control (≤120 mmHg) or standard blood pressure control (≤140 mmHg). The trial excluded individuals with diabetes, stroke, polycystic kidney disease, and several other characteristics (SPRINT Research Group, N Engl J Med 2015; 373:2103–2116).

Now, Tisha Joerla Tan, MD, of Loyola University Medical Center, and her colleagues have used data from the National Health and Nutrition Examination Survey (NHANES), an annual nationally representative survey of the US population, to estimate how many US individuals would benefit if the right blood pressure control were applied to those who meet the criteria used in the SPRINT trial. The analysis included adults age 50 or older with a systolic blood pressure between 130 and 180 mmHg depending on how many antihypertensives they were taking, and one or more risk factors for cardiovascular disease. Individuals with diabetes, a history of stroke, proteinuria greater than 1g/d, heart failure, or an estimated glomerular filtration rate (eGFR) ≤20 mL/min/1.73 m² were excluded from the analysis.

About 18 million US adults met SPRINT criteria and Dr. Tan and her colleagues estimated that applying intensive blood pressure control to these individuals would prevent about 100,000 deaths each year. The researchers also estimated the number of deaths that could be prevented among adults with eGFRs between 20 and 59 mL/min/1.73 m².

“Our analyses also showed that more than 4 million adults with stage 3–4 chronic kidney disease meet SPRINT criteria, and intensive systolic blood pressure lowering was projected to prevent 32,800 deaths per year in this group,” said Dr. Tan in a press release.

The SPRINT trial has demonstrated that intensive lowering of blood pressure can provide cardiovascular benefits and reduce deaths, said George Thomas, MD, director of the Center for Blood Pressure Disorders at the Cleveland Clinic in Ohio. But he also noted it is important to remember that patients with uncontrolled hypertension on multiple medications, diabetes, past strokes, or with severe kidney disease were excluded. And NHANES doesn’t provide all the information needed to determine all SPRINT exclusion criteria, he said.

“Additionally, the risks of intensive therapy need to be kept in mind,” he said. “It is not possible to predict who would experience a benefit and who would experience harm.”

Patients who were intensively treated in the SPRINT trial had higher rates of hypotension, syncope events, electrolyte abnormalities, and acute kidney injury compared with the standard group, explained Dr. Thomas. Additionally, it may be more difficult to monitor for potential adverse events in practice than in the trial.

“Patients in the trial were very closely followed and blood pressure measurements were done with an automated device following a very strict protocol for measurement,” Dr. Thomas said. “In real-world practice, this may not happen and the adverse events may potentially be higher.”

Longer-term data from the SPRINT trial on quality of life, neurologic effects, and long-term kidney outcomes in intensively treated patients may help clinicians decide who might benefit from tighter blood pressure control, Dr. Thomas said.

In the meantime, he recommended that clinicians carefully measure patients’ blood pressure, and closely monitor patients whose blood pressure is being tightly controlled. This monitoring should include kidney function and electrolyte levels. “Pros and cons of intensive therapy need to be discussed with patients, and blood pressures goals should be individualized rather than taking a one-size-fits-all approach,” Dr. Thomas said.

“Intensive Blood Pressure Lowering Will Prevent Over 100,000 Deaths Annually” (Abstract 2229)
Use of Palliative Care Lags Among Minority Patients at the End of Life

Use of palliative care among patients with end stage renal disease (ESRD) has increased steadily since 2004, but use among minority patients lags behind whites, according to a study presented at Kidney Week 2016.

Palliative care, which focuses on comfort measures and may include discontinuing dialysis, may ease the burden for patients with ESRD who are nearing the end of life. To help ensure that patients are advised about the option of palliative care, the Centers for Medicare & Medicaid Services included voluntary end-of-life counseling in the 2016 physician fee schedule, wrote lead author Haytham Alkhaimy, MD, of Augusta (Georgia) University and his colleagues in their abstract.

“In medicine, unfortunately we sometimes prolong suffering,” said Alkhaimy. “We shouldn’t be shy about talking about palliative care at some point.”

Alkhaimy and his colleagues analyzed all deaths of patients receiving dialysis between 2004 and 2011 in the United States Renal Data System (USRDS) to see how many received palliative care or discontinued dialysis at least 4 days before death. Among the 874,777 patients who initiated dialysis during that period, 52% had died by the end of 2012.

Use of palliative care increased from 4% to 20% of dialysis patients in the database between 2004 and 2011, according to the analysis. “This is good news,” Alkhaimy said. “We have been using palliative care more.”

Patients who received palliative care were significantly more likely to be older at the start of dialysis (72±12 vs. 67±14 years). Women made up 47% of the palliative care patients vs. 44% of nonpalliative care patients.

Patients who had more hospitalizations were also more likely to receive palliative care (RR 1.04), likely because these patients had exposure to more physicians or to hospitals with palliative care units, suggested Alkhaimy.

Palliative care did not appear to hasten death, as there was no significant difference in the time to death between the two groups.

“If you go into palliative care you may think your life will be shorter, but this shows it will be the same,” Alkhaimy said. The analysis included all patients who had a palliative care code under ICD9, he said. Some may have continued dialysis while receiving palliative care, which may have prolonged life.

Patients whose causes of death were coded as cardiovascular, gastrointestinal, metabolic, vascular, or infection-related were less likely to receive palliative care. “If you have a heart attack or something immediate there may not be time to go into palliative care,” Alkhaimy explained.

There were also significant differences between the use of palliative care by minority patients and white patients. About 80% of the patients receiving palliative care were white, 17% were black, and only 3% were from other minority groups.

The study could not explain the reasons behind the differences in palliative care utilization between groups, noted Alkhaimy. He said there is a need for more studies, including prospective studies, about the use of palliative care to help understand its use in patients with ESRD.

There are likely multiple factors that might contribute to disparities in the use of palliative care, said L. Ebony Boulware, MD, MPH, chief of the division of general internal medicine at Duke University School of Medicine.

“Evidence shows that there are differences in patient preferences, patient-provider communication, education, and lack of trust among minorities, all of which could influence receipt and use of palliative care,” Boulware said.

Studies aimed at understanding patient, provider, and system level factors that influence use of palliative care in dialysis patients are warranted, she said. In particular, identifying barriers to palliative care, especially for minorities, might help explain the patterns identified in the study.

“Efforts to educate patients as well as providers and to make both aware of the role of palliative care in the context of dialysis may be critically needed,” Boulware said.

In the meantime, Alkhaimy suggested that clinicians educate themselves about palliative care so they can discuss the option with patients who might benefit. He acknowledged that end-of-life care options are a difficult topic to discuss, which may cause physicians to hesitate.

“You don’t want to be uncomfortable,” he said. “You don’t want the patient to be uncomfortable.”

But he noted that if a patient is nearing the end of life and has a poor quality of life as a result of dialysis or other treatments, failing to discuss palliative care may prolong their suffering.

“Palliative care is sometimes needed for comfort measures and to improve a patient’s quality of life,” he said.

“Racial Disparities in the Utilization of Palliative Care in Dialysis Patients from the United States Renal Data System” (Abstract 4963)

Poor Sleep Increases Kidney Failure Risk

Chicago—Too little and poor quality sleep are associated with a greater risk of kidney failure, according to results from the Chronic Renal Insufficiency Cohort Study (CRIC) presented at Kidney Week 2016.

While sleep disorders are common in patients with chronic kidney disease (CKD), how poor sleep may affect disease progression is not clear, according to the study’s lead author Ana C. Ricardo, MD, MPH, an assistant professor in the division of nephrology at the University of Illinois College of Medicine at Chicago.

So Ricardo and her colleagues conducted a prospective study of 432 adults enrolled in the CRIC study at 2 centers. The CRIC study is a longitudinal, multicenter study that has followed nearly 4000 people with CKD for several years. Participants in the sleep study wore a wrist activity monitor for 5–7 days to record their sleep duration and sleep quality. They also filled out questionnaires about their sleep quality, daytime sleepiness, and risk of sleep apnea. The participants were then followed for an average of 5 years during which 70 developed end stage renal disease (ESRD) and 48 died.

An average night of sleep for participants in the study was 6.5 hours, and about 1 in 5 participants experienced sleep interruptions. For every extra hour of sleep, the researchers found a 19% lower risk of developing ESRD when they controlled for several factors, including body mass index, blood pressure, baseline kidney function, and cardiovascular disease (HR 0.81, 95% CI 0.67–0.99 per hour increased sleep length). Patients who had more interrupted sleep also had increased risk of developing ESRD with a 4% increase in risk for every 1% increase in sleep fragmentation (HR 1.04, 95% CI 1.01–1.07 per 1% increase in sleep fragmentation). More fragmented sleep was also linked to declines in eGFR (-0.17 mL/min/1.73 m²/ year, p=0.016).

“Short sleep and fragmented sleep are significant, yet unappreciated risk factors for CKD progression,” Ricardo said. “Our research adds to the accumulating knowledge regarding the importance of sleep on kidney function, and underscores the need to design and test clinical interventions to improve sleep habits in individuals with CKD.”

Earlier this year, another study that followed 4238 participants in the Nurses’ Health Study for 11 years found that nurses who reported sleeping less were at higher risk for more rapid declines in their estimated glomerular filtration rate (McMullen CJ, et al. Kidney Int 2016; 89:1524–1530).

While the previous study suggested a link between shorter sleep duration and earlier stages of CKD, the Ricardo study strengthens the evidence by linking sleep duration to ESRD, said Mark J. Sarnak, MD, MS, Director of Research in the Division of Nephrology at Tufts Medical Center. The CRIC Study also used more objective measures of sleep duration and quality than the previous study.

How reduced or poor quality sleep might contribute to declining kidney function is less clear, Sarnak noted.

“A valid question is whether quantity or quality of sleep is a causal risk factor for kidney function decline or have we not sufficiently adjusted for covariates that may be associated with both poor sleep and kidney function decline,” Sarnak said.

Larger studies that adjust for such factors as well as additional mechanistic studies may help answer these questions and lay the groundwork for studies of potential interventions that improve sleep quality and slow progression of kidney disease, he said.

Although there is not yet enough evidence to definitively say that sleeping better will reduce the progression of kidney disease, there is sufficient evidence to show that sleep is important for overall health, Sarnak noted.

“Clinicians should be asking questions about sleep and educating patients about healthy sleep hygiene,” he said.

“The Association of Sleep Duration and Quality with Chronic Kidney Disease Progression” (Abstract 3754).
Positive Results for Transplant Intervention and Liraglutide

By Bridget M. Kuehn

A safe, inexpensive pre-transplant intervention can reduce graft loss and mortality, according to late-breaking trial results presented during Kidney Week 2016.

During the late-breakers session at the meeting, the positive results from the REPAIR study of remote ischemic preconditioning (RIPC) were accompanied by reassuring data on the renal outcomes from the LEADER trial of Liraglutide in type 2 diabetes. Other preliminary studies presented at the meeting found positive results for medications for lupus nephropathy and focal segmental glomerulosclerosis (FSGS), as well as some positive results for rapid withdrawal of steroids in transplant patients. But a trial of low-sodium dialysate did not find a benefit.

Transplant protection

Together, the rush of blood that flows into a newly transplanted kidney and the period of reduced oxygen just before transplant may permanently damage the organ. This damage may reduce kidney function and the life of the transplant.

But some evidence has suggested that preconditioning the organ by briefly limiting blood flow prior to the transplant can protect against these injuries by triggering the body's protective mechanisms (Veighey K and MacAllister R. *Pediatr Nephrol* 2015; 30:1749–1759).

Now, Kristin Veighey, MB, MRCP, a nephrologist and research fellow at the University College London Centre for Nephrology, and her colleagues have shown that using a blood pressure cuff to briefly limit blood flow to the upper arm in the living donor and recipient just before surgery can reduce graft loss and substantially cut recipient mortality.

In the REPAIR study (http://repair.lshtm.ac.uk/), Veighey and her colleagues randomized 406 live donor/recipient pairs to placebo, RIPC just prior to surgery, RIPC 24 hours before surgery, or both. At the meeting, Veighey presented 5-year follow-up data that found sustained improvements in adjusted average eGFRs at 1 year in the RIPC group compared to placebo at 2, 3, 4, and 5 years, although the overall eGFR difference was not significant. The study also found reduced graft loss in the early RIPC group compared with placebo (5% vs. 6%), and reduced mortality in the early vs. placebo groups (2% vs. 5%). No adverse events were documented in the intervention groups.

“Based on the fact that this is safe, it is easy to deliver, and it is virtually cost-neutral at the point of delivery, we would advocate that this is something we should be offering to our patients as part of routine practice in this setting,” Veighey said.

The potential benefits of RIPC were first shown in cardiology, and we are now starting to see them in nephrology, said Gretchen Brandt, MD, a nephrologist at Kaiser Permanente in Washington, DC. She noted that it is remarkable to see a clinically significant improvement in mortality and graft function in live donor patients, who already tend to do well.

“The potential benefits of RIPC were first shown in cardiology, and we are now starting to see them in nephrology, said Gretchen Brandt, MD, a nephrologist at Kaiser Permanente in Washington, DC. She noted that it is remarkable to see a clinically significant improvement in mortality and graft function in live donor patients, who already tend to do well.

The trial was well designed, said Brandt, though she noted the trial used dialysate sodium levels that were on the ends of the spectrum to see a difference. At her institution, for example, she noted that the standard dialysate sodium level is somewhere in the middle at 137 mEq/L. She also noted that left ventricular mass is a surrogate marker and that it might be difficult to see a difference in a 9-month trial.

“I wouldn't give up hope that there are future studies that see a difference 2 to 5 years out,” Brandt said.

In the meantime, she suggested that clinicians watch for hypotension in patients during dialysis.

“Patients in the low-dialysate arm were often hypoensive,” she explained.

Other studies presented at the meeting suggested benefits to rapid steroid withdrawal in low-risk kidney transplant patients, and provided preliminary evidence for the safety and efficacy of new agents for lupus nephropathy and FSGS.

- **The HARMONY Trial**, which enrolled 615 low-risk Caucasian kidney transplant patients, and tested the effect of rapid steroid withdrawal with standard immunosuppressive therapy, did not meet its primary endpoint of reduced acute rejections at 12 months. But rapid withdrawal did nearly cut diabetes among transplant recipients in half.

- **The phase 2 AURA-LV trial** of calcitriol-inhibitor voroclosporin for lupus nephritis (LN) (n=265) met its primary endpoint, with 32.6% of low-dose treated patients and 27.5% of high-dose patients achieving complete remission at 24 weeks compared with 19.3% of the placebo group. It also met its secondary endpoints. But the treatment group also had more adverse events and a higher mortality rate than placebo. A phase 3 trial is planned.

- **Sparsenta**, a dual angiotensin II and endothelin type A receptor antagonist, had more of an effect on proteinuria, a surrogate endpoint, than angiotensin II antagonist with ibrsartan in patients with focal segmental glomerulosclerosis in the phase 2 DUET trial, which enrolled 96 patients. Sparsartan was also well tolerated.
**Higher BMI May Explain Women’s Lower Risk of End Stage Renal Disease Compared with Men**

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ifestyle factors, particularly higher body mass index (BMI), appear to explain the lower risk of end stage renal disease (ERSD) in women compared with men, according to data from the Chronic Renal Insufficiency Cohort (CRIC) Study presented at Kidney Week 2016.

The incidence of ERSD is 1.5 times higher in US men than women even though women live longer and are more likely to have chronic kidney disease (CKD), said Ana C. Ricardo, MD, MPH, MS, assistant professor of medicine at the University of Illinois at Chicago. Some studies have shown that men with CKD progress more quickly (Neugarten J, et al. Am Soc Nephrol 2000; 11:319–29). The effect of gender on CKD progression has been hotly debated for years. Until about 15 years ago there was a consensus that gender had no effect, then the prevailing view shifted to see female gender as protective, said Joel Neugarten, MD, JD, professor of medicine at Albert Einstein College of Medicine. A large meta-analysis published 2 years ago reignited the debate when it found no gender-based difference in CKD progression (Ninth D, et al. BMJ 2013; 346:f3524), a result Neugarten attributed to the high number of patients with diabetic renal disease in the study.

Now, Ricardo and her colleagues are wading in to the debate with an analysis of the relationship between gender and progression to ERSD (determined based on dialysis or transplant and estimated glomerular filtration rate) in the Chronic Renal Insufficiency Cohort (CRIC). The CRIC study followed 1778 women and 2161 men for an average of about 7 years. The average age of study participants was 58; 42% were non-Hispanic black and 13% were Hispanic. They found that at the start of the study women were more likely than men to be physically inactive (33% vs. 28%), never have smoked (53% vs. 39%), and have a higher BMI (33 vs. 31 kg/m²). During the study follow-up period, 844 participants developed ERSD, and women’s risk was lower, but nearly disappeared when the researchers adjusted for lifestyle factors, including smoking, physical activity, and BMI.

“In the unadjusted analysis, in men kidney function tended to get worse over time at a more rapid rate than women,” Ricardo said. But after the researchers adjusted for baseline kidney function and markers of bone and mineral metabolism, the gender differences in progression became less significant. Adjusting for lifestyle factors also reduced the differences.

Adjusting for BMI alone appeared to attenuate the risk of ERSD on its own in women. This “obesity paradox” has also been documented in previous studies, Ricardo noted. “We know that in the general population obesity is a risk factor for cardiovascular disease and death; however, in dialysis patients having higher weight or BMI is protective,” she explained.

Higher rates of smoking among men did not appear to explain the differences.

“In other studies, we’ve seen that smoking has a deleterious effect [on the kidney],” Ricardo said. “But for this particular study it didn’t appear to play a significant role in terms of gender disparities.”

The risk of mortality in women was 40% lower than in men, Ricardo said, so more women were not dying before reaching dialysis or transplant. “It’s a well-studied, well-followed cohort that confirms a relationship between gender and renal disease,” said Neugarten.

But it also raises questions about the role of sex hormones in CKD progression. For example, if estrogen were protecting women from faster progression of renal disease you would expect younger women to be protected and older women to progress more quickly. “But younger women had accelerated progression compared to older women,” Neugarten said. “That’s contrary to what I would have predicted.”

The findings on BMI were also surprising. There isn’t a clear mechanism to explain this relationship, Neugarten noted. Also, BMI as a measure is considered by many to be flawed, he said. But other studies that have used waist circumference or other measures of obesity have found contradictory results as well.

“The consensus is that high BMI accelerates renal disease, but many investigations have found that it is protective,” he explained. “We don’t know.”

In future analyses, Ricardo and her colleagues plan to look at whether estrogen helps protect women from ERSD. They also plan to look at whether gender differences in endothelial function between men and women play a role.

In the meantime, she noted that many of the factors that appear to put men at greater risk based on her analysis are modifiable. For example, interventions might include management of phosphorus, calcium, or addressing issues related to socioeconomic status.

“We could potentially bring the risk of men down,” Ricardo said.

She said her analysis also identified important disparities in the care women receive. Women were less likely to receive cardioprotective medications, like ACE inhibitors, angiotensin inhibitors, statins, or aspirin. They were also less likely to be seen by a nephrologist.

“We nephrologists need to see if we are treating women the same way as men,” she said.

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**Organoids Derived from Patients with Kidney Disease May Aid Research**

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icago—Stem cells from patients with polycystic kidney disease have been coaxed into growing into kidney-like structures, which may aid researchers studying the disease, according to a study presented at Kidney Week 2016.

Ryuji Morizane, MD, PhD, an instructor and scientist in the Brigham and Women’s Hospital Renal Division in Boston, and his colleagues presented data on how they grew the kidney-like structures, called kidney organoids. They also described the features of the kidney organoids and the disease features they recreate.

Improvements in cell culturing technology have allowed scientists to coax stem cells into growing into organoids that recapitulate many of the features of kidneys, lungs, the gut, brain, and retina (Clevers H. Cell 2016; 165:1586–97). Scientists can use organoids to study organ development and disease processes in the laboratory, noted Hans Clevers, MD, PhD, professor of molecular genetics at the Hubrecht Institute in Utrecht, Netherlands, in his review. Organoids derived from the cells of patients with diseases, in particular, hold the promise to aid personalized medicine, he noted.

Morizane and his colleagues had previously developed a method to grow kidney organoids from human pluripotent stem cells that have the basic features of the kidney, including segmented nephron structures containing podocytes, proximal tubules, loops of Henle, and distal tubules juxtaposed to interstitial cells. Now, they have applied this method to pluripotent stem cells collected from patients with autosomal recessive polycystic kidney disease (ARPKD). The patients’ cells grew into kidney organoids that had large cysts in the tubules, just like those seen in patients with ARPKD.

“Establishment of a novel platform to model ARPKD using human kidney organoids will facilitate studies on mechanisms of cyst formation and contribute to the development of chemical screening systems to find potential therapeutic agents for polycystic kidney disease,” said Morizane.

The work may also lay the groundwork for one day growing transplantable kidneys in the laboratory.

“Our organoid system enables in vitro studies of kidney pathophysiology, nephrotoxicity assays, and disease modeling, and ultimately will lead to development of bioengineered kidneys for regenerative medicine,” Morizane said.

Cleviers said Morizane’s study builds on work by another laboratory that has generated kidney organoids from human stem cells (Takasato M, et al. Nat Proc 2016; 11:1681–1692). It also demonstrates the potential of stem cells to form remarkably organ-like structures.

“This beautiful study builds on earlier work by Melissa Little and her colleagues in Melbourne,” Clevers said. “It is amazing to witness again the self-organizing capacity of stem cells. The only thing missing from these mini-kidneys is the plumbing: blood vessels and ureter.”

“Kidney organoids derived from human pluripotent stem cells contain multiple kidney compartments and model polycystic kidney disease” (Abstract 2139).
Raising Awareness during Nephrology Rounds

By Lourdes Gonzalez Suarez, MD, PhD

The US nephrology community has been concerned about lower numbers of trainees in Nephrology in recent years. A trend of fewer applicants to nephrology has been noted since 2011. Between 2013 and 2014, there were a slightly higher number of Nephrology Programs and fellowship positions opening. This led to a higher number of available positions than the number of applicants available to fill those positions in 2014 and 2015. This problem, if it remains unsolved, could translate into a possible future decline of the nephrology workforce and of nephrologists’ ability to meet the needs of patient care in the US.

Fortunately, several measures are improving this situation. The fellowship Match timeline changed in 2013: Instead of choosing a specialty at some early point during PGY-2 and matching in the spring of that same academic year, we now have more time to choose a specialty up to the beginning of the PGY-3, and the Match has been delayed until December of that academic year. This change has allowed more time to evaluate options, which may be beneficial, especially for those residency programs where nephrology rotation may have been included at a later time in the PGY-2. Following institution of the ASN initiative for all nephrology fellowship programs to participate in the Match, and to fill all their positions through the Match, an increase in filled positions was seen for the 2016 academic year. There was a slight increase in the number of applicants during this year alone. If this trend continues, potentially in upcoming years this “crisis” of unfilled positions may become history.

As nephrology fellows, we may be able to contribute to solutions to the challenge of ensuring a robust nephrology workforce. We play an important role in introducing nephrology to medical students and residents. We usually spend more time with our team members in training than do our attending staff. Therefore, we have an additional opportunity to make an impact and inspire our peers to consider nephrology.

We need to remind ourselves of the particular aspects of nephrology that caught our attention and inspired us to pursue a career in the field. Our interest might have been piqued in different stages of our medical training. To some of us it occurred when we were medical students; to others it may have been while working as hospitalists for some years before deciding to train in Nephrology. This exercise may help us find key elements of our own experience in choosing nephrology that we may share with others.

Several small changes can make a difference in how the nephrology rotation is experienced. Here I summarize some of the most common scenarios that we can take advantage of to engage our peers in our specialty:

• Take a walk. During walking rounds, we may be able to take advantage of those moments in between patients to share our knowledge in a collegial and learning environment. Topics shared may vary according to the clinical cases being seen. Any spare moment may be full of fun facts about nephrology history, ranging from how the first dialysis came to be, to how the first transplants were performed. These facts and conversations may help increase interest in the field.

• Ask questions. It is important to keep questions short and to the point and to base them on clinical scenarios of patients seen by the team, especially those concepts that are tested. Asking questions may help our peers recognize possible gaps in knowledge, tailor their study sessions, and perhaps focus their interest. This will help in board exam preparation as well.

• Engage in hands-on activities. In many instances, it is better to practice skills than just learn the theory. Engage your team in the physical exam. At the bedside, teach them how to examine fistulas and how to differentiate them from grafts. This tool is specific to nephrology and may be interesting for our peers in training to familiarize themselves with. If a point-of-care ultrasound is available, take a look at the kidneys. Placing central venous access for hemodialysis may be another important skill to learn during nephrology rotation.

• Don’t miss an opportunity to use formulas. Formulas are one of the most challenging parts of our specialty, and are certainly considered when deciding whether or not to apply to nephrology. Given the opportunity to practice them, our peers in training may feel more comfortable using these calculations and learning their merits. Some of the barriers to understanding may be overcome if time is spent working on these formulas and sharing tips on how to simplify and solve acid–base disorders, for example.

• Visit the lab. It should be interesting to all the members of the team to take a look at urine samples under the microscope to make a diagnosis. Urinalysis is a fundamental and inexpensive diagnostic tool, providing a great amount of information that can lead to diagnosis of certain pathologies. Visiting the lab is a good opportunity to emphasize the importance of our field.

Remember, if we are able to transmit our joy and passion for nephrology, we may inspire our peers to enter the field. The future of nephrology is now in our hands; let’s make the best of it.

Lourdes Gonzalez Suarez, MD, PhD, is a third year nephrology fellow at Mayo Clinic in Rochester, MN.

New Drug for Secondary Hyperparathyroidism Approved in Europe

Amgen’s drug etelcalcetide (“Parsabiv”) has been approved for marketing in Europe, through a decision by the European Commission announced in November 2016. Applications are also pending in the United States and Japan for etelcalcetide, which treats secondary hyperparathyroidism (SHPT) in adult patients with chronic kidney disease (CKD) who are on hemodialysis. In Europe, the prevalence of SHPT within dialysis populations ranges from 30% to 49%. Medscape reports. The EC approval covers 28 countries in the EU; Norway, Iceland, Liechtenstein, and members of the European Economic Area (EEA), can take corresponding decisions based on the EC decision.

The drug is the first calcimimetic agent to be given intravenously by a healthcare provider at the end of a hemodialysis session, three times weekly.

John Canningham, MD, professor of nephrology at University College London Medical School, noted in Amgen’s announcement that treatment failures among patients with SHPT are common. “Parsabiv provides a new tool that should give physicians more confidence that patients are getting the medication they need to treat their SHPT,” Cunningham said.

In SHPT, excessive parathyroid hormone is secreted by the parathyroid gland and promotes phosphorus and calcium movement from bone, which can cause joint pain. The new medication binds to and activates the calcium-sensing receptor on the parathyroid gland and decreases parathyroid hormone levels.

The marketing application for etelcalcetide included data from three phase 3 studies, all of which met their primary endpoints, including two pooled placebo-controlled trials in more than 1000 patients and a head-to-head study comparing Parsabiv with cinacalcet (Sensipar, manufactured by Amgen).

Amgen submitted a new drug application for etelcalcetide to the US Food and Drug Administration in August 2015, but the FDA has yet to look favorably on the drug application. In August, the FDA issued a Complete Response Letter for the New Drug Application (NDA) for Parsabiv”.

According to the FDA website, a complete response letter provides a more consistent and neutral mechanism “to convey that our initial review of an application is complete and we cannot approve the application in its present form.” The agency said the letter provides a more consistent approach to informing applicants of changes that must be made before an application can be approved, with no implications about whether the drug will ultimately be approved. Amgen says it is reviewing the Complete Response Letter and anticipates a meeting with the FDA late in 2016.

In January 2016, Japanese drugmaker Ono Pharmaceuticals filed a manufacturing and marketing approval application in Japan for etelcalcetide, for the same indication, Pharmaletter.com reported. Ono has been working to commercialize the medication since 2011, when it entered into an exclusive licensing agreement with former KAI Pharmaceuticals (now a subsidiary of Amgen) to develop etelcalcetide.
Dysproteinemias and Glomerular Disease

By Paisit Pauksakon and Agnes B. Fogo

What is the current terminology for dysproteinemia-related kidney disease?

Dysproteinemias are characterized by abnormal Ig molecules or fragments and result from clonal proliferation of plasma cells or B lymphocytes. Thus, an alternative term for dysproteinemia is plasma cell dyscrasia (PCD). PCDs are classified clinically on the basis of several external parameters, including percentage of plasma cells in the bone marrow, the presence of a monoclonal (M) spike on serum protein electrophoresis (SPEP) or urine protein electrophoresis (UPEP), osteolytic lesions on skeletal survey, and hypercalcemia. When the combination of findings meets precise criteria, patients may be classified as having multiple myeloma.

In 2012, the term monoclonal gamopathy of renal significance (MGRS) was introduced by the International Kidney Monoclonal Gamopathy Research Group. This approach distinguishes monoclonal gamopathy of undetermined significance, which has an isolated monoclonal spike on serum and/or urine electrophoresis without end organ damage, from MGRS, which is defined as kidney dysfunction due to monoclonal Ig (M Ig) deposition.

Where do monoclonal proteins deposit in the kidneys?

PCDs can cause disease in any compartment of the renal parenchyma, including glomeruli, tubules, interstitium, and blood vessels. These distribution patterns are mostly determined by the physicochemical properties of the pathogenic M Ig. Light chain cast nephropathy (LCNN) is a purely tubulointerstitial pattern of renal injury due to the precipitation of light chain (LC) initially in the lumens of distal tubules, causing inflammatory reaction and injury. Approximately 90% of patients with LCNN have multiple myeloma, often with a high tumor burden. In contrast, LC proximal tubulopathy (LC Fanconi syndrome) is characterized by proximal tubular injury and intracellular crystalline deposits of monoclonal LC.

Occasionally, LC proximal tubulopathy occurs in combination with AL amyloidosis (LCDD). The spectrum of renal diseases induced by M Ig also includes Ig-related amyloidosis (Alg); monoclonal Ig deposition disease (MIDD), which includes light chain deposition disease (LCDD), light and heavy chain deposition disease, and heavy chain deposition disease; most patients with immunotactoid glomerulopathy; and proliferative glomerulonephritis with monoclonal IgG deposits (PGN-MID). Many cryoglobulins also have a monoclonal component. Most of these diseases have glomerular deposits, with varying deposits elsewhere. Amyloid deposits have randomly arranged fibrils, usually only light chain (AL) but rarely with heavy chain components or light and heavy chain components. These deposits are predominantly present in glomeruli and blood vessels and occasionally present in the interstitium. Nonorganized, punctate, powdery deposits are characteristic of MIDD; classically, they are along the inner aspect of glomerular basement membranes (Figure 1), causing nodular sclerosis, and they are also seen on the outer aspect of the collecting ducts. AL amyloidosis is a purely tubulointerstitial disease with no glomerular deposits. In immunotactoid glomerulopathy, the deposits are localized to glomeruli, causing focal proliferative or mesangio-proliferative lesions, with microtubular substructure. PGN-MID shows granular electron-dense mesangial and/or subendothelial deposits with no substructure, mimicking usual immune complex deposits, but composed of only a single light chain and β heavy chain subclass without tubular basement membrane deposits (1–11).

M Ig may also trigger other injuries due to complement activation triggering C3 glomerulopathy or membranous nephropathy due to M Ig reacting to the phospholipase A2 receptor (11). Of note, multiple patterns of paraprotein deposition frequently coexist in a single renal biopsy specimen. In our experience, almost 50% of patients with LCDD show coexistent LCCN. Combined LCDD and AL amyloidosis are also relatively common, whereas combined LCDD and AL amyloidosis are rare due to the underlying mechanisms promoting specific organization and deposition (e.g., β-pleated sheet formation in amyloid versus partial unfolding in LCDD).

How do patients with MGRS present?

The spectrum of renal manifestations in patients with PCDs is wide and varies according to the disease type and molecular characteristics of the pathogenic M Ig. Acute kidney injury (AKI) and proteinuria with or without hematuria are the most common presenting findings. Patients with major glomerular involvement, such as AL amyloid, MIDD, immunotactoid glomerulopathy, and PGN-MID, classically present with nephrotic-range proteinuria. Recently, a subset of patients with LCDD has been recognized to have limited proteinuria with dominant tubular deposits. Cryoglobulinemic GN often presents as mixed nephritic/nephrotic syndrome, often with systemic signs of vasculitis. In contrast, patients with LCNN present with less proteinuria and ALK, whereas those with LC proximal tubulopathy often show partial Fanconi syndrome. Of note, testing for monoclonal proteins in urine and serum (SPEP and/or UPEP) is a routine part of the prebiopsy evaluation of proteinuric adult middle-aged or older patients. However, in our practice, about 50% of patients undergoing renal biopsy with some evidence of a monoclonal protein had kidney disease unrelated to monoclonal protein.

What factors predict outcome?

Insufficient data on the outcome of patients with dysproteinemia-associated glomerular disease are available. A recent report from The International Kidney Monoclonal Gammopathy Research Group identified several independent factors associated with poor renal outcome in patients with dysproteinemia. In the multiple logistic regression model, the strongest predictor of renal outcome was the presence of monoclonal proteinuria. The presence of monoclonal proteinuria was associated with a higher risk of renal failure, death, or transplantation. This finding highlights the importance of early detection and treatment of dysproteinemia to prevent renal damage.

What novel therapies are emerging?

In the future, the development of novel therapies for dysproteinemia-associated glomerular disease is likely to be accelerated by advances in our understanding of the pathophysiology of these diseases. One promising approach is the use of monoclonal antibodies that can selectively target the monoclonal protein. These antibodies can inhibit the binding of the monoclonal protein to its receptors, thereby preventing the formation of immune complexes and the deposition of monoclonal protein in the renal tissue. Additionally, the development of new drugs that can disrupt the immune response to the monoclonal protein is also an area of active research. This approach has the potential to reduce the formation of immune complexes and the deposition of monoclonal protein in the renal tissue, thereby preventing the progression of glomerular disease.
Figure 1. Light chain deposition disease

Extensive powdery deposits along inner aspect of the glomerular basement membranes (transmission electron microscopy; original magnification, 5600).

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