ASN LEADING THE FIGHT AGAINST KIDNEY DISEASE

KidneyNews

March 2012 | Vol. 4, Number 3

Researchers Look to Solar Power to Make Dialysis Greener

By Tracy Hampton

Solar power can help offset the high utility costs of hemodialysis, making the treatments more environmentally friendly, report scientists in Australia. The findings, published recently in the *Clinical Journal of the American Society of Nephrology*, point the way to a "green dialysis" future when resources are used and reused wisely.

Hemodialysis treatments for kidney failure patients require a considerable amount of basic utilities such as water and power, leaving a vast carbon footprint behind that is sure to grow as the incidence and prevalence of dialysis use inevitably rise worldwide. "As our planet's population continues to grow, so does the sustainable growth rate of the dialysis patient population. This annual growth rate is now expected to be 6 percent, which will give us roughly 4 million patients by 2025," said Faissal Tarrass, MD, head of the department of hemodialysis at the Hospital Princessa Lala Meriem, in Morocco.

Demands of dialysis

Research indicates that each hemodialysis treatment uses more than one half the daily power consumption of an average Australian four-person home, and power prices are predicted to soar to two to three times the current rate over the coming decade in Australia. Yet little thought has yet been given to addressing the resource demands of dialysis.

To see whether solar energy might be used to help meet the power demands of dialysis equipment, John Agar, MBBS, Anthony Perkins, and Alwie Tjipto, MBBS, of Geelong Hospital, Barwon Health, in Victoria, Australia, established a solar-assisted dialysis program in Geelong (located in southeastern Australia) that included four home dialysis machines. For solar comparison, Geelong is comparable with St. Louis, Missouri.

Previously, the investigators conducted other resource conservation initiatives that addressed water reuse practices and recycling of reject water. They successfully developed interventions that have reduced water losses of up to 100,000 L per week across their facility and home hemodialysis sites. For example, reject water from the hospital-based dialysis unit provides

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No Reduction from Paracalcitol on Left Ventricular Mass in CKD Patients, but Other Outcomes Hint at Benefit

Forty-eight weeks of paracalcitol, the active hormonal form of vitamin D, doesn't reduce left ventricular mass or most measures of cardiac function in patients with stage 3 or 4 chronic kidney disease (CKD), according to a study published in the Feb. 15 *Journal of the American Medical Association*. But there was one intriguing finding: treatment reduced left atrial volume and improved some clinical outcomes, setting the stage for larger studies to explore whether treatment with paracalcitol has a role in treatment of CKD patients.

"Cardiac hypertrophy is exceedingly common in patients with chronic kidney disease, both before and on dialysis," according to Ravi Thadhani, MD, lead investigator and director for clinical research in nephrology at the Massachusetts General Hospital in Boston. CKD patients are "profoundly deficient" in vitamin D, and observational studies and animal models have suggested that vitamin D might reduce left ventricular hypertrophy. It was that hypothesis that Thadhani and colleagues set out to test

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Solar Power

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autoclave steam for instrument sterilization, ward toilet flushing, janitor stations, and garden maintenance. Satellite center reject water is tanker-trucked to community sporting fields, schools, and gardens. Home-based nocturnal dialysis patient reuse reject water is used for home domestic utilities, gardens, and animals. A natural progression for the team was to move from water to power.

The group chose solar power above wind power for this study because solar radiation is silent and, because it penetrates clouds, more dependable. Wind is unpredictable, and harnessing its power can cause noise and visual pollution. This study represents the first known and reported solar project in dialysis.

For their study, the investigators used the simplest solar model: array donation to, and service draw from, the national grid. The power generated by the solar array was metered and recorded before being directed to the national grid, permitting weekly tracking of all grid-donated power and power drawn specifically for dialysis-related use.

Cutting costs, saving resources

After the first 12 months of the program (from July 26, 2010, to July 25, 2011), power costs were reduced by 76.5 percent. Interestingly, the authors report that from a "what has the weather been like" assessment of Geelong, the 12-month study period was one of the worst remembered; however, solar exposure is not entirely dependent on sunshine and sunlight.

In the coming years, the system is expected to turn a profit in addition to generating effectively free power. A solar array is estimated to have a lifespan of approximately 30 years.

"Geelong Hospital is showing that renewable power for dialysis is both practical and cost-effective," said Frances Mortimer, MRCP, who was not involved with the research and is the medical director of the Centre for Sustainable Healthcare in Oxford, UK.

"Professor Agar's article provides a timely reminder of the environmental impacts of the delivery of health care and of renal medicine in particular," said Andrew Connor, MD, who was the Centre for Sustainable Healthcare's first Green Nephrology Fellow (2009–2010). "It's inspiring to see practical measures being put into place to reduce these impacts and to realize financial benefits simultaneously." Connor, who is in the department of renal medicine at Derriford Hospital, in Plymouth, UK, has published widely in the field of sustainable health care.

Directors of dialysis services may wish to investigate whether they can take similar steps toward greener dialysis, taking into account that charges for grid-provided power and reimbursement rates for grid-donated power from alternative sources such as the sun or wind will vary from place to place and from power company to power company.

"Although not all locations, purchasing environments, or local administrations will be suitable or supportive, the twin issues of environmental degradation and climate change demand that simple ecoassessment is made and solutions sought," the authors wrote.

They encourage the dialysis community to assess the solar exposure records at their home geographic position, which can be done at http://www.wunderground.com/calculators/solar. With local latitude and longitude coordinates, investigators can obtain tables and graphs for the mean daily, weekly, monthly, or annual solar exposure of a particular location.

"Knowing the expected local solar exposure, available solar arrays, local purchase and installation costs, power rates charged by local utilities, any predicted price changes, and local reimbursement rates for grid-contributed power, a simple calculation can determine whether solar-assisted power might be financially viable," the authors wrote.

The researchers also advocate for applying water conservation and improved waste management systems (such as those that use steam sterilization of post-dialysis plastic waste before shredding) to dialysis programs. "For too long, we have (ab)used but have not considered the environmental consequences of that (ab) use. It is time to change that paradigm," they wrote.

Connor has worked to spread this same message in recent years by leading work to determine the carbon footprints of renal services and different dialysis regimens. In the UK, his work within the Green Nephrology Programme has included recruiting a network of Green Nephrology Local Representatives in over half of the nations' kidney units, surveying the environmental practices of these units, and developing tools to reduce their impacts through case studies.

"One of the challenges for the future must now be to drive down the emissions generated in the production of dialysis consumables," Connor said.

Protecting the environment is a worthy cause in itself, but there may be additional motivation to green nephrology because patients with kidney disease are particularly vulnerable to the effects of climate change. For example, extremes of weather can disrupt dialysis services and negatively affect the health of these patients, who are particularly at risk in very hot weather.

Disclosure: Fresenius Medical Care (Australia) provided the funding and secured the technical advice to resource the project.

The article "Solar-Assisted Hemodialysis" is available online at http://cjasn.asnjournals.org/, doi: 10.2215/CJN.09810911.

Paracalcitol

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in the study. He chose to use paracalcitol, rather than the dietary form of vitamin D, because the conversion to the hormonal form takes place in the kidneys, and is impaired in CKD.

The primary endpoint in the study was left ventricular mass index (LVMI) as determined by cardiac MRI, "the gold standard," Thadhani said. Prespecified secondary endpoints included changes in diastolic mitral annular relaxation velocity (E'), changes in B-type natriuretic peptide (BNP), and several measures of left ventricular function. The trial, known as PRIMO (Paracalcitol Capsule Benefits in Renal Failure-Induced Cardiac Myopathy) was investigator-initiated, and funded by Abbott Laboratories.

The study took place at 60 centers in 11 countries, which required a coordination and standardization effort Thadhani characterized as "very labor-intensive." It enrolled 227 patients, with a mean age of approximately 65. Most patients had hypertension, and many were receiving medication for it. Patients were randomized to receive either placebo or paracalcitol for 48 weeks. Early and sustained reduction in parathyroid hormone levels in the active-treatment group indicated good compliance throughout the study.

At the study's end, there was no significant difference between the treatment arms in LVMI, even after a sensitivity analysis to account for patients with missing data or those lost to follow-up. While unexpected, Thadhani said, "I think it is an important result, because it gives us an idea of where the signal may not be," and therefore will guide the design of future studies. There was also no difference in E', a measure of left ventricular relaxation.

There were, however, clear differences between the groups on other secondary endpoints. B-type natriuretic peptide increased in both groups, but favored active treatment. While total hospitalizations did not differ between groups, there was only one cardiovascular event requiring hospitalization in the active treatment group, but eight in the placebo group, five of them for congestive heart failure.

Perhaps most intriguingly, there was a significant reduction in left atrial volume in patients receiving paracalcitol compared to placebo-treated patients (p=0.003), with the change occurring gradually and steadily over the 48 weeks. This outcome measure was not prespecified but instead was exploratory, Thadhani noted, "so we have to be cautious. But all together, the hospitalizations, the BNP, and the left atrial volume begin to define a treatment signal pointing to diastolic function." The change in atrial volume was not accompanied by any changes in blood pressure.

"What we think is happening is that the drug is allowing better relaxation during diastole, therefore allowing the heart to have a stronger squeeze. The heart's ability to relax is better, and as a result its ability to pump is better. The signal is a functional, rather than structural, change." He noted that animal studies suggested this effect from paracalcitol as well.

"We are cautiously optimistic that we have a signal, one that could explain the outcomes. It was not the signal we were expecting, but one could argue that we could not plan a larger study without knowing where the signal lay, and now we have that better understanding." Planning for a larger trial is now underway. Thadhani noted that if the effect on atrial relaxation is confirmed, it would make paracalcitol unique among cardiac drugs, most of which reduce blood pressure as they relax the heart.

Thadhani cautioned that therapy with paracalcitol was associated with more episodes of elevated calcium, and that paracalcitol, like other agents that activate the vitamin D receptor, can elevate serum creatinine without changing glomerular filtration rate. "Clinicians need to be aware of these two consequences of the therapy," he said.

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ASN LEADING THE FIGHT AGAINST KIDNEY DISEASE

Kidney News

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ASN Kidney News is published by the American Society of Nephrology
1510 H Street NW, Suite 800, Washington, DC 20005. Phone: 202-659-0599

www.asn-online.org

Postmaster: Please send address changes to *ASN Kidney News*, c/o Customer Service, American Society of Nephrology 1510 H Street NW, Suite 800, Washington, DC 20005.

Publications mail agreement No. 40624074. Return undeliverable Canadian addresses to PO Box 503, RPO West Beaver Creek, Richmond Hill ON L4B 4R6

ASN Kidney News (ISSN print 1943-8044 and online 1943-8052) is an official publication of the American Society of Nephrology, 1510 H Street NW #800, Washington DC 20005, and is published monthly. Periodicals postage paid at Washington, DC and at additional mailing offices. Subscription rates: $12 per year. To order, please email bhenkel@asn-online.org. Subscription prices subject to change. Annual ASN membership dues include $12 for *ASN Kidney News* subscription.

ASN News

ASN Geriatric Nephrology Advisory Group Awarded Prestigious Grant

By Grant Olan

ASN's Geriatric Nephrology Advisory Group (GNAG) recently won a $25,000 grant from the Association of Specialty Professors (ASP) for improving competency in palliative end-of-life care among nephrology fellows.

GNAG is pleased to announce that the ASP grant will support the Dimitrios G. Oreopoulos Visiting Professor Program. This program, named in honor of the longtime GNAG chair and lifetime leader in the field of geriatric nephrology, will help foster exposure of fellows and faculty in Accreditation Council for Graduate Medical Education (ACGME)-certified nephrology fellowship training programs to issues related to palliative and end-of-life care.

Nephrology training programs have not traditionally emphasized training in end-of-life care, and research suggests that nephrologists are often not comfortable addressing the end-of-life needs of their patients. Nephrologists and other providers involved in the care of older patients with advanced kidney disease have a unique opportunity to improve the quality of end-of-life care for this population. Training a future generation of nephrologists how to manage the end-of-life needs of their older patients with kidney disease is a critical component in achieving this goal.

The program will provide $1425 in travel support for visits from a nationally recognized expert in end-of-life care for up to five nephrology fellowship programs ($7125 total). GNAG is now accepting applications. The deadline to apply is 11 p.m. ET on May 1, 2012. For more information, please visit www.asn-online.org.

The visiting professor program builds on GNAG's longstanding commitment to advancing nephrologists' understanding of end-of-life care, including GNAG's development of the ASN Geriatrics Nephrology Online Curriculum in 2009. The curriculum addresses the most significant aspects of caring for aging patients with kidney disease (including assessing GFR in the elderly, drug dosing and renal toxicity, management of ESRD in elderly patients, and end of life decision making) and is free for all members of ASN and the renal community, physicians, students, and other providers at http://www.asn-online.org/education_and_meetings/distance-learning/curricula/geriatrics/.

The ASP grant will also support GNAG's efforts to update and enhance the end-of-life and palliative care content in the ASN Geriatrics Nephrology Online Curriculum, and to improve access to this resource and other online educational resources related to end-of-life care for fellows and faculty in ACGME-certified nephrology fellowship training programs.

ASN Presents Award to Dimitrios G. Oreopoulos, MD, PhD

By Grant Olan

On February 1, 2012, Vanita Jassal, MD, PhD, presented Dimitrios G. Oreopoulos, MD, PhD, an ASN Award of Recognition for his many contributions to ASN and the nephrology community. The award was presented in Ontario during a citywide nephrology rounds webcast. Dr. Jassal read notes from Dr. Oreopoulos's colleagues, including a recognition letter from current ASN President Ronald J. Falk, MD, FASN, that calls Dr. Oreopoulos "a tireless advocate for the needs of patients with kidney disease."

Dr. Oreopoulos has been a mentor to several generations of nephrologists and inspired many others to do the same. Among his many accomplishments and achievements, Dr. Oreopoulos helped create the ASN Geriatric Nephrology Advisory Group. In a few short years, the advisory group has become a robust forum dedicated to improving the care of older adults with kidney disease, produced several signature activities (including ASN's Geriatric Nephrology Online Curriculum, the ASN Annual Meeting Geriatric Program, and the NephSAP issue on geriatric nephrology), and ensured that geriatric nephrology is strongly represented within ASN.

Dr. Oreopoulos's influence and legacy will continue in the many initiatives that he established. To watch the award presentation, visit: http://mediasite.otn.ca/mediasite41/Viewer/?peid=4bcb4ce6c25c44d4accbe2de6110a2d41d

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Prognostic Indices Offered for Decisions with Older Patients

By Eric Seaborg

Many clinical guidelines—including a recent one on dialysis—recommend taking a patient's life expectancy into account in selecting treatments, but accurate prognostic tools are hard to find and use, especially amid the time constraints of a busy practice.

A new website could make life expectancy judgments for older patients easier and more accurate by offering automated calculators that provide patient-specific statistical likelihoods after a few clicks of a mouse. The calculators are backed up by a recent review article in the *Journal of the American Medical Association* (1).

"Ignoring prognosis and life expectancy can lead to poor care," said study coauthor Sei Lee, MD. Patients are often treated with therapies that they will not live long enough to benefit from. Those with life-threatening conditions are often referred to hospice too late to appreciate its benefits. And age-based recommendations may withhold appropriate treatment from those who are unusually hale and hearty for their chronologic age.

"Life expectancy is often not accounted for in medical decision-making, so we tried to make it easier for doctors and other health-care providers by collecting all of the life-expectancy calculators that we could find in a systematic review and putting them in one place so that people could just go to one place and find what they needed," Lee told *ASN Kidney News*. He is an assistant professor of medicine in the geriatrics division at the University of California, San Francisco.

After a literature search, the researchers screened some 20,000 prognostic indices. They ruled out disease-specific indices, focusing on all-cause mortality in patients over 60 years old. They found 16 indices that passed the test of being developed in one cohort and validated in another with a level of accuracy deemed "moderate" to "very good." The indices apply to different populations, including those living at home, in nursing homes, and in hospitals.

The researchers then used the parameters delineated in each report to create automated calculators and published them at a website, Eprognosis.org. The researchers urge caution in their use because none of the prognostic indices has been completely tested for routine use, but they propose that the indices provide some objective information beyond a physician's intuition and experience.

None is specific to nephrology, but measures of kidney health are important contributors to some. For example, the Inouye burden-of-risk illness score for nonterminal hospitalized persons 65 years and older has an accuracy rating of "good." It gives a patient who on admission has chronic renal failure, an albumin level of 3.5 g/dL or lower, a creatinine level above 1.5 mg/dL, and no other risk factors (such as cancer, stroke, congestive heart failure, diabetes with end-organ damage, or dementia) a 32 percent 1-year mortality risk. The addition of a single additional risk factor raises this risk to 61 percent.

"I think that it is a very important review," said Mark A. Swidler, MD, a nephrologist and associate professor of medicine, geriatrics, and palliative medicine at Mt. Sinai School of Medicine in New York City, who was not involved in the review.

"It draws attention to the importance of prognostic indices because we have an aging population that is living longer with a greater amount of comorbid conditions and geriatric syndromes, some of whom are facing dialysis decisions or are on dialysis. It is important to have methods to quantify the contributions of those conditions and syndromes to the patients' survival. However, we're not only talking about survival. Geriatric decision-making is also about quality of life, which is most reflected in optimizing mental function and functional status. Eprognosis is useful because it provides calculators, so all you have to do is put in the appropriate numbers and then you get an answer," Swidler said. A clinician could bring up the calculator on a smart phone while talking to a patient but would be unlikely to perform the calculations required otherwise.

Swidler agreed with the review authors, who noted that more work remains to be done to make prognostic indices more helpful for routine use. Also, although prognostic information is important in a patient's decision to choose or forego dialysis therapy, these indices have not been validated in dialysis or other nephrology populations.

Prognosis is especially relevant to high-impact treatments such as dialysis and transplantation. The 2010 edition of the Renal Physicians Association guideline on initiating and withdrawing dialysis emphasizes the need to estimate prognosis and survival time. The chair of the panel that drew up the guideline, Alvin H. Moss, MD, told *ASN Kidney News,* "The physician should learn the patient's values, wishes, and goals for care and make a treatment recommendation, also taking into account the patient's prognosis and overall condition. It is a shared decision-making process, about what course of treatment the patient would want given the patient's condition. The prognostic information is very helpful in that process."

Although some indices have been developed that are more applicable to nephrology patients than are those at Eprognosis.org, most are not as accessible as calculators. However, Moss helped create an easy-to-use calculator for patients already undergoing dialysis, "The Surprise Question—Dialysis Mortality Predictor."

Rethinking dialysis in the elderly?

The consideration of prognosis could lead to some rethinking about dialysis, especially because the fastest-growing age group to be starting dialysis is made up of those 75 and older. The average life expectancy of a 75-year-old starting dialysis is 1.5–2 years, so the wisdom of the treatment was called into question by a study showing that the start of dialysis is associated with a substantial and sustained decline in functional status in nursing home residents with ESRD, published in 2009 in the *New England Journal of Medicine* by Manjula Kurella Tamura, MD, and associates (2).

An assistant professor of medicine at Stanford University, Kurella Tamura has a prognosis-oriented article coming out in *Kidney International* that provides a framework for individualizing ESRD management decisions in older patients by incorporating life expectancy and patient preferences to assess the risks and benefits of competing treatment strategies (3). "We tried to look at decisions like vascular access placement or referrals for kidney transplant, because life expectancy has a substantial effect on the potential benefits of those interventions," she told *ASN Kidney News*.

Most guidelines recommend an arteriovenous (AV) fistula rather than an AV graft or a catheter as the first access type in patients beginning hemodialysis, but the recommendation may not apply equally to all. AV fistulas have

Calculator Estimates Prognosis of Dialysis Patients

At least one nephrology-centric mortality calculator is available on the Internet for estimating the prognosis of dialysis patients.

"There has been a real need to have these types of prognostic indices when you are sitting down to talk to a patient about advance care planning," said the index co-developer, Alvin H. Moss, MD. "In conversations with the patient and the patient's family about what type of treatment the patient would want at the end of life, it's very helpful to have some background objective information to give them an idea of how things look for them for the future." Dr. Moss is director of the Center for Health Ethics and Law and professor of medicine at West Virginia University.

The calculator can be found at www.touchcalc.com as "The Surprise Question—Dialysis Mortality Predictor." The simple questionnaire consists of "the surprise question" ("I would [or would not] be surprised if my patient died in the next 6 months") as well as the patient's serum albumin level, age, presence or absence of dementia, and presence or absence of peripheral vascular disease. It provides percentages for predicted 6-month survival, 12-month survival, and 18-month survival.

The index has a c-statistic accuracy of 0.8, which is about as good as any of the calculators on Eprognosis. It was developed in a cohort of 512 patients and validated in a cohort of 514.

The index has not been validated in patients with chronic kidney disease before dialysis, but that is the next step on Moss's research agenda. "There is every reason to believe that it would be accurate and helpful, but we haven't confirmed that," he said.

The research behind the calculator is found in "Predicting six-month mortality for patients who are on maintenance hemodialysis," *Clin J Am Soc Nephrol* 2010; 5:72–79.

fewer complications like access-related bloodstream infections than do AV grafts or catheters, but they take longer to mature, so patients with limited life expectancies may not realize the benefits. Kurella Tamura and her team estimated that for the average 75-year-old patient, one would need to treat 25 patients with an AV fistula rather than an AV graft to prevent one episode of access-related infection. "That to us seems like quite a large number of patients. In contrast, you would only have to treat two patients with an AV graft vs. a catheter in order to prevent one bloodstream infection. That suggests that a fistula may not be the access of first choice for some patients," she said.

The article says that perfectly accurate predictions of life expectancy are not needed: "Reasonable estimates of whether a patient is above or below the median life expectancy for his or her age will allow clinicians to make better assessments of the risks and benefits of various management strategies."

The article also contains life expectancy estimates for dialysis patients of different ages broken into quartiles. For example, in the 75–79 age group, 25 percent of the patients can be expected to live 3.7 years, 50 percent to live 1.7 years, and 25 percent to live 6 months or less. Swidler said that the Eprognosis indices could be helpful in placing patients into these quartiles and talking meaningfully to them about how they want to optimize their quality of life and spend their remaining time.

In an editorial in *JAMA* that accompanied the prognostic indices review, Thomas M. Gill, MD, of Yale cautions, "Despite the proliferation of prognostic indices for mortality, there is currently no evidence that their routine use improves patient outcomes. To determine whether use of a previously validated prognostic index is better than usual care, an impact study must be conducted."

The review article agrees that "further research is needed before general prognostic indices for elderly individuals can be recommended for routine use." But Lee said that he would "absolutely encourage" clinicians to use the indices "with a grain of salt" to improve on the use of clinical experience alone.

Physicians too optimistic?

Studies have shown that physicians tend to be too optimistic in estimating life expectancy. "When you compare clinician intuition vs. an index vs. a combination of both, the combination always wins, and so I would argue that this piece of information is a valuable adjunct to clinical intuition and has been shown to lead to more accurate predictions," Lee said.

A potentially controversial aspect of Eprognosis.org is that its presence on the Internet makes it accessible to the general public. Patients can access it simply by clicking the button saying that they are health professionals. The researchers left it accessible because anything that would have made it harder for the public to use would have made it less accessible to physicians. Lee acknowledged that even sophisticated patients may not understand the limitations of the indices.

Public accessibility can be seen as a part of the movement toward shared decision-making, observers said. "We're moving toward an age where consumers are better informed," said Moss, a nephrologist and medical ethicist at West Virginia University. "But drawing conclusions from Eprognosis.org is not something that patients should do independent of having a discussion with their doctor."

"I think families and patients have to be involved and be given the choice of getting the information," Swidler said. "Dialysis in certain subgroups of the elderly ESRD population is very challenging. You are signing up for a treatment program that is a big commitment. And up until now, I don't think there has been enough available information for the public to really know what the reality is and make good decisions."

Lee said that he has been using prognostic indices for years in his geriatrics and palliative care practice for discussions with patients: "It really opens the door. Some patients quickly let me know that they don't want to talk about it, and I recommend specific care incorporating life expectancy into my recommendations, but I don't ever explicitly talk about it. For other patients, they have been thinking about it, and it feels like flood gates are opening."

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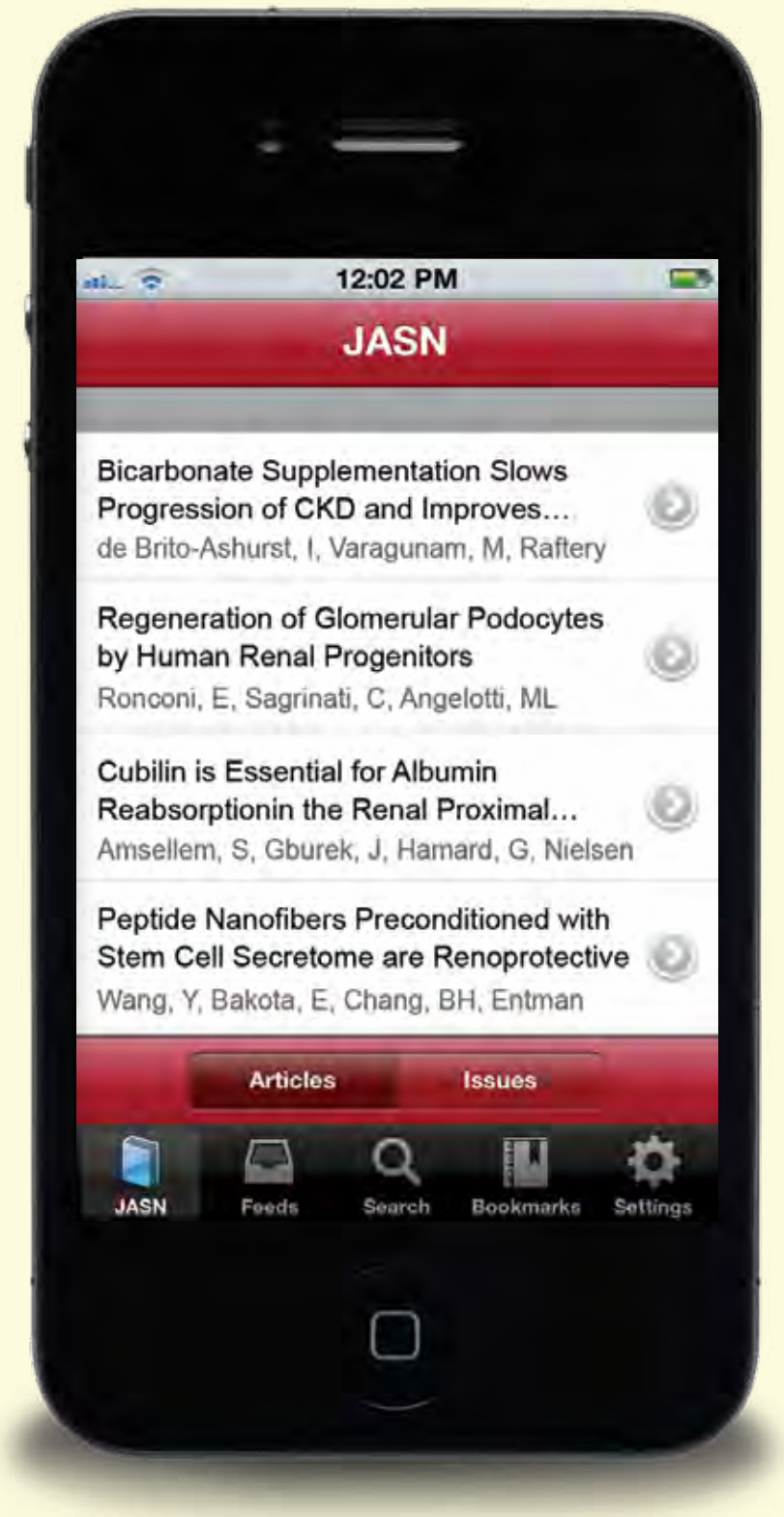

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FSGS' Link to Neurologic Disorder Probed

By Richard Robinson

The recent discovery of inverted formin 2 (*INF2*) as a major gene for focal segmental glomerulosclerosis (FSGS) focused the spotlight on this gene as important for understanding renal disease. New findings reveal that the same gene causes an uncommon neurologic disease, Charcot-Marie-Tooth disease (CMT), in a subset of the same patients.

The finding has important clinical implications for FSGS patients, and it sheds light on the crucial role of the actin cytoskeleton in the structure and function of the podocyte, a property it appears to share with the Schwann cells that insulate axons.

"We do not know exactly why some mutations lead only to the renal disease, while others cause renal plus neurologic disease," said Corinne Antignac, MD, PhD, lead author of the study and a researcher at the French National Institute of Health and Medical Research and the Necker Hospital in Paris. However, she said, it appears possible that the exact location of the mutation along the gene determines whether the kidneys and nervous system, or the kidneys alone, are affected. The study was published late last year in the *New England Journal of Medicine*.

The clinical implication of the finding is quite clear, Antignac said. "If you have patients with familial-dominant FSGS, you have to check whether they might have a neurologic disorder." Patients suspected of having peripheral neuropathy should be referred to a neurologist for further evaluation and treatment.

The CMT disease causes progressive weakness and atrophy of distal muscles and reduced tendon reflexes. Over time, patients typically experience deformities of the foot, including high arches and hammertoe, along with hand deformities.

Mutations in the *INF2* gene were originally linked to FSGS in 2010 by Martin Pollak, MD, and colleagues. In early 2011, Antignac and her team reported that out of 54 French families with autosomal-dominant FSGS, 17 percent carried *INF2* mutations. By contrast, only one patient in 84 sporadic cases carried a mutation. These results indicated that *INF2* mutations are a major cause of autosomal-dominant FSGS but are unlikely to account for a significant fraction of sporadic disease.

The gene encodes a formin protein, a family of proteins involved in remodeling of the actin and microtubule cytoskeletons. In fulfilling this role, *INF2* interacts with myelin and lymphocyte protein (MAL), which, as its name implies, is found in both myelin and lymphocytes, along with podocytes. "When we read the literature, we saw that *INF2* was interacting with MAL, and that reminded me that we had heard about patients with both FSGS and Charcot-Marie-Tooth disease," Antignac said.

That led her to wonder whether the two diseases might have a common cause in these patients. She and her colleagues enrolled 16 patients with both FSGS and CMT from 16 unrelated families, including seven with autosomal-dominant FSGS and nine with sporadic disease. They also obtained DNA from an additional four families from previously published cases. They ruled out mutations in the two genes that account for the large majority of CMT cases, called PMP22 and MPZ, both of which are crucial for myelin stability in Schwann cells.

They found heterozygous mutations in *INF2* in 12 of the 16 patients. In most patients, though not all, symptoms of CMT developed earlier than or at the same time as proteinuria, in patients ranging from age 5 to age 28 (median, age 13). Several patients had both sensorineural hearing loss and muscle weakness. Patients were classified as having an intermediate CMT phenotype, with a combination of both axonal and demyelinating changes.

The nine different mutations were all located in exons 2 and 3 of the gene, which encode a protein domain crucial for interacting with multiple other proteins.

"All of the mutations for both CMT and FSGS are located in a more central part of the protein" compared with those causing FSGS alone, Antignac said. This may account for the more widespread clinical phenotype arising from these mutations, although much work remains to be done to test that hypothesis.

In the kidney, *INF2* is predominantly expressed in podocytes, where it interacts with MAL, among other targets, as it does in Schwann cells. In Schwann cells, the disease-causing mutations do not interrupt *INF2*-MAL binding but instead, Antignac showed, cause MAL to be mislocalized away from the nucleus and diffused throughout the cytoplasm. Cells with mutant *INF2* had less cortical actin and a reduced number of long actin stress fibers, and their microtubule network was disorganized.

"*INF2* is involved in polymerization and depolymerization of actin," Antignac said, "and it is well known that the cytoskeleton is crucial for the shape of the podocyte. You can very well imagine if this system is interrupted, it could lead to abnormalities of the cytoskeleton, and to disease."

Her group is currently investigating the role of the *INF2*-MAL complex in intracellular transport in the podocyte.

"It has been shown that the complex is involved in transport in lymphocytes, and we are trying to figure out whether it is critical for the podocyte. It is very important to try to understand how *INF2* works," she said, and how it goes awry when mutated, because it may give clues to the development of treatments for both primary and secondary FSGS.

"I think this is a fascinating finding," said Pollak, who discovered the *INF2*-FSGS link. "It emphasizes the importance of taking a careful family history." Pollak is chief of nephrology at Beth Israel Deaconess Medical Center in Boston.

"It's a great paper," Pollak said. "People have long noted there are certain similarities between podocytes and some cells of the nervous system, in terms of structure and biology, and this is consistent with that at a genetic level." Those similarities are especially acute in the "architectural complexity" of the two cell types, made possible by actin and other cytoskeletal elements.

James Lupski, MD, PhD, professor and vice chairman of molecular and human genetics and professor of pediatrics at Baylor College of Medicine in Houston, who is an expert on CMT, agreed that the article is important.

"In both the neuropathy and the glomerular disorder, you are dealing with cells that have had to specialize, creating very unusual membrane structures. The Schwann cell wraps many times around the axon, while the podocyte must have a very large surface area to deal with filtration." The remarkable thing, he said, "is that one protein is involved in solving this problem in both."

Suggested Reading

Boyer O, et al. INF2 mutations in Charcot-Marie-Tooth disease with glomerulonephropathy. *N Engl J Med 2012*; 365:2377–2388.

In Advanced Renal Cell Carcinoma...

Indication

VOTRIENT is indicated for the treatment of patients with advanced renal cell carcinoma (RCC).

Important Safety Information

WARNING: HEPATOTOXICITY
Severe and fatal hepatotoxicity has been observed in clinical studies. Monitor hepatic function and interrupt, reduce, or discontinue dosing as recommended. See "Warnings and Precautions," Section 5.1, in complete Prescribing Information.

- **Hepatic Effects:** Patients with pre-existing hepatic impairment should use VOTRIENT with caution. Treatment with VOTRIENT is not recommended in patients with severe hepatic impairment. Increases in serum transaminase levels (ALT, AST) and bilirubin were observed. Severe and fatal hepatotoxicity has occurred. Transaminase elevations occur early in the course of treatment (92.5% of all transaminase elevations of any grade occurred in the first 18 weeks). Before the initiation of treatment and regularly during treatment, **monitor hepatic function and interrupt, reduce, or discontinue dosing as recommended**.
- **QT Prolongation and Torsades de Pointes:** Prolonged QT intervals and arrhythmias, including torsades de pointes, have been observed with VOTRIENT. Use with caution in patients at higher risk of developing QT interval prolongation, in patients taking antiarrhythmics or other medications that may prolong QT interval, and those with relevant pre-existing cardiac disease. Baseline and periodic monitoring of electrocardiograms and maintenance of electrolytes within the normal range should be performed.
- **Hemorrhagic Events:** Fatal hemorrhagic events have been reported (all Grades [16%] and Grades 3 to 5 [2%]). VOTRIENT has not been studied in patients who have a history of hemoptysis, cerebral, or clinically significant gastrointestinal hemorrhage in the past 6 months and should not be used in those patients.
- **Arterial Thrombotic Events:** Arterial thrombotic events have been observed and can be fatal. In clinical RCC studies of VOTRIENT, myocardial infarction, angina, ischemic stroke, and transient ischemic attack (all Grades [3%] and Grades 3 to 5 [2%]) were observed. Use with caution in patients who are at increased risk for these events.
- **Gastrointestinal Perforation and Fistula:** Gastrointestinal perforation or fistula has occurred. Fatal perforation events have occurred. Use with caution in patients at risk for gastrointestinal perforation or fistula. Monitor for symptoms of gastrointestinal perforation or fistula.
- **Hypertension:** Hypertension, including hypertensive crisis, has been observed. Blood pressure should be well-controlled prior to initiating VOTRIENT. Monitor for hypertension and treat as needed. Hypertension was observed in 47% of patients with RCC treated with VOTRIENT. Hypertension occurs early in the course of treatment (39% of cases occurred by Day 9 and 88% of cases occurred in the first 18 weeks). In the case of persistent hypertension despite anti-hypertensive therapy, the dose of VOTRIENT may be reduced. VOTRIENT should be discontinued if there is evidence of hypertensive crisis or if hypertension is severe and persistent despite

Move Forward With VOTRIENT

In a phase 3, randomized, double-blind, placebo-controlled trial, VOTRIENT provided significant improvement in progression-free survival (PFS) in both treatment-naïve and cytokine-pretreated patients with advanced RCC[1,2]

All patients
9.2 months
(95% CI, 7.4-12.9)
overall median PFS with VOTRIENT (n=290) vs **4.2 months** (95% CI, 2.8-4.2) with placebo (n=145) (*P*<0.001)[1,3]

Treatment-naïve patients
11.1 months
(95% CI, 7.4-14.8)
median PFS with VOTRIENT (n=155) vs **2.8 months** (95% CI, 1.9-5.6) with placebo (n=78) (*P*<0.001)[1,3]

Cytokine-pretreated patients
7.4 months
(95% CI, 5.6-12.9)
median PFS with VOTRIENT (n=135) vs **4.2 months** (95% CI, 2.8-5.6) with placebo (n=67) (*P*<0.001)[1,3]

NCCN Guidelines® Category 1 recommendation[4]

- As a first-line therapy for relapsed or Stage IV unresectable RCC of predominant clear cell histology . These Guidelines also include therapies other than VOTRIENT as first-line treatment options

WARNING: HEPATOTOXICITY
Severe and fatal hepatotoxicity has been observed in clinical studies. Monitor hepatic function and interrupt, reduce, or discontinue dosing as recommended.
See "Warnings and Precautions," Section 5.1, in complete Prescribing Information.

VOTRIENT: Safety Profile Summary[1]

- Most common adverse events observed with VOTRIENT were diarrhea, hypertension, hair color changes (depigmentation), nausea, anorexia, and vomiting
  - — Grade 3/4 fatigue occurred in 2% of patients; all grades, 19% of patients
  - — Grade 3/4 asthenia occurred in 3% of patients; all grades, 14% of patients
- For any individual adverse reaction in the VOTRIENT arm, the rate of Grade 3/4 adverse events is ≤4%

Most common laboratory abnormalities were ALT and AST increases[1]

- Grade 3 ALT increases occurred in 10% of patients; grade 4, 2% of patients
- In clinical trials, 92.5% of all transaminase elevations of any grade occurred in the first 18 weeks of treatment with VOTRIENT
- Monitor serum liver tests before initiation of treatment with VOTRIENT and at least once every 4 weeks for at least the first 4 months of treatment or as clinically indicated. Periodic monitoring should then continue after this time period

Votrient™
pazopanib tablets (200 mg)

anti-hypertensive therapy and dose reduction of VOTRIENT.

- **Wound Healing:** VOTRIENT may impair wound healing. Temporary interruption of therapy with VOTRIENT is recommended in patients undergoing surgical procedures. VOTRIENT should be discontinued in patients with wound dehiscence.
- **Hypothyroidism:** Hypothyroidism was reported as an adverse reaction in 26/586 (4%). Monitoring of thyroid function tests is recommended.
- **Proteinuria:** Monitor urine protein. Proteinuria was reported in 44/586 (8%) (Grade 3, 5/586 [<1%] and Grade 4, 1/586 [<1%]). Baseline and periodic urinalysis during treatment is recommended. Discontinue for Grade 4 proteinuria.
- **Pregnancy Category D:** VOTRIENT can cause fetal harm when administered to a pregnant woman. Women of childbearing potential should be advised of the potential hazard to the fetus and to avoid becoming pregnant while taking VOTRIENT.
- **Drug Interactions:** CYP3A4 Inhibitors (eg, ketoconazole, ritonavir, clarithromycin): Avoid use of strong inhibitors. Consider dose reduction of VOTRIENT when administered with strong CYP3A4 inhibitors.

  CYP3A4 Inducers (such as rifampin): Consider an alternate concomitant medication with no or minimal enzyme induction potential or avoid VOTRIENT.

  CYP Substrates: Concomitant use of VOTRIENT with agents with narrow therapeutic windows that are metabolized by CYP3A4, CYP2D6, or CYP2C8 is not recommended.

- **Adverse Reactions:** The most common adverse reactions (>20%) for VOTRIENT versus placebo were diarrhea (52% vs. 9%), hypertension (40% vs. 10%), hair color changes (depigmentation) (38% vs. 3%), nausea (26% vs. 9%), anorexia (22% vs. 10%), and vomiting (21% vs. 8%).

  Laboratory abnormalities occurring in >10% of patients and more commonly (≥5%) in the VOTRIENT arm versus placebo included increases in ALT (53% vs. 22%), AST (53% vs. 19%), glucose (41% vs. 33%), and total bilirubin (36% vs. 10%); decreases in phosphorus (34% vs. 11%), sodium (31% vs. 24%), magnesium (26% vs. 14%), and glucose (17% vs. 3%); and leukopenia (37% vs. 6%), neutropenia (34% vs. 6%), thrombocytopenia (32% vs. 5%), and lymphocytopenia (31% vs. 24%).

  VOTRIENT has been associated with cardiac dysfunction (such as a decrease in ejection fraction and congestive heart failure) in patients with various cancer types, including RCC. In the overall safety population for RCC (N=586), cardiac dysfunction was observed in 4/586 patients (<1%).

Please see Brief Summary of Prescribing Information on adjacent pages.

References: 1. VOTRIENT Prescribing Information. Research Triangle Park, NC: GlaxoSmithKline; 2011. **2.** Sternberg CN, et al. *J Clin Oncol.* 2010;28(6):1061–1068. **3.** Data on file, GlaxoSmithKline. **4.** Referenced with permission from The NCCN Clinical Practice Guidelines in Oncology® for Kidney Cancer V.1.2012. © National Comprehensive Cancer Network, Inc 2011. All rights reserved. Accessed November 17, 2011. To view the most recent and complete version of the guideline, go online to www.nccn.org.

www.VOTRIENT.com

GlaxoSmithKline
Oncology

Journal View

Aliskiren plus ACEI or ARB May Increase Hyperkalemia Risk

Combining the direct renin inhibitor aliskiren with an angiotensin-converting inhibitor (ACEI) or an angiotensin receptor blocker (ARB) may lead to an increased risk of hyperkalemia, reports a meta-analysis in the *British Medical Journal*.

A systematic review identified 10 randomized trials comparing aliskiren combined with ACEIs or ARBs versus ACEIs or ARBs alone. Data on 4814 patients were pooled for meta-analysis, focusing on the risk of hyperkalemia and acute kidney injury. Most of the trials compared aliskiren plus ARB versus ARB monotherapy.

Patients receiving aliskiren plus either an ACEI or an ARB were at increased risk of hyperkalemia: relative risk 1.58, compared with ACEI or ARB alone. Treatment with aliskiren alone was also associated with an increased rate of hyperkalemia: relative risk 1.67. The rates of acute kidney injury were similar among the various treatments.

Recent studies have raised concerns about the safety of dual inhibition of the renin-angiotensin system, leading to cautions about using ACEIs and ARBs together. With the rising use of aliskiren, it's important to determine whether it has similar safety problems in combination with other drugs.

The new analysis suggests that combining aliskiren with an ACEI or an ARB may increase the risk of hyperkalemia. Further studies of the clinical role and safety of using aliskiren in combination therapy are needed. Until then, the authors urge careful monitoring of serum potassium in patients receiving combinations of renin-angiotensin system blockers [Harel Z, et al. The effect of combination treatment with aliskiren and blockers of the renin-angiotensin system on hyperkalemia and acute kidney injury: systematic review and meta-analysis. *BMJ* 2012; 344:e42].

Postoperative Change in Serum Creatinine Helps Predict AKI Risk

Measuring the change in serum creatinine immediately after cardiac surgery may help in predicting acute kidney injury (AKI), suggests a study in the *American Journal of Kidney Diseases.*

The prospective study included 350 patients undergoing elective coronary artery bypass grafting or valve replacement surgery in Winnipeg, Canada, from 2007 to 2009. Serum creatinine was measured at baseline and within 6 hours after the end of surgery, and then each day during the remaining hospital stay. The immediate postoperative change in serum creatinine (ΔSCr) was evaluated as a predictor of AKI, based on Kidney Disease: Improving Global Outcomes (KDIGO) criteria.

The ΔSCr was decreased by more than 10 percent of baseline in 52 percent of patients. Fourteen percent met the KDIGO criteria for AKI during their hospitalization. The factors associated with AKI in a base model were bypass pump time, baseline estimated GFR, and European System for Cardiac Risk Evaluation score.

The ΔSCr was strongly associated with the development of AKI. The c statistic, an indicator of discrimination, increased from 0.69 in the base model to 0.78 after the addition of ΔSCr. The risk of AKI was more than six times higher (odds ratio 6.38) for patients with a 10 percent or greater reduction in serum creatinine. In contrast, AKI was significantly reduced (odds ratio 0.37) for those with a 10 percent or greater increase in serum creatinine.

New approaches are needed to identify patients at increased risk of AKI after cardiac surgery. Recent studies suggest that changes in creatinine before and after surgery may have better predictive ability than single baseline measurements.

Patients with an increase of more than 10 percent in serum creatinine measured within 6 hours after elective cardiac surgery are at high risk of AKI, the new study suggests. A model including the ΔSCr shows increased predictive ability. The authors note that their study used a surrogate marker of AKI, rather than clinical events [Ho J, et al. Serum creatinine measurement immediately after cardiac surgery and prediction of acute kidney injury. *Am J Kidney Dis* 2012; 59:196–201].

New Calcineurin Inhibitor Shows Promise

Voclosporin, a novel calcineurin inhibitor, compares well with tacrolimus in primary kidney transplant recipients—including a possible reduction in new-onset diabetes after transplantation (NODAT), reports a trial in the *American Journal of Transplantation*.

The phase 2, open-label trial included 334 low-risk patients undergoing initial renal transplantation. Patients were randomly assigned to receive low, intermediate, or high doses of voclosporin or standard-dose tacrolimus. At 6 months, the rates of biopsy-proven acute rejection were 10.7 percent, 9.1 percent, and 2.3 percent in the low- to high-dose voclosporin groups compared with 5.8 percent in the tacrolimus group. This was within the study margin of noninferiority.

Analysis of secondary outcomes found a significant reduction in NODAT with voclosporin: 1.6 percent, 5.7 percent, and 17.7 percent, compared with 16.4 percent with tacrolimus. The high-dose voclosporin group had a small but significant increase in estimated GFR compared with those receiving tacrolimus. Pharmacokinetic and pharmacodynamic studies showed excellent correlation between the voclosporin trough and area under the curve. There were no significant differences in mycophenolic acid exposure.

Voclosporin was developed as a new calcineurin inhibitor for organ transplantation that would reduce toxicity with similar or better efficacy. The new trial suggests that voclosporin is noninferior to tacrolimus in preventing acute rejection after de novo kidney transplantation. Further trials are needed to confirm these results, including the effects on renal function and NODAT risk [Busque S, et al. The PROMISE study: a phase 2b multicenter study of voclosporin (ISA247) versus tacrolimus in de novo kidney transplantation. *Am J Transpl* 2011;11:2675–2684].

vomiting. The data described below reflect the safety profile of VOTRIENT in 290 RCC patients who participated in a randomized, double-blind, placebo-controlled study *[see Clinical Studies (14) of full prescribing information]*. The median duration of treatment was 7.4 months (range 0 to 23) for patients who received VOTRIENT and 3.8 months (range 0 to 22) for the placebo arm. Forty-two percent (42%) of patients on VOTRIENT required a dose interruption. Thirty-six percent (36%) of patients on VOTRIENT were dose reduced. Table 1 presents the most common adverse reactions occurring in ≥10% of patients who received VOTRIENT.

Table 1. Adverse Reactions Occurring in ≥10% of Patients who Received VOTRIENT

	VOTRIENT (N = 290)			Placebo (N = 145)		
	All Grades[a]	Grade 3	Grade 4	All Grades[a]	Grade 3	Grade 4
Adverse Reactions	%	%	%	%	%	%
Diarrhea	52	3	<1	9	<1	0
Hypertension	40	4	0	10	<1	0
Hair color changes	38	<1	0	3	0	0
Nausea	26	<1	0	9	0	0
Anorexia	22	2	0	10	<1	0
Vomiting	21	2	<1	8	2	0
Fatigue	19	2	0	8	1	1
Asthenia	14	3	0	8	0	0
Abdominal pain	11	2	0	1	0	0
Headache	10	0	0	5	0	0

[a] National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.

Other adverse reactions observed more commonly in patients treated with VOTRIENT than placebo and that occurred in <10% (any grade) were alopecia (8% versus <1%), chest pain (5% versus 1%), dysgeusia (altered taste) (8% versus <1%), dyspepsia (5% versus <1%), facial edema (1% versus 0%), palmar-plantar erythrodysesthesia (hand-foot syndrome) (6% versus <1%), proteinuria (9% versus 0%), rash (8% versus 3%), skin depigmentation (3% versus 0%), and weight decreased (9% versus 3%). Table 2 presents the most common laboratory abnormalities occurring in >10% of patients who received VOTRIENT and more commonly (≥5%) in patients who received VOTRIENT versus placebo.

Table 2. Selected Laboratory Abnormalities Occurring in >10% of Patients who Received VOTRIENT and More Commonly (≥5%) in Patients who Received VOTRIENT Versus Placebo

	VOTRIENT (N = 290)			Placebo (N = 145)		
	All Grades[a]	Grade 3	Grade 4	All Grades[a]	Grade 3	Grade 4
Parameters	%	%	%	%	%	%
Hematologic						
Leukopenia	37	0	0	6	0	0
Neutropenia	34	1	<1	6	0	0
Thrombocytopenia	32	<1	<1	5	0	<1
Lymphocytopenia	31	4	<1	24	1	0
Chemistry						
ALT increased	53	10	2	22	1	0
AST increased	53	7	<1	19	<1	0
Glucose increased	41	<1	0	33	1	0
Total bilirubin increased	36	3	<1	10	1	<1
Phosphorus decreased	34	4	0	11	0	0
Sodium decreased	31	4	1	24	4	0
Magnesium decreased	26	<1	1	14	0	0
Glucose decreased	17	0	<1	3	0	0

[a] National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.

Hepatic Toxicity: In a controlled clinical study with VOTRIENT for the treatment of RCC, ALT >3 X ULN was reported in 18% and 3% of the VOTRIENT and placebo groups, respectively. ALT >10 X ULN was reported in 4% of patients who received VOTRIENT and in <1% of patients who received placebo. Concurrent elevation in ALT >3 X ULN and bilirubin >2 X ULN in the absence of significant alkaline phosphatase >3 X ULN occurred in 5/290 (2%) of patients on VOTRIENT and 2/145 (1%) on placebo. *[See Dosage and Administration (2.2) of full prescribing information and Warnings and Precautions (5.1).]* **Hypertension:** In a controlled clinical study with VOTRIENT for the treatment of RCC, 115/290 patients (40%) receiving VOTRIENT compared with 15/145 patients (10%) on placebo experienced hypertension. Grade 3 hypertension was reported in 13/290 patients (4%) receiving VOTRIENT compared with 1/145 patients (<1%) on placebo. The majority of cases of hypertension were manageable with anti-hypertensive agents or dose reductions with 2/290 patients (<1%) permanently discontinuing treatment with VOTRIENT because of hypertension. VOTRIENT has been associated with hypertensive crisis in patients with various cancer types including RCC. In the overall safety population for RCC (N = 586), one patient had hypertensive crisis on VOTRIENT. *[See Warnings and Precautions (5.6).]* **QT Prolongation and Torsades de Pointes:** In a controlled clinical study with VOTRIENT, QT prolongation (≥500 msec) was identified on routine electrocardiogram monitoring in 3/290 (1%) of patients treated with VOTRIENT compared with no patients on placebo. Torsades de pointes was reported in 2/586 (<1%) patients treated with VOTRIENT in the RCC studies. *[See Warnings and Precautions (5.2).]* **Arterial Thrombotic Events:** In a controlled clinical study with VOTRIENT, the incidences of arterial thrombotic events such as myocardial infarction/ischemia [5/290 (2%)], cerebral vascular accident [1/290 (<1%)], and transient ischemic attack [4/290 (1%)] were higher in patients treated with VOTRIENT compared to the placebo arm (0/145 for each event). *[See Warnings and Precautions (5.4).]* **Hemorrhagic Events:** In a controlled clinical study with VOTRIENT, 37/290 patients (13%) treated with VOTRIENT and 7/145 patients (5%) on placebo experienced at least 1 hemorrhagic event. The most common hemorrhagic events in the patients treated with VOTRIENT were hematuria (4%), epistaxis (2%), hemoptysis (2%), and rectal hemorrhage (1%). Nine (9/37) patients treated with VOTRIENT who had hemorrhagic events experienced serious events including pulmonary, gastrointestinal, and genitourinary hemorrhage. Four (4/290) (1%) patients treated with VOTRIENT died from hemorrhage compared with no (0/145) (0%) patients on placebo. *[See Warnings and Precautions (5.3).]* In the overall safety population in RCC (N = 586), cerebral/intracranial hemorrhage was observed in 2/586 (<1%) patients treated with VOTRIENT. **Hypothyroidism:** In a controlled clinical study with VOTRIENT, more patients had a shift from thyroid stimulating hormone (TSH) within the normal range at baseline to above the normal range at any post-baseline visit in VOTRIENT compared with the placebo arm (27% compared with 5%, respectively). Hypothyroidism was reported as an adverse reaction in 19 patients (7%) treated with VOTRIENT and no patients (0%) in the placebo arm. *[See Warnings and Precautions (5.8).]* **Diarrhea:** Diarrhea occurred frequently and was predominantly mild to moderate in severity. Patients should be advised how to manage mild diarrhea and to notify their healthcare provider if moderate to severe diarrhea occurs so appropriate management can be implemented to minimize its impact. **Proteinuria:** In the controlled clinical study with VOTRIENT, proteinuria has been reported as an adverse reaction in 27 patients (9%) treated with VOTRIENT. In 2 patients, proteinuria led to discontinuation of treatment with VOTRIENT. *[See Warnings and Precautions (5.9).]* **Lipase Elevations:** In a single-arm clinical study, increases in lipase values were observed for 48/181 patients (27%). Elevations in lipase as an adverse reaction were reported for 10 patients (4%) and were Grade 3 for 6 patients and Grade 4 for 1 patient. In clinical RCC studies of VOTRIENT, clinical pancreatitis was observed in 4/586 patients (<1%). **Cardiac Dysfunction:** Pazopanib has been associated with cardiac dysfunction (such as a decrease in ejection fraction and congestive heart failure) in patients with various cancer types, including RCC. In the overall safety population for RCC (N = 586), cardiac dysfunction was observed in 4/586 patients (<1%).

7 DRUG INTERACTIONS

7.1 Drugs That Inhibit or Induce Cytochrome P450 3A4 Enzymes

In vitro studies suggested that the oxidative metabolism of pazopanib in human liver microsomes is mediated primarily by CYP3A4, with minor contributions from CYP1A2 and CYP2C8. Therefore, inhibitors and inducers of CYP3A4 may alter the metabolism of pazopanib. **CYP3A4 Inhibitors:** Coadministration of pazopanib with strong inhibitors of CYP3A4 (e.g., ketoconazole, ritonavir, clarithromycin) may increase pazopanib concentrations. A dose reduction for VOTRIENT should be considered when it must be coadministered with strong CYP3A4 inhibitors *[see Dosage and Administration (2.2)]*. Grapefruit juice should be avoided as it inhibits CYP3A4 activity and may also increase plasma concentrations of pazopanib. **CYP3A4 Inducers:** CYP3A4 inducers such as rifampin may decrease plasma pazopanib concentrations. VOTRIENT should not be used if chronic use of strong CYP3A4 inducers can not be avoided *[see Dosage and Administration (2.2)]*.

Does Lowering Dialysate Sodium Affect Patient Outcomes?

Decreasing dialysate sodium prescription (DNa) reduces interdialytic weight gain (IDWG) but doesn't lead to reduced mortality, according to a report in the *Clinical Journal of the American Society of Nephrology*.

The researchers analyzed data on nearly 26,000 patients from the Dialysis Outcomes and Practice Patterns Study (DOPPS). Morbidity and mortality were assessed at different levels of DNa, accounting for both IDWG and the risk of death associated with lower predialysis serum sodium levels.

At all levels of predialysis serum sodium, higher DNa was associated with increased IDWG. For each 2 mEq/L increase in DNa, there was a 0.17 percent increase in body weight. However, the final model—including adjustment for predialysis serum sodium—found no association between higher DNa and higher mortality.

This remained so even after further adjustment for IDWG. In facilities where at least 90 percent of patients had the same DNa (56 percent), the association with mortality was significant: adjusted hazard ratio 0.88 per 2 mEq/L increase. Because of the nature of the data, confounding by indication was considered unlikely.

Recent studies have suggested that reducing DNa may reduce IDWG. Before any such change in clinical practice is made, it's important to assess the impact on patient outcomes.

The new analysis of DOPPS data does not support the theory that lowering DNa to reduce IDWG will translate to better patient outcomes. The researchers write, "In the absence of randomized prospective studies, the benefit of reducing IDWG by decreasing DNa prescriptions should be carefully weighed against an increased risk for adverse outcomes" [Hecking M, et al. Dialysate sodium concentration and the association with interdialytic weight gain, hospitalization, and mortality. *Clin J Am Soc Nephrol* 2012; 7:92–100].

Journal View

Composite Biomarker Can Track Inflammation in Lupus Nephritis

A combination of three biomarkers may be useful for monitoring interstitial inflammation in patients with lupus nephritis, according to a report in *Kidney International*.

The researchers collected urine samples from 61 patients with lupus nephritis, at or around the time of renal biopsy. All patients met at least four American College of Rheumatology criteria for systemic lupus erythematosus, including immune complex glomerulonephritis. A renal pathologist graded interstitial inflammation and interstitial fibrosis in 64 biopsy specimens. Linear discriminant analysis was performed to evaluate various urinary biomarkers for inclusion in a "composite biomarker" of interstitial inflammation.

The composite biomarker of tubulointerstitial inflammation consisted of monocyte chemotactic protein-1; hepcidin, which reflects lupus nephritis flares; and liver fatty acid–binding protein. Sensitivity was 100 percent, specificity 81 percent, positive predictive value 67 percent, and negative predictive value 100 percent. The composite biomarker had a misclassification rate of only 14 percent.

Renal biopsy is typically performed at diagnosis of lupus nephritis but not for subsequent disease flares. An accurate, noninvasive indicator of kidney injury—particularly interstitial inflammation—would be helpful in planning and monitoring medical treatment.

The new composite biomarker shows promise for use in monitoring tubulointerstitial inflammation in lupus nephritis. Although further validation is needed, the authors believe that the biomarker could provide useful information about the renal interstitium in other kidney diseases as well [Zhang X, et al. A composite urine biomarker reflects interstitial inflammation in lupus nephritis biopsies. *Kidney Int* 2012; 81:401–406].

Switching to Sirolimus Doesn't Slow Chronic Changes after Transplantation

For kidney transplant patients going through rapid steroid withdrawal, switching from tacrolimus to sirolimus doesn't reduce the rate of long-term changes on subsequent renal biopsy specimens, according to a report in *Transplantation*.

The randomized controlled trial included 122 kidney transplant recipients undergoing rapid steroid withdrawal. At 1 month, the patients were assigned to switch from tacrolimus to sirolimus or to remain taking tacrolimus. Protocol biopsy specimens were obtained at 1 month, 1 year, and 2 years for assessment of long-term changes, including interstitial fibrosis and tubular atrophy (IFTA) and the sum of Banff chronic scores (Total Score). The influence of previous rejection episodes on the long-term scores was assessed as well.

One-year biopsy specimens were obtained from 90 percent of patients in both groups. The two groups had similar and significant increases in long-term changes—i.e., proportion of biopsy specimens with IFTA scores of 2 or greater and Total Scores greater than 2. At 1 year, patients who had previous episodes of rejection and who continued to receive tacrolimus had higher IFTA scores and were more likely to have Total Scores greater than 2. Among those without previous rejection, both the IFTA and the Total Score showed significant progression from 1 to 2 years.

Chronic calcineurin inhibitor nephrotoxicity contributes to the development of IFTA after kidney transplantation. In a previous report, the authors found no difference in 1-year kidney function among patients who were converted from tacrolimus to sirolimus 1 month after transplantation.

The new analysis showed no reduction in the progression of IFTA and other long-term changes through 2 years in kidney recipients switched to sirolimus, compared with those continuing with tacrolimus. This was so even in patients with no previous episodes of rejection. Further study of the progression of long-term changes after early steroid withdrawal is needed [Heilman RL, et al. Impact of early conversion from tacrolimus to sirolimus on chronic allograft changes in kidney recipients on rapid steroid withdrawal. *Transplantation* 2012; 93:47–53].

Industry Spotlight

Fresenius Teams with Insurer to Slow Progression of Chronic Kidney Disease

In 2011, Fresenius successfully concluded a 5-year pilot project that showed costs could be lowered with an integrated provider program focusing on patients with chronic kidney disease (CKD). By capturing patients earlier in the course of CKD, the provider of dialysis services and products was able to show noteworthy savings in the project sponsored by the Centers for Medicare & Medicaid Services (CMS).

Now Fresenius and Aetna are bringing the same program to a wider group of patients, beginning in the Northeast and phasing it in to more regions over time.

The CMS pilot project brought in health care costs 12 percent below the Medicare Advantage and 4 percent below Medicare fee-for-service benchmarks for this population, and the hope is that this will continue in the new collaboration. The 1-year and 2-year survival rates were also higher in the groups receiving additional monitoring and care, from California to Connecticut.

Health indicators improved, too. Patients in the program prospered, with clinical measures showing a 24 percent improvement in the mortality rate and a 20 percent reduction in all-cause hospitalization in comparison with national benchmarks.

The new care program is structured to enhance coordination of care among specialists, primary care providers, and nurses. Together, they identify members at risk and improve clinical management in earlier stages of kidney disease to help slow the progression to kidney failure.

The program's success relies on daily measures from patients coming in through a wireless communication system that lets the care team members identify, make suggestions, or even remotely intervene to prevent complications versus national benchmarks. Other features of the program include expanded management of the various comorbidities such as congestive heart failure and cardiac disease, with particular attention to nutritional status, infection risks, vascular access, and psychosocial needs that affect kidney patients.

The pilot program achieved this expanded patient care by adding personal nurse care managers to work with patients and their care providers on these nondialysis focus areas.

Peter Sauer, president at Fresenius Health Partners, said the collaboration with Aetna fits well with the company's focus and expertise in comprehensive renal therapy management. "As rates of diabetes, obesity, and heart disease climb and threaten to dramatically increase the incident rates for renal disease, we want to assist payers, doctors, and patients by providing the highest quality and most cost-effective care now," Sauer said. The hope is that the program will work on a large scale to slow the progression of CKD in patients by catching evidence of the disease early and by "facilitating gentler, less costly transitions to dialysis or pretransplant care," according to a story about the program launch on the Medical Express site.

"If dialysis becomes necessary, we want to help members begin dialysis with the lowest risk for complications," said Roger London, MD, Aetna's Northeast Region medical director. "We believe the model will improve our members' quality of life by helping them and their doctors better manage the conditions contributing to or resulting from chronic kidney disease."

New Options for Advanced Kidney Cancer

Several kidney cancer drugs made the news lately.

The U.S. Food and Drug Administration (FDA) recently approved Inlyta (axitinib) for treating advanced renal cell carcinoma (RCC) after treatment with a systemic therapy has failed. An oral drug made by Pfizer, Inlyta blocks certain receptors that can influence tumor growth and also the progression of kidney cancer. Forty percent to 65 percent of patients whose cancer progresses after first-line therapy go on to receive a second-line treatment, the company said.

In its January announcement, the FDA said that the safety and effectiveness of Inlyta were evaluated in a randomized, open-label, multicenter clinical study of 723 patients whose disease had progressed during or after treatment with an initial systemic therapy. The study was designed to measure the time a patient lived without the cancer progressing. The results showed a median progression-free survival period of 6.7 months, compared with 4.7 months with a standard treatment (sorafenib).

A study presented at the 2012 Genitourinary Cancers Symposium in early February showed that some patients with metastatic RCC may need a higher than standard dose of the newly approved axitinib to achieve optimal benefit, according to an analysis of data from the phase III AXIS trial.

A new combination therapy is also under development. An immunotherapy (AGS-003) agent from Argos Therapeutics combined with the drug sunitinib may help prolong the lives of men with unfavorable-risk, metastatic RCC, according to new data from an open-label, phase 2 study. The study found that the combination of AGS-003 plus sunitinib was linked with a longer survival period than that for sunitinib alone in these patients. The study enrolled 21 patients (16 men) with newly diagnosed metastatic clear-cell RCC.

Multiple partial responses were observed with this combination regimen: 11 of 15 patients (73 percent) who had immune assessments over time showed increases in their CD28+ memory T immune cells, according to Argos. These immune responses correlated directly with longer survival.

Overall, the median progression-free survival was 11.2 months, and the estimated median overall survival was 29.3 months, on the basis of follow-up through January 2012. The combination of immunotherapy and drug is designed to stimulate a patient's immune response to the tumor. Each production of a patient's fully personalized immunotherapy generates up to 5 years of treatment for each patient, said Argos.

Lead investigator Robert Figlin, MD, who directs the division of hematology/oncology at the Cedars-Sinai Samuel Oschin Comprehensive Cancer Institute in Los Angeles, and colleagues found that the combination was tolerated well. Observed adverse events were as expected with sunitinib toxicities, but a notable exception was injection site reactions in approximately 50 percent of study participants.

Preliminary data have been shared about the use of the drug cabozantinib in pretreated patients with metastatic refractory RCC. The patients participated in an ongoing phase 1b trial of cabozantinib, an inhibitor of both MET and VEGFR2 factors. The drug was developed to block metastasis and blood vessel growth in order to kill tumor cells while blocking their escape pathways, *Drug Discovery News* reported.

The investigators looked at data from patients enrolled in a drug interaction study of cabozantinib in patients with advanced solid tumors. The 25 RCC patients in the trial received 140 mg oral cabozantinib administered daily, and the study endpoints were safety, tolerability, and antitumor activity.

The rate of disease control at week 16 for all 25 patients was 72 percent. An estimate of median progression-free survival was 14.7 months (95 percent confidence interval; lower limit 7.3 months; upper limit was not reached). Ten patients remain in the study and are progression-free, with treatment durations ranging up to 16.4 months, according to *Drug Discovery News*.

The FDA lists recently approved drugs for the treatment of kidney cancer as sorafenib (2005), sunitinib (2006), temsirolimus (2007), everolimus (2009), bevacizumab (2009), and pazopanib (2009). It looks as though more are on the way.

Policy Update

ASN Task Force Answers Questions about Accountable Care Organizations

Ever since the Centers for Medicare and Medicaid Services (CMS) released the Accountable Care Organization (ACO) final rule in October 2011, the American Society of Nephrology (ASN) ACO Task Force has been analyzing the rule to determine how it may affect patients with kidney disease and the nephrologists who care for them. This Q & A with Amy Williams, MD, and Emily Robinson, MD, is the first in a series of Q & A articles with task force members about ACOs and other approaches to new health care delivery models.

What were the biggest changes from the proposed rule that CMS made to the final ACO rule?

Amy Williams: CMS received extensive feedback on the initial ACO rules, including comments from ASN related to the care of individuals with chronic kidney disease (CKD), ESRD, and kidney transplants. In response to the general comments, CMS made changes that will make it easier for some organizations to form and participate in ACOs. However, the task force was dismayed that CMS did not make any substantial changes to the rule based on the ASN's recommendations. Table 1 summarizes the most important modifications. You may access a complete list of the 33 quality measures on the ASN website.

What were the biggest nephrology-specific changes between the proposed and final rules?

Amy Williams: Although the changes to the ACO rules may allow more entities to participate in ACOs, few changes to the rule will have a direct impact on nephrologists or on individuals with nephrologic diseases. The goal of delivering patient-centered, collaborative, coordinated health care should improve the care of patients with CKD, but to accomplish this, the nephrology community must partner with the ACO primary care providers to provide appropriate guidance in the care of CKD patients and the primary prevention of renal disease.

Unfortunately, the quality metrics, although decreased in number, do not reflect priority outcomes or quality measures for patients with advanced CKD, ESRD, or recent renal transplants. Educating the ACO providers in appropriate use of the routine health maintenance and cancer screening tests in patients with advanced CKD, ESRD, and limited life expectancy will prevent unnecessary testing, possible adverse events, and unnecessary costs.

How are patients attributed to an ACO?

Amy Williams: The final process of patient assignment to an ACO has two steps:

1. Patients are preliminarily assigned to an ACO on the basis of the historical (prior 12 months) plurality of primary care G-code charges associated with an annual wellness visit or Welcome to Medicare visit attributed to the patient by a primary care provider.

2. If the patient has not had any primary care services from any primary care provider, he or she will be assigned to the specialist and the specialist's ACO that has provided the plurality of primary care services. This "preliminary prospective assignment" allows ACOs to know which patients they are likely responsible for managing and should help them identify high-risk patients, such as those with advanced CKD and renal transplants, and facilitate early implementation of evidence-based management to improve patient outcomes and manage the cost of care. Final reconciliation of patient assignments will occur at the end of the performance period and will be based on which ACO provided the plurality of the patient's primary services.

What are the potential positive developments for my dialysis patients if they are attributed to an ACO?

Emily Robinson: There would be pros and cons for a dialysis patient attributed to an ACO. ACOs are charged with developing processes to promote evidence-based medicine, promote beneficiary engagement, and coordinate care, all of which could help all patients, including dialysis patients. ACOs also are mandated to have systems in place to identify high-risk individuals and develop individualized care plans.

Dialysis patients specifically may benefit from improved efforts to coordinate care and efforts at medication reconciliation, one of the quality measures, because they often have medical records in many different locations and different physicians who prescribe their medications. Other quality measures, including vaccination for influenza and pneumonia as well as screening for risk of falling, may be helpful for these patients, although likely they are already being done in the dialysis units.

Amy Williams: Partnering with ACO providers to develop and implement patient education materials and best practices for treating patients with CKD, ESRD, and renal transplants could prevent adverse patient and renal outcomes from nephrotoxic medications, polypharmacy complications, and missed opportunities for renal-preserving interventions. Such co-

Table 1. Modifications to ACO proposed rule

Aspect of ACO program	Detailed changes
Financial provisions	The final rule reduces financial risk and allows for all ACOs to earn savings from the first dollar saved. CMS initially proposed a rule that only ACOs that shared financial risk in the "two-sided" model could share in savings from the first dollar their ACO saved Medicare. The final rule also eliminates a 25 percent withhold of savings for all participants.
Application and structural changes	The final rule eliminates the initial application requirement to obtain a mandatory Antitrust Agency review and instead provides a voluntary expedited review. The requirement to undergo an Antitrust Agency review each time an ACO adds a provider or supplier was also eliminated.
Eligible entities	The proposed rule listed the four groups outlined in the Affordable Care Act, and stated that critical access hospitals paid through Method II were eligible to apply as ACOs. The final rule added Federally Qualified Health Centers and Rural Health Clinics to the list of eligible entities. For all entities, the beneficiaries of established ACO will be assigned on the basis of use of primary care services. Thus, all entities applying must provide a list of practitioners who provide primary care services in their facilities.
Patient assignment	The initial proposal assigned patients retrospectively on the basis of the plurality of primary services. This approach was changed to incorporate a hybrid of preliminary prospective assignment with quarterly beneficiary identification and reconciliation of assignment at the end of each performance year, based on the patient's plurality of primary care during that year. This allows for the identification of beneficiaries after the initial ACO application, not waiting until after 1 year of management as initially proposed. The final rule outlined not only assignment based on plurality of primary care services rendered by a primary care physician, but also assignment for beneficiaries who have not had care from any primary care physician. These patients will be assigned on the basis of plurality of primary services provided by any ACO professional (i.e., nephrologists). CMS will monitor avoidance of high-risk patients and, as stated in the proposed rule, will terminate ACO agreements if this behavior is revealed.
Beneficiary data sharing	In addition to sharing limited patient data (name, date of birth, sex, and health insurance claim number) at initiation of application, the frequency of beneficiary data reports to the ACO was increased from yearly to quarterly. Established ACOs will have the opportunity to ask CMS for additional patient-specific data after receiving a patient's consent. The ACOs are required to notify the beneficiaries of data sharing and give them the opportunity to decline. If the assigned beneficiary declines data sharing with the ACO, the ACO is still responsible for his or her care (quality, cost, outcomes).
Quality measures	The initial 65 quality measures in five domains have been decreased to 33 measures in four domains. Unfortunately, the only measure with significant impact on CKD management, microalbuminuria screening, was eliminated. During the first year, CMS will pay for reporting the measures and, during the second and third years of the agreement period, will pay for both reporting and performance. Although declaring that 50 percent of the primary care physicians as meaningful users of the electronic medical record (EMR) is no longer a condition for participation, the EMR remains a quality measure now weighted higher than the other measures. This change will allow practices to apply for inclusion in the ACO program while developing the EMR tools.

ordination may lead to better preparation and appropriate referral for renal replacement therapy or conservative care, ultimately achieving better patient outcomes.

What are the potential risks or downsides for my dialysis patients if they are attributed to an ACO?

Emily Robinson: Some aspects of the ACO program may not be so positive for dialysis patients. Some of the quality measures, such as mammograms, colonoscopies, aggressive lipid management, or even aggressive blood pressure control, may not apply to dialysis patients. We may find that instead of careful consideration of the risks and benefits of these interventions in each individual patient based on specific evidence in dialysis patients, these patients may be given the interventions only to satisfy quality measures, even if they are unnecessary and potentially harmful.

If a patient is in a dialysis unit that is not associated with the primary care physician's ACO, it is possible that the primary care physician will encourage a change of dialysis unit to one within the ACO for better control of costs and savings, even if it is not close to the patient's home. There may be perverse incentives to hold off on access planning with CKD patients as long as possible to avoid unnecessary costs, thus increasing catheter rates among patients who are beginning dialysis.

Amy Williams: The rule states that difficult patients must be included in the ACO, and an ACO can be terminated for discriminating against these patients. However, the potential for ACOs to avoid assignment of high-risk patients is a concern. Most individuals with advanced CKD and ESRD have multiple comorbidities and require complex care. It is unclear how successful CMS will be in detecting ACOs that avoid enrolling these patients. Nephrologists will need to continue to be advocates for these patients and have a significant role in their medical management.

Emily Robinson: We hope that CMS's efforts truly safeguard against cherry-picking of patients, and that individuals receiving dialysis, whose care is often complex, will not have a harder time finding a primary care physician willing to accept them as patients.

In the next issue the ASN ACO Task Force will address more questions, including these: Can my nephrology practice join an ACO? What will it mean for me as a nephrologist if my dialysis patients are attributed to an ACO? What other kinds of new care delivery models exist?

If you have questions about ACOs you'd like the task force to address, please email the ASN Manager of Policy and Government Affairs, Rachel Shaffer, at rshaffer@asn-online.org.

Amy Williams is affiliated with the Mayo Clinic in Rochester, NY, and Emily Robinson is affiliated with the Brigham and Women's Hospital in Boston.

Detective Nephron

Detective Nephron, world-renowned for his expert analytic skills, trains budding physician-detectives in the diagnosis and treatment of kidney diseases. L.O. Henle, a budding nephrologist, presents a new case to the master consultant.

Nephron I am craving a good case today. Wonder what Henle has in store for me.

L. O. Henle enters the room.

Nephron What do you want?

Henle I… have a case for us.

Nephron Is it another electrolyte disorder?

Henle Hyperphosphatemia.

Nephron Hmm…well, let's take that one, then.

Henle (prepared) A 67-year-old man with multiple myeloma presents with acute kidney injury secondary to obstruction. They placed a Foley catheter in the emergency room, and his renal function is improving. Initially he had a creatinine level of 4.0 mg/dL, and over the past 2 days it is down to 1.3 mg/dL. Interestingly, the phosphorus level is rising. It was 6 mg/dL on presentation and now it is up to 15 mg/dL.

Nephron (chuckling) Near-normal renal function and elevated phosphorus… always an interesting combination.

Henle The medical team wants to start binders as soon as possible.

Nephron (confused) Ahah! This is going be exciting.

Henle (with caution) Just some more information, if you will allow, sir.

Nephron (chuckling) Sure—I hope it is the information I am looking for.

Henle The calcium and magnesium levels are normal. The patient doesn't have any signs of tumor lysis syndrome, or acidosis of any kind. Lactate was normal. Also, he has not been getting any vitamin D supplementation or any phosphate enemas.

Nephron Wow, you really are taking the fun out of this by giving me a laundry list of differential diagnoses that can cause elevated phosphorus. It seems that you have already ruled out the major common causes. What bothers me is that this is rising in the setting of improving renal function.

Henle We repeated the tests multiple times.

Nephron (laughing) I believe you!

Henle To me this is very confusing. What could be causing such high levels of phosphorus?

Nephron Is it the kidney?

Henle The kidneys, I know, are highly efficient in maintaining phosphate balance even when the dietary intake of phosphorus is increased severalfold. If, however, there is an acute phosphate load (i.e., an increase in phosphate concentration over a few hours rather than days), then the entry of phosphate into the extracellular compartment exceeds the rate at which it is excreted, and hyperphosphatemia results.

Nephron Exactly! So, think of the causes of hyperphosphatemia in three ways. (1) You gave him too much (we caused it) (i.e., a phosphate load sufficient enough to overwhelm the ability of the kidney to excrete it). (2) His kidneys stopped working (acute renal or chronic renal injury). (3) The kidney is deciding to enhance proximal tubular phosphate reabsorption (very rare).

Henle Seems like we had ruled out causes of acute phosphate load.

Nephron Well. the phosphate load can be endogenous or exogenous. No exogenous causes (i.e., ingestion of phosphate-containing laxatives) were found in your case. Endogenous causes can be from cell breakdown—so tumor lysis, rhabdomyolysis, and marked hemolysis can do it. In your particular case, the myeloma history does concern me a bit. Hmmm!

Henle (astounded) But with normal calcium, potassium, creatine kinase, and uric acid, less likely any of the above.

Nephron (calm) Fascinating!

Henle The other causes of mobilization of intracellular phosphate into the extracellular fluid are lactic acidosis and diabetic ketoacidosis. Severe metabolic acidosis can cause cellular phosphate utilization because of inhibition of glycolysis. There is no tissue hypoxia in this case, to our knowledge.

Nephron And it's not renal failure; this man's GFR is actually improving and most likely will be normal soon. Now, let's look at the third set of causes and perhaps come up with a diagnosis. What in this patient's history might have warranted a medication that can have direct effects on phosphorus absorption?

Henle (chuckling) You mean bisphosphonates? No, he didn't get that one. I know—they can cause mild hyperphosphatemia because they stimulate phosphate transport directly. His parathyroid hormone (PTH) is around 50 pg/mL, so hypoparathyroidism is less likely, and he has no signs of clinical acromegaly. Thought you might like that one, given your prior cases.

Nephron Good work, my apprentice. Either deficient PTH secretion or renal resistance to PTH

(pseudohypoparathyroidism) results in increased phosphate reabsorption and leads to hyperphosphatemia. Usually in this case the calcium is low, too. Tumoral calcinosis might be rare in this case because that is more of a genetic disease. Hmm… tough case, but I think I might have just thought of the answer. Like I said, the myeloma history bothers me.

Henle (puzzled) What could this possibly be, given that the renal function is getting better and the phosphorus level is getting worse?

Nephron How controlled is his myeloma? And what light chain is it?

Henle Hmm… Not so well controlled. A multiple regimen is failing, and it's IgM kappa type.

Nephron (confident) All right, then, go ahead and reassure the team to do nothing, and make sure they don't start any binders because that might be harmful.

Henle exits without questioning.

Nephron (to himself) Wonder why he just left without asking me "why"?

Before Detective Nephron can go down to get coffee, Henle returns to the office.

Nephron You're back.

Henle I am puzzled. I think you are getting at pseudohyperphosphatemia from paraproteins? Is that right? Should I ask the lab to de-proteinate?

Nephron Good work!

Henle So this is all a factitious result.

Nephron Spurious hyperphosphatemia due to interference with analytic methods may occur in patients with hyperglobulinemia, hyperlipidemia, hemolysis, and hyperbilirubinemia. Phosphate can be determined accurately by reanalysis of the specimen after removal of protein by ultrafiltration. Classically this can be seen with IgM-related diseases rather than IgG, but even in IgG-related paraprotein diseases, this has been recorded. Paraproteins can cause Na, creatinine, CO_2, and Ca values to be spurious. When dealing with large molecules like IgM, one has to be extremely careful about these spurious results.

Henle Yes, you are correct.

Nephron (with confidence) Now, go and get the real result.

Henle exits, and Detective Nephron starts reading* ASN Kidney News. *A few days later, the detective is sipping away at his coffee when Henle enters the office.

Nephron Nothing is better than a cup of warm coffee. And a great case.

Henle After removal of the proteins, a phosphorus level came back 4.0 mg/dL, and the regular blood work still reads 13–14 mg/dL. This is fascinating.

Nephron Great work, Henle (with a smirk). Again, my dear apprentice, never underestimate the power of the nephrologist. Not every electrolyte disorder is real, and not every number should be treated. By not treating here, you prevented harm. Pseudoelectrolyte disorders are a common finding in paraproteinemias.

Detective Nephron was developed by Kenar Jhaveri, MD, assistant professor of medicine at Hofstra North Shore LI School of Medicine. Thanks to Dr. Rimda Wanchoo, clinical instructor, division of nephrology, Weill Cornell Medical Center, New York, for her editorial assistance. Send correspondence regarding this section to kjhaveri@nshs.edu or kdj200@gmail.com.

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