ASN LEADING THE FIGHT AGAINST KIDNEY DISEASE

KidneyNews

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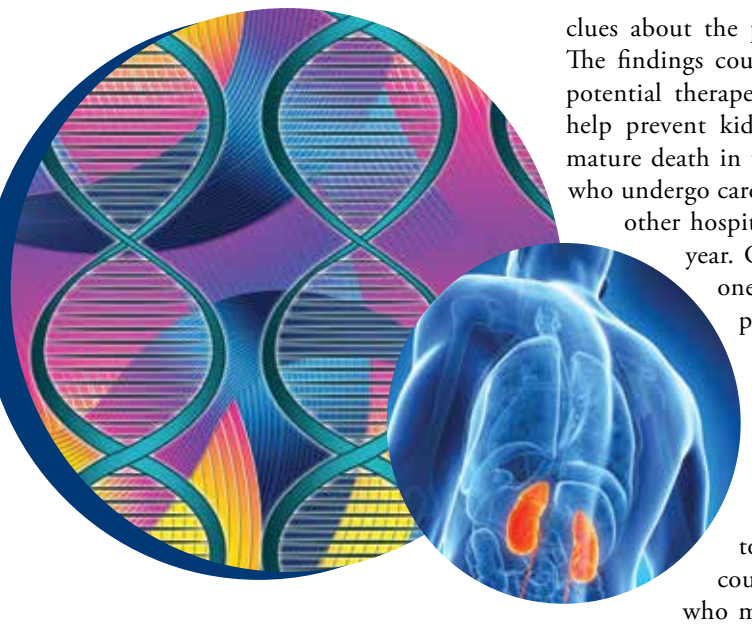
Genetic Markers Could Help Identify Hospital Patients at Risk for AKI

By Kurtis Pivert



Researchers have isolated several genetic markers that could help identify individuals at risk for acute kidney injury (AKI) in the hospital setting (1). Results from the study presented at ASN Kidney Week 2014 in Philadelphia, PA, offer new clues about the pathogenesis of AKI. The findings could eventually lead to potential therapeutic interventions to help prevent kidney failure and premature death in thousands of patients who undergo cardiovascular surgery or other hospital interventions each year. Currently, AKI affects one in five hospitalized patients worldwide.

Collaborators from Yale University, Vanderbilt University, and the University of Western Ontario wanted to determine if they could identify patients who may have a higher genetic risk for developing AKI in the hospital. Doing so could uncover novel pathways that could be targeted for therapeutic interventions, said senior author Chirag R. Parikh, MD, PhD, FASN of Yale.

Investigators in this multicenter study weren't alone in their clinical suspicion that some individuals could have a genetic predisposition for developing AKI in the hospital setting. "What is clear is that patients of similar age and health status can have drastically different kidney outcomes after a potential insult like cardiopulmonary bypass surgery," said Benjamin Humphreys, MD, PhD, FASN, of Brigham and Women's Hospital and Director of the Harvard Stem Cell Institute Kidney Group in Boston. "Many patients do just fine, but others develop AKI. The absence of obvious clinical factors to explain these divergent outcomes suggests a role for genetic predisposition."

Until recently, analysis methods limited the scope of genetic AKI studies. "The putative genetic components of AKI have until recent years been mainly investigated by hypothesis-driven research (of candidate genes)," Parikh said. "But technological progress in genotyping has opened the possibilities

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Most Americans Aren't Healthy Enough to Be Kidney Donors

Just over half of adults in the United States—including nearly two-thirds of African Americans—have health conditions that would preclude their becoming living kidney donors, according to a study presented at Kidney Week 2014.

Anthony J. Bleyer, Jr., and colleagues of Wake Forest School of Medicine, Winston-Salem, NC, performed a population-based study to estimate the percentage of Americans healthy enough for kidney donation. The analysis included data on adults aged 21 to 70 years, drawn from The National Health and Nutrition Examination Survey 2010–2011. The investigators studied the presence of common factors that are used to exclude volunteers from donating a kidney in a representative sample of the United States population.

They found that 55.2 percent of the United States population would be ineligible to donate a kidney because of health conditions. A history of hypertension, the most common excluding condition, was present in 19.2 percent of participants. This was followed by obesity, 15.0 percent; excessive alcohol intake (more than four drinks per day), 11.6 percent; and diabetes, 11.5 percent.

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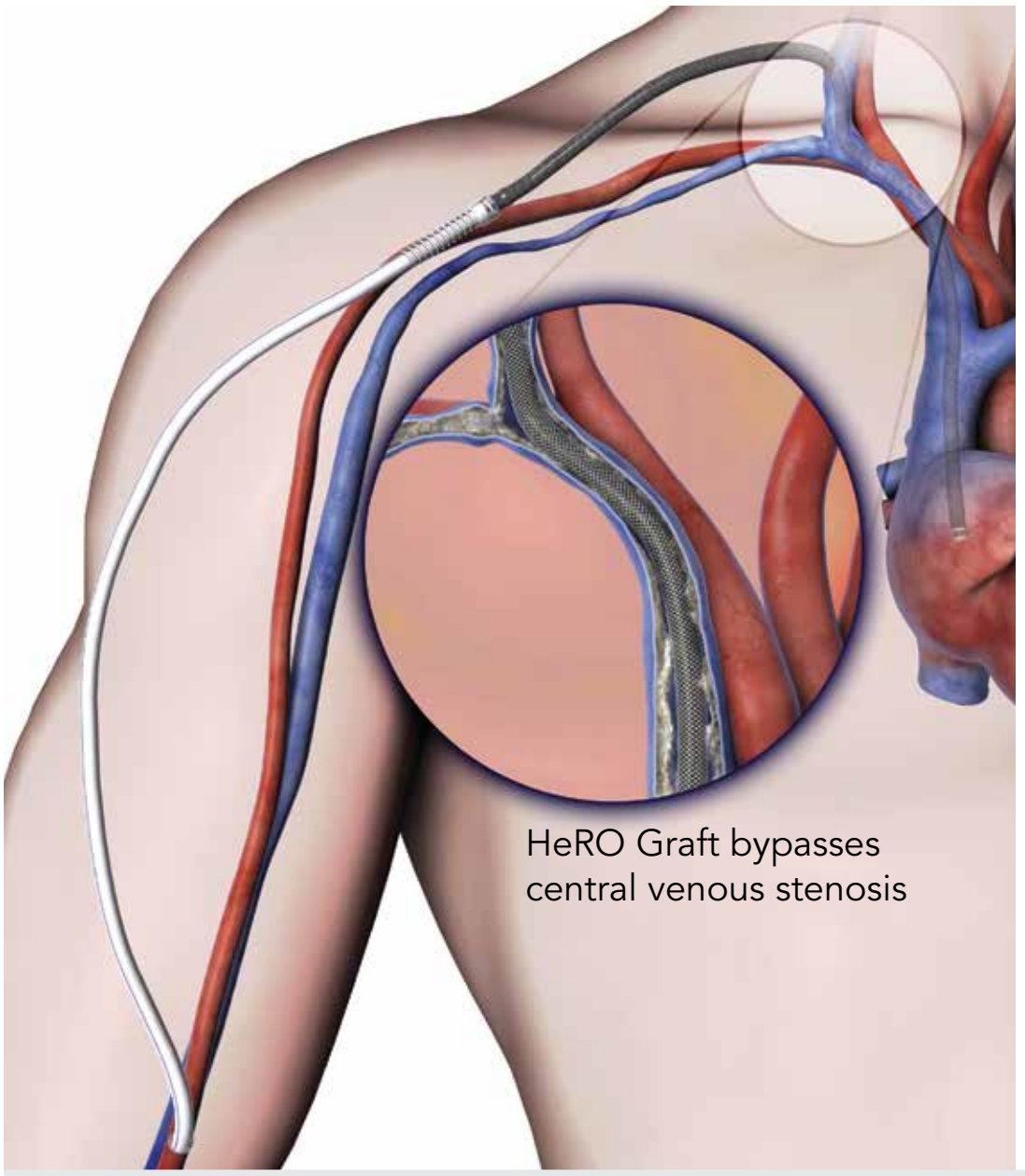

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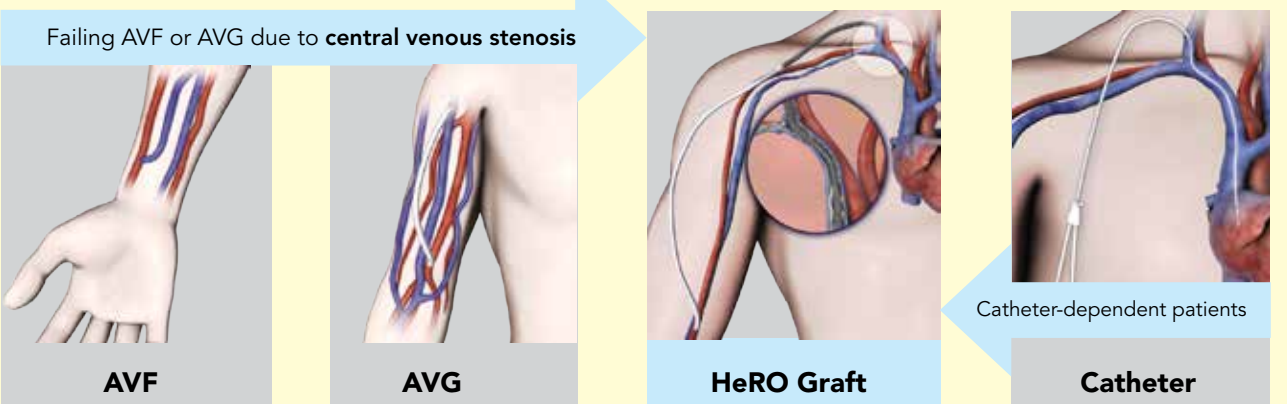

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1) Katzman et al., J Vasc Surg 2009. 2) Gage et al., EJVES 2012. 3) Dageforde et al., JSR 2012.

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Kidney Donors

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The rates of medical ineligibility were higher at lower levels of household income: 60.1 percent of individuals with an income below $35,000 would be unable to donate, versus 49.3 percent with an income above $100,000.

Financial pressures and immigration status are nonmedical factors that often affect the ability to be a kidney donor. With the addition of income below the poverty line and non–United States citizenship, 68.5 percent of the United States population would be ineligible to donate. The figure rose to 75.8 percent after the exclusion of smokers and of individuals with shortness of breath when walking up an incline.

There were significant racial and ethnic differences in the distribution of exclusionary medical conditions, with African Americans having the highest rates of obesity, hypertension, diabetes, and microalbuminuria. Overall, 63.9 percent of African Americans would be ineligible to donate, compared with 54.8 percent of whites.

There is a well-recognized shortage of living kidney donors in the United States. The new report is the first population-based study to evaluate the rates of specific medical conditions and social factors that would exclude individuals from living kidney donation.

"It is well known that African Americans and individuals with lower incomes are at an increased risk of kidney failure. Unfortunately, their potential donors—who are very likely to come from the same social groups—are also much less likely to be kidney donors due to comorbid conditions," said Anthony Bleyer, the senior investigator in the study. "Increasing the number of living donors will require addressing this important issue."

Increasing obesity and worsening health of the general population decrease the pool of potential donors. "Financial compensation for time lost at work and lost income would likely improve the ability to donate in 36.1 percent of the eligible donor pool that has an adjusted family household income of less than $35,000," Bleyer said.

Passing the Torch

By Pascale H. Lane

Six years ago *ASN Kidney News* did not exist. The magazine came to life in January 2009. Over the years it has grown and developed, much like a child. Despite some early stumbles and falls, it has now learned to walk and talk and live.

As with my own children, *ASN Kidney News* has matured and readied itself to live without me. I know our new editor-in-chief, Richard Lafayette, MD, FACP, will help it mature further; however, I will miss my baby just the same. I have learned so much from this job, and it has provided me hours of joy (and some frustration) over the past six years.

This swan song would be incomplete without expressing my thanks to a number of people. First, the editorial advisory board provided inspiration and ideas for content and features. Next, I must thank those who wrote and edited articles and feature sections. I know many of you performed these tasks at least somewhat reluctantly, but your efforts made the magazine successful. I must thank the executive editor, Dawn McCoy. She will be continuing in her role, but I will miss our calls. I must also thank *Kidney News* designer Lisa Cain, who conceived the magazine's original design and continues to work wonders with each monthly issue.

Finally, I want to encourage all members of the American Society of Nephrology to get involved in its efforts. The organization does a lot for us, but it needs the input and energy of its members to get it right. Volunteer for a group or committee. Sign up for political action alerts. And always read *ASN Kidney News*.

Pascale H. Lane, MD, FASN, is the outgoing editor-in-chief of ASN Kidney News. *She will remain on the* KN *Editorial Advisory Board.*

Genetic Markers

Continued from page 1

toward hypothesis-generating genomic screens and novel opportunities to explore polygenetic perspectives, now spanning a wide array of possible analyses falling under the term Genome-Wide Association Study (GWAS)."

With GWAS scientists can analyze genetic variants in multiple individuals to determine if a disease or trait is linked to any single-nucleotide polymorphisms (SNPs). The method has been utilized to investigate numerous disease conditions from chronic kidney disease to cardiovascular disease to cancer. According to Parikh, it provides an excellent approach to discover genetic factors in a population because of the high number of recombinant events the population represents.

Using GWAS methods, the investigators analyzed data from patients at risk for AKI in the hospital setting—760 adults with AKI and 669 adult controls who underwent surgery or received care in the intensive care unit (ICU)—to determine if any SNPs were associated with the development of AKI. The study population was selected from the surgical ICU (TRIBE-AKI study) and the medical ICU (VALID ICU cohort). AKI was defined as a rise in creatinine of 0.3 mg/dL or 50 percent from baseline for at least two days.

After genotyping a total of 992,895 SNPs, the researchers identified six clusters of three or more SNPs on six different chromosomes that are associated with a patient's risk of developing AKI. Among these clusters, four (SOX2-OT, IL33, RAB20, and TAOK1) are intronic (not coding information for protein synthesis) and the remaining 2 are intergenic (involving more than one gene). "All six SNP clusters are protective against AKI, with odds ratios ranging from 0.55 to 0.72," said Parikh.

Brigham and Women's Humphreys found the results very intriguing and noted that they could certainly lead to a better understanding of AKI pathophysiology. "Most of the SNP clusters identified appear to protect against AKI," he said. "Understanding how certain gene variants confer renal protection could lead to new therapeutic strategies as well as new risk prediction tools."

"AKI is a heterogeneous disease and genetic studies need to be continued to fully capture the host risk," Dr. Parikh emphasized. "It is recommended that sequencing can be used as a complement to GWAS, to obtain a better map of the genetic variants in GWAS-significant genes or well-established candidate genes."

Although it was a relatively small study by GWAS standards, the results are promising, Humphreys said. "They clearly call for a much larger analysis to rigorously evaluate the association of these candidate SNPs with risk of AKI."

Parikh agreed, adding that "further collaborative research is required utilizing larger cohorts to confirm these findings and identify candidate genes that are mechanistically linked to pathogenesis of AKI."

This study was supported by the National Institutes of Health R01HL085757 and P30 DK079310 O'Brien Kidney Center Grant.

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CORRECTION

The article, “20 Things to Know about Your ASN” in the October/November issue of *Kidney News* included incorrect numbers for ASN’s membership. Item 19 in the article should have read: “Of ASN’s 15,560 members, 5306 (34 percent) are from outside the United States.”The article incorrectly stated: “Of ASN’s 14,928 members, 6184 (41 percent) are from outside the United States.”*Kidney News* apologizes for the error. The numbers are stated correctly in the online *KN*.

RRT Can Play a Critical Role in Treating Ebola Patients

By Eric Seaborg

Recent Ebola cases have shown that dialysis can play a key role in the survival of critically ill patients. Given the potential importance of renal replacement therapy (RRT) for these patients—and the need for biocontainment procedures to protect caregivers—nephrologists should take active roles in creating treatment plans at their facilities, experts said.

The recovery of a patient at Emory University Hospital shows that even patients at the point of organ failure can recover from Ebola virus disease if given aggressive supportive therapy, according to Harold A. Franch, MD, a nephrologist who helped treat this first Ebola patient known to have received RRT. Franch presented this case study at a special session at Kidney Week as well as in a recent article in the *Journal of the American Society of Nephrology*.

"Now we know that you can recover kidney function, so the damage is not irreversible," Franch said. Supportive therapy—especially fluid replacement—can buy the time needed for a patient's body to mount an immune response to overcome the viral attack, at least in some cases.

Ebola has several effects that can lead to acute kidney injury (AKI) and the need for RRT. These effects include massive fluid loss from vomiting and diarrhea leading to hypovolemia, a systemic inflammatory response syndrome, hemorrhagic fever and clotting abnormalities that increase susceptibility to bleeding, and more, said Sarah Faubel, MD, professor of medicine at the University of Colorado, Denver, and head of ASN's AKI Advisory Group. Faubel also spoke at the Kidney Week special session. "The medical indications for renal replacement therapy in Ebola virus are similar to those in other patients with acute kidney injury, and involve considerations such as volume control, electrolyte balance, and the severity of kidney dysfunction," Faubel said. "In critically ill patients, nephrologists have great experience in considering the risks and benefits of RRT, and the medical decision to start it should follow the usual course."

The decision may follow standard considerations, but the implementation is different because of the need to isolate the patient. A unique aspect of Ebola treatment is that staff protection is as important as the patient outcome. "You will not succeed unless you have an isolation environment that protects your staff safety and the safety of the community," Franch said.

"The biggest lesson in terms of treatment of Ebola patients is that you have to play by the rules of the isolation unit," Franch told *Kidney News*. "When you are in an operating room, you have to do everything according to operating room standards to protect the patient. When you are in an isolation room, you have to do everything according to isolation procedures to protect the staff from infection."

A hospital should develop its plan for dealing with an Ebola patient well before any patient arrives. These plans should follow Centers for Disease Control and Prevention (CDC) guidelines and local community health department recommendations, Faubel said. "Given the potential need for dialysis and the complexity of performing dialysis in patients with Ebola virus disease (EVD), nephrologist involvement is essential in the planning phases of hospitals intending to care for patients with EVD," a guidance document developed by ASN recommends. The plan should address questions such as the use of anticoagulation, an approach for laboratory testing, and how to handle dialysis effluent and the other medical wastes. (Many of these treatment resources can be found online—see sidebar.)

For effective planning, nephrologists need a realistic idea of the infectivity of the virus. Ebola virus is spread through direct contact with blood from infected patients, but can also spread via contact with other fluids such as urine, sweat, vomit, and diarrhea.

Franch said that Ebola is more like hepatitis B than HIV: "It can survive on surfaces about as long as hepatitis B, which isn't that long, but is long enough. It is not like HIV, which dies pretty much as soon as it gets on a surface. Ebola is a lipid-coated virus, so once you really dry it out, it dies. In a dialysis unit, you have to isolate hepatitis B patients, but you don't have to isolate HIV patients."

One factor that makes Ebola so infectious is its very high levels—in the billions of viruses per milliliter of blood—and it can also be present on the patient's skin. It is not transmitted through the respiratory route like influenza, but aerosolized bodily fluids are infectious. These characteristics call for extra caution in dialysis set-up, and argue for the use of continuous RRT to minimize blood spill possibilities.

The case of Thomas Eric Duncan in Dallas, in which two nurses treating him became infected, led the CDC to tighten its guidelines to recommend that personal protective equipment have full body coverage for all workers caring for Ebola patients.

The Emory team adopted procedures designed to minimize the possibility of healthcare worker exposure. "We dedicated a pressure-controlled room, used point-of-care laboratory testing, [and used] dedicated ultrasound and x-ray machines that never left the room. Blood cultures were performed in the room and consulting physicians did not enter the room unless absolutely required," Franch said.

Much of the care relied on ICU nurses with specialized training in isolation protocols and in continuous RRT who volunteered for the duty, but some on-the-spot training was unavoidable. They followed isolation procedures such as checking the integrity of the protective gear of those entering and exiting the isolation unit.

The team used a single dialysis machine "with a small footprint that could stay in the room and had the flexibility to perform both continuous and intermittent modes of dialysis," Franch said, and anything that went into the isolation unit stayed there.

In keeping with Kidney Disease Improving Global Outcomes AKI guidelines, the team put the cannula in the right internal jugular, which is their local practice. Line placement is considered a center-specific consideration, and hospitals should stick with practices they have experience with. This is no time to experiment with new procedures, Faubel said.

Franch said that to minimize filter changes in the dialysis unit, the patient received anticoagulation therapy, which has its own problems because Ebola is a hemorrhagic disease. "For this reason, we used regional citrate anticoagulation with peripheral calcium replacement and regular ionized calcium measurements. While this approach worked extremely well, alkalosis from metabolism of the citrate does become a problem," Franch said.

Emory University Hospital successfully treated a pair of other patients whose kidney function remained normal despite arriving from Africa on day 10 and day 14 of their illnesses. The RRT patient was admitted much earlier, on day 4 of his disease, and developed AKI despite the aggressive supportive therapy. Some observers have doubted whether continued treatment could work when the disease has progressed this far. But with RRT and other support, the patient's immune system responded. "The biggest lesson is that someone can recover from this," Franch concluded.

Resources for Ebola Preparation and Treatment

As the Ebola epidemic reached beyond Africa with patients in the United States and Europe, ASN responded quickly with a wealth of resources, from a podcast on Ebola and dialysis to a well-attended special session at Kidney Week.

The Centers for Disease Control and Prevention and other healthcare leaders reacted as well, and ASN has gathered links to every topic related to nephrology at the page: http://www.asn-online.org/news/2014/1017-ebola.aspx

Some of the most important links on the page are to:

- ASN Frequently Asked Questions Regarding Ebola Virus Disease and Dialysis.
- CDC Recommendations for Safely Performing Acute Hemodialysis in Patients with Ebola Virus Disease in U.S. Hospitals
- A podcast featuring Harold Franch, MD, who successfully dialyzed a patient with Ebola, and Sarah Faubel, MD, chair of ASN's Acute Kidney Injury Advisory Group, discussing Ebola's effects on kidney function and considerations nephrologists should take into account when treating a patient with Ebola.

The page also includes links to a CDC fact sheet on personal protective equipment for Ebola, a CDC hospital checklist for Ebola preparedness, CDC Ebola resources, and the World Health Organization Ebola portal.

Emory University, where a patient was successfully treated using dialysis, has a webpage with "Emory Healthcare Ebola Preparedness Protocols": http://www.emoryhealthcare.org/ebola-protocol/ehc-message.html

Details on the treatment of this patient along with proposed clinical practice guidelines can be found in "Successful Delivery of RRT in Ebola Virus Disease," epublished in *Journal of the American Society of Nephrology*: http://jasn.asnjournals.org/content/early/2014/11/13/ASN.2014111057.abstract

Another recent article about two other Emory patients, "Clinical Care of Two Patients with Ebola Virus Disease in the United States," was published in the *New England Journal of Medicine* and can be found at: http://www.nejm.org/doi/full/10.1056/NEJMoa1409838

High-Impact Clinical Trials Offer New Insights into ADPKD and AKI

By Tracy Hampton with Kurtis Pivert

A total of 27 late-breaking clinical trials were presented at ASN Kidney Week 2014 in Philadelphia. These studies detailed new understandings and innovations in multiple therapeutic areas, including acute kidney injury (AKI), autosomal dominant polycystic kidney disease (ADPKD), dialysis, and diabetic nephropathy. This article highlights some of the leading science presented at the oral plenary High-Impact Clinical Trials session that potentially could influence the clinical approach of kidney health professionals in the United States and beyond.

HALT PKD trials

Two new prospective, multicenter randomized clinical trials sought to understand the influence of blood pressure control on disease progression and comorbidities in patients with ADPKD, the fourth leading cause of end stage renal disease (ESRD). A combination of two studies, the HALT PKD trials first evaluated the effects of rigorous blood pressure control on disease progression and whether combined antihypertensive therapies conferred an additional benefit.

The HALT A study enrolled 558 patients with early ADPKD to determine if rigorous blood pressure control conferred benefits over standard blood pressure control related to a reduced rate of increase in total kidney volume and greater declines in measures of heart and kidney problems (1). Healthy patients between 15 and 49 years old (with an eGFR greater than 60 mL/min/1.73 m^2) were randomized to either standard blood pressure control (120–130/70–80 mm Hg) or low blood pressure control (95–110/60–75 mm Hg) groups. The primary end point was disease progression measured as percent change in total kidney volume.

Low blood pressure control was well tolerated and resulted in a 14.2 percent slower growth of total kidney volume over five years, while conferring some cardiovascular benefits. "Hypertension was very well controlled in both treatment groups," said lead author Arlene Chapman, MD. "The results emphasize the potential importance of early detection and aggressive treatment of hypertension in ADPKD."

In the HALT B study, researchers included 486 ADPKD patients with chronic kidney disease (CKD) stage 3 to find out if treatment with an angiotensin-converting enzyme (ACE) inhibitor was safe and by itself sufficient to achieve blood pressure control in the majority of patients (2). This time, patients were randomized to either ACE inhibitor monotherapy or ACE inhibitor plus an angiotensin-receptor blocker (ARB).

Although both treatment regimens were well tolerated, dual therapy didn't confer any additional treatment benefit. "Both studies showed that ACE inhibitors alone or in combination with ARBs are safe and well tolerated and achieve excellent blood pressure control in the majority of patients with ADPKD," said lead author Vincente Torres, MD, PhD. "However, both failed to demonstrate any superiority of dual blockade with an ACE-I and an ARB compared to an ACE inhibitor alone." Hypertension in ADPKD develops early and associates with disease progression.

Glucose control could help reduce diabetic nephropathy incidence

Longitudinal data obtained in a post-trial observational study suggest that glucose control may be a key determinant for ESRD risk. The ADVANCE-ON Trial found patients who maintained strict glucose control demonstrated evidence of a sustained and significant reduction in ESRD over a long period of time with a median of nearly 10 years.

Follow-up of 8494 patients in the Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) trial, which is the largest clinical trial on diabetes, revealed that intensive glucose control leads to long-term reductions in the risk of developing ESRD (3).

"Our study also suggests that the benefits are greater when treatment is begun early in the course of the disease, and in people in whom blood pressure is well-controlled," said lead author Vlado Perkovic, MBBS, PhD, FASN. "These results suggest that finding better ways to control glucose levels is key to preventing the epidemic of kidney failure due to type 2 diabetes around the world."

New understandings in AKI

Two studies evaluated potential therapies for AKI in the hospital setting, a common complication that can lead to kidney failure and in some cases death.

The first examined the use of aspirin and clonidine with non-cardiac surgery to determine if it could reduce the incidence of AKI. "We need treatments to prevent AKI in the surgical setting, and early data suggested taking aspirin in this regard might be beneficial," said Amit Garg, MD, the study's author. The substudy of the PeriOperative ISchemic Evaluation-2 (POISE-2) Trial included 6905 patients undergoing non-cardiac surgery. Investigators found that use of aspirin around the time of surgery increased the risk of major bleeding, which was associated with a greater risk of subsequent AKI. The use of clonidine (a medication used to treat hypertension) around the time of surgery increased the risk of low blood pressure, which was associated with a greater risk of subsequent AKI.

Compared with placebo, neither aspirin nor clonidine altered the risk of most AKI observed after major non-cardiac surgery. "Approximately 200 million adults undergo major non-cardiac surgery each year, and among patients taking aspirin prior to surgery there is substantial practice variability as to whether it is held or not in the perioperative period," the study investigators noted (4).

Another AKI study evaluated the use of mesenchymal stem cells in patients undergoing cardiac bypass surgery. The ACT-AKI study built on previous work that demonstrated the cells' potential to prevent AKI and promote recovery of renal function after it occurred. A trial of 156 patients who developed AKI following cardiac surgery found that treatment with certain stem cells did not shorten the time it took patients to achieve complete kidney recovery, nor did it decrease their risk of dying prematurely or needing dialysis. Unfortunately, "AKI is a common condition and there is no effective treatment," the researchers said (5).

Advances in dialysis reported

Several studies reported research on innovations in care for patients on dialysis. The first study examined a new approach to in-stent restenosis, a common problem in this population. It included 265 dialysis patients, and found that the Fluency® Plus Endovascular Stent Graft—which is placed inside a blocked stent to re-open it and allow adequate blood to flow and dialysis to take place—was superior to balloon angioplasty alone through 6 months. The Fluency® Plus Endovascular Stent Graft was better for restoring blood flow and keeping the area open longer. "In-stent restenosis is a common problem in the care of ESRD patients. This study represents the first level-1 evidence for the use of stent-grafts in the treatment of both arteriovenous fistula and arteriovenous graft stenosis," said lead author Alexander Yevzlin, MD (6).

Another, ACTIVE Dialysis Multinational Trial, examined the use of extended hemodialysis hours to determine if it would improve patient outcomes. Among 200 patients on dialysis, extending weekly dialysis hours for 12 months did not improve quality of life, but was linked with improvements in some laboratory measures (such as potassium and phosphate blood levels) and a reduced need for blood pressure medications (7).

Disclosure information is available at http://www.asn-online.org/education/kidneyweek/2014/program-faculty.aspx. Funding information is available in the Kidney Week 2014 Abstract Supplement at http://www.asn-online.org/abstracts.

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Our Roots Go Deep

Exercise May Slow Kidney Disease Progression

Patients with stage 3 to 4 chronic kidney disease (CKD) assigned to an exercise/rehabilitation intervention have better maintenance of kidney function at one-year follow-up, according to preliminary research presented at Kidney Week 2014.

In a pilot study, consultant renal physiotherapist Sharlene A. Greenwood of King's College London and colleagues evaluated an exercise training program for patients with predialysis CKD. Ten patients received the study intervention, which consisted of thrice-weekly exercise sessions at a gym setting in a community hospital. Another 10 patients received usual care.

The exercise programs were individualized, accounting for patient choice and aiming for a combination of aerobic and resistance exercises. Aerobic exercise was predominantly performed on recumbent stationary exercise cycles, at an intensity corresponding to 80 percent heart rate reserve with maximum heart rate, based on incremental exercise testing. Resistance training was prescribed at 80 percent of one repetition maximum. The intervention also included an individual session with a senior renal physiotherapist for discussion of exercise and personal goals with use of a motivational interviewing approach.

Kidney function was assessed by comparing the rate of change in serum creatinine-based estimated GFR (eGFR) for each participant for 12 months before the study versus during the 12-month intervention period. Other outcomes of interest included pulse wave velocity, exercise capacity (VO_2 peak), waist circumference, and body weight. Eight patients in the intervention group and 10 control individuals completed the study.

At the end of 12 months, patients assigned to the exercise/rehabilitation group had better-preserved kidney function. The mean difference in eGFR was 7.8 mL/min/1.73 m^2/year, compared with the usual care group.

Exercise/rehabilitation was also associated with reduced body weight and improved exercise capacity. After adjustment for baseline differences, patients in the intervention group had a 5.6 kg reduction in body weight and a 7.1 cm reduction in waist circumference, with a 5.7 mL/kg/min increase in relative VO_2 peak.

There was also a significant 2.30 m/second reduction in pulse wave velocity in the intervention group. The eGFR benefit was inversely correlated with the changes in pulse wave velocity and waist circumference.

Patients with stage 3 to 4 CKD have reduced exercise capacity, which may contribute to their risk of cardiovascular disease—the leading cause of death in CKD. Exercise training has the potential to preserve kidney function and improve cardiovascular risk factors in predialysis patients with CKD.

This pilot study suggests substantial benefits of an exercise/rehabilitation program for patients with stage 3 to 4 CKD. The benefits include a slower decline in kidney function after 12 months of exercise training, compared with usual care.

Together with improvements in exercise capacity and body weight, the exercise/rehabilitation program may be associated with improved quality of life in this group of patients. "Although small, our study suggests that long-term tailored exercise prescription with motivational interviewing is a feasible approach for exercising patients with progressive CKD, and sets the scene for a large multicenter study," Greenwood said.

New Findings on Diet and Kidney Disease

Research presented at Kidney Week 2014 highlights dietary factors affecting kidney disease outcomes—including a study reporting that a "healthy diet" and lower sodium intake are associated with a reduced risk of major renal outcomes. Another report draws attention to the potentially high levels of potassium added to some "reduced-sodium" foods.

Nephrologist Andrew Smyth, MB, of National University of Ireland Galway and his colleagues presented the results from the Diet and Health Study of the National Institutes of Health and the American Association of Retired Persons. On the basis of findings on food frequency questionnaires completed by nearly 545,000 participants, the researchers evaluated the relationship between diet quality, sodium and potassium intake, and major renal outcomes—dialysis or death from renal causes. The study evaluated several different definitions of a "healthy diet": the Healthy Eating Index, the Alternate Healthy Eating Index, the Mediterranean Diet Score, and the Recommended Food Score, along with sodium and potassium intake.

On three of four diet quality measures, a healthy diet was associated with a lower risk of dialysis or death from a renal cause; there was no association with the Recommended Food Score. On multivariate analysis, the risk of the combined outcome was 16 to 23 percent lower for participants in the highest quintile of dietary quality, compared with the lowest quintile.

Said Smyth: "We found that high sodium intake, average 4.7 g/day, was associated with an increased risk, but no difference between low and moderate intakes: average 2.0 and 3.1 g/day." High potassium intake was associated with a reduced risk.

The risk was 19 percent higher for participants in the highest quintile of sodium/potassium ratio. The researchers conclude, "Our findings extend the known benefits of healthy eating and show that the consumption of a healthy diet, including reducing sodium intake from high levels and increasing potassium intake, may protect from future major renal endpoints."

Arti Sharma Parpia, RD, of St. Michael's Hospital, Toronto, and colleagues from the University of Toronto evaluated the protein, sodium, phosphorus, and potassium content of "reduced-sodium" meat and poultry products sold at grocery stores. "Food manufacturers may use phosphate and potassium additives to replace the functional and flavor properties of sodium, and the amount is usually not listed on food labels," the researchers write.

They found that sodium-reduced products contained 25 to 55 percent less sodium than their non–sodium-reduced counterparts: the mean difference was 460 mg per 100 g. The sodium-reduced products also contained on average 47 percent more potassium, with a wide variability in potassium content: from 210 to 1500 mg per 100 g. Potassium-containing additives were found on the ingredients list of 63 percent of sodium-reduced products, compared with 25 percent of non–sodium-reduced products.

Phosphorus and protein levels did not differ for the two groups of products. "Potassium additives are frequently added to sodium-reduced meat and poultry products in amounts that significantly contribute to the potassium load for CKD patients," the researchers conclude. "Patients requiring a potassium restriction should limit their intake of sodium-reduced meat and poultry products."

Poor Air Quality Linked to CKD Risk

Could differences in air quality contribute to the observed regional variations in chronic kidney disease (CKD)? A study presented at Kidney Week 2014 finds a higher prevalence of recognized CKD in counties of the United States with higher particulate air pollution.

Epidemiologist Jennifer L. Bragg-Gresham, PhD, of the University of Michigan and colleagues evaluated differences in pollutant levels—specifically, fine particles smaller than 2.5 µm ($PM_{2.5}$)—as potentially contributing to regional differences in CKD prevalence.

On the basis of Medicare claims data from 1.1 million persons aged 65 years and older, the prevalence of CKD by county ranged from zero to 60 percent, with a median of 16 percent. Associations between levels of $PM_{2.5}$, determined from U.S. Environmental Protection Agency air-quality data made publicly available through the WONDER online database of the Centers for Disease Control and Prevention, and prevalence of recognized CKD in the Medicare data were analyzed.

"We found that poorer air quality was associated with a higher prevalence of CKD," Bragg-Gresham and coauthors write. With $PM_{2.5}$ treated as a continuous variable, each increment of 4 µg/m^3 in $PM_{2.5}$ was associated with a 3 percent higher CKD prevalence, after adjustment for individual-level confounders.

When counties were grouped by quartiles of $PM_{2.5}$, a threshold at approximately14 µg/m^3 was observed for higher CKD prevalence. This is much lower than the level typically considered unhealthy (40 µg/m^3) for sensitive groups, such as children, the elderly, and people with cardiorespiratory disease.

Well recognized individual risk factors, such as age, diabetes, and hypertension explain some, but not all, of the wide regional variation in CKD prevalence. As yet unrecognized environmental factors, such as air pollution, might account for some part of the additional variability.

Although observational studies cannot show causal relationships, this large cross-sectional study suggests that higher $PM_{2.5}$ levels in a county are associated with higher rates of diagnosed CKD. The researchers call for further studies to clarify this relationship, including laboratory diagnosis of CKD, longitudinal designs, assessment of other air and environmental pollutants, and measures of individual pollutant exposure.

"If this association is borne out by future studies, it would have implications for reducing air pollution exposure for those with CKD and also for those at risk for the condition," Bragg-Gresham said. "The potential public health significance of this finding is even greater for regions and countries with much higher levels of air pollution than the United States."

Industry Spotlight

DaVita Activates Compliance after $400 Million Settlement

DaVita announced in May 2013 that it had set aside $300 million in case the company would be required to pay a federal fine, revealed CEO Kent Thiry, during what he termed a "sober" conference call to announce quarterly results. Eventually, the company had set aside a total of $414 million, so it would be prepared to pay for a potential violation of the False Claims Act when the time came.

The settlement money has finally come due, and amounted to $387 million plus interest accrued between February and October of this year.

In late October, the U.S. Department of Justice (DoJ) announced that DaVita had agreed to pay $350 million to resolve claims that the company had violated the False Claims Act. The claims included paying kickbacks to induce the referral of patients to DaVita dialysis clinics. Headquartered in Denver, DaVita has dialysis clinics in 46 states and the District of Columbia.

A fine of $39 million was also part of the settlement to the federal government, payment for two particular deals. In addition, another $11.5 million has to be paid to cover Medicaid (state) compensation. Interest charges on the settlement amount began in Feb. 2014 at the rate of 2.25 percent per year, the DoJ announced.

For its part, DaVita announced that the investigation, which covered a period from March 2005 to February 2014, was resolved with findings that "patient care was never at issue, nor were billing or payment practices." The DaVita statement added: "We are proud of our commitment to compliance over our 15-year history. We have worked incredibly hard to get things right and it is our belief there was no intentional wrongdoing."

The DoJ statement noted that DaVita had joint ventures with and eventually acquired Gambro in 2005. Gambro was accused of fraud, had to pay more than $300 million in a settlement, and had to unwind its own joint venture agreements as part of that settlement. DaVita had compliance agreements in place related to its Gambro relationship and eventual ownership.

In the current settlement, DaVita said it would "undo 11 joint venture transactions covering 26 of our 2,119 clinics." According to the *Denver Business Journal*, the U.S. Attorney's Office also announced that, "in conjunction with today's announcement," it was closing a criminal probe into two joint ventures involving DaVita and doctors. The $39 million civil forfeiture agreed to by DaVita was "based upon conduct related to two specific joint venture transactions entered into in Denver," the office said, implying that ownership although crimes were not discovered in relation to the two joint ventures. (Forfeiture describes the process wherein a civil court, after all the interested parties have had a chance to make their case, orders a change in ownership of the property, without criminal charges.)

DaVita also will institute a strictly outlined compliance program through a Corporate Integrity Agreement that includes many required elements and potential fines if compliance requirements fail to be established, such as: "unwinding of the Subject Joint Venture Clinics, except to the extent covered by a Monitor's certification." The program calls for an independent monitor, a written code of conduct, detailed training of DaVita staff and others covered under the settlement, including board members; and hiring a chief compliance officer.

Now DaVita will have to start entering into transactions that uncouple 11 of the same clinics that it worked to partner with. The settlement noted that for 9 years, until February 2014, DaVita had identified physicians or physician groups with patient populations suffering from renal disease. DaVita, the claim said, "offered them (the physicians) lucrative opportunities to partner with DaVita by acquiring or selling an interest in the dialysis clinics to which their patients would be referred," and the physicians also could not compete with the DaVita clinics nor refer patients to other dialysis providers.

Policy Update

CMS Final Rule for 2015 Holds No Surprises

By Mark Lukaszewski

On Friday, October 31, 2014, the Centers for Medicare & Medicaid Services (CMS) released its 2015 End-Stage Renal Disease (ESRD) Prospective Payment System (PPS) and Quality Incentive Program (QIP) final rule for calendar years 2017 and 2018. This article provides a basic overview of the key takeaways of the rule.

After close inspection, ASN has concluded that the final rule did not contain any unexpected adjustments to the ESRD PPS or QIP and does not differ substantially from the proposed rule. The society determined it is likely that the 2015 rulemaking cycle will have a more pronounced effect on the program, as CMS is expected to provide further clarity on how new drugs may be added to the bundle, as well as make changes to the low-volume adjuster.

ESRD PPS

CMS finalized every aspect of the Protecting Access to Medicare Act (PAMA) pertaining to the ESRD PPS, including setting the base rate at a 0.1 percent increase from 2014 and delaying the inclusion of oral-only drugs until 2024. CMS noted that it believes the agency has the authority to add new services to the bundle, an issue that has recently been debated within the kidney community.

CMS addressed the provision of dialysis beyond the standard three times per week, restating its position that facilities must furnish medical justification for more frequent dialysis, and that dialysis modality choice does not constitute medical justification. The agency also stated that while it is not changing its policy regarding payment for drugs that are included in the PPS but are furnished for the treatment of ESRD, it recognizes that there is ongoing concern regarding patient access to prescription medications. CMS is considering various alternatives for dealing with this issue and plans to put out guidance in the near future.

Quality Improvement Program

In terms of the QIP, CMS finalized a proposal to implement a risk-standardized 30-day all-cause hospital readmissions (SRR) measure. ASN strongly supported this measure in concept but recommended against finalizing the measure owing to numerous concerns with the measure and methodology as designed. Notably, the National Quality Forum voted against the SRR measure when it was considered for endorsement this fall.

On a more positive note, CMS decided against adding a new measure to assess conditions treated by oral-only drugs, which is consistent with ASN's encouragement to utilize a few highly meaningful measures rather than adding more watered-down measures. In addition, CMS finalized its proposal to remove the "Hgb >12 g/dL anemia management measure," a change ASN has supported for several years because the measure is topped out.

ASN, together with the greater kidney community, will continue to work together with CMS in order to make sure that the measures being developed guarantee the highest quality care possible for the millions of Americans with kidney disease. To learn more about this issue, or to read the ASN comment letter to CMS, please visit the ASN advocacy page at http://www.asn-online.org/policy/.

Final Physician Fee Rule Includes Wins for Kidney Community

By Mark Lukaszewski

On Halloween Eve 2014, CMS released the 2015 Physician Fee Schedule final rule, finalizing several important victories for ASN and other advocates in the kidney community.

A top ASN priority, also supported by other stakeholders, was to modify the billing rules to allow nephrologists to bill the full month of care when a home dialysis patient has been hospitalized during that month. CMS finalized the proposal it laid out in the proposed rule that would allow nephrologists who complete monthly assessment of home dialysis patients and at least one face-to-face patient visit to bill for the full monthly MCP code for home dialysis patients who are hospitalized that month. Previously, nephrologists had to bill the per diem code in months when their home dialysis patients were hospitalized. ASN and other advocates, including the Home Dialysis Alliance and Kidney Care Partners, supported this change,.

Also in the final rule, CMS addressed concerns raised by ASN and others in the Continuing Medical Education (CME) community that physicians attending certified CMS programs like ASN Kidney Week could get unfairly reported in the Open Payments program. The Open Payments program is an online federal initiative to increase transparency regarding physicians' financial relationships with industry, such as gifts and travel.

CMS established reporting rules that *specifically exclude* CME payments from the Open Payments program, including speaker-related payments and tuition support for attendees, so long as they are not directed by a commercial supporter.

Although CMS does not yet have the legal authority from Congress to designate patients' homes as qualifying telehealth sites, ASN has and will continue to encourage both CMS and Congress to consider the potential benefits of adding the monthly capitation payment (MCP) services for home dialysis patients to the Medicare telehealth list as federal statute regarding telehealth sites evolves. This could enable more patients to consider dialysis at home, and reduce the travel burden for both patients and providers. CMS did note that it could pilot telehealth MCP care through its Innovation Center, opening up a new advocacy angle for 2015.

For more information on the final rule, please visit ASN's policy webpage at http://www.asn-online.org/policy/

Journal View

Dabigatran Linked to Excess Bleeding Risk

The risk of bleeding complications is increased for patients with atrial fibrillation taking dabigatran compared with warfarin—and patients with chronic kidney disease are among the highest-risk subgroups, according to a report in *JAMA Internal Medicine*.

The retrospective cohort study used pharmacy and medical claims data for a random 5 percent sample of Medicare beneficiaries in 2010 to 2011. Two groups of patients who started anticoagulant treatment within 60 days after diagnosis of atrial fibrillation were identified: 1302 receiving dabigatran and 8102 receiving warfarin. Episodes of major and minor bleeding by site were compared between groups, with propensity score weighting to account for differences in patient characteristics.

Patients starting treatment with dabigatran had higher bleeding rates than did those starting warfarin: hazard ratio (HR) 1.30 for any bleeding event and 1.58 for major bleeding. The adjusted rates of major bleeding were 9.0 percent with dabigatran versus 5.9 percent with warfarin. The risk of gastrointestinal bleeding was also higher with dabigatran: HR 1.85.

The rates of most types of bleeding complications were higher with dabigatran, including hematuria (HR 1.41), vaginal bleeding (HR 2.27), hemarthrosis (HR 2.78), and hemoptysis (HR 1.49). The exception was intracranial hemorrhage: HR 0.32 with dabigatran.

The excess bleeding risk remained significant in defined high-risk subgroups. The rates of major bleeding with dabigatran were particularly high for African American patients (HR 2.12) and for patients with chronic kidney disease (HR 2.07).

Soon after the approval of dabigatran, there were reports of severe bleeding events, particularly among elderly patients and those with renal impairment. Subsequent studies of this risk have yielded conflicting results.

This large analysis of Medicare beneficiaries with atrial fibrillation supports concerns about higher bleeding risk with dabigatran, compared with warfarin. The authors urge caution in prescribing dabigatran, especially to African Americans and patients with chronic kidney disease renal impairment. They also highlight the elevated risk of gastrointestinal bleeding across all patient subgroups [Hernandez I, et al. Risk of bleeding with dabigatran in atrial fibrillation. *JAMA Intern Med* doi:10.1001/jamainternmed.2014.53980].

ASN LEADING THE FIGHT AGAINST KIDNEY DISEASE

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Policy Update

ASN Goes to NIH and PCORI

By Grant Olan

On September 19, 2014, ASN Secretary-Treasurer and Research Advocacy Committee Chair John R. Sedor, MD, FASN, joined other members of the committee and several of the society's advisory groups to visit the National Institutes of Health (NIH) and Patient-Centered Outcomes Research Institute (PCORI) for "Kidney Research Advocacy Day."

ASN began annual visits to NIH in 2012 to raise the profile of kidney disease, promote more kidney-related research, and encourage more cross-institute collaboration. This year, Kidney Research Advocacy Day participants met with leaders of the National Heart Lung and Blood Institute (NHLBI), National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), National Institute of Biomedical Imaging and Bioengineering (NIBIB), National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), and National Institute on Aging (NIA). The NIAMS and PCORI meetings were the first one-on-one meetings ASN has had with their leaders.

An internal ASN study of kidney research revealed that less than 1 percent of what the federal government spends on the cost of care for patients with kidney disease is invested in kidney research (approximately $80 billion in Medicare expenditures vs. $650 million for kidney research). The cost of just the Medicare End Stage Renal Disease (ESRD) program is nearly $35 billion, which is more than the entire budget for NIH (less than $30 billion in 2014).

Moreover, in 2013 NIH spent less per patient on kidney research vs. heart disease, cancer, and HIV/AIDS ($30 on kidney research per patient compared to $61, $534, and $2,898, respectively).

U.S. Congressional Kidney Caucus Co-Chair Rep. Tom Marino (R-PA) recently requested a review of federal investments in kidney research from the Government Accountability Office (GAO), a bipartisan agency that is highly regarded by Congress. Obtaining a congressional request for a GAO report on this topic is the cornerstone of ASN's aggressive new Research Advocacy Strategic Plan to bolster support for more federal kidney research funding.

"I believe the GAO report is a crucial first step in understanding the current kidney research landscape, and anticipate it will confirm that kidney research is underfunded," Dr. Sedor said.

"I believe the report will pay dividends for research funding down the line," ASN President Jonathan Himmelfarb, MD, FASN added. "Once complete, ASN looks forward to sharing the results with the entire kidney community."

PCORI and each of the NIH institutes were receptive to ASN's concerns and expressed interest in working with the society to advance kidney-related research. Below are some takeaways from the Kidney Research Advocacy Day meetings.

National Heart Lung and Blood Institute (NHLBI)

ASN met with Lawrence J. Fine, MD, Branch Chief, Clinical Applications and Prevention Branch, NHLBI, and other senior staff at the institute. NHLBI supports collaboration with NIDDK and kidney-related initiatives, such as an Ischemia-Chronic Kidney Disease ancillary study. Most heart trials exclude patients with advanced kidney disease despite the fact that heart disease is the leading cause of death for that population. ASN encouraged the institute to also measure albuminuria as well as collect and archive urine samples (for use by the research community) in the study and as many other studies as possible.

National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS)

ASN met with NIAMS Deputy Director Robert H. Carter, MD, and other senior staff. NIAMS supports lupus nephritis research. A new NIH initiative called Accelerating Medicines Partnership (AMP) will explore possible biological pathways for treating lupus nephritis. AMP is a public-private partnership between NIH, industry, and nonprofit groups to increase the number of new diagnostics and therapies for patients and reduce the time and cost of developing them.

National Institute of Biomedical Imaging and Bioengineering (NIBIB)

ASN met with NIBIB Acting Deputy Director William J. Heetderks, MD, PhD, and other senior staff. NIBIB supports an initiative called the Quantum Grants Program. The goal is to make a "profound (quantum) impact on the prevention, diagnosis, or treatment of a major disease or national public health problem through the development and implementation of biomedical technologies within 10 years." The program is funding a project to develop an implantable bioartificial kidney.

National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)

ASN met with NIDDK Director Griffin P. Rodgers, MD, Deputy Director Gregory G. Germino, MD, Kidney Urologic and Hematologic Diseases Division Director Robert A. Star, MD, and other senior staff. In addition to the issues outlined above, ASN and NIDDK discussed expanding NIH's loan repayment to include adult bench research, a possible 2015 NIDDK health disparities initiative and other institute research funding priorities, and the Kidney Research National Dialogue.

National Institute on Aging (NIA)

ASN met with NIA Deputy Director Marie A. Bernard, MD, and other senior staff. NIA has supported kidney-related initiatives on acute kidney injury, organ donation, and renal function in older Americans. NIA has also supported initiatives to advance research on multiple chronic conditions such as the request for applications on "Behavioral Interventions to Address Multiple Chronic Health Conditions in Primary Care." ASN encouraged the institute to also consider initiatives in other areas where there has been little study, such as best management practices for older Americans nearing ESRD and kidney–mineral bone disorders.

Patient-Centered Outcomes Research Institute (PCORI)

ASN met with PCORI Chief Science Officer Bryan Luce, PhD, and other senior staff. PCORI is a new institute with a relatively small research grant portfolio and has provided more than $16 million in grants for kidney-related projects to date. PCORI recently announced a joint collaboration with NHLBI on a comparative effectiveness research initiative to study how to reduce disparities in treating hypertension. The initiative is only the second PCORI–NIH collaboration. The first was for a study on falls among the elderly with NIH. ASN encouraged PCORI and NHLBI to consider kidney disease phenotypes given the significant association between the two.

Kidney Research Advocacy Day Participants

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Efforts to Address Health Disparities: A Multipronged Approach

By Rachel Meyer

In many ways, kidney disease is the poster child for health disparities in the United States. In 2012, African Americans were nearly four times as likely and Native Americans nearly twice as likely as whites to experience kidney failure (1). African Americans, Hispanics, Native Americans, and Alaska Natives are twice as likely as whites to have diabetes, the leading cause of kidney disease. The incidence of ESRD in people with diabetes is six times as high in Native Americans compared with the incidence in the general population of diabetes patients. Moreover, minority populations spend more time on the wait list for a kidney transplant and are less likely to utilize a home dialysis modality (2).

Addressing these health disparities was a top ASN Public Policy priority in 2014, and in 2015 the society will continue to prioritize efforts at the federal legislative, regulatory, and profession-sanctioned levels to raise awareness and reduce disparities. Table 1 depicts ASN's efforts to integrate health disparities advocacy into every aspect of the society's 2014 policy priorities. ASN endeavors to ensure that Congress, federal research funding agencies, and Medicare are aware of these discrepancies and take every opportunity to confront them on behalf of the millions of Americans who are at disproportionate risk for kidney disease or compromised access to kidney care.

Table 1. 2014 ASN Policy Efforts to Address Health Disparities

2014 ASN Public Policy Priorities	Efforts to Address Health Disparities
1. Influence the evolution of the ESRD Quality Incentive Program and participate, in collaboration with the entire kidney community, in the bundle rebasing process.	• Highlighted effects of proposed changes to the ESRD bundle and QIP on underrepresented minorities in all comment letters. • Encouraged development and selection of QIP measures and risk-adjustment strategies that properly account for the unique needs and characteristics of underrepresented minorities.
2. Shape the implementation and evaluation of the ESRD Seamless Care Organization (ESCO) program.	• Promoted the need for providers and practices of all sizes and types, serving all patient populations and geographic regions, to be able to participate in the ESCO program. • Advocated for strong oversight to prevent cherry-picking of vulnerable patient populations. • Emphasized need for vigilance regarding equitable access to transplant.
3. Develop and implement a long-range strategic plan regarding interactions with NIH and NIDDK, and continue to expand ASN's research advocacy beyond NIH.	• Promoted health disparities research among and collaboration between federal research agencies and programs as ASN's key research recommendation, including NIH and the VA's research office, • Asked the GAO to specifically assess gaps in health disparities research as part of GAO's assessment of the overall federal investment in kidney research funding.
4. Collaborate with other stakeholder coalitions to ensure a successful launch of the NIDDK Coalition.	• Advocated that the Friends of the NIDDK join ASN in emphasizing the importance of disparities research as a crucial, cross-cutting area in all interactions with NIDDK.
5. Promote recognition of Kidney Health Initiative (KHI) within FDA and Congress, and begin to develop policy positions on legislation related to the FDA.	• Highlighted the fact that significant health disparities exist in kidney disease as an important reason to promote innovative technologies and therapies that could potentially help reduce inequities in risk, diagnosis, and care of underrepresented minorities.
6. Foster the interest of younger and more diverse nephrologists in public policy issues, including establishing a policy track at Kidney Week.	• Ensure diversity in terms of speaker and moderator selection in public policy sessions.
7. Identify potential legislative or regulatory strategies to address the declining interest in nephrology careers.	• Explored developing federal loan repayment programs that support underrepresented minorities • Encouraged federal funding agencies, especially NIMHD and NIDDK, to continue to expand programs that specifically fund underrepresented minorities

1. USRDS, 2014.
2. DPC Education Center. http://dpcedcenter.org/kidney-health-disparities

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SAMSCA® (tolvaptan) tablets for oral use

Brief Summary of Prescribing Information. Please see Full Prescribing Information for complete product information.

WARNING: INITIATE AND RE-INITIATE IN A HOSPITAL AND MONITOR SERUM SODIUM

SAMSCA should be initiated and re-initiated in patients only in a hospital where serum sodium can be monitored closely. Too rapid correction of hyponatremia (e.g., >12 mEq/L/24 hours) can cause osmotic demyelination resulting in dysarthria, mutism, dysphagia, lethargy, affective changes, spastic quadriparesis, seizures, coma and death. In susceptible patients, including those with severe malnutrition, alcoholism or advanced liver disease, slower rates of correction may be advisable.

INDICATIONS AND USAGE: SAMSCA is indicated for the treatment of clinically significant hypervolemic and euvolemic hyponatremia (serum sodium <125 mEq/L or less marked hyponatremia that is symptomatic and has resisted correction with fluid restriction), including patients with heart failure and Syndrome of Inappropriate Antidiuretic Hormone (SIADH).

Important Limitations: Patients requiring intervention to raise serum sodium urgently to prevent or to treat serious neurological symptoms should not be treated with SAMSCA. It has not been established that raising serum sodium with SAMSCA provides a symptomatic benefit to patients.

CONTRAINDICATIONS: SAMSCA is contraindicated in the following conditions:

Urgent need to raise serum sodium acutely: SAMSCA has not been studied in a setting of urgent need to raise serum sodium acutely.

Inability of the patient to sense or appropriately respond to thirst: Patients who are unable to auto-regulate fluid balance are at substantially increased risk of incurring an overly rapid correction of serum sodium, hypernatremia and hypovolemia.

Hypovolemic hyponatremia: Risks associated with worsening hypovolemia, including complications such as hypotension and renal failure, outweigh possible benefits.

Concomitant use of strong CYP 3A inhibitors: Ketoconazole 200 mg administered with tolvaptan increased tolvaptan exposure by 5-fold. Larger doses would be expected to produce larger increases in tolvaptan exposure. There is not adequate experience to define the dose adjustment that would be needed to allow safe use of tolvaptan with strong CYP 3A inhibitors such as clarithromycin, ketoconazole, itraconazole, ritonavir, indinavir, nelfinavir, saquinavir, nefazodone, and telithromycin.

Anuric patients: In patients unable to make urine, no clinical benefit can be expected.

Hypersensitivity: SAMSCA is contraindicated in patients with hypersensitivity (e.g. anaphylactic shock, rash generalized) to tolvaptan or any component of the product *[see Adverse Reactions (6.2)]*.

WARNINGS AND PRECAUTIONS:

Too Rapid Correction of Serum Sodium Can Cause Serious Neurologic Sequelae (see BOXED WARNING): Osmotic demyelination syndrome is a risk associated with too rapid correction of hyponatremia (e.g., >12 mEq/L/24 hours). Osmotic demyelination results in dysarthria, mutism, dysphagia, lethargy, affective changes, spastic quadriparesis, seizures, coma or death. In susceptible patients including those with severe malnutrition, alcoholism or advanced liver disease, slower rates of correction may be advisable. In controlled clinical trials in which tolvaptan was administered in titrated doses starting at 15 mg once daily, 7% of tolvaptan-treated subjects with a serum sodium <130 mEq/L had an increase in serum sodium greater than 8 mEq/L at approximately 8 hours and 2% had an increase greater than 12 mEq/L at 24 hours. Approximately 1% of placebo-treated subjects with a serum sodium <130 mEq/L had a rise greater than 8 mEq/L at 8 hours and no patient had a rise greater than 12 mEq/L/24 hours. Osmotic demyelination syndrome has been reported in association with SAMSCA therapy *[see Adverse Reactions (6.2)]*. Patients treated with SAMSCA should be monitored to assess serum sodium concentrations and neurologic status, especially during initiation and after titration. Subjects with SIADH or very low baseline serum sodium concentrations may be at greater risk for too-rapid correction of serum sodium. In patients receiving SAMSCA who develop too rapid a rise in serum sodium, discontinue or interrupt treatment with SAMSCA and consider administration of hypotonic fluid. Fluid restriction during the first 24 hours of therapy with SAMSCA may increase the likelihood of overly-rapid correction of serum sodium, and should generally be avoided.

Liver Injury: SAMSCA can cause serious and potentially fatal liver injury. In a placebo-controlled and open label extension study of chronically administered tolvaptan in patients with autosomal dominant polycystic kidney disease, cases of serious liver injury attributed to tolvaptan were observed. An increased incidence of ALT greater than three times the upper limit of normal was associated with tolvaptan (42/958 or 4.4%) compared to placebo (5/484 or 1.0%). Cases of serious liver injury were generally observed starting 3 months after initiation of tolvaptan although elevations of ALT occurred prior to 3 months. Patients with symptoms that may indicate liver injury, including fatigue, anorexia, right upper abdominal discomfort, dark urine or jaundice should discontinue treatment with SAMSCA. Limit duration of therapy with SAMSCA to 30 days. Avoid use in patients with underlying liver disease, including cirrhosis, because the ability to recover from liver injury may be impaired. *[see Adverse Reactions (6.1)]*.

Dehydration and Hypovolemia: SAMSCA therapy induces copious aquaresis, which is normally partially offset by fluid intake. Dehydration and hypovolemia can occur, especially in potentially volume-depleted patients receiving diuretics or those who are fluid restricted. In multiple-dose, placebo-controlled trials in which 607 hyponatremic patients were treated with tolvaptan, the incidence of dehydration was 3.3% for tolvaptan and 1.5% for placebo-treated patients. In patients receiving SAMSCA who develop medically significant signs or symptoms of hypovolemia, interrupt or discontinue SAMSCA therapy and provide supportive care with careful management of vital signs, fluid balance and electrolytes. Fluid restriction during therapy with SAMSCA may increase the risk of dehydration and hypovolemia. Patients receiving SAMSCA should continue ingestion of fluid in response to thirst.

Co-administration with Hypertonic Saline: Concomitant use with hypertonic saline is not recommended.

Drug Interactions:

Other Drugs Affecting Exposure to Tolvaptan:

CYP 3A Inhibitors: Tolvaptan is a substrate of CYP 3A. CYP 3A inhibitors can lead to a marked increase in tolvaptan concentrations *[see Dosage and Administration (2.3), Drug Interactions (7.1)]*.

Do not use SAMSCA with strong inhibitors of CYP 3A *[see Contraindications (4.4)]* and avoid concomitant use with moderate CYP 3A inhibitors.

CYP 3A Inducers: Avoid co-administration of CYP 3A inducers (e.g., rifampin, rifabutin, rifapentin, barbiturates, phenytoin, carbamazepine, St. John's Wort) with SAMSCA, as this can lead to a reduction in the plasma concentration of tolvaptan and decreased effectiveness of SAMSCA treatment. If co-administered with CYP 3A inducers, the dose of SAMSCA may need to be increased *[see Dosage and Administration (2.3), Drug Interactions (7.1)]*.

P-gp Inhibitors: The dose of SAMSCA may have to be reduced when SAMSCA is co-administered with P-gp inhibitors, e.g., cyclosporine *[see Dosage and Administration (2.3), Drug Interactions (7.1)]*.

Hyperkalemia or Drugs that Increase Serum Potassium: Treatment with tolvaptan is associated with an acute reduction of the extracellular fluid volume which could result in increased serum potassium. Serum potassium levels should be monitored after initiation of tolvaptan treatment in patients with a serum potassium >5 mEq/L as well as those who are receiving drugs known to increase serum potassium levels.

ADVERSE REACTIONS:

Clinical Trials Experience: Because clinical trials are conducted under widely varying conditions, adverse reactions rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The adverse event information from clinical trials does, however, provide a basis for identifying the adverse events that appear to be related to drug use and for approximating rates. In multiple-dose, placebo-controlled trials, 607 hyponatremic patients (serum sodium <135 mEq/L) were treated with SAMSCA. The mean age of these patients was 62 years; 70% of patients were male and 82% were Caucasian. One hundred eighty nine (189) tolvaptan-treated patients had a serum sodium <130 mEq/L, and 52 patients had a serum sodium <125 mEq/L. Hyponatremia was attributed to cirrhosis in 17% of patients, heart failure in 68% and SIADH/other in 16%. Of these patients, 223 were treated with the recommended dose titration (15 mg titrated to 60 mg as needed to raise serum sodium). Overall, over 4,000 patients have been treated with oral doses of tolvaptan in open-label or placebo-controlled clinical trials. Approximately 650 of these patients had hyponatremia; approximately 219 of these hyponatremic patients were treated with tolvaptan for 6 months or more. The most common adverse reactions (incidence ≥5% more than placebo) seen in two 30-day, double-blind, placebo-controlled hyponatremia trials in which tolvaptan was administered in titrated doses (15 mg to 60 mg once daily) were thirst, dry mouth, asthenia, constipation, pollakiuria or polyuria and hyperglycemia. In these trials, 10% (23/223) of tolvaptan-treated patients discontinued treatment because of an adverse event, compared to 12% (26/220) of placebo-treated patients; no adverse reaction resulting in discontinuation of trial medication occurred at an incidence of >1% in tolvaptan-treated patients.

Table 1 lists the adverse reactions reported in tolvaptan-treated patients with hyponatremia (serum sodium <135 mEq/L) and at a rate at least 2% greater than placebo-treated patients in two 30-day, double-blind, placebo-controlled trials. In these studies, 223 patients were exposed to tolvaptan (starting dose 15 mg, titrated to 30 and 60 mg as needed to raise serum sodium). Adverse events resulting in death in these trials were 6% in tolvaptan-treated-patients and 6% in placebo-treated patients.

Table 1. Adverse Reactions (>2% more than placebo) in Tolvaptan-Treated Patients in Double-Blind, Placebo-Controlled Hyponatremia Trials

System Organ Class MedDRA Preferred Term	Tolvaptan 15 mg/day-60 mg/day (N = 223) n (%)	Placebo (N = 220) n (%)
Gastrointestinal Disorders		
Dry mouth	28 (13)	9 (4)
Constipation	16 (7)	4 (2)
General Disorders and Administration Site Conditions		
Thirst[a]	35 (16)	11 (5)
Asthenia	19 (9)	9 (4)
Pyrexia	9 (4)	2 (1)
Metabolism and Nutrition Disorders		
Hyperglycemia[b]	14 (6)	2 (1)
Anorexia[c]	8 (4)	2 (1)
Renal and Urinary Disorders		
Pollakiuria or polyuria[d]	25 (11)	7 (3)

The following terms are subsumed under the referenced ADR in Table 1:

[a]polydipsia; [b]diabetes mellitus; [c]decreased appetite; [d]urine output increased, micturition, urgency, nocturia

In a subgroup of patients with hyponatremia (N = 475, serum sodium <135 mEq/L) enrolled in a double-blind, placebo-controlled trial (mean duration of treatment was 9 months) of patients with worsening heart failure, the following adverse reactions occurred in tolvaptan-treated patients at a rate at least 2% greater than placebo: mortality (42% tolvaptan, 38% placebo), nausea (21% tolvaptan, 16% placebo), thirst (12% tolvaptan, 2% placebo), dry mouth (7% tolvaptan, 2% placebo) and polyuria or pollakiuria (4% tolvaptan, 1% placebo).

Gastrointestinal bleeding in patients with cirrhosis: In patients with cirrhosis treated with tolvaptan in the hyponatremia trials, gastrointestinal bleeding was reported in 6 out of 63 (10%) tolvaptan-treated patients and 1 out of 57 (2%) placebo treated patients. The following adverse reactions occurred in <2% of hyponatremic patients treated with SAMSCA and at a rate greater than placebo in double-blind placebo-controlled trials (N = 607 tolvaptan; N = 518 placebo) or in <2% of patients in an uncontrolled trial of patients with hyponatremia (N = 111) and are not mentioned elsewhere in the label: *Blood and Lymphatic System Disorders: Disseminated intravascular coagulation; Cardiac Disorders: Intracardiac thrombus, ventricular fibrillation; Investigations: Prothrombin time prolonged; Gastrointestinal Disorders: Ischemic colitis; Metabolism and Nutrition Disorders: Diabetic ketoacidosis; Musculoskeletal and Connective Tissue Disorders: Rhabdomyolysis; Nervous System: Cerebrovascular accident; Renal and Urinary Disorders: Urethral hemorrhage; Reproductive System and Breast Disorders (female): Vaginal hemorrhage; Respiratory, Thoracic, and Mediastinal Disorders: Pulmonary embolism, respiratory failure; Vascular disorder: Deep vein thrombosis.*

Postmarketing Experience: The following adverse reactions have been identified during post-approval use of SAMSCA. Because these reactions are reported voluntarily from a population of an unknown size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Neurologic: Osmotic demyelination syndrome; *Investigations:* Hypernatremia. Removal of excess free body water increases serum osmolality and serum sodium concentrations. All patients treated with tolvaptan, especially those whose serum sodium levels become normal, should continue to be monitored to ensure serum sodium remains within normal limits. If hypernatremia is observed, management may include dose decreases or interruption of tolvaptan treatment, combined with modification of free-water intake or infusion. During clinical trials of hyponatremic patients, hypernatremia was reported as an adverse event in 0.7% of patients receiving tolvaptan vs. 0.6% of patients receiving placebo; analysis of laboratory values demonstrated an incidence of hypernatremia of 1.7% in patients receiving tolvaptan vs. 0.8% in patients receiving placebo. *Immune System Disorders:* Hypersensitivity reactions including anaphylactic shock and rash generalized *[see Contraindications (4.6)]*.

DRUG INTERACTIONS:

Effects of Drugs on Tolvaptan:

Ketoconazole and Other Strong CYP 3A Inhibitors: SAMSCA is metabolized primarily by CYP 3A. Ketoconazole is a strong inhibitor of CYP 3A and also an inhibitor of P-gp. Co-administration of SAMSCA and ketoconazole 200 mg daily results in a 5-fold increase in exposure to tolvaptan. Co-administration of SAMSCA with 400 mg ketoconazole daily or with other strong CYP 3A inhibitors (e.g., clarithromycin, itraconazole, telithromycin, saquinavir, nelfinavir, ritonavir and nefazodone) at the highest labeled dose would be expected to cause an even greater increase in tolvaptan exposure. Thus, SAMSCA and strong CYP 3A inhibitors should not be co-administered *[see Dosage and Administration (2.3) and Contraindications (4.4)]*.

Moderate CYP 3A Inhibitors: The impact of moderate CYP 3A inhibitors (e.g., erythromycin, fluconazole, aprepitant, diltiazem and verapamil) on the exposure to co-administered tolvaptan has not been assessed. A substantial increase in the exposure to tolvaptan would be expected when SAMSCA is co-administered with moderate CYP 3A inhibitors. Co-administration of SAMSCA with moderate CYP3A inhibitors should therefore generally be avoided *[see Dosage and Administration (2.3) and Warnings and Precautions (5.5)]*. **Grapefruit Juice:** Co-administration of grapefruit juice and SAMSCA results in a 1.8-fold increase in exposure to tolvaptan *[see Dose and Administration (2.3) and Warnings and Precautions (5.5)]*. **P-gp Inhibitors:** Reduction in the dose of SAMSCA may be required in patients concomitantly treated with P-gp inhibitors, such as e.g., cyclosporine, based on clinical response *[see Dose and Administration (2.3) and Warnings and Precautions (5.5)]*. **Rifampin and Other CYP 3A Inducers:** Rifampin is an inducer of CYP 3A and P-gp. Co-administration of rifampin and SAMSCA reduces exposure to tolvaptan by 85%. Therefore, the expected clinical effects of SAMSCA in the presence of rifampin and other inducers (e.g., rifabutin, rifapentin, barbiturates, phenytoin, carbamazepine and St. John's Wort) may not be observed at the usual dose levels of SAMSCA. The dose of SAMSCA may have to be increased *[Dosage and Administration (2.3) and Warnings and Precautions (5.5)]*. **Lovastatin, Digoxin, Furosemide, and Hydrochlorothiazide:** Co-administration of lovastatin, digoxin, furosemide, and hydrochlorothiazide with SAMSCA has no clinically relevant impact on the exposure to tolvaptan.

Effects of Tolvaptan on Other Drugs: Digoxin: Digoxin is a P-gp substrate. Co-administration of SAMSCA with digoxin increased digoxin AUC by 20% and Cmax by 30%. **Warfarin, Amiodarone, Furosemide, and Hydrochlorothiazide:** Co-administration of tolvaptan does not appear to alter the pharmacokinetics of warfarin, furosemide, hydrochlorothiazide, or amiodarone (or its active metabolite, desethylamiodarone) to a clinically significant degree. **Lovastatin:** SAMSCA is a weak inhibitor of CYP 3A. Co-administration of lovastatin and SAMSCA increases the exposure to lovastatin and its active metabolite lovastatin-β hydroxyacid by factors of 1.4 and 1.3, respectively. This is not a clinically relevant change.

Pharmacodynamic Interactions: Tolvaptan produces a greater 24 hour urine volume/excretion rate than does furosemide or hydrochlorothiazide. Concomitant administration of tolvaptan with furosemide or hydrochlorothiazide results in a 24 hour urine volume/excretion rate that is similar to the rate after tolvaptan administration alone. Although specific interaction studies were not performed, in clinical studies tolvaptan was used concomitantly with beta-blockers, angiotensin receptor blockers, angiotensin converting enzyme inhibitors and potassium sparing diuretics. Adverse reactions of hyperkalemia were approximately 1-2% higher when tolvaptan was administered with angiotensin receptor blockers, angiotensin converting enzyme inhibitors and potassium sparing diuretics compared to administration of these medications with placebo. Serum potassium levels should be monitored during concomitant drug therapy. As a V_2 receptor antagonist, tolvaptan may interfere with the V_2 agonist activity of desmopressin (dDAVP). In a male subject with mild Von Willebrand (vW) disease, intravenous infusion of dDAVP 2 hours after administration of oral tolvaptan did not produce the expected increases in vW Factor Antigen or Factor VIII activity. It is not recommended to administer SAMSCA with V_2 agonist.

USE IN SPECIFIC POPULATIONS: There is no need to adjust dose based on age, gender, race, or cardiac function *[see Clinical Pharmacology (12.3)]*.

Pregnancy: Pregnancy Category C. There are no adequate and well controlled studies of SAMSCA use in pregnant women. In animal studies, cleft palate, brachymelia, microphthalmia, skeletal malformations, decreased fetal weight, delayed fetal ossification, and embryo-fetal death occurred. SAMSCA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. In embryo-fetal development studies, pregnant rats and rabbits received oral tolvaptan during organogenesis. Rats received 2 to 162 times the maximum recommended human dose (MRHD) of tolvaptan (on a body surface area basis). Reduced fetal weights and delayed fetal ossification occurred at 162 times the MRHD. Signs of maternal toxicity (reduction in body weight gain and food consumption) occurred at 16 and 162 times the MRHD. When pregnant rabbits received oral tolvaptan at 32 to 324 times the MRHD (on a body surface area basis), there were reductions in maternal body weight gain and food consumption at all doses, and increased abortions at the mid and high doses (about 97 and 324 times the MRHD). At 324 times the MRHD, there were increased rates of embryo-fetal death, fetal microphthalmia, open eyelids, cleft palate, brachymelia and skeletal malformations *[see Nonclinical Toxicology (13.3)]*.

Labor and Delivery: The effect of SAMSCA on labor and delivery in humans is unknown.

Nursing Mothers: It is not known whether SAMSCA is excreted into human milk. Tolvaptan is excreted into the milk of lactating rats. Because many drugs are excreted into human milk and because of the potential for serious adverse reactions in nursing infants from SAMSCA, a decision should be made to discontinue nursing or SAMSCA, taking into consideration the importance of SAMSCA to the mother.

Pediatric Use: Safety and effectiveness of SAMSCA in pediatric patients have not been established.

Geriatric Use: Of the total number of hyponatremic subjects treated with SAMSCA in clinical studies, 42% were 65 and over, while 19% were 75 and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. Increasing age has no effect on tolvaptan plasma concentrations.

Use in Patients with Hepatic Impairment: Moderate and severe hepatic impairment do not affect exposure to tolvaptan to a clinically relevant extent. No dose adjustment of tolvaptan is necessary. Avoid use of tolvaptan in patients with underlying liver disease.

Use in Patients with Renal Impairment: No dose adjustment is necessary based on renal function. There are no clinical trial data in patients with CrCl <10 mL/min, and, because drug effects on serum sodium levels are likely lost at very low levels of renal function, use in patients with a CrCl <10 mL/min is not recommended. No benefit can be expected in patients who are anuric *[see Contraindications 4.5) and Clinical Pharmacology (12.3)]*.

Use in Patients with Congestive Heart Failure: The exposure to tolvaptan in patients with congestive heart failure is not clinically relevantly increased. No dose adjustment is necessary.

OVERDOSAGE: Single oral doses up to 480 mg and multiple doses up to 300 mg once daily for 5 days have been well tolerated in studies in healthy subjects. There is no specific antidote for tolvaptan intoxication. The signs and symptoms of an acute overdose can be anticipated to be those of excessive pharmacologic effect: a rise in serum sodium concentration, polyuria, thirst, and dehydration/hypovolemia. The oral LD50 of tolvaptan in rats and dogs is >2000 mg/kg. No mortality was observed in rats or dogs following single oral doses of 2000 mg/kg (maximum feasible dose). A single oral dose of 2000 mg/kg was lethal in mice, and symptoms of toxicity in affected mice included decreased locomotor activity, staggering gait, tremor and hypothermia.

If overdose occurs, estimation of the severity of poisoning is an important first step. A thorough history and details of overdose should be obtained, and a physical examination should be performed. The possibility of multiple drug involvement should be considered. Treatment should involve symptomatic and supportive care, with respiratory, ECG and blood pressure monitoring and water/electrolyte supplements as needed. A profuse and prolonged aquaresis should be anticipated, which, if not matched by oral fluid ingestion, should be replaced with intravenous hypotonic fluids, while closely monitoring electrolytes and fluid balance.

ECG monitoring should begin immediately and continue until ECG parameters are within normal ranges. Dialysis may not be effective in removing tolvaptan because of its high binding affinity for human plasma protein (>99%). Close medical supervision and monitoring should continue until the patient recovers.

PATIENT COUNSELING INFORMATION: As a part of patient counseling, healthcare providers must review the SAMSCA Medication Guide with every patient *[see FDA-Approved Medication Guide (17.3)]*.

Concomitant Medication: Advise patients to inform their physician if they are taking or plan to take any prescription or over-the-counter drugs since there is a potential for interactions.**Strong and Moderate CYP 3A inhibitors and P-gp inhibitors:** Advise patients to inform their physician if they use strong (e.g., ketoconazole, itraconazole, clarithromycin, telithromycin, nelfinavir, saquinavir, indinavir, ritonavir) or moderate CYP 3A inhibitors (e.g., aprepitant, erythromycin, diltiazem, verapamil, fluconazol) or P-gp inhibitors (e.g., cyclosporine) *[see Dosage and Administration (2.3), Contraindications (4.4), Warnings and Precautions (5.5) and Drug Interactions (7.1)]*.

Nursing: Advise patients not to breastfeed an infant if they are taking SAMSCA *[see Use In Specific Populations (8.3)]*.

For more information about SAMSCA, call 1-877-726-7220 or go to www.samsca.com.

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Distributed and marketed by Otsuka America Pharmaceutical, Inc., Rockville, MD 20850

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INDICATION and Important Limitations

- SAMSCA is indicated for the treatment of clinically significant hypervolemic and euvolemic hyponatremia (serum sodium <125 mEq/L or less marked hyponatremia that is symptomatic and has resisted correction with fluid restriction), including patients with heart failure, and Syndrome of Inappropriate Antidiuretic Hormone (SIADH)
- Patients requiring intervention to raise serum sodium urgently to prevent or to treat serious neurological symptoms should not be treated with SAMSCA. It has not been established that raising serum sodium with SAMSCA provides a symptomatic benefit to patients

IMPORTANT SAFETY INFORMATION

SAMSCA should be initiated and re-initiated in patients only in a hospital where serum sodium can be monitored closely. Too rapid correction of hyponatremia (e.g., >12 mEq/L/24 hours) can cause osmotic demyelination resulting in dysarthria, mutism, dysphagia, lethargy, affective changes, spastic quadriparesis, seizures, coma and death. In susceptible patients, including those with severe malnutrition, alcoholism or advanced liver disease, slower rates of correction may be advisable

Contraindications: Urgent need to raise serum sodium acutely, inability of the patient to sense or appropriately respond to thirst, hypovolemic hyponatremia, concomitant use of strong CYP 3A inhibitors, anuric patients, and hypersensitivity (e.g. anaphylactic shock, rash generalized) to tolvaptan or its components

Warnings and Precautions:

- Subjects with SIADH or very low baseline serum sodium concentrations may be at greater risk for too-rapid correction of serum sodium. In patients receiving SAMSCA who develop too rapid a rise in serum sodium or develop neurologic sequelae, discontinue or interrupt treatment with SAMSCA and consider administration of hypotonic fluid. Fluid restriction should generally be avoided during the first 24 hours
- SAMSCA can cause serious and potentially fatal liver injury. Avoid use in patients with underlying liver disease, including cirrhosis, because the ability to recover may be impaired. Limit duration of therapy with SAMSCA to 30 days
- Dehydration and hypovolemia can occur, especially in potentially volume-depleted patients receiving diuretics or those who are fluid restricted. In patients who develop medically significant signs or symptoms of hypovolemia, discontinuation is recommended
- Co-administration with hypertonic saline is not recommended
- Avoid concomitant use with: CYP 3A inhibitors and CYP 3A inducers. The dose of SAMSCA may have to be reduced if co-administered with P-gp inhibitors
- Monitor serum potassium levels in patients with a serum potassium >5 mEq/L and in patients receiving drugs known to increase serum potassium levels

Adverse Reactions - The most common adverse reactions (SAMSCA incidence ≥5% more than placebo, respectively): thirst (16% vs 5%), dry mouth (13% vs 4%), asthenia (9% vs 4%), constipation (7% vs 2%), pollakiuria or polyuria (11% vs 3%) and hyperglycemia (6% vs 1%)

Gastrointestinal Bleeding in Patients with Cirrhosis – In patients with cirrhosis in the hyponatremia trials, GI bleeding was reported in 10% of tolvaptan-treated patients vs 2% for placebo

Please see Brief Summary of FULL PRESCRIBING INFORMATION, including Boxed WARNING, on following page.

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