ASN LEADING THE FIGHT AGAINST KIDNEY DISEASE

Kidney Week Edition

KidneyNews

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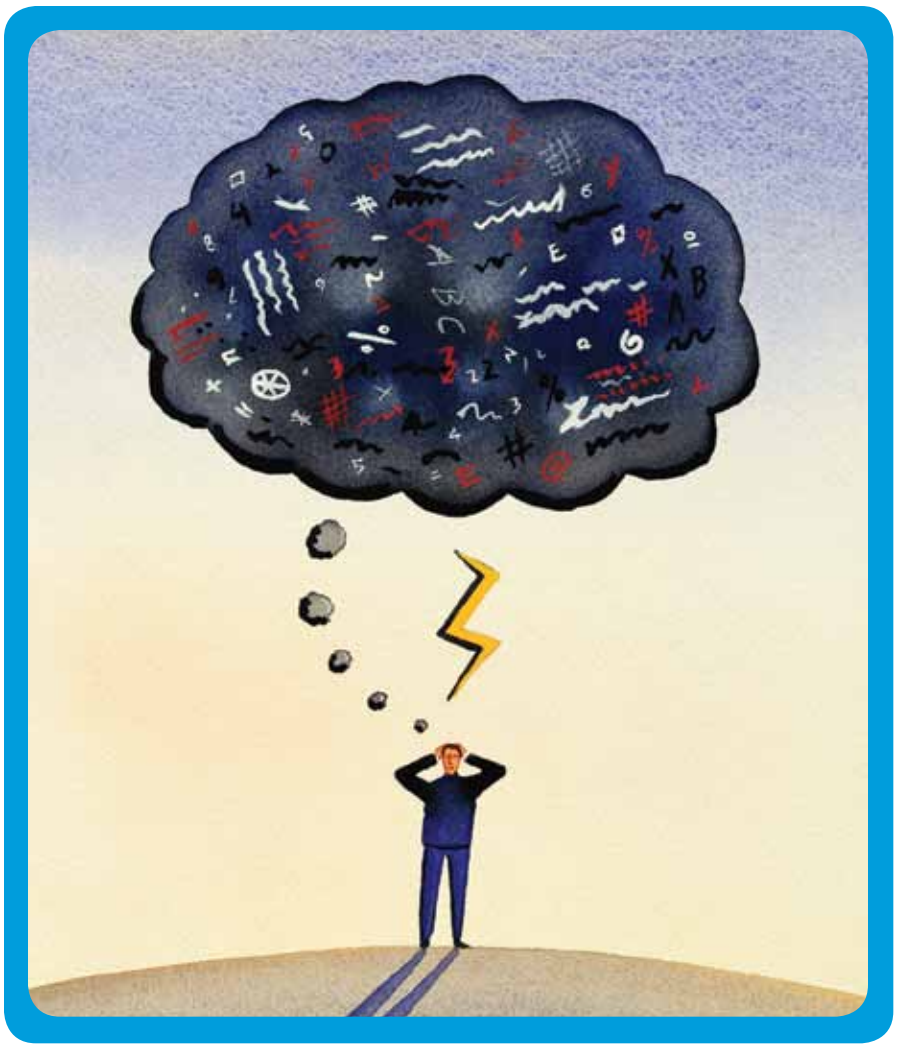
Dialysis Patients: Ready for Disasters?



By Tracy Hampton

Most dialysis patients are not prepared to effectively handle man-made or natural disasters, finds a study appearing in the October *Clinical Journal of the American Society of Nephrology*. The findings held even for patients receiving relevant educational materials from dialysis centers.

"A dialysis patient is reliant on frequent visits to a dialysis facility to maintain his or her health, and when this cannot be achieved due to lack of clean water, lack of electricity, impassable roadways, etc., severe medical complications leading to significant morbidity and mortality can occur quite quickly," said medical student Mark Foster of the University of North Carolina School of Medicine, who led the study. "This research is important because it sheds light on this lack of preparation and can serve as a stimulus to enact measures to ensure better preparation for future disasters."

Mitigating the effects of disaster on dialysis patients will require local, regional, and national leadership. Because disaster preparedness was not related to level of education, literacy, socioeconomic status, or age, it is clear that the lack of preparation is a systemic problem that will require coordinated efforts from dialysis facilities, large dialysis organizations, and national foundations, the authors said.

"If these findings are representative of the dialysis community at large, and they may well be, the dialysis community needs to develop and validate innovative educational approaches that will improve disaster preparedness for our patients," said Jeffrey Kopp, MD, of the Kidney Community Emergency Response Coalition (KCERC) and the National Institute of Diabetes and Digestive and Kidney Diseases.

Other experts agree. "The educational materials have been disseminated, but perhaps we need to explore what are the other barriers to preparedness, including financial and motivational," said Richard Zoraster, MD, medical director of the National Hospital Preparedness Program at the Los Angeles County Emergency Medical Services Agency.

Disasters and dialysis

Patients on dialysis depend on technology to keep them alive, and they must take certain steps to avoid becoming seriously sick or dying in the face of a disaster such as the recent tornadoes in the Midwest or the earthquake in Japan. Several years

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Disasters

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ago, the KCERC developed a disaster response plan that addresses the particular needs of dialysis patients and includes implementation and dissemination of best practices at the state, local, and individual level (http://www.ncbi.nlm.nih.gov/pubmed/17699500). The KCERC and the National Kidney Foundation have provided information to both dialysis clinics and patients regarding the necessary steps for disaster preparedness.

"KCERC and large dialysis organizations have done a very good job by educating dialysis patients about what to do in the case of a disaster," said Didier Portilla, MD, a member of the American Society of Nephrology's Disaster Relief Task Force and a professor at the University of Arkansas College of Medicine.

Disaster scenarios fall along two lines of response. Often, people must evacuate their homes and seek shelter in other locations. Dialysis patients should know where alternative dialysis clinics are, have medications on hand, and carry medical documentation of their kidney condition. Other events such as severe snowstorms require people to stay in their homes. When this happens, dialysis patients should be careful how much they drink, have a stockpile of appropriate foods and medications, and notify local police, fire, electric, water, and emergency services.

Dialysis patients' preparedness

To assess how well dialysis centers and their patients are prepared for disasters, Foster and his colleagues—including Jane Brice, MD, Maria Ferris, MD, PhD, and others—surveyed 311 end stage kidney disease patients who received care at six different regional dialysis centers in central North Carolina between June and August 2009. They also interviewed dialysis administrators to ascertain their centers' disaster preparedness activities.

The researchers asked questions regarding demographics, general disaster preparedness using Homeland Security recommended item lists, dialysis specific preparation for an individual to shelter in place, and preparatory steps for a forced evacuation. The cross-sectional analysis revealed that all dialysis centers had a disaster preparedness program in place, but most patients were not well-prepared for a disaster. Only 43 percent of patients knew of alternative dialysis centers. Only 42 percent had adequate medical records at home that they could take with them on short notice. Only 40 percent had discussed the possibility of staying with a friend or relative during a disaster, and only 15 percent had a medical bracelet or necklace they could wear if they were forced to leave their homes. Also, while individuals should maintain personal stores of potassium exchange resins along with instructions for use to mitigate hyperkalemia, only 13 percent of patients had any knowledge of the medication, and only 6 percent had the medication in their homes.

"These results were found to be independent of age, gender, race, education, household income, and literacy level, indicating that all sorts of people were unprepared no matter what their socioeconomic status," Foster said.

Preparedness was slightly better when patients were asked about their plans for disasters that would force them to stay in their homes, the researchers found. Fifty-seven percent knew what diet they should follow during a disaster, and 63 percent had a two-week supply of extra medications.

Home peritoneal dialysis patients were significantly more likely to be prepared for a disaster than hemodialysis patients. All 27 home peritoneal dialysis patients studied knew how to order extra supplies. Still, only 40 percent had an extra supply of antibiotics, only 38 percent had notified the local power company of their health condition, and 20 percent had notified the local water company.

"This is an excellent and timely paper pointing out the vulnerability of dialysis patients who experience a natural disaster," said Allen Nissenson, MD, chief medical officer of DaVita Inc. "With experts now stating that climate change will drive an increase in extreme weather throughout the country, it is essential that patients and providers understand the risks and the key role of education and preparation to minimize the impact on patient health."

Ways to Improve

The findings about dialysis patients' disaster preparedness may apply to other patients as well, said study author Mark Foster. "With the recent string of natural disasters, including the recent tornadoes of the spring of 2011, the earthquake in Japan, Hurricane Katrina in 2005, and many others, it is quite relevant for all folks, especially those who are living with chronic illnesses who require frequent monitoring and intervention to maintain their health."

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Kidney News

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Changing More than the Name: ASN Kidney Week 2011

ASN's annual meeting (previously called Renal Week) is now Kidney Week, reflecting the mission of ASN members and the society in leading the fight against kidney disease. Changing more than the name, this year's meeting includes several exciting new features and resources.

Kidney Week Mobile Application

Access Kidney Week information in the palm of your hand. Use ASN's Kidney Week mobile application for on-the-go access to meeting information on your smartphone or handheld device. Features include a customizable calendar and itinerary builder, exhibitor listing with interactive booth map, social media interaction, and special meeting alerts. Download the app online at www.asn-online.org/KidneyWeek.

Support for the Kidney Week Mobile Application is provided by Amgen.

Kidney Week Posters On-Demand

Fully paid participants can access electronic versions of the Kidney Week posters at no additional cost. Search and locate posters easily by authors, categories, or keywords during and after the meeting. The Posters On-Demand computer kiosk is located onsite in the Hall A Foyer, or posters can be accessed online at www.asn-online.org/KidneyWeek/PostersOnDemand.

CME credit will not be awarded for these materials.

Amgen, Genentech, a Member of the Roche Group, and Mitsubishi Tanabe Pharma provide support for Posters On-Demand.

Hot Topics Sessions in Hall D

On Friday, November 11, from 10:30 a.m. to 12:30 p.m., the "Hot Topics" session will address HUS epidemiology/bacteriology and eculizumab experience as well as provide an update on the SYMPLICITY clinical trial with editorial comments.

On Saturday, November 12, from 2 to 4 p.m., attendees may hear updates on hemodiafiltration trials and FHN trials and from the Chronic Kidney Disease Prognosis Consortium in the "Beyond Conventional Hemodialysis and Beyond eGFR" session.

Top Abstracts

ASN is pleased to award 46 Top Abstracts for young investigators and physicians-in-training as lead authors. Check out the list of Top Oral Abstracts and Top Posters in the Kidney Week *Onsite Program*. The Top Posters will be located in the front center of the poster area in the Exhibit Hall.

Meetings-Within-a-Meeting on Diabesity and Bioengineering

Diabesity refers to diabetes and obesity, a global epidemic contributing to kidney disease worldwide. Bioengineering is the interface between nanotechnology and biology, applying the most advanced technologies to understand kidney disease and targeted therapies.

ASN offers Meetings-Within-a-Meeting (MWM) for featured topics to encourage a sense of community and to promote scientific interchange. Each MWM consists of Basic and Clinical Science Symposia, Clinical Nephrology Conferences, Special Sessions, Oral Abstract Sessions, and Poster Sessions. Each MWM generally takes place in the same location throughout the Annual Meeting.

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The ASN Corporate Support Program recognizes supporters year round for their generous contributions to the Society. Through this program, supporters help ASN lead the fight against kidney disease. ASN gratefully acknowledges the following companies for their contributions in 2011.

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ASN in Review

ASN Addresses Key Challenges in Kidney Community in 2011

During the past year, ASN's membership, leaders, and staff have worked together to begin to implement the society's new mission: "ASN leads the fight against kidney disease by educating health professionals, sharing new knowledge, advancing research, and advocating the highest quality care for patients."

In its role as the society's governing body, the ASN Council constantly aligns the society's mission, goals, and initiatives with the key opportunities and challenges in the kidney community. ASN responded to many opportunities and challenges since last year's annual meeting, such as:

- As a result of the current global economic challenges, governments are beginning to cut funding for medical care, research, and education. In addition to the ongoing efforts of the ASN Public Policy Board related to funding for medical care and education, ASN also created a Research Advocacy Committee during the past year.
- Health care regulation is expanding, the profession is slowly losing its prerogative to self-govern, and the government and other payers are demanding higher quality care as well as linking payment to performance. Besides its ongoing efforts related to the implementation of the Medicare Improvements for Patients and Providers Act, which included the Quality Incentive Program (QIP), ASN helped create two Practice Improvement Modules (PIMs) that the American Board of Internal Medicine (ABIM) introduced in 2011.
- Globalization and expanded access to medical information is changing health care in the United States and abroad. ASN Highlights were held in Brazil, Germany, and Panama, while the society expanded its number of members and meeting participants from throughout the world. ASN established a Patient Education task force and is expanding the venues by which it disseminates information, to better inform the public, patients, legislators, policymakers, and providers.

In addition to these responses to opportunities and challenges, ASN continued to educate medical professionals, address issues in patient care and health care regulation, support and advocate for kidney disease research, address nephrology workforce and professional development concerns, and expand outreach during the past year.

Educating medical professionals

ASN expanded its role in educating medical professionals in 2011. The society:

- Held ASN Kidney Week 2011, the premier meeting of kidney professionals in the world, as well as Renal WeekEnd meetings in Dallas, Chicago, New York, and Washington, DC.
- Expanded distance learning with Renal Week on Demand (300 hours of content from Renal Week 2010) and the Board Review Course and Update (BRCU) Online (64.75 hours of CME in seven modules).
- Launched the six-year term of the new editorial team for the *Clinical Journal of the American Society of Nephrology (CJASN)*, led by Editor-in-Chief Gary C. Curhan, MD, ScD.
- Produced the top-ranked journal in nephrology and urology; this year the *Journal of the American Society of Nephrology (JASN)* increased its impact factor to 8.288.
- Published six issues of the *Nephrology Self-Assessment Program (NephSAP)* and enhanced audio NephSAP; future issues will focus on transplantation (November 2011), pediatric nephrology (January 2012), and hypertension (March 2012).
- Administered the ASN In-Training Examination for Nephrology Fellows to 803 fellows and held the 2011 ASN BRCU with more than 400 participants.

Patient care and health care regulation

ASN addressed the top issues in patient care and health care regulation:

- Testified at a Medicare committee meeting on use of erythropoiesis stimulating agents in patients with chronic kidney disease.
- Formed the ASN Accountable Care Organizations (ACOs) Task Force and submitted comments to the Centers for Medicare and Medicaid Services (CMS) regarding the ACO proposed rule.
- Submitted comments to the United Network for Organ Sharing on the proposed kidney allocation concept document.
- Responded to the proposed rule concerning the Medicare End-Stage Renal Disease Program Prospective Payment System and Quality Improvement Program.
- Launched the ASN Patient Education Task Force and ASN Quality and Patient Safety Task Force.
- Submitted comments to the Centers for Medicare and Medicaid Services regarding a proposed vascular access quality measure.

Kidney disease research

In 2011, ASN continued to expand the breadth and scope of its support and advocacy for kidney disease research.

- Advocated to prevent cuts to the National Institutes of Health (NIH) budget for 2011.
- Awarded seven Gottschalk Research Scholar Grants, one John Merrill Grant in Transplantation, one Norman Siegel Research Scholar Grant, and two ASN-Association of Specialty Professors-National Institute of Aging Junior Development Grants in Geriatric Nephrology.
- Awarded 10 ASN Student Scholar Grants to provide medical students support for full-time nephrology research.
- Launched ASN's first freestanding ASN Hill Day: ASN leaders and staff conducted meetings with 60 congressional offices.
- Helped plan and promote the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) acute kidney injury workshop.
- Created the ASN Research Advocacy Committee.

Nephrology workforce and professional development

ASN addressed nephrology workforce and professional development concerns.

- Convened the ASN Workforce Committee, and presented at the Association of American Medical Colleges' Annual Physician Workforce Conference.
- Published "The Future of the Nephrology Workforce: Will There Be One?" in *CJASN*.
- Promoted the Chronic Kidney Disease PIM, which ASN helped ABIM develop, and initiated the Dialysis PIM, which ASN produced and ABIM approved.
- Helped launch a new website for Women in Nephrology (WIN), which reflected a stronger relationship between ASN and WIN.
- Held the ASN Training Program Directors meeting and participated in the Alliance for Academic Internal Medicine Fellowship Match Task Force.
- Added new members to ASN's advisory groups based on requests from nearly 300 volunteers.

Expanding outreach

In 2011, the society joined the Council of Medical Specialty Societies and:

- Reached the 13,000-member milestone for the first time in ASN's history, and recorded more than two million unique visits to the ASN website in 2010 (a 42 percent increase from the previous year).
- Participated in nearly 20 joint leadership meetings with the leaders of other kidney-related organizations.
- Held an ASN Highlights meeting in Berlin, in Ouro Preto, Brazil, and in Panama City, Panama (in conjunction with the Sociedad Latino-Americana de Nefrologia e Hipertension).
- Received funding from the Association of Specialty Professors to produce and distribute podcasts and videos for geriatric nephrology grand rounds.
- Exhibited at the World Congress of Nephrology, the American Transplant Conference, the Annual Dialysis Conference, and the American Nephrology Nurses Association.
- Released the new dynamic edition of *ASN Kidney News*, the *CJASN* eJournalClub forum and the attendant iPhone app, completed plans for journal smartphone apps and mobile websites, and initiated the ASN media blog to expand outreach to journalists and expanded ASN's social media.

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Meet ASN's Next President

Ronald Falk, MD, FASN, will begin his year as ASN President November 13, 2011. Dr. Falk, Allen Brewster Distinguished Professor of Medicine at the University of North Carolina at Chapel Hill, is also Chief of the UNC Division of Nephrology and Director of the UNC Kidney Center.

Dr. Falk's research probes questions focused on immune-mediated kidney diseases, especially glomerulonephritis. His clinical and basic science interests include both ANCA glomerulonephritis and small vessel vasculitis. A central objective of Falk's research is elucidating the causes of ANCA necrotizing and crescentic glomerulonephritis. Unraveling the cause of this disease requires considering a number of factors involved in the development of ANCA glomerulonephritis. Falk conceptualizes this process as opening the vasculitis lock with a key that has a number of "ridges and valleys" analogous to those factors that contribute to the development of this autoimmune disease. He participates in a research group that, in a large study over the last four years, has revealed a number of avenues of investigation and new approaches to ongoing questions that pertain not only to ANCA glomerulonephritis, but to the general fields of autoimmunity, inflammation, and basic neutrophil and monocyte biology.

Ronald Falk

Why did you become a nephrologist?

When I was studying medicine, I found that the questions asked of kidney patients, and about kidney patients, were complicated and intriguing and I found the science behind the questions fascinating. I still do. I consider it such a privilege to care for people with chronic disease.

When I encounter young people who are considering nephrology as a career, I tell them they cannot be in a better position than to enter into the lifelong study of kidney medicine. Now is an especially exciting time to be working in nephrology because of the rapid pace of change, because kidney professionals are at the forefront of many recent healthcare changes, and because of the exciting opportunities scientists and clinicians in kidney medicine have to make a positive difference in the lives of millions of patients.

Are you already planning for ASN Kidney Week 2012?

I'm excited about the 2012 meeting in San Diego. ASN Kidney Week is the premier kidney meeting in the world, the highlight of the year. Planning for the meeting is well under way under the able leadership of Manikkam Suthanthiran, MD, FASN, Chair-Elect of the ASN Program Committee, and Mark E. Rosenberg, MD, FASN, Chair of the ASN Postgraduate Education Committee. The Program and PGE Committees have developed a truly spectacular infrastructure and are so well supported by ASN staff that I really don't need to worry about the process. We are looking forward to fantastic presentations, policy discussions, and unparalleled professional exchange.

As Chair of the ASN Education Committee, you worked hard to see that ASN developed Practice Improvement Modules (PIMs). What do you consider the importance of PIMs?

Until recently there were no practice improvement modules aimed at kidney providers. These are excellent tools and provide a realistic approach to improving the care of patients. They are designed to engage learners, and many doctors say they have changed their approaches based on their experiences with the PIM process. ASN has just released a dialysis PIM and hopes to make more of these available as possible to meet the needs of kidney professionals.

During your time at ASN you have added scientists with nursing and pharmaceutical expertise to the Program and Education Committees. Why is this important to ASN?

Advanced practice nurses, nurse practitioners, and pharmacists are among the many professionals who are integral to the teams taking care of patients with kidney disease, and their expertise is invaluable. In recognition of this, the American Society of Nephrology is planning to expand its continuing education credits to encompass continuing education for advanced practice nurses and doctors of pharmacy.

You have served on Council for several years. What have you learned from your experience on Council?

ASN Council is composed of individuals with diverse backgrounds and interests, representative of most of the constituencies within the kidney space. Council discussions are always interesting and informative, and I have been impressed over the years with how Council members coalesce diverse perspectives and band together to do what is best for the society.

In recent years I have seen tremendous change as the society has expanded the number of high-quality expert staff. Bringing in additional experts has allowed ASN to expand its educational offerings, add distance learning tools, reach new media, add members, and enhance the impact ASN makes on global kidney policy.

You direct the University of North Carolina Kidney Center. What impact has the Kidney Center had on the state of North Carolina?

The Kidney Center is committed to advancing research in kidney disease, and to serving the citizens of North Carolina. One of the Center's goals is for all North Carolinians to ask their physicians "How are my kidneys?" when they visit their doctors. Especially in counties where kidney disease is increasing, primarily in the rural parts of the state, we are working hard to increase awareness of the risks of developing kidney disease and how to manage kidney disease. Kidney Center staff interact closely with local leaders across the state to achieve the most effective outreach in each community. We have learned that different approaches work better in different parts of the state, and we work hard to target the messaging and reach the maximum number of people in each community, through local leaders, screenings, and other forms of communication. The Kidney Center also works hard to make sure more North Carolinians consider becoming organ donors.

You are well known as a fervent Carolina basketball fan. Will your duties as ASN President interfere with your ability to watch every Carolina game?

Absolutely not. And it is going to be a great year for our team.

ASN President Joseph V. Bonventre reflects on his term leading the society in a flier to be distributed at Kidney Week.

Kidney Week Mobile Application

New for 2011

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Kidney Patients' HDL Loses Vasoprotective Function

HDL cholesterol from patients with chronic kidney disease (CKD) loses its protective effect on the cells lining blood vessels, the vascular endothelium. In patients with CKD, HDL appears to lose its anti-inflammatory effects and to become a proinflammatory substance, said Timo Speer, MD, of Saarland University Hospital in Hamburg, Germany.

The rate of cardiovascular (CV) events increases in patients with CKD long before they need dialysis. Dr. Speer called renal disease "a cardiovascular risk factor per se." Epidemiologic studies have shown that in healthy people, the risk of coronary heart disease decreases 3 percent for every 1 percent increase in the normally protective HDL. Although HDL helps remove LDL, or bad, cholesterol from the circulation, it also has direct effects on the endothelium, including increased production of nitric oxide (which helps relax arteries) and antioxidant, anti-inflammatory, and antithrombotic effects. It also facilitates the healing of damaged endothelium.

CKD HDL limits endothelial nitric oxide production and increases adhesion molecules

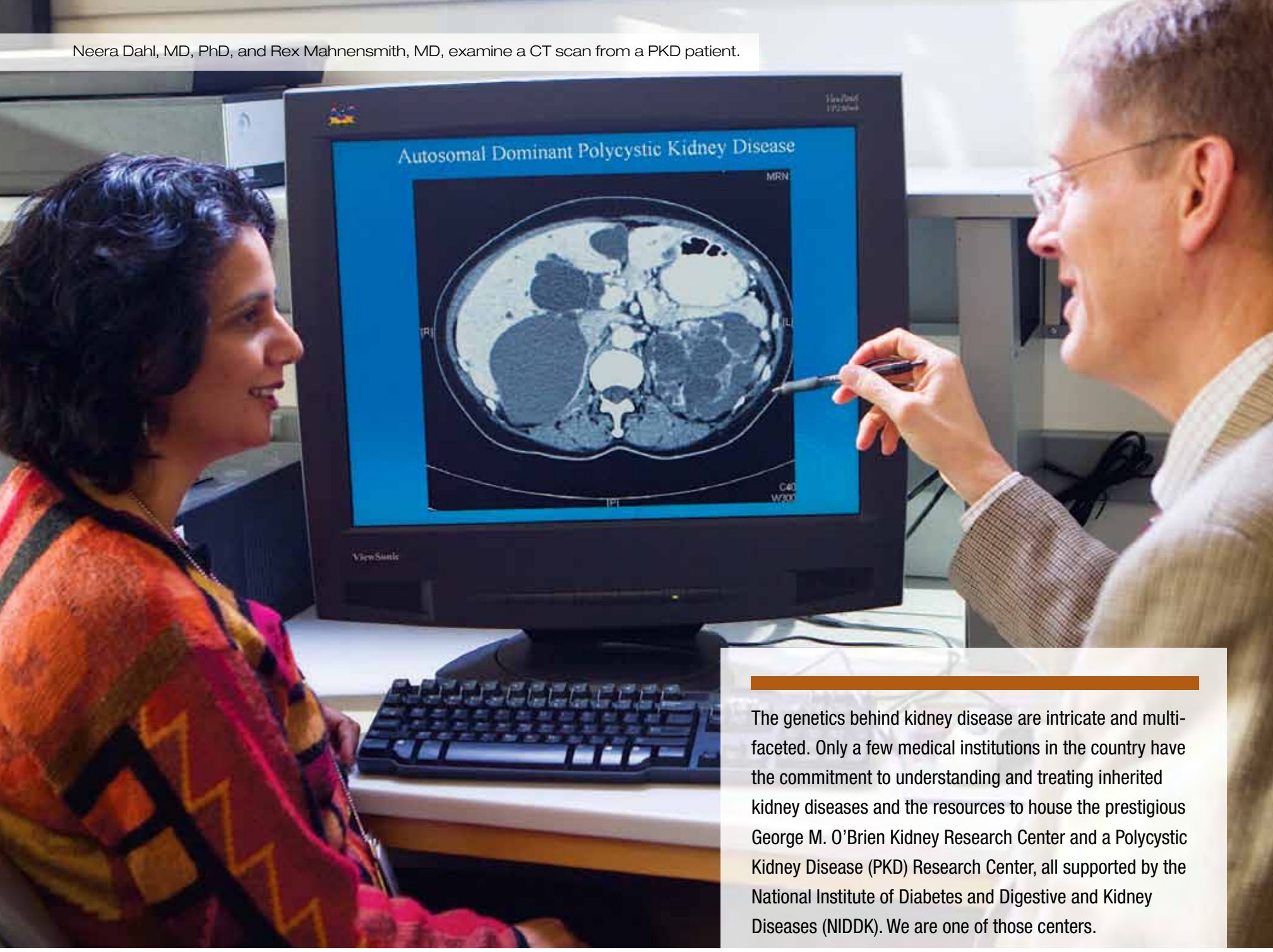
Dr. Speer and colleagues isolated HDL from healthy control individuals and from patients with different stages of CKD to evaluate the effects of their HDL on endothelial function. The researchers first exposed aortic endothelial cells in vitro to the HDL that they had isolated, and they measured nitric oxide production. HDL from healthy volunteers increased production by about 10 percent, but HDL from patients with stage 5 CKD inhibited production by 40 percent compared with buffer-treated control individuals. The same levels of inhibition of nitric oxide production were seen when HDL from stage 2 or stage 3/4 patients was used. The more HDL that was added to the cultures, the greater were the effects: inhibition of nitric oxide production with HDL from patients with CKD or stimulation with HDL from healthy control individuals.

The researchers investigated the molecular mechanisms of the effects on nitric oxide production and found that CKD HDL increased phosphorylation of an inhibitory site and decreased phosphorylation of stimulatory sites on an enzyme, endothelial nitric oxide synthase. Healthy HDL promoted phosphorylation of stimulatory sites. Endothelial nitric oxide synthase is an enzyme that controls nitric oxide production, and phosphorylation of a site on the molecule promotes that site's function—either inhibitory or stimulatory.

Healthy HDL decreased the production of vascular cell adhesion molecule-1 (VCAM-1) in the presence of the inflammatory mediator tumor necrosis factor-α (TNF-α), but CKD HDL was associated with a rise in VCAM-1 expression. VCAM-1 makes the endothelium sticky, promotes the adherence of certain kinds of blood cells, and may play a role in the development of atherosclerosis. Even without TNF-α, "HDL from end stage renal disease patients becomes a proinflammatory particle," Dr. Speer said.

HDL also affects healing of the endothelium after injury. Damaged endothelium may be dangerous because it loses its vascular protective functions and allows clots to form in the vessels. HDL from healthy volunteers reduced the apoptosis rate of endothelial cells, Dr. Speer said, "while HDL from dialysis patients had no effect." Apoptosis is a natural process of programmed cell death, so a high rate of apoptosis limits the ability of the endothelium to regenerate.

Experimentally injured endothelium exposed to healthy HDL showed a rate of healing almost threefold higher than did control samples, but exposure to CKD HDL inhibited healing by about 20 percent compared with control samples.



Neera Dahl, MD, PhD, and Rex Mahnensmith, MD, examine a CT scan from a PKD patient.

The genetics behind kidney disease are intricate and multi-faceted. Only a few medical institutions in the country have the commitment to understanding and treating inherited kidney diseases and the resources to house the prestigious George M. O'Brien Kidney Research Center and a Polycystic Kidney Disease (PKD) Research Center, all supported by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK). We are one of those centers.

Research Excellence, Clinical Leadership and a Commitment to Our Patients

Our researchers have discovered over fifteen genes for human diseases affecting the kidney and blood pressure. These discoveries cover the gamut from rare disorders of blood pressure regulation through sodium and potassium handling such as Liddle's syndrome, pseudohypoaldosteronism type II and Bartter's and Gittelman's syndromes to such common inherited kidney diseases as polycystic kidney disease (PKD). While our researchers are now seeking to translate these findings to treatments for PKD and other disorders, our nephrologists are using these discoveries to help our patients lead healthy and fulfilling lives.

Being at the forefront of clinical research and treatments means that our physicians and surgeons are furthering the current understanding of kidney disease. Most importantly, it means they are positioned to provide the best care possible to our patients.

Yale-New Haven Hospital is the primary teaching hospital of Yale School of Medicine. Nephrology services at Yale-New Haven were ranked 35th by *U.S.News & World Report* in 2011-12.

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Plenary Session

Leptin Researcher to Describe Its Role in Obesity

Jeffrey Friedman

State-of-the-Art Lecture

The contribution of the relatively newly discovered hormone leptin to obesity will be the subject of the state-of-the-art lecture by Jeffrey M. Friedman, MD, PhD, on Thursday, November 10, beginning at 8 a.m.

Dr. Friedman is a professor at the Rockefeller University, an investigator at the Howard Hughes Medical Institute, and the director of the Starr Center for Human Genetics in New York City.

Dr. Friedman's research received national attention in 1994 when he and his colleagues isolated a gene linked to mouse obesity and its human homologue. They subsequently found that injections of the protein leptin decrease body weight in mice by reducing food intake and increasing energy expenditure. In his lecture, "Leptin and the Biological Basis of Obesity," Dr. Friedman will describe the current state of research in the area, including his approach to understanding the genetic basis of obesity in humans and the mechanisms by which leptin transmits its weight-reducing signal.

Leptin, a hormone made in fat tissue, plays a key role in regulating weight by modulating food intake relative to energy expenditure to maintain weight within a relatively narrow range. Defects in the leptin gene are associated with severe obesity in animals and humans. Leptin acts on neurons in brain centers that control energy balance, and it plays a general role in regulating many of the physiological responses observed with changes in nutritional states, with clear effects on female reproduction, immune function, and the function of other hormones, including insulin.

Dr. Friedman's lab is active in elucidating the molecular mechanisms responsible for the regulation of gene expression associated with weight change. The amount of leptin expressed from fat is strongly regulated, which suggests that the fat cell knows how much fat it has. To address this question, the lab is using transgenic mice to identify DNA regulatory elements that change expression of a receptor gene controlled by the leptin gene in parallel with changes in adipose tissue mass.

Diet-induced weight loss in humans decreases leptin concentration, which may explain the high failure rate of dieting. Recent clinical studies at Rockefeller University Hospital explored the possibility that administering leptin to dieting patients can alter their response to weight.

Dr. Friedman received his PhD from the Rockefeller University in 1986. He was appointed assistant investigator with the Howard Hughes Medical Institute at Rockefeller in 1986, promoted to associate investigator in 1991, and investigator in 1997. He received his MD from Albany Medical College.

He was elected to the National Academy of Sciences and is a member of its Institute of Medicine. He has received numerous national and international awards, including the Albert Lasker Basic Medical Research Award and the Endocrinology Transatlantic Medal from the United Kingdom's Society for Endocrinology.

Susan Wall to Deliver Brenner Endowed Lectureship

Susan M. Wall

Susan M. Wall, MD, will present the Barry M. Brenner Endowed Lectureship on Thursday, November 10. The topic of her presentation will be "Modulation of ENaC function by pendrin-dependent Cl-/HCO_3- exchange."

Dr. Wall is professor of medicine and physiology at Emory University School of Medicine in Atlanta. For the past 25 years, she has studied the renal physiology of H+/OH- transporters along the collecting duct.

The focus of her attention recently has been the renal physiology of the Cl-/HCO_3- exchanger, pendrin. While pendrin's critical role in hearing and thyroid function is well known, this transporter is also highly expressed in the apical regions of type B and non-A, non-B intercalated cells in the cortical collecting duct and connecting tubule, where it plays an important role in the renal regulation of blood pressure.

Dr. Wall and her colleagues have shown that pendrin mediates the absorption of chloride and the secretion of bicarbonate in the cortical collecting duct and that it is greatly upregulated by aldosterone, which stimulates chloride absorption and bicarbonate secretion in these segments. The researchers observed that in mice given a high-salt diet, in which circulating aldosterone concentration is low, blood pressure, serum electrolytes, and serum bicarbonate are similar in pendrin-null and wild-type mice. However, the pressor response to aldosterone is greatly blunted in pendrin-null mice, presumably due to the absence of pendrin-mediated chloride absorption. Moreover, when pendrin-null mice are changed from a high- to a low-sodium diet, they excrete more sodium and chloride than pair-fed wild-type mice. The chloriuresis observed in the salt-restricted pendrin-null mice could be readily explained by the absence of pendrin-mediated chloride absorption. However, because pendrin does not transport sodium, the researchers explored the cause of the natriuresis further. Although pendrin and the epithelial sodium channel (ENaC) localize to different cell types, Dr. Wall and her colleagues made the surprising observation that ENaC abundance and function are greatly reduced in pendrin-null mice. They demonstrated that pendrin modulates ENaC abundance and function in aldosterone-treated mice, at least in part by secreting bicarbonate into the luminal fluid, which stimulates ENaC abundance and function.

Dr. Wall received her undergraduate degree in chemistry from the University of Seattle and her MD from St. Louis University School of Medicine. She did her postgraduate medical training in internal medicine and nephrology at the University of California, Los Angeles, hospitals. She did research fellowships at UCLA and the National Heart, Lung, and Blood Institute. After a year on the faculty at the University of Texas Medical School at Houston, Dr. Wall moved to Emory in 2002.

ASN gratefully acknowledges Monarch Pharmaceuticals for support of the Barry M. Brenner Endowed Lectureship.

Plenary Session

Prolific Medical Inventor to Discuss Range of Innovations

Robert S. Langer

State-of-the-Art Lecture

The Friday state-of-the-art lecture will feature one of the most amazing and prolific inventors in the history of biomedicine, Robert S. Langer, ScD. His talk, "Biomaterials and Biotechnology: From the Discovery of Angiogenesis Inhibitors to the Development of Controlled Drug Delivery Systems and the Foundation of Tissue Engineering," will share insights from a unique career as part of the plenary session on Friday, November 11.

Dr. Langer is the David H. Koch Institute Professor at the Massachusetts Institute of Technology, an institute professor being the highest honor that MIT awards its faculty members. He is the most cited engineer in history.

He has been a pioneer in applying materials science and engineering to drug delivery and tissue engineering. His career began in the 1970s when as a graduate student at MIT, he began working on a way to use plastics to administer cancer drugs at a controlled pace inside patients' bodies. At that time, the scientific community believed that only small molecules could pass through a plastic delivery system in a controlled manner. Dr. Langer developed polymer materials that allowed the large molecules of a protein to pass through membranes over time to inhibit angiogenesis, and thereby fight cancer by blocking the recruitment of new blood vessels by tumors. This breakthrough allowed for cancer treatment with large molecules that could not previously be used therapeutically because the body's enzymes attacked and destroyed them when they were given orally or injected.

Dr. Langer's innovative products include a chemotherapy wafer for the treatment of brain cancer, a device that cuts the pain associated with needles and IVs, and transdermal patches for the delivery of drugs such as nicotine and birth control hormones. He is also a pioneer in tissue engineering, helping start the field of regenerative medicine and tissue engineering to address the problem of donor-organ shortages. Dr. Langer and his colleagues designed degradable polymer scaffolds that could support growth of human cells, leading to artificial skin, muscles, nerves, cartilage, bone, and organs that are now used to treat patients.

His research has spawned more than a dozen biotechnology firms and more than 35 products that are currently on the market or in human testing. He has published nearly 1130 articles and has about 800 patents issued and pending worldwide. His patents have been licensed to more than 220 pharmaceutical, chemical, biotechnology, and medical device companies.

A graduate of Cornell University, he received his ScD from MIT in chemical engineering in 1974, and then joined the faculty as a visiting professor. He has received more than 180 scientific awards, including the Millennium Technology Prize, the world's largest award for technology innovation; the Charles Stark Draper Prize, considered the equivalent of the Nobel Prize for engineers; the Lemelson-MIT Prize, the nation's most prestigious prize for invention; and the U.S. National Medal of Science. He will receive the 2012 Priestley Medal, the highest honor of the American Chemical Society.

Sodium Pump Researcher to Receive Homer W. Smith Award

Anita Aperia

Anita Aperia, MD, PhD, will receive the Homer W. Smith Award, which will be followed by delivery of the Homer W. Smith Address titled "To Serve and Protect: Classical and Novel Roles for Na,K-ATPase" on Friday, November 11.

Dr. Aperia is professor of pediatrics at Karolinska Institutet in Stockholm. The Smith Award recognizes individuals who contribute to our basic understanding of how the kidneys function in health and disease, and Dr. Aperia's discoveries concerning the sodium pump have greatly advanced this knowledge.

She started her research career studying renal function in newborn infants. To elucidate the mechanisms behind the low capacity of the infant kidney to adapt to physiological needs, her experimental studies focused on the function and plasticity of the sodium pump, Na,K-ATPase. Her discovery that the sodium pump is regulated by dopamine led to a fruitful collaboration with professor Paul Greengard, aimed at settling questions concerning dopamine signaling through parallel studies on renal tubule cells and striatal neurons.

Her recent work has focused on the implications of her serendipitous finding that the sodium pump gives rise to a signal that protects the kidney from damage by disease and cell death.

A native of Sweden, Dr. Aperia received her PhD training at Yale University, where she studied effects of hypoxia on renal function. She graduated from the Karolinska Institutet medical school, where she was appointed professor of pediatrics in 1987.

Dr. Aperia chaired the Karolinska Institutet's department of pediatrics from 1987 to 1999. During this time she initiated and planned the building of the Astrid Lindgren Children's Hospital. She currently directs a multidisciplinary research group specializing in live cell imaging, a joint initiative of the Karolinska Institutet and the Royal Swedish Institute of Technology.

A dedicated teacher, she has supervised 47 doctoral and 30 postdoctoral students.

Dr. Aperia is a member of the Nobel Assembly for Physiology or Medicine and chaired the Nobel Assembly in 2001. She is a member of the Royal Swedish Academy of Science, where she chaired the class of medicine from 2003 to 2010. She has been a councilor of the International Society of Nephrology and of the European Society of Pediatric Nephrology.

She has received numerous awards, including the Torsten and Ragnar Söderberg Prize in Medicine from the Swedish Society of Medicine, the Hamburger Award from the International Society of Nephrology, and another Swedish honor, His Majesty the King's Medal.

Homer W. Smith

Homer W. Smith was chairman of physiology at the University of Virginia before moving in 1928 to New York University (NYU). As director of the Physiology Laboratories at NYU, he developed and refined the concepts of glomerular filtration and tubular absorption and secretion of solutes.

The clarity of Dr. Smith's logic and the skill with which he explained his ideas transformed them into vivid and powerful concepts that are the cornerstones of our present understanding of normal and abnormal renal function. He attracted the best and brightest to the field, to NYU, and to the Mount Desert Island Biological Laboratory, where he spent many summers studying renal physiology in fish.

The Homer W. Smith award recognizes individuals who contribute to our basic understanding of how the kidneys function in health and disease.

Schrier Lectureship to Focus on Biologic Memory in Acute Renal Failure

Eric G. Neilson

Eric G. Neilson, MD, FASN, will present the Robert W. Schrier Endowed Lectureship on Friday, November 11, on the subject, "The Origins of Fibroblasts: From Tissue Injury to Fibrosis." Dr. Neilson is the From Lewis Landsberg Professor of Medicine and Cell and Molecular Biology and vice president for medical affairs and dean of the Feinberg School of Medicine at Northwestern University in Chicago.

Over the course of his career, Dr. Neilson has studied renal basement membranes and the pathogenesis of interstitial nephritis leading to fibrosis, work that has resulted in more than 280 publications. His talk will describe the origins of fibroblasts focusing on epithelial and endothelial plasticity as well as other mechanisms of fibrogenesis.

Dr. Neilson is a member of the American Society for Clinical Investigation, the Association of American Physicians, the American Clinical and Climatological Association, the Interurban Clinical Club, and the Association of Professors of Medicine. He was the founding president of the Association of Subspecialty Professors. He has received the Young Investigator Award, the Barry M. Brenner Lectureship, the President's Medal, and the John P. Peters Award from ASN as well as a MERIT Award from the National Institutes of Health. He has received an A. N. Richards Distinguished Achievement Award from the University of Pennsylvania School of Medicine, the Distinguished Professor Award from the Association of Subspecialty Professors, and the Robert H. Williams, MD, Distinguished Chair of Medicine Award from the Association of Professors of Medicine. He is currently editor-in-chief of the *Journal of the American Society of Nephrology.*

A medical graduate of the University of Alabama in Birmingham, Dr. Neilson trained in internal medicine and nephrology at the hospital of the University of Pennsylvania in Philadelphia, where he rose to become the C. Mahlon Kline Professor of Medicine, chief of the renal-electrolyte and hypertension division, and director of the Penn Center for Molecular Studies of Kidney Diseases. He came to Vanderbilt in 1998 as the Hugh Jackson Morgan Professor and chairman of the department of medicine. He finished his term in the latter position in 2010.

ASN gratefully acknowledges Otsuka America Pharmaceutical, Novartis, Astellas Pharma US, and several individuals for support of the Robert W. Schrier Endowed Lectureship.

Health-Care Reform to be Subject of Blagg Lectureship

Mark B. McClellan

Mark B. McClellan, MD, PhD, will present the Christopher R. Blagg Endowed Lectureship in Renal Disease and Public Policy on Friday, November 11, on the topic of "What Are the Essential Elements for Reform of a Care Delivery System?"

Dr. McClellan is a senior fellow, director of the Engelberg Center for Health Care Reform, and Leonard D. Schaeffer Chair in Health Policy Studies at the Brookings Institution in Washington, D.C. Established in 2007, the Engelberg Center provides practical solutions to achieve high-quality, innovative, affordable health care with particular emphasis on identifying opportunities on the national, state, and local levels.

A physician and an economist by training, Dr. McClellan has a distinguished record in public service and academic research. He is a former administrator of the Centers for Medicare and Medicaid Services and a former commissioner of the U.S. Food and Drug Administration. He served as a member of the President's Council of Economic Advisers and as senior director for health-care policy at the White House under President George W. Bush. He also served in the Clinton administration as deputy assistant secretary of the treasury for economic policy and supervised economic analysis and policy development on a variety of domestic policy issues.

Dr. McClellan's experience includes serving as associate professor of economics and associate professor of medicine at Stanford University, where he directed Stanford's Program on Health Outcomes Research. He was associate editor of the *Journal of Health Economics* and co-principal investigator of the Health and Retirement Study, a longitudinal study of the health and economic status of older Americans.

Dr. McClellan holds a medical doctor degree from the Harvard University–Massachusetts Institute of Technology (MIT) Division of Health Sciences and Technology, a doctorate in economics from MIT, a master's degree in public administration from Harvard, and a bachelor of arts degree from the University of Texas at Austin.

ASN gratefully acknowledges the Northwest Kidney Centers and its contributors for support of the Christopher R. Blagg Endowed Lectureship in Renal Disease and Public Policy.

Vascular Calcification Expert to Deliver Coburn Endowed Lectureship

Cecilia M. Giachelli

Mechanisms and Regulation of Vascular Calcification" will be the subject of the Jack W. Coburn Endowed Lectureship on Friday, November 11. The lecturer will be Cecilia M. Giachelli, PhD, professor of bioengineering, adjunct professor of pathology, and adjunct professor of oral biology at the University of Washington in Seattle.

Dr. Giachelli is internationally recognized for her work investigating the molecular mechanisms of vascular calcification and extracellular matrix control of cell function. Her studies have led to the discovery of key inducers and inhibitors that contribute to vascular calcification in chronic kidney disease, atherosclerosis, and medial arterial calcification. These discoveries are currently being translated to therapeutic strategies to block inappropriate calcification in disease and biomaterials development.

Dr. Giachelli's studies of the basic adhesive interactions required for cellular growth and movement feature an emphasis on integrins and their ligands. Under normal conditions, adhesive interactions control tissue development and maintain mature tissue integrity. During wound repair, adhesive interactions change to facilitate healing and remodeling. In diseases such as atherosclerosis, cancer, and renal tubulointerstitial fibrosis, cellular growth and movement are aberrant, leading to invasion and pathological accumulation of cells and their byproducts. Her research has a particular focus on the role of specific adhesive ligands, especially secreted products such as osteopontin and other extracellular matrix proteins, as well as integrins, in vascular and renal models of normal homeostasis, regeneration, and disease.

Dr. Giachelli is on the editorial boards of *Circulation Research* and *Cardiovascular Pathology*. She has published more than 100 articles in top journals, including *Circulation Research, Kidney International, Journal of Clinical Investigation*, and *Journal of Biological Chemistry*. She was awarded the American Heart Association Established Investigator Award and is an elected fellow of the American Institute for Medical and Biological Engineering. She has received both public and private funding for her vascular calcification research.

She received her undergraduate training in biochemistry from the University of California at Davis and her doctoral degree in pharmacology from the University of Washington. She completed postdoctoral fellowships in pathology and pharmacology at the University of Washington School of Medicine.

ASN gratefully acknowledges Amgen for support of the Jack W. Coburn Endowed Lectureship.

Plenary Session

Researcher to Present Genetic Effects Related to Increased Lifespan

Cynthia Kenyon

State-of-the-Art Lecture

Aging was assumed to be a passive consequence of molecular wear and tear until discoveries in the 1990s revealed the existence of genetic mechanisms that influence and even control the process. One of the leaders in unveiling these new mechanisms, Cynthia Kenyon, PhD, will deliver the state-of-the-art lecture, "From *C. Elegans* to Mammals: Genes that Can Increase Lifespan," at the plenary session on Saturday, November 12.

Dr. Kenyon is an American Cancer Society Professor in the department of biochemistry and director of the Hillblom Center for the Biology of Aging at the University of California, San Francisco (UCSF).

In 1993, the discovery by Dr. Kenyon and colleagues that a single-gene mutation could double the lifespan of the tiny roundworm, *Caenorhabditis elegans*, sparked an intensive study of the molecular biology of aging. The finding challenged the widely held assumption that aging is a random and haphazard process of the body wearing out. Dr. Kenyon was skeptical of this idea, thinking that something as universal and fundamental as aging might well be subject to control by genes.

Dr. Kenyon's discoveries have led to the realization that genetic circuits exist to control aging, involving hormones as well as proteins that regulate the activities of entire groups of cell-protective genes. The long-lived mutants that Dr. Kenyon and others have identified are resistant to many age-related diseases, raising the possibility of a new strategy for combating many diseases by targeting aging itself. By manipulating genes and cells, Dr. Kenyon and her colleagues extended the lifespan of healthy, active *C. elegans* by sixfold, demonstrating the extraordinary plasticity of aging.

Dr. Kenyon graduated as the valedictorian in chemistry and biochemistry from the University of Georgia in 1976. She received her PhD from the Massachusetts Institute of Technology in 1981, where she was one of the first to look for genes on the basis of their expression profiles, discovering that DNA-damaging agents activate a battery of DNA repair genes in *E. coli*. Her postdoctoral studies involved studying the development of *C. elegans* with Nobel laureate Sydney Brenner at the MRC Laboratory of Molecular Biology in Cambridge, United Kingdom.

She has been at UCSF since 1986, serving as the Herbert Boyer Distinguished Professor until her appointment to her present position. Dr. Kenyon has received many honors and awards for her productive research. She is a member of the U.S. National Academy of Sciences, the American Academy of Arts and Sciences, and the Institute of Medicine. She is a past president of the Genetics Society of America.

ASN Presents Education Award to Agnes Fogo

Agnes B. Fogo

The Robert G. Narins Award, which honors those who have made substantial contributions to education and teaching, will be presented to Agnes B. Fogo, MD, on Saturday, November 12.

Dr. Fogo is the John L. Shapiro Professor of Pathology, professor of medicine and pediatrics, and director of the Renal Pathology/Electron Microscopy Laboratory at Vanderbilt University Medical School in Nashville, Tenn.

She has a long-standing interest in teaching. Her particular accomplishments in this area include developing and leading the basic renal pathology course, which is an annual feature of ASN Kidney Week. She also developed another annual feature of Kidney Week, the ASN Renal Biopsy Short Course, which brings together nephrologists, pathologists, and microscopists to study challenging renal biopsies and discuss clinical correlations. She created a widely used resource for teaching renal pathology in the form of a web-based free Atlas of Renal Pathology for the National Kidney Foundation, and is an author of two textbooks on renal pathology.

She is currently a member of the ASN Glomerular Disease Advisory Group, chairs the International Society of Nephrology Renal Pathology Advisory Committee, and is an ISN councilor. She has taught at numerous ISN renal pathology courses.

Dr. Fogo has served as pathology editor for the *American Journal of Kidney Disease* and associate editor of the *American Journal of Pathology* and *Journal of the American Society of Nephrology*. She is currently section editor for nephrology dialysis and transplantation and section editor for renal immunology and pathology in *Current Opinion in Nephrology and Hypertension*, and associate editor of *Laboratory Investigation*.

Fogo has also served on the ASN postgraduate committee and program committees and numerous grant review committees of the National Institutes of Health and American Heart Association. Her research interest focuses on progression and potential regression of chronic kidney disease, and is funded by the National Institute of Diabetes and Digestive and Kidney Diseases. Her major clinical interests focus on hypertension-related renal injury and focal segmental glomerulosclerosis.

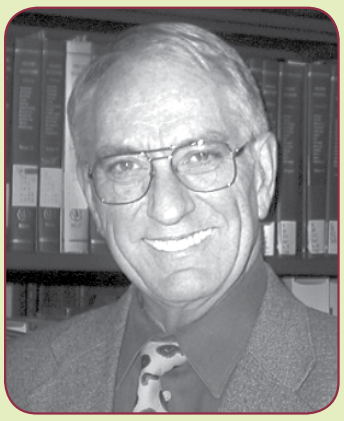
Dr. Fogo received her undergraduate education at the University of Oslo in Norway and the University of Tennessee in Chattanooga. She attended medical school at Vanderbilt, where she also did her pathology residency and fellowship training. She has been on the faculty there continuously since her residency.

Robert G. Narins

Robert G. Narins, MD, was the first recipient of the award bearing his name. He taught and mentored countless students, serving on the faculties of the University of Pennsylvania, UCLA, Harvard University, Temple University, and Henry Ford Hospital.

Well recognized for his contributions in the fields of fluid-electrolyte and acid-base physiology, Dr. Narins has also led numerous education efforts at the national and international levels. Among these, he has chaired the American Board of Internal Medicine's Nephrology Board and worked on the American College of Physicians' Annual Program Committee. From 1994 to 2006, he developed and guided ASN's educational programs, including working to expand educational programs during Renal Week. In addition, he was instrumental in the development of ASN's newest journal, the *Clinical Journal of the American Society of Nephrology*; in establishing the Fellow of the American Society of Nephrology program; and in negotiating ASN's partnership agreements with Hypertension, Dialysis, & Clinical Nephrology (HDCN) and UpToDate. Dr. Narins is also credited with working with organizations in Europe and Asia to help promote education and teaching in nephrology.

Jared Grantham to Receive John P. Peters Award



Jared J. Grantham

Jared J. Grantham, MD, FACP, is this year's recipient of the John P. Peters Award, to be presented on Saturday, November 12. The award recognizes Dr. Grantham's outstanding contributions to improving the lives of patients with kidney disease and to furthering the understanding of the kidney in health and disease.

Dr. Grantham is the Harry Statland Professor of Nephrology at the University of Kansas in Lawrence. In 2000, he was selected to be the founding director of The Kidney Institute at the University of Kansas Medical Center, an interdisciplinary renal research and training program comprised of 20 physician- and basic scientists, where he is now director emeritus.

His life work in nephrology falls into two major categories: defining the cellular mechanisms of salt and fluid transport across renal epithelial membranes and exploring the pathogenesis and treatment of polycystic kidney disease. The former work was recognized by ASN with the Homer W. Smith Award and the latter work was recognized by the International Society of Nephrology and Polycystic Kidney Disease Foundation with the Lillian Jean Kaplan Prize. With Kansas City businessman Joseph Bruening, Dr. Grantham co-founded the PKD Foundation in 1982. That organization has grown to have a national and international reach that has promoted awareness and research funding directed at understanding the basis and the treatment of polycystic kidney disorders. In 2009, for example, the PKD Foundation gave nearly $2 million in grants to fund 32 projects in five countries.

Dr. Grantham currently serves as treasurer of ASN, and was the founding editor of the *Journal of the American Society of Nephrology*. He is a member of the American Society of Clinical Investigation, Association of American Physicians, American Clinical and Climatological Association, American Association for the Advancement of Science (Fellow), and International Society of Nephrology, where he serves on the executive committee. He has received the David Hume Award from the National Kidney Foundation, the Award of Merit from the American Heart Association, and the Jean Hamburger Award from the International Society of Nephrology.

A life-long Kansan, he graduated from the University of Kansas School of Medicine. He did his residency in internal medicine at the Kansas University Medical Center followed by a research fellowship at the National Heart Institute's laboratory of kidney and electrolyte metabolism. After his fellowship, he served as a staff investigator for three years before returning to the University of Kansas to establish a renal research laboratory in the department of internal medicine, where he has received continuous National Institutes of Health funding. In 1970, he became director of nephrology, a position he held for 25 years.

Belding H. Scribner Award to Honor Neil Powe

Neil R. Powe

Presented to those who have made outstanding contributions to the care of patients with renal disorders or have substantially changed the clinical practice of nephrology, the 2011 Belding H. Scribner Award will be presented to Neil R. Powe, MD, FASN, on Saturday, November 12. Dr. Powe has published a plethora of incisive studies that have explored the effectiveness of therapies in kidney disease patients, illuminated kidney disease disparities and their causes, and advanced kidney disease awareness and prevention..

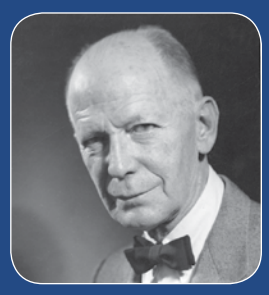
Dr. Powe is the Constance B. Wofsy Distinguished Professor at the University of California, San Francisco (UCSF), chief of medicine at San Francisco General Hospital, and vice chair of medicine at UCSF. He has made fundamental contributions in more than 350 publications that have catalyzed rigorous clinical investigation in kidney disease and shaped science in outcomes and disparities research. He has also mentored a large cadre of investigators who are conducting clinical epidemiology and patient outcomes research in kidney disease at leading academic institutions.

Some of his noteworthy studies include investigations of early referral of kidney disease patients, dialysis modality effectiveness, patient-physician contact in dialysis care, conduct of rounds in dialysis units, dialysis care by type of ownership, septicemia in dialysis patients, proteinuria screening cost-effectiveness, racial differences in cardiovascular procedure use, access to transplantation, determinants of organ donation, kidney disease management in primary care, the public health burden of kidney disease, and national surveillance of chronic kidney disease.

Dr. Powe led one of the first large, prospective cohort studies of incident end stage renal disease (ESRD) patients, the Choices for Healthy Outcomes in Caring for ESRD (CHOICE) study. CHOICE, with its careful characterization of 1041 patients in dialysis facilities in 18 U.S. states, has been a resource over the past 15 years for generating important answers to pressing problems in kidney disease. Dr. Powe's body of work has had a remarkable impact on the care of patients with kidney disease, has substantially raised public consciousness of kidney disease, and has changed the clinical practice of nephrology.

Dr. Powe earned his medical degree at Harvard Medical School. He completed his residency and fellowship at the University of Pennsylvania. Prior to joining UCSF, Dr. Powe served as the James Fries University Distinguished Service Professor of Medicine and director of the Welch Center at Johns Hopkins University. He is a member of the American Society of Clinical Investigation, the Association of American Physicians, and the Institute of Medicine.

John P. Peters



John P. Peters, MD, was one of the fathers of nephrology and former chief of the Metabolic Division in the Department of Medicine at Yale University. He transformed clinical chemistry from a discipline of qualitative impressions to one in which precise quantitative measurements of body fluids comprise a vital part of the patient examination and provide great explanatory value.

He advanced the view that disease is a quantitative abnormality of normal physiological processes and that, by understanding disease, one could gain a deeper understanding of normal physiology. His enduring scientific contributions paralleled his intense commitment to the care of the sick, as well as his fervent mission to ensure that the physician be an advocate for the patient.

Belding H. Scribner

Belding H. Scribner, MD, developed the arteriovenous shunt, which made possible long-term hemodialysis for chronic renal failure.

Dr. Scribner served as head of the University of Washington's Division of Nephrology in the Department of Medicine from 1958 to 1982. He and his co-workers at the Seattle university made numerous contributions to helping patients with end stage renal disease, including establishing the world's first out-of-hospital dialysis unit, developing a home hemodialysis program, improving techniques and equipment for hemodialysis and peritoneal dialysis, and studying the adequacy and complications of chronic renal disease treated by dialysis. Dr. Scribner's work made a significant contribution to transforming nephrology into a major subspecialty of internal medicine.

Plenary Session

Space Expert to Describe Medicine "Off the Earth"

State-of-the-Art Lecture

Jonathan B. Clark

Jonathan B. Clark, MD, MPH, will deliver the Sunday state-of-the- art lecture on "Up in Space: Medicine Off the Earth." Dr. Clark is an assistant professor of neurology and space medicine at Baylor College of Medicine and Center for Space Medicine. He is also clinical assistant professor at the University of Texas Medical Branch.

Dr. Clark's avid interest in space medicine—especially the neurologic effects caused by extreme environments and crew survival in space—is apparent in his many professional endeavors. He serves as Space Medicine Advisor for the National Space Biomedical Research Institute (NSBRI). He is board certified in neurology and aerospace medicine and is an Aerospace Medical Association Fellow. Dr. Clark is also medical director of the Red Bull Stratos Project, a manned stratospheric balloon freefall parachute flight test program, and chief medical officer for Excalibur Almaz, an orbital commercial space company.

From 1997 to 2005, Dr. Clark worked at NASA as a Space Shuttle Crew Surgeon. He was a member of the NASA Spacecraft Survival Integrated Investigation Team from 2004 to 2007 and a member of the NASA Constellation Program EVA Standing Review Board from 2007 to 2010. He served 26 years on active duty with the U.S. Navy and qualified as a Naval Flight Officer, Naval Flight Surgeon, Navy Diver, and Special Forces Military Freefall parachutist.

Young Investigator Wins Award for Kidney Fibrosis Findings

Katalin Susztak

The ASN Young Investigator Award will be presented to Katalin Susztak, MD, PhD, for her groundbreaking research on the mechanisms of progressive chronic kidney disease.

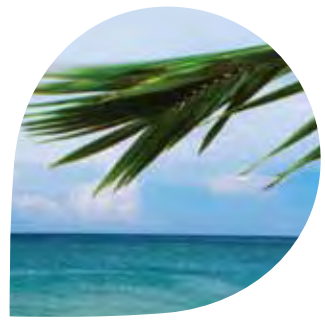
Dr. Susztak is an associate professor of medicine and genetics at the Albert Einstein College of Medicine in New York City.

The work in her laboratory is aimed at understanding the cellular and molecular mechanisms that lead to progressive renal fibrosis in chronic kidney diseases. She performs translational research to identify novel genetic, genomic, and epigenomic biomarkers of chronic kidney disease. She has shown that an integrative analysis of epigenetic and genetic determinants in diseased cells can provide a basis for more accurately modeling the critical biological pathways involved in mediating the progressive phenotype in individual patients.

Dr. Susztak's genetic approaches use a mouse model to test the role of candidate signaling molecules directly in vivo. Specifically, her work has highlighted the role of the Notch and Wnt/beta-catenin pathways, renal epithelial cell homeostasis, and renal stem or progenitor cell function and differentiation in progressive chronic kidney disease. Her recent results revealed the role of embryonic programs in the development of adult disease-causing alterations in renal epithelial cells and in causing kidney fibrosis. These studies have a broad clinical significance because they could be used to develop novel therapeutic strategies.

Dr. Susztak received her doctoral and medical degrees from Semmelweis University School of Medicine in Budapest, Hungary, in 1997. She completed her clinical fellowship in nephrology at the Albert Einstein College of Medicine in 2002. She conducted her postdoctoral work with Dr. Erwin Bottinger, where her observations led to the recognition that injury and apoptosis of podocytes are the earliest lesions in progressive diabetic nephropathy.

Dr. Susztak serves on the ASN Glomerular Disease Advisory Group. She will receive the award and deliver the Young Investigator Address titled "Kidney Fibrosis: Where Kidney Repair Went Awry" on Sunday, November 13.



Experience

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30 mg
tablets

Experience the first and only oral vasopressin V_2-receptor antagonist that increases

FREE WATER CLEARANCE

and serum sodium concentrations.

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, cirrhosis, 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.

- 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
- 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
- Gastrointestinal bleeding in patients with cirrhosis: Use in cirrhotic patients only when the need to treat outweighs this risk
- Avoid use with: CYP 3A inhibitors and CYP 3A inducers. Reduced dose of SAMSCA may be needed if used with P-gp inhibitors
- Co-administration with hypertonic saline is not recommended
- Monitor serum potassium in patients with levels >5 mEq/L and in those receiving drugs known to increase serum potassium

Commonly observed adverse reactions: (SAMSCA vs placebo) 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%).

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

For more information please visit www.samsca.com

Otsuka
Otsuka America Pharmaceutical, Inc.

Samsca® (tolvaptan) 15 mg 30 mg tablets

SELECTIVE. CORRECTIVE.

March 2010

0710A-0589B

SAMSCA® (tolvaptan) tablets for oral use

Brief Summary of Prescribing Information. For complete prescribing information consult official package insert.

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, cirrhosis, 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.

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. None of the patients in these studies had evidence of osmotic demyelination syndrome or related neurological sequelae, but such complications have been reported following too-rapid correction of serum sodium. 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.

Gastrointestinal Bleeding in Patients with Cirrhosis: In patients with cirrhosis treated with tolvaptan in hyponatremia trials, gastrointestinal bleeding was reported in 6 out of 63 (10%) tolvaptan-treated patients and 1 out of 57 (2%) placebo-treated patients. SAMSCA should be used in cirrhotic patients only when the need to treat outweighs this risk.

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: There is no experience with concomitant use of SAMSCA and 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 (2.4), 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 (2.4), 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 (2.4), 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).

SAMSCA® (tolvaptan)

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.*

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 (2.4) 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 (2.4) 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 (2.4) 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 (2.4) 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 (2.4) 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 and SAMSCA is a P-gp inhibitor. Co-administration of SAMSCA and digoxin results in a 1.3-fold increase in the exposure to digoxin.

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.

USE IN SPECIFIC POPULATIONS:

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.

Use in Patients with Renal Impairment: Exposure and response to tolvaptan are similar in patients with a creatinine clearance 10-79 mL/min and in patients without renal impairment. No dose adjustment is necessary. Exposure and response to tolvaptan in patients with a creatinine clearance <10 mL/min or in patients on chronic dialysis have not been studied. No benefit can be expected in patients who are anuric *[see Contraindications (4.5)]*.

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 LD_{50} 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 Pg-p 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 (2.4), 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.

Manufactured by Otsuka Pharmaceutical Co., Ltd., Tokyo, 101-8535 Japan

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

US Patent Nos.: 5,258,510 and 5,753,677.

SAMSCA is a trademark of Otsuka Pharmaceutical Co., Ltd., Tokyo, 101-8535 Japan

Otsuka

Otsuka America Pharmaceutical, Inc. 0708L-0023B Rev. 05/2009

ASN SCIENTIFIC EXPOSITION

Thursday, November 10 – Saturday, November 12 | 9:30 a.m. – 2:30 p.m.

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Exhibitor Spotlights

ASN has built a special theater in the scientific exposition hall to spotlight industry's latest advances in nephrology practices, products, services, and technologies during 60 minute presentations (no continuing medical education credit). Seating is first come, first served and limited to 100 participants.

All presentations include breakfast (morning presentations) or lunch (afternoon presentations).

Spotlight Schedule

Thursday, November 10, 2011

10:00 a.m. – 11:00 a.m.
Importance of Early Diagnosis and Management of Hyperphosphatemia in CKD Patients on Dialysis

Presented by SANOFI

12:30 p.m. – 1:30 p.m.
Blood Management in Clinical Context: Perspectives in Nephrology

Presented by janssen PHARMACEUTICAL COMPANIES OF Johnson & Johnson

Friday, November 11, 2011

10:00 a.m. – 11:00 a.m.
Protocol Management of Secondary Hyperparathyroidism (HPT) and Appropriate Insurance Coverage and Co-Pays

Presented by AMGEN®

12:30 p.m. – 1:30 p.m.
Understanding Hyponatremia: Treating Beyond the Primary Diagnosis

Presented by Otsuka Otsuka America Pharmaceutical, Inc.

Saturday, November 12, 2011

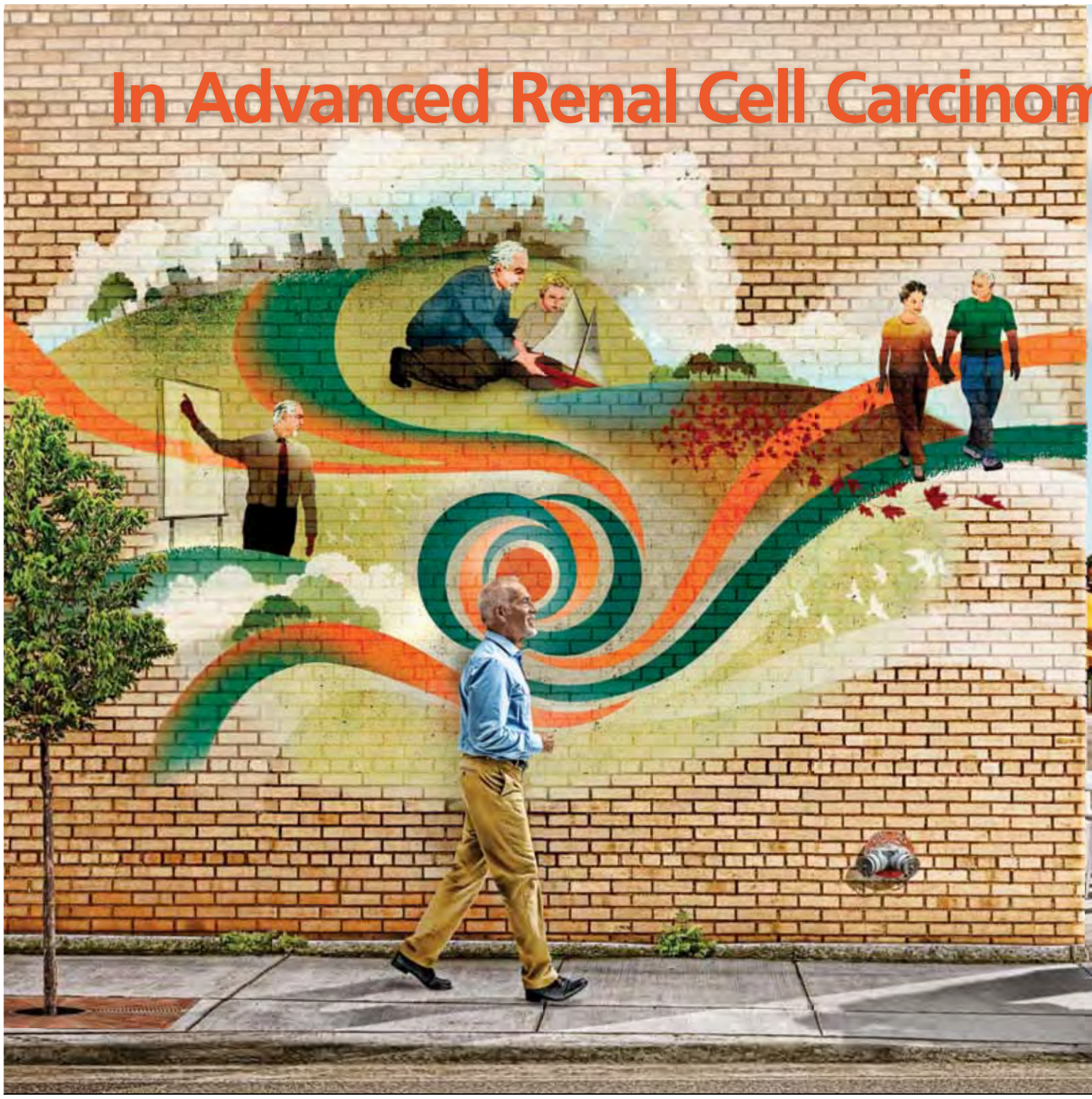
10:00 a.m. – 11:00 a.m.
Renal Replacement Therapy for AKI: Current Status and Future Challenges

Presented by GAMBRO®

12:30 p.m. – 1:30 p.m.
Understanding Crystal Burden and Treating Refractory Chronic Gout

Presented by SAVIENT PHARMACEUTICALS, INC.

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 has been observed. Hypertension was observed in 47% of patients with RCC treated with VOTRIENT. Hypertension occurs early in the course of treatment (88% occurred in the first 18 weeks). Blood pressure should be well-controlled prior to initiating VOTRIENT. Monitor for hypertension and treat as needed. If hypertension persists despite antihypertensive therapy, the dose of VOTRIENT may be reduced or discontinued as appropriate.

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)[2,3]

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)[2,3]

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)[2,3]

NCCN Guidelines Category 1 recommendation[4]

- First-line therapy for relapsed or Stage IV unresectable RCC of predominant clear cell histology

Proven safety profile[1,2]

- Most common adverse events observed with VOTRIENT (>20%) were diarrhea, hypertension, hair color changes (depigmentation), nausea, anorexia, and vomiting
  - — Grade 3/4 fatigue occurred in 2% of patients; all grades, 19%
  - — Grade 3/4 asthenia occurred in 3% of patients; all grades, 14%

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

- Grade 3 ALT increases occurred in 10% of patients; grade 4, 2%
- 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

Once-daily oral dosing[1]

- The recommended dosage of VOTRIENT is 800 mg once daily without food (at least 1 hour before or 2 hours after a meal)
- Dose modifications, interruptions, and discontinuations may be required in patients with hepatic impairment, drug interactions, and following adverse events
- Forty-two percent of patients on VOTRIENT required a dose interruption; 36% of patients on VOTRIENT were dose-reduced

VOTRIENT is a multitargeted tyrosine kinase inhibitor that is indicated for the treatment of patients with advanced RCC.

Votrient™
pazopanib tablets (200 mg)

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%); 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: GlaxoSmith-Kline; 2010. **2.** Sternberg CN, et al. *J Clin Oncol*. 2010;28(6):1061–1068. **3.** Data on file, GlaxoSmithKline. **4.** Referenced with permission from ©National Comprehensive Cancer Network, Inc 2010. All Rights Reserved. NCCN Guidelines™: Kidney Cancer, V.1.2011. NCCN.org Accessed January 12, 2011. NCCN® and NCCN GUIDELINES™ are trademarks owned by the National Comprehensive Cancer Network, Inc.

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GlaxoSmithKline
Oncology

Multifactorial Intervention with Nurse Practitioners May Control Cardiac Risk Factors in CKD

By Daniel M. Keller

Nurse practitioners did as well as physicians when they were part of a multifactorial program to improve management of some cardiovascular (CV) risk factors. They lessened the need for physician visits for patients with chronic kidney disease (CKD) but were unable to modify lifestyle risk factors such as smoking, body weight, physical activity, or sodium intake.

Researchers performed the Multifactorial Approach and Superior Treatment Efficacy in Renal Patients with the Aid of Nurse Practitioners (MASTERPLAN) study to investigate whether a multifactorial intervention based on guidelines with the added support of specialized nurse practitioners to augment physician visits could reduce CV risk, slow the loss of renal function, and improve the quality of care. Studies of single interventions achieved at best only moderate success in reducing the high CV morbidity and mortality accompanying CKD.

Arjan van Zuilen, MD, head of the kidney transplant unit at University Medical Center Utrecht in Utrech, Netherlands, presented the findings of the MASTERPLAN study in a late-breaking trial recently.

MASTERPLAN was a randomized controlled clinical trial that recruited patients with CKD from nine Dutch hospitals between 2004 and 2005 and followed them up through 2010. The participants' estimated GFR had to be between 20 and 70 mL/min per 1.73 m^2. They were randomly assigned to a traditional care control group (n = 393) or to an interventional group (n = 395). The primary outcome was a composite of CV death, myocardial infarction, and stroke.

At baseline, participants in the two groups were well matched for age (59 years), gender (about 68 percent men), kidney transplants (14 percent), blood pressure, estimated GFR, and laboratory parameters. However, there was more history of CV disease in the intervention group (34 percent) than in the control group (25 percent).

CV risk factors other than lifestyle improved in intervention group

At 5 years, most laboratory parameters had improved and the use of risk-reducing drugs rose in both groups, but the intervention group showed greater improvement than did the control group. It had greater decreases in systolic and diastolic blood pressure, LDL cholesterol, proteinuria, and prevalence of anemia. It also made more use of statin drugs, aspirin, and active vitamin D.

The use of angiotensin converting enzyme inhibitors or angiotensin receptor blockers increased in both arms, with more than 80 percent of participants in each arm using them, so there was no significant difference between the groups. They also did not differ in their hemoglobin A1c levels, which were already below the treatment goal of 7.0 percent at baseline.

Although the CV risk factors improved in the intervention group compared with the control group, the intervention group had no lower incidence of the primary composite endpoint of CV death, myocardial infarction, and stroke or of any of the secondary endpoints of the risk of each individual component of the composite endpoint, or in the risk of reaching ESRD.

The intervention did not help to modify any lifestyle risk factors, such as physical activity, body mass index, or sodium intake. Both the intervention and control groups had a decrease in the proportion of smokers—the difference between groups was not significant.

Patients in the intervention group made more visits to health care provid-

ers each year (7.2 versus 4.7 visits, respectively, but they visited the physician less often than did those in the control group (2.8 versus 3.7, respectively).

Study was underpowered for primary outcome

Dr. van Zuilen explained the lack of a significant difference in the primary outcome as a result of too few CV events occurring, with a 5-year event incidence rate of 8.9 percent in both arms. When the study was planned, the estimated event rate in the control arm was 13.5 percent, based on the results of previous studies.

Johannes Mann, MD, of the department of nephrology at Munich General Hospital in Munich, Germany, said he calculated that to be sufficiently powered to show a difference in the primary endpoint, the study would have required 10 times the number of individuals involved in the MASTERPLAN trial.

In explaining the results, Dr. van Zuilen further noted that perhaps not all the treatment goals were beneficial, and that possibly, because some of the risk factors were well controlled in both groups, the differences between groups were small.

He concluded that nurse practitioners can perform as well as physicians to improve CV risk factors if they follow established guidelines and that they "can then take away some of the burden of the very big patient loads we have in our outpatient departments."

Despite MASTERPLAN being underpowered to show an effect between groups in the primary outcome of CV death, myocardial infarction, and stroke, Dr. Mann commented to *ASN Kidney News* that it was "a very important study because... the nurse practitioner intervention was, in absolute terms, effective in reducing the primary outcome, which was a hard outcome."

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

	VOTRIENT (N = 290)			Placebo (N = 145)		
Adverse Reactions	All Grades[a] %	Grade 3 %	Grade 4 %	All Grades[a] %	Grade 3 %	Grade 4 %
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. 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)		
Parameters	All Grades[a] %	Grade 3 %	Grade 4 %	All Grades[a] %	Grade 3 %	Grade 4 %
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) 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. In the overall safety population for RCC (N = 586), one patient had hypertensive crisis on VOTRIENT. [*See Warnings and Precautions (5.2).*] 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 (5.3).]* 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 (5.5).]* 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 (5.7).]* 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. 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)]*. **7.2 Effects of Pazopanib on CYP Substrates:** Results from drug-drug interaction studies conducted in cancer patients suggest that pazopanib is a weak inhibitor of CYP3A4, CYP2C8, and CYP2D6 in vivo, but had no effect on CYP1A2, CYP2C9, or CYP2C19 *[see Clinical Pharmacology (12.3) of full prescribing information]*. Concomitant use of VOTRIENT with agents with narrow therapeutic windows that are metabolized by CYP3A4, CYP2D6, or CYP2C8 is not recommended. Coadministration may result in inhibition of the metabolism of these products and create the potential for serious adverse events. *[See Clinical Pharmacology (12.3) of full prescribing information.]*

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy: Pregnancy Category D *[see Warnings and Precautions (5.10)]*. VOTRIENT can cause fetal harm when administered to a pregnant woman. There are no adequate and well-controlled studies of VOTRIENT in pregnant women. In pre-clinical studies in rats and rabbits, pazopanib was teratogenic, embryotoxic, fetotoxic, and abortifacient. Administration of pazopanib to pregnant rats during organogenesis at a dose level of ≥3 mg/kg/day (approximately 0.1 times the human clinical exposure based on AUC) resulted in teratogenic effects including cardiovascular malformations (retroesophageal subclavian artery, missing innominate artery, changes in the aortic arch) and incomplete or absent ossification. In addition, there was

Paricalcitol Versus Cinacalcet in Lowering Parathyroid Hormone Levels in Chronic Kidney Disease

By Daniel M. Keller

Paricalcitol allowed the achievement of target parathyroid hormone levels better than cinacalcet in patients with secondary hyperparathyroidism (SHPT), a complication of chronic kidney disease (CKD). Both a vitamin D receptor activator such as paricalcitol and a calcimimetic such as cinacalcet effectively treat SHPT, which is characterized by elevated serum levels of intact parathyroid hormone (iPTH). Elevated iPTH levels can lead to skeletal and cardiovascular complications.

Speaking at the 48th Congress of the European Renal Association—European Dialysis and Transplant Association in Prague, Markus Ketteler, MD, of the division of nephrology at the Coburg Clinic in Coburg, Germany, told the congress that the effectiveness of these treatments had never before been compared in patients undergoing hemodialysis.

So he and coworkers performed the Improved Management of iPTH with Paricalcitol-centered Therapy versus Cinacalcet Therapy with Low-dose Vitamin D in Hemodialysis Patients with Secondary Hyperparathyroidism (IMPACT SHPT) study to assess the optimal dose titration of paricalcitol (adding cinacalcet if hypercalcemia occurred) in comparison with a combination of cinacalcet with low-dose vitamin D for the treatment of SHPT. The phase 4 study was open label and multinational.

After a screening and washout period, the investigators randomly assigned 272 patients receiving hemodialysis to paricalcitol or to cinacalcet with low-dose vitamin D for 28 weeks. The evaluation period was the final eight weeks of the trial. Patients received paricalcitol intravenously (iv stratum at United States and Russian sites) or orally (oral stratum at all sites other than in the United States or Russia). Patients taking cinacalcet received low-dose vitamin D intravenously (iv) or orally.

At baseline, the patients were well matched within each stratum for age, gender, duration of dialysis, serum calcium, and serum iPTH level (iv stratum, 521 pg/mL and 526 pg/mL;

Continued on page 26

Parathyroid Hormone

Continued from page 25

oral stratum, 495 pg/mL and 510 pg/mL for the paricalcitol and cinacalcet arms, respectively). Comorbidities were common and possibly reflected the characteristics of the larger population of patients receiving hemodialysis. Significantly more participants in the paricalcitol group iv stratum had type 1 diabetes, and those in the oral stratum had more type 2 diabetes.

Paricalcitol was initially dosed at 0.07 µg/kg iv or PTH/80 orally. The cinacalcet dose was 30 mg initially. The study inclusion criteria were hemodialysis three times a week for at least three months before entry; an iPTH level between 300 and 800 pg/mL, inclusive; a calcium level of 8.4–10.0 mg/dL; and phosphorus at or below 6.5 mg/dL at baseline.

The primary outcome of the trial was the proportion of participants attaining a mean iPTH value of 150–300 pg/mL during weeks 21 to 28 (normal iPTH is 10–65 pg/mL). A secondary outcome was the proportion of participants with hypocalcemia, defined as a mean serum calcium level of less than 8.4 mg/dL, or with hypercalcemia, defined as a mean calcium level of at least 10.5 mg/dL.

More people receiving paricalcitol achieved iPTH target

In the primary efficacy analysis of reaching the target iPTH level, iv paricalcitol was superior to iv cinacalcet, with fewer patients outside the normal serum calcium range. In the iv stratum, 58 percent of patients receiving paricalcitol achieved the iPTH endpoint versus 33 percent receiving cinacalcet (p = 0.016). However, the patients taking the oral drugs showed no significant difference in the proportion achieving the iPTH target (54 percent with paricalcitol versus 43 percent with cinacalcet; p = 0.26).

In a secondary efficacy analysis that controlled for strata, paricalcitol was superior to cinacalcet, with 56 percent and 38 percent of participants, respectively, falling in the iPTH efficacy range during the evaluation period (p = 0.01).

When the wholesale costs in the United States of paricalcitol, cinacalcet, and vitamin D preparations were calculated, the medication costs for paricalcitol treatment were 40 percent lower than for cinacalcet treatment.

Adverse events

Hypocalcemia occurred in about half of the cinacalcet patients in either the iv or the oral stratum but in only 4 percent in the oral paricalcitol stratum and in none in the iv stratum. Minimal hypercalcemia was observed and was not significantly different between the two drugs taken either iv or orally.

In all, 69–81 percent of subjects in the four groups completed the study. Serious adverse events led to interruption of the study drugs in 22–27 percent of the patients in any of the four arms. When the iv and oral strata were combined, three times as many major adverse cardiovascular events occurred with paricalcitol (9/134) as with cinacalcet (3/134), possibly because of differences in risk factors between the groups at baseline.

In conclusion, Dr. Ketteler said "Paricalcitol showed superiority over cinacalcet in achieving the primary efficacy endpoint" when strata were controlled for. He noted that hypocalcemia occurred in almost half of the patients treated with cinacalcet and that in paricalcitol-treated patients the incidence of hypercalcemia was not significantly different from that in people treated with cinacalcet.

ASN **Kidney Week** 2011

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Thursday, November 10 • 12:45 p.m. – 1:45 p.m.

Clinical Approach to Syndromes of Hyponatremia: An Update on Pathophysiology, Diagnosis, and Treatment
Support for this symposium is provided by an educational grant from Otsuka America Pharmaceutical, Inc.

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Support for this symposium is provided by an educational grant from Mitsubishi Tanabe Pharma

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ASN LEADING THE FIGHT AGAINST KIDNEY DISEASE

Journal View

For Dialysis Patients, No Survival Gain with Earlier Nephrologist Care

In older adults starting dialysis, earlier initiation of nephrology care hasn't led to improved first-year survival, reports a study in the *Archives of Internal Medicine*.

The researchers analyzed U.S. Renal Data System data on 323,977 patients aged 67 or older who started dialysis between 1996 and 2006. Trends in the timing of the earliest identifiable nephrology visit and in one-year mortality after dialysis initiation were analyzed, with consideration of changes in case mix.

In 2006, about 35 percent of patients first saw a nephrologist less than three months before the start of dialysis, compared to nearly 50 percent in 1996. Mean estimated glomerular filtration rate at the start of dialysis was 12 mL/min/1.73 m^2 in 2006, compared to 8 mL/min/1.73 m^2 in 1996. Rates of anemia and initial peritoneal dialysis also decreased during the period studied.

Despite these trends, there was no reduction in mortality during the first year on dialysis. With adjustment for shifts in sociodemographic characteristics and comorbidity, the estimated annual reduction in one-year mortality was 0.9 percent. The change was even smaller, 0.4 percent per year, after adjustment for earlier nephrology consultation.

Consistent with current recommendations, there is a trend toward earlier nephrology care before the start of dialysis. However, this trend does not appear to have resulted in any substantial improvement in survival during the first year on dialysis. The results highlight the need to test the benefits versus costs of earlier dialysis and other "nephrologist-driven health care interventions." [Winkelmayer WC, et al: Predialysis nephrology care of older patients approaching end-stage renal disease. *Arch Intern Med* 2011; 171: 1371–1378].

Serum Cystatin C May Help Predict AKI Risk in Children

In children undergoing heart surgery, increases in serum cystatin C during the early postoperative period are associated with an increased rate of acute kidney injury (AKI), suggests a study in *Kidney International*.

The prospective study included 288 children undergoing cardiac surgery at three children's hospitals. One-half were aged 2 years or younger. Preoperative and postoperative cystatin C were evaluated as predictors of AKI. The predictive value of cystatin C was compared with that of serum creatinine-based estimates of glomerular filtration rate.

Stage 1 AKI or worse developed in 42 percent of the children and stage 2 AKI or worse in 11 percent. Children with higher preoperative creatinine-based estimated glomerular filtration rates were at higher risk of AKI: adjusted odds ratio (OR) 1.5 for stage 1 and 1.9 for stage 2 AKI.

Preoperative cystatin C was unrelated to AKI risk. However, children in the highest quintile of postoperative cystatin C were at significantly increased risk: OR 6.0 for stage 1 and 17.2 for stage 2 AKI. Being in the highest tertile of percent change in cystatin C was independently associated with AKI risk; being in the highest tertile of serum creatinine predicted stage 1 but not stage 2 AKI. Postoperative change in both cystatin C and creatinine predicted longer ICU stay, while postoperative change in cystatin C also predicted duration of mechanical ventilation.

Early diagnosis of AKI is particularly challenging in children. The new study suggests that early postoperative increases in serum cystatin C may predict the development of AKI in children undergoing cardiac surgery. Postoperative cystatin C may be useful for risk stratification in AKI treatment trials. More study of the association between preoperative renal function and AKI risk is needed [Zappitelli M, et al: Early postoperative serum cystatin C predicts severe acute kidney injury following pediatric cardiac surgery. *Kidney Int* 2011; 80: 655–662].

Loss to Analysis—a Problem in CKD Trials

Randomized trials of treatment for chronic kidney disease (CKD) have important quality shortcomings—including a high rate of loss of patients from the analysis, according to a study in the *American Journal of Kidney Diseases*.

The researchers performed a systematic evaluation of loss to analysis for primary outcomes of randomized controlled trials of patients with CKD undergoing dialysis or kidney transplantation. The analysis included 196 trials published in 2007 and 2008. Studies in which not all randomized patients were included in the primary outcome analysis were considered to have loss to analysis.

Twenty-seven percent of the trials specified no clear primary outcome. Five percent did not report numbers of patients randomized and analyzed, while 12 percent used time-to-event analysis. Of the remaining 110 studies, 58 percent had some loss to analysis. The median loss to analysis was 10 percent, with a range of one to 41 percent.

Fifty-four percent of trial reports said that analysis was by intention to treat. Yet 44 percent of studies making this claim did not include all randomized patients in the analysis. Imputation of missing data was reported by five percent of studies. Studies without loss to analysis tended to have smaller sample sizes: 128 versus 229.

Randomized trials of treatment for CKD pose unique challenges. Based on the new review, many CKD studies do not meet current standards for clinical trial reporting. Many trials do not specify a primary outcome of interest; those which do have high rates of data loss to analysis. Efforts to improve the quality of CKD randomized trials should include increased attention to transparency and reporting loss to analysis. [Deo A, et al: Loss to analysis in randomized controlled trials in *CKD. Am J Kidney Dis* 2011; 58: 349–355].

Low Sodium Beats Dual Blockade for Nondiabetic Nephropathy

In patients with nondiabetic nephropathy, guideline-based reductions in sodium intake are more effective than the combination of lisinopril and valsartan in lowering proteinuria and blood pressure, reports a trial in the *British Medical Journal*.

The randomized controlled trial included 52 outpatients with nondiabetic nephropathy. In four 6-week periods, patients were treated with the angiotensin receptor blocker (ARB) valsartan 320 mg/d or placebo (in random order) plus a low- and regular-sodium diet (in sequential order): target intake 50 versus 200 mmol Na^+/d. Patients took the angiotensin-converting enzyme (ACE) inhibitor lisinopril 40 mg/d throughout the study.

Mean urinary sodium excretion was 106 mmol Na^+/d on the low-sodium diet and 184 mmol Na^+/d on the regular-sodium diet. Proteinuria decreased from 1.68 g/d on ACE inhibitor plus regular-sodium diet, to 1.44 with ACE inhibitor plus ARB, to 0.85 with ACE inhibitor plus low-sodium diet, to 0.67 g/d with ACE inhibitor plus ARB plus low-sodium diet. The 51 percent reduction in proteinuria with ACE inhibitor plus low-sodium diet was significantly greater than the 21 percent reduction with ARB plus ACE inhibitor.

Mean systolic blood pressure was 134 mm Hg with ACE inhibitor plus regular-sodium diet. There was a 2 percent reduction on ACE inhibitor plus ARB, compared to a 7 percent reduction with ACE inhibitor plus low-sodium diet. Adding dual blockade to low-sodium diet did not produce further significant reductions in proteinuria or blood pressure.

The results suggest that adding a low-sodium diet to an ACE inhibitor reduces proteinuria and blood pressure to a greater extent than the combination of ACE inhibitor and ARB in patients with nondiabetic nephropathy. Efforts to reduce sodium intake to recommended levels will enhance the efficacy of renoprotective strategies in this group of patients. [Slagman MCJ, et al: Moderate dietary sodium restriction added to angiotensin converting enzyme inhibition compared with dual blockade in lowering proteinuria and blood pressure: randomised controlled trial. *BMJ* 2011; 343: d4366].

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Dietary Factors and Chronic Kidney Disease

By Amaka Eneanya and Julie Lin on behalf of the ASN CKD Advisory Group

The role of diet in maintaining a healthy weight in decreasing the risk for diabetes and hypertension—the leading causes of kidney failure worldwide—is undoubtedly important. Recent evidence suggests that dietary factors may also directly influence decline in kidney function. Nutritional epidemiology has traditionally focused on the development of diabetes and cardiovascular disease. Logically, the same dietary factors implicated in macrovascular coronary or cerebral vascular disease will also manifest in microvascular disease of the kidneys.

Several challenges arise in studying the role of diet in kidney disease progression in humans. First, as in any investigation of dietary factors and the development or progression of chronic medical conditions, adherence in an interventional diet study is difficult to maintain in randomized participants over several weeks or years. Second, kidney disease progression usually requires several years to manifest in community-dwelling adults in the general population. So the majority of studies with the requisite long-term follow-up in this area are observational and subject to potential confounding by unmeasured entities that may reflect an overall healthier lifestyle. Nonetheless, longitudinal observational studies currently provide the majority of information for associations between diet and kidney disease.

In critical evaluation of the published medical literature, additional considerations such as how kidney disease progression is defined and how diet is administered or measured are also important. Here we summarize the major relevant research studies and divide "kidney disease" into two main entities: 1) directly measured GFR or estimated GFR (eGFR), widely considered to be the primary measure of kidney "function" (Table 1), and 2) the presence of microalbuminuria, which is commonly considered to represent early kidney disease as well as reflect systemic vascular dysfunction (Table 2). A variety of kidney outcomes have been examined by different investigators, which may make direct comparisons between studies difficult. Notably, almost all published studies looking at microalbuminuria are cross-sectional.

How dietary intake is measured and quantified in observational studies also deserves attention. In longitudinal cohort studies, a common evaluation tool is the semi-quantitative food frequency questionnaire, which assesses average food intake over the preceding year in approximately 130 items. Responders are given a standard portion size and choose one of nine possible frequency-of-consumption responses, ranging from "never or less than once per month" to "six or more times per day" for each food item. Total energy and nutrient intake can then be calculated by summing up energy or nutrients from all foods. Whereas traditional nutritional epidemiology has focused on individual nutrients or foods, their additive or interactive influence perhaps may be better observed when overall diet patterns are considered for incident chronic diseases. Therefore, nutritional epidemiology studies in recent years have included analyses of healthful dietary patterns (e.g., prudent-style and Dietary Approaches to Stop Hypertension [DASH]-style, both high in whole grain, fruit, and vegetable intake) and of unhealthful dietary patterns (e.g., Western-style, high in red meat, refined grains, and sweets).

Historically, the role of dietary protein in kidney disease has been dominant because of a number of longstanding reports that protein restriction delays the progression of

Table 1

Studies of diet and kidney function by measured or estimated GFR

Reference	Patient population	Study design/follow-up	Results	Outcome
Walker JD, et al. *Lancet* 1989; 334:1411-1415	32 patients (age 26–62) with IDDM and GFR >20 mL/min per 1.73 m²	Crossover intervention study of patients with type I diabetes: normal-protein diet (1.13 g/kg per day) followed by low-protein diet (0.67 g/kg per day), 62-month follow-up	Mean rate of GFR fell from 0.61 (SEM 0.14) mL/min per month with normal-protein diet to 0.14 (SEM 0.08) mL/min per month with low-protein diet (p = 0.001)	Measured GFR change (clearance of Cr-labeled edetic acid)
Klahr S, et al. *N Engl J Med* 1994; 330:877–884	840 patients (age 18–70): group 1 (GFR 25–55 mL/min per 1.73 m²); group 2 (GFR 13–24 mL/min per 1.73 m²)	Multicenter randomized controlled trial; randomized to usual-protein (1.3 g/kg per day), low-protein (0.58 g/kg per day), and very-low-protein diet (0.28 g/kg per day); 2.2-year follow-up	No significant difference between diet groups in projected mean GFR decline	Measured GFR change (clearance of I-iothalamate)
Levey AS, et al. *Am J Kidney Dis* 1996; 27:652–663	255 patients (age 18–70) with baseline GFR 13–24 mL/min per 1.73 m²	Correlation analysis of multicenter randomized controlled trial; randomized to low-protein (0.58 g/kg per day) or very-low-protein diet (0.28 g/kg per day) supplemented with keto-amino acids (0.28 g/kg per day); 2.2-year follow-up	0.2 g/kg per day lower achieved total protein intake associated with a 1.15 mL/min per year slower mean decline in GFR (p = 0.011); no meaningful benefit of the prescribed very low-protein/keto-amino acid diet vs. low-protein diet on slower progression of renal disease	(1) Measured GFR change (clearance of I-thalamate) (2) Time to renal failure (initiation of dialysis or renal transplantation or death)
Knight EL, et al. *Ann Intern Med* 2003; 138:460–467	1623 women (age 42–68) participating in Nurses' Health Study	Prospective observational cohort study; protein intake measured by food frequency questionnaires; 11-year follow-up	Normal renal function (eGFR >80 mL/min per 1.73 m²); high protein intake not significantly associated with change in eGFR; mild renal insufficiency (eGFR 55–80 mL/min per 1.73 m²); every 10-g increase in nondairy animal protein intake associated with decrease in eGFR of 1.69 mL/min per 1.73 m² (95% CI, −2.93 to −0.45)	eGFR (≥25% decline between 1989 and 2000)
Lin J, et al. *Clin J Am Soc Nephrol* 2010; 5:836–843	3296 women (median age 56) participating in Nurses' Health Study	Prospective observational cohort study; nutrients over 14 years assessed by food frequency questionnaires; 11-year follow-up	Highest quartile of sodium directly associated with eGFR decline (OR = 1.52; 95% CI, 1.10–2.09); higher β-carotene intake inversely associated with eGFR decline (OR = 0.62; 95% CI, 0.43–0.89)	eGFR (≥30% decline between 1989 and 2000)
Lin J, et al. *Am J Clin Nutr* 2010; 4:897–904	19,256 participants (age ≥45) in REGARDS study	Cross-sectional study; dietary fat intake assessed by food frequency questionnaire	No significant association with any dietary fats and presence of eGFR <60 mL/min per 1.73 m²	eGFR (< 60 mL/min per 1.73 m²)
Bomback AS, et al. *Kidney Int* 2010; 77:609–616	15,745 participants (age 45–64) in ARIC study	Prospective observational cohort study; baseline soda beverage intake assessed by food frequency questionnaires; 9-year follow-up	No significant associations between sugar or diet soda intake and incidence of chronic kidney disease	eGFR (incident eGFR <60 mL/min per 1.73 m² at 3 or 9 years follow-up)
Lin J, et al. *Clin J Am Soc Nephrol* 2011; 6:160–166	3318 women (median age 56) participating in Nurses' Health Study	Prospective observational cohort study; cumulative soda beverage intake assessed by food frequency questionnaires; 11-year follow-up	Consumption of ≥2 servings per day of artificially sweetened (diet) soda associated with eGFR decline ≥30% (OR = 2.02; 95% CI, 1.36–3.01) and ≥3 mL/min per 1.73 m² per year (OR = 2.20; 95% CI, 1.36–3.55); no associations seen with sugar-sweetened soda	eGFR (≥ 30 % decline or >3 mL/min per 1.73 m² between 1989 and 2000)
Lin J, et al. *Am J Kidney Dis* 57 (2): 245-254, 2011	3071 women (median age 56) participating in Nurses' Health Study	Prospective observational cohort study; dietary intake assessed by food frequency questionnaires; Western vs. DASH vs. prudent dietary patterns; 11-year follow-up	Highest quartile of Western pattern score associated directly with rapid eGFR decline (OR = 1.77; 95% CI, 1.03–3.03); top quartile of DASH score had decreased risk of rapid eGFR decline (OR = 0.55; 95% CI, 0.38–0.80); prudent dietary pattern not associated with eGFR decline	eGFR (≥ 30 % decline or >3 mL/min per 1.73 m² per year between 1989 and 2000)

Abbreviations: ARIC = Atherosclerosis Risk in Communities; CI = confidence interval; DASH = Dietary Approaches to Stop Hypertension; eGFR = estimated GFR; IDDM = insulin-dependent diabetes mellitus; OR = odds ratio; REGARDS = Reason for Geographic and Racial Differences in Stroke; SEM = standard error of the mean.

kidney function decline in laboratory animals. In 1994, results were published from the Modification of Diet in Renal Disease study, a multicenter randomized controlled trial of 840 adults with chronic kidney disease (GFR 25–55 mL/min per 1.73 m^2) who were randomized to usual-protein (1.3 g/kg per day), low-protein (0.58 g/kg per day), or very-low-protein (0.28 g/kg per day) diets. The primary finding was that there was no significant difference between the diet groups in mean GFR decline over 2.2 years. Limitations of this study include the short follow-up time and the exclusion of all but diet-controlled diabetic participants. By contrast, subsequent analyses of the Nurses' Health Study observational cohort by Knight et al. (Table 1) reported that higher dietary animal (but not total, dairy, or vegetable) protein intake was associated with faster eGFR decline over 11 years in women (only ~4% diabetic) with baseline mild renal insufficiency (defined as eGFR 55–80 mL/min per 1.73 m^2). The Modification of Diet in Renal Disease study did not distinguish between different types of dietary protein, which may have differential effects on eGFR decline.

Over recent years, additional studies on dietary factors and chronic disease have been published in the Nurses' Health Study, the Multi-Ethnic Study of Atherosclerosis, the Atherosclerosis Risk in Communities, and the Reason for Geographic and Racial Differences in Stroke cohorts (Tables 1 and 2). Overall, the majority of the findings suggest that diets considered "heart healthful" (low in saturated animal fats and protein, sodium, and sweetened beverages but high in fruit, vegetables, high-fiber whole grains, low-fat dairy, and fish) are inversely associated with the presence and progression of chronic kidney disease.

A potential pathophysiologic link between diet and kidney disease (as well as heart disease) is inflammation. Interestingly, inflammatory markers such as C-reactive protein, intracellular adhesion molecule-1, and vascular cellular adhesion molecule-1—which have been associated with subsequent coronary heart disease, the presence of albuminuria, and faster decline of kidney function in multiple studies—are significantly more elevated in people eating unhealthful diets than those eating healthful diets. More research is needed, however, to further assess the role of diet in modifying the risk for chronic kidney disease progression.

Amaka Eneanya, MD, (nephrology fellow) and Julie Lin, MD, MPH, FASN, (faculty physician) are members of the Renal Division, Department of Medicine at Brigham and Women's Hospital and Harvard Medical School in Boston.

Table 2

Studies of diet and albuminuria/microalbuminuria

Reference	Patient population	Study design/follow-up	Results	Outcome
Walker JD, et al. *Lancet* 1989; 334:1411–1415	32 patients (age 26–62) with IDDM and GFR >20 mL/min per 1.73 m^2	Crossover intervention study of patients with type I diabetes; normal-protein diet (1.13 gm/kg per day) followed by low-protein diet (0.67 gm/kg per day); 24-hour urine collected for urinary albumin; 62-month follow-up	Significant fall in mean albumin excretion ratio from 467 mg/24 hours to 349 mg/24 hours with low-protein diet compared with normal-protein diet ($p < 0.01$)	Urinary albumin excretion rate: (>300 mg/day)
Metcalf PA, et al. *Clin Chem* 1993; 39:2191–2198	5416 participants (age 40–78) in New Zealand health screen survey	Cross-sectional study; 3-month dietary intake assessed by food frequency questionnaire; random urine collection for urinary albumin	Relative risk for albuminuria: dietary cholesterol >226 mg/day directly associated with presence of microalbuminuria (OR = 1.32; 95% CI, 1.02–1.70); dietary fiber >26 g/day inversely associated with presence of microalbuminuria (OR = 0.74; 95% CI, 0.58–0.95)	Urinary albumin excretion rate: (normal albuminuria: men <28 mg/L, women <29 mg/L; slight albuminuria: men 29–299 mg/L, women 30–299 mg/L; clinical albuminuria >300 mg/L)
Toeller M, et al. *Diabetologia* 1997; 40:1219–1226	2696 participants (age 15–60) with IDDM in EURODIAB Complication Study	Cross-sectional study of patients with type I diabetes; standard 3-day dietary record obtained; 24-hour urine collected for urinary albumin	Total protein intake associated with higher albumin excretion rate (β = 0.02; 95% CI, 0.01–0.04); animal protein intake associated with higher albumin excretion rate (β = 0.02; 95% CI, 0.003–0.03)	Urinary albumin excretion rate (defined as a continuous variable)
Riley MD, et al. *Am J Clin Nutr* 1998; 67:50–57	178 Tasmanian adults (mean age 39.4) with IDDM and no previous albuminuria	Cross-sectional study of patients with type I diabetes; dietary macronutrient intake over 1 year as measured by food frequency questionnaires; overnight urine collection for urinary albumin	Microalbuminuria in highest quintile of energy-adjusted saturated fat vs. lowest (OR = 4.9; 95% CI, 1.2–20.0); microalbuminuria in highest quintile of energy-adjusted protein vs. lowest (OR = 0.10; 95% CI, 0.02–0.56)	Urinary albumin excretion rate (microalbuminuria: 20–200 µg/min)
Wrone EM, et al. *Am J Kidney Dis* 2003; 41:580–587	12,422 participants (age 20–80) in NHANES III	Cross-sectional cohort study; 24-hour dietary recall; random urine collection for urinary albumin	Microalbuminuria associated with highest quintile of dietary protein intake vs. lowest in patients with hypertension and diabetes mellitus (OR = 3.3; 95% CI, 1.4–7.8); dietary protein intake not associated with microalbuminuria in normotensive or nondiabetic persons	Urinary albumin-to-creatinine ratio (>300 mg/g)
Daviglus ML, et al. *Am J Kidney* Dis 2005; 45:256–266	4381 participants (age 40–59) in INTERMAP	Cross-sectional study; 24-hour dietary data collected at four visits; two 24-hour urine collections for urinary albumin	Total estimated sugar (OR = 0.67, p = 0.029), ω-6 fatty acid (OR = 0.75, p = 0.039), polyunsaturated fatty acid (OR = 0.77, p = 0.039), calcium (OR = 0.65, p = 0.015, vitamin E (OR = 0.67, p = 0.011), vitamin C (OR = 0.66, p = 0.009), and iron intake (OR = 0.60, p = 0.007) associated inversely with presence of microalbuminuria in men; alcohol intake (OR = 1.20, p = 0.024) and 24-hour urinary sodium excretion (OR = 1.35, p = 0.009) directly associated with microalbuminuria in women	Urinary albumin excretion rate (microalbuminuria negative: albumin <30 mg/day; microalbuminuria positive: albumin ≥30 to <300 mg/day)
Nettleton JA, et al. *Am J Clin Nutr* 2008; 87:1825–1836	5042 participants (age 45–84) in Multi-Ethnic Study	Cross-sectional study; diet assessed by food frequency questionnaire; one spot urine sample to assess albumin and creatinine	Dietary pattern characterized by high consumption of whole grains, fruit, vegetables, and low-fat dairy foods associated with 20% lower albumin-to-creatinine ratio across quintiles ($\beta = -0.042 \pm 0.01$, p (trend) = 0.004)	Urinary albumin-to-creatinine ratio (25–249 mg/g)
Shoham DA, et al. *Plos One* 3:e3431	9358 participants (age 20–80) in NHANES, 1999–2004	Cross-sectional study; diet assessed by questionnaire	≥2 servings of sugar-sweetened soda associated with presence of microalbuminuria (OR 1.40; 95% CI, 1.13–1.74); no association between diet soda and microalbuminuria	Urinary albumin-to-creatinine ratio (>25 mg/g in women, >17 mg/g in men)
Lin J, et al. *Clin J Am Soc Nephrol* 2010; 5:836–843	3296 women (median age 67) participating in Nurses' Health Study	Subgroup analysis of prospective observational cohort study, cross-sectional study of microalbuminuria; nutrients assessed by repeated food frequency questionnaires, cumulative average approach; spot urinary samples collected in 2000 to assess albumin and creatinine	Highest quartile of animal fat vs. lowest directly associated with microalbuminuria (OR = 1.72; CI, 1.12–2.64); intake of two or more servings per week of red and processed meat directly associated with microalbuminuria (OR = 1.51; CI, 1.01–2.26)	Urinary albumin-to-creatinine ratio (25–355 µg/mg)
Lin J, et al. *Am J Clin Nutr* 2010; 4:897–904	19,256 participants (age ≥45) in REGARDS study	Cross-sectional study; dietary fat intake assessed by food frequency questionnaire	Highest quintile of saturated fat intake vs. lowest associated with high albuminuria (OR = 1.33; CI, 1.07–1.66, p = 0.04)	Urinary albumin-to-creatinine ratio (25–355 mg/g for women, 17–250 mg/g for men)
Lin J, et al. *Clin J Am Soc Nephrol* 2011; 6:160–166	3318 women (median age 67) participating in Nurses' Health Study	Subgroup analysis of prospective observational cohort study, cross-sectional study of microalbuminuria; cumulative soda beverage intake assessed by food frequency questionnaires	No associations seen with diet or sugar soda and microalbuminuria	Urinary albumin-to-creatinine ratio (25–355 µg/mg)
Lin J, et al. *Am J Kidney Dis* 2011; 57:245–254	3121 women (median age 67) participating in Nurses' Health Study	Subgroup analysis of prospective observational cohort study, cross-sectional study of microalbuminuria; dietary intake assessed by food frequency questionnaires; Western vs. DASH vs. prudent dietary pattern	Highest quartile of Western pattern score directly associated with microalbuminuria (OR = 2.17; 95% CI, 1.18–3.66) top quartile of DASH score had no association with microalbuminuria; prudent dietary pattern not associated with microalbuminuria	Urinary albumin-to-creatinine ratio (25–354 µg/mg)

Abbreviations: CI = confidence interval; DASH = Dietary Approaches to Stop Hypertension; EURODIAB = collaborative European study of childhood insulin-dependent diabetes; IDDM = insulin-dependent diabetes mellitus; INTERMAP = international study of dietary patterns and blood pressure; NHANES III = National Health and Nutrition Examination Survey; OR = odds ratio; REGARDS = Reason for Geographic and Racial Differences in Stroke.

The Influence of Obesity on Kidney Health

By Allon Friedman, MD, on behalf of the ASN CKD Advisory Group

Obesity is a major challenge to domestic and international public health. As of 2008 in the United States nearly one in four adults was obese (1). In that same year, the World Health Organization estimated that approximately 500 million adults throughout the globe were obese (with an additional 1 billion being overweight) (2).

Obesity is widely considered a harbinger for a multitude of diseases, particularly diabetes and hypertension. In recent years a growing body of evidence has suggested that kidney disease, too, may be included in this list of illnesses. In fact, one published report estimates that up to one third of kidney disease in the United States could be related to obesity (3). But how strong is the evidence that obesity has deleterious effects on kidney health, and what therapeutic interventions are available? These questions are increasingly relevant to every practicing nephrologist.

An association between obesity and kidney disease was noted in the modern medical literature as early as 1923, when Boston practitioner William Preble described a high rate of albuminuria and nephritis in his large cohort of obese patients (4). From the 1970s onward, a series of case reports described the existence of proteinuria and glomerular hyperfiltration in severely obese individuals. Interestingly, weight loss almost immediately reversed these conditions. Subsequent animal studies have confirmed that renal changes accompany obesity. In one such study, Henegar and colleagues induced obesity in a cohort of dogs and noted structural and immunohistochemical changes in the kidney, although they could not isolate the independent effects of obesity from the development of other pathologic states such as hypertension and insulin resistance (5). More recently many, but not all, observations in humans have confirmed a link between obesity and glomerular hypertrophy/hyperfiltration and proteinuria (6). A minority of obese individuals also appear to develop obesity-related glomerulopathy, a process that can be associated with focal segmental glomerular sclerosis and progression to end stage renal disease (ESRD)(7).

A growing body of epidemiologic evidence supports the direct association between obesity and kidney disease, even after accounting for intermediate disease states like hypertension and diabetes. In one such study, conducted in a cohort of over 300,000 Kaiser Permanente patients, increasing body mass index was linked with a stepwise increase in the risk of ESRD during decades of follow-up (8). Individuals with extreme obesity (body mass index ≥40) actually had more than a seven times greater risk of developing ESRD over the follow-up period than did persons of normal weight. Adjustment for the presence of diabetes and hypertension attenuated the relationship somewhat, but the risk conferred by obesity was still greatly elevated. Similar findings have been documented in other populations (9, 10). Obesity has also been implicated as an independent risk factor leading to the accelerated progression of other primary renal diseases, such as IgA nephropathy (11).

Scientific data increasingly support the hypothesis that obesity has adverse effects on kidney health, yet several central questions remain. For example, the mechanisms are poorly understood. Investigators have implicated several possible factors (Table 1), including alterations in levels of adipocyte-related cytokines such as leptin and adiponectin (as well as other hormones), upregulation of the renin-angiotensin axis and sympathetic nervous activity, insulin resistance, renal-associated lipotoxicity, protein consumption, and hemodynamic factors such as hyperfiltration and hypertension. However, the exact pathogenesis is still unknown. Of note, it is also not well understood whether the hallmark hemodynamic changes

and increased proteinuria observed in obese individuals are simply functional, benign adaptations, or truly pathologic. Why obesity affects kidney health in some but not all obese individuals is yet another mystery. Preliminary research raises the possibility that preterm birth may predispose certain obese individuals to renal disease, perhaps through the underdevelopment of nephron mass (12).

A final question relates to identifying effective treatment strategies. Some insight into this issue has been gleaned from the study of bariatric surgery patients before and after surgery-induced weight loss. The advantage of using this model, which is not without limitations, is that investigators can compare changes in renal function and health within individual patients after guaranteed (and usually profound) weight loss.

Studies performed in relatively healthy bariatric surgery patients essentially confirm the findings from animal models that weight loss reduces glomerular hyperfiltration and proteinuria (13). It is not known whether this effect is renoprotective because so few patients with pre-existing kidney disease have been studied before and after bariatric surgery. Yet a fairly consistent proteinuria-reducing effect has been noted from nonsurgical weight loss therapies in patients with proteinuric nephropathies (14). Thus, the intuitive concept that weight loss ameliorates obesity-related kidney disease (or at least proteinuria) is supported by the limited scientific data currently available, although the minimum weight loss required is not known, nor is the persistence of this effect over time.

Researchers have also focused on blockade of the renin-angiotensin axis as a potential treatment, given the acknowledged deleterious effects of an upregulated renin-angiotensin system common in obesity. A recent post-hoc analysis of a randomized, controlled trial found that the angiotensin-converting enzyme inhibitor ramipril had disproportionately greater effects on reducing proteinuria and the risk of ESRD in overweight and obese grossly proteinuric kidney disease patients than it did in similarly diseased lean patients (15).

The intimate connection between the obesity crisis and the growth of the chronic kidney disease population makes it likely that this topic will become increasingly prominent in coming years. It is also expected that the many unanswered questions surrounding both the causes of obesity-related kidney disease and its optimal treatment will be tackled with greater urgency.

Allon Friedman, MD, FASN, is a nephrologist and clinical investigator at Indiana University School of Medicine.

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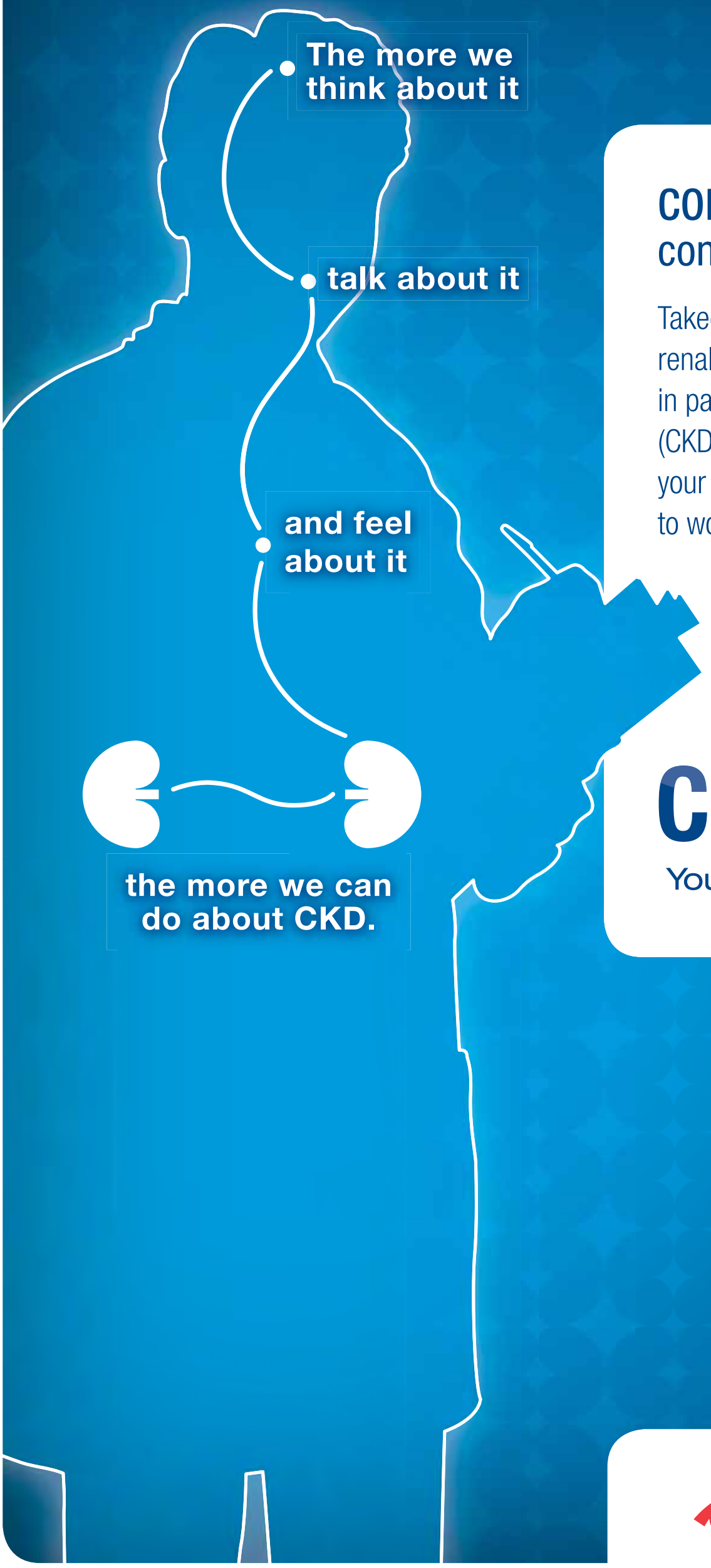
Table 1

Potential causes underlying influence of obesity on kidney health

- ☐ Adipocyte-related molecules: adiponectin, leptin, and others
- ☐ Renin-angiotensin activation
- ☐ Increased sympathetic activity
- ☐ Insulin resistance
- ☐ Protein consumption
- ☐ Lipotoxicity
- ☐ Hypertension
- ☐ Hemodynamic factors
- ☐ Nephron underdevelopment



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Physical Activity and Kidney Disease

By Cassianne Robinson-Cohen and Ian de Boer, MD, on behalf of the ASN CKD Advisory Group

A growing body of evidence suggests that lifestyle approaches can yield significant benefits for patients with chronic kidney disease (CKD). Although exercise is not routinely advocated in patients with CKD, it delivers a broad range of health benefits and may prevent cardiovascular complications and disease progression in this patient population. Regular aerobic and resistance training exercise of an intensity and duration tailored to the patient should be considered as an integral treatment option in all patients with CKD.

Physical inactivity is an underlying cause of cardiovascular disease (CVD). Observational studies in the general population have consistently reported that greater physical activity is associated with lower risks of myocardial infarction, stroke, and cardiovascular death (1–3). Physical inactivity contributes to obesity, diabetes mellitus, and hypertension, which are each independently associated with the development of CVD and a decline in functional status.

Exercise stimulates glucose uptake by skeletal muscle, thereby reducing insulin secretion and promoting lipolysis (4). Exercise also contributes to a fall in systemic blood pressure and a reduction in body mass (5, 6). In controlled trials in the general population, moderate physical activity consisting of aerobic, resistance, and combination training improves fasting and postprandial glucose levels, induces and maintains weight loss, raises HDL cholesterol, lowers LDL cholesterol and triglycerides, lowers blood pressure, and probably lowers inflammation and improves endothelial function. On the basis of these results, guidelines from the American Heart Association and the American College of Sports Medicine recommend either moderate-intensity exercise 5 days per week for a minimum of 30 minutes, strenuous exercise 3 days per week for 20 minutes, or a combination of these activities.

The presence of CKD is associated with substantial increased risks of cardiovascular events, disability, and a shortened lifespan. This increased risk can be partly explained by a concomitant increase in traditional risk factors for CVD, such as diabetes mellitus and hypertension. But chronic renal dysfunction alone is also an independent risk factor for CVD. In fact, the majority of individuals with moderate CKD die of CVD rather than progress to ESRD. The major cardiovascular events seen in CKD patients include myocardial infarction and cardiac arrest, stroke, and peripheral vascular disease. Efforts focused on the prevention and management of CVD in patients with CKD are imperative.

Diabetes, obesity, hypertension, and the presence of kidney dysfunction per se lead to activation of the renin-angiotensin system, oxidative stress, endothelial dysfunction, elevated asymmetric dimethyl arginine, low-grade inflammation with increased circulating cytokines, and dyslipidemia (7). These metabolic disturbances are highly prevalent both in CKD patients (8, 9) and in physically inactive individuals (10), and they augment the risks of microvascular and macrovascular disease. Inasmuch as exercise is well recognized as a therapeutic intervention that can improve the physiologic, functional, and psychological deterioration that accrues as a result of a sedentary lifestyle, it is plausible that greater physical activity may temper the metabolic disturbances of CKD and reduce the risks of kidney disease progression and cardiovascular events (Figure 1).

In patients with ESRD, several randomized controlled trials have reported that performing aerobic and/or resistance training during dialysis time, during nondialysis time, or at home can improve many indices of health and function, such as peak oxygen consumption, HDL and LDL cholesterol concentrations, left ventricular mass index, ejection fraction, cardiac output index, stroke volume index, heart rate, quality of life, depression, physical functioning, bodily pain, and work capacity (Table 1) (11). In these trials, aerobic exercise training was typically prescribed for three to four sessions/week for 30–60 minutes per session, at moderate intensity, and was composed of cycle ergometer training, walking/jogging, aerobics, calisthenics, swimming, or ball games. These studies demonstrate that exercise can counteract the physiologic, functional, and psychological wasting associated with ESRD.

In the predialysis CKD setting, a few small trials have investigated the effects of physical activity interventions on a broad spectrum of physiologic indices (Table 1). Studies that have investigated the effects of resistance training programs in CKD patients have found that muscle endurance programs administered three times per week for 12 weeks cause a significant reduction in levels of inflammation markers (C-reactive protein and IL-6) (12) and a significant increase in muscular strength, dynamic endurance, walking capacity, and functional mobility (13).

In addition to the beneficial effects on risk for CVD, physical function, and psychological well-being, physical activity may slow the progression of CKD. One small study of the effect of regular aquatic exercise in patients with moderate chronic renal failure assigned 17 adults with chronic renal failure to low-intensity aerobic exercise in the pool for 12 weeks, twice a week, with sessions lasting for 30 minutes, and matched them to nine control participants who remained sedentary (14). The participants in the exercise group showed significant reduction in serum cystatin-C levels and enhancement of creatinine clearance, whereas no such change was noted in the control group.

Recent evidence also suggests that greater physical activity is associated with a lower risk of rapid kidney function decline among older adults (15). In this large study of community-based older adults, the two highest physical activity groups had a 28 percent lower risk of rapid kidney function decline, defined by the loss of more than 3 mL/min per 1.73 m^2 per year in the GFR (calculated using serum cystatin C), compared with the two lowest physical activity groups, accounting for potential confounding characteristics. Additionally, in the Nurses' Health Study, women in the highest physical activity group were 35 percent less likely to have albuminuria than were women in the lowest physical activity group (16).

Modalities to delay or prevent the onset of cardiovascular complications and to slow the progressive loss of kidney function in the CKD population are urgently needed. A large body of evidence suggests that regular aerobic and resistance training exercises of moderate intensity and medium duration could help correct the disease processes underlying these adverse outcomes. Even without randomized controlled trials proving that physical activity prevents cardiovascular and renal events, this body of evidence is sufficiently robust to motivate action. We recommend that physical activity tailored to the individual should be routinely advocated in patients with CKD.

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Figure 1

Exercise and kidney health

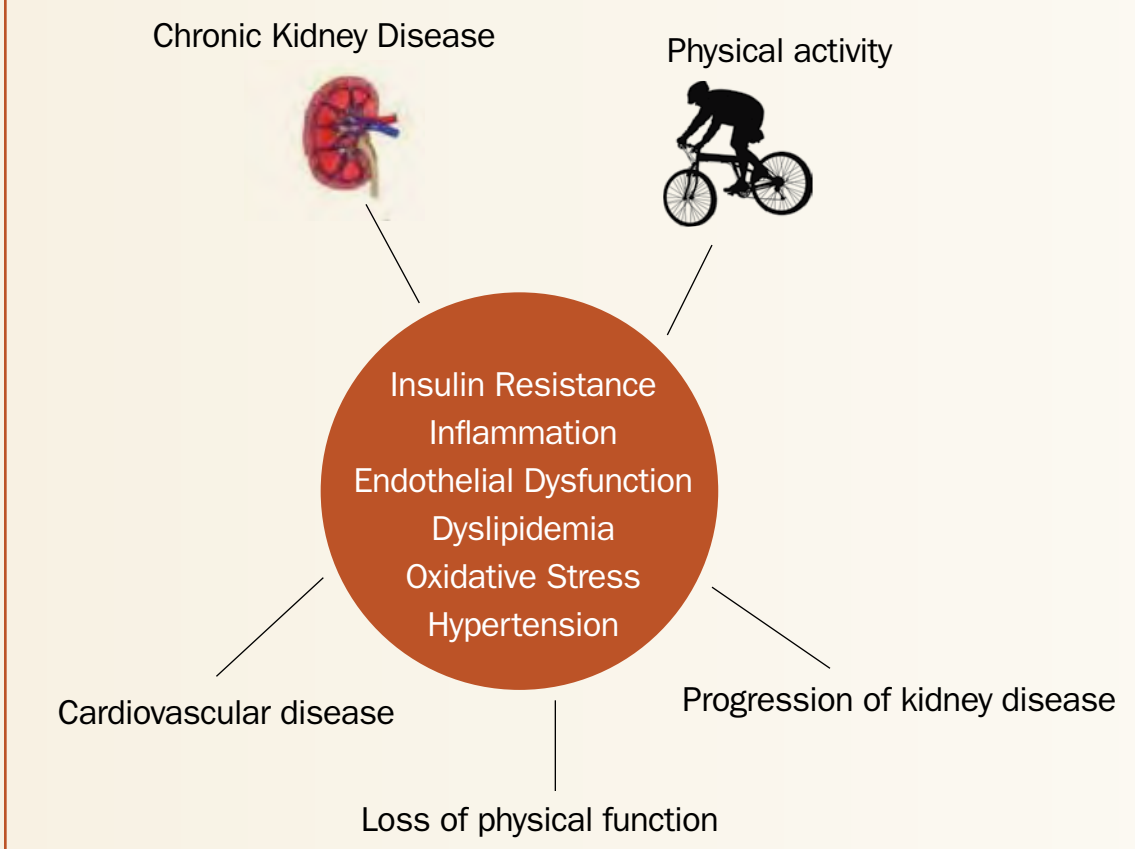

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Table 1

Summary of studies on physical activity in CKD or ESRD

Setting	Modality, frequency and duration of exercise treatment	Outcomes
End-stage renal disease, intradialytic	Aerobic training • Cycle ergometer (17, 18) 30–45 min, 3–4 times per week for 6–20 weeks	• Increase in peak oxygen consumption • Increase in peak heart rate • Increase in duration of graded exercise stress test • Increase in physical performance
	Strength training • Lower body strength exercise (19, 20)	• Knee extension strength • Increase in self-reported physical functioning
End-stage renal disease, interdialytic/home-based therapy	Aerobic training • Walking (21) • Calisthenics (22, 23) • Cycle ergometer (21) • Swimming (23) 45–60 min, 3–4 times per week for 6–20 weeks	• Increase in maximal aerobic capacity • Decrease in total triglyceride levels • Increase in HDL cholesterol • Decrease in fasting plasma insulin levels • Improvement in glucose disappearance rates • Reduction in coronary risk factors • Increase in self-reported quality of life • Decrease in prevalence of clinical depression
	Strength training • Upper and lower body strength exercise (23) 3–4 times per week, 45 min per session	• Increase in cross-sectional area of muscle fibers • Increased exercise capacity • Increased likelihood of returning to work
Chronic kidney disease, home or training center	Aerobic training • Aquatic exercise (14) 3–4 times per week, 45–60 min per session for 6–20 weeks	• Reduction in cystatin C levels • Reduction in blood pressure • Enhancement of creatinine clearance
	Strength training: • Upper and lower body resistance training (12) 3–4 times per week, 45 min per session	• Reduction in serum C-reactive protein and IL-6 • Increase in type I and type II muscle fiber cross-sectional areas • Decrease in heart rate • Increase in thigh muscular function • Increased muscular strength • Increased dynamic endurance • Increased walking capacity • Increased functional mobility

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Dialysis Data Submission Migrates Online

By Kurtis Pivert

The next generation in electronic records management will arrive at all Centers for Medicare & Medicaid Services (CMS)–certified end stage renal disease (ESRD) dialysis clinics by February 2012, affecting facilities, clinicians, and patients. The new system, CROWNWeb, promises to streamline the data submission process for dialysis providers and provide up-to-the-minute clinical and facility information to assist nephrologists, help improve oversight, and guide patient care decisions.

As highlighted in the January 2011 issue of *Kidney News*, CROWNWeb was developed for CMS-certified dialysis facilities to help them comply with the electronic submission guidelines in the updated Conditions for Coverage (CfC) for ESRD. The program is entirely web-based and adheres with federal security requirements to ensure the confidentiality of patient and facility records.

Certified dialysis providers will be able to submit and track patient admission history and forms, required CMS facility documentation, and clinical dialysis data online anytime. Due to the sensitive nature of this information, CROWNWeb incorporates a tiered security structure to ensure that the site and its critical data remain safeguarded. In addition to login credentials, users must obtain a unique one-time system-generated pass code each time they visit CROWNWeb, which is delivered via email or text message, valid for a 12-hour session before gaining access to the site. This security measure is a second layer of protection that goes beyond what's offered in many web sites.

Originally unveiled in 2009 to a test group, CROWNWeb has undergone constant improvements in preparation for national release. The test group ultimately comprised some of the largest dialysis organizations, and they were able to use the program's unique batching capabilities. However, many small and medium-sized dialysis organizations may not be able to utilize this technology, which led the National Renal Administrators Association to collaborate with the CMS to fill the gap. A pilot project will allow these providers to use a third-party Health Information Exchange to access the Nationwide Health Information Network and deliver data to CROWNWeb and the CMS, an infrastructure that still meets the stringent security requirements of the National Institute of Standards and Technology.

Patient care and accountability

The impact of the new data submission and management system will be felt beyond the dialysis clinic. Patients and clinicians will benefit in several different ways from the new program. For one, the dramatic reduction in time needed to process CMS forms and analyze data with CROWNWeb, compared with the current paper-based system, will increase the efficiency of the CMS in addressing provider accountability in meeting patient care goals.

One of the quality initiatives for ESRD patients, Dialysis Facility Compare, will now have real-time facility and clinical data to enhance the search results patients and caregivers use to make informed decisions when choosing a dialysis provider. Moreover, instead of a small fraction of patient information currently accessible, the CMS will now have access to data from all certified dialysis facilities, giving researchers and clinicians a more complete picture of the ESRD population.

An additional advantage for patients is the continuity of care that a central database like CROWNWeb affords. The system creates a centralized archive of the patient's records after admission to a facility. With this archive, CROWNWeb reduces potential treatment interruptions owing to missing treatment data and provides for a seamless transition if a patient relocates to another clinic. Once a transfer is initiated, the new facility will receive a report from CROWNWeb outlining whether the patient is receiving hemodialysis or peritoneal dialysis; a summary of their weekly sessions data; and whether they are at-home or in-clinic patients.

If a natural disaster or other event prevents a patient from accessing his or her current facility, the system also provides a new "transient patient" feature, supplying an interim provider with the patient's treatment summary and their recently submitted CMS forms.

For more information about CROWNWeb, please visit www.projectcrownweb.org.

Policy Update

By Rachel Shaffer

ASN Discusses ESA Label Changes with FDA

When the Food and Drug Administration (FDA) changed the label on erythropoiesis-stimulating agents (ESAs) in July, ASN raised concerns about the modifications to the agency. FDA met with ASN this October to discuss the society's reservations.

FDA significantly revised the ESA label, most importantly by removing the recommended target hemoglobin range of 10–12 g/dL. The new label states that the dose of ESAs should be "reduced or interrupted" if hemoglobin levels exceed 11 g/dL. The label also states that "In controlled trials, patients experienced greater risks for death, serious adverse cardiovascular reactions, and stroke when administered ESAs to target a hemoglobin level of greater than 11 g/dL." The revised label caused concern among nephrologists, including those on ASN's Public Policy Board, on multiple levels. First, no study has ever demonstrated that risk does in fact exist above the specific threshold of 11 g/dL, as stated on the label. Second, the label generates uncertainty about how ESAs should actually be administered. "Interrupting" a medication is not typical when treating patients with chronic disease and variable follow up. How low is it safe to let hemoglobin levels go? And would exceeding 11 g/dL generate risk of a malpractice lawsuit in the case of an adverse event?

Given the confusion and alarm among the nephrology community regarding the changes, ASN was pleased that FDA suggested an in-person meeting to discuss the already-published label—a rare move for the agency. ASN Public Policy Board chair Tom Hostetter, MD, and Public Policy Board member Wolfgang Winkelmayer, MD, ScD, FASN, represented the society at the FDA, along with ASN Manager of Policy and Government Affairs Rachel Shaffer. The key points ASN's contingent emphasized centered on the agency's assertion that hemoglobin levels above 11 g/dL have conclusively been proven to increase risk of adverse events.

ASN emphasized that since adverse events were consistently observed in randomization groups targeting only hemoglobin concentrations >13 g/dL, no scientific data are currently available that would either justify dropping the previous hemoglobin target of 10–12 g/dL, or substantiate the statement of risk at 11g/dL (Table 1). An accurate statement would instead read that "In controlled trials, patients experienced greater risks for death, serious adverse cardiovascular reactions, and stroke when administered ESAs to target a hemoglobin level of greater than **13 g/dL**."

"We recognize that FDA is doing its best to ensure patient safety in an area where evidence is sparse, and with a product that is known to increase safety risks when hemoglobins of 13 g/dL or more are aggressivley targeted," said Winkelmayer. "But it is fundamentally not true that evidence suggests those risks start at 11 g/dL. It would be more reasonable for the label to state that — based on available trial evidence—the risks of any treatment strategies targeting the range between 11 g/dL and 13 g/dL are currently unknown relative to lower or higher targets. That change would allow patients and their nephrologists to have a conversation about the potential risks and benefits."

ASN also pointed out the on-the-ground reality that the new dosing recommendation terminology could result in overly conservative, more rigidly enacted ESA dosing practice patterns in some dialysis units, especially in light of recent changes to the ESRD Quality Incentive Program by the Centers for Medicare and Medicaid Services. The label change may place patients at increased risk of anemia and blood transfusions, which could adversely affect health and candidacy for transplantation.

The society also explained that physicians treating chronic disease rarely consider *interrupting* treatment as it may lead to adverse health outcomes. In the setting of anemia in CKD patients, interruption may place patients at increased risk of transfusions.

ASN's key request to FDA—a request shared by the Renal Physicians' Association, which also attended the meeting—is that FDA consider revising the label to reflect that studies actually show that greater risk exists when ESAs target a hemoglobin level of greater than 13 g/dL.

At press time (within a week of the meeting) FDA had not issued any formal responses to ASN. The society will keep members updated about additional communications with the FDA regarding the label. You may view ASN's letter to the FDA on this issue at www.asn-online.org.

Table 1

Available evidence from randomized controlled trials showing adverse cardiovascular outcomes in patients With CKD

	Target hemoglobin (g/dL)		Achieved hemoglobin (g/dL)	
	Low	High	Low	High
NHT	10	14	10.3	13.3
CHOIR	11.3	13.5	11.4	12.8
TREAT	>9 *	13	10.6	12.5

* Not a hemoglobin target, but a threshold group; placebo group with darbepoetin rescue below a hemoglobin concentration of 9 g/dL. Adapted from *Sem in Dial*

Debt Committee Urged to Protect Kidney Disease Funding

The Joint Committee on Deficit Reduction, or the "super committee" is without question the most talked-about—and feared and revered—entity in Washington, DC, this fall. Tasked by the Budget Control Act of 2011 with developing a plan by November 23 to trim at least $1.2 trillion from the national debt over the next decade, the super committee's job is daunting. However, the committee possesses no shortage of options to meet that $1.2 trillion goal: everything is "on the table" for reductions. ASN is leading the way in making sure that funding affecting kidney patients and physicians is not among the reduced.

ASN identified the funding streams pertinent to kidney disease most likely to be endangered by the committee's search for programs to trim, and together with the American Society of Pediatric Nephrology (ASPN) and the Renal Physicians' Association (RPA), sent a letter to the super committee outlining the vital importance of their preservation for patient care, job preservation, and economic stability. "It's critical that the super committee recognize the significance of these programs, especially at this time," said ASN Public Policy Board chair Thomas H. Hostetter, MD. "Our letter emphasizes that it's not just doctors, or even just doctors and patients, who benefit—it is every American whose job, community or local economy is affected by these issues."

Discretionary workforce programs are considered to be among the most vulnerable. In the letter, ASN emphasized that decreasing federal support for physician training would result in a host of unintended consequences for patients and the nation's healthcare workforce. The society urged the super committee to avoid any cuts to physician training programs, which would exacerbate the problem of Americans' access to care, worsen the physician shortage already recognized by Congress, and endanger thousands of jobs. According to the economic consulting firm Tripp Umbach, cuts to graduate medical education at the nation's largest teaching hospitals alone would trigger the elimination of over 70,000 jobs and the loss of $10 billion to the U.S. economy.

Similarly, ASN highlighted the crucial role the research activities funded through the National Institutes of Health (NIH), Agency for Healthcare Research and Quality, and the Veterans' Administration play in maintaining the health of the U.S. population and the nation's economy. Besides enabling important medical discoveries, according to a 2010 study, investment in the NIH led to the creation of 487,900 new jobs and produced more than $68 billion in new economic activity.

The letter also urged the super committee to account for the needs of ESRD patients, the most vulnerable of all Medicare patient populations, by maintaining funding for ESRD care at current levels and not subjecting ESRD care to possible payment reductions. It further encouraged the super committee to consider incorporating the "Comprehensive Immunosuppressive Drug Coverage for Kidney Transplant Patients Act of 2011" into its recommendations to Congress, noting that this bipartisan legislation would save lives and protect Medicare's investment in kidney transplants. ASN, ASPN, and RPA also advocated that at this juncture in particular, repeal and replacement of the flawed sustainable growth rate (SGR) formula would be the most appropriate and fiscally responsible course of action in the effort to preserve Medicare beneficiary access to care.

Looking Ahead

Should the bipartisan group fail to reach agreement on a plan to reduce the deficit, or if Congress fails to enact the committee's recommendations, sequestration is automatically triggered. Spending cuts to the tune of 50 percent would be applied to all defense, non-defense discretionary, and mandatory spending. Exemptions exist for certain programs, including Social Security, Medicare, military retirement, unemployment insurance, and low-income programs. An across-the-board 2 percent cut to Medicare would go into effect. And as doubt grows regarding the committee's ability to reach a bipartisan consensus, the 2 percent cap is increasingly looking like a bright spot for the patients and physicians affected by the Medicare program.

For programs other than Medicare, failure to achieve a plan that Congress can agree upon would potentially be devastating. The good news is that several members of the super committee, including Rep. Max Baucus (D-MT) and Rep. Chris Van Hollen (D-MD)—whose district includes the NIH in Bethesda, MD—have voiced their continued support for the NIH. "It would be very short-sighted to make cuts to NIH because the history has [sic] that the discoveries that they've come up with have helped to reduce costs because they've developed treatments to various diseases, so I'm very hopeful that we'll be able to protect that very important national investment," said Rep. Van Hollen in a recent interview.

Finally, it is significant that if the super committee is unable to develop a plan that Congress supports, the actual automatic cuts would not be implemented until January 2013. Conceivably, Congress would still have another year to devise a different plan or otherwise prevent the automatic cuts—something it has proven adept at pulling off before. For the time being, ASN will continue to urge the committee to reach agreement while protecting certain key health training, research, and patient care programs. Join ASN in advocating for sensible protections for these programs by visiting ASN's Legislative Action Center at http://capwiz.com/asn/home.

ASN Launches Quality and Patient Safety Task Force

Advancing the quality of care and improving patient safety are two of the most important issues for healthcare professionals and policymakers alike. Reducing preventable injuries and illnesses in hospitals is now recognized not only to be an important goal from a patient perspective but also key to slowing the rising cost of care. Meanwhile, quality improvement initiatives—both voluntary and as a component of Medicare payment programs—are proliferating.

In concert with the growing attention to these issues, ASN recently established the ASN Quality and Patient Safety Task Force. The task force, chaired by Amy Williams, MD, is tasked with the following charge:

1. Draft ASN's response to the American Board of Internal Medicine (ABIM) "Choosing Wisely" Campaign.
2. Identify current trends in quality improvement and patient safety initiatives.
3. Develop online tools to help nephrologists conduct quality improvement studies and improve patient safety.
4. Raise ASN member awareness of quality and patient safety issues and the resources available to help address them, including the development of a "quality" abstract category at ASN Kidney Week.
5. Consider opportunities for alignment with the Department of Health and Human Services "Partnership for Patients" initiative.

The task force's first major initiative is to participate in the ABIM's "Choosing Wisely" campaign, which is focused on the concept that more care is not necessarily high-quality care, and in some cases excess tests, procedures, or prescriptions can lead to patient harm.

"As medical professionals, we are entrusted by our patients and society to provide quality care that is evidence based, safe, and achieves the best outcomes," said task force chair Amy Williams, MD. "Managing the explosion of medical knowledge, increasing complexity of clinical care, and new external pressures demanding innovative, effective, and efficient care models to achieve benchmarks and quality standards can be confusing and overwhelming. The goal of this task force is to provide tools and guidance to meet the expectations of delivering safe, effective, patient-centered, timely, efficient and equitable care to all patients with kidney disease in an environment of constant change as well as to develop partnerships with CMS, ABIM and other governing bodies to appropriately influence change to improve the value of care delivered."

Besides Dr. Williams and Council Liaison Ron Falk, MD, FASN, the task force is comprised of 10 members, each representing one of ASN's 10 advisory groups (Table 1).

Table 1

ASN Patient Quality & Safety Work Group Roster

- Amy Williams, Chair
- Amy Dwyer - Interventional Nephrology Advisory Group
- Allison Eddy - Physiology and Cell Biology Advisory Group
- Ronald Falk - ASN Council Liaison
- Jeffrey Fink - CKD Advisory Group
- Bertrand Jaber - AKI Advisory Group
- Stuart Linas - Hypertension Advisory Group
- Beckie Michael - Practicing Nephrologists Advisory Group
- Ann O'Hare - Geriatric Nephrology Advisory Group
- Rachel Shaffer - ASN Staff Liaison
- Heidi Schaefer - Transplant Advisory Group
- Howard Trachtman - Glomerular Diseases Advisory Group
- Dan Weiner - Dialysis Advisory Group

Immunosuppressive Drug Coverage Bill Gains Support

Extending lifetime immunosuppressive drug coverage for kidney transplant recipients is a top ASN legislative advocacy priority. On Capitol Hill, the efforts of ASN and other advocates have paved the way for Congress to again consider providing the much-needed lifetime coverage.

All patients with end stage renal disease are entitled to Medicare coverage for dialysis or kidney transplants. While Medicare pays for most kidney transplants, it only provides 36 months of immunosuppressive drug coverage for patients who do not qualify for Medicare due to age or disability. Patients who cannot afford immunosuppressive drugs lose the transplanted kidney and then require dialysis to stay alive. Immunosuppressive drugs cost Medicare $19,000 per year per patient; dialysis costs Medicare more than $77,000 per year per patient. This bill would provide Medicare coverage for immunosuppressive drugs only—protecting Medicare's investment in the transplant—and all other Medicare coverage would cease after 36 months, as under current law.

On July 29, Sen. Richard Durbin (D-IL) introduced the Comprehensive Immunosuppressive Drug Coverage for Kidney Transplant Patients Act of 2011 (S. 1454). ASN worked behind the scenes with Rep. Michael Burgess, MD, (R-TX) and other members of the kidney advocacy community to recruit a bipartisan group of congressmen in the House to co-sponsor a companion bill to be introduced by Rep. Burgess. Supported by 18 cosponsors from both sides of the aisle, Rep. Burgess introduced the House companion bill (H.R. 2969) on September 21.

With both House and Senate bills now available for legislative consideration, ASN has redoubled its advocacy efforts in support of the Act. Public Policy Board Chair Thomas Hostetter, MD, Public Policy Board member Wolfgang Winkelmayer, MD, ScD, FASN, ASN President Joseph V. Bonventre, MD, PhD, FASN, and ASN Manager of Policy and Government Affairs Rachel Shaffer participated in a series of meetings with key Republican and Democratic leaders in the House and Senate to discuss the legislation this October. These meetings included discussions with Rep. Tom Marino (R-PA) and Rep. John Fleming, MD (R-LA), the Republican co-chair and vice-chair of the Congressional Kidney Caucus, a House caucus dedicated to educating Congress and the public about the problem kidney disease poses for our society. As a direct result of these discussions with ASN, Rep. Marino and Rep. Jim McDermott—the Democratic co-chair of the Congressional Kidney Caucus—stated that they would sign on as co-sponsors of the bill.

For the first time, ASN also incorporated social media into its advocacy efforts, posting updates about the bill's introduction on Facebook and Twitter pages, and encouraging followers to send a message in support of the bill to their congressional representatives through ASN's Legislative Advocacy Center (http://capwiz.com/asn/issues/alert/?alertid=53775511). At press time, ASN members had sent more than 500 messages to Congress—an ASN record for member advocacy communications. If you haven't sent in a message yet, please take a minute to do so today.

Broad support exists on both sides of the aisle for the bill, and ASN anticipates that many more members will support the bill in the coming weeks and months. So, a bill that would protect transplants and help more patients receive the gift of life—with broad bipartisan support—sounds like a slam dunk, right? Not so fast. As seen this summer with the debt ceiling debacle, nothing is certain on Capitol Hill at this time. Several potential impediments lurk, most importantly, the debt "super committee," which is tasked with trimming the deficit by up to $1.5 trillion. There is a distinct possibility that the debt-reduction process could effectively paralyze Congress, preventing consideration and passage of smaller (though worthwhile) bills. Moreover, the Congressional Budget Office (CBO) most recently estimated the bill to cost $600 million over 10 years—although the actual cost is actually likely much lower, especially since the two most commonly used drugs have gone generic since CBO made that estimate. Getting new spending legislation passed is an uphill battle given the increased controversy around the nation's debt issues.

Nonetheless, ASN is hopeful that its advocacy efforts, together with those of other members of the kidney and transplant communities, will come to fruition this year. The bill is generally recognized by both parties as a common-sense piece of legislation that would provide considerable benefit to society. Building upon this accord, lawmakers stand a legitimate chance of overcoming the current political climate to provide the lifetime drug coverage that patients need. You may view the joint ASN, ASPN, and RPA letter to the debt super committee at www.asn-online.org. To send a letter to your congressional representatives in support of the bill, please visit http://capwiz.com/asn/home/.

Online ASN Resource Center for Investigators Aims to Simplify Research Approval Process

Recognizing the challenges of navigating the complex maze of steps necessary to obtain approval to conduct patient-oriented research in dialysis units, the ASN Dialysis Advisory Group (DAG) created a new online resource for researchers. The "ASN Investigator Resource Center" is a clearinghouse for forms and policies regarding the research application process in national dialysis chains. Intended to be a "one-stop shopping" resource, the webpage contains all the information a researcher would need to initiate and complete the approval process. The Investigator Resource Center also provides the names and contact information of staff at each provider whom investigators with questions may contact. Although currently limited to DaVita and Fresenius Medical Care (FMC), the DAG anticipates expanding the site to include comprehensive resources for other dialysis providers—including DCI, Satellite, US Renal Care and others—in the coming months.

Besides housing forms, policies, and contact information, the website also contains an open letter from each dialysis provider to ASN members as well as provider-specific answers to a list of "Frequently Asked Questions" developed by members of the ASN DAG. "Part of what we wanted to do was demystify the approval process for ASN members, especially junior investigators," said DAG chair Raj Mehrotra, MD, FASN. "The DAG put their heads together and came up with all the questions they've found themselves asking about the research application process over the years, or questions they are still asking. DaVita and FMC were quite forthcoming in their responses to our questions, and I think even seasoned investigators could learn something new by taking a look."

"Clarifying the process for research applications is just one more thing ASN is doing to facilitate cutting-edge medical research and support the next generation of investigators," commented DAG Council Liaison Sharon Moe, MD, FASN.

The ASN Investigator Resource Center can be accessed at http://www.asn-online.org/irc/.

Kidney Week 2011
Public Policy Sessions

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Pragmatic Clinical Trials: Improving Design and Conduct of Clinical Studies Including Pragmatic Trials in Nephrology

Early Program: November 8 and 9

Bringing Policy to Practice: The Case for Comparative Effectiveness Research

Thursday, November 10, 2:00 – 4:00 PM, 115 A/B

Accountable Care Organizations: A New Model of Care for Patients with Chronic Kidney Disease

Friday, November 11, 2:00 – 4:00 PM, 115 A/B

ASN Educational Symposium:
Accountable Care Organizations: Can They Fulfill Their Promise?

Saturday, November 12, 6:45 – 7:45 AM, Philadelphia Marriott Downtown, Grand Ballroom, Salon E

Breakfast will be served.

Support for this session is provided by educational grants from

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ASN Educational Symposium:
Entering the Era of Pay-for-Performance: Observational versus Randomized Clinical Trial Data and the ESRD Quality Incentive Program

Saturday, November 12, 12:45 – 1:45 PM, Philadelphia Marriott Downtown, Grand Ballroom, Salon A

Lunch will be served.

Support for this session is provided by an educational grant from

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Quality Improvement Program for ESRD:
An Experiment in Payment for Quality

Saturday, November 12, 2:00-4:00PM, 115 A/B

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