ASN LEADING THE FIGHT AGAINST KIDNEY DISEASE

KidneyNews

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Research Provides Insights into Connections Between Sleep and Diabetes

Diabetes and sleep problems often go hand in hand. It has been known for some time that diabetes-associated factors such as neuropathy and nighttime hypoglycemia can contribute to sleep problems in patients. Research is now providing growing evidence that insufficient sleep can also contribute to diabetes risk. The most recent studies reveal some of the potential mechanisms behind this link.

"Sleep can affect diabetes, and diabetes can affect sleep," said Elizabeth Bashoff, MD, of the Joslin Diabetes Center in Boston. "For everyone, but especially for patients with chronic conditions such as diabetes, it's important to take care of your health overall to improve sleep, and to take steps to get a good night's sleep to restore the body."

How diabetes affects sleep

Fluctuations in blood glucose can be particularly disruptive to sleep for many individuals with diabetes. "It's not uncommon for people to experience hypoglycemia in the middle of the night, which can cause headaches, sweating, and nightmares," Bashoff said. "Blood glucose that is too high can also be a problem because it may cause people to wake up repeatedly to use the bathroom."

Sleep apnea is also a major cause of sleep problems, and it is more common in individuals with diabetes than in the general population. Sleep apnea is linked to obesity, and weight loss is by far the most effective treatment for individuals with sleep apnea who have high BMIs.

Leg pain due to neuropathy can also keep diabetics up at night. Controlling blood sugar levels can help. Also, there are many medications to treat the condition, some of which also have a beneficial sedative effect at bedtime.

How sleep affects diabetes

While diabetes and its associated com-

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Study Questions Phosphate Binders' Cardiovascular Benefits for Patients with Mild Kidney Disease

Elevated phosphate levels in the blood—even when levels are in the high normal range—carry increased heart-related risks, but taking a phosphate binder did not improve cardiovascular measures in patients with mild kidney disease in a recent study published in the *Journal of the American Society of Nephrology*.

"It would appear that for now it would be better to lower the amount of phosphate in the diet rather than rely on pharmacological interventions," said senior author Charles Ferro, MBChB, MD, of the University Hospitals Birmingham NHS Foundation Trust and the University of Birmingham, in England.

Because adherence to the study medication was low, though, additional studies are warranted to test the true potential of phosphate binders for protecting the heart health of patients with mild kidney disease.

Chronic kidney disease (CKD) is the most common condition associated with deranged phosphate homeostasis. Ferro and his colleague Colin Chue, MBChB, led a research team that conducted a double-blind, randomized, placebo-controlled trial of 120 patients with stage 3 CKD to test the effects of the phosphate binder sevelamer carbonate, which is approved only for patients with kidney failure. Sevelamer carbonate holds promise for improving cardiovascular health because high blood levels of phosphate promote calcification and stiffening of blood vessels and can cause structural changes in the heart, such as increased wall thickness.

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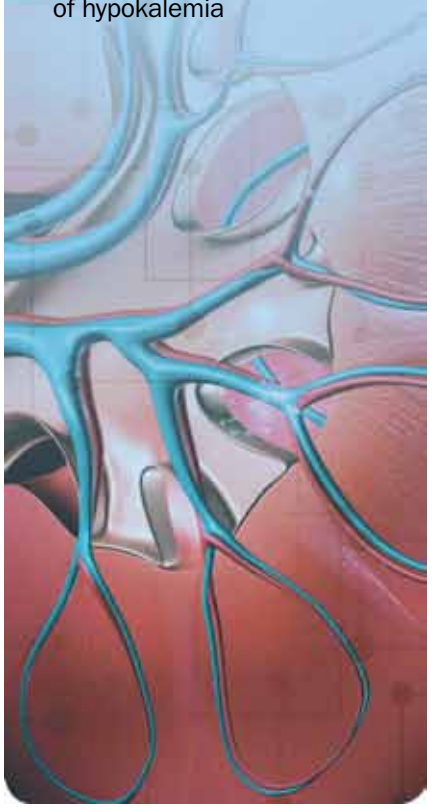

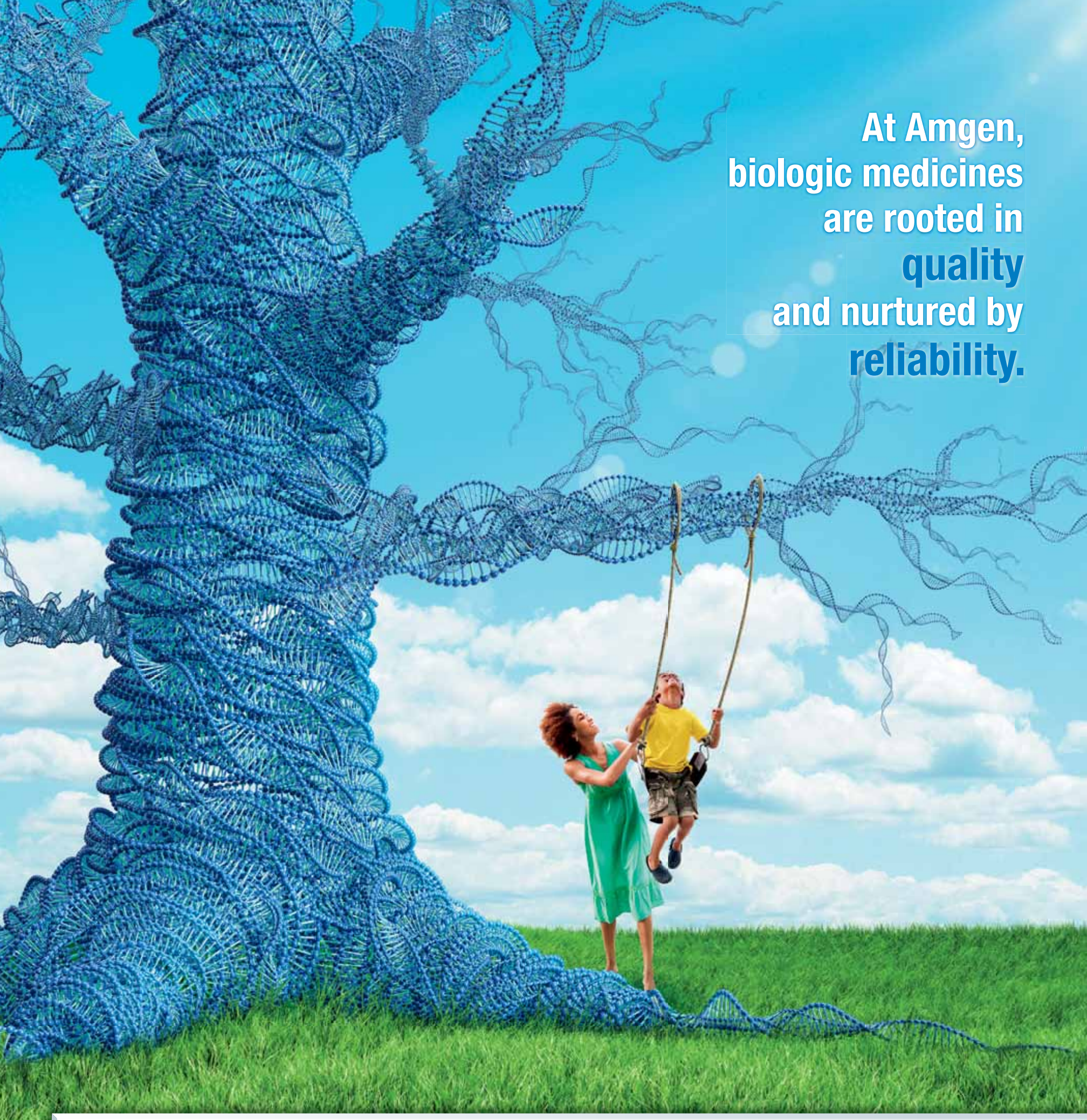

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Sleep and Diabetes

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plications can have clear impacts on sleep quality, sleep quality may also impact diabetes and diabetes risk.

The first clue to this connection came from a 1999 study published in *The Lancet*. The study found that restricting healthy young people's sleep to just four hours for six nights in a row produced striking changes in glucose tolerance and endocrine function (Spiegel K et al. *Lancet* 1999; 354:1435–1439).

Since then, studies have generated additional evidence that disrupted sleep affects insulin resistance, and that individuals with diabetes who keep regular sleep schedules seem to maintain better blood sugar control, perhaps in part due to circadian rhythms connected to glucose metabolism. Also, research suggests that people who get less sleep tend to be heavier than those who sleep well, which puts them at increased risk for developing type 2 diabetes.

Research is starting to tease out the mechanisms by which sleep affects diabetes risk. A new *Journal of the American Medical Association* study found that individuals who secrete low levels of melatonin at night have about twice the risk of developing type 2 diabetes as individuals who secrete high levels of the hormone (McMullan CJ et al. *JAMA* 2013; 309:1388–1389). The study included 370 women who developed diabetes and 370 controls. Melatonin secretion was measured at the start of the study, when none of the participants had diabetes. Women in the highest category of melatonin secretion had an estimated diabetes incidence rate of 4.27 cases/1000 person-years compared with 9.27 cases/1000 person-years in the lowest category.

"This is the first time that an independent association has been established between nocturnal melatonin secretion and type 2 diabetes risk," said first author Ciaran McMullan, MD, a nephrologist at Brigham and Women's Hospital in Boston. "Hopefully this study will prompt future research to examine what influences a person's melatonin secretion and what is melatonin's role in altering a person's glucose metabolism and risk of diabetes."

New evidence presented at SLEEP 2012, the 26th annual meeting of the Associated Professional Sleep Societies, links sleep apnea with carbohydrate craving. Researchers screened 55 individuals (more than half of whom had diabetes) for sleep apnea and carbohydrate cravings. They found that among the diabetic patients, the prevalence of sleep apnea was 82 percent, and they had almost twice the risk of carbohydrate craving than nondiabetics. In addition, patients with sleep apnea were almost twice as likely to have high carbohydrate craving than were patients without sleep apnea.

"Previous studies have shown that sleep deprivation may lead to changes in hormones that regulate appetite and hunger. These hormonal changes can lead to significant craving for high-calorie carbohydrates," said study co-investigator Mahmood Siddique, DO, of the department of medicine at the Robert Wood Johnson Medical School in New Brunswick, NJ. "This study supports previous findings by validating this in a community sample of diabetics."

Getting a good night's sleep

While some aspects of sleep may be out of one's control, experts agree that certain measures can help improve sleep for most people, leading to considerably better health.

"Maintaining a regular schedule, getting exercise, avoiding alcohol at night—and for people with diabetes, testing blood sugar at bedtime—can lead to a better night's sleep," said Bashoff. "I often see patients who are so busy that they don't think of these simple steps."

Individuals who sleep poorly are susceptible to depression and other mood disorders, changes in eating, decreases in physical activity—and as indicated by the latest evidence, perhaps an increased risk of developing diabetes.

Cardiovascular Benefits

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After a 4-week open label run-in period, during which all patients received sevelamer carbonate, 109 patients were randomly assigned to sevelamer or placebo for an additional 36 weeks. The investigators assessed left ventricular mass and systolic and diastolic function with cardiovascular magnetic resonance imaging and echocardiography, and they assessed arterial stiffness by carotid–femoral pulse wave velocity.

"We hoped that by asking a very motivated group of patients with early stage chronic kidney disease to take phosphate binders with every meal, we would be able to reduce the amount of phosphate absorbed from the diet," Ferro said. However, at the end of the study, the investigators found no differences in any of the measures of cardiovascular structure and function between the groups.

Yet despite repeated reminders and suggested methods to maximize compliance, adherence to treatment was low, with only 56 percent of patients taking more than 80 percent of the study medication. Also, several patients withdrew from the study because of difficulty with the frequency (two tablets taken three times daily) and tolerability of the study agents. When the subgroup of patients with more than 80 percent compliance was analyzed separately, the group taking sevelamer excreted significantly smaller amounts of phosphate in their urine compared with those taking placebo. The sevelamer group also had reduced levels of the hormone fibroblast growth factor 23, which is critical for maintaining phosphate balance but is also toxic to the cardiovascular system. No changes were noted in any of the measures of cardiovascular structure nor in serum levels of phosphate, klotho, and vitamin D, though.

"Although only 56 percent of patients took 80 percent or more of the prescribed medications in this controlled study, which is a legitimate limitation to the results, this level of adherence is very commonly seen in clinical practice, which makes the findings of this study translatable to the real clinical setting," said Jeannie Kim Lee, PharmD, BCPS, CGP, of the University of Arizona College of Pharmacy. Lee, who was not involved with the study, has conducted extensive research addressing patients' medication adherence.

More research needed

In an accompanying editorial, Rajiv Agarwal, MD, of the Indiana University School of Medicine, noted that the study "should not serve as a death knell to investigations on phosphorus in progressive CKD, but should instead serve as a crèche for future investigations on the value of phosphorus reduction in preventing cardiovascular disease and CKD progression."

He noted that it is unlikely that sevelamer is ineffective because the drug is approved with adequate trial data to support its use in people with hyperphosphatemia.

He added that while the drug in the doses used in this trial was not effective in reducing an already normal level of phosphorus concentration, perhaps the participants increased their dietary phosphorus intake, which would prevent an overall decline in serum phosphorus.

Until more information is available about the potential heart-related benefits of phosphate binders for individuals with mild CKD, these patients should focus on dietary changes to reduce their phosphate levels. Foods with large amounts of added phosphate are processed meat, ham, sausages, canned fish, baked goods, cola drinks, and other soft drinks.

"Fast food and ready-to-eat processed foods are the main contributors to today's rising dietary consumption of phosphate," Ferro noted. He suggested that a comprehensive public education effort that explains the harmful effects of high phosphate intake and provides clear labeling of the phosphate content of food could help limit the damage done by this cardiovascular risk factor.

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Policy Update

Fewer Patients Now Required for Groups to Apply for ESRD Seamless Care Organizations

By Rachel Shaffer

CMS recently relented on its requirement that ESRD programs applying to form ESRD Seamless Care Organizations (ESCOs) must have at least 500 matched beneficiaries. Applicants must now have 350 matched beneficiaries, and the deadline to submit a formal application has been pushed back to July 1, 2013.

The change came after requests for greater flexibility on the threshold from many in the kidney care community—including ASN. CMS stated that the reduction was in response to stakeholder feedback and suggestions from organizations interested in new models of ESRD care.

"The lower threshold is welcome news," said Doug Johnson, MD, vice chair of the board at Dialysis Clinic, Inc. "It will permit more providers to participate, leading to greater innovation and ultimately better care for patients with kidney disease.

CMS had originally emphasized in written communications and in conference calls with the kidney community that the 500-patient threshold was selected to ensure a statistically accurate shared savings calculation, and therefore could not be reduced.

However, some potential applicants noted that it would not be possible to achieve that minimum in a given "market"—which CMS defined as limited to just two Medicare Core-Based Statistical Areas—especially given that patients who had already been matched to a Medicare ACO or another Medicare program involving shared savings would be excluded from attribution to an ESCO.

"ASN applauds CMS and the Innovation Center for making this important change," said ASN Public Policy Board chair Thomas H. Hostetter, MD. "The society will continue to work with other kidney community stakeholders to encourage the agency to consider what we believe are further modifications that would strengthen the program's ability to deliver innovative, higher-quality care, support further research, and allow more nephrologists and providers to participate in the ESCO program. For instance, ASN believes it is important for CMS to describe a plan to develop dialysis-specific quality metrics in a transparent manner that allows for community input, as well as to prospectively describe the criteria it will use to determine whether an ESCO is a success or a failure."

Also welcoming the news were stakeholders who are not eligible to apply as participants, but who are invested in the success of the program given its potential to improve care for patients on dialysis.

"The American Nephrology Nurses Association (ANNA) was delighted that CMS reconsidered the minimum number of ESRD participants in an ESRD Seamless Care Organization (ESCO) to allow smaller providers to participate in these innovative programs," said ANNA immediate past president Glenda Payne. "Having broader representation in this project increases the potential for innovation. ANNA believes that registered nurses and Advanced Practice Registered Nurses (APRN) will play critical roles in every ESCO, as nurses are traditionally the primary coordinators of care, and APRNs will provide close oversight of patients, working with nephrologists to improve the care patients receive and taking action to prevent complications and reduce the need for hospitalizations."

"The National Kidney Foundation is hopeful that reducing the minimum beneficiary requirement will encourage a greater range of providers to develop innovative care coordination models that target the specific health care needs of the patients in their community," said NKF President Beth Piraino, MD. "Having a diversity of models will help inform future strategies for broadly delivering higher quality care that serves patients' health, lifestyle, and community support needs."

CMS said in its announcement of the lower threshold that participants' savings rates will have to change to maintain the same level of statistical accuracy in calculating shared savings or losses. Owing to the lower threshold, the minimum savings rate in the payment track for non-Large Dialysis Organizations (LDO) will increase from 4 percent to 4.75 percent for those non-LDO participants that have between 350 to 499 matched beneficiaries in performance years 1 and 2.

Kidney Disease Research at VA Advances Care

By Grant Olan

The Department of Veterans Affairs (VA) kicked off National VA Research Week—May 13–17, 2013—with a briefing at the Washington, DC, VA Medical Center. VA Research Week celebrates the contributions of VA researchers to high quality care for veterans and medical progress. This year's theme was "VA Research Inspires".

The VA maintains a comprehensive research portfolio aimed at advancing the treatment of kidney failure, as well as preventing and slowing the progression of kidney disease. VA leadership, including VA Chief Research and Development Officer Joel Kupersmith, MD, spoke at the briefing.

Kupersmith provided an overview of research at the Washington VA Medical Center and highlighted the Million Veterans Program, which is the largest longitudinal study ever undertaken. The program will study how genes affect diseases and has already collected blood samples and health information from more than 150,000 veterans.

The VA sponsored 59 events showcasing other VA discoveries nationwide, emphasizing that sustained funding is needed for the VA research, including kidney disease, that will lead to discoveries that advance health care not just for veterans, but for all Americans.

Posttransplant diabetes; predialysis dietician care

For example, Boston VA researchers recently found that men—but not women—with certain forms of two genes were more than twice as likely to develop diabetes after transplant compared with men with other gene forms. Scientists can use this information to help predict risk for diabetes and to better understand its root causes.

Minneapolis VA researchers also recently found that patients with kidney disease who see a dietitian before starting dialysis have a better chance at survival. Patients who saw a dietician for at least a year before starting dialysis had a nearly 10 percent lower mortality rate compared with those who had no care by a dietician.

"ASN strongly supports the VA research mission and wants to highlight its critical role in advancing medical science and quality care for America's veterans," said John R. Sedor, MD, ASN Research Advocacy Committee Chair. "There are also significant economic benefits to the nation. Medical research generates jobs, supports local businesses, and stimulates the economy."

ASN is on the Executive Committee of the Friends of VA Medical Care and Health Research (FOVA), which collaborates with The Independent Budget to recommend funding levels for VA research. This year FOVA and The Independent Budget are requesting $611 million for VA research and $225 million for critical infrastructure needs at VA research facilities in 2014. That $611 million is necessary to keep pace with the rising cost of research and to support new investigation into conditions that can affect veterans returning from Iraq and Afghanistan, including polytrauma, or multiple traumatic injuries such as a serious head injury in addition to limb and vision loss or serious burns.

Many VA research facilities are also in dire need of maintenance and repairs. A $225 million investment in construction and infrastructure projects in 2014 would help address the most serious deficiencies. For instance, some labs lack crucial safety features such as emergency showers. A congressionally mandated VA report details the condition of all VA research facilities at www.aamc.org/varpt.

ASN participated in FOVA congressional meetings and launched a grassroots email campaign during VA Research Week in support of these budget requests. The society is also co-sponsoring a FOVA congressional briefing in June highlighting the benefits and importance of VA research.

Correction

The May *Kidney News* article on the Congressional Kidney Caucus Reception failed to note that the American Nephrology Nurses Association was a cosponsor of the March 20 event. ASN is proud to partner with ANNA to advance the care of patients with kidney disease and regrets the oversight.

ANNA members, left, were a strong presence at the reception.

ANNA Washington Representative Jim Twaddell speaks with Kidney Caucus co-chair Rep. Tom Marino.

Journal View

Tubulointerstitial Nephropathies in Patients with HIV

Tubulointerstitial nephropathies are found in more than one-fourth of kidney biopsy specimens obtained from HIV-infected patients, reports a study in the *Clinical Journal of the American Society of Nephrology*.

The retrospective study included 59 consecutive renal biopsy specimens showing predominantly tubular lesions, interstitial lesions, or both in patients with HIV infection. The patients were referred to the nephrology department of a French hospital between 1995 and 2011; the analysis excluded patients with HIV-associated nephropathy and vascular diseases. Patterns of tubulointerstitial nephropathies in HIV-infected patients were analyzed, along with their therapeutic implications.

The cases of tubulointerstitial nephropathy represented 26.6 percent of 222 native renal biopsies performed in HIV-infected patients. Approximately equal numbers of tubulopathy cases and interstitial nephritis cases were included.

At referral, about three-fourths of patients had acute kidney injury, and close to 60 percent had high-grade proteinuria. A little more than half had drug-related nephrotoxicity. Other identified causes included infections, dysimmune disorders, and malignancies. Acute and chronic tubulointerstitial nephropathies of unknown origin accounted for 10 percent of cases each.

Toxic effects of antiretroviral drugs accounted for three-fourths of tubulopathies. Tenofovir toxicity was involved in more than half of these cases, causing proximal tubular dysfunction in nearly 90 percent of cases. Other manifestations included overt Fanconi's syndrome and nephrogenic diabetes inspidus. The causes and pathologic findings were more variable in cases of interstitial nephritis.

With advances in HIV treatment and improved patient outcomes, patterns of HIV-related renal complications have changed. This study finds a high rate of tubulointerstitial nephropathies among HIV-infected patients referred for nephrology evaluation. Drug toxicity is the most common diagnosis, but other causes are possible. The findings highlight the need for monitoring of renal function in patients with HIV infection and the importance of renal biopsy for accurate diagnosis [Zaidan M, et al. Tubulointerstitial nephropathies in HIV-infected patients over the past 15 years: a clinico-pathological study. *Clin J Am Soc Nephrol* 2013, in press].

Evidence Supports Health Benefits of Lower Sodium and Higher Potassium

Two updated meta-analyses show cardiovascular and other health benefits of decreased sodium and increased potassium intake, reports the *British Medical Journal*.

The researchers performed systematic reviews to identify randomized trials and cohort studies of lower sodium intake and higher potassium intake. In adults, lower sodium intake was associated with decreased systolic and diastolic blood pressure. Reducing sodium intake to less than 2 g/d was associated with a decrease of 3.47/1.81 mm Hg in blood pressure, with no evidence of adverse effects on blood lipid or catecholamine levels or kidney function.

The data were insufficient to show reduced mortality or cardiovascular morbidity associated with lower so-

dium intake. However, higher sodium intake was associated with increased risks of stroke, risk ratio (RR) 1.24; fatal stroke, RR 1.63; and fatal coronary heart disease, RR 1.32.

Higher potassium intake was linked to a significant reduction in blood pressure, but only in people with hypertension. A potassium intake between 90 and 120 mmol/d was associated with a reduction of 7.16 mm Hg in systolic blood pressure, with no dose–response effect. Individuals with higher potassium intake had a decreased incidence of stroke, RR 0.76, but not cardiovascular disease or coronary heart disease.

"[M]ost people will likely benefit from reducing sodium intake," the researchers write. In patients free of kidney problems that would impair potassium handling, increasing potassium may help to prevent and control hypertension and stroke risk. The evidence shows reduced blood pressure in children with lower sodium intake but not higher potassium intake [Aburto NJ, et al. Effect of lower sodium intake on health: systematic review and meta-analyses. *BMJ* 2013; 346:f1326; Aburto NJ, et al. Effect of increased potassium intake on cardiovascular risk factors and disease: systematic review and meta-analyses. *BMJ* 2013; 346:f1378].

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Journal View *continued*

Younger Age at Weight Gain Increases Later CKD Risk

People who are overweight by their mid-30s are more than twice as likely to experience chronic kidney disease (CKD) by their mid-60s, reports a study in the *Journal of the American Society of Nephrology*.

The study included data on 5362 singleton children born during a single week in March 1946, drawn from a national health survey in the United Kingdom. A sample of 1794 participants with complete data was expanded to 4584 by multiple imputation analysis. Body mass index at age 20 to 26 (self-reported) and in subsequent decades of life (measured) was analyzed for association with CKD at age 60 to 64. The presence of CKD was based on estimated GFR (eGFR) of less than 60 mL/min/1.73 m^2, urine albumin-to-creatinine ratio of 3.5 mg/mmol or greater, or both.

With adjustment for social class in childhood and adulthood, being overweight at younger ages was associated with a higher risk of CKD at age 60 to 64. Cohort members who were overweight at age 26 or 36 had a twofold increase in risk of CKD before age 65, compared with those who never became overweight or who became overweight in their 60s.

The association between overweight in young adulthood and later CKD was only partly explained by adjustment for diabetes and hypertension. An increased waist-to-

hip ratio at age 43 or 53 was also a risk factor for CKD at age 60 to 64. The associations were similar across different definitions of CKD.

The study is one of the first to assess the relationship between body weight at different ages and the risk of CKD later in life. On the basis of their data, the researchers estimate that in the United States, more than 36 percent of cases of CKD in the population aged 60 to 64 could be avoided if weight gain were prevented or delayed [Silverwood RJ, et al. Association between younger age when first overweight and increased risk for CKD. *J Am Soc Nephrol* 2013; 24:813–821].

Nephrologist Care Improves Outcomes after AKI

For patients with an episode of acute kidney injury (AKI), early nephrology follow-up is associated with improved survival 2 years later, according to a report in *Kidney International*.

Ontario health data were used to identify hospitalized adults receiving temporary inpatient dialysis after an episode of AKI between 1996 and 2008. The analysis included 3877 patients who survived for 90 days after discharge free of dialysis, with follow-up information through 2 years after discharge. Of these, 1583 patients received early follow-up with a nephrologist and could be matched to a patient without a nephrologist. The risk of all-cause mortality was compared on propensity-matched analysis.

All-cause mortality was 8.4 per 100 patient-years for patients with early nephrologist follow-up versus 10.6 per 100 patient-years for those without nephrologist follow-up: hazard ratio 0.76. Within 2 years, 15.5 and 18.9 percent of patients had died, respectively. In subgroup analyses, the survival benefit was significant for men, patients younger than 65 years, those with a history of diabetes, and those with no previous nephrology consultation.

Even if kidney function recovers, patients with AKI remain at increased risk of death. Care after discharge may affect the prognosis; yet, only 8 percent of patients see a nephrologist within 1 year.

The new study suggests improved survival with early nephrologist follow-up of hospitalized patients who survive an episode of AKI. The authors call for further studies to clarify optimal care for AKI survivors, including the role of nephrology care [Harel Z, et al. Nephrologist follow-up improves all-cause mortality of severe acute kidney injury. *Kidney Int* 2013; 83:901–908].

New Data on Perioperative β-Blockade for Noncardiac Surgery

For patients with multiple risk factors undergoing noncardiac, nonvascular surgery, perioperative β-blockers reduce mortality and cardiac morbidity, according to a study in the *Journal of the American Medical Association*. The protective effect is larger for patients with more risk factors, the authors found.

Using Veterans Health Administration (VA) databases, the researchers identified 37,805 propensity score–matched pairs of patients undergoing major noncardiac surgery who did and did not receive perioperative β-blockade, defined as an active outpatient prescription or receipt of β-blockers on the day of or the day after surgery. The 30-day mortality and cardiac morbidity (cardiac arrest or Q-wave myocardial infarction) were compared between groups.

In this VA population, the rates of perioperative β-blocker exposure were 40.3 percent overall, 66.7 percent for patients undergoing vascular surgery, and 37.4 percent for those undergoing nonvascular surgery. The likelihood of perio-

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Perioperative β-Blockade

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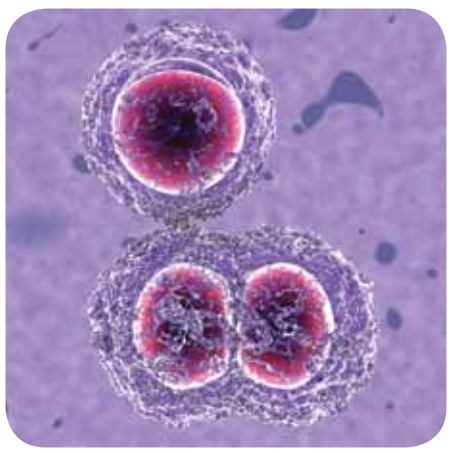
perative β-blockade increased from 25.3 percent for patients with no revised cardiac risk index factors to 71.3 percent for those with four or more risk factors. The overall 30-day mortality was 1.1 percent, and cardiac morbidity was 0.9 percent.

On propensity-matched analysis, perioperative β-blockers were associated with lower mortality among higher-risk patients. The relative risk (RR) was 0.63 for patients with two revised cardiac risk index factors, with a number needed to treat (NNT) of 105. For patients with the risk factors, the RR was 0.54 and the NNT 41; for those with four or more risk factors, RR was 0.40 and the NNT 18.

Perioperative β-blockade reduced mortality risk only for patients undergoing nonvascular surgery. The nonvascular surgery group also had a significant reduction in cardiac morbidity: RR 0.67, NNT 339.

There is continued controversy over the use of perioperative β-blockers for patients undergoing major noncardiac surgery. Current class I recommendations call only for continuation of pre-existing β-blocker therapy [London MJ, et al. Association of perioperative β-blockade with mortality and cardiovascular morbidity following major noncardiac surgery. *JAMA* 2013; 309:1704–1713].

Nasal MRSA Carriage Predicts Worse Outcomes in Hemodialysis Patients



Even without clinical signs of infection, hemodialysis patients who are methicillin-resistant *Staphylococcus aureus* (MRSA) carriers are at increased risk of death, reports a study in *BMC Nephrology*.

The prospective cohort study included 289 hemodialysis outpatients at an urban dialysis unit. All underwent nasal swabs for MRSA culture at admission to the unit, after transfer from another unit, or on readmission after a hospital stay. Patients found to be nasal MRSA carriers were kept in a separate ward and treated with nasal muciprocin; appropriate treatments for extranasal (throat and skin) MRSA colonization were used as well. Clinical characteristics and outcomes were compared for MRSA carriers versus noncarriers.

Nasal MRSA carriage was identified in 11.7 percent of patients. About one-third of nasal MRSA carriers also had extranasal colonization. Patients with a history of cancer and those with increased comorbidity were more likely to be nasal MRSA carriers. Traditional MRSA risk factors were not significant, nor were markers of inflammation or malnutrition.

During follow-up, death occurred in 55.9 percent of patients whose test results for MRSA were positive versus 37.4 percent of MRSA-negative patients. The mortality difference was significant on Kaplan-Meier analysis. Muciprocin treatment eradicated nasal MRSA colonization in 73.5 percent of patients. For patients in whom eradication therapy was unsuccessful, all-cause mortality exceeded 85 percent.

Nasal MRSA carriage is a known risk factor for bacteremia and death in various patient groups. There is ongoing controversy regarding its clinical impact on patients receiving long-term hemodialysis.

About one of eight hemodialysis patients may be nasal MRSA carriers, the new study suggests. These patients are at increased risk of death during follow-up, especially if muciprocin is not effective in eradicating MRSA. The authors call for further study of nasal MRSA colonization as an independent outcome predictor in hemodialysis patients [Schmid H, et al. Persistent nasal methicillin-resistant staphylococcus aureus carriage in hemodialysis outpatients: a predictor of worse outcome. *BMC Nephrol* 2013; 14:93].

Simultaneous Pancreas-Kidney Transplantation May Reverse Microvascular Damage in Patients with Type 1 Diabetes

In patients with type 1 diabetes and diabetic nephropathy (DN), microvascular structural abnormalities are reversed within 1 year after simultaneous pancreas-kidney transplantation (SPK), reports a study in the *American Journal of Transplantation*.

The investigators used sidestream dark field (SDF) imaging—an emerging technology for noninvasive visualization of the microcirculation—to study the microvascular morphology of the oral mucosa. Imaging studies were performed in various groups, including 26 patients with DN, 38 patients undergoing SPK, 15 patients with type 1 diabetes, 15 DN patients undergoing kidney transplantation, and 20 healthy control individuals.

The study also included longitudinal SDF imaging in 21 patients with DN undergoing SPK. The microvascular findings were correlated with markers of endothelial dysfunction, including angiopoeitin-1 and angiopoeiten-2 (Ang-1 and Ang-2) and soluble thrombomodulin.

The SDF imaging studies showed increased capillary tortuosity in the DN patients and in the type 1 diabetes group: 1.83 and 1.55, respectively. This value was significantly reduced in patients undergoing SPK, 1.31, compared with no change after kidney transplantation, 1.64. Levels of soluble thrombomodulin and the Ang-2/Ang-1 ratio also normalized after SPK, compared with no change after kidney transplantation. The reversal of capillary tortuosity and decreased markers of endothelial dysfunction were observed within 12 months after SPK.

Simultaneous pancreas-kidney transplantation is an advanced treatment alternative for patients with type 1 diabetes and DN or other forms of microvascular disease. This study, using SDF imaging, suggests that reversal of systematic microvascular abnormalities occurs within 1 year after SPK in patients with DN. No such effect is noted in patients undergoing kidney transplantation only [Khairoun M, et al. Microvascular damage in type 1 diabetic patients is reversed in the first year after simultaneous pancreas-kidney transplantation. Am J Transplant 2013; 13:1272–1281].

MMF for Lupus Nephritis Patients with Poor Kidney Function

For lupus nephritis patients with a very low eGFR, mycophenolate mofetil (MMF) may lead to faster recovery of kidney function compared with cyclophosphamide, reports a study in the *American Journal of Kidney Diseases*.

The study was a post hoc analysis of data from patients enrolled in the Aspreva Lupus Management Study, a large randomized trial of MMF versus cyclophosphamide for lupus nephritis. Of 370 patients enrolled, 32 had severely decreased kidney function: eGFR less than 30 mL/min/1.73 m^2. Of those, 20 received MMF, target dosage 3 g/d; and 12 received cyclophosphamide, given in monthly intravenous pulses of 0.5 to 1.0 g/m^2. Response was defined as decreased proteinuria and stabilization or improvement in serum creatinine levels.

Over 24 weeks, the response rate was similar between groups: 20.0 percent with MMF and 16.7 percent with cyclophosphamide. However, MMF was associated with more rapid improvement in kidney function, with a between-group difference of 1.51 mL/min/1.73 m^2 per week. Serious adverse events occurred in 45.0 percent of patients with MMF versus 63.6 percent with cyclophosphamide.

Randomized trials suggest that oral MMF is an effective alternative to intravenous cyclophosphamide for the treatment of lupus nephritis. It has been unclear whether MMF is adequate therapy for patients with very low kidney function.

The new analysis finds similar response rates—but faster improvement in renal function—with MMF for lupus nephritis patients with low eGFR, compared with cyclophosphamide. The authors hope that their hypothesis-generating study will lead to further studies of the efficacy and safety of MMF for this group of patients [Walsh M, et al. Mycophenolate mofetil or intravenous cyclophosphamide for lupus nephritis with poor kidney function: a subgroup analysis of the Aspreva Lupus Management Study. *Am J Kidney Dis* 2013; 61:710–715].

versus none on placebo), and require treatment with oral or topical antifungal agents and anti-microbial agents than patients on comparators. In the pooled analysis of 8 controlled trials, phimosis was reported in 0.3% of uncircumcised male patients treated with INVOKANA and 0.2% required circumcision to treat the phimosis *[see Warnings and Precautions]*.

Hypoglycemia: In all clinical trials, hypoglycemia was defined as any event regardless of symptoms, where biochemical hypoglycemia was documented (any glucose value below or equal to 70 mg/dL). Severe hypoglycemia was defined as an event consistent with hypoglycemia where the patient required the assistance of another person to recover, lost consciousness, or experienced a seizure (regardless of whether biochemical documentation of a low glucose value was obtained). In individual clinical trials *[see Clinical Studies (14) in full Prescribing Information]*, episodes of hypoglycemia occurred at a higher rate when INVOKANA was co-administered with insulin or sulfonylureas (Table 4) *[see Warnings and Precautions]*.

Table 4: Incidence of Hypoglycemia* in Controlled Clinical Studies

Monotherapy (26 weeks)	**Placebo (N=192)**	**INVOKANA 100 mg (N=195)**	**INVOKANA 300 mg (N=197)**
Overall [N (%)]	5 (2.6)	7 (3.6)	6 (3.0)
In Combination with Metformin (26 weeks)	**Placebo + Metformin (N=183)**	**INVOKANA 100 mg + Metformin (N=368)**	**INVOKANA 300 mg + Metformin (N=367)**
Overall [N (%)]	3 (1.6)	16 (4.3)	17 (4.6)
Severe [N (%)]†	0 (0)	1 (0.3)	1 (0.3)
In Combination with Metformin (52 weeks)	**Glimepiride + Metformin (N=482)**	**INVOKANA 100 mg + Metformin (N=483)**	**INVOKANA 300 mg + Metformin (N=485)**
Overall [N (%)]	165 (34.2)	27 (5.6)	24 (4.9)
Severe [N (%)]†	15 (3.1)	2 (0.4)	3 (0.6)
In Combination with Sulfonylurea (18 weeks)	**Placebo + Sulfonylurea (N=69)**	**INVOKANA 100 mg + Sulfonylurea (N=74)**	**INVOKANA 300 mg + Sulfonylurea (N=72)**
Overall [N (%)]	4 (5.8)	3 (4.1)	9 (12.5)
In Combination with Metformin + Sulfonylurea (26 weeks)	**Placebo + Metformin + Sulfonylurea (N=156)**	**INVOKANA 100 mg + Metformin + Sulfonylurea (N=157)**	**INVOKANA 300 mg + Metformin + Sulfonylurea (N=156)**
Overall [N (%)]	24 (15.4)	43 (27.4)	47 (30.1)
Severe [N (%)]†	1 (0.6)	1 (0.6)	0
In Combination with Metformin + Sulfonylurea (52 weeks)	**Sitagliptin + Metformin + Sulfonylurea (N=378)**		**INVOKANA 300 mg + Metformin + Sulfonylurea (N=377)**
Overall [N (%)]	154 (40.7)		163 (43.2)
Severe [N (%)]†	13 (3.4)		15 (4.0)
In Combination with Metformin + Pioglitazone (26 weeks)	**Placebo + Metformin + Pioglitazone (N=115)**	**INVOKANA 100 mg + Metformin + Pioglitazone (N=113)**	**INVOKANA 300 mg + Metformin + Pioglitazone (N=114)**
Overall [N (%)]	3 (2.6)	3 (2.7)	6 (5.3)
In Combination with Insulin (18 weeks)	**Placebo (N=565)**	**INVOKANA 100 mg (N=566)**	**INVOKANA 300 mg (N=587)**
Overall [N (%)]	208 (36.8)	279 (49.3)	285 (48.6)
Severe [N (%)]†	14 (2.5)	10 (1.8)	16 (2.7)

* Number of patients experiencing at least one event of hypoglycemia based on either biochemically documented episodes or severe hypoglycemic events in the intent-to-treat population

† Severe episodes of hypoglycemia were defined as those where the patient required the assistance of another person to recover, lost consciousness, or experienced a seizure (regardless of whether biochemical documentation of a low glucose value was obtained)

Laboratory Tests: *Increases in Serum Potassium:* Dose-related, transient mean increases in serum potassium were observed early after initiation of INVOKANA (i.e., within 3 weeks) in a trial of patients with moderate renal impairment *[see Clinical Studies (14.3) in full Prescribing Information]*. In this trial, increases in serum potassium of greater than 5.4 mEq/L and 15% above baseline occurred in 16.1%, 12.4%, and 27.0% of patients treated with placebo, INVOKANA 100 mg, and INVOKANA 300 mg, respectively. More severe elevations (i.e., equal or greater than 6.5 mEq/L) occurred in 1.1%, 2.2%, and 2.2% of patients treated with placebo, INVOKANA 100 mg, and INVOKANA 300 mg, respectively. In patients with moderate renal impairment, increases in potassium were more commonly seen in those with elevated potassium at baseline and in those using medications that reduce potassium excretion, such as potassium-sparing diuretics, angiotensin-converting-enzyme inhibitors, and angiotensin-receptor blockers *[see Warnings and Precautions]*.

Increases in Serum Magnesium: Dose-related increases in serum magnesium were observed early after initiation of INVOKANA (within 6 weeks) and remained elevated throughout treatment. In the pool of four placebo-controlled trials, the mean change in serum magnesium levels was 8.1% and 9.3% with INVOKANA 100 mg and INVOKANA 300 mg, respectively, compared to -0.6% with placebo. In a trial of patients with moderate renal impairment *[see Clinical Studies (14.3) in full Prescribing Information]*, serum magnesium levels increased by 0.2%, 9.2%, and 14.8% with placebo, INVOKANA 100 mg, and INVOKANA 300 mg, respectively.

Increases in Serum Phosphate: Dose-related increases in serum phosphate levels were observed with INVOKANA. In the pool of four placebo controlled trials, the mean change in serum phosphate levels were 3.6% and 5.1% with INVOKANA 100 mg and INVOKANA 300 mg, respectively, compared to 1.5% with placebo. In a trial of patients with moderate renal impairment *[see Clinical Studies (14.3) in full Prescribing Information]*, the mean serum phosphate levels increased by 1.2%, 5.0%, and 9.3% with placebo, INVOKANA 100 mg, and INVOKANA 300 mg, respectively.

Increases in Low-Density Lipoprotein Cholesterol (LDL-C) and non-High-Density Lipoprotein Cholesterol (non-HDL-C): In the pool of four placebo-controlled trials, dose-related increases in LDL-C with INVOKANA were observed. Mean changes (percent changes) from baseline in LDL-C relative to placebo were 4.4 mg/dL (4.5%) and 8.2 mg/dL (8.0%) with INVOKANA 100 mg and INVOKANA 300 mg, respectively. The mean baseline LDL-C levels were 104 to 110 mg/dL across treatment groups *[see Warnings and Precautions]*.

Dose-related increases in non-HDL-C with INVOKANA were observed. Mean changes (percent changes) from baseline in non-HDL-C relative to placebo were 2.1 mg/dL (1.5%) and 5.1 mg/dL (3.6%) with INVOKANA 100 mg and 300 mg, respectively. The mean baseline non-HDL-C levels were 140 to 147 mg/dL across treatment groups.

Increases in Hemoglobin: In the pool of four placebo-controlled trials, mean changes (percent changes) from baseline in hemoglobin were -0.18 g/dL (-1.1%) with placebo, 0.47 g/dL (3.5%) with INVOKANA 100 mg, and 0.51 g/dL (3.8%) with INVOKANA 300 mg. The mean baseline hemoglobin value was approximately 14.1 g/dL across treatment groups. At the end of treatment, 0.8%, 4.0%, and 2.7% of patients treated with placebo, INVOKANA 100 mg, and INVOKANA 300 mg, respectively, had hemoglobin above the upper limit of normal.

DRUG INTERACTIONS

UGT Enzyme Inducers: Rifampin: Co-administration of canagliflozin with rifampin, a nonselective inducer of several UGT enzymes, including UGT1A9, UGT2B4, decreased canagliflozin area under the curve (AUC) by 51%. This decrease in exposure to canagliflozin may decrease efficacy. If an inducer of these UGTs (e.g., rifampin, phenytoin, phenobarbital, ritonavir) must be co-administered with INVOKANA (canagliflozin), consider increasing the dose to 300 mg once daily if patients are currently tolerating INVOKANA 100 mg once daily, have an eGFR greater than 60 mL/min/1.73 m^2, and require additional glycemic control. Consider other antihyperglycemic therapy in patients with an eGFR of 45 to less than 60 mL/min/1.73 m^2 receiving concurrent therapy with a UGT inducer and require additional glycemic control *[see Dosage and Administration (2.3) and Clinical Pharmacology (12.3) in full Prescribing Information]*.

Digoxin: There was an increase in the area AUC and mean peak drug concentration (C_{max}) of digoxin (20% and 36%, respectively) when co-administered with INVOKANA 300 mg *[see Clinical Pharmacology (12.3) in full Prescribing Information]*. Patients taking INVOKANA with concomitant digoxin should be monitored appropriately.

USE IN SPECIFIC POPULATIONS

Pregnancy: Teratogenic Effects: Pregnancy Category C: There are no adequate and well-controlled studies of INVOKANA in pregnant women. Based on results from rat studies, canagliflozin may affect renal development and maturation. In a juvenile rat study, increased kidney weights and renal pelvic and tubular dilatation were evident at greater than or equal to 0.5 times clinical exposure from a 300 mg dose *[see Nonclinical Toxicology (13.2) in full Prescribing Information]*.

These outcomes occurred with drug exposure during periods of animal development that correspond to the late second and third trimester of human development. During pregnancy, consider appropriate alternative therapies, especially during the second and third trimesters. INVOKANA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: It is not known if INVOKANA is excreted in human milk. INVOKANA is secreted in the milk of lactating rats reaching levels 1.4 times higher than that in maternal plasma. Data in juvenile rats directly exposed to INVOKANA showed risk to the developing kidney (renal pelvic and tubular dilatations) during maturation. Since human kidney maturation occurs *in utero* and during the first 2 years of life when lactational exposure may occur, there may be risk to the developing human kidney. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from INVOKANA, a decision should be made whether to discontinue nursing or to discontinue INVOKANA, taking into account the importance of the drug to the mother *[see Nonclinical Toxicology (13.2) in full Prescribing Information]*.

Pediatric Use: Safety and effectiveness of INVOKANA in pediatric patients under 18 years of age have not been established.

Geriatric Use: Two thousand thirty-four (2034) patients 65 years and older, and 345 patients 75 years and older were exposed to INVOKANA in nine clinical studies of INVOKANA *[see Clinical Studies (14.3) in full Prescribing Information]*.

Patients 65 years and older had a higher incidence of adverse reactions related to reduced intravascular volume with INVOKANA (such as hypotension, postural dizziness, orthostatic hypotension, syncope, and dehydration), particularly with the 300 mg daily dose, compared to younger patients; more prominent increase in the incidence was seen in patients who were 75 years and older *[see Dosage and Administration (2.1) in full Prescribing Information and Adverse Reactions]*. Smaller reductions in HbA1C with INVOKANA relative to placebo were seen in older (65 years and older; -0.61% with INVOKANA 100 mg and -0.74% with INVOKANA 300 mg relative to placebo) compared to younger patients (-0.72% with INVOKANA 100 mg and -0.87% with INVOKANA 300 mg relative to placebo).

Renal Impairment: The efficacy and safety of INVOKANA were evaluated in a study that included patients with moderate renal impairment (eGFR 30 to less than 50 mL/min/1.73 m^2) *[see Clinical Studies (14.3) in full Prescribing Information]*. These patients had less overall glycemic efficacy and had a higher occurrence of adverse reactions related to reduced intravascular volume, renal-related adverse reactions, and decreases in eGFR compared to patients with mild renal impairment or normal renal function (eGFR greater than or equal to 60 mL/min/1.73 m^2); patients treated with INVOKANA 300 mg were more likely to experience increases in potassium *[see Dosage and Administration (2.2) in full Prescribing Information, Warnings and Precautions, and Adverse Reactions]*.

The efficacy and safety of INVOKANA have not been established in patients with severe renal impairment (eGFR less than 30 mL/min/1.73 m^2), with ESRD, or receiving dialysis. INVOKANA is not expected to be effective in these patient populations *[see Contraindications and Clinical Pharmacology (12.3) in full Prescribing Information]*.

Hepatic Impairment: No dosage adjustment is necessary in patients with mild or moderate hepatic impairment. The use of INVOKANA has not been studied in patients with severe hepatic impairment and is therefore not recommended *[see Clinical Pharmacology (12.3) in full Prescribing Information]*.

OVERDOSAGE

There were no reports of overdose during the clinical development program of INVOKANA (canagliflozin).

In the event of an overdose, contact the Poison Control Center. It is also reasonable to employ the usual supportive measures, e.g., remove unabsorbed material from the gastrointestinal tract, employ clinical monitoring, and institute supportive treatment as dictated by the patient's clinical status. Canagliflozin was negligibly removed during a 4-hour hemodialysis session. Canagliflozin is not expected to be dialyzable by peritoneal dialysis.

PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Medication Guide).

Instructions: Instruct patients to read the Medication Guide before starting INVOKANA (canagliflozin) therapy and to reread it each time the prescription is renewed.

Inform patients of the potential risks and benefits of INVOKANA and of alternative modes of therapy. Also inform patients about the importance of adherence to dietary instructions, regular physical activity, periodic blood glucose monitoring and HbA1C testing, recognition and management of hypoglycemia and hyperglycemia, and assessment for diabetes complications. Advise patients to seek medical advice promptly during periods of stress such as fever, trauma, infection, or surgery, as medication requirements may change.

Instruct patients to take INVOKANA only as prescribed. If a dose is missed, advise patients to take it as soon as it is remembered unless it is almost time for the next dose, in which case patients should skip the missed dose and take the medicine at the next regularly scheduled time. Advise patients not to take two doses of INVOKANA at the same time.

Inform patients that the most common adverse reactions associated with INVOKANA are genital mycotic infection, urinary tract infection, and increased urination.

Inform female patients of child bearing age that the use of INVOKANA during pregnancy has not been studied in humans, and that INVOKANA should only be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Instruct patients to report pregnancies to their physicians as soon as possible.

Inform nursing mothers to discontinue INVOKANA or nursing, taking into account the importance of drug to the mother.

Laboratory Tests: Due to its mechanism of action, patients taking INVOKANA will test positive for glucose in their urine.

Hypotension: Inform patients that symptomatic hypotension may occur with INVOKANA and advise them to contact their doctor if they experience such symptoms *[see Warnings and Precautions]*. Inform patients that dehydration may increase the risk for hypotension, and to have adequate fluid intake.

Genital Mycotic Infections in Females (e.g., Vulvovaginitis): Inform female patients that vaginal yeast infection may occur and provide them with information on the signs and symptoms of vaginal yeast infection. Advise them of treatment options and when to seek medical advice *[see Warnings and Precautions]*.

Genital Mycotic Infections in Males (e.g., Balanitis or Balanoposthitis): Inform male patients that yeast infection of penis (e.g., balanitis or balanoposthitis) may occur, especially in uncircumcised males and patients with prior history. Provide them with information on the signs and symptoms of balanitis and balanoposthitis (rash or redness of the glans or foreskin of the penis). Advise them of treatment options and when to seek medical advice *[see Warnings and Precautions]*.

Hypersensitivity Reactions: Inform patients that serious hypersensitivity reactions such as urticaria and rash have been reported with INVOKANA. Advise patients to report immediately any signs or symptoms suggesting allergic reaction or angioedema, and to take no more drug until they have consulted prescribing physicians.

Urinary Tract Infections: Inform patients of the potential for urinary tract infections. Provide them with information on the symptoms of urinary tract infections. Advise them to seek medical advice if such symptoms occur.

Active ingredient made in Belgium

Finished product manufactured by:
Janssen Ortho, LLC
Gurabo, PR 00778

Manufactured for:
Janssen Pharmaceuticals, Inc.
Titusville, NJ 08560

Licensed from Mitsubishi Tanabe Pharma Corporation

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A New Team at JASN

By Karl A. Nath

I am privileged to serve as the new Editor-in-Chief of the *Journal of the American Society of Nephrology* (*JASN*), and I am delighted to introduce our new team. Thanks to the leadership of Dr. Eric Neilson and his team, and prior leadership, *JASN* holds a premier position among kidney journals, dedicating itself to both the scientific and clinical communities by publishing the very best work in relevant fields. *JASN* will maintain this important commitment and publish cutting-edge scientific studies and the best in translational studies, epidemiology, clinical trials and research, renal therapies, and renal transplantation. In addition, *JASN* will be a vibrant voice for issues that are of broad and timely interest to the nephrology community in these challenging times.

To fulfill this mission, a roster of distinguished individuals with expertise encompassing these areas has been assembled, with Dr. Anupam Agarwal serving as Deputy Editor (University of Alabama at Birmingham; AKI, molecular biology, mutant mouse models). Associate editors are listed in Table 1.

The new team at JASN: Standing left to right are Fernando Fervenza, MD, PhD; Matthew Griffin, MBChB; Keith Norris, MD; Robert Gaston, MD; Ariel Gomez, MD; Agnes Fogo, MD; Alfred Cheung, MD. Sitting from left to right are David Salant, MD; Anupam Agarwal, MD; Karl A. Nath, MBChB; Bonnie O'Brien; Phylllis August, MD, MPH; and Peter Harris, PhD.

JASN is most fortunate to have as its Managing Editor, Ms. Bonnie O'Brien, who has served this role with every distinction from the very first issue of the journal, which was published in July 1990.

Special appreciation and thanks go to Dr. Eric Neilson and Dr. Gary Curhan, Editor-in-Chief of *CJASN*, for quite helpful discussions, particularly during this transition period, and to Ms. Adrienne Lea, ASN Director of Communications, and Dr. Sharon Moe, President-Elect, ASN, and former Chair of the ASN Communications Committee, for their continued support and input.

The mission of the ASN is to "lead the fight against kidney disease." *JASN* actively participates in this mission by publishing new, important, and influential literature pertaining to the science and practice of nephrology, and by engaging the nephrology community in dialog. The new team at *JASN* is honored to serve this journal and this community, and warmly welcomes feedback so that this remarkable journal can best serve our discipline, our community, and, ultimately, the welfare of patients with kidney disease.

Karl A. Nath, MBChB, is affiliated with the Division of Nephrology & Hypertension, Department of Medicine, and Department of Physiology and Biomedical Engineering, Mayo Clinic, Rochester, MN

Table 1. *JASN*'s Associate Editors and their specialties

- **Phyllis August, MD, MPH**, Weill Cornell Medical Center
  hypertension, pregnancy-related kidney disease, epidemiology
- **Alfred Cheung, MD**, University of Utah
  end-stage kidney disease, vascular access, CKD, clinical trials
- **David Ellison, MD**, Oregon Health and Science University
  renal physiology, tubular disease, molecular pathogenesis of hypertension, edema
- **Robert Gaston, MD**, University of Alabama, Birmingham
  transplantation
- **Fernando Fervenza, MD, PhD**, Mayo Clinic, Rochester
  human glomerulonephritis and other parenchymal diseases
- **Agnes Fogo, MD**, Vanderbilt University
  renal pathology, mechanisms of renal injury
- **Ariel Gomez, MD**, University of Virginia
  renal development, renin-angiotensin system, renal autocoids, pediatrics
- **Matthew Griffin, MBChB**, National University of Ireland, Galway
  immunology, transplant biology, AKI, regenerative medicine
- **Peter Harris, PhD**, Mayo Clinic, Rochester
  molecular genetics of kidney disease
- **Keith Norris, MD**, Charles R. Drew University of Medicine and Science
  CKD, renal epidemiology and outcomes, hypertension, health care disparities
- **David Salant, MD**, Boston University
  glomerular biology and pathobiology, glomerulonephritis
- **Amy Williams, MD**, Mayo Clinic, Rochester
  dialysis, CKD, public policy, career development, and professionalism

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- **Geriatric Nephrology:** Basic, clinical, and health services research relevant to the field of geriatric nephrology (1001)
- **Nutrition and Metabolism:** Basic and patient-based studies addressing the metabolic and physiologic responses to nutrients and how they interface with kidney disease and its treatment (1401)

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Fellows can submit clinical cases or pedigrees that demonstrate novel clinical findings, illustrate classic conditions in new or unusual ways, or illuminate and expand knowledge concerning physiology, cell biology, genetics, or molecular mechanisms. These case reports should reflect an understanding of the relevant science and are eligible for poster presentation and publication only. Select abstract category 1302 Fellows Case Reports during the submission process.

The full list of abstract categories and their descriptions are available at www.asn-online.org/KidneyWeek

Please note that ALL abstract authors (including co-authors) must have current disclosures on file with ASN at time of submission.

ASN LEADING THE FIGHT AGAINST KIDNEY DISEASE

IMPORTANT DATES (2013)

Abstracts

Wednesday, April 10
Abstract Submission Site Opens

Tuesday, June 11
Abstract Submission Site Closes
(11:59 p.m. EDT)

Wednesday, July 31
Late-Breaking Clinical Trial
(Phases II & III only) Submission Site Opens

Wednesday, September 11
Late-Breaking Clinical Trial
(Phases II & III only) Submission Site Closes
(11:59 p.m. EDT)

Registration & Housing

Wednesday, June 5
Registration and Housing Opens

Wednesday, September 11
Early Registration Closes

Friday, October 4
Housing Closes

Wednesday, October 23
Advance Registration Closes

Tuesday, November 10
Onsite Registration Opens

Kidney Week

Tuesday, Nov. 5 – Wednesday, Nov. 6
Early Programs

Thursday, Nov. 7 – Sunday, Nov. 10
Annual Meeting

Centers for Disease Control Debuts CKD Surveillance System

Chronic kidney disease (CKD) is a growing public health problem affecting 10–15 percent of the general U.S. population. Yet until recently, the United States lacked a comprehensive surveillance system to document the burden of CKD and its risk factors over time. To address this need, the Centers for Disease Control and Prevention (CDC), as a major part of its CKD Initiative, commissioned two research teams led by Neil Powe, MD, at the University of California, San Francisco, and Rajiv Saran, MD, of the University of Michigan to develop and implement a national CKD Surveillance System. The surveillance system was successfully launched in the fall of 2012 and is currently available on the CDC's website at www.cdc.gov/ckd/surveillance.

The surveillance system tracks "the progress of our efforts to prevent, detect, and manage CKD," the CDC writes on the website. It also "provides the means for evaluating, monitoring, and implementing quality improvement efforts by both federal and nonfederal agencies." Highlights of the surveillance system include a national CKD fact sheet and a specific section to evaluate progress toward achieving Healthy People 2020 objectives for CKD.

Data is arranged within categories, so that specific indicators, such as "percentage of patients seeing a nephrologist by stage," are nested within broader topics, such as "processes and quality of care in CKD." There are currently nine broad topics: incidence, prevalence, awareness, burden of risk factors, health consequences, processes and quality of care, health care system capacity, CKD in children and adolescents, and CKD in the solid organ transplant population. Each broad topic contains multiple indicators. Tables and figures are downloadable.

"What's novel about this surveillance system is that it brings CKD data from disparate data sources together into one location," Powe said. "Integration of multiple data sources is one of the main goals of this project, enabling us to help provide a complete picture of national trends in CKD."

The current surveillance system contains data from many resources, including measures derived from the National Health and Nutrition Examination Surveys (NHANES), the Veterans Affairs Healthcare System (National VA), the United States Renal Data System (USRDS), the National Kidney Disease Education Program (NKDEP), the College of American Pathologists (CAP), and the American Medical Association (AMA), to name a few. Data sources are rigorously evaluated for characteristics that would make them useful to include in a surveillance system, including representativeness and stability over time.

"Key goals of this surveillance system are to monitor trends, promote CKD prevention and stimulate improvement of CKD care," Powe said. "We're hoping to disseminate the data as widely as possible so that it may be used to its fullest public health potential."

ASN LEADING THE FIGHT AGAINST KIDNEY DISEASE

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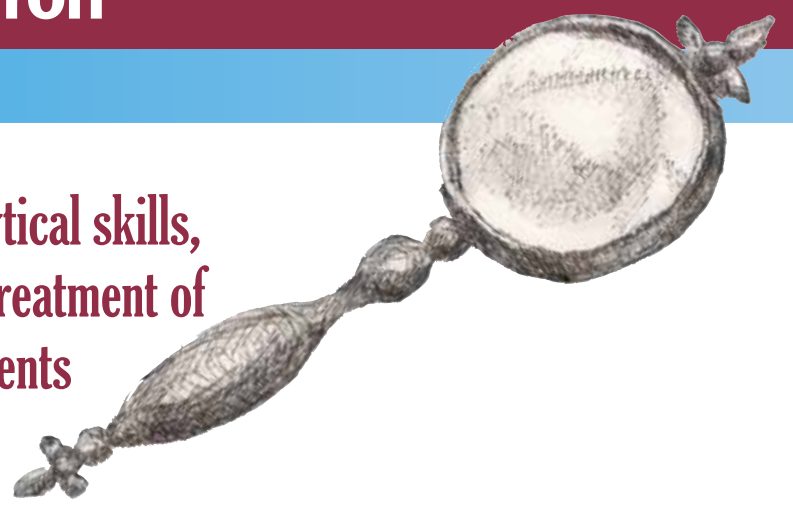
ALEXION

Detective Nephron



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

Ms. Curious Tubule enters the room along with L.O. Henle to present a case.

Nephron My apprentice, what do you have for me? And we have our medical student back. Good!

Henle and Tubule look at each other.

Henle I have a patient with a potassium level of 1.8 mmol/L.

Nephron *(chuckling)* Hmm. That is really low. Can the patient walk?

Tubule *(confidently)* No, that is why this 43-year-old woman is here with profound lower extremity weakness leading to being bedridden for the past 2 days.

Nephron That's always the problem. Figuring out the cause is more important. I am assuming the medical team has started replacing her potassium. What do you think is causing all this?

Henle Broadly speaking, hypokalemia can result from potassium losses or translocation.

Nephron Good place to start.

Tubule *(curiously)* Can you elaborate on translocation?

Nephron Good! And?

Henle Well, translocation refers to shifting of potassium into cells. This can result from two major mechanisms. The first is from increased work of Na-K ATPase, which can be noticed in patients with hyperinsulinemia. This is also the reason why patients in refeeding syndrome can become hypokalemic. An increase in β-2 adrenergic activity also increases the activity of this pump, leading to hypokalemia. The second mechanism is stimulation of the cellular H+ and K+ exchange that can be sometimes seen in alkalemia leading to potassium being pumped into the cells and hypokalemia. Also, sometimes in leukocytosis (e.g., in acute myeloid leukemia), there may be uptake of potassium by the leukocytes, leading to pseudohypokalemia.

Tubule Also, I have heard that increased blood cell production, as seen in treatments with folate and vitamin B12 for anemia and GM-CSF for neutropenia, can result in hypokalemia.

Henle I doubt this patient has any of them, because the leukocyte count, hemoglobin, and platelets are completely normal. She has been eating a regular diet, has normal blood glucose levels, and has not recently been using β-2 adrenergic agents. She really didn't have many symptoms except for this weakness and perhaps some dry eyes and mouth for the past 3 months.

Nephron Good thought process. Since you've started, let us now complete the other side of the equation.

Tubule You mean potassium losses? Well potassium losses can be from extrarenal causes or renal causes.

Nephron Why don't we talk about her diarrhea?

Tubule She has none! She has no medical history for any such causes of nonrenal losses.

Henle I would consider moving to renal causes of losses, given that she has a non–anion gap metabolic acidosis, might I add.

Tubule Oh, I missed that part of her laboratory examination.

Nephron Did you confirm the metabolic acidosis with an arterial blood gas determination? A compensatory response *to* respiratory alkalosis can look exactly like metabolic acidosis, meaning a low serum bicarbonate. We need to see a low arterial pH to be sure.

Henle Yes, we did. Her pH was 7.21.

Tubule *(confidently)* In terms of renal losses, that's a long list.

Nephron Her 24-hour urine potassium must be more than 20 mmol.

Tubule Of course you can guess the number correctly. Actually, it was 41 mmol in 24 hours. Also, her urine pH is 6.5, and her random urine electrolytes are Na, 34 mmol/L; K, 21 mmol/L; and Cl, 35 mmol/L. Therefore, her urine anion gap is +20.

Henle Wait a second! Clearly, we know there are urinary losses here, and there is a positive anion gap, which suggests possibly a renal tubular acidosis (RTA), given that she had normal renal function. But there are other mechanisms we need to consider. Nephron: Please enlighten us, my friend.

Nephron Please enlighten us, my friend.

Henle I look at renal causes in physiology-based mechanisms. Increased distal sodium delivery as a cause of the K+ losses is one category (diuretics, vomiting, Bartter and Gitelman syndromes), but in those cases mostly there is some degree of alkalosis, which this patient lacks. I doubt this is Liddle syndrome, with increased epithelial sodium channel activity.

Nephron Do you want to know the magnesium level?

Henle Of course I do. That is another mechanism via decreased renal outer medullary potassium inward rectification.

Tubule And the magnesium was 1.02 mmol/L (2.5 mg/dL).

Nephron Is hypertension present?

Tubule No, which rules out increased mineralocorticoid activity increase (again mostly with some metabolic alkalosis).

Nephron It seems that a much more practical way to think might be to divide your causes with acidosis versus alkalosis. Isn't it? Let's stop listing all non–acidosis related causes, please!

Henle I think this is a distal RTA.

Tubule I think it is a proximal RTA.

Nephron Oh well, you will both have to defend your diagnoses.

Tubule The pathophysiology of hypokalemia in RTA is not well known, but given the degree of hypokalemia, I think this is too low for just a distal RTA.

Henle How do you explain the alkaline urinary pH then, in the absence of active treatment of a proximal RTA with bicarbonate? If you had proximal RTA in steady state, the distal component is still working, and you should be able to acidify the urine, but here your urine pH is high. Hence, I think this is a classic case of distal RTA.

Nephron In distal RTA, you are unable to excrete the daily acid load. In the absence of bicarbonate therapy, this results in progressive hydrogen ion retention. The serum bicarbonate levels are rarely below 10 meq/L. To enable you to make a diagnosis of distal RTA, the urine pH should be 5.5 or higher, the urine sodium concentration should be above 25 mmol/L, and the urine anion gap should be consistent with low rates of ammonium excretion (hence positive). The urine osmolal gap has been shown to be more useful, but I assume that wasn't done in this case.

Henle That is correct, and the serum bicarbonate was 15 mmol/L, which suggests against proximal RTA in this individual.

Nephron In proximal RTA, there is a reduced capacity to reclaim filtered bicarbonate in the proximal tubule. The serum bicarbonate concentration in untreated patients with proximal RTA is usually between 12 and 20 mmol/L. When the serum bicarbonate is low, virtually all of the filtered bicarbonate can be reabsorbed, and distal acidification proceeds normally, with a urine pH that is appropriate for the patient's diet.

Tubule Hmm... I guess this is distal RTA.

Henle Great. Let's go and treat her with repletion.

Nephron Stop by in a few days and tell me the cause of her distal RTA. It doesn't occur in isolation.

Tubule The major causes of distal RTA include autoimmune diseases, malignancy, and hypercalciuria. Perhaps we should look for those causes.

Henle Hmm…she did describe having dry eyes and mouth. What autoimmune diseases cause distal RTA?

Tubule I think she might have Sjogren syndrome (SS), which might complete the entire presentation: dry eyes, dry mouth, distal RTA.

Nephron Come back in 2 weeks, please.

Two weeks later

Henle Aggressive potassium repletion was initiated with combined oral potassium tablets and intravenous fluids. By day 2 of hospitalization, the patient reported marked improvement in overall strength, and her potassium had risen to 3.5 mmol/L. She was discharged on hospital day 6, receiving potassium replacement with potassium citrate.

Nephron Tubule, I am curious; what did you do next?

Henle (*jumping in*) We ordered a 24 hour urinary calcium concentration, and it was not elevated.

Henle We determined that the antinuclear antibody was speckled, and the antinuclear factor titer was 1:2560.

Nephron I see.

Tubule Perhaps this is lupus, so we got a double-strand DNA determination, and it was negative. Her normal lactate dehydrogenase level suggested against a malignancy. Her levels of Sjogren syndrome A at 518 AU/mL and Sjogren syndrome B at 530 AU/mL clinched the diagnosis of SS. A follow-up revealed a potassium level of 3.8 mmol/L and complete resolution of her previous symptoms.

Nephron Nice work, team!

Henle While it is common for patients with an established diagnosis of SS to have distal RTA, it is rare for patients to present with severe hypokalemia and acidosis as their initial presentation, especially in such a dramatic and severe manner.

Tubule Would we treat the underlying SS?

Nephron Good question; unlikely, if kidney function is normal. The indications for treatment of SS with steroids include symptoms (i.e., joint pain, dry mouth and eyes). There is evidence that steroids may resolve the distal RTA because it may be an antibody-mediated process that steroids can curtail, perhaps targeting the hydrogen ATPase pump in the distal nephron. It's a tough decision. Usually these patients do relatively well with potassium and alkali preparations like potassium citrate.

Nephron (*lecturing mode*) Again, from a single entity of hypokalemia you diagnosed a systemic illness. Remember, besides laboratory data and clinical acumen, you need a good history and physical examination because that will never be replaced! No online tool or laboratory test is going to give you the most information as well as the patient can!

Detective Nephron was developed by Kenar Jhaveri, MD, assistant professor of medicine at Hofstra North Shore LIJ School of Medicine and an attending nephrologist at North Shore University and Long Island Jewish Medical Center in Great Neck, NY.
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Industry Spotlight

Medgenics' Biopump Shows Good Early Results

Medgenics has announced early data from its phase II clinical trial with the EPODURE biopump device. This trial used the company's proprietary biopump to deliver the drug erythropoietin, or EPO, to anemic patients with chronic kidney disease who had not yet begun dialysis.

The company, based in Karmiel, Israel, has produced biopump applications for treating several chronic diseases, including hepatitis C, and is in the early stages of developing a biopump application that would treat hemophilia.

The biopump allows patients to produce, in their bodies on a long-term basis, their own natural human protein therapy. Cells are taken from patients, treated, placed in the biopump, and then the sterilized pump is implanted.

The recent trial results showed that the EPODURE pump produced an environment that let hemoglobin remain in a desired range for 2 to 4 months without any additional injections. The company noted that that the treatment never went past the typical normal range for hemoglobin.

The company plans a larger phase II trial for later this year, according to the firm's website.

"We believe that EPODURE could improve the safety and efficacy of anemia treatments while enhancing patient quality of life by providing a more reliable treatment that reduces or eliminates the need for frequent EPO or ESA injections," said Medgenics chief executive Andrew Pearlman. He added that the system "could provide clear cost benefits to payers."

In recent years EPO drugs have been in the news for several reasons, including investigations into dialysis provider DaVita for overuse of the drug Epogen (made by Amgen), and double billing the government for drug that is left in vials and reused, according to a July 2012 *Denver Post* story. DaVita agreed to pay $55 million to settle over allegations of drug overuse; the company denied any wrongdoing.

Amgen also has settled suits, entering a guilty plea at the U.S. District Court in Brooklyn for misbranding its anemia drug, Aranesp, which meant that the company was accused of selling it for uses not approved by the FDA.

NxStage Gets FDA Clearance for New High-Flow Capabilities

On April 30, the U.S. Food and Drug Administration (FDA) granted NxStage Medical clearance for its new high-flow capabilities with the NxStage System One, a portable hemodialysis system cleared for home use. With this clearance, NxStage Medical, based in Lawrence, Mass., expects to begin offering its System One with new higher flow capabilities in the United States later in 2013.

The higher flow capabilities will allow practitioners to adjust the duration and frequency of patient prescriptions for dialysis at home.

"This latest regulatory milestone reflects strong and systematic execution against our product pipeline," said Jeffrey Burbank, chief executive officer at NxStage Medical, Inc. "NxStage therapy may be prescribed less frequently, for example, three times per week or every other day, at treatment times consistent with those that patients and physicians experience in-center (in dialysis centers) today."

NxStage's high flow capabilities also received CE mark approval (CE marking is the manufacturer's declaration that a product meets the requirements of the applicable European Union rules for marketing a product freely in those areas).

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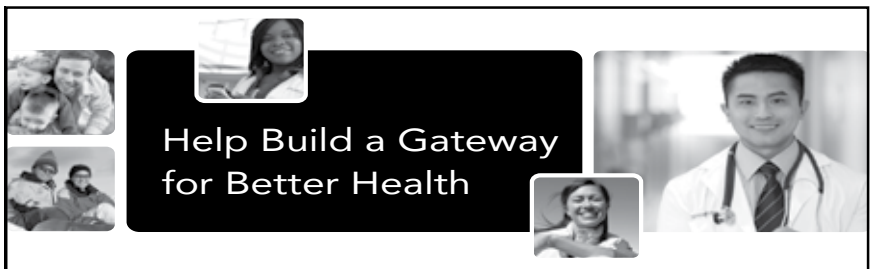

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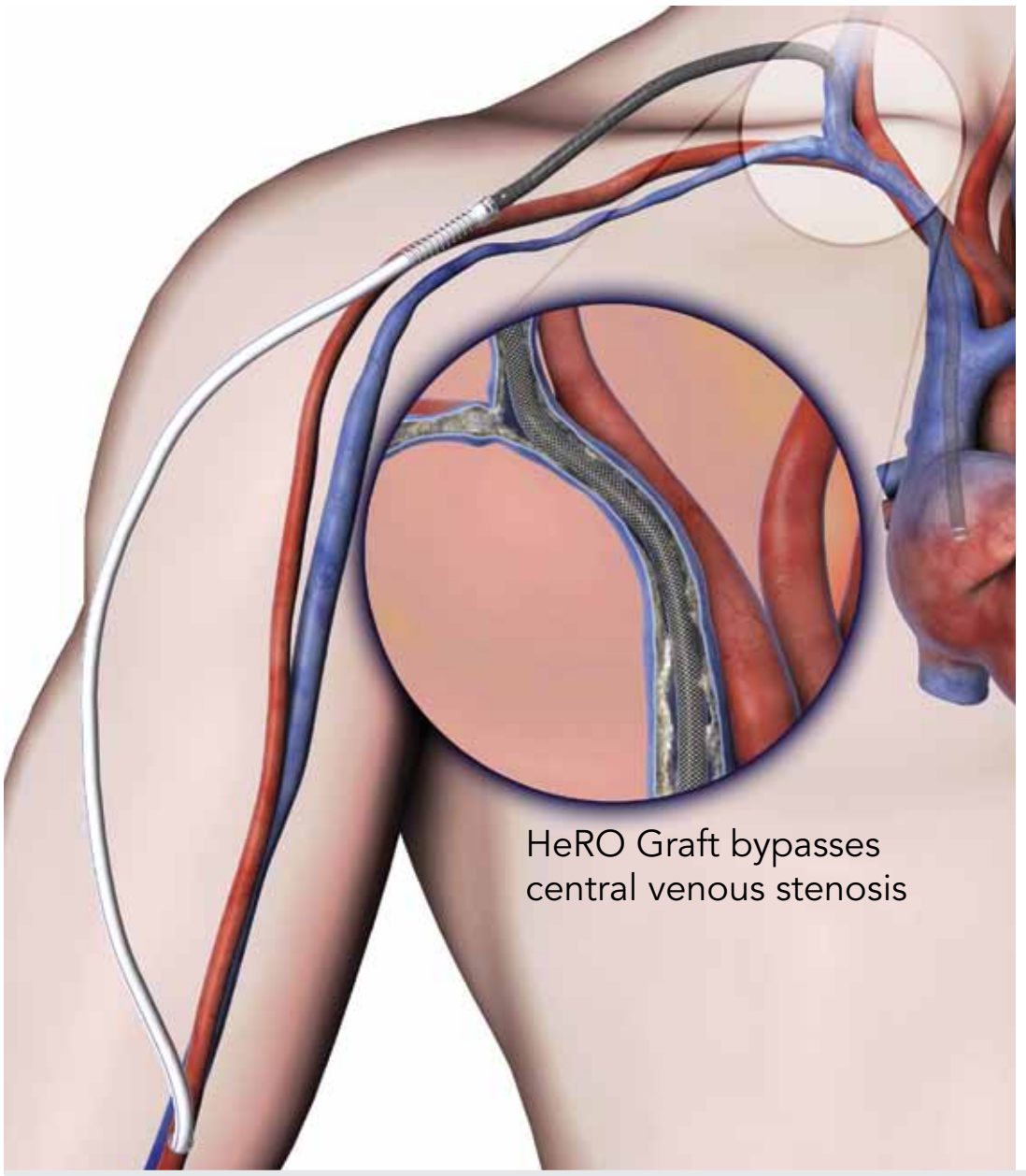

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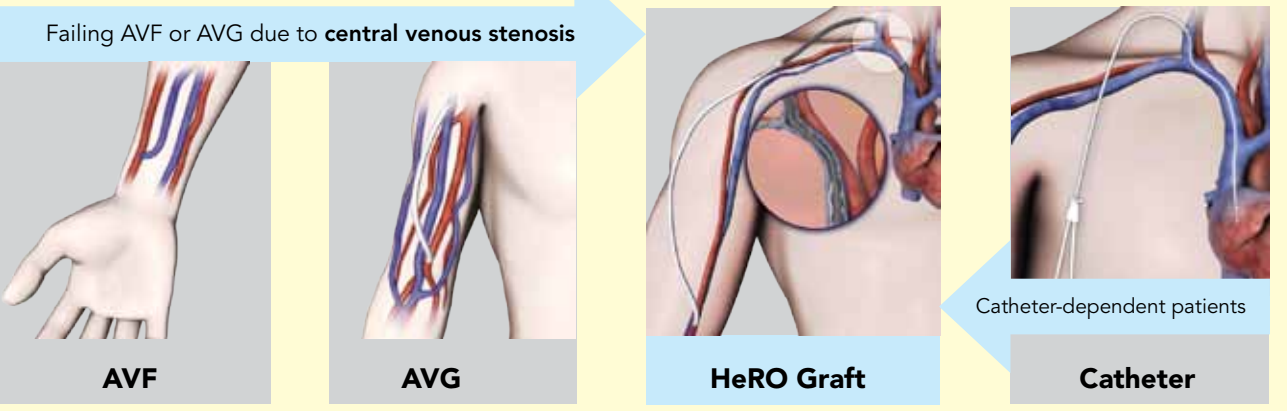

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References:
1) Katzman et al., J Vasc Surg 2009. 2) Gage et al., EJVES 2012. 3) Dageforde et al., JSR 2012.

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