ASN LEADING THE FIGHT AGAINST KIDNEY DISEASE

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Electronic Health Records Vulnerable to Security Breaches

By Eric Seaborg

A study of data breaches reported to the California state attorney general's office in 2012 found that the health care sector was third in the number of data breaches, after the retail sector and finance and insurance sector. And although the data breaches in the health care industry so far have resulted primarily from inadvertent lapses, such as the loss of a laptop or mobile device, some security consultants warn that the personal information in the files is seen as increasingly valuable for identity thieves and others.

Medical records command a much higher black market price than credit card numbers, which is why Rick Kam, president of the data-security consulting firm ID Experts in Portland, Ore., foresees fraudsters paying much more attention to medical information than they have in the past.

Two Kinds of Problems

The problems fall into two general categories, the software itself and human failure to adopt good practices.

Many studies have found very basic vulnerabilities in EHR software, said Laurie Williams, PhD, a computer science professor at North Carolina State University. Her research team's examination of a pair of EHR systems found they were open to "almost beginner level security attacks."

Poor security is an endemic problem with software in many industries, and "the software itself is probably not any worse than in other domains," Williams said. Many other kinds of software contain similar vulnerabilities, but the EHR problems are troubling because they contain such sensitive and personal information. Williams said that if a hacker obtains credit card information, a user can repair the damage by closing the account and getting a new credit card, "but with health records, if someone's private information gets out, you can't withdraw that knowledge."

Potential problems range from identity theft from the release of information such as Social Security numbers to malicious tampering with records themselves.

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The Kidney Research National Dialogue: NIDDK's New Model for Advancing Kidney Science

By Kurtis Pivert

Until recently, NIH identified new investigational areas by gathering small groups of experts at face-to-face meetings scheduled months in advance. Besides the costs involved, this method limited discussion to a narrow topic among a few researchers. To improve this process, the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) developed a novel model to determine future research priorities through broad engagement with the kidney community. Currently in its second year, the Kidney Research National Dialogue (KRND) is a web-based forum where stakeholders interactively propose, evaluate, and select investigational objectives to improve understanding of renal biology and disease. The project entered its second phase with the recent publication of the first of 12 planned commentaries on research priorities selected by KRND participants.

Expanding the conversation

The first online strategic planning initiative launched by NIH, KRND was created to expand discussion of research priorities beyond the confines of NIDDK's Bethesda campus.

"We are constantly looking to identify investigational opportunities, and it's always been important to the NIDDK to

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Kidney Research National Dialogue

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engage as many people as possible," said Chris Ketchum, PhD, deputy director of NIDDK's Division of Kidney, Urologic, & Hematologic Diseases.

KRND is extremely important for the kidney research community, said ASN President Bruce Molitoris, MD, FASN: "Giving investigators around the country the opportunity to fully participate in KRND has led to a common vision of the future research needed to benefit patients with kidney disease."

KRND addresses the need to improve outcomes by advancing knowledge—from the molecular basis of kidney disease to the characteristics predisposing patients to developing it, said Mark Okusa, MD, FASN. "The novel web-based system facilitates engagement of basic and clinical scientists, practitioners, and advocacy and professional groups in a dialogue that fosters new ideas and reinforces important recurring concepts," Okusa said.

"The interactive platform was designed to overcome the expense and logistics of conventional strategic planning," said Krystyna Rys-Sikora, PhD, program director and project leader of KRND.

Previously, NIDDK gathered experts for 1-day discussions of important areas for future research. "These centered on a few discussions and had clearly defined objectives," said Molitoris. "However, they were limited to a select number of individuals, and there was a general tendency to believe their research interests were the most important areas to fund and advance."

Limited productivity was also a concern. Even if 100 researchers met in person, breaking into smaller working groups can limit the ideas generated from each area and prevent cross-fertilization, said Ketchum. "If an expert seated in the CKD group had relevant information for the AKI group, they wouldn't be able to share," he added.

KRND's instantaneous feedback could help shorten the research timeline. "If we can identify opportunities more quickly, distribute that information to the community faster, and get people thinking about the important research questions sooner, this could accelerate the pace of science," said Rys-Sikora.

Molitoris agreed: "By quickly establishing investigative priorities, cooperative studies and large interactive team-science grants can be developed, allowing kidney disease research to rapidly advance."

An open online forum

KRND's online social network has expanded to 1600 members from the United States and abroad, representing the entire spectrum of the kidney community. In addition to proposing and weighing research objectives, KRND members rank ideas through an anonymous voting system.

Stakeholder interaction is critical because different groups see kidney disease from different points of view, said Okusa, who with Molitoris and colleagues coauthored KRND's acute kidney injury (AKI) commentary.

"With AKI, patient advocates are interested in what the outcomes of these interactions mean to them," Okusa said. "Basic scientists are interested in the biological mechanisms responsible for AKI. Clinical scientists are interested in employing these concepts in testable hypotheses that may lead to clinical trials. And advocacy groups can gain an understanding of the potential public health impact and lead efforts to improve public awareness and, potentially, funding and legislation that could impact care for patients with AKI."

Participants saw advantages to NIDDK's new approach. "KRND has opened up the spectrum of input tremendously," said Molitoris.

"KRND's interactive design permits a 'real-time' dialogue to refine and build consensus around important topics that would ordinarily take much longer," said Okusa.

NIDDK's experimental approach did have some disadvantages, including a lack of input from investigators outside the kidney research arena.

"These ideas were created within a narrow framework and may potentially not benefit from the large team science approaches and ideas emanating outside of nephrology," said Molitoris. "Particularly, this may result in limiting the translational importance and abilities of the vision to be generated." But he added that NIDDK has been very proactive and successful in planning small focused meetings bringing in outside experts to help nephrology think bigger, think differently, and create a new vision for future research.

A research blueprint

In 2011, working groups were formed in each of KRND's 12 topic areas (see sidebar), responsible for compiling KRND objectives into commentaries—road

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maps for advancing kidney research. These commentaries—the first of which (AKI and diabetic nephropathy) were published in *CJASN*—will be disseminated to the global research community and to NIDDK for potential projects and funding (1).

The AKI commentary covered a wide range of topics—from identifying biomarkers and improving our understanding of pathophysiology to determining the optimal timing of dialysis initiation and cessation (2).

"Stakeholder consensus on KRND's AKI commentary provides a blueprint for researchers by identifying the most important direction for AKI research," said Okusa. "Although there are a number of areas to investigate in AKI, there are only limited resources and these need to be channeled to the most important areas."

The development of patient registries was a key factor outlined in the diabetic nephropathy commentary (3). Identifying genetic and epigenetic risk factors for the disease, as well as developing new models for testing hypotheses, were among other key priorities for KRND participants.

A need for collaboration

Beyond individual research objectives, KRND participants identified a need for more collaboration. "Science is evolving to require a more collaborative approach and more diverse expertise," said Ketchum. "We need more of those types of interactions, more multidisciplinary teams to tackle complex problems that face the nephrology community. NIDDK is paying close attention to the feedback, and going forward I'm hopeful that we'll support those types of collaborative teams in the future."

Molitoris agreed on the need for a collaborative approach. "Although NIH has always been a leader in discovery science, the current funding—especially for kidney research within NIDDK—limits the depth and breadth of research that can be undertaken," he said. "It is essential for commercial entities that have the necessary funding to be involved in large clinical studies that could identify future therapies in the fight against kidney disease."

One example Molitoris points to is the NIH Public-Private Partnership Program, adding that it needs to be advanced in NIDDK.

"This will promote interactions between nephrology researchers and industry to advance potential devices and therapies to the level of diagnosing and treating patients," Molitoris said. "It is these types of interactions, which have been fostered by NIDDK in AKI meetings, that will benefit our patients the most."

For more information about KRND visit http://www2.niddk.nih.gov/KUH/KUHHome/KRND.htm.

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Kidney Research National Dialogue Topic Areas

- Acute Kidney Injury
- Chronic Kidney Disease
- Diabetic Nephropathy
- National Kidney Disease Education Program/ Translation
- End Stage Renal Disease/Dialysis
- Glomerulonephritis/ Inflammation
- Hypertension
- Normal Biology/ Development/Physiology
- Polycystic Kidney Disease
- Training
- Transplantation
- Other

Electronic Health Records

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"You could possibly change someone's blood type and then they'd get a transfusion of the wrong type," Williams said.

Rubin noted that victims of identity theft can have money stolen and their credit ruined, but medical disclosures pose special dangers. "There are a lot of risks to people having their medical data exposed," he said. There is a risk about not being able to get a job because [you] have a certain genetic makeup, or just shame from having certain diseases."

People problems

But the majority of the health care breaches that have happened so far appear to relate more to human practices in health care settings that tend to make matters worse.

"In terms of security management, the health care industry is particularly bad. A lot of the security problems in the health care industry are people management issues as opposed to software issues," said Avi Rubin, PhD, professor of computer science at Johns Hopkins University and technical director of its Information Security Institute.

Rubin toured hospitals to study their practices and noted a general disregard for computer security, such as passwords commonly posted on computers using sticky notes. In one hospital, a nurse went from computer to computer typing in a particular physician's password so the physician would not time out. That practice left the machines unattended and unprotected most of the time.

The accepted practice of distributing to patients disks containing their x-rays—along with executable programs for reading them—is dangerous because when patients walk into a facility with these disks, practitioners have no idea what is really on them. They could contain malware that could infect whole systems, Rubin said.

Williams noted that in the interest of easing the transition to electronic records, some practices have taken shortcuts such as having a single log-in ID for doctors and another for nurses, rather than having individual user IDs.

"If they do that, they will have no way to trace who did what. So to use the blood example again, they should be able to go back and see who changed the blood type," Williams said.

Another advantage of individual user IDs is to track access within a practice, to discourage workers from accessing records they should not access, for example, out of curiosity that a neighbor came in and looking up why, Williams said.

Security tips

EHR software users' options are limited because they must buy a system certified by government regulators, and Williams and Rubin agreed that the certification process has not paid adequate attention to security. They recommended that practitioners pressure vendors and government regulators to make security a higher priority.

Rubin recommended that practices trying to improve security not try to do it on their own: "They need to have access to a real security professional, whether it is somebody that just consults with them or, if they are a large organization, somebody that works in-house."

The increasing use of smartphones and other devices offers another avenue for data to be compromised. Physicians and other health care workers are probably leaders in the adoption of these technologies, emphasizing the need for good computer hygiene.

With most health care security breaches still resulting from mistakes such as the loss or theft of laptops, the U.S. Department of Health and Human Services' cybersecurity website lists 10 tips for improving practices in the small health care environment (Table 1).

Rubin and Williams both stressed that creating a culture of data security awareness is a key step in protecting patient records, which should be considered one more part of patient care in the digital world.

Table 1. Cybersecurity tips for the health care environment

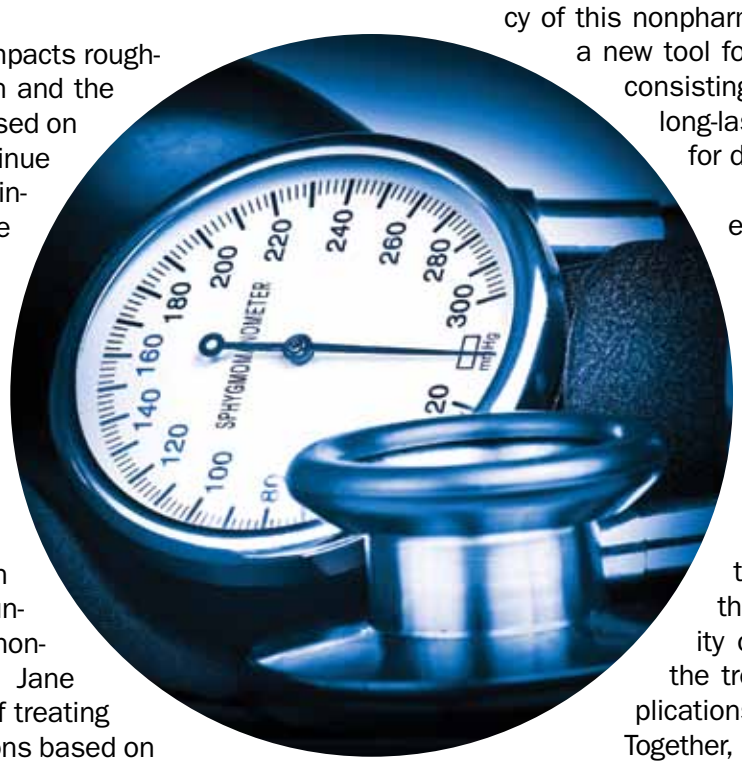
- Use strong passwords and change them regularly.
- Keep anti-virus software current.
- Use a firewall, particularly a hardware firewall between a local area network and the Internet.
- Control access so that protected health information is accessible only to people who need to know it.
- Control physical access to prevent the loss or theft of devices such as portable storage media, laptops, and handhelds.
- Limit network access, including operating wireless routers in encrypted mode.
- Plan for the unexpected by creating backups and having a data recovery plan.
- Maintain good computer habits, including uninstalling any nonessential software and keeping software up-to-date with security patches and new features.
- Protect mobile devices from physical theft and signal theft. Encrypt any information they contain.
- Establish a culture in which everyone takes security as seriously as practices like hand washing and disinfection.

For more information, visit http://www.healthit.gov/providers-professionals/cybersecurity.

Hypertension: The Good, the Bad, and the Unknown

For this issue's focus on hypertension, we have assembled a small portfolio of articles describing recent provocative advances in the study of hypertension.

But first, the bad news. Hypertension impacts roughly 30 percent of the adult U.S. population and the majority of Americans aged 65 or older, based on NHANES surveys. The prevalence will continue to rise rapidly as the U.S. population continues to get older. Moreover, although there have been improvements over the past 10 years, less than 50 percent of patients under treatment for hypertension reach target for blood pressure control. A similar level of poor control is seen in hypertensive patients with chronic kidney disease (CKD), where hypertension is known to promote progression of kidney damage. Laura Svetkey and Crystal Tyson address the prevalence of hypertension in CKD, treatment goals, and the debates underlying choices in pharmacologic and nonpharmacologic therapies. In her piece, Jane Reckelhoff describes the potential risks of treating men and women with the same interventions based on her studies identifying gender-specific mechanisms underlying the pathogenesis of hypertension.



Among the obstacles to improving outcomes in patients with hypertension is the lack of new therapies. One could argue that there has not been a truly novel drug for hypertension since the development of ACE inhibitors in the 1980s, considering that angiotensin receptor blockers and renin inhibitors also target the renin-angiotensin system. In another article in our series, Svetkey and Tyson detail potentially good news regarding progress in developing a novel approach for hypertension treatment: renal nerve ablation. If ongoing prospective randomized controlled trials confirm the efficacy of this nonpharmacologic intervention, we would have a new tool for patients with resistant hypertension consisting of a single intervention with apparent long-lasting effects circumventing the need for daily medication dosing.

And now for the unknown. Jens Titze explains new concepts of sodium homeostasis whereby macrophages can regulate non-osmotic sodium storage in the skin to influence blood pressure responses to increased dietary salt intake. Finally, Steven Crowley summarizes the growing literature that supports a role for the immune system to regulate blood pressure and target organ damage in hypertension through effects on the vasculature and the kidney. This work raises the possibility of targeting inflammatory pathways in the treatment of hypertension and its complications.

Together, the articles in this series highlight opportunities to turn the bad news about hypertension into good news for our patients.

Thomas Coffman, MD, FASN, and Steven Crowley, MD, edited this special section of ASN Kidney News *and are affiliated with the Division of Nephrology at Duke University Medical Center in Durham, NC.*

Treatment of Hypertension in Patients with Chronic Kidney Disease

By Laura P. Svetkey and Crystal C. Tyson

Most people with chronic kidney disease (CKD) have high blood pressure. Treatment of hypertension in patients with CKD is considered critical to prevent CKD progression and related cardiovascular events. However, questions remain about the appropriate BP goal. Most evidence indicates there is no benefit of treating to a goal any lower than 140/90 mm Hg, but there is some suggestion that such a goal may be appropriate for patients with albuminuria. Given recent evidence that a lower goal in patients with diabetes (without CKD) actually increases risk, and the subsequent change in American Diabetes Association guidelines from 130/80 mm Hg to 140/80 mm Hg, it may be prudent to consider other factors—such as presence or absence of albuminuria and comorbid disease—in order to individualize BP management in patients with CKD.

The evidence is somewhat more clear-cut with regard to choice of antihypertensive medication: treatment with angiotensin converting enzyme (ACE) inhibitors (and possibly angiotensin receptor blockers [ARBs] as well) is more effective than other classes at slowing CKD progression, and possibly preventing incident heart failure.

However, no clinical outcomes trial has carried out head-to-head comparison between ACE inhibitors and ARBs, or between ACE inhibitors and diuretics. Most patients with CKD have some degree of volume-dependent hypertension, arguing for use of diuretic (specifically a loop diuretic if their eGFR is less than 30 mL/min/1.73 m^2). Furthermore, many patients with CKD have resistant hypertension, a condition in which diuretic is critical for achieving BP control.

In addition, the evidence favoring ACE inhibitors or ARBs comes from studies comparing classes of agents for the initial treatment of hypertension (i.e., the first drug). Most patients with CKD require at least two antihypertensive medications to achieve goal BP. There is no clinical trial evidence to guide the choice of the second, third, fourth, or more medication.

Therefore, a reasonable strategy involves initial treatment with an ACE inhibitor (or an ARB) with a diuretic added as the second agent, or vice versa.

There is no evidence base to guide the use of nonpharmacologic antihypertensive therapy in patients with CKD. The effective lifestyle strategies for lowering BP (weight loss in the overweight/obese, DASH [Dietary Approaches to Stop Hypertension] dietary pattern, reduced sodium intake, physical activity, and moderation of alcohol intake) have not been tested specifically in patients with CKD, but most are likely to be effective and safe in this population. The possible exception is the DASH dietary pattern, which is high in potassium, calcium, magnesium, and phosphorus. With an eGFR greater than 45 mL/min/1.73 m^2, excretion of these minerals is likely to be sufficiently preserved to comfortably recommend DASH; however, additional laboratory surveillance is prudent. Despite the fact that the BP-lowering effects and safety of DASH and other lifestyle interventions have not yet been tested in the setting of CKD, they are nonetheless "heart healthy" behaviors appropriate for any population with high cardiovascular risk.

Overall, when treating hypertension in patients with CKD the therapeutic goal should be to effectively lower BP while simultaneously slowing progression of disease and reducing cardiovascular risk. Blood pressure targets should be individualized, taking into account degree of albuminuria and presence of comorbidities. Using an ACE inhibitor (or ARB) and diuretic should be the cornerstones of drug therapy, and nonpharmacologic lifestyle strategies should be encouraged.

Laura P. Svetkey, MD, and Crystal C. Tyson, MD, are affiliated with the Division of Nephrology at Duke University Medical Center in Durham, NC.

Women Are Not Just Small Men! Sex Differences in Blood Pressure Control

By Jane F. Reckelhoff

Hypertension is a common condition that is a significant risk factor for development of other cardiovascular diseases. The prevalence of hypertension is higher in men than women until after menopause, when the prevalence reverses and is higher in women. In addition, more women die of cardiovascular disease each year than do men.

There is mounting evidence that blood pressure in women is less well controlled than in age-matched men, despite the facts that women see their physicians more frequently and are often more compliant with their medications than men. This statistic makes one consider that either physicians are not as aggressive in treating hypertension in women, which is possibility, or that what causes hypertension in women may not be the same as what causes hypertension in men. Yet the guidelines for treatment for hypertension are the same for men and women based on data mostly collected in men, or if women were included in the studies, there were no analyses of the data to separate responses to antihypertensive therapy in men and women.

This leads to the notion in hypertension treatment that "women are just small men"—we treat their hypertension the same, even the doses of drugs are the same despite significant body weight differences between men and women that may suggest that kinetics and utilization of drugs may also be different.

The reason I think this is important is based on our animal experiments. We have studied aged male and female spontaneously hypertensive rats and found that the blood pressure in old males can be well controlled to normotensive levels by angiotensin receptor blockers (ARBs) or angiotensin I converting enzyme (ACE) inhibitors, suggesting that the renin-angiotensin system is the major system that affects blood pressure in the males.

In the old females, however, ARBs or ACE inhibitors reduce blood pressure but don't normalize it. Also, endothelin ETA receptor antagonists reduce blood pressure but don't normalize it. 20-hydroxyeicosatetraeonic acid (20-HETE) synthesis inhibitors reduce blood pressure but don't normalize it. The combination of ARBs, endothelin ETA receptor antagonists, and 20-HETE inhibitors given together significantly reduce blood pressure in the old females, but still doesn't normalize it (their blood pressure remains at 110 mm Hg mean blood pressure, measured by 24-hour telemetry, where the definition of "normal" is 100 mm Hg). These old females are no longer estrous cycling, which is similar to menopause in women. Also, bear in mind that these rats are inbred and raised in barriers, and so have little genetic variation or environmental confounding effects compared to humans. Based on these data, it's not surprising that blood pressure control in women, especially postmenopausal women, confounded by genetics and environmental conditions may be difficult to manage! It also surprising that very few human studies have been done in which gender differences in responses to antihypertensive therapies have even been evaluated!

So what can we do as clinicians and scientists? First of all, make the NIH put teeth into their rules for human subject studies and require that all studies be powered to evaluate gender-specific differences. This is as important for men as for women, and the finding that there is no gender difference in responses is as important as finding them. The second thing is to advocate that women are not just "little men," with different genetics and environmental conditions that may differentially affect their incidence of diseases, disease progression, treatment, and responses to that treatment. Finally, as new drug therapies for hypertension, or any other disease for that matter, come on the market we should advocate for gender differences studies in responses to make certain we are treating women and men with the best available therapies for their "differences" or "similarities."

Jane F. Reckelhoff, PhD, is the Director of the Women's Health Research Center at the University of Mississippi Medical Center in Jackson, MS..

The Role of Renal Denervation in the Management of Hypertension

By Laura P. Svetkey and Crystal C. Tyson

Renal denervation is an emerging and promising new therapy for resistant hypertension. Although 54 percent of all hypertension is "uncontrolled" (1), not all uncontrolled hypertension is considered resistant. The American Heart Association (AHA) definition of resistant hypertension is BP above goal on at least three antihypertensive medications of different classes, one of which is a diuretic, or BP that requires four or more medications to get to goal. Prevalence in the general hypertensive population is relatively low, but resistant hypertension is commonly seen in nephrology offices.

In evaluating a patient with resistant hypertension, it's important to consider reversible underlying causes, titrate current medications to maximum tolerated dose, and optimize adherence to both pharmacologic and lifestyle treatments. Thereafter, management involves the addition of one more medication after another. If each subsequent addition significantly lowers BP, even if it never gets to goal, then this treatment strategy is advantageous. However, taking four or more medications involves both financial and potential side effect burdens. A potential new treatment for resistant hypertension is on the horizon: renal denervation.

Renal denervation, achieved by radiofrequency ablation through an intra-arterial catheter, directly addresses the extent to which resistant hypertension is due to sympathetic overactivity. Denervation reduces efferent nerve activity (i.e., from the central nervous system [CNS] to the kidney) thus lowering renin secretion, stimulating natriuresis, and improving renal hemodynamics. It also reduces renal afferent nerve activity (i.e., from the kidney to the CNS) thus reducing outflow to the CNS and contralateral kidney, which further dampens sympathetic activity.

Human trials conducted outside the United States are very promising: in one randomized, controlled trial of 106 hypertensive patients, net reduction in BP 6 months after denervation was 33/11 mm Hg compared to control (2). Blood pressure reduction persisted for 12 months. There was no excess risk of renal damage or hypotension.

Larger trials in the United States, involving at least three different ablation devices, are either ongoing or planned for the near future. If these trials replicate the non–U.S. trials, it is reasonable to expect U.S. Food and Drug Administration (FDA) approval within the next year or two.

In considering implementation of this new treatment modality, there are several questions to consider:

Is renal denervation effective and safe in patients with chronic kidney disease (CKD)? The failing, ischemic kidney contributes to sympathetic hyperactivity, suggesting that patients with CKD may have greater BP lowering from denervation than those with normal kidney function. Pilot data in small numbers of patients with stage 3 to 4 CKD (3) and in ESRD (4,5) suggest favorable results, but in ESRD small renal arteries may limit feasibility. Results are promising in CKD, but clearly additional research is needed.

Is renal denervation a reasonable treatment option in patients with less severe hypertension? Most trials to date have enrolled patients with AHA-defined resistant hypertension and systolic BP greater than or equal to 160 mm Hg. Trials in resistant hypertension with systolic BP 140 mm Hg to 160 mm Hg are planned.

Are the benefits long lasting? Are there renal risks that become apparent several years after denervation? Patients in non–U.S. studies were followed for 3 years, with sustained BP response and kidney function. An ongoing U.S. trial will follow patients for 5 years, and a postmarketing registry will be an FDA requirement.

Can the results in relatively homogeneous non–U.S. populations be generalized to patients in the United States? Presumably, ongoing and planned studies in the United States will reflect our racial/ethnic and clinical diversity.

Will renal nerves regenerate after radioablation? From transplant experience we know that, to some extent, renal nerves grow back. Although 3-year follow-up after denervation in a limited number of patients suggests persistent BP effects, additional information will be available from ongoing and planned studies, which are longer and larger.

Will the cost of denervation be offset by savings in prescription drugs, outpatient visits, hypertension-related

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Renal Denervation

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events, and quality of life? To date there is no formal cost-benefit analysis, but this analysis could potentially be estimated with mathematical modeling.

In summary, the preliminary data suggest that renal denervation in patients with resistant hypertension and relatively preserved renal function has a dramatic impact on BP and an acceptable safety profile. Additional data are accruing to substantiate (or not) these findings, determine long-term effects, and clarify the range of BP and level of kidney function that is appropriate for treatment of resistant hypertension with renal denervation.

Laura P. Svetkey, MD, and Crystal C. Tyson, MD, are affiliated with the Division of Nephrology at Duke University Medical Center in Durham, NC.

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New Concepts of Sodium Homeostasis

By Jens Titze

Body sodium content is most intimately coupled with extracellular water content. The idea is that body fluids inside and outside the cells readily equilibrate, resulting in constant electrolyte concentrations in extra- and intracellular fluids. This concept of constancy of internal environment composition is perhaps one of the hallmarks of medical physiology established by Claude Bernard in the 19th century (1). Sodium homeostasis seems to perfectly fit into this model. Sodium is the major cation in the extracellular fluid compartment where it acts to hold water, thereby determining the extracellular volume. Elaborated from this model, three major assumptions dominate our clinical and physiological approach towards sodium balance. First, sodium homeostasis is primarily restricted to the extracellular space. Second, any extracellular sodium accumulation or loss will inevitably lead to commensurate changes in extracellular fluid content (equilibrium theory). Third, to ensure constancy of extracellular volume, our body's sodium content is to be maintained within very narrow limits. Dietary sodium will be completely excreted when the extracellular volume is normal (steady state theory).

Our thinking on sodium balance is largely based on textbook teachings (2): "If dietary intake is abruptly increased from a low-sodium diet, only about one-half is excreted on the first day. This state of affairs elevates the plasma osmolality, stimulating both thirst and secretion of antidiuretic hormone. The increments in water intake and renal water reabsorption produce water retention, resulting in increases in effective circulating volume and weight. After 3-4 days, a new steady state is achieved in which renal sodium excretion matches intake. The same sequence occurs in reverse if sodium intake is reduced." This experiment, which was first described by the 19th century physiologist Carl Ludwig, places renal sodium handling into the very center of sodium homeostasis (3). Today's molecular exploration of mechanisms of sodium excretion and reabsorption by renal glomerular or tubular systems in response to abrupt changes in salt intake is the most logical continuation of this experimental approach.

However, recent evidence from experiments in humans and in animals suggests that there are limitations with this well-established concept. Our research on salt and water balance has traditionally relied on the study of renal short-term adjustment in response to dietary extremes. The reverse experiment during a simulated long-term space flight to Mars, namely study of renal excretion of sodium in response to long-term constant salt intake, showed astounding results. We found that humans rhythmically retain and excrete sodium in their urine over weeks and months, resulting in significant accumulation and release of body sodium—without the expected changes in body weight. This finding was highly anomalous, because it neither supported the model that dietary salt is excreted by the kidneys within 24 hours (steady-state theory), nor that sodium accumulation invariably leads to fluid retention (equilibrium theory). Sodium had been stored in tissues. Additional animal experiments have revealed that sodium can be stored in muscle and in the skin. While the mechanisms of sodium storage in muscle have not yet been addressed, skin sodium storage to our surprise leads to osmotic stress, which triggers an even more surprising regulatory response by immune cells. Apparently, macrophages act as onsite controllers of interstitial sodium and blood pressure homeostasis. The cells sense sites of sodium storage in the skin and most presumably modulate electrolyte and fluid transport by cutaneous lymph capillaries, thereby enhancing removal of interstitial sodium- and chloride-rich fluid from the skin tissue. Failure of this physiological extrarenal regulatory homeostatic immune cell response leads to local electrolyte accumulation in the skin and salt-sensitive hypertension. Investigation of tissue sodium content has shown that this storage phenomenon is not an animal-research curiosity, but also exists in humans. Visualization of reservoir sodium by ^{23}Na magnetic resonance imaging technology revealed sodium storage in human muscle and skin, which increases with age, is more pronounced in men than in women and is directly associated with blood pressure levels.

Emerging basic research questions are how sodium storage is organized at the cellular level, and whether the immune/lymph system forms a homeostatic regulatory network for tissue electrolyte balance. Clinicians may ask whether humans with

increased sodium storage are at risk for developing cardiovascular disease, and whether tissue sodium content can be modified by lifestyle changes or medical treatment. The concept of extrarenal regulation of sodium homeostasis provides new avenues for the preclinical and clinical research community.

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Hypertension: An Autoimmune Disease?

By Steven Crowley

Although cardiologists and nephrologists have debated for years about the relative contributions of the vasculature and the kidney to the pathogenesis of hypertension, new data have emerged that may recast essential hypertension as an autoimmune disease. These studies do not discount the importance of vascular tone and regulation of intravascular volume in the determination of blood pressure. Rather, these novel experiments illustrate that immune cells and inflammatory mediators can influence blood pressure precisely by impacting vascular function and renal sodium handling. Moreover, these recent findings have stimulated renewed interest in earlier, pioneering studies that first hinted at a role for immunity in hypertension.

Long before the era of transgenic models, researchers first drew a link between lymphocyte functions and blood pressure elevation. For example, adoptive transfer of lymph node cells from a rat made hypertensive by renal infarction recapitulated the hypertensive response in the recipient. Conversely, mice lacking a thymus, the organ in which T lymphocytes mature through selective processes, were protected from blood pressure elevation in a model of spontaneous hypertension, and thymectomy in genetically hypertensive rats reduced blood pressure. Later, during the study of atherogenesis, the walls of resistance vessels undergoing remodeling in the setting of hypertension were noted to contain inflammatory cell clusters. Furthermore, in several animal models of hypertension, broad pharmacologic blockade of inflammatory signaling pathways such as those involving NF-κB could reduce the infiltration of immune cells into the vascular wall, limit blood pressure elevation, and protect the heart and kidney from damage (1). However, only recently have the specific mononuclear cell types and their aberrant functions to stimulate blood pressure elevation received more intense scrutiny.

In the modern era, adoptive transfer studies using purified immune cell populations have uncovered a novel role for adaptive immune responses to regulate the susceptibility to blood pressure elevation. For example, work from the group of David Harrison has established that mice lacking functional lymphocytes have a muted blood pressure response to hypertensive stimuli that is restored by transfer of T but not B lymphocytes (2). Preliminary experiments further indicate that CD8+ rather than CD4+ T cells are the key prohypertensive T cell subpopulation. These T cells may promote hypertension by potentiating vascular dysfunction and/or sodium retention in the kidney. Activated T cells appear to promote vascular dysfunction by potentiating local oxidative stress, a key function of inflammatory cells that protects the host in the setting of infection but becomes "autoimmune" in the setting of hypertension. Regarding renal mechanisms of hypertension, mice lacking functional T cells have enhanced expression in the kidney of cyclooxygenase-2, leading to exaggerated generation of the vasodilator prostaglandins E2 and I2 and preserved natriuresis in face of a hypertensive stimulus. Thus, activated T lymphocytes mediate blood pressure elevation by coordinately augmenting vasoconstriction and renal sodium retention.

These actions of T lymphocytes would imply that an adaptive immune response to a specific antigen promotes hypertension. Although no such putative antigen has been definitively established, the group of Rodriguez-Iturbe has put forth heat shock protein 70 as one possible candidate. Moreover, protection from hypertension in animals genetically deficient of key costimulatory receptors required to mobilize a full antigen-dependent T cell response represents further evidence of a directed antigen-mediated process. On the other hand, innate immunity that seeks to protect the host before it can identify and process a specific antigen may also play a role in hypertension. For example, monocytes are the precursors for the macrophages that can propagate broad inflammatory responses even in the absence of a processed antigen, and mice lacking monocytes have a muted blood pressure response to hypertensive stimuli. On the other hand, monocytes can also differentiate into dendritic cells that potently activate adaptive immune responses by presenting processed antigens to T cells, and inflammatory cytokines such as TNF-α that exacerbate blood pressure elevation can be produced by both innate and adaptive immune cell lineages. Thus, the relative participation of the innate versus adaptive immune response in the pathogenesis of hypertension will require further elucidation.

The clinical application of these new research findings also awaits further validation. Reports of reduced blood pressure levels in HIV-infected patients deficient in functional T cells and elevated blood pressure levels in patients suffering from autoimmune diseases such as psoriatic arthritis support a role for immune responses in human hypertension. Moreover, in kidney biopsies from patients with malignant hypertension, perivascular inflammatory cell clusters figure prominently. Nevertheless, particularly given the potential toxicities of broad immunosuppression, a more precise understanding of immune mechanisms in hypertension through additional preclinical studies will likely yield the greatest potential for the development of novel and safe immune-based therapies to limit blood pressure elevation and/or prevent the emergence of target organ damage in the setting of hypertension.

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ASN Hosts PhD Summit

By Grant Olan and Lisa Bryan

In June, ASN hosted its first-ever PhD Summit. Chaired by ASN Physiology and Cell and Molecular Biology Advisory Group Chair Jeffrey H. Miner, PhD, and ASN President Bruce A. Molitoris, MD, FASN, the summit focused on identifying ways the society can advance PhD interest in kidney research and improve the environment for its PhD members.

Dr. Miner and Dr. Molitoris were joined by a diverse group of 16 PhDs. Participants included ASN members and nonmembers from academia, industry, and the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK). Prior to attending the summit, participants completed a survey to identify barriers to PhD trainees pursuing careers in nephrology research. The survey highlighted several common themes, including the perception of kidney research as less important and respected compared to other basic science or clinically relevant disciplines (such as cardiology and oncology), poor integration of renal physiology in student programs, and concerns about research funding.

Today, there is greater competition within NIDDK and across the National Institutes of Health (NIH) to secure research funding than in the past. Since the doubling of NIH's budget ended in 2002, the agency's budget has essentially been undoubled after adjusting for biomedical research inflation. As a result, research budgets have been slashed, programs have been axed, and grant application success rates have fallen from 31.2% of grants funded in 2002 to 17.6% of grants funded in 2012 (Figure 1). As a consequence, scientists are leaving the research field, and the best young minds may never enter the profession.

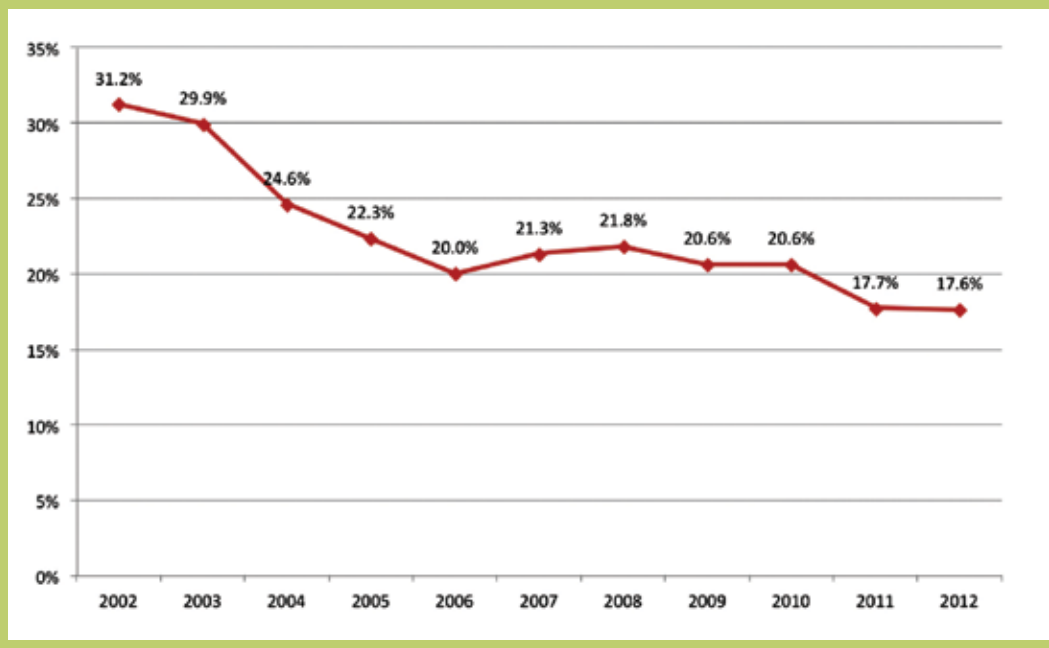
"Today there is a decline in PhDs entering kidney research, and that must change if we want to find a cure for kidney disease," Dr. Miner said. "The purpose of the ASN PhD Summit was to figure out ways to do that. The list of participants was impressive. All of them are at the top of their professions, and all of them came to the summit with excellent ideas for generating more interest in kidney research."

ASN Council commended the summit participants for developing a number of high-quality recommendations that it will soon consider. The list of recommendations includes ways to raise awareness about the kidney and research, foster entry into PhD careers in kidney research, and create a more welcoming environment for

PhDs at ASN Kidney Week, the society's annual scientific meeting.

"ASN represents the entire spectrum of kidney health professionals and scientists, including PhDs," Dr. Molitoris said. "I am confident that the recommendations of the ASN PhD Summit will ensure that the society is meeting the needs of its PhD members. PhDs play a crucial role in achieving the mission of ASN to lead the fight against kidney disease. Their research unlocks the mysteries of how the kidney works and functions, which is key for identifying opportunities for better treatments and possible cures for kidney disease."

Figure 1. Percentage of NIH grant applications funded from 2002 to 2012



ASN PhD Summit Participants

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Leslie A. Bruggeman, PhD
Greg R. Dressler, PhD
Iain A. Drummond, PhD
Kathleen S. Hering-Smith, PhD
Deborah K. Hoshizaki, PhD
Alicia A. McDonough, PhD
Jeffrey H. Miner, PhD
Bruce A. Molitoris, MD, FASN
Ji-Bin Peng, PhD
Jennifer S. Pollock, PhD
Ambra Pozzi, PhD
Nick Pullen, PhD
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Something to Say?

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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

10282400

K02CAN13080B

janssen

Journal View

Hemodialysis Patients Overestimate Survival

Especially after 1 year, patients receiving hemodialysis tend to rate their chances of survival higher than their nephrologists do, reports a study in *JAMA Internal Medicine*.

Using medical records data and validated prognostic tools, the researchers identified 150 hemodialysis patients (out of a group of 207) with predicted 1-year mortality of at least 20 percent. The patients and their nephrologists were then interviewed regarding their expectations for survival. The patients' and physicians' perceptions of the prognosis and likelihood of transplantation were compared with each other and with actual survival.

The analysis included interviews with 62 of 80 eligible patients. Eighty-one percent of patients believed they had at least a 90 percent chance of being alive 1 year later. By contrast, nephrologists estimated that only 25 percent of patients stood a 90 percent chance of surviving for 1 year.

Just 6 percent of patients said they had less than a 50 percent chance of surviving for 5 years, whereas nephrologists rated the chances of 5-year survival at less than 40 percent for 56 percent of patients. Sixty-six percent of patients believed they were candidates for kidney transplantation, whereas nephrologists thought so for only 39 percent.

None of the patients reported discussing their estimated life expectancy with their nephrologists. Of patients who expected to survive for 1 year, only 44 percent said they would want life-extending treatments if it meant increased discomfort. Actual survival was 93 percent at 1 year but dropped sharply with longer follow-up times: to 79 percent at 17 months and 56 percent at 23 months.

The mortality risk for hemodialysis patients exceeds 20 percent per year, a risk similar to that for some types of cancer. Studies have shown that cancer patients overestimate their chances of survival.

The new study suggests that the same is true of hemodialysis patients. Although patients' estimates of 1-year survival are accurate, their expectations of longer-term survival are much higher than their nephrologists' predictions. The researchers call for "interventions to help providers communicate effectively with patients about prognosis" [Wachterman MW, et al. Relationship between the prognostic expectations of seriously ill patients undergoing hemodialysis and their nephrologists. *JAMA Intern Med* 2013; 173:1206–1214].

Kidney Stones May Increase Women's CHD Risk

A history of kidney stones is associated with an increased risk of coronary heart disease (CHD) in women but not in men, reports a study in the *Journal of the American Medical Association*.

The analysis included data on a combined group of more than 45,000 men and 196,000 women from three prospective follow-up studies of health care professionals, all initially free of CHD. A history of kidney stones was analyzed as a risk factor for CHD, defined as fatal or nonfatal myocardial infarction (MI) or coronary revascularization.

Overall, 8.1 percent of participants had a history of kidney stones. At follow-up times of up to 24 years in men and 18 years in women, there were nearly 17,000 incident cases of CHD.

A history of kidney stones was associated with a higher risk of CHD in women. The CHD incidence rate was 754 versus 514 per 100,000 in one cohort of female registered nurses and 144 versus 55 per 100,000 person-years in a second cohort. In multivariable analyses, the hazard ratios for CHD associated with kidney stones were 1.18 and 1.48, respectively.

For women, kidney stones were associated with the individual outcomes of fatal and nonfatal MI and revascularization. Men showed no association between kidney stones and CHD risk.

The prevalence of kidney stones appears to be increasing. Some previous studies have found an increased risk of MI among patients with a history of kidney stones.

The new analysis supports the association between kidney stones and CHD in women, although not in men. The authors discuss possible explanations, including cardiovascular risk factors, shared dietary risks, and deterioration of kidney function related to kidney stones. Further study will be needed to evaluate these mechanisms and to determine whether an association is truly sex specific [Ferraro PM, et al. History of kidney stones and the risk of coronary heart disease. *JAMA* 2013; 310:408–415].

Early Invasive Treatment for ACS Increases Risk of AKI

For patients with acute coronary syndrome (ACS), early catheterization may increase the risk of acute kidney injury (AKI) but is also associated with better long-term survival, concludes a study in the *British Medical Journa*l.

Health data from Alberta were used to identify about 10,500 patients treated for non-ST elevation ACS between 2004 and 2009. Patients with AKI and control individuals free of AKI were stratified by baseline estimated GFR and then matched according to a propensity score for early invasive treatment—i.e., coronary catheterization within 2 days. Early invasive treatment was analyzed as a risk factor for AKI, kidney injury requiring dialysis, progression to ESRD, and death of any cause.

Overall, about 41 percent of patients underwent early invasive treatment. Compared with similar patients treated conservatively, the group receiving early invasive treatment had a modest but significant increase in AKI risk: 10.3 versus 8.7 percent, risk ratio 1.18. The rate of AKI patients requiring dialysis was low in both groups: 0.4 and 0.3 percent, respectively. At a median 2.5 years of follow-up, the rate of progression to ESRD was also similar between groups: 0.3 and 0.4 events per 100 person-years.

However, all-cause mortality was significantly lower in the group receiving early invasive treatment: 2.4 versus 3.4 events per 100 person-years, risk ratio 0.69. Analyses of patients with reduced kidney function at baseline and with the use of different definitions of early invasive treatment showed similar patterns.

When indicated, early invasive treatment for ACS improves long-term survival. The new study is one of the first to compare AKI risks and consequences in ACS patients undergoing early invasive versus conservative treatment.

The results show a small but significant increase in AKI risk with early invasive treatment. However, there was no difference in the rates of AKI requiring dialysis or progression to ESRD, whereas early invasive treatment was associated with improved survival. "[T]hese results suggest that invasive treatments should not be withheld solely because of concern they might increase the risk of kidney injury," the researchers write [James MT, et al. Renal outcomes associated with invasive versus conservative management of acute coronary syndrome: propensity matched cohort study. *BMJ* 2013; 347:f4151].

Androgen Deprivation Therapy Linked to AKI Risk

Men with prostate cancer undergoing androgen deprivation therapy (ADT) may be at increased risk for acute kidney injury (AKI), according to a report in the *Journal of the American Medical Association*.

British general practice and hospital databases were used to identify 10,250 men with newly diagnosed, nonmetastatic prostate cancer. Patients with incident AKI were matched with as many as 20 control individuals. The association between receipt of ADT—classified as gonadotropin-releasing hormone agonists, oral antiandrogens, combined androgen blockade, bilateral orchiectomy, estrogens, or a combination of these—and the occurrence of AKI was assessed.

A total of 232 incident cases of AKI occurred during a mean follow-up time of 4.1 years, for a rate of 5.5 cases per 1000 person-years. Current ADT users were at increased risk for AKI, compared with those who never received ADT: odds ratio (OR) 2.48. The difference in incidence associated with AKI was 4.43 per 1000 persons per year. With adjustment for all potential confounders, the OR was 2.68.

The ADT-associated increase in risk mainly reflected the use of combined androgen blockade with gonadotropin-releasing hormone agonists plus oral antiandrogens (OR 4.50), estrogens (OR 4.00), other ADT combinations (OR 4.04), and gonadotropin-releasing hormone agonists (OR 1.93). The association weakened after the first year of ADT use but remained significant at longer follow-up times.

Androgen deprivation therapy can delay progression in men with advanced prostate cancer. However, ADT-induced testosterone suppression may adversely affect renal function.

This study found an increased rate of AKI among men with nonmetastatic prostate cancer receiving various types of ADT, with evidence of a possible additive effect. The authors call for further studies to confirm the association between AKI and ADT and to determine its clinical significance [Lapi F, et al. Androgen deprivation therapy and risk of acute kidney injury in patients with prostate cancer. *JAMA* 2012; 310:289–296].

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Industry Spotlight

A New Type of Anemia Drug

A new type of erythropoietin product may be coming soon for patients with chronic and advanced kidney disease in whom anemia may develop.

AstraZeneca, the second largest pharmaceuticals firm in the United Kingdom, had a dwindling drug pipeline and has completed a deal with FibroGen, a biotechnology company in the United States, for an experimental anemia drug, several news outlets reported recently. AstraZeneca paid for rights to a drug that could be worth more than $815 million.

FG-4592 is the name of the new compound, which is delivered in pill form rather than the conventional injection for anemia brought on by chronic kidney (CKD) disease and end stage renal disease (ESRD).

The treatment is the first of a new type of drug for kidney patients that boosts the production of red blood cells by making the body react as if it is at high altitude and needs more cells for oxygen delivery.

Pharmaceutical researchers believe that such drugs could create a new market in treating anemia and other serious conditions, including circulatory problems and wound damage, Reuters reported. The drug may someday be developed for other anemia conditions, AstraZeneca said on its website.

Right now, AstraZeneca will pay $350 million up front, plus development-related milestone payments of up to $465 million, for a total of $815 million for rights to FG-4592 in the United States, China, and selected markets. The Reuters news service said that there could be additional payments "if use of the drug is expanded beyond the initial target of treating anaemia [sic] in patients with chronic kidney disease and end stage renal disease."

The drug is a small-molecule compound that stops the activity of hypoxia-inducible factor prolyl hydroxylase in anemia patients with CKD. According to AstraZeneca, the drug brings about a natural response to conditions of low oxygen and turns on the process of making red blood cells. FG-4592 has been shown to correct anemia and maintain hemoglobin levels "without the need for supplementation with intravenous iron in CKD patients not yet receiving dialysis and in end stage renal disease patients receiving dialysis," the company noted.

Thomas B. Neff, chief executive officer of FibroGen, said that FG-4592 could offer anemia patients an easier oral therapy "that provides coordinated erythropoiesis [production of red blood cells], that increases natural erythropoietin within the normal physiological range, and that is effective without intravenous iron supplementation and without an increased risk for hypertension."

Neff said that AstraZeneca and FibroGen would make China the first-to-launch country for FG-4592 and that the companies want to innovate in the area of anemia therapy to CKD and ESRD patients in the United States, where clinical trials would be fully funded under the terms of the agreement.

Pascal Soriot, AstraZeneca's chief executive officer, said that the collaboration on FG-4592 is "an important addition to AstraZeneca's growing late-stage portfolio in cardiovascular and metabolic disease," one of the company's core therapy areas. "We know from our research into complications of renal disease that anemia continues to be a challenge for patients with chronic kidney disease, due in part to the inconvenience and complexity of existing injectable and intravenous therapies and the safety concerns associated with them," Soriot said.

U.S. Renal Care Makes Acquisition

U.S. Renal Care (USRC), based in Plano, TX, has nearly doubled its business reach by acquiring Ambulatory Services of America (ASA), an evidence-based practice of dialysis and radiation oncology services in Brentwood, TN.

The merger will nearly double USRC's current patient volume to about 14,000 with operations in more than 200 outpatient, home, and specialty hospital dialysis programs and facilities, business website Modern Healthcare reported. ASA had 79 dialysis centers at the time of the merger.

"Doubling the size of U.S. Renal Care means both greater access for patients and greater operational efficiency," USRC CEO Chris Brengard said. "We could not have chosen a better partner than ASA, given our mutual commitment to personal, professional dialysis care and our emphasis on physician-led facilities."

But even after doubling its dialysis business, the merged company stands at less than 10 percent of the total dialysis services market, according to ASA executive vice president and general counsel Doug Chappell, *Modern Healthcare* reported. The lion's share comes from Fresenius Medical Care, based in Germany, and DaVita, based in Denver. According to the Fresenius website, Fresenius North America has 64 percent of the parent company's approximately 257,916 patients, or about 165,000 patients.

As of June 30, 2013, DaVita reported operating or providing "administrative services at 2010 outpatient dialysis centers located in the United States serving approximately 159,000 patients."

Nxstage has a Record-Breaking Quarter, New Project

NxStage, which is a maker of home-based dialyzers as well as models for health care setting use, set a revenue record in its last financial quarter and had noteworthy sales of its home-use dialysis systems.

Revenue for the second quarter of 2013 increased 11 percent to $65.5 million. The same quarter in 2012 showed revenue of $59 million.

The company's financial report said that "higher revenues were driven by increased adoption of the NxStage System One" model, designed for home use. Home sector revenue increased to $32.7 million for the second quarter of 2013, compared with revenue of $30.7 million for the second quarter of 2012.

"Our results reflect solid progress and early benefit from our strategic growth initiatives, including our new, direct to patient marketing programs," said Jeffrey H. Burbank, who is NxStage's founder and CEO. Looking ahead, he said that the company believes its efforts to "further penetrate both the United States and international markets are on track to deliver 15 percent annual revenue growth in 2014 and beyond."

Although the home sector had the largest percentage increase in revenues, the company's other sectors also grew: critical care revenue increased to $10.8 million for the second quarter of 2013 compared with revenue of $9.4 million for the same quarter in 2012. In-center revenue (in dialysis centers) increased to $21.2 million for the second quarter of 2013, up from revenue of $18.2 million for the second quarter of 2012.

In late July, NxStage, based in Lawrence, MA, and other partners announced that they would team up on a new filtering device to remove harmful bacteria from blood. That project is part of the Defense Advanced Research Projects Agency (DARPA) and its goal is to develop an innovative medical filtration device that could save the lives of soldiers—and civilians—by treating them for sepsis. Up to 10 percent of combat wounds result in life-threatening infections that ultimately lead to sepsis conditions, announced Battelle, lead and coordinating partner in the project. Sepsis is also a problem for some patients in hospitals, especially those in septic shock.

DARPA created the Dialysis-Like Therapeutics (DLT) program to develop a portable device that creates a treatment for sepsis. The plan is for a final device that can remove blood from the body, separate harmful "dirty" agents from the blood and return "cleaned" blood to the body in a manner similar to dialysis treatment for kidney failure. Several organizations are working on various aspects of a system that will work in the field.

Subcontractor NxStage will design, develop, and ultimately manufacture and distribute the medical device once it obtains the proper regulatory approvals, after the device successfully passes through clinical trials in both military and nonmilitary settings.

Technology website Gizmodo said DARPA has made significant investments in its DLT effort to date to multiple contractors for the development of key blood purification and diagnostic technologies that could contribute to the device. For example, Harvard's Wyss Institute is developing a device that accepts blood infused with nanotubules designed to attract harmful bacteria. The nanotubule-bound bacteria are magnetized to stay in the device, and the cleaned blood is returned to the body.

Kick off ASN Kidney Week 2013 with Early Programs

The following 1- or 2-day courses (November 5–6) require separate registration from the ASN Annual Meeting (November 7–10).

- Advances in Research Conference: From Molecules to Man to Main Street: The Impact of Innovations in Translational Science
- Business of Nephrology: Emerging Fronts and Opportunities
- Critical Care Nephrology: 2013 Update
- CVD in CKD: What's in the Toolbox...and What to Do with Results
- Diagnosis and Management of Disorders of Acid-Base, Fluid, and Electrolyte Balance
- Dialysis Facility Medical Directorship
- Fundamentals of Renal Pathology
- Geriatric Nephrology: Patient-Centered Care for Elderly Patients with CKD
- Glomerulonephritis Update: Diagnosis and Therapy 2013
- In-Service Exam
- Kidney Transplantation
- Maintenance Dialysis: Principles, Practical Aspects, and Case-Based Workshops
- Maintenance of Certification: NephSAP Review and ABIM Modules
- NephroPrevention
- Onco-Nephrology: What the Nephrologist Needs to Know about Cancer and the Kidney
- Professional Development Seminar
- Update on Polycystic Kidney Disease: Translating Mechanism into Therapy

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Policy Update

Bringing HOPE to a Divided Congress

HOPE Act Would Lift Ban on Transplanting HIV+ Organs in HIV+ Patients

By Mark Lukaszewski

Legislation to end a 1980s-era federal ban on the transplantation of organs from deceased HIV+ donors to patients with HIV is moving forward in Congress. At a time when reaching across the aisle is rare, the overwhelming bipartisan support for the HIV Organ Policy Equity Act (HOPE Act) and its rapid advancement in the House and Senate underscore the importance of this legislation.

Research indicates that lifting this medically outdated ban could add up to 600 organs per year for HIV-infected transplant candidates. That means patients with HIV could get faster access to a new supply of HIV+ organs. This would not only help individuals with HIV, but would reduce the organ shortage for the more than 95,000 Americans currently on a transplant waitlist—with or without HIV—who are in the same organ pool.

Momentum in the Senate and House

In a political environment where very little legislation is being passed, the HOPE Act has quickly advanced since its introduction on February, 14, 2013, by Sen. Tom Coburn (R-OK) and Sen. Barbara Boxer (D-CA) in the Senate, and by Rep. Lois Capps (D-CA) and Rep. Andy Harris (R-GA) in the House. Less than 5 months later, the bill had passed the Senate with one amendment by unanimous consent on June 17, 2013. Building off this momentum, the House of Representatives Energy & Commerce Committee slated the HOPE Act for markup—the final hurdle before reaching the House floor for a vote—on July 17, 2013, where it was again unanimously approved with no objections.

ASN has made the HOPE Act a policy priority, and in doing so, ASN staff has met with nearly one in three of the members of the House of Representatives offices who ultimately cosponsored the HOPE Act. ASN has been working with an extremely diverse group of advocacy organizations, ranging from the HIV and LGBT communities to medical and transplant societies. This broad support is not limited to the public sector. Because of the tremendous bipartisan support, it is possible that the House version of the HOPE Act will be passed under suspension of the rules—a procedure used to quickly pass noncontroversial bills. Since the HOPE Act has already passed the Senate, and looks to be able to pass the House of Representatives, the next step would be the President's desk, making the Hope Act one of only a handful of bills to be signed into law in the 113th Congress.

Benefits for patients, physicians, and taxpayers

The HOPE Act is a scientifically sound, no-cost bill, which could increase access to transplantation, potentially saving lives and millions of dollars by eliminating the need for dialysis, which can cost upwards of $80,000 annually per patient. Most important, passage of this bill could make a significant difference for patients and their families who are waiting for the gift of life.

ASN will remain in close contact with the staff of the bill's sponsors and will provide consistent updates to ASN members as further developments occur.

A Preview of This Fall's Congressional Budget Showdown

By Grant Olan

These days, it seems that Congress lurches from one fiscal crisis to the next with another one set for this fall. The clock for passing a budget for Fiscal Year 2014, which begins on October 1, is quickly running out. If Congress fails to pass a budget or appropriations funding government services beyond that date, non-essential federal offices will be closed and non-essential employees furloughed. While the impact on health care would be minimal—Medicare and other mandatory federal programs would still operate—public health and medical research programs would be in jeopardy.

Congress faces a number of challenges. For one, the House of Representatives and Senate are unable to agree on funding levels for each of the 13 appropriation bills. The Senate budget levels are above funding caps established by the 2011 Budget Control Act passed by Congress to cut the federal deficit. The House and Senate have not had a conference to reconcile their funding levels for each of the appropriation bills. Complicating matters, the United States will again hit the "debt ceiling" this fall, the legal limit of how much debt the government can assume. Some Republicans say they will refuse to raise the debt ceiling unless there are more federal budget cuts.

If Congress does manage to pass a budget that raises funding levels beyond the existing caps, lawmakers must also amend the 2011 Budget Control Act. Otherwise there will be an across-the-board cut, known as "sequestration," to bring federal discretionary spending program budgets in line with the caps, including budgets for the Agency for Healthcare Research and Quality (AHRQ) and National Institutes of Health (NIH)." The FDA and NIH have already sustained significant cuts. NIH's budget in 2013 was $29.1 billion compared to $30.6 billion in 2012. The budget for the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), the largest source of federal funding for kidney research, was cut $99 million in 2013 (Table 1).

"These cuts will mean fewer and smaller research projects aimed at finding treatments and cures for kidney disease, and lost jobs," said John R. Sedor, MD, ASN Research Advocacy Committee chair. "ASN remains committed to protecting NIH, NIDDK, and the rest of the medical research enterprise from more cuts under sequestration and has teamed up with NDD United, a national coalition of 3200 organizations, to fight back."

"We are facing a time where prominent scientists in the field of nephrology are unsure how and if they will be able to maintain their laboratories over the next several years," added ASN Research Advocacy Committee Member Jordan A. Kreidberg, MD, PhD. "The field was already in crisis before the sequester, now it is in uncharted territory."

How have NIH budget cuts affected your research?

ASN recently launched a survey to collect feedback from its members on how cuts might affect (or have affected) them to share with Congress. The society is also looking for volunteers to provide tours of their labs and/or institutions for members of Congress and their congressional staff so they can learn about the benefits of research. To complete the survey and volunteer, go to http://www.surveymonkey.com/s/XYBFX6Q.

Table 1. Impact of sequestration on federal research budgets

*Dollars in Millions	FY13 Budget (operating under FY12)	After Sequestration (VA exempt)	Difference
AHRQ	$369	$350	**$19**
CDC	$5, 657	$5,368	**$289**
FDA	$2,506	$2,378	**$128**
NIH	$30,632	$29,070	**$1,562**
NIDDK	$1,947	$1,848	**$99**
VA Research	$581	$581	**$0**

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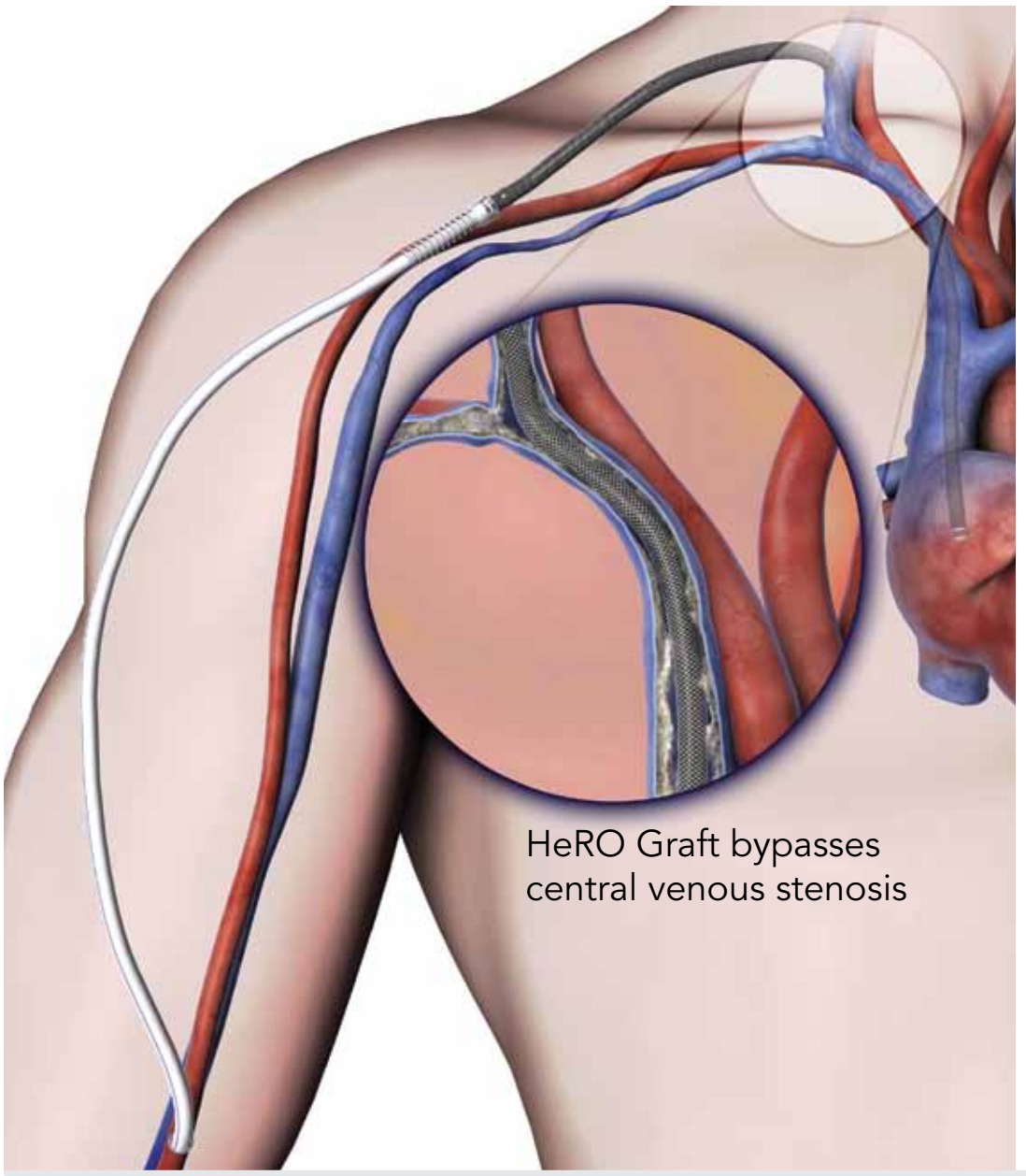

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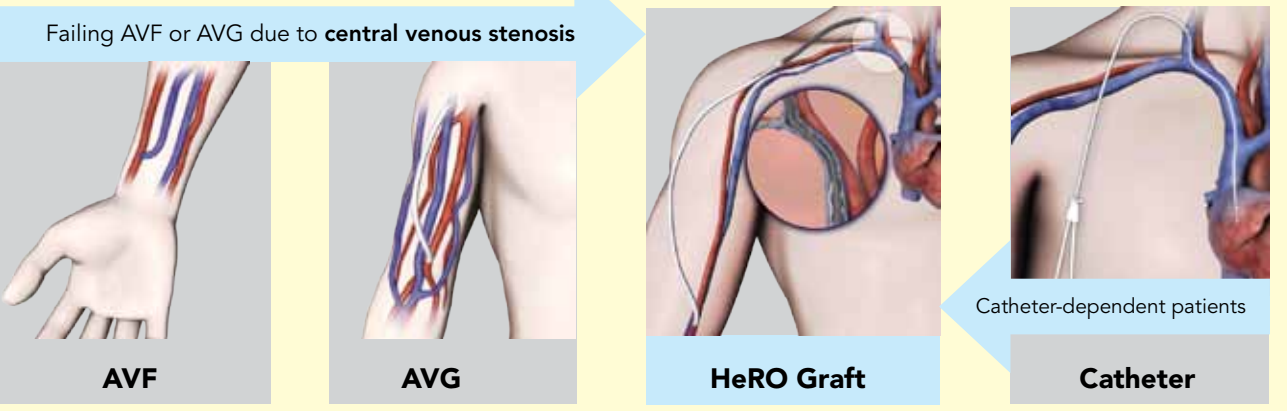

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References:
1) Katzman et al., J Vasc Surg 2009. 2) Gage et al., EJVES 2012. 3) Dageforde et al., JSR 2012.

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