ASN LEADING THE FIGHT AGAINST KIDNEY DISEASE

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Slow Walking Speed Linked with Premature Death in Patients with Chronic Kidney Disease

Because chronic kidney disease (CKD) leads to the retention of metabolic waste products and hormonal disturbances, patients often experience skeletal muscle loss and dysfunction. New research published in the *Journal of the American Society of Nephrology* looks into a potential link between CKD patients' impaired mobility and reduced physical performance and their risk of dying prematurely.

"Physical performance tests are objective measures used in gerontology to assess frailty, risk of disability, and to measure global comorbid burden," said first author Baback Roshanravan, MD, of the University of Washington. "Little is known about physical performance and its association with all-cause mortality in younger CKD patients not treated with renal replacement therapy who are free of stroke and disability in their activities of daily living."

Trial results

Roshanravan and his colleagues followed 385 patients with CKD without a history of stroke or disability and with an average age of 61 years and an average estimated GFR of 41 mL/min per 1.73 m^2. Through various tests, the researchers compared handgrip strength, usual walking speed, six-minute walking distance, and timed up and go (the time that a person takes to rise from a chair, walk 4 meters, turn around, walk back to the chair, and sit down). The researchers were hoping to characterize patients' physical performance and evaluate the utility of physical performance assessment in a referred clinic-based population of patients with CKD.

"First, CKD is associated with poor

Continued on page 3

New HIPAA Compliance Requirements Take Effect

By Kurtis Pivert

Newly enacted legislation has changed requirements for compliance with the Health Insurance Portability and Accountability Act (HIPAA). The new provisions of the Health Information Technology for Economic and Clinical Health (HITECH) Act strengthen security measures for Protected Health Information (PHI) and step up auditing and enforcement.

Although the law took effect March 26, physicians and other covered entities have until September 23, 2013, to comply with the new, wide-ranging regulations. The provisions are outlined in the Omnibus Final Rule.

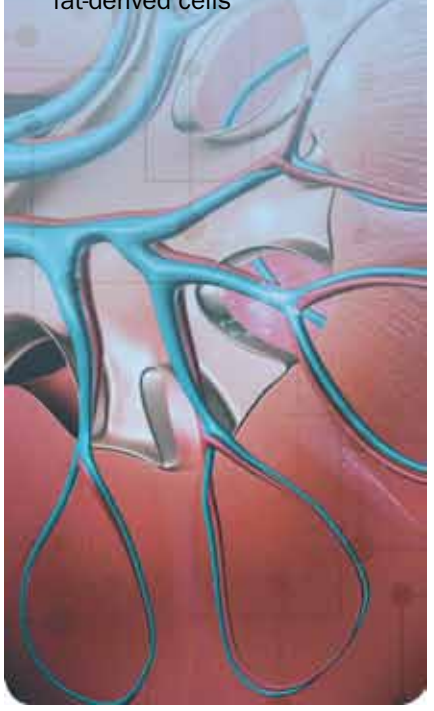
Changes for providers and patients

Among the legislation's significant changes is the broadened definition of a "business associate" (and extension of HIPAA compliance and liability under the law) to include any vendor storing PHI (e.g., electronic health record [EHR] companies) or any subcontractor that uses PHI to generate payments. These entities are now liable even if the practice doesn't have a business agreement with them. The law also requires that existing contracts with business associates be updated to reflect the new regulations.

The criteria for a PHI breach have been revised from the subjective "risk of harm" standard to a more objective test. A breach is now presumed to have occurred unless the covered entity can

Continued on page 3

Inside



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Slow Walking Speed

Continued from page 1

physical performance compared to the healthy population," Roshanravan said. "Second, objective physical performance testing is an important bedside clinical tool that adds to the value of regular laboratory assessment of kidney function in discriminating those at high risk of mortality even among those without a history of stroke or disability in their activities of daily living."

During an average of three years of follow-up, the investigators found that measures of lower extremity performance were at least 30 percent lower than predicted. Each 0.1-meter-per-second slower walking speed was linked with a 26 percent higher risk for death, and each one-second longer timed up and go was linked with an 8 percent higher risk for death. These associations were also seen even after excluding the subgroup with baseline self-reported mobility disability.

Walking speed and timed up and go more strongly predicted three-year mortality than kidney function or common blood tests. Adding walking speed to common laboratory tests of kidney function significantly improved the prediction of three-year mortality.

"We discovered that even after accounting for renal function, diabetes, and coronary artery disease, worse lower extremity physical performance was associated with all-cause mortality, but unexpectedly, this association after adjusting for renal function and comorbid illness was not seen with handgrip strength," Roshanravan said. "Our findings suggest that lower extremity physical performance testing in chronic kidney disease patients may help identify those individuals who are more burdened by their CKD."

Other experts agree that the findings may have a significant clinical impact.

"This novel study demonstrates that physical performance measures can improve the health assessment of persons with advanced chronic kidney disease. The key advantages of these measures are that they are low cost, non-invasive, and highly informative," said Michelle Odden, PhD, who was not involved with the study and is an assistant professor of epidemiology at Oregon State University. "Additionally, these physical performance measures may provide insight into the systemwide health effects of chronic kidney disease."

Odden's research focuses mostly on kidney disease, cardiovascular outcomes, and loss of physical function in older adults.

Additional studies needed

As with any observational study, caution must be taken in this case against ascribing a causal relationship between lower extremity physical performance. The study provides no insights on whether lower physical activity may be a consequence of or a cause of lower physical performance in individuals with CKD.

Roshanravan also noted that the follow-up time in the study may not have been sufficiently long enough to detect significant differences in survival between those with strong and weak grip strength.

While more research is needed, the study's findings suggest that measuring lower extremity physical performance may capture a complex set of skeletal muscle and neurologic impairments that develop in CKD patients and substantially affect their survival. The authors encourage additional investigations that look into the biological mechanisms underlying decreased physical performance in patients with CKD and that evaluate whether interventions that improve physical performance in CKD translate to improvements in health and longevity.

Study co-authors include Cassianne Robinson-Cohen, PhD, Kushang Patel, PhD, Ernest Ayers, Alyson Littman, PhD, Ian de Boer, MD, T. Alp Ikizler, MD, Jonathan Himmelfarb, MD, Leslie Katzel, MD, PhD, Bryan Kestenbaum, MD, and Stephen Seliger, MD.

Disclosures: Dr. Baback Roshanravan was funded by a Ruth L. Kirschstein National Research Service Award (NRSA) and T32 grant from the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK). The authors reported no other financial disclosures.

HIPAA

Continued from page 1

demonstrate, through a risk assessment, that there was a low probability that PHI was disclosed. Provisions in the HITECH Act also strengthen compliance and enforcement of HIPAA regulations by instituting audits for all covered entities—large and small—and by increasing civil and criminal penalties for unauthorized disclosure of PHI.

Other sections of the HITECH Act directly affect patients, who now have to provide additional authorization before their PHI can be disclosed for payment of services. If a medical practice uses EHRs, patients now have the right to obtain an electronic copy of their records.

Preparing for compliance

Before the September 23 deadline, physicians, office staff, and business associates will have to take several steps to meet the new HIPAA compliance requirements.

One of the first actions covered entities will need to take is to appoint a privacy officer and security officer. The practice's current privacy and security policies and procedures will need to be revised to align with new provisions, and be updated on a regular basis. These should include policies on securing portable electronic devices that may store PHI, as well as protocols to destroy any information on devices that may become compromised. Procedures for encrypting and securely transferring PHI electronically should also be included.

Staff members who use PHI (e.g., those working in the coding or billing departments) must become familiar with new office policies and HIPAA requirements. To ensure that practices are prepared for the new enforcement mechanisms, in-house audits and risk assessments should be conducted to identify and correct any potential compliance issues.

Patient privacy notices

Patient privacy notices must be revised to reflect the requirements for additional authorization before disclosure of PHI for processing payment of services. Entities must also prepare methods to provide copies of a patient's electronic PHI when requested.

Procedures for how staff should identify, investigate, and report a potential breach of PHI should be drafted and reviewed regularly. Finally, all agreements with business associates need to be updated to reflect the extended HIPAA definition and liability.

Designed to protect and secure sensitive patient data, the new HITECH Act provisions will affect all health care providers this year. For more information on HIPAA and the requirements implemented under the Omnibus Final rule, visit http://www.hhs.gov/ocr/privacy/index.html.

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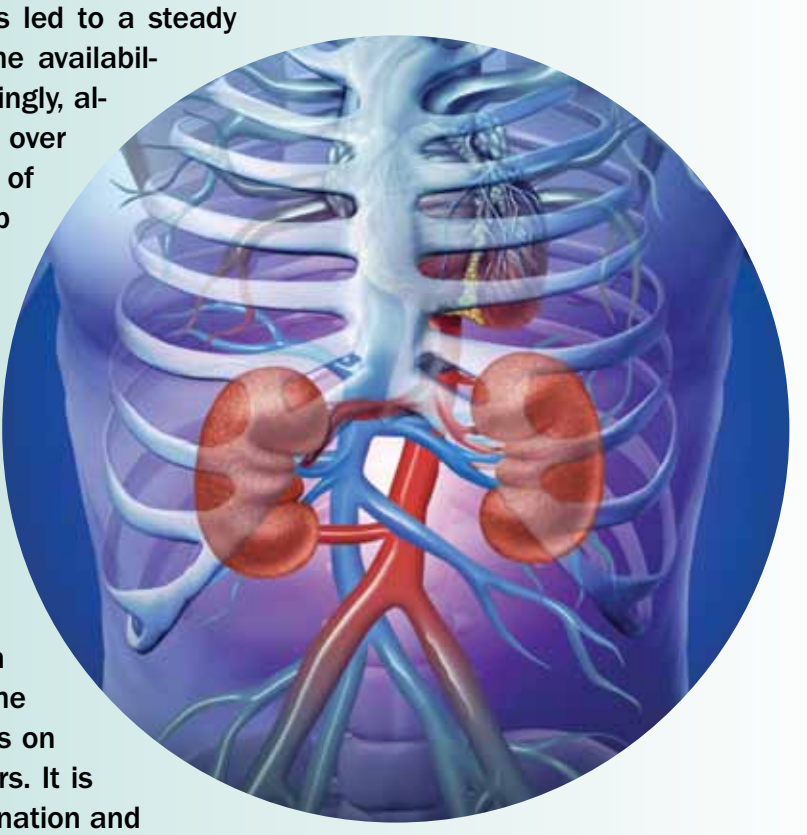
The Living Kidney Donor

By Sindhu Chandran and David Wojciechowski



The increasing prevalence of end stage renal disease (ESRD) has led to a steady growth in the kidney transplant waiting list, rapidly outpacing the availability and transplantation of organs from deceased donors. Interestingly, although overall living donation rates have remained relatively static over the last several years the one exception is a rise in the number of living non-spouse unrelated donors, including altruistic donors. The first step in addressing the disparity between the waiting list and access to living donation involves education of the public about the process of living kidney donation. It is our responsibility as a medical community to emphasize donor safety and insist upon data to support the appropriate medical counseling of donors.

In this special issue of *ASN Kidney News*, we address issues pertinent to donor health and safety by drawing upon the experience and knowledge of experts in the field. First, we bring you the latest trends in donor screening and advances in the donor surgical procedure. In order that physicians may better counsel potential donors, long-term outcomes in living kidney donors are discussed next. Given the disproportionately high incidence of ESRD in racial and ethnic minorities, we then review unique issues associated with the evaluation of potential donors in these vulnerable groups, with an emphasis on long-term donor health. We then discuss the appropriate follow-up of donors. It is our hope that this series will improve your understanding of living kidney donation and better equip you to counsel patients and families about living donation.

Sindhu Chandran, MBBS, and David Wojciechowski, DO, editors of this special section, are assistant clinical professors of medicine in the division of nephrology at the University of California, San Francisco.

Trends in the Screening and Acceptance of Living Kidney Donors

By Didier A. Mandelbrot

The use of living donors for kidney transplantation in the United States has become increasingly common, with recipients of a living donor kidney demonstrating better outcomes and shorter waiting times. Substantial differences exist between transplant centers in their choice of protocols and exclusion criteria for potential living donors. Nevertheless, certain trends in living donation practices over the past 20 years, reflecting a relaxation of some acceptance criteria and a tightening of others, have become apparent from surveys of transplant programs (1) and analysis of registry data collected by the United Network for Organ Sharing (UNOS) (2).

Donor-recipient relationships

One of the most dramatic trends among living donors is in the relationships between donors and recipients. Over the past 12 years, genetically unrelated, nonspousal donors have more than doubled (Figure 1). In a 1986 survey, only 16 percent of transplant programs in the United States reported that they would accept living unrelated donors—compare this to 31 percent in 1995 and 100 percent in 2007. The acceptance of nondirected (altruistic or Good Samaritan) donors has also increased, from 8 percent of programs in 1989 to 38 percent in 2000 to 61 percent in 2007.

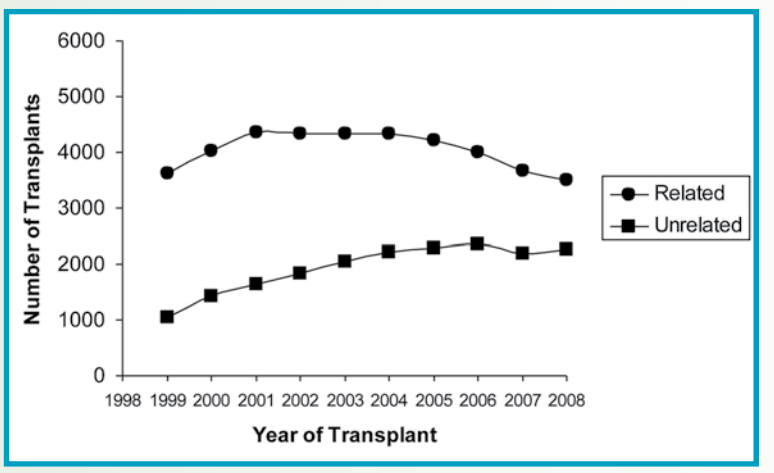
Donor age

Living kidney donors are now older. In 2008, 1.5 percent of living kidney donors were over the age of 65, compared to 0.7 percent in 1988. Between 1995 and 2007, the percentage of programs without a set upper-age limit more than doubled to 59 percent. In contrast, programs became stricter with respect to younger candidates. No programs reported an age cutoff of 14 or 16 years in 2007, and almost none reported having no lower age limit at all. Quantitatively, however, young donors are less common than older donors, so the increase in the median age of donors from 35 to 41 years between 1988 and 2008 suggests an overall trend toward less restrictive age criteria for donors.

Kidney function

Most transplant programs in the United States continue to use a 24-hour collection to measure creatinine clearance, although some use a direct measure of GFR (e.g., iodinated marker) or an estimated GFR formula. Although UNOS data suggest no statistically significant changes in the mean serum creatinine or eGFR of donors over the past decade, surveys indicate changes in specific practices. In contrast to1995, when some programs reported using lower creatinine clearance cutoffs of 60 mL/min/1.73 m^2 or even 40 mL/min/1.73 m^2, by 2007 no programs reported using a cutoff below 80 mL/min/1.73 m^2.

Figure 1. Trends in living related versus living unrelated, nonspousal donors in the United States.



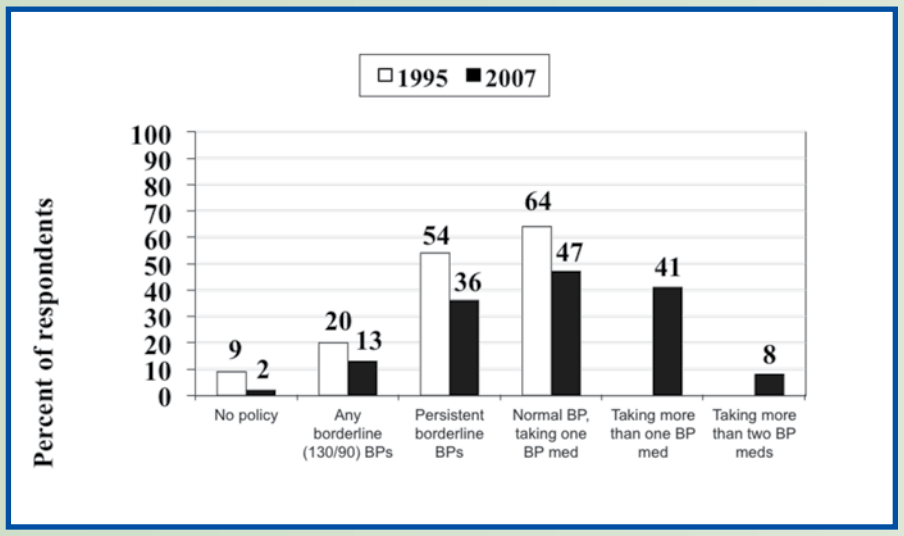
Data from www.UNOS.org.

Continued on page 6

Trends

Continued from page 5

Figure 2. Exclusion criteria by category of blood pressure reported in surveys from 1995 and 2007.



From Mandelbrot et al. (1). Abbreviation: BP = blood pressure.

Hypertension

Exclusion criteria for blood pressure have become less restrictive, although they remain highly variable among centers. In 1995, most programs excluded candidates taking antihypertensive medications or having borderline hypertension. By 2007, 47 percent of programs excluded candidates on any antihypertensive medication, but 41 percent excluded donors only if they were taking more than one medication, and 8 percent excluded donors only if they were taking more than two medications (Figure 2). This trend may be partly due to data suggesting that donation by selected patients with well-controlled hypertension appears to be safe in the short term.

Thus, significant variability remains among transplant programs in the medical criteria used to evaluate donors, but there are clear overall trends. Protocols for the evaluation of potential donors will continue to evolve as more data on outcomes emerge, especially regarding medically complex donors.

Didier A. Mandelbrot, MD, is medical director of the Living Kidney Donor Program at Beth Israel Deaconess Medical Center, director of clinical trials at the Transplant Institute, and associate professor of medicine at Harvard Medical School, in Boston.

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Advances in Living Donor Nephrectomy

By Dorry Segev

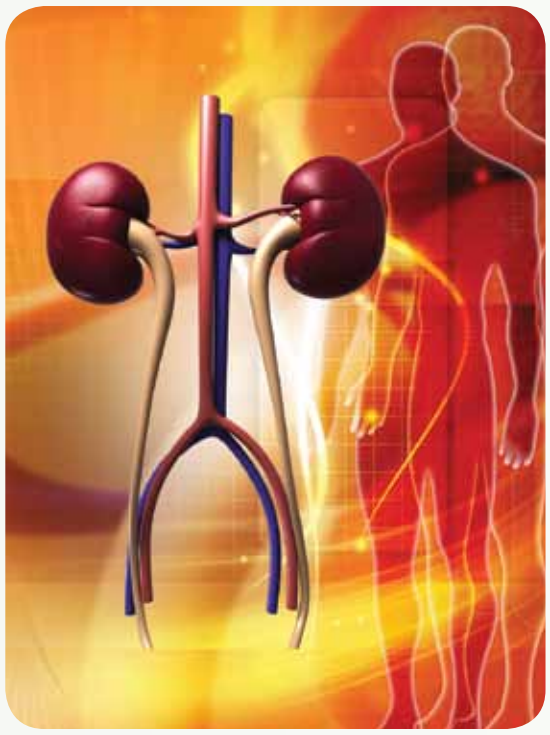
In 1995, Ratner, Kavoussi, and colleagues at Johns Hopkins University revolutionized live kidney donor transplantation through the development of the laparoscopic donor nephrectomy (1). Since then, the number of live donor transplants in the United States doubled, the number of live donors who are not biologically related to the recipient rose by more than fivefold, and the proportion of donor nephrectomies performed laparoscopically (or laparoscopically assisted) neared 100 percent. Today, approximately one-third of donor nephrectomies are performed using pure laparoscopic techniques, and approximately two-thirds are performed with the additional insertion of one of the surgeon's hands into the abdomen.

In an effort to further minimize the already minimally invasive donor nephrectomy, several approaches have been recently explored. One concept reported by multiple centers, first among urologists excising diseased kidneys and later for the purposes of donation, is the single-port approach (2). Instead of separate ports for dissection and an additional (usually Pfannenstiel) incision for extraction of the kidney, a multiport device is placed through a peri-umbilical incision, and through this device are introduced all of the dissecting instruments. When the kidney is ready for extraction, it is removed through the same peri-umbilical incision after removing the multiport device. Obviously, the size of this incision is the Achilles heel of this approach, and the size can vary based on the size of the kidney and the size of the patient. In the setting of excising diseased kidneys, the kidney can be removed piecemeal and generally does not require an umbilical incision larger than the smallest possible dissecting multiport. However, in the setting of kidney donation, obviously the kidney must be removed intact without any compromise to its anatomic integrity, and this defines the length of the incision. While patients are reportedly pleased with the cosmetic results, demonstrating medical benefits has been more challenging in the early experience of this operation. It remains unclear if the risks associated with this technique, including the narrower window of laparoscopic instrument triangulation, are outweighed by its benefits.

We recently described a modified laparoscopic technique that maintains the traditional dissection ports (and hence the window of triangulation) but obviates the larger incision for extracting the kidney. Instead of using the traditional Pfannensteil extraction, our team, led by Robert Montgomery, removed the kidney transvaginally through a posterior colpotomy used to communicate with the abdomen (3). Patient outcomes were excellent, including a very short postsurgical hospital stay, minimal need for analgesia, and no apparent sequelae of the colpotomy; however, the total world experience with this procedure remains very small.

While surgical innovations are exciting and possibly compelling, they must be explored in the context of maximizing patient safety. Recent reports by Friedman, Ratner, and Peters of persistent use of Hem-o-Lok clips, despite clear evidence that these non-transfixing clips have on multiple occasions dislodged from the renal artery and led to donor deaths, are sobering reminders of the need to maintain patient safety above all else (4). Unfortunately, given the extreme rarity of major adverse events in the context of live kidney donation (5), it will likely require large experiences with given innovative surgical approaches before enough evidence can be accumulated to support (or call into question) their safety.

Dorry Segev, MD, PhD, is associate professor of surgery and epidemiology and director of Clinical Research Transplant Surgery at Johns Hopkins University in Baltimore, MD.



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Long-Term Outcomes in Kidney Donors

By Scott Reule and Hassan N. Ibrahim

As donor nephrectomy is entirely performed for the beneficence of the recipient, minimizing surgical morbidity and preserving long-term mortality is a priority. Currently, laparoscopic nephrectomy is associated with less pain, shorter hospital stay and faster return to work, and a calculated mortality rate of 3.1 per 10,000 donors, controlled for age, race, and sex (1,2).

Does kidney donation, with its associated loss of glomerular mass, impart a risk profile similar to that of patients with chronic kidney disease (CKD)? Many studies have demonstrated no significant increase in mortality among donors in comparison to variably matched controls and variable follow-up times. In a larger study, Ibrahim et al. reported on the vital status of approximately 3700 kidney donors, matched for age, sex, race, and BMI over a 40-year time frame. In their analysis, there appeared to be no significant decrease in lifespan and in fact, the donors seemed to outlive their controls (3). Segev et al. demonstrated no significant change in overall survival among more than 80,000 kidney donors compared to age- and comorbidity-matched controls using national registry data (2). Studies in older donors demonstrate similar findings. Berger et al. demonstrated no significant increase in mortality among donors older than 70 years of age (4).

In general, kidney donors are in excellent health as they undergo extensive medical and surgical screening; however, the evidence suggests that reduced GFR may be an independent predictor of all-cause and cardiovascular mortality. Although GFR decline due to nephrectomy versus GFR decline in the setting of comorbid disease are mechanistically different, concerns regarding kidney donation and a possible increased cardiovascular risk remain. Mjoen et al. followed 2269 Norwegian donors for a median of 14.3 years and revealed that overall as well as cardiovascular mortality was lower in donors than the general population matched for age and gender (5). More recently, Garg et al. used extensive exclusion criteria to select for "the healthiest segment" of the general population for comparison with kidney donors. They were able to demonstrate no increased risk of death or cardiovascular event in kidney donors over a median follow-up of 6.5 years with maximum follow-up of 18 years (6).

Current literature suggests that donor outcomes are excellent and the appropriate screening of candidates may contribute to the decreased risk observed. Regardless, considerable interest remains in long-term outcomes among kidney donors as efforts are being made to expand the donor transplantation pool, including use of non-ideal donors. Creation of prospective studies of the less than ideal donors is crucial.

Scott Reule, MD, and Hassan N. Ibrahim, MD, MS, are affiliated with the division of renal diseases and hypertension at the University of Minnesota in Minneapolis, MN.

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Outcomes of Living Kidney Donation in Racial and Ethnic Minority Donors

By Krista L. Lentine and Dorry L. Segev

The expansion of kidney transplantation from living donors over the last several decades has included greater racial and ethnic diversification of the donor population. In the United States, the fraction of non-white living kidney donors rose from 24 percent in 1988 to 30 percent in 2011, representing more than 1700 donors. Currently, 12 percent of living kidney donors in the United States are African American and 13 percent are Hispanic. Because most countries, including the United States, do not currently maintain national registries that effectively track long-term donor outcomes, much of the information on postdonation health has been drawn from single-center, retrospective studies. The largest cohort study of living kidney donors published to date found no adverse impacts of donation on survival or end stage renal disease (ESRD) compared with general population registry controls (1), but notably, more than 98 percent of the sample was white. Racial differences in the burden and consequences of health complications among non-white persons in the general U.S. population are well documented. However, disparities in health after kidney donation have only recently raised attention.

In addition to more complete national collection of postdonation follow-up data, strategies to expand the evidence base for donor counseling and informed consent include database integration projects. Recent linkage of Organ Procurement and Transplantation Network (OPTN) registry data with the Social Security Death Master File demonstrated that while surgical and long-term mortality were higher in African American donors compared with white donors, long-term mortality did not exceed that of matched healthy non-donor controls (2).

Race-related differences in the frequency of ESRD and medical comorbidity after donation are also becoming apparent. Integration of OPTN donation records with Centers for Medicare & Medicaid Services (CMS) ESRD reporting forms revealed that while ESRD is uncommon after kidney donation, the ESRD rate in African American donors is nearly five times that of white donors (3). We linked administrative data from a private insurance provider with OPTN donor registration data and found that compared with white donors, African American donors had a 50 percent higher risk for postdonation hypertension and more than twice the risks of medication-treated diabetes and chronic kidney disease (CKD) diagnoses. Hispanic donors also had twice the risk of CKD and nearly three times the risk of drug-treated diabetes (4). Preliminary data presented at ASN Kidney Week 2012 using similar methods also support consistently higher rates of medical complications in African American and Hispanic donors compared with white donors regardless of sample or payer source (5). While novel methods of risk stratification such as apolipoprotein L1 genotyping in African Americans hold promise for identifying certain high-risk donors in the evaluation phase, the direct impact of donation on medical and renal outcomes after donation remains uncertain.

As policies for the informed consent, medical evaluation, and follow-up of living organ donors are receiving more attention and formalization by the organizations that guide and regulate transplantation practice, continued efforts to strengthen the evidence that underlies best practices applicable to donors with diverse demographic profiles are needed. These efforts should include assembly of healthy controls for assessment of risks directly attributable to donation as an important priority. In the meantime, practitioners should be frank with potential donors about what is currently known and what remains unknown about health outcomes after living donation across racial and ethnic groups.

Krista L. Lentine, MD, MS, is affiliated with the Center for Outcomes Research and the Abdominal Transplant Program at the Saint Louis University School of Medicine in St. Louis, MO. Dorry L. Segev, MD, PhD, is affiliated with the Abdominal Transplant Program, Department of Surgery, Johns Hopkins University, Baltimore, MD.

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Follow-Up of the Living Kidney Donor

By Sindhu Chandran

Transplantation from a living kidney donor provides the best outcomes in recipients with end stage renal disease. However, our knowledge regarding the effects of kidney donation on long-term mental and physical health of the living donor remains incomplete. Published data are largely derived from single-center retrospective studies in young, healthy, and mostly white populations (1), whereas donors in today's environment are increasingly older, larger, racially diverse, and medically complex (2).

We also suffer from a paucity of information on the psychological and socioeconomic consequences of donation, including the long-term health-related quality of life, financial consequences of donation, and potential issues unique to participation in exchange programs or altruistic donation. Since 1999, transplant centers have been required to submit donor follow-up data at 6 and 12 months to the Organ Procurement and Transplantation Network (OPTN), and in 2008 a 24-month follow-up was added. Unfortunately, nationally collected United Network for Organ Sharing (UNOS) living donor follow-up data are often incomplete (3) and do not allow meaningful interpretations of safety and outcomes.

Why do we need better living donor follow-up? Potential donors, particularly if they are nontraditional, need accurate outcomes information on which to base informed consent. Programs need this information to provide reliable counseling during the evaluation process as well as to assess and improve center performance. Surveillance of the donor may also identify individual problems allowing for early intervention.

What are the barriers to living donor follow-up? A survey of transplant centers in the United States (4) found that the most commonly reported barrier was donors not wanting to return to the program, cited by 87 percent of programs. Out-of-date contact information (73 percent) was next, followed by lack of program (54 percent) or donor (49 percent) reimbursement for follow-up costs.

How can we improve the follow-up of living kidney donors? Ideally, longitudinal prospective cohort studies would be conducted to answer our questions regarding donor health. These studies would follow and compare clinical outcomes in donors to a control group of similarly screened and examined individuals who did not donate. However, since kidney donors are generally healthy and have low event rates, the long duration of follow-up needed makes it difficult to recruit subjects and sustain funding for such studies. Retrospective cohort studies are more efficient in terms of time and cost, but limited by response bias and low inclusion rates of minorities. Linkage of UNOS donor registration forms to large databases such as the U.S. Renal Data System or health insurance databases can allow us to track major events, but not all outcomes.

It has been argued that a national donor follow-up registry would achieve a greater degree of follow-up, obtain data on a larger and more diverse donor population, and permit the examination of a broader range of health outcomes (5). The recommendations of a living donor follow-up conference included mandating more complete data collection by transplant centers in the immediate postdonation period, setting up a system of incentives and penalties that would motivate transplant center compliance with the standards, and delegating lifelong follow-up of the living kidney donor to a separate third-party organization that would be responsible for maintaining the registry and for any costs of follow-up (3). Obtaining comprehensive knowledge of the outcomes of donation is critical to providing safe and ethical care to our living kidney donors and building community trust in the system of living kidney donation.

Sindhu Chandran, MBBS, is affiliated with the Division of Nephrology–Kidney Transplant Service at the University of California, San Francisco.

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Introducing a
NEW approach in
type 2 diabetes
treatment...

INVOKANA™ (canagliflozin) is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

INVOKANA™ is not recommended in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis.

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

- History of a serious hypersensitivity reaction to INVOKANA™.
- Severe renal impairment (eGFR <30 mL/min/1.73 m^2), end stage renal disease, or patients on dialysis.

WARNINGS and PRECAUTIONS

- **Hypotension:** INVOKANA™ causes intravascular volume contraction. Symptomatic hypotension can occur after initiating INVOKANA™, particularly in patients with impaired renal function (eGFR <60 mL/min/1.73 m^2), elderly patients, and patients on either diuretics or medications that interfere with the renin-angiotensin-aldosterone system (eg, angiotensin-converting-enzyme [ACE] inhibitors, angiotensin receptor blockers [ARBs]), or patients with low systolic blood pressure. Before initiating INVOKANA™ in patients with one or more of these characteristics, volume status should be assessed and corrected. Monitor for signs and symptoms after initiating therapy.

Please see additional Important Safety Information and Brief Summary of full Prescribing Information on the following pages.

In adults with type 2 diabetes,

NOW AVAILABLE

ENVISION NEW POSSIBILITIES

Introducing INVOKANA™—the first and only treatment option approved in the United States that reduces the reabsorption of glucose in the kidneys via sodium glucose co-transporter-2 (SGLT2) inhibition[1]

A1C Reductions as Monotherapy

INVOKANA™ monotherapy provided statistically significant A1C reductions vs placebo at 26 weeks[1]

A1C Change From Baseline With INVOKANA™ Monotherapy[1]

Effect on Weight*

Statistically significant weight reductions vs placebo at 26 weeks (*P*<0.001)[1]

» Difference from placebo†:
100 mg: −2.2%; 300 mg: −3.3%

Impact on Systolic Blood Pressure (SBP)*

Statistically significant SBP lowering vs placebo at 26 weeks (*P*<0.001)[2]

» Difference from placebo†:
100 mg: −3.7 mm Hg; 300 mg: −5.4 mm Hg

INVOKANA™ is not indicated for weight loss or as antihypertensive treatment.

***Prespecified secondary endpoint.**

†Adjusted mean.

A1C Reductions vs Sitagliptin

INVOKANA™ 300 mg demonstrated greater A1C reductions vs sitagliptin 100 mg, in combination with metformin + a sulfonylurea, at 52 weeks (*P*<0.05)[1]

» Difference from sitagliptin†: −0.37%

Incidence of Hypoglycemia

Monotherapy over 26 weeks:
100 mg: 3.6%; 300 mg: 3.0%; placebo: 2.6%[1]

With metformin and a sulfonylurea over 52 weeks:
INVOKANA™ 300 mg: 43.2%; sitagliptin 100 mg: 40.7%[1]

» Insulin and insulin secretagogues are known to cause hypoglycemia. INVOKANA™ can increase the risk of hypoglycemia when combined with insulin or an insulin secretagogue

Convenient Once-Daily Dosing[1]

» Recommended starting dose: INVOKANA™ 100 mg

» Dose can be increased to 300 mg in patients tolerating 100 mg, who have an eGFR of ≥60 mL/min/1.73 m^2, and require additional glycemic control

The most common (≥5%) adverse reactions were female genital mycotic infection, urinary tract infection, and increased urination.

References: 1. Invokana [prescribing information]. Titusville, NJ: Janssen Pharmaceuticals, Inc; 2013. **2.** Stenlöf K, Cefalu WT, Kim KA, et al. Efficacy and safety of canagliflozin monotherapy in subjects with type 2 diabetes mellitus inadequately controlled with diet and exercise. *Diabetes Obes Metab*. 2013;15(4):372-382.

Learn more at INVOKANAhcp.com/journal

Invokana™
canagliflozin tablets

IMPORTANT SAFETY INFORMATION *(continued from first page)*

WARNINGS and PRECAUTIONS *(cont'd)*

- **Impairment in Renal Function:** INVOKANA™ (canagliflozin) increases serum creatinine and decreases eGFR. Patients with hypovolemia may be more susceptible to these changes. Renal function abnormalities can occur after initiating INVOKANA™. More frequent renal function monitoring is recommended in patients with an eGFR below 60 mL/min/1.73 m^2.
- **Hyperkalemia:** INVOKANA™ can lead to hyperkalemia. Patients with moderate renal impairment who are taking medications that interfere with potassium excretion, such as potassium-sparing diuretics, or medications that interfere with the renin-angiotensin-aldosterone system are more likely to develop hyperkalemia. Monitor serum potassium levels periodically after initiating INVOKANA™ in patients with impaired renal function and in patients predisposed to hyperkalemia due to medications or other medical conditions.
- **Hypoglycemia With Concomitant Use With Insulin and Insulin Secretagogues:** Insulin and insulin secretagogues are known to cause hypoglycemia. INVOKANA™ can increase the risk of hypoglycemia when combined with insulin or an insulin secretagogue. Therefore, a lower dose of insulin or insulin secretagogue may be required to minimize the risk of hypoglycemia when used in combination with INVOKANA™.
- **Genital Mycotic Infections:** INVOKANA™ increases the risk of genital mycotic infections. Patients with a history of genital mycotic infections and uncircumcised males were more likely to develop genital mycotic infections. Monitor and treat appropriately.
- **Hypersensitivity Reactions:** Hypersensitivity reactions (eg, generalized urticaria), some serious, were reported with INVOKANA™ treatment; these reactions generally occurred within hours to days after initiating INVOKANA™. If hypersensitivity reactions occur, discontinue use of INVOKANA™; treat per standard of care and monitor until signs and symptoms resolve.
- **Increases in Low-Density Lipoprotein (LDL-C):** Dose-related increases in LDL-C occur with INVOKANA™. Monitor LDL-C and treat per standard of care after initiating INVOKANA™.
- **Macrovascular Outcomes:** There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with INVOKANA™ or any other antidiabetic drug.

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 (eg, rifampin, phenytoin, phenobarbitol, 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 60mL/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 requiring additional glycemic control.
- **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. Patients taking INVOKANA™ with concomitant digoxin should be monitored appropriately.

USE IN SPECIFIC POPULATIONS

- **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 ≥0.5 times clinical exposure from a 300-mg dose.

  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.

- **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™. 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 of age. 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 <50 mL/min/1.73 m^2). 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 ≥60 mL/min/1.73 m^2); patients treated with INVOKANA™ 300 mg were more likely to experience increases in potassium.

  The efficacy and safety of INVOKANA™ have not been established in patients with severe renal impairment (eGFR <30 mL/min/1.73 m^2), with end-stage renal disease (ESRD), or receiving dialysis. INVOKANA™ is not expected to be effective in these patient populations.

- **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 it is therefore not recommended.

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, eg, 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.

ADVERSE REACTIONS

- The most common (≥5%) adverse reactions were female genital mycotic infections, urinary tract infections, and increased urination. Adverse reactions in ≥2% of patients were male genital mycotic infections, vulvovaginal pruritis, thirst, nausea, and constipation.

Please see Brief Summary of full Prescribing Information on the following pages.

K02CAN13149

Invokana™
canagliflozin tablets

Janssen Pharmaceuticals, Inc.

Canagliflozin is licensed from Mitsubishi Tanabe Pharma Corporation.

April 2013 K02CAN13075B

INVOKANA™

(canagliflozin) tablets, for oral use

Brief Summary of Prescribing Information.

INDICATIONS AND USAGE

INVOKANA™ (canagliflozin) is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus *[see Clinical Studies (14) in full Prescribing Information].*

Limitation of Use: INVOKANA is not recommended in patients with type 1 diabetes mellitus or for the treatment of diabetic ketoacidosis.

CONTRAINDICATIONS

- History of a serious hypersensitivity reaction to INVOKANA *[see Warnings and Precautions].*
- Severe renal impairment (eGFR less than 30 mL/min/1.73 m^2), end stage renal disease or patients on dialysis *[see Warnings and Precautions and Use in Specific Populations].*

WARNINGS AND PRECAUTIONS

Hypotension: INVOKANA causes intravascular volume contraction. Symptomatic hypotension can occur after initiating INVOKANA *[see Adverse Reactions]* particularly in patients with impaired renal function (eGFR less than 60 mL/min/1.73 m^2), elderly patients, patients on either diuretics or medications that interfere with the renin-angiotensin-aldosterone system (e.g., angiotensin-converting-enzyme [ACE] inhibitors, angiotensin receptor blockers [ARBs]), or patients with low systolic blood pressure. Before initiating INVOKANA in patients with one or more of these characteristics, volume status should be assessed and corrected. Monitor for signs and symptoms after initiating therapy.

Impairment in Renal Function: INVOKANA increases serum creatinine and decreases eGFR. Patients with hypovolemia may be more susceptible to these changes. Renal function abnormalities can occur after initiating INVOKANA *[see Adverse Reactions].* More frequent renal function monitoring is recommended in patients with an eGFR below 60 mL/min/1.73 m^2.

Hyperkalemia: INVOKANA can lead to hyperkalemia. Patients with moderate renal impairment who are taking medications that interfere with potassium excretion, such as potassium-sparing diuretics, or medications that interfere with the renin-angiotensin-aldosterone system are more likely to develop hyperkalemia *[see Adverse Reactions].*

Monitor serum potassium levels periodically after initiating INVOKANA in patients with impaired renal function and in patients predisposed to hyperkalemia due to medications or other medical conditions.

Hypoglycemia with Concomitant Use with Insulin and Insulin Secretagogues: Insulin and insulin secretagogues are known to cause hypoglycemia. INVOKANA can increase the risk of hypoglycemia when combined with insulin or an insulin secretagogue *[see Adverse Reactions].* Therefore, a lower dose of insulin or insulin secretagogue may be required to minimize the risk of hypoglycemia when used in combination with INVOKANA.

Genital Mycotic Infections: INVOKANA increases the risk of genital mycotic infections. Patients with a history of genital mycotic infections and uncircumcised males were more likely to develop genital mycotic infections *[see Adverse Reactions].* Monitor and treat appropriately.

Hypersensitivity Reactions: Hypersensitivity reactions (e.g., generalized urticaria), some serious, were reported with INVOKANA treatment; these reactions generally occurred within hours to days after initiating INVOKANA. If hypersensitivity reactions occur, discontinue use of INVOKANA; treat per standard of care and monitor until signs and symptoms resolve *[see Contraindications and Adverse Reactions].*

Increases in Low-Density Lipoprotein (LDL-C): Dose-related increases in LDL-C occur with INVOKANA *[see Adverse Reactions].* Monitor LDL-C and treat per standard of care after initiating INVOKANA.

Macrovascular Outcomes: There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with INVOKANA or any other antidiabetic drug.

ADVERSE REACTIONS

The following important adverse reactions are described below and elsewhere in the labeling:

- Hypotension *[see Warnings and Precautions]*
- Impairment in Renal Function *[see Warnings and Precautions]*
- Hyperkalemia *[see Warnings and Precautions]*
- Hypoglycemia with Concomitant Use with Insulin and Insulin Secretagogues *[see Warnings and Precautions]*
- Genital Mycotic Infections *[see Warnings and Precautions]*
- Hypersensitivity Reactions *[see Warnings and Precautions]*
- Increases in Low-Density Lipoprotein (LDL-C) *[see Warnings and Precautions]*

Clinical Studies Experience: Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to the rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

Pool of Placebo-Controlled Trials: The data in Table 1 is derived from four 26-week placebo-controlled trials. In one trial INVOKANA was used as monotherapy and in three trials INVOKANA was used as add-on therapy *[see Clinical Studies (14) in full Prescribing Information].* These data reflect exposure of 1667 patients to INVOKANA and a mean duration of exposure to INVOKANA of 24 weeks. Patients received INVOKANA 100 mg (N=833), INVOKANA 300 mg (N=834) or placebo (N=646) once daily. The mean age of the population was 56 years and 2% were older than 75 years of age. Fifty percent (50%) of the population was male and 72% were Caucasian, 12% were Asian, and 5% were Black or African American. At baseline the population had diabetes for an average of 7.3 years, had a mean HbA1C of 8.0% and 20% had established microvascular complications of diabetes. Baseline renal function was normal or mildly impaired (mean eGFR 88 mL/min/1.73 m^2).

Table 1 shows common adverse reactions associated with the use of INVOKANA. These adverse reactions were not present at baseline, occurred more commonly on INVOKANA than on placebo, and occurred in at least 2% of patients treated with either INVOKANA 100 mg or INVOKANA 300 mg.

Table 1: Adverse Reactions From Pool of Four 26–Week Placebo-Controlled Studies Reported in ≥ 2% of INVOKANA-Treated Patients*

Adverse Reaction	Placebo N=646	INVOKANA 100 mg N=833	INVOKANA 300 mg N=834
Female genital mycotic infections†	3.2%	10.4%	11.4%
Urinary tract infections‡	4.0%	5.9%	4.3%
Increased urination§	0.8%	5.3%	4.6%
Male genital mycotic infections¶	0.6%	4.2%	3.7%
Vulvovaginal pruritus	0.0%	1.6%	3.0%
Thirst#	0.2%	2.8%	2.3%
Constipation	0.9%	1.8%	2.3%
Nausea	1.5%	2.2%	2.3%

* The four placebo-controlled trials included one monotherapy trial and three add-on combination trials with metformin, metformin and sulfonylurea, or metformin and pioglitazone.

† Female genital mycotic infections include the following adverse reactions: Vulvovaginal candidiasis, Vulvovaginal mycotic infection, Vulvovaginitis, Vaginal infection, Vulvitis, and Genital infection fungal. Percentages calculated with the number of female subjects in each group as denominator: placebo (N=312), INVOKANA 100 mg (N=425), and INVOKANA 300 mg (N=430).

‡ Urinary tract infections includes the following adverse reactions: Urinary tract infection, Cystitis, Kidney infection, and Urosepsis.

§ Increased urination includes the following adverse reactions: Polyuria, Pollakiuria, Urine output increased, Micturition urgency, and Nocturia.

¶ Male genital mycotic infections include the following adverse reactions: Balanitis or Balanoposthitis, Balanitis candida, and Genital infection fungal. Percentages calculated with the number of male subjects in each group as denominator: placebo (N=334), INVOKANA 100 mg (N=408), and INVOKANA 300 mg (N=404).

Thirst includes the following adverse reactions: Thirst, Dry mouth, and Polydipsia.

Abdominal pain was also more commonly reported in patients taking INVOKANA 100 mg (1.8%), 300 mg (1.7%) than in patients taking placebo (0.8%).

Pool of Placebo- and Active-Controlled Trials: The occurrence of adverse reactions was also evaluated in a larger pool of patients participating in placebo- and active-controlled trials.

The data combined eight clinical trials *[see Clinical Studies (14) in full Prescribing Information]* and reflect exposure of 6177 patients to INVOKANA. The mean duration of exposure to INVOKANA was 38 weeks with 1832 individuals exposed to INVOKANA for greater than 50 weeks. Patients received INVOKANA 100 mg (N=3092), INVOKANA 300 mg (N=3085) or comparator (N=3262) once daily. The mean age of the population was 60 years and 5% were older than 75 years of age. Fifty-eight percent (58%) of the population was male and 73% were Caucasian, 16% were Asian, and 4% were Black or African American. At baseline, the

population had diabetes for an average of 11 years, had a mean HbA1C of 8.0% and 33% had established microvascular complications of diabetes. Baseline renal function was normal or mildly impaired (mean eGFR 81 mL/min/1.73 m^2).

The types and frequency of common adverse reactions observed in the pool of eight clinical trials were consistent with those listed in Table 1. In this pool, INVOKANA was also associated with the adverse reactions of fatigue (1.7% with comparator, 2.2% with INVOKANA 100 mg, and 2.0% with INVOKANA 300 mg) and loss of strength or energy (i.e., asthenia) (0.6% with comparator, 0.7% with INVOKANA 100 mg and 1.1% with INVOKANA 300 mg).

In the pool of eight clinical trials, the incidence rate of pancreatitis (acute or chronic) was 0.9, 2.7, and 0.9 per 1000 patient-years of exposure to comparator, INVOKANA 100 mg, and INVOKANA 300 mg, respectively.

In the pool of eight clinical trials with a longer mean duration of exposure to INVOKANA (68 weeks), the incidence rate of bone fracture was 14.2, 18.7, and 17.6 per 1000 patient years of exposure to comparator, INVOKANA 100 mg, and INVOKANA 300 mg, respectively. Upper extremity fractures occurred more commonly on INVOKANA than comparator.

In the pool of eight clinical trials, hypersensitivity-related adverse reactions (including erythema, rash, pruritus, urticaria, and angioedema) occurred in 3.0%, 3.8%, and 4.2% of patients receiving comparator, INVOKANA 100 mg and INVOKANA 300 mg, respectively. Five patients experienced serious adverse reactions of hypersensitivity with INVOKANA, which included 4 patients with urticaria and 1 patient with a diffuse rash and urticaria occurring within hours of exposure to INVOKANA. Among these patients, 2 patients discontinued INVOKANA. One patient with urticaria had recurrence when INVOKANA was re-initiated.

Photosensitivity-related adverse reactions (including photosensitivity reaction, polymorphic light eruption, and sunburn) occurred in 0.1%, 0.2%, and 0.2% of patients receiving comparator, INVOKANA 100 mg, and INVOKANA 300 mg, respectively.

Other adverse reactions occurring more frequently on INVOKANA than on comparator were:

Volume Depletion-Related Adverse Reactions: INVOKANA results in an osmotic diuresis, which may lead to reductions in intravascular volume. In clinical studies, treatment with INVOKANA was associated with a dose-dependent increase in the incidence of volume depletion-related adverse reactions (e.g., hypotension, postural dizziness, orthostatic hypotension, syncope, and dehydration). An increased incidence was observed in patients on the 300 mg dose. The three factors associated with the largest increase in volume depletion-related adverse reactions were the use of loop diuretics, moderate renal impairment (eGFR 30 to less than 60 mL/min/1.73 m^2) and age 75 years and older (Table 2) *[see Dosage and Administration (2.2) in full Prescribing Information, Warnings and Precautions, and Use in Specific Populations].*

Table 2: Proportion of Patients With at Least one Volume Depletion-Related Adverse Reactions (Pooled Results from 8 Clinical Trials)

Baseline Characteristic	Comparator Group* %	INVOKANA 100 mg %	INVOKANA 300 mg %
Overall population	1.5%	2.3%	3.4%
75 years of age and older†	2.6%	4.9%	8.7%
eGFR less than 60 mL/min/1.73 m^2†	2.5%	4.7%	8.1%
Use of loop diuretic†	4.7%	3.2%	8.8%

* Includes placebo and active-comparator groups

† Patients could have more than 1of the listed risk factors

Impairment in Renal Function: INVOKANA is associated with a dose-dependent increase in serum creatinine and a concomitant fall in estimated GFR (Table 3). Patients with moderate renal impairment at baseline had larger mean changes.

Table 3: Changes in Serum Creatinine and eGFR Associated with INVOKANA in the Pool of Four Placebo-Controlled Trials and Moderate Renal Impairment Trial

			Placebo N=646	INVOKANA 100 mg N=833	INVOKANA 300 mg N=834
Pool of Four Placebo-Controlled Trials	Baseline	Creatinine (mg/dL)	0.84	0.82	0.82
		eGFR (mL/min/1.73 m^2)	87.0	88.3	88.8
	Week 6 Change	Creatinine (mg/dL)	0.01	0.03	0.05
		eGFR (mL/min/1.73 m^2)	-1.6	-3.8	-5.0
	End of Treatment Change*	Creatinine (mg/dL)	0.01	0.02	0.03
		eGFR (mL/min/1.73 m^2)	-1.6	-2.3	-3.4
			Placebo N=90	**INVOKANA 100 mg N=90**	**INVOKANA 300 mg N=89**
Moderate Renal Impairment Trial	Baseline	Creatinine (mg/dL)	1.61	1.62	1.63
		eGFR (mL/min/1.73 m^2)	40.1	39.7	38.5
	Week 3 Change	Creatinine (mg/dL)	0.03	0.18	0.28
		eGFR (mL/min/1.73 m^2)	-0.7	-4.6	-6.2
	End of Treatment Change*	Creatinine (mg/dL)	0.07	0.16	0.18
		eGFR (mL/min/1.73 m^2)	-1.5	-3.6	-4.0

* Week 26 in mITT LOCF population

In the pool of four placebo-controlled trials where patients had normal or mildly impaired baseline renal function, the proportion of patients who experienced at least one event of significant renal function decline, defined as an eGFR below 80 mL/min/1.73 m^2 and 30% lower than baseline, was 2.1% with placebo, 2.0% with INVOKANA 100 mg, and 4.1% with INVOKANA 300 mg. At the end of treatment, 0.5% with placebo, 0.7% with INVOKANA 100 mg, and 1.4% with INVOKANA 300 mg had a significant renal function decline.

In a trial carried out in patients with moderate renal impairment with a baseline eGFR of 30 to less than 50 mL/min/1.73 m^2 (mean baseline eGFR 39 mL/min/1.73 m^2) *[see Clinical Studies (14.3) in full Prescribing Information],* the proportion of patients who experienced at least one event of significant renal function decline, defined as an eGFR 30% lower than baseline, was 6.9% with placebo, 18% with INVOKANA 100 mg, and 22.5% with INVOKANA 300 mg. At the end of treatment, 4.6% with placebo, 3.4% with INVOKANA 100 mg, and 3.4% with INVOKANA 300 mg had a significant renal function decline.

In a pooled population of patients with moderate renal impairment (N=1085) with baseline eGFR of 30 to less than 60 mL/min/1.73 m^2 (mean baseline eGFR 48 mL/min/1.73 m^2), the overall incidence of these events was lower than in the dedicated trial but a dose-dependent increase in incident episodes of significant renal function decline compared to placebo was still observed.

Use of INVOKANA was associated with an increased incidence of renal-related adverse reactions (e.g., increased blood creatinine, decreased glomerular filtration rate, renal impairment, and acute renal failure), particularly in patients with moderate renal impairment.

In the pooled analysis of patients with moderate renal impairment, the incidence of renal-related adverse reactions was 3.7% with placebo, 8.9% with INVOKANA 100 mg, and 9.3% with INVOKANA 300 mg. Discontinuations due to renal-related adverse events occurred in 1.0% with placebo, 1.2% with INVOKANA 100 mg, and 1.6% with INVOKANA 300 mg *[see Warnings and Precautions].*

Genital Mycotic Infections: In the pool of four placebo-controlled clinical trials, female genital mycotic infections (e.g., vulvovaginal mycotic infection, vulvovaginal candidiasis, and vulvovaginitis) occurred in 3.2%, 10.4%, and 11.4% of females treated with placebo, INVOKANA 100 mg, and INVOKANA 300 mg, respectively. Patients with a history of genital mycotic infections were more likely to develop genital mycotic infections on INVOKANA. Female patients who developed genital mycotic infections on INVOKANA were more likely to experience recurrence and require treatment with oral or topical antifungal agents and antimicrobial agents *[see Warnings and Precautions].*

In the pool of four placebo-controlled clinical trials, male genital mycotic infections (e.g., candidal balanitis, balanoposthitis) occurred in 0.6%, 4.2%, and 3.7% of males treated with placebo, INVOKANA 100 mg, and INVOKANA 300 mg, respectively. Male genital mycotic infections occurred more commonly in uncircumcised males and in males with a prior history of balanitis or balanoposthitis. Male patients who developed genital mycotic infections on INVOKANA were more likely to experience recurrent infections (22% on INVOKANA

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

Could High-Potency Statins Increase Risk of Acute Kidney Injury?

Patients taking high-potency statins may have a higher rate of hospitalization for acute kidney injury (AKI), according to a study in the *British Medical Journal*.

Drawing on nine population-based cohort studies and a meta-analysis from North America and the United Kingdom, the researchers analyzed data from more than two million adults (40 years or older) who began taking statin therapy between 1997 and 2008. Treatment with high-potency statins—rosuvastatin 10 mg or higher, atorvastatin 20 mg or higher, or simvastatin 40 mg or higher—was evaluated for association with hospitalization for AKI. Patient cohorts with and without chronic kidney disease (CKD) were analyzed, with each case matched to 10 controls.

Within 120 days after the start of statin therapy, there were 4691 hospitalizations for AKI in patients without CKD and 1896 in patients with CKD. In the non-CKD cohort, the risk of hospitalization for AKI was 34 percent higher for patients taking high-potency statins (compared with lower doses). For the CKD cohort, the 10 percent excess risk associated with high-potency statins was nonsignificant. An analysis of heterogeneity showed robust associations across study sites.

Previous studies have suggested possible adverse renal effects of lipid-lowering statin therapy. However, the specific nature of this relationship—including whether there is any dose–response effect—remains unclear.

The new study shows a possible increase in hospitalization for AKI among patients starting high-potency statin therapy, especially during the first few months. Although the absolute risk appears small, the association may have clinical implications for prescribing of high-potency statins, "particularly when treatment with a low potency statin is an option" [Dormuth CR, et al. Use of high potency statins and rates of admission for acute kidney injury: multicenter, retrospective observational analysis of administrative databases. *BMJ* 2013; 346:f880].

Aliskiren Doesn't Improve Outcomes in Heart Failure

In patients with heart failure and decreased ejection fraction, aliskiren does not improve postdischarge outcomes—but does increase the risk of renal function decline and other key adverse events, reports a trial in the *Journal of the American Medical Association*.

The international Aliskiren Trial on Acute Heart Failure Outcomes study included 1615 hemodynamically stable patients with heart failure. All had decreased left ventricular function, with left ventricular ejection fraction 40 percent or lower (mean 28 percent), signs and symptoms of fluid overload, and elevated natriuretic peptides. In the hospital, patients were randomly assigned to treatment with aliskiren, 150 mg/day (increasing to 300 mg/day as tolerated), or placebo in addition to standard therapy.

Forty-one percent of patients had diabetes, and the mean estimated GFR was 67 mL/min/1.73 m^2. Baseline medications included diuretics in about 96 percent of patients, β-blockers in 82 percent, and angiotensin-converting enzyme inhibitors or angiotensin receptor blockers in 84 percent.

Aliskiren did not reduce the follow-up risk of cardiovascular death or heart failure readmission, compared with placebo. The primary outcome rates were 24.9 percent versus 26.5 percent at 6 months and 35.0 percent versus 37.3 percent at 12 months, respectively.

Aliskiren was associated with an increased likelihood of decline in estimated GFR to less than 30 mL/min/1.73 m^2: 10.9 percent versus 9.1 percent. The patients receiving aliskiren also had increased rates of hyperkalemia, severe hyperkalemia, and hypotension.

Adding direct renin inhibition to standard treatment for chronic heart failure and reduced ejection fraction might further improve outcomes by reducing "aldosterone escape." The new multicenter trial finds no such improvement in outcomes with aliskiren, but it does show increased rates of hypotension, hyperkalemia, and worsening renal function. More study is needed to evaluate the possible benefits of aliskiren for nondiabetic patients with heart failure [Gheorghiade M, et al. Effect of aliskiren on postdischarge mortality and heart failure readmissions among patients hospitalized for heart failure: the ASTRONAUT randomized trial. *JAMA* 2013; 309:1125–1135].

Policy Update

President Reaches for Middle Ground in His Budget Request

By Grant Olan

President Barack Obama released his budget request for fiscal year 2014 on April 10, 2013. In a departure from his grand and ambitious budget proposals of the past, the president made some significant concessions to meet congressional Republicans halfway.

Specifically, the president proposed to replace the $1.2 trillion sequester cuts to discretionary spending with $1.8 trillion in deficit reduction achieved through entitlement reform and nearly $1 trillion in new revenue that includes a new minimum tax of 30 percent on households earning more than $1 million after charitable giving, known as the "Buffett Rule."

The president's proposal includes a modest increase in the National Institutes of Health's (NIH) funding, and small increases to programs for organ donation activities.

Of the $1.8 trillion in deficit reduction, $400 billion would be achieved through health care–related savings, such as cuts to Medicare providers' graduate medical education payments, bad debt reimbursement reductions, and increases in Medicare drug rebates. The $400 billion also includes Medicare structural reforms and new measures to reduce Medicare and Medicaid fraud.

The President's proposal contains some new initiatives, including:

- $100 billion for roads and railways
- $8 billion to help community colleges prepare students for existing jobs
- $1 billion to promote innovation in manufacturing
- $130 million to expand mental health treatment and prevention services

The president's proposal also includes modest increases for existing federal programs and federal research agencies. For instance, included is $26 million for coordinating organ donation activities and for state grants to develop and improve donor registries, an increase of $2 million.

The budget would increase $471 million, or 1.5 percent over 2012, to $31.3 billion. Included in that funding is a new $100 million initiative called BRAIN, short for Brain Research through Advancing Innovative Neurotechnologies, to uncover new ways to prevent, treat, and cure neurological disorders. The overall NIH budget increase would also include new funding of $18 million for the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) over 2012 for a total of $1.8 billion.

"The president should be commended for his proposed investments in NIH and other federal research agencies," said John R. Sedor, MD, ASN Research Advocacy Committee Chair. "However, ASN is calling for Congress to provide $32 billion for NIH and $2 billion for NIDDK, the minimum amounts needed to avoid loss of promising research, like a groundbreaking discovery that helps explain racial/ethnic disparities that increase risks for kidney disease. African Americans are more than 4 times as likely as Caucasians to progress to advanced kidney failure. Now we know, thanks to recent NIDDK-funded research, that African Americans with two variants of the APOL1 gene face greater risk of kidney failure. This finding could lead to new interventions to improve the kidney health of African Americans."

ASN has been working with the Ad Hoc Group of Medical Research, Coalition for Health Funding, and the kidney community to advocate for these NIH and NIDDK requests. The society is also supporting the Friends of AHRQ's request for $433.7 million for the Agency for Healthcare Research and Quality, which is a 7 percent increase over 2012 and in line with the president's request.

VA funding

While the president also requested a slight increase for medical and prosthetic research for veterans in 2014 of $586 million, ASN is supporting the Friends of VA Medical Care and Health Research's (FOVA) more robust request of $611 million. This new funding would support new research into conditions veterans returning from Iraq and Afghanistan face, including polytrauma, multiple traumatic injuries such as a serious head injury in addition to a serious burn.

ASN is on the Executive Committee of FOVA, which is also requesting at least $50 million for up to five major Department of Veterans Affairs (VA) research facility construction projects and $175 million in nonrecurring maintenance and minor construction funding to address deficiencies identified in a VA congressionally requested report last year detailing an in-depth survey and analysis of the physical condition of all VA research facilities (www.aamc.org/varpt). For more information about the VA, FOVA, and FOVA's 2014 requests, see the March issue of *ASN Kidney News* (http://www.asn-online.org/publications/kidneynews/).

Despite the new initiatives and budget increases for federal research agencies the president proposed, taken together with his deficit reduction recommendations, annual federal budget deficits would dip from the current level of $937 billion to just $439 billion in 2023, or 1.7 percent of the gross domestic product. The nation's debt would continue to grow, however, climbing from $16.8 trillion today to $25 trillion in 2023.

Of course, Congress controls the purse strings and Republican responses to the president's budget request have been mixed. As lawmakers negotiate the 2014 budget, ASN will continue highlighting the importance of supporting innovative kidney disease research that will improve patient care, cut costs, and preserve the investigator pipeline.

ASN Joins Forces with Patient Advocates to Advance Kidney Health on Capitol Hill

By Grant Olan and Rachel Shaffer

Continuing an annual tradition, ASN leaders went to Capitol Hill for Kidney Health Advocacy Day on April 25, 2013. In a first for ASN, society leaders teamed up with patient advocates from the American Association of Kidney Patients (AAKP) and Dialysis Patient Citizens (DPC) for meetings with congressional offices in the House and Senate about issues of importance to ASN and the kidney care community. ASN, AAKP, and DPC met with more than 40 congressional offices, and met personally with members of Congress in one of every four meetings. ASN, AAKP, and DPC participants advocated for three key issues:

- Transplant legislation
- Medical research funding
- The Kidney Health Initiative (KHI)

Besides meeting with lawmakers from their own states, advocates also met with congressional leaders and members of Congress who sit on committees that have jurisdiction over the issues discussed, either from an "authorizing" perspective (meaning that the committee can tell a certain program or agency what it is allowed to or must do), or from an "appropriations" perspective (meaning that the committee is in charge of determining how much funding an agency or a program receives).

"ASN was thrilled to partner with AAKP and DPC to advance these important issues on Capitol Hill," said ASN President Bruce A. Molitoris, MD, FASN. "A collaborative effort to present both patient and physician perspectives strengthens our advocacy case for what we are asking Congress to do for those affected by and at risk for kidney disease."

DPC President Eric Edwards commented, "Giv-

Continued on page 18

Policy Update

Capitol Hill

Continued from page 17

en that ASN and DPC share many of the same policy priorities, joining forces for Kidney Health Advocacy Day was a natural partnership that I believe advanced our goals for patients. We look forward to continuing to work together."

"Collaborating to raise congressional awareness about kidney disease and ask lawmakers to take the steps our organizations believe would help patients with kidney disease was a great success," said AAKP President Sam Pederson.

Making the case for transplant legislation

Advocating for the passage of two transplant-related bills is a top ASN public policy priority for 2013. ASN leaders and patient advocates discussed the Comprehensive Immunosuppressive Drug Coverage Act and the HIV Organ Policy Equity (HOPE) Act in meetings and encouraged members of Congress to support these common-sense pieces of legislation.

The Comprehensive Immunosuppressive Drug Coverage Act (or "Immuno Bill") would guarantee lifetime immunosuppressive drug coverage to the thousands of Americans who receive kidney transplants through the Medicare End Stage Renal Disease (ESRD) Program. Although patients who receive a kidney transplant must take the immunosuppressive drugs every day for the rest of their lives to prevent organ rejection, Medicare only provides the drugs for 36 months. After that time, many patients who are no longer eligible for Medicare have difficulty obtaining coverage or purchasing the drugs themselves. Patients who can't take their drugs lose their kidney and wind up back on dialysis, which costs Medicare more than the immunosuppressive drugs otherwise would and reduces many patients' quality of life.

"Some patients don't even apply to be wait-listed on the transplant list as they know they can't afford the drugs and continue on dialysis indefinitely," DPC member and patient advocate Michael Dickerson pointed out in congressional meetings. Dickerson, a college student who plans a career in nephrology, was diagnosed with CKD at an early age and after two kidney transplants is now back on dialysis.

"I have personally cared for patients who have lost their transplant because they could not afford the drugs they needed and were devastated to lose their gift of life," said ASN Transplant Advisory Group chair Michelle Josephson, MD. "It was gratifying to advocate for legislation that would prevent other patients from going through that hardship."

By making sure all patients get the drugs they need to keep their kidneys healthy, the Immuno bill would provide a cost-effective solution that will not only improve the lives of countless kidney transplant patients, but also use limited federal resources more effectively. AAKP, ASN, and DCP are committed to continuing to press for passage of this bill beyond Kidney Health Advocacy Day and in collaboration with the larger transplant and kidney communities.

Urging Congress to sustain medical research funding

In meetings with House and Senate appropriators and other lawmakers, ASN leaders and AAKP and DPC patient advocates discussed the significant prevalence of kidney disease and the expense of treating it and highlighted the imperative of supporting the National Institutes of Health (NIH), including the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), and the Department of Veterans Affairs (VA) research budgets. Advocates also highlighted the significant racial and ethnic disparities in kidney disease, and encouraged more research to elucidate and eliminate them.

More than 20 million children, adults, and veterans have kidney disease, the eighth leading cause of death in the United States today. The nearly 600,000 individuals who have end stage renal disease (ESRD) comprise less than 1 percent of Medicare beneficiaries but account for nearly 7 percent of Medicare's budget. Investing in medical research is crucial to improve patients' lives and give health care professionals the tools they need to reduce these costly statistics.

Moreover, the combination of an aging population and epidemic increases in obesity and diabetes means the number of Americans with kidney disease will continue to escalate without investments in research. Research advances that can halt or slow progression to ESRD—or make dialysis more efficient—can yield significant savings to Medicare.

"Highlighting the fact that publicly funded research supports one in 500 full-time U.S. jobs, and every dollar invested in medical research generates $2.60 of economic activity, was a very effective way to help congressional staff visualize the benefits that research is bringing to their communities back home today," said Public Policy Board chair Thomas H. Hostetter, MD.

In discussing the VA, advocates highlighted the Million Veterans Program, the largest longitudinal study ever undertaken to study how genes affect diseases. Blood samples and health information have already been collected from more than 150,000 veterans. At a recent Friends of VA Medical Care and Health Research (FOVA) briefing on Capitol Hill, VA Chief Research and Development Officer Joel Kupersmith, MD, said new funding is needed for the cutting edge research, including kidney disease, that will lead to discoveries that advance health care not just for our nation's veterans, but for all Americans.

Kupersmith also noted that kidney disease affects a great number of veterans disprortionate to the general population and highlighted the importance of continued VA research funding for efforts such as studying the deleterious pharmacokinetic effects that medications for treating diabetes, hypertension, and other diseases often have on the kidney.

In their meetings, ASN, DPC, and AAKP urged support for the research and kidney communities' requests of at least $32 billion for NIH, including $2 billion for NIDDK, and $611 million for VA research in the 2014 fiscal year, the minimum investments necessary to avoid the loss of promising research like APOL1 and the Million Veterans Program. They also addressed concerns related to sequestration and the importance of ensuring it does not undercut investments in research.

Leading up to Kidney Health Advocacy Day, ASN laid the groundwork on the medical research advocacy front by:

- Joining nearly 300 organizations in opposing continued cuts to NIH in a letter to the President and Congress.
- Joining 425 organizations in a letter to the House and Senate Budget Committees requesting $65 billion for all discretionary public health and health research programs in 2014.
- Submitting written testimony about the value of NIH and NIDDK research to the House and Senate Appropriations Committees.
- Collaborating with the American Society of Pediatric Nephrology (ASPN) to send the House and Senate Appropriations Committees a letter requesting $2 billion for NIDDK that was signed by numerous other members of the kidney community representing patients, providers, and industry.
- Participating in FOVA meetings with House and Senate VA Committees to urge support of at least $611 million for VA research, as well as $50 million for up to five major research facility construction projects and another $175 million for minor construction and non-reoccurring maintenance.

Advancing the Kidney Health Initiative (KHI)

In addition to advocating for the Immuno Bill and HOPE Act, and trumpeting the value of investing in medical research, some ASN leaders—and AAKP President and Kidney Health Initiative Board of Directors member Sam M. Pederson—highlighted the Kidney Health Initiative. Focusing on members of Congress who sit on committees with jurisdiction over the FDA, advocates explained the goals, structure, and progress of the public-private partnership between ASN and FDA that aims to bring the kidney community together to improve patient safety and foster innovation in nephrology.

"It's important that Congress know what FDA and the kidney community are doing to try to advance the therapies available to people with kidney disease," commented Mr. Pederson, a kidney transplant recipient and previous CAPD patient.

ASN is grateful to the society's leaders and the AAKP and DPC patient advocates for helping make Kidney Health Advocacy Day a success. The society will continue to engage Congress in the months to come as the budget process plays out and other legislation important to society members and the patients ASN serves moves forward.

ASN and ASPN Host Kickoff Reception for the Congressional Kidney Caucus

By Grant Olan

On Wednesday, March 20, 2013, ASN and the American Society of Pediatric Nephrology (ASPN) hosted a reception on Capitol Hill to launch the activities of the Congressional Kidney Caucus in the 113th Congress. Co-chaired by Rep. Tom Marino (R-PA) and Rep. Jim McDermott (D-WA), the bipartisan Congressional Kidney Caucus was founded by Rep. McDermott and former Representative, now Senator, Mark Kirk (R-IL) in March 2002 to raise awareness in Congress about the prevalence and burden of kidney disease and advance kidney patient health.

This year, the Caucus is focusing on increasing the visibility of kidney disease in Congress and advancing kidney patient health initiatives, including:

- The "Comprehensive Immunosuppressive Drug Coverage for Kidney Transplant Patients Act of 2013" (H.R. 1438 / S. 323) that would extend Medicare coverage for immunosuppressive drugs over a recipient's lifetime—protecting Medicare's investment so no patient ends up back on dialysis after losing a transplant.
- Rebasing ESRD bundled payments for costs associated with each dialysis treatment in a way that is good for patients and fair for providers.
- Promoting home dialysis as a safe and convenient alternative to in-center treatment for certain patient populations.

Co-sponsors of the reception included the American Association of Kidney Patients, American Kidney Fund, Dialysis Patient Citizens, Home Dialyzors United, National Kidney Foundation, and Renal Physicians Association. Nearly 100 people attended the event, including congressional staff, professors and medical researchers from top academic institutions, and professionals from patient and health professional organizations.

Both Rep. Marino—a two-time survivor of kidney cancer—and Rep. McDermott—who represents the "birthplace of modern dialysis," Seattle, WA—spoke at the reception about the important role patients, their caregivers, and advocates play in calling attention to and building support for these issues. Rep. Elijah Cummings (D-MD) and Rep. Charlie Rangel (D-NY) also attended the reception and gave moving speeches about family members and members of their communities affected by kidney disease, and the responsibility of the public to ensure patients receive the best care.

Co-Chair Rep. Jim McDermott hands the podium over to his colleague and Kidney Caucus member Rep. Charlie Rangel.

Co-Chair Rep. Tom Marino speaks about his personal experience with kidney cancer.

Kidney Caucus member Rep. Elijah Cummings and ASN Public Policy Board Chair Thomas H. Hostetter, MD.

ASN Manager of Policy and Government Affairs Rachel Shaffer and American Kidney Fund Executive Director LaVarne Burton.

American Society of Pediatric Nephrology Washington Representative Katie Schubert and member Jonathan Heiliczer, MD.

KIDNEYWEEK 2013

Atlanta, GA | Nov 5 - 10

Call for Abstracts

Submit your abstract for ASN Kidney Week 2013: The world's premier nephrology meeting

NEW ABSTRACT CATEGORIES FOR 2013

- **Pediatric Nephrology:** Clinical, epidemiological, and management studies of pediatric diseases (403)
- **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)

Fellows Case Reports

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

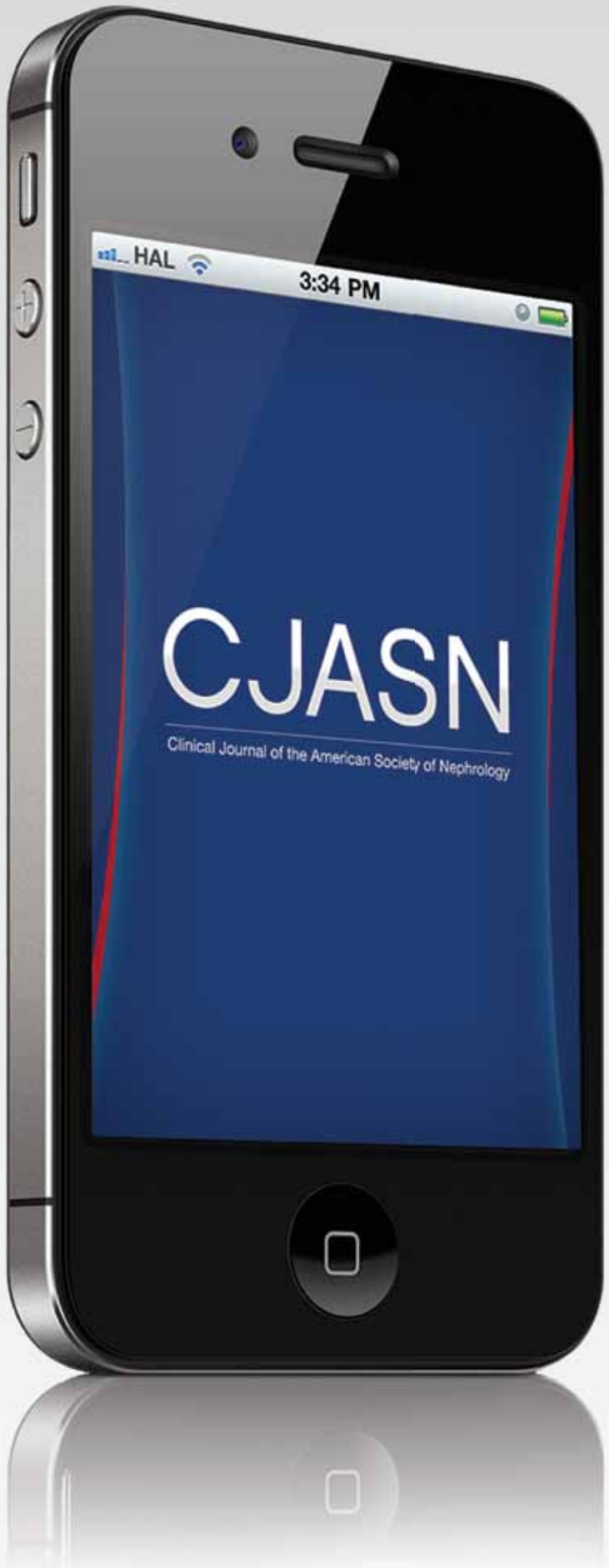
Wednesday, October 23
Advance Registration Closes

Tuesday, November 10
Onsite Registration Opens

Kidney Week

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

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



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ASN LEADING THE FIGHT AGAINST KIDNEY DISEASE

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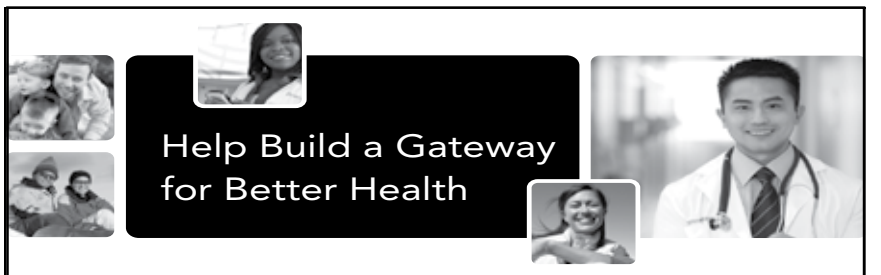

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Industry Spotlight

NICE Issues New Guidance on Kidney Diseases

The U.K.'s National Institute for Health and Clinical Excellence (NICE) has issued a final appraisal decision and rejected the drug axitinib (marketed by Pfizer as Inlyta) for the treatment of advanced kidney cancer. NICE also recently provided management guidance for patients with hyperphosphatemia, which often accompanies chronic kidney disease (CKD).

The decision on axitinib mirrored NICE's initial recommendations about the medication. In comments to the National Health Service (NHS)—which delivers publicly funded health throughout the U.K.—about the draft guidance on axitinib, NICE's Chief Executive Sir Andrew Dillon said, "We do not want to divert NHS funds to a treatment that costs more but doesn't help people live longer."

The precise decision by the independent NICE appraisal committee was that axitinib shouldn't be recommended for use after failure of prior treatment with sunitinib or a cytokine.

The Department of Health instructed NICE to examine the use of axitinib for the two populations specified in drug labeling, those previously treated with sunitinib, and those previously treated with a cytokine therapy. Experts told the appraisal committee that the use of cytokines is decreasing in clinical practice because most patients now start treatment with NICE-recommended sunitinib or pazopanib.

The data that Pfizer submitted for evaluation hurt the drug's case. The trial data provided included a direct comparison of the drug to sofafenib, a drug not recommended by NICE and not identified in the scope of the case. The trial also lacked a comparison to "best supportive care"—the care that the majority of patients receive currently. Thus, an indirect and simulated comparison was made using separate data from another trial, according to documents on the NICE website.

When the committee considered this comparison, they noted that limited analysis was completed to identify uncertainties within this simulated method of comparison, and thus, they were concerned about its validity and reliability. The draft guidance is now with a named group of consultees, who can appeal the decision. Until NICE issues final guidance, NHS bodies will make decisions locally on the funding of specific treatments. This draft guidance does not mean that people currently taking axitinib will stop receiving it. They have the option to continue treatment until they and their clinicians consider it appropriate to stop.

Earlier in March, NICE issued guidelines for the management of increased serum phosphate level in the blood, or hyperphosphatemia, which is a common comorbidity among people who have CKD.

The NICE recommendations include offering calcium acetate as the first-line treatment in adults to control serum phosphate in addition to dietary management. For children, doctors should offer a calcium-based phosphate binder. The guideline also makes recommendations on second-line phosphate binder usage. The guidelines further call for giving individualized information on dietary phosphate management and assessing a patient's serum phosphate control during every routine clinical visit.

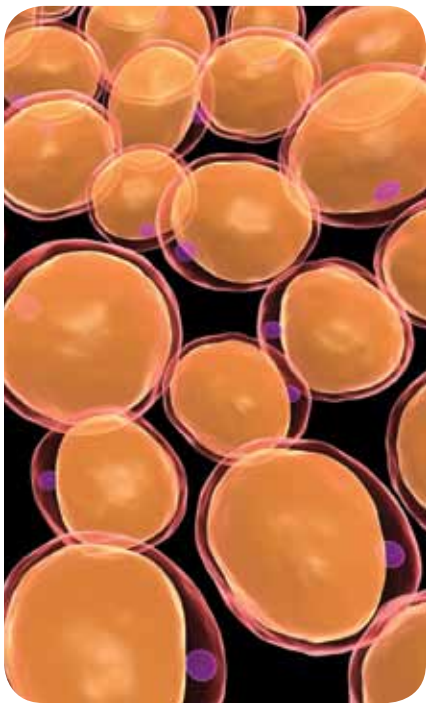
Fat-Derived Regenerative Cells Patented to Treat Kidney Disease

Cytori Therapeutics, Inc., has received a patent for a new method of treating renal diseases using adipose-derived regenerative cells (ADRCs), cells derived from fat tissue. The company announced that the patent covers treatment of a broad range of renal disorders, including acute kidney disease as well as chronic kidney disease (CKD).

The patent also covers several ways of delivering the cells, including directly to the kidney or to the renal blood vessels.

Cytori won the U.S. patent in part with data from a preclinical study showing that ADRCs improve renal function and reduce the death rate in acute kidney injury. In the study, animals received either ADRCs or delivery of a control material after a renal injury. Survival in the ADRC-treated group was 100 percent, which was a statistically significant outcome compared to only 57 percent survival in the control group. Functional and histologic improvements in serum creatinine, blood urea nitrogen, and renal cell necrosis in the ADRC group were also statistically significant.

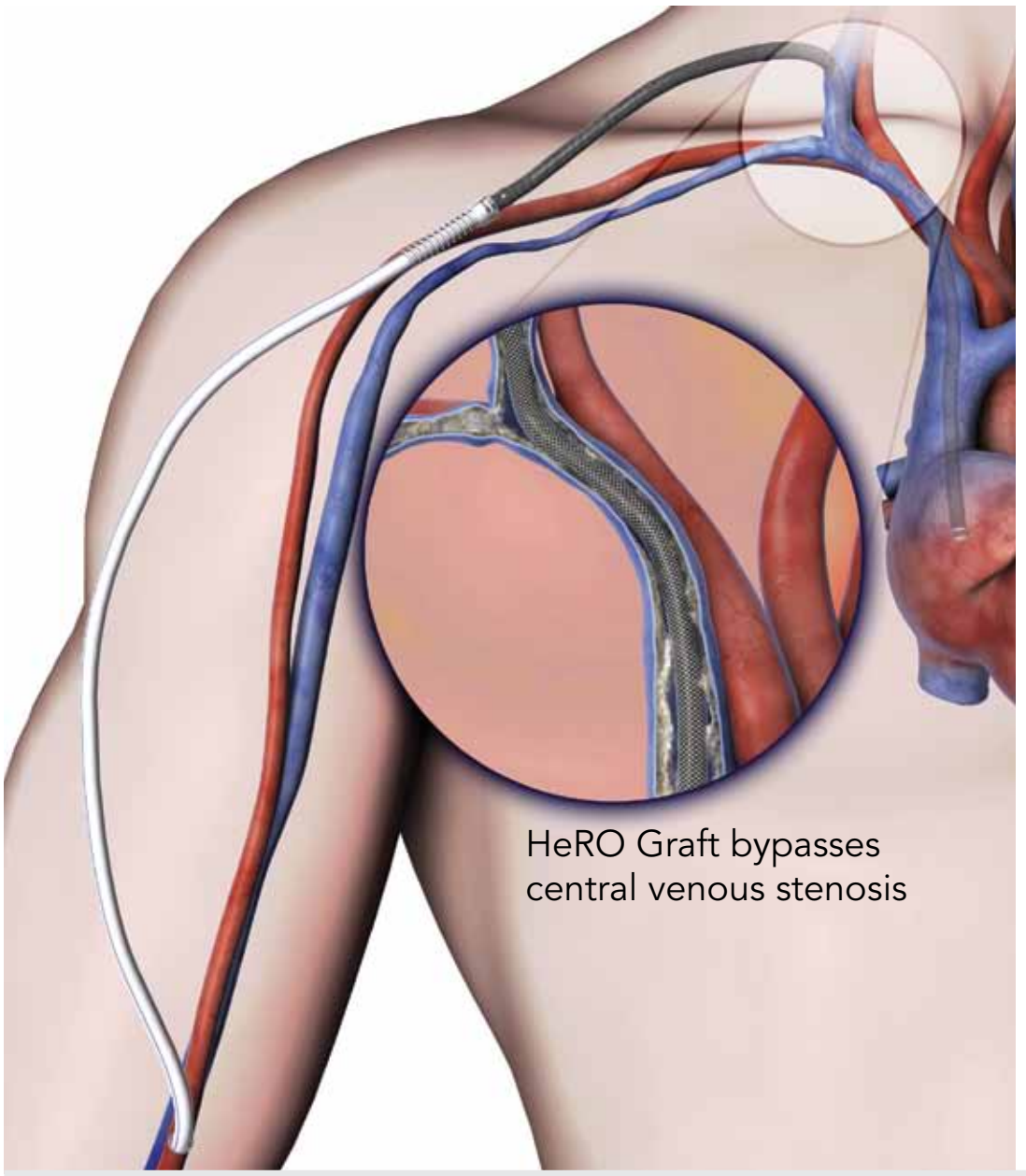
Based in San Diego, Cytori is a regenerative medicine company that develops and manufactures medical devices that allow for therapeutic use of adult stem and regenerative cells that naturally occur in fat tissue. Until now, the company's commercial activities have been focused on cosmetic and reconstructive surgery, cell banking, and tools for medical research.



"The renal patents are an important addition to our growing portfolio of ADRC patents," said Cytori CEO Chris Calhoun. "CKD is an important comorbidity of cardiovascular disease, Cytori's core focus."

Calhoun said Cytori potentially could find a partner on this new indication to bring the therapy to market. The company has related patents in Europe to cover treatment of a broad range of renal disorders.

In 2012, Cytori's operations had total product and contract revenue growth of 14 percent year-over-year, with $4.4 million coming from Japan out of the annual total of $14.5 million. In the fourth quarter of 2012, the company had a quarterly gross profit of $2.6 million, which was greater than sales and marketing expenses of $2.1 million.



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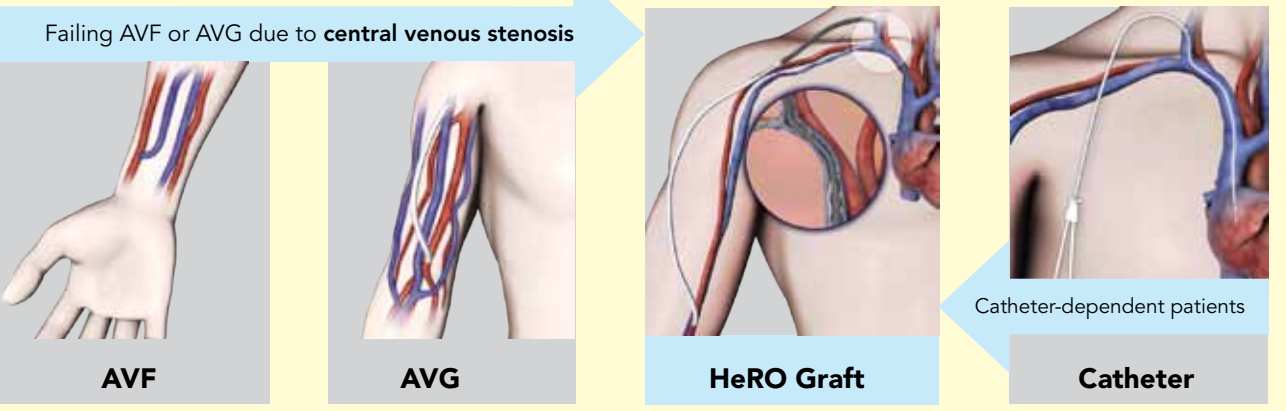

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References:
1) Katzman et al., J Vasc Surg 2009. 2) Gage et al., EJVES 2012. 3) Dageforde et al., JSR 2012.

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