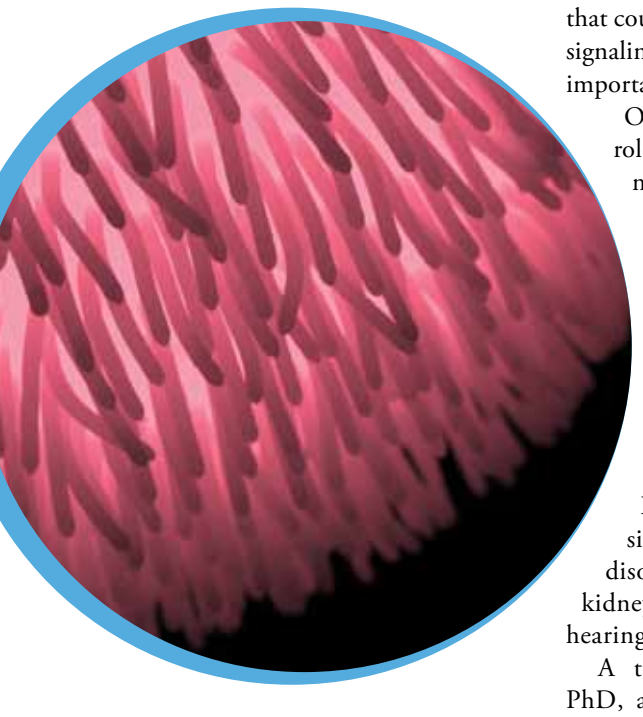
ASN LEADING THE FIGHT AGAINST KIDNEY DISEASE

Kidney News

July 2013 | Vol. 5, Number 7

Cilia Admit Larger Proteins Than Thought

By Eric Seaborg



A new fluorescence visualization technique reveals that cilia admit much larger molecules than has previously been seen—a finding that could provide new insights into cell signaling systems from what could be an important new research tool.

Often called antennae for their roles in signaling processes, cilia monitor the cell's exterior environment, translating mechanical and chemical forces into molecular signals so the cell can respond appropriately. In the kidney, cilia monitor the flow of urine. They sense the wavelength of light in the eye, pressure in cartilage, and blood flow in the heart. Defects in the hairlike protrusions have been implicated in disorders ranging from polycystic kidney disease to loss of vision and hearing.

A team led by Takanari Inoue, PhD, assistant professor of cell biology at the Johns Hopkins University School of Medicine, found that molecules as large as 650 kDa can enter the cilia, which is some 10 times larger than was heretofore thought. That size limit means that 90 percent of the proteins in mammalian cells can make their way into cilia and perhaps affect signaling functions.

In their study in Nature *Chemical Biology*, the team said that the gateway is not a pore of fixed size but a sieve-like process, in which small molecules transfer through more quickly than do larger ones. Inoue said that a key point may not simply be which molecules can make their way into the cilia, but what happens to them once they are there. Inoue told *Kidney News* that one "highly speculative thought" is that "under some disease conditions, primary cilia get clogged at the base, so that the proteins cannot go in and out, so … they cannot send a signal."

The only way into a cilium is through the base from which it protrudes from the cell, so several recent studies have looked into how proteins traffic in and out. Last year, a study in the *Proceedings of the National Academy*

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ASN Holds Summit on Diversity

In June, ASN held its first-ever summit on diversity. Chaired by Jonathan Himmelfarb, MD, FASN, and Donald E. Wesson, MD, FASN, the summit focused on what ASN can do to improve diversity at all levels of the society, encourage more students from underrepresented minorities to pursue careers in nephrology, and better support all nephrologists.

Ten nephrologists joined the meeting organizers, ASN Councilors Himmelfarb and Wesson, incoming ASN President Sharon M. Moe, MD, FASN, and several ASN staff members. In advance of the summit, ASN solicited input from key leaders in nephrology and diversity programs, and shared that input with the summit participants. These leaders provided information on mentoring and professional development programs, described ongoing initiatives such as the NIH BUILD consortium, and offered suggestions for how ASN might better incorporate inclusiveness into the fabric of all ASN activities.

During the summit, participants discussed successful diversity programs, career challenges in nephrology, and opportunities for change at ASN. A number of those attending shared their motivations for becoming nephrologists. Several singled out senior nephrologists who piqued and encouraged their interest in kidney disease, helped them advance in their careers, network at ASN Kidney Week and other meetings, and provided formal and informal leadership training. Others noted their first introduction to kidney medicine came via family members with kidney disease, and the group discussed the importance of medical and research careers as avenues to giving back to communities and improving society.

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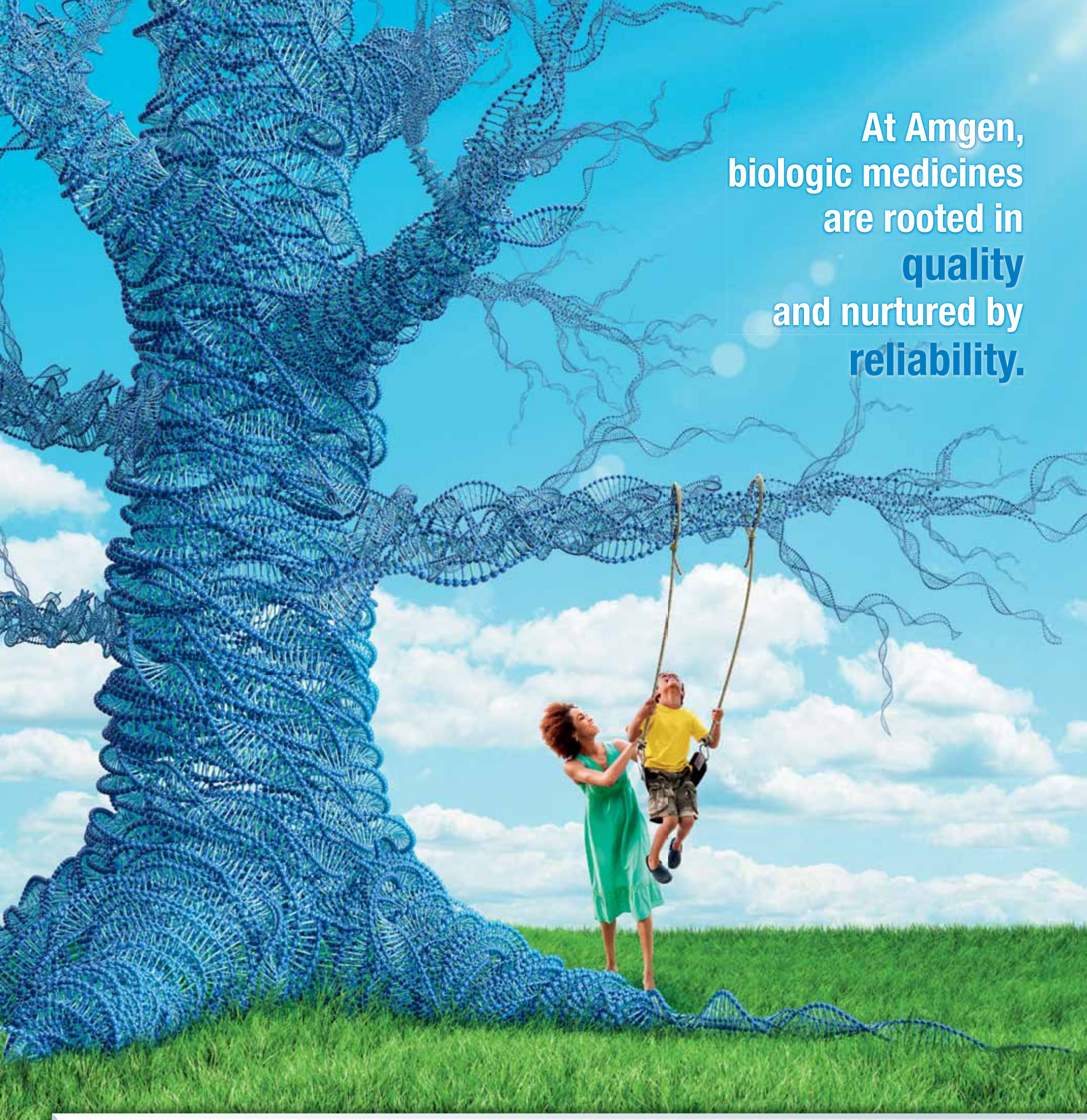

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Cytosolic Proteins

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of Science USA concluded that photoreceptor primary cilia have no fixed pore that limits the diffusion of soluble proteins, at least up to 80 kDa. By contrast, a study in *Nature Cell Biology* concluded that the ciliary base does contain a fixed pore that excludes molecules larger than 67 kDa. These researchers termed the barrier a ciliary pore complex, believing it to be analogous to the nuclear pore complex (NPC), but Inoue's team overcame some limitations of that study and found a way to document that larger molecules could enter the cilia.

The Johns Hopkins team developed a variation on the chemically inducible dimerization technique that is often used to manipulate signaling molecules. In dimerization, two proteins that would otherwise not interact are each induced to attach to different sides of the same enzyme or other dimerization agent and thereby form a ternary complex. This experiment used rapamycin as the dimerizer.

Inoue's team engineered a molecule with a cyan fluorescent tag targeted to embed itself in the cilia's membranes. One end anchored itself to the membrane and the other end contained a rapamycin-binding domain. They then introduced into the cytoplasm their particular "proteins of interest," molecules with yellow fluorescent tags engineered with an end that would attach to the rapamycin. When they introduced rapamycin, they waited to see what would diffuse into the cilia.

They call their technique a chemically induced diffusion trap because the cilia become the equivalent of a roach motel, where the molecules can check in separately but, once bound together, cannot check out. The researchers repeated the experiment with molecules of increasing size and found that everything they tried, up to the largest size their technique would permit—650 kDa, or 7.9 nm—made it into the cilia.

Small molecules entered more quickly than did larger molecules. The researchers performed calculations on the speed at which the various sizes of molecules diffused, and they proposed that the barrier was more like a sieve than a simple pore.

They proposed "two important implications for how ciliary protein composition is regulated." First, over long time scales, the exclusion of proteins may not be as important as what happens once they are in—the binding interactions with other cilia-resident molecules that lead to the selective retention of proteins. Second, because signaling reactions are rapid, the sieve-like barrier's role in limiting protein entry could play an important regulatory role.

"I think the surprising thing here is that even large soluble proteins seem to be able to get through this kind of barrier," said Peter C. Harris, PhD, professor of medicine and biochemistry and molecular biology at the Mayo Clinic.

However, Harris did not see an obvious link to polycystic kidney disease because the experiment dealt with soluble proteins rather than membrane proteins: "The proteins that are involved in simple polycystic kidney disease, like polycystin-1 and polycystin-2, and fibrocystin for the recessive form of polycystic kidney disease, are fairly large and all membrane proteins. So they are not going to get into the cilia in the way that is described in this paper."

Terry Watnick, MD, director of the Baltimore Polycystic Kidney Disease Research and Clinical Core Center, which funded the study with a grant from the National Institute of Diabetes and Digestive and Kidney Diseases, agreed that most work on polycystic disease has involved membrane proteins, but said, "There is an intimate tie between the cilia and cystic kidney disease. There could be unidentified soluble molecules that may be required for ciliary-based signal transduction pathways."

Watnick was excited by the possibilities the diffusion trap offers for further research: "You could adapt this methodology to bring other signaling compounds to the cilia to perturb the system and see what the downstream effects are. This could be a useful tool for exploring signaling systems in cilia because it allows you to target molecules to cilia, and Inoue has shown that he is able to do that effectively."

Summit on Diversity

Continued from page 1

Eddie Greene, MD, FASN, Director of the Office of Diversity at Mayo Clinic, described the rapid pace of demographic change in the United States (Figure 1), and emphasized that "identifying, recruiting and employing outstanding and talented people from the pool of diverse individuals present in our society has the potential to be our strongest asset in assuring that we achieve sustainable excellence and success." He also provided information on how organizational performance improves as organizational diversity increases.

The relatively low numbers of medical school graduates entering nephrology training garnered much discussion, and a number of summit members provided insights into ways to increase interest in kidney medicine, research, and policy. Dr. Moe presented information on current ASN activities and outreach to students and trainees, such as Kidney TREKS (Tutoured Research and Education for Kidney Scholars).

Highly successful characteristics of a number of career development programs to increase diversity in research and academic medicine were discussed and evaluated, including the Robert Wood Johnson Harold Amos Medical Faculty Development Program, the NIDDK Network of Minority Research Investigators program, and mentoring programs developed by the J. Robert Gladden Society of the American Academy of Orthopedics.

Participants also discussed the importance of establishing appropriate measures of success for diversity and mentoring programs. Challenges to robust evaluation of program performance include establishing baseline demographics and adequate resource support for programs.

By the conclusion of the summit, participants reached consensus on a number of recommendations that will be presented to the ASN Council later this summer. Dr. Himmelfarb discussed the interest of all Council members in the outcomes from this summit.

"To accomplish its mission, ASN will expand opportunities for all members to participate fully, meaningfully, and personally," said ASN Executive Director Tod Ibrahim. "This participation will go beyond ASN Kidney Week to include helping the society develop high-quality programs, formulate policy initiatives to improve care for every person with kidney disease, and make decisions that enrich the lives of kidney patients worldwide."

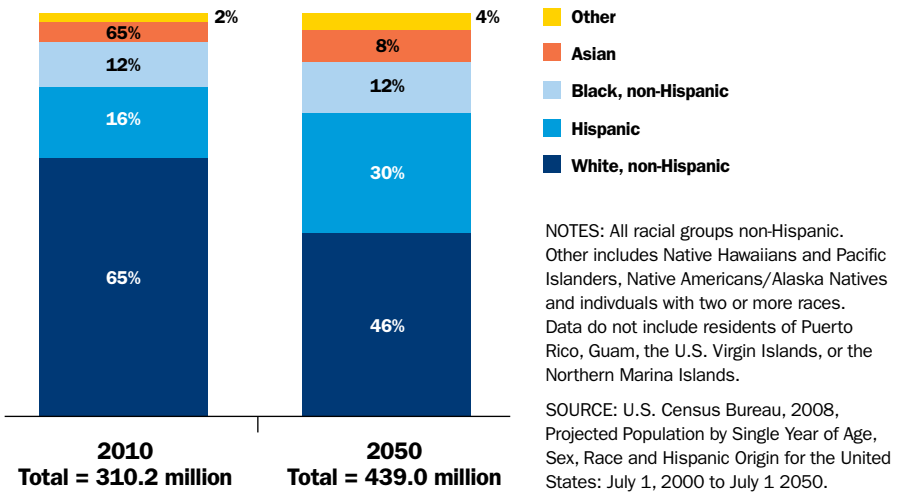
Initiatives that promote diversity in its broadest sense strengthen institutions. ASN has chosen to be proactive in this spirit and successfully brought together a diverse group of individuals to have an honest and innovative exchange of how to best promote diversity in our organization.

Keisha L. Gibson, MD, MPH, summit participant

The call to enhance diversity within health care professional societies, including the ASN, is often based on moral grounds and there is certainly a moral case to be made for doing so. Nevertheless, quoting the late Herb Nickens, 'it is not just the right thing to do, it is the smart thing to do.' At ASN we recognize that enhancing our diversity makes us better able to lead the fight against kidney disease.

Donald E. Wesson, MD, FASN

Figure 1. Distribution of U.S. Population by Race, Ethnicity, 2010 and 2050



NOTES: All racial groups non-Hispanic. Other includes Native Hawaiians and Pacific Islanders, Native Americans/Alaska Natives and indivduals with two or more races. Data do not include residents of Puerto Rico, Guam, the U.S. Virgin Islands, or the Northern Marina Islands.

SOURCE: U.S. Census Bureau, 2008, Projected Population by Single Year of Age, Sex, Race and Hispanic Origin for the United States: July 1, 2000 to July 1 2050.

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ASN Kidney News is published by the American Society of Nephrology
1510 H Street NW, Suite 800, Washington, DC 20005. Phone: 202-640-4660

www.asn-online.org

Postmaster: Please send address changes to *ASN Kidney News*, c/o Customer Service, American Society of Nephrology 1510 H Street NW, Suite 800, Washington, DC 20005.

Publications mail agreement No. 40624074. Return undeliverable Canadian addresses to PO Box 503, RPO West Beaver Creek, Richmond Hill ON L4B 4R6

ASN Kidney News (ISSN print 1943-8044 and online 1943-8052) is an official publication of the American Society of Nephrology, 1510 H Street NW #800, Washington DC 20005, and is published monthly. Periodicals postage paid at Washington, DC and at additional mailing offices. Subscription rates: $12 per year. To order, please email bhenkel@asn-online.org. Subscription prices subject to change. Annual ASN membership dues include $12 for *ASN Kidney News* subscription.

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ALEXION

Kidney Health Initiative Announces Pilot Projects, Leadership

KIDNEY HEALTH INITIATIVE

ASN and FDA launched the Kidney Health Initiative (KHI), a new public-private partnership in September 2012. In less than one year, KHI has made significant progress moving the partnership forward.

The Board of Directors for KHI was appointed in February 2013 (Table 1). Members of the Board of Directors were selected from the initiative's Pioneer Members. An important strength of the Board is that it represents the richly diverse interests of stakeholders. The Board met by conference call twice prior to hosting its first face-to-face meeting on May 8, 2013. Topics discussed at these first meetings have included defining key mission areas for KHI, identifying topics for KHI to address, and building a collaborative project submission process for KHI members to submit their concepts.

To date, the response to KHI from the nephrology community has been overwhelmingly positive. Membership has currently surpassed 40 Pioneer Members and includes patients, health professionals, and research institutes as well as the biotechnology, dialysis, medical device, and pharmaceutical industries from the United States and abroad. To view a complete and updated list of members, please visit the KHI website (http://www.kidneyhealthinitiative.org).

While the infrastructure of KHI was being established, the leadership identified and initiated two pilot projects with the hope that these pilot projects will serve as examples of the strength of KHI and a model for future proposals. A pilot project on pharmacokinetics in patients receiving continuous renal replacement therapy (CRRT) is underway and is being led by co-chairs George R. Aronoff, MD, FACP, and Thomas D. Nolin PhD, PharmD, FASN. The objective is to improve the process of studying drug dosing in CRRT patients. The workgroup will generate a white paper that will concisely report on multiple considerations in performing pharmacokinetics studies in CRRT patients.

Brad H. Rovin, MD, FASN. is leading the second pilot project examining clinical trial endpoints in lupus nephritis. This project is a partnership with the Lupus Nephritis Trial Network (LNTN) and includes both nephrologists and rheumatologists focused on treating lupus nephritis. The project has three components: a comprehensive literature review to identify lupus nephritis outcome measures currently and previously used, an analysis of primary data from completed clinical trials and observational databases, and the derivation of consensus recommendations.

The study group will recommend a core set of outcome measures, biomarkers, surrogate markers, and clearly defined terms that should be incorporated into all lupus nephritis trials such that these trials represent best practices in this area. By establishing a core set of measures, this work will also provide a basis for comparison of results across future trials.

The final pilot project initiated by KHI members will be a white paper aimed at identifying barriers to innovation in kidney disease. For more information on the pilot projects or publications, please visit the KHI website (http://www.kidneyhealthinitiative.org).

Starting this summer, KHI will begin accepting ideas for projects from its members, which is its main focus. In September, members of KHI will come together for an annual stakeholder's meeting. This conference is intended to help KHI members discuss ongoing projects, identify new projects for collaboration, and learn more about the linkages and collaborations between the renal community and the FDA.

KHI looks forward to updating the nephrology community as ongoing and future projects generate important data for the continued scientific advancement of patients with kidney disease.

To learn more about KHI, pilot projects, or membership, please visit http://www.kidneyhealthinitiative.org, or contact KHI Project Director Melissa West at mwest@asn-online.org.

Table 1. Kidney Health Initiative Board of Directors

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Center for Drug Evaluation and Research (CDER), U.S. Food and Drug Administration (FDA)

Prabir Roy-Chaudhury, MD, PhD, FASN
University of Cincinnati / American Society of Nephrology

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Stuart Goldstein, MD, *Cincinnati Children's Hospital Medical Center*

Jula K. Inrig, MD, FASN, *Duke University/ Quintiles Global Clinical Research Organization*

Reshma Kewalramani, MD, FASN, *Amgen*

Alan S. Kliger, MD, *Yale University*

Kristine Kuus, PhD, *The Binding Site*

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Shawne Suggs-Anderson, MMSc, RD, *Center for Food Safety & Applied Nutrition (CFSAN), FDA*

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Melissa West, Project Director

NIA Deputy Director Speaks with *ASN Kidney News*

In March 2013, ASN Kidney News kicked off a Q and A series with NIH institute directors. In this month's issue KN interviewed National Institute on Aging (NIA) Deputy Director Marie Bernard, MD, a clinician and geriatrician, about NIA's research portfolio.

KN:

You have been in your post at NIA for 5 years. How have the institute's priorities changed over those years?

Bernard:

In the almost 5 years that I have been deputy director of NIA, and the more than 25 years that I have followed NIA research, I have been impressed that aging research has gone beyond the "bean counting" stage, that is, qualitative descriptions of aging-related phenomena, as it was characterized in the past, to in-depth exploration of the mechanisms underlying aging and disease. This includes the mechanisms that lead to aging, cognitive health and decline, behavior and social interactions, and the maintenance of health and development of disease. Additionally, there is very thoughtful exploration of means to intervene to maintain and enhance health, both physical and cognitive, with aging.

KN:

As a geriatrician and clinician, you have had experience diagnosing and treating hypertension, diabetes, and other conditions common among older adults. What advances do you deem noteworthy since the early days of your career and how can NIA speed further development in these areas?

Bernard:

As a board-certified geriatrician I have relied upon information from NIA and NIH to guide my care of patients and teaching of students, residents, and fellows. Noteworthy findings during that time related to the impact of lifestyle modification, including exercise and diet, to limit the likelihood of the development of diabetes mellitus and to delay the development of frailty. For example, were it not for the partnering of NIA with NIDDK for the Diabetes Prevention Program (DPP), we might not have known that people who were 60 years and older only responded to lifestyle modification for the prevention of diabetes, whereas the younger participants responded to lifestyle modification and metformin.

Other NIA research has shown that exercise is useful even in the very elderly in nursing homes. It was a great patient motivator when I counseled them to modify their habits to benefit their medical conditions. NIA is making every effort to further develop areas relevant to enhancing health and quality of life. I have been particularly impressed with the efforts to leverage NIA resources by collaborative initiatives with other Institutes and Centers (ICs) within NIH, such as the support of the DPP, and in public-private partnerships such as the Alzheimer's Disease Neuroimaging Initiative.

KN:

As the elderly population in the United States continues to grow, so will the importance of prevention initiatives to contain escalating health care costs. How does NIA balance its research portfolio between prevention and treatment, and what research opportunities are on the horizon for strengthening health literacy and wellness programs for this population?

Bernard:

NIA has a number of means of obtaining input from the scientific community to help balance its research portfolio between prevention and treatment. There is of course the core of the research enterprise—peer-reviewed, investigator-initiated projects—which make up the vast majority of the research funded by our institute. Peer reviewers are asked to rank research proposals based not only on the science, but also on innovation, as well as importance to public health. Additionally, our National Advisory Council provides a second level of review of all grants considered for funding, and provides guidance regarding priorities for research.

As we consider the development of special initiatives to encourage research in developing fields, we start with workshops and other outreach to the scientific community for input regarding appropriate priorities. These always provide a lively exchange of ideas and insights. Finally, we have periodic reviews of the research portfolios of each of our four extramural funding divisions by our National Advisory Council, seeking advice regarding the current direction of specific research areas and how they can be enhanced in the future. By these means we attempt to maintain a balanced approach to the many opportunities in aging research.

KN:

Elderly patients often experience more than one chronic condition at a time. Older kidney patients may have heart disease, hypertension, or diabetes. How does NIA work with other institutes and centers to maximize efficiencies in the research of co-morbid conditions?

Bernard:

NIA is particularly interested in studies of the impact of multiple chronic conditions (MCCs), given their high prevalence among the elderly. To this end, we collaborate extensively with other NIH institutes to evaluate the impact of various chronic conditions in this population. For example, we are working with the National Heart, Lung, and Blood Institute and the National Institute of Diabetes and Digestive and Kidney Diseases in the Systolic Blood Pressure Intervention Trial (SPRINT), which examines the impact of blood pressure reduction in people with hypertension and chronic renal insufficiency. I have mentioned our joint initiatives in diabetes. We have also assembled a group of experts to develop universal outcomes for assessment of individuals with MCCs, as reported last year in the *Journal of the American Geriatrics Society*.(1). We are also working with the trans-DHHS (Department of Health and Human Services) working group on MCCs, and with the Centers for Medicare & Medicaid Services and the National Quality Forum to consider how MCC outcomes might become quality measures.

KN:

How does NIA plan to ensure that the educational continuum for medical students, resi-

dents, and fellows prepares the next generation of physicians to provide the best possible care for the growing elderly population?

Bernard:

We are very concerned about the pipeline of future scientists and clinicians specializing in the care and treatment of older people. In research, we support traditional F, T, and K training and career development awards. We also have the Paul B. Beeson award that provides additional support to clinicians to assure protected time to conduct research. This K08 and K23 opportunity is provided as a request for application (RFA) each year, in collaboration with the National Institute of Neurological Disorders and Stroke, the American Federation for Aging Research, the John A. Hartford Foundation, and others. Recent review of the Beeson program found a high success rate in obtaining subsequent R01 research project grant funding. We have been very pleased that several Beeson Scholars have focused on issues related to chronic kidney disease.

We also recently developed the Grants for Early Medical/Surgical Specialists' Transition to Aging Research (GEMSSTAR) program. This R03 is designed for medical and surgical specialists who are new to aging research. The award is contingent on the applicant demonstrating protected time and resources for career development from another source. The ASN Foundation for Kidney Research and the Alliance for Academic Internal Medicine (AAIM) offer junior development grants in geriatric nephrology (http://www.asn-online.org/foundation/career-development.aspx) as a source of support. Other sources can include the applicant's institution or affiliated Veterans Administration hospital; a Clinical and Translational Science Award; NIH K12 or R25 program; specialty societies, such as the Association of Specialty Professors or the American Geriatrics Society; Older Americans Independence Center Research Career Development Core; or other government, public, or private sources. The goal of the program is to assist new faculty members in gathering the data needed to successfully compete for a K award. Both the GEMSSTAR and Beeson RFAs are issued in the late spring of each year.

Our Medical Student Training in Aging Research (MSTAR) program encourages medical students, particularly those interested in research, to consider a career in academic geriatrics. NIA partners with the American Federation for Aging Research and several foundations to offer 8- to 12-week MSTAR Program scholarships to first- and second-year medical students, providing hands-on and didactic research training in aging and geriatrics. We also fund training programs that reserve slots for medical students or physicians interested in basic, clinical, and translational geriatric research.

Information about all of NIA's training and career development awards can be found at http://www.nia.nih.gov/research/dea/research-training-and-career-award-support.

We hope that these initiatives will help with the admittedly leaky pipeline of future aging researchers. There are also a number of initiatives to better prepare clinicians for the demands of our progressively aging society, led by the Health Resources Services Administration (HRSA) and enhanced by enabling legislation and funding as a result of the Affordable Care Act. Review of the HRSA website should be helpful in getting a full sense of the scope of those activities.

KN:

One of NIA's initiatives is "Minority Aging and Health Disparities." Studies have shown that African Americans have a disproportionate share of kidney disease compared to Caucasians. What is the institute doing to address health disparities in general, and disparities in kidney disease in particular?

Bernard:

In approaching health disparities, NIA looks at both diversifying the research workforce and exploring health disparities that may exist, in an effort to narrow gaps. NIA's National Advisory Council recently conducted a review of our health disparities research and minority aging researcher training. We were found to have a strong program for the development of researchers—ranging from the annual Summer Institute on Aging Research to the GEMSSTAR and Beeson programs described earlier. We also have programs to encourage undergraduates interested in aging research through our NIA MSTEM Advancing Diversity in Aging Research through Undergraduate Education program. These grants are made to institutions that propose creative and innovative research education programs to diversify the workforce in aging. And our Aging Research Dissertation Awards to Increase Diversity offer dissertation support to eligible doctoral students through awards to their institutions.

In approaching health disparities, NIA looks at both diversifying the research workforce and exploring health disparities that may exist, in an effort to narrow gaps.

Additionally, we have an Office of Special Populations in the Office of the NIA Director that is responsible for further enhancing our health disparities research portfolio. NIA's innovative Research Centers on Minority Aging Research (RCMARS) continue to provide leadership in disparities research. We also have a number of specific initiatives looking at health care systems and disparities in care within those systems. A number of clinical studies with oversampling of underrepresented minority groups have allowed us to examine differences in Alzheimer's disease presentation and osteoporosis by race/ethnicity. The advent of the new trans-NIH health disparities strategic plan, due to be unveiled this fall, will also intensify our efforts in this area. However, our overall efforts related to health disparities have not specifically focused on disparities in kidney disease.

KN:

What do you consider the greatest opportunities for researchers in aging over the next decade?

Bernard:

Researchers in aging have the distinct advantage of the demographic imperative. As more and more of our population turns 65 and older with aging of the baby boomer generation, there will be increased demands for better understanding of the aging process and development of interventions to prevent diseases and disability associated with growing older. That is already being seen in the demands for an invigorated effort in Alzheimer's disease. In 2011, President Obama signed into law the National Alzheimer's Project Act (http://aspe.hhs.gov/daltcp/napa/). This calls for a national plan for the approach to Alzheimer's disease, and NIA/NIH leads the research component of that plan. Aging research itself is entering a new era. There is growing interest among most of the NIH ICs in the basic biology underlying aging and age-related disease, as demonstrated by the development of the trans-NIH Geroscience Interest Group, supported by 20 of the 27 ICs. (http://sigs.nih.gov/geroscience/Pages/default.aspx). The time is right for focus on aging research, and scientists in the field are likely to find support for their interests owing to these converging forces.

KN:

The scientific community is concerned not only about the mandatory automatic spending cuts to NIH that went into effect March 1, but also about the shrinking federal dollars for medical research overall. How will NIA minimize the impact of the cuts and allocate its budget to maximize the scientific impact?

Bernard:

The NIA will move forward with a balanced program funding a spectrum of basic, translational, clinical, and social and behavioral research as best we can. Certainly, we know that cuts and ongoing budget constraints will reduce our ability to capitalize on many scientific opportunities presented to us, as the percentage of investigator-initiated proposals we are able to fund remains quite low. This means that many highly meritorious proposals, which have the promise of moving research on aging and age-related diseases forward in important ways, simply cannot be funded.

Each of the NIH ICs has been given the authority to decide how the sequestration cuts will be made. Different ICs have different priorities and conditions that factor into their decisions. In NIA's case, we will look at both competing and non-competing grants and strike a balance between funding new studies and maintaining important research projects to which we have already committed.

Reference

1. Working Group on Health Outcomes for Older Persons with Multiple Chronic Conditions. University health outcomes measures for older persons with multiple chronic conditions. *J Am Geriatr Soc* 2012; 60 (12); 2333–2341.

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Practice Pointers

Hypertension and Blood Pressure Goals in the Dialysis Unit

In this month's issue, Jula K. Inrig of the ASN Dialysis Advisory Group and Kevin Griffiths of the ASN Practicing Nephrologists Advisory Group converse about how to handle hypertension in the dialysis unit and about blood pressure goals for patients.

By Jula K. Inrig and Kevin Griffiths

JKI: Please tell us about intradialytic hypertension. Why is it so difficult to define it? What are the proposed mechanisms?

Clinically, intradialytic hypertension is defined as a rise in blood pressure (BP) that occurs during dialysis; you tend to recognize it when you see it (or get called by the nurse about it).

In research, most studies define intradialytic hypertension based on an increase in BP occurring from before to after dialysis, using systolic BP (SBP), mean arterial pressure, or both. However, research definitions of intradialytic hypertension do not always take into consideration measurements made during dialysis, because these are not always readily available, and these more modest increases in BP may be less recognized by clinicians.

Proposed mechanisms for intradialytic hypertension include volume overload, sodium excess, excess endothelin-1 relative to nitric oxide, sympathetic overactivity, dialyzability of medications, and overactivity of the renin-angiotensin-aldosterone system. Evidence suggests that intradialytic hypertension is caused by an imbalance in vasoregulators endothelin-1 and nitric oxide. What causes that imbalance is yet to be determined.

JKI: What is the clinical significance of BP increases during dialysis? Prevalence, morbidity and mortality, outcomes data, and so on? Is there any correlation between intradialytic hypertension and dialysis adequacy?

An increase in SBP above 10 mm Hg from before to after dialysis has been associated with increased hospitalizations and higher mortality. However, evolving research suggests that even small increases in BP from before to after dialysis are associated with adverse outcomes. Although most patients have occasional increases in SBP under these conditions, approximately10 percent have persistent increases in BP that exceed 10 mm Hg from before to after dialysis, observed over the course of 6 months.

There is no correlation between dialysis adequacy (traditionally defined by urea kinetics) and the presence of intradialytic hypertension. However, when we look broadly at sodium and water balance, sodium solute removal may be inadequate among patients with intradialytic hypertension.

KG: According to current published guidelines, what is the recommended BP target for hemodialysis patients? Peritoneal dialysis patients? Is there any evidence pointing to different BP goals for young and old dialysis patients?

The current Kidney Disease Outcome Quality Initiative guidelines recommend a predialysis target BP value of less than 140/90 mm Hg and a postdialysis value of less than 130/80 mm Hg for either hemodialysis or peritoneal dialysis patients. However, a dialysis patient's age may alter these parameters. Recent evidence suggests that dialysis patients over age 50 with SBP under 140 mm Hg have a higher mortality rate than do patients with SBP greater than 160 mm Hg. Dialysis patients under age 50 whose SBP is under 140 mm Hg had a lower mortality rate than when their SBP was above 160 mm Hg.

KG: Are there any studies that examine the use of predialysis or postdialysis BP or other BP measurements as guides to manage therapy? Is there any role for ambulatory BP monitoring in dialysis patients?

Predialysis and postdialysis BP readings are unreliable measurements on which to base antihypertensive therapy. Evidence suggests that predialysis SBP readings overestimate SBP by 10 mm Hg, whereas postdialysis SBP may underestimate SBP by 7 mm Hg. An ongoing pilot randomized clinical trial (RCT) is being conducted (BP in Dialysis, BID) to determine the safety and feasibility of targeting different predialysis BP levels.

Ambulatory BP monitoring and home BP readings are effective tools to guide therapy for dialysis patients because both are more reflective of true BP burden and have stronger relationships with adverse outcomes. These tools are particularly useful for patients who have large variability in dialysis unit BP measurements or discrepancies between home and dialysis unit readings. Thus, they can be used to help minimize overdosing or underdosing of antihypertensive medications.

KG: Are there preferred BP medications for hemodialysis or peritoneal dialysis patients, considering their specific characteristics, as well as dialyzability?

Angiotensin II receptor antagonists or ACE inhibitors, β-blockers, and calcium channel blockers are recommended as first-choice drugs depending on the patient's other comorbidities. Peritoneal dialysis patients who have residual renal function (RRF) and hemodialysis patients with RRF benefit most from ACE inhibitors because this class regresses LVH and preserves RRF. Carvedilol or another β-blocker is recommended for patients who have had a recent heart attack and for those with systolic heart failure. Finally, evidence shows that diuretics are associated with preservation of RRF and lower all-cause mortality. Most ACE-I agents are dialyzable (except fosinopril), but angiotensin-receptor blockers, calcium channel blockers, and combination α-β-blockers are not dialyzable and should be preferred for those with high BP during hemodialysis.

JKI: How effective is dry weight reduction alone in controlling BP in patients receiving conventional thrice-weekly hemodialysis?

Solid evidence to support dry weight reduction for short-term control of BP comes from the Dry-Weight Reduction in Hypertensive HD Patients (DRIP) study. In this 8-week study, systematically lowering dry weight reduced ambulatory BP by an additional 7 mm Hg beyond usual care. However, these patients still required antihypertensive therapy and were not normotensive at the end of the study. Although achieving euvolemia is very important for BP control and cardiovascular protection, thrice-weekly dialysis is not typically adequate for controlling BP.

JKI: What therapies (e.g., dialysis prescription alterations) can be used to treat a patient who experiences a hypertensive episode during dialysis? What role do dialysate sodium and dialysate calcium have in BP control?

Dry weight reduction should be tried before other therapies. However, I have not found this to be very effective among patients with persistent intradialytic increases in BP. A recent uncontrolled study of 25 patients with intradialytic hypertension demonstrated that the use of carvedilol (at doses up to 50 mg twice daily) abrogated the intradialytic rise in BP among two-thirds of these patients. The improvement in intradialytic hypertension corresponded with improvements in endothelial cell function. Although RCTs are needed to confirm this, carvedilol is certainly a good option for BP control among those who do not improve with dry weight reduction.

Two potential dialysis alterations have been suggested to help control BP among those with intradialytic hypertension: lowering dialysate sodium (by stabilizing nitric oxide and endothelin-1 release) and lowering dialysate calcium (by reducing cardiac contractility). Both measures have been tested in early stages and have been pre-

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Practice Pointers

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sented as abstracts at the American Society of Nephrology Kidney Week meetings in 2011 and 2012, and they may be beneficial. More formal studies are under way.

KG: What are the best treatment options for refractory hypertension in dialysis patients?

Multiple reasons exist for refractory hypertension in a dialysis patient, ranging from noncompliance with medications, nonadherence to dialysis prescriptions, administration of Epogen and nonsteroidal anti-inflammatory drugs, and renovascular hypertension. The best treatment options include minoxidil and also transdermal clonidine for patients whom the nephrologists have deemed noncompliant. Physicians may consider converting the patient to peritoneal dialysis, or transferring the patient to nocturnal hemodialysis, in which more consistent maintenance of dry weight can be achieved. Finally, some smaller studies suggest that bilateral nephrectomy may lead to better blood pressure control after 3 months. However, with the improvement in oral antihypertensive therapy and control of volume status, this method is not widely used.

JKI: What nonpharmacologic interventions may optimize BP control in dialysis patients?

High dietary sodium intake increases thirst, interdialytic weight gain, and BP. Thus, dietary sodium restriction is very important for BP control among dialysis patients, particularly for those receiving conventional thrice-weekly dialysis. Small studies also suggest that lowering dialysate sodium may help control interdialytic BP. Several nonpharmacologic interventions are being tested in phase II and phase III trials among patients with resistant hypertension, including renal denervation and baroreflex activation therapy, but these treatments have not been tested in dialysis patients.

KG and JKI: With the Joint National Committee Guidelines (JNC) VIII soon to be released, do you foresee any changes that may be applicable to dialysis patients?

In the absence of RCTs, it is unlikely that JNC VIII will give specific recommendations for either BP agents or targets for dialysis patients. Based on more recent trial data, the guideline BP targets for chronic kidney disease patients and elderly patients may be higher than those in JNC VII. Although the data reviewed for JNC VIII will not come from trials that enrolled dialysis patients, we think that using higher BP targets (particularly in elderly patients) is relevant to dialysis patients.

KG and JKI: Is there any role for diuretics in dialysis patients in terms of BP control or amelioration of heart failure?

Among incident dialysis patients with residual renal function, diuretics can be useful to help remove salt and water in the interdialytic period to minimize the amount needed to be ultrafiltered during dialysis. One observational study suggested the use of diuretics during the first year of hemodialysis to be associated with improved outcomes, however this is likely highly confounded. Among patients on peritoneal dialysis, it is unclear whether or not the use of diuretics affects RRF. Personally, we individualize the use of diuretics. If a patient has good urine output that is enhanced by the use of diuretics without contributing to intradialytic hypotension, then we will continue them. But there is concern about diuretics contributing to hemodynamic instability and faster loss of RRF. Thus, their use needs to be individualized and more studies are needed in this area.

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

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

Table 4: Incidence of Hypoglycemia* in Controlled Clinical Studies

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

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

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

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

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

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

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

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

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

DRUG INTERACTIONS

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

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

USE IN SPECIFIC POPULATIONS

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

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

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

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

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

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

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

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

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

OVERDOSAGE

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

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

PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Medication Guide).

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

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

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

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

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

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

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

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

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

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

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

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

Active ingredient made in Belgium

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

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

Licensed from Mitsubishi Tanabe Pharma Corporation

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janssen

Atrasentan with Current Optimal Therapy Reduces Albuminuria in Type 2 Nephropathy

Atrasentan, an oral endothelin receptor antagonist, reduces albuminuria and improves the lipid profile in patients with diabetic nephropathy when given with optimal therapy using an angiotensin converting enzyme (ACE) inhibitor or an angiotensin II receptor blocker (ARB), a recent study shows.

"It has a nearly 40 percent reduction of albuminuria over the full 12-week stretch [of the trial], with minimal side effects," Dick de Zeeuw, MD, PhD, professor and chair of the department of clinical pharmacology at University Medical Center Groningen in The Netherlands, reported at the 50th Congress of the European Renal Association—European Dialysis and Transplant Association in Istanbul. Besides being a marker of kidney damage, albuminuria is also a promoter of kidney damage and a cardiovascular risk factor, possibly because it indicates generalized vascular and endothelial dysfunction.

Atrasentan is an investigational compound that blocks the effect of endothelin-1 at the endothelin-A receptor. Endothelin-1 is a peptide that constricts blood vessels in the kidney and has a negative effect on kidney function.

Although optimal therapy with compounds that target the renin-angiotensin-aldosterone system, such as ACE inhibitors and ARBs, help protect the kidneys and reduce albuminuria, some risk persists. "There is a pressing need for new medications to treat nephropathy in patients with type 2 diabetes who have a high risk to end up in dialysis," de Zeeuw said.

He presented the results of two parallel, double blind, placebo-controlled, multinational phase 2b studies (total n = 211) in which patients with type 2 diabetes and nephropathy received maximum tolerated labeled doses of ACE inhibitors or ARBs. They also received atrasentan at 0.75 mg/day (n = 78), 1.25 mg/day (n = 83), or placebo (n = 50) to evaluate the efficacy of the compound in lowering albuminuria and its safety. At baseline, patients in the three groups all had macroalbuminuria, as determined by the urinary albumin-to-creatinine ratio (878 mg/g, 826 mg/g, and 671 mg/g, respectively).

At the end of the 12-week trials, patients experienced sustained reductions in the primary endpoint of the urinary albumin-to-creatinine ratio: a 36 percent geometric mean decrease in the group receiving the 0.75-mg dose and a 44 percent decrease at the 1.25-mg dose versus a 2 percent increase in the placebo group (both $p < 0.001$ vs. placebo). Just over half of the patients in each group experienced a decrease of more than 30 percent in urinary albumin-to-creatinine ratio. Significant decreases ($p < 0.001$) were evident as early as 2 weeks for the atrasentan groups. There were also decreases in low-density lipoprotein cholesterol and triglyceride levels in the active drug groups.

Adverse events similar to placebo

The rates of adverse events were similar among the three groups. Peripheral edema occurred in 35 percent of patients in the 0.75-mg group and in 42 percent in the 1.25-mg and placebo groups. Diarrhea and constipation occurred in 13, 21, and 14 percent of the people in the three arms, respectively. Adverse events caused 8 percent of participants to drop out of the low-dose group and 15 percent to discontinue the study in the high-dose group. Edema was the most common reason for participants to discontinue the study. None discontinued in the placebo group.

Estimated GFRs dropped by less than 1 mL/min per 1.73 m^2 in both of the atrasentan groups, but these changes were no different from those in the placebo group ($p = 0.412$ and $p = 0.355$ for the 0.75-mg and 1.25-mg doses, respectively).

A phase 3 randomized, double-blind, placebo-controlled trial is planned using the 0.75-mg daily dose of atrasentan, which was determined in the phase 2b trials to have the best balance of efficacy and safety. The trial will investigate renal as well as cardiovascular outcomes when atrasentan is given on top of current optimal standard of care to patients with type 2 diabetic nephropathy. It is planned to involve more than 4000 patients and to run for 4 years.

As noted by de Zeeuw, other endothelin antagonists have been tested in type 2 diabetes and have lowered albuminuria. A trial of avosentan was stopped early because of fluid retention leading to congestive heart failure. He said that this adverse effect was blamed on the high dose of the drug, and current trials are looking at a lower dose that might retain the albumin-lowering effects but avoid fluid retention.

Mediterranean Diet Linked to Lower Mortality in Older Men with Chronic Kidney Disease

For people with chronic kidney disease (CKD) who followed a Mediterranean-style diet, renal function improved. The more these people adhered to such a diet, the more improvement was seen in survival, according to the results of a study presented at the 50th Congress of the European Renal Association—European Dialysis and Transplant Association in Istanbul, Turkey, in May.

The Mediterranean diet consists largely of plant-based foods such as fruits and vegetables, whole grains, legumes, and nuts; healthful oils such as olive and canola; and some fish and poultry but limits red meat and saturated fats. Red wine in moderation is optional; it has been associated in various populations with lower risks of illness and mortality. However, few data exist regarding kidney function in community-dwelling adults who follow such a diet.

Juan Carrero, PhD, of the Karolinska Institute in Stockholm and co-workers conducted an observational study on a population-based cohort (the Uppsala Longitudinal Study of Adult Men) of 1110 Swedish men around 70 years old to see whether the men who followed a Mediterranean diet had improved kidney function, lower cardiometabolic risks, and reduced mortality. From 7-day diet diaries that the men recorded, the researchers determined their dietary habits, from which they calculated a Mediterranean Diet Score, allowing classification of the participants as low, medium, or high adherents to such a diet.

Within the cohort, 506 men had GFRs of less than 60 mL/min per 1.73 m^2 and were therefore considered to have CKD. Deaths were recorded during a median follow-up time of 9.9 years.

During follow-up, 168 of the 506 individuals with CKD died. Better adherence to the diet was independently associated with better survival. For every two-point increase in the Mediterranean Diet Score, the investigators observed an 18 percent lower risk of death, with a stronger association in those individuals who had adequate dietary intakes.

Of the individuals who died, the adherence groups did not differ in their cardiometabolic risk factors. "Most potential explanatory risk factors for the mortality association, such as obesity, blood pressure, lipoproteins, glucose, insulin, or inflammation, did not associate with a greater or poorer adherence to the diet," Carrero said. To some extent, this lack of association with such risk factors may be attributable to the homogeneous nature of the cohort: men of about the same age, from the same region, and of the same ethnicity. "In addition…the benefits of the Mediterranean diet may be mainly accounted for by individual nutrients, such as high fiber intake and high PUFA [polyunsaturated fatty acids] but low SFA [saturated fatty acid] intake rather than by the score as a whole," he said.

In comparison with low adherents to the diet, high adherents had a 42 percent lower risk of CKD after adjustment for body mass index, physical activity, smoking, education, hypertension, hyperlipidemia, and diabetes (adjusted odds ratio 0.58; 95 percent confidence

interval 0.38–0.87; p for trend = 0.04).

Carrero pointed out that adherence to a Mediterranean diet is not very common among older individuals in Scandinavia, so the adherence scores were relative within that population. "Thus, a high adherence to this diet means that among the individuals studied, they had an intake of food most in accordance with the Mediterranean style," he explained. A potential confounding factor in the study is that individuals with low adherence to a Mediterranean diet may also have been less compliant with other lifestyle and medical advice.

The strengths of the study are its prospective nature; the use of the 7-day dietary record, which is the preferred method for dietary assessment; and the use of a national mortality registry with 100 percent inclusion. The limitations include a lack of data on the use of dietary supplements and the fact that about half of the participants did not provide adequate dietary recall results. Finally, because the study involved elderly men with moderate CKD from a rather homogeneous population, the results may not be applicable to other populations.

Because of the observational nature of the study, one cannot draw a causal link between adherence to a Mediterranean diet and improved kidney function or lower mortality. The investigators therefore suggest initiating interventional studies to formally test such a link.

Cardiovascular Risk Profile Improves with Sevelamer Use in Diabetic Nephropathy

Markers of cardiovascular protection rose when diabetic patients with chronic kidney disease were treated with the phosphate binder sevelamer carbonate (sevelamer). In a randomized trial comparing sevelamer with the phosphate binder calcium carbonate, the group receiving sevelamer experienced increased levels of estrogen receptor-α (ER-α), two markers of antioxidant activity, and defenses against advanced glycation end products.

Phosphate is a component of diet and is absorbed in the small intestine. The kidneys excrete excess phosphate, but in the case of impaired renal function, they cannot maintain proper phosphate balance. Studies have shown that the resulting hyperphosphatemia correlates with increased mortality. Dietary restriction of phosphate intake and the use of oral phosphate binders can help control phosphate balance.

Sevelamer is a non–calcium-containing phosphate binder that may also have additional beneficial effects on other factors that promote cardiovascular disease, a major cause of mortality in chronic kidney disease.

Oxidative stress and inflammation are part of the process of cardiovascular disease. ER-α is known to reduce these factors in men and women, but ER-α activity is reduced in diabetic kidney disease, suggesting that decreased ER-α may contribute to the increased risk and prevalence of cardiovascular disease in this population. Simply put, less ER-α leads to more oxidative stress and inflammation, leading to more cardiovascular damage. In addition, advanced glycation end products, the result of hyperglycemia in diabetes, elevate the levels of oxidative stress and inflammation.

Besides binding phosphate, sevelamer is also thought to block the absorption of advanced glycation end products from food, further helping to limit oxidative stress and inflammation. Given that sevelamer does not contain calcium, it may also lower the progression of vascular calcification in comparison with calcium-containing phosphate binders.

Testing effect of sevelamer on cardiovascular risk factors

To test the hypothesis that sevelamer restores the levels of ER-α and has beneficial effects on other risk factors, Gary Striker, MD, research professor of geriatrics and medicine at the Mount Sinai School of Medicine in New York City, and colleagues compared the effects of sevelamer and calcium carbonate on the levels of ER-α and other markers of antioxidant and anti–advanced glycation end products in peripheral blood mononuclear cells (white blood cells). They presented their findings at the 50th Congress of the European Renal Association—European Dialysis and Transplant Association.

The trial randomly assigned men and women with type 2 diabetes to sevelamer 4800 mg/day (n = 56) or to calcium carbonate 1950 mg/day (n = 50) for 6 months. The inclusion criteria were hemoglobin A1c level greater than 6.5 percent, an estimated GFR of 25–80 mL/min per 1.73 m^2, and albumin excretion greater than 300 mg/day. The mean ages of the men and women in the sevelamer and calcium carbonate groups ranged from 60.1 to 67.5 years.

In an analysis at 3 months assessing the amount of change from baseline in the biomarkers, the group as a whole (both men and women analyzed together) showed a marked increase in ER-α if they received sevelamer as opposed to calcium carbonate (p = 0.003). There were also significant increases in two biomarkers of antioxidant effects, Nrf2 and advanced glycated end-product receptor 1 (AGER1) (p = 0.009, p = 0.028, respectively). Nrf1 activates multiple pathways within cells to protect against oxidative stress and inflammation, and AGER1 suppresses oxidative stress caused by cellular oxidants.

The levels of two inflammatory markers predictive of cardiovascular disease and progression of diabetic kidney disease (tumor necrosis factor receptor 1 and RAGE) decreased in the group receiving sevelamer.

There were differences between men and women in some of the various markers when the sexes were analyzed separately, but the major finding of increased levels of ER-α was consistent regardless of sex.

The investigators concluded that sevelamer carbonate restored levels of ER-α in both men and women and that this effect was associated with a reduction in markers of oxidative stress, inflammation, progression of diabetic kidney disease, and risk factors for cardiovascular disease, as well as improvements in antioxidant defenses.

It is important to note that the study involved surrogate markers that indicate risk. It did not directly investigate clinical outcomes such as cardiovascular events or progression of kidney disease. Larger trials of longer duration are planned to see whether the findings in this trial will be reflected in a reduction in clinical events.

Policy Update

ASN and Patient Advocates Advance Kidney Health on Capitol Hill

By Grant Olan

On April 25, 2013, the American Society of Nephrology (ASN) met with nearly 60 congressional offices for Kidney Health Advocacy Day. In a first for ASN, the society partnered with the American Association of Kidney Patients (AAKP) and Dialysis Patient Citizens (DPC) to build support for the following three key issues of mutual importance to the three organizations.

Passage of transplant legislation that will ease access to organ donations and provide kidney transplant recipients lifetime coverage of immunosuppressive drugs:

The HIV Organ Policy Equity Act, or HOPE Act, passed by unanimous consent in the Senate on June 17 after vigorous advocacy by ASN and more than 50 other organizations (see story, next page). The bill, which must still pass the House before President Barack Obama can sign it into law, would end a 1984 federal ban on the transplantation of organs from deceased HIV+ people to people with HIV who are on the transplant list. Because lifting this ban would free up organs of all types, patients with HIV would get organs faster than they would on the waitlist, and that would make more organs available for all patients.

The "Comprehensive Immunosuppressive Drug Coverage for Kidney Transplant Patients Act of 2013" (S. 323 / H.R. 1438) would extend Medicare coverage for immunosuppressive drugs over a recipient's lifetime, protecting Medicare's investment in the transplant and ensuring that no patients will lose their kidney.

Sustained funding for medical research

Sequestration cut National Institutes of Health (NIH) funding in 2013 by 5.1 percent, or $1.6 billion, affecting all NIH institutes and centers, including the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK). That means that approximately 700 fewer competitive research project grants will be issued this year than in 2012. These cuts are on top of NIH's already shrinking purchasing power. AAKP, ASN, and DPC urged Congress to protect NIH from more budget cuts that are planned between 2014 and 2021. The three organizations also urged Congress to increase funding for the medical research and infrastructure budgets of the U.S. Department of Veterans Affairs, which, while exempt from sequestration, have not kept up with the pace of inflation.

ASN's new partnership with the U.S. Food and Drug Administration (FDA): the Kidney Health Initiative (KHI)

Formed in September 2012, KHI allows ASN and the FDA to bring together stakeholders, including industry, academia, and patients, to foster the development of new therapies for diseases that affect the kidney (see story, page 5). Numerous barriers prevent or discourage companies from investing in this space. KHI, which covers every FDA division (drugs, devices, biologics, and food safety), will help innovators or companies bring ideas from concept to cure.

"Pairing kidney health professionals with patient advocates was a successful model that ASN hopes to replicate in future years," said ASN public policy board chair Thomas H. Hostetter, MD. "The society is grateful to AAKP and DPC for their participation in Kidney Research Advocacy Day, and hopeful that Congress will take positive steps to enact long overdue transplant legislation and protect medical research funding. Members of the Kidney Health Initiative have already hit the ground running on several projects, and we look forward to keeping Congress informed of their progress."

Nearly 40 AAKP, ASN, and DPC leaders, patient advocates, and staff participated in Kidney Health Advocacy Day 2013.

(left to right) ASN Past President Ronald Falk, MD, FASN, KHI Project Director Melissa West, JST's Andrew Shore, KHI Co-Chair Prabir Roy-Chaudhury, MD, PhD, FASN, and AAKP President and KHI Board of Directors Member Sam Pederson meeting on KHI.

Senator Susan Collins (R-ME) with ASN Workforce Committee Chair Mark Parker, MD, (left) and ASN Policy Assistant Mark Lukaszewski (right) discuss kidney disease and the importance of sustained research funding.

(right to left) ASN Chronic Kidney Disease Advisory Group Chair Uptal Patel, MD, ASN Physiology and Cell and Molecular Biology Advisory Group Chair Jeffrey Miner, PhD, DPC Patient Ambassador Diane Brisbane, Senator Roy Blunt (R-MO), DPC Patient Ambassador William Shireman and DPC Policy Assistant Stephen Campbell after meeting to discuss the immunosuppressives bill and HOPE Act.

(right to left) ASN President Bruce Molitoris, MD, FASN, and AAKP Vice President Paul Conway explain the value of NIH and NIDDK funding with Peter Gwynn-Sackson, Legislative Assistant for Senator Mary Landrieu (D-LA).

(left to right) JST's Jim Jochum, KHI Project Director Melissa West, ASN Councilor Mark Okusa, MD, FASN, ASN Public Policy Board Member Wolfgang Winkelmayer, MD, ScD, FASN.

Senate Passes Bill to Allow HIV Organ Donations

The Senate in June passed a bill that would reverse a decades-old ban and allow research on organ donations from HIV-positive individuals.

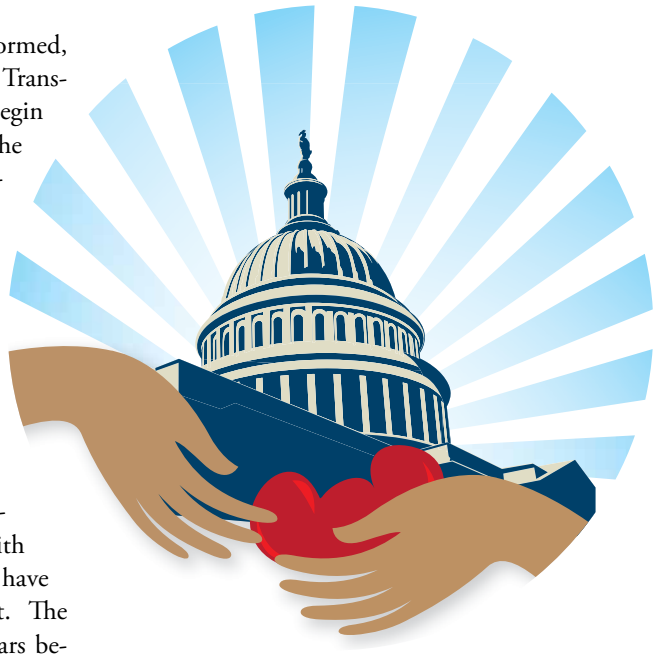
The bill (S 330) could pave the way for organs from HIV-positive donors to be transplanted into patients who are also HIV-positive and ultimately free up organs for other individuals. Sen. Barbara Boxer (D-Calif.) introduced the HIV Organ Policy Equity (HOPE) Act in February. A related House bill (HR 698) awaits committee action.

"The passage of the HOPE act is wonderful news," said Michelle Josephson, MD, of the University of Chicago section of nephrology. "The ban on using organs from individuals infected with HIV was put in place years ago, prior to the availability of drugs that effectively treat HIV. We now know that patients who have been infected with HIV can be managed with antiretroviral drugs and benefit from kidney transplantation."

Under the HOPE Act, the Department of Health and Human Services (HHS) would routinely evaluate the progress of medical research into possible health risks for people with HIV who receive organ transplants from HIV-positive donors. If research demonstrates that transplants from HIV-positive donors to HIV-positive recipients can be safely and successfully performed, HHS could direct the Organ Procurement and Transplantation Network to establish procedures to begin such transplantations. A study published in the *American Journal of Transplantation* found that allowing organ transplants from HIV-positive donors to HIV-positive recipients could increase the organ donation pool by 500-600 donors a year and save hundreds of lives.

"The HOPE Act is significant because it provides more kidneys for the donation pool," said Thomas Hostetter, of the division of nephrology at the Case Western Reserve University Department of Medicine. "Even though we now know that people infected with HIV disease benefit from a kidney transplant, like everyone else with end stage kidney disease, unless these individuals have a living donor they wait for years on the waitlist. The waitlist for a deceased donor kidney is many years because there is a large gap between supply of available organs and the number of people waiting for a kidney transplant. This Act will help close that gap."

"Thanks and credit go to the individuals and organizations, including ASN, that supported and lobbied for passage of the Act," Josephson said. "The Act benefits all of our end stage kidney patients needing a kidney transplant and gives the doctors more tools and strategies with which to help their patients."



Update on the Immunosuppressive Bill

By Rachel Shaffer

Advocating for passage of the Comprehensive Lifetime Immunosuppressive Drug Coverage Bill—in collaboration with the transplant and kidney communities (particularly the American Society of Transplantation)—is one of ASN's top public policy priorities this year.

In June, ASN responded to a request from the House and Senate offices of the bill's co-sponsors, Rep. Michael Burgess, MD, (R-TX), Rep. Ron Kind (D-WI), and Sen. Richard Durbin (D-IL), for information that could be helpful in reducing the Congressional Budget Office's (CBO) estimate of how much the bill would cost.

ASN conducted a comprehensive review of every state's individual "benchmark plans"—which define the minimum amount of coverage all insurance companies operating in that state will have to provide patients as of October 1, 2013—to assess the extent to which they cover immunosuppressive drugs. Fortunately, it appears that every benchmark plan covers at least one of every type of drug in the immunosuppressive regimen.

With the help of former Centers for Medicare and Medicaid Services (CMS) Chief Medical Officer and ASN member Barry M. Straube, MD, the society also examined trends in generic immunosuppressive drug utilization, and found that the average cost of the two most commonly used types of immunosuppressive drugs has declined by 55% and 57%, respectively, since the CBO last estimated the bill's cost.

The implications of these two findings could potentially have significant ramifications for the bill's likelihood of passage. Because Americans are supposed to purchase health insurance starting in 2014—and it appears that most states will cover at least some immunosuppressive drugs—fewer people will need Medicare to provide their drug coverage. And, because the cost of the drugs has decreased due to increased utilization of generic products, the drugs Medicare does need to cover will be less expensive than in the past.

The net result: CBO could determine that the bill costs less than previous estimates, thereby increasing its likelihood of being passed into law in a difficult economic climate. "From a policy perspective, the Immuno bill already enjoys strong bipartisan support," said ASN Public Policy Board Chair Thomas H. Hostetter, MD. "Most members of Congress agree that providing lifetime coverage is the right choice and the bill enjoys bipartisan support in the House and Senate."

However, CBO, the independent entity that estimates how much legislation will cost, does not take into account downstream savings from keeping patients with healthy transplants off dialysis as a result of covering their immunosuppressive drugs. CBO focuses primarily on the up-front cost (the drugs) rather than the long-term savings achieved by keeping patients off dialysis. "As a result, even though we and many members of Congress recognize that the bill is the right thing for patients, the CBO's cost estimate is a challenge at this time," Hostetter added.

"The last time CBO officially estimated the cost, it concluded that the bill would cost approximately $600 million over 10 years. Given the challenging economic climate in Washington, DC, it is difficult to extend any Medicare benefits or other entitlement programs that have any cost associated with their implementation," said Troy Zimmerman of the National Kidney Foundation. "Anything we can do to lower the cost would be beneficial."

"With strong bipartisan champions for the bill on both the House and Senate side and this new information that could potentially reduce the score, we are hopeful that the bill's odds of passage are better this year than in the past—and we're all committed to working collaboratively as a community to help move it forward," said Kathryn Schubert, the American Society of Pediatric Nephrology's Washington representative.

Look for more updates on the Immuno Bill in future issues of Kidney News, and please visit the ASN Public Policy webpage to communicate with your members of Congress encouraging them to support this crucial legislation.

About the "Immuno Bill"

The Comprehensive Lifetime Immunosuppressive Drug Coverage Bill, also known as the "Immuno Bill," would provide lifetime anti-rejection medication coverage for patients who receive a kidney transplant, enabling them to keep the kidney healthy and live dialysis-free. Currently, Medicare only provides this coverage for 36 months. Patients who receive a kidney and cannot afford the drugs or don't have insurance are at risk for losing the transplant and returning to dialysis—which Medicare covers again, at a much greater cost. Dialysis costs approximately $88,000 on average, whereas the immunosuppressive drugs cost less than a quarter of that, on average. Protecting Medicare's investment in the transplant makes good sense for patients' quality of life, and good sense from an economic perspective.

Journal View

Kidney and Cardiovascular Disease Risk Genes Aren't the Same

For the most part, gene variants associated with kidney disease and cardiovascular disease are different from one another, according to a report in the *American Journal of Kidney Diseases*.

Two targeted single-nucleotide polymorphism (SNP) analyses were performed by the use of data from many thousands of participants enrolled in six different disease consortia. The first analysis looked for associations between 19 SNPs known to be associated with kidney function and a series of vascular phenotypes. The second analysis sought associations of 64 validated vascular SNPs with markers of kidney damage.

One kidney disease–related SNP—rs653178 near the SH2B adaptor protein 3 gene *(SH2B3)*—was also associated with systolic and diastolic blood pressure and coronary artery disease, as previously reported. Otherwise, the kidney disease variants were not significantly associated with vascular phenotypes, with nonsignificant results in 127 out of 133 tests.

Likewise, most SNPs associated with vascular phenotypes were unrelated to kidney phenotypes, with nonsignificant results in 187 out of 192 tests. The only exceptions were two highly correlated SNPs at the *SH2B3* locus.

Given the strong associations between chronic kidney disease and cardiovascular disease, a shared genetic basis is possible. But the new study finds little overlap among the gene variants associated with kidney disease versus cardiovascular disease, with the notable exception of the SH2B3 locus. Rather than a genetic explanation, the associations between kidney and cardiovascular disease may reflect "a function of the disease milieu itself," the researchers write [Olden M, et al. Overlap between common genetic polymorphisms underpinning kidney traits and cardiovascular disease phenotypes: The CKDGen Consortium. *Am J Kidney Dis* 2013; 61:889–898].

Tobacco Smoke Linked to Lower eGFR in Teens

Active or passive exposure to tobacco smoke is associated with decreased kidney function in adolescents, according to a study in *Pediatrics*.

The study included data on 7516 participants, aged 12 to 17 years, in the National Health and Nutrition Examination Survey from 1999 to 2010. All had available data on serum creatinine and cotinine. Active and secondhand smoking were assessed on the basis of self-report or serum cotinine levels above 10 ng/mL or at least 0.05 ng/mL, respectively. The relationships between either type of smoking and estimated GFR (eGFR) were analyzed.

The adolescents had a median eGFR of 96.8 mL/min per 1.73 m^2 and a median serum cotinine concentration of 0.07 ng/mL. With multivariable adjustment, each interquartile range increase in serum cotinine (0.03 to 0.59 ng/mL) was associated with a 1.1 mL/min per 1.73 m^2 decrease in eGFR.

In comparison with unexposed adolescents, the mean differences in eGFR were –0.4 mL/min per 1.73 m^2 in the first tertile of serum cotinine concentration, –0.9 mL/min per 1.73 m^2 in the second tertile, and –2.2 mL/min per 1.73 m^2 in the third tertile. Among active smokers, the differences by tertile were 0.2, –1.9, and –2.6 mL/min per 1.73 m^2, respectively. The association between cotinine and eGFR appeared stronger in boys and in younger and lighter adolescents.

Active and passive smoking are demonstrated risk factors for kidney disease in adults. This cross-sectional study links tobacco smoke exposure to reduced eGFR in adolescents, suggesting that the adverse effects of smoking on kidney function may start in childhood. The authors note that although the associations are modest, they could have a major impact on kidney disease at the population level [Garcia-Esquinas E, et al. Kidney function and tobacco smoke exposure in US adolescents. *Pediatrics* 2013; 131:e1415–e1423].

Even After "Black Box" Warning, For-Profit Dialysis Centers Used More ESAs

After a "black box" warning to use the lowest possible dose of erythropoiesis-stimulating agents (ESAs), for-profit dialysis facilities continued to prescribe higher ESA doses, according to a report in *JAMA Internal Medicine.*

The researchers analyzed U.S. Renal Data System data on more than 275,000 patients receiving in-center hemodialysis before and after a 2007 black box warning on ESA use. This safety directive from the U.S. Food and Drug Administration called for use of the lowest possible ESA dose to avoid the need for blood transfusion and for withholding ESAs in patients with hemoglobin levels higher than 12 g/dL. The researchers analyzed the effects of the black box warning on ESA dosing and hematocrit for both for-profit and nonprofit dialysis facilities.

At both times and across hematocrit categories, for-profit dialysis facilities used higher doses of ESAs than did nonprofit facilities, after adjustment for case mix. At for-profit centers, the median weekly ESA dose was 9020 U before the black box warning and 8322 U afterward. At nonprofit centers, the figures were 5670 U and 5063 U, respectively.

The median weekly ESA dose increased 54.7 percent for patients who switched from a nonprofit to a for-profit facility from before to after the black box warning, compared with a 50.9 percent decrease for those who switched from a for-profit to a nonprofit facility. After the warning, for-profit dialysis centers performed no better than nonprofit centers in avoiding hematocrit levels below 30 percent.

The findings suggest that "financial considerations may have played a role" in ESA dosing at for-profit centers. The authors discuss the need for ongoing monitoring of dialysis care and outcomes since implementation of the bundled reimbursement system [Ishida JH, et al. Dialysis facility profit status and compliance with a black box warning. *JAMA Intern Med* 2013; May 13:1–2. doi:10.1001/jamainternmed.2013.979].

Choice of Statins May Affect Diabetes Risk

Patients taking certain higher-potency statin drugs may be at increased risk for the development of diabetes, suggests a study in the *British Medical Journal*.

Using Ontario health data, the researchers identified a population of more than 470,000 nondiabetic patients aged 66 years or older who started statin therapy between 1997 and 2010. All were new users who had not been prescribed a statin for at least 1 year previously. The indication for statins was primary prevention in 48 percent of patients and secondary prevention in 52 percent. The use of individual statins was analyzed for association with the development of new-onset diabetes.

With pravastatin as the reference drug, three higher-potency statins—atorvastatin, rosuvastatin, and simvastatin—were associated with an increased risk of incident diabetes. The adjusted hazard ratios were 1.22, 1.18, and 1.10, respectively. Diabetes risk was not increased for users of fluvastatin or lovastatin.

The absolute increases in risk per 1000 person-years were 31 with atorvastatin and 34 with rosuvastatin, compared with 26 with simvastatin and 23 with pravastatin. The associations were similar in the primary and secondary prevention groups and when statins were grouped by potency. However, the increase in risk with rosuvastatin became nonsignificant after adjustment for dose.

Some studies have suggested that statin treatment may be associated with an increased incidence of new-onset diabetes. Amid conflicting results, few studies have compared the effects of different statins.

These population-based data suggest increased diabetes risk among older patients taking higher-potency statins—particularly atorvastatin and simvastatin. The risk associated with rosuvastatin may depend on dose. The authors acknowledge some important limitations of their study, including a lack of information on key diabetes risk factors [Carter AA, et al. Risk of incident diabetes among patients treated with statins: population based study. *BMJ* 2012; 346:f2610].

Long-Chain n-3 Fatty Acids Affect Sudden Cardiac Death Risk

During the first year of receiving hemodialysis, patients with higher levels of long-chain n-3 fatty acids are at lower risk of sudden cardiac death, reports a study in *Kidney International*.

The study included a nationally representative cohort of patients from more than 1000 hemodialysis units in 2004 to 2005. The researchers identified 100 cases of sudden cardiac death within the first year after the patients had started dialysis, along with 300 patients who survived the first year. The risk of sudden cardiac death was compared for patients in differing quartiles of long-chain n-3 fatty acid level during their first year of receiving dialysis.

Baseline long-chain n-3 fatty acid level was inversely associated with the risk of sudden cardiac death, even after adjustment for comorbid diseases, biochemical variables, and dietary fats. In comparison with the lowest quartile of long-chain n-3 fatty acids, the odds ratios for sudden cardiac death were 0.37 in the second quartile, 0.22 in the third quartile, and 0.20 in the fourth quartile. The protective effect was apparent even during the first few months of dialysis, when the risk of sudden cardiac death is highest.

Experimental and clinical studies suggest that long-chain n-3 fatty acids may protect against sudden cardiac death, the leading cause of death in hemodialysis patients. The new analysis suggests that long-chain n-3 fatty acids are "strongly and independently" associated with risk of sudden cardiac death during the first year of hemodialysis. The authors call for a randomized controlled trial of long-chain n-3 fatty acid supplementation for hemodialysis patients [Friedman AN, et al. Inverse relationship between long-chain n-3 fatty acids and risk of sudden cardiac death in patients starting hemodialysis. *Kidney Int* 2013; 83:1130–1135].

Urinalysis Is More Specific for AKI than NGAL

For early detection of acute kidney injury (AKI), urinalysis is a more specific test than urinary neutrophil gelatinase-associated lipocalin (NGAL), reports a study in *Nephrology Dialysis Transplantation*.

A rapid enzyme-linked immunosorbent assay (ELISA) for urinary NGAL underwent analytic validation by the use of random and 24-hour urine samples from 125 healthy volunteers. The results showed that NGAL levels were stable for up to 7 days, including ambient and frozen samples. The ELISA showed linear performance at concentrations from 0.24 to 10,000 ng/mL, with a quantitation limit of 0.24 ng/mL. Inter- and intra-assay precision were excellent, although the presence of white blood cells was associated with higher NGAL levels. The ninety-fifth percentile reference values were 65.0 ng/mL or less in women and 23.4 ng/mL or less in men.

In a clinical validation study, NGAL measurement and urinalysis were performed on samples from 363 emergency department patients who were admitted to the hospital. Urinary NGAL concentrations increased with AKI stage according to the Acute Kidney Injury Network criteria. However, the ELISA had only fair performance in differentiating absence of AKI versus stage 1, 2, or 3 AKI. Sensitivity and specificity were both 65 percent, with an area under the curve of 0.70. By comparison, urinalysis with microscopy offered excellent specificity of 91 percent but sensitivity of only 22 percent: area under the curve 0.57.

Urinary NGAL is a promising biomarker for earlier detection of AKI. The new ELISA reliably measures NGAL in clinical urine samples, although pyuria is a potential confounder.

Higher urinary NGAL is an indicator of AKI; its diagnostic performance is only fair, but it might be improved by excluding patients with prerenal causes of AKI. Meanwhile, microscopic urinalysis is a readily available and inexpensive test with high specificity for AKI [Schinstock CA, et al. Urinalysis is more specific and urinary neutrophil gelatinase-associated lipocalin is more sensitive for early detection of acute kidney injury. *Nephrol Dial Transplant* 2013; 28:1175–1185].

Eculizumab for Atypical Hemolytic-Uremic Syndrome

For patients with atypical hemolytic-uremic syndrome, treatment with the terminal complement inhibitor eculizumab can improve renal function, even allowing some patients to discontinue dialysis, reports a study in the *New England Journal of Medicine*.

The report describes two prospective phase 2 trials of eculizumab in patients with atypical hemolytic-uremic syndrome, aged 12 years or older. Trial 1 included 17 patients with low platelet counts and kidney damage. Trial 2 included 20 patients with kidney damage but no more than a 25 percent reduction in platelet count during at least 8 weeks of plasma exchange or infusion. Both trials included 26 weeks of eculizumab; with long-term extension phases, treatment continued for a median of 64 and 62 weeks, respectively.

In trial 1, platelet count increased by a mean of 73×10^9 over 26 weeks. In trial 2, 80 percent of patients remained free of thrombotic microangiopathy events—including dialysis initiation—while receiving eculizumab.

Eculizumab was also associated with time-dependent improvement in estimated GFR, particularly in patients receiving earlier treatment. In trial 1, four out of five patients were able to discontinue dialysis. Long-term treatment with eculizumab had no cumulative toxicity or serious infection-related adverse events, including meningococcal infections.

Atypical hemolytic-uremic syndrome—caused by genetic defects in complement system regulation—puts patients at risk of complement-mediated thrombotic microangiopathy affecting the kidneys and other organs. The new trials support previous case reports showing benefits of complement inhibitor therapy with eculizumab.

These benefits include improved renal function even in patients with significant, long-standing renal damage. The researchers conclude, "The results of eculizumab therapy appear to represent a substantial advancement in the treatment of patients who have this severe and life-threatening systemic disease" [Legendre CM, et al. Terminal complement inhibitor eculizumab in atypical hemolytic-uremic syndrome. *N Engl J Med* 2013; 368:2169–2181].

Industry Spotlight

Fresenius Making inroads with ACOs

Dialysis provider Fresenius Medical Care has announced its second accountable care organization (ACO) arrangement. The latest deal is with ApolloMed ACO of Glendale, CA, announced in May. Fresenius will provide integrated health care management for its patients with ESRD.

As part of the agreement, ApolloMed ACO and Fresenius Medical Care will share in the operations and financial cost savings gained from the partnership. The agreement is built on the 5-year demonstration project that Fresenius Health Partners, a subsidiary of Fresenius Medical Care, conducted with Medicare beneficiaries receiving dialysis.

In April, Fresenius similarly teamed up with Heritage California ACO (HCACO) and its ESRD patients. The agreement lets Fresenius Medical Care work with HCACO to manage the overall health and coordination of care of these HCACO beneficiaries, with the goal of improving their health outcomes and reducing their total cost of care, according to Fresenius Medical Care, the world's largest provider of dialysis services.

DaVita has been more cautious in its approach to ACO partnerships. DaVita executives said during an investor conference call in February that it wouldn't participate in the Centers for Medicare & Medicaid Services' new renal ACO demonstration unless the agency changed some of its rules. What were the issues? Several things: the ACO method penalizes dialysis providers who have had better outcomes in the past; there isn't time to make an investment and see return before the ESRD bundle rebasing begins; and there are some economic penalties for larger dialysis organizations, noted DaVita, the second largest dialysis provider in the United States.

But by May 22, DaVita had announced a shift, by buying a pioneering ACO, HealthCare Partners of Torrance, CA, for $4.42 billion. The *Los Angeles Times* reported that HealthCare Partners, with more than 50 medical offices and 550,000 patients across southern California, has been a national leader in coordinating patient care.

"Medicare is searching desperately for ways to make the delivery system more cost effective, and groups like HealthCare Partners have been doing just that for 20-plus years, so they have particular value going forward," said Glenn Melnick, a health economist for Rand Corporation. "But I must say DaVita comes out of left field." The latter comment refers to the fact that most of the big buyers of ACOs have been insurers.

HealthCare Partners notes that it had $2.4 billion in revenue last year, and its operating income was $488 million, according to company documents.

Aveo: Partner Opted Not to Seek European Union Approval of Kidney Cancer Drug

Aveo Pharmaceuticals of Cambridge, MA, said that its partner Astellas Pharma, whose world headquarters is in Japan, would not seek marketing approval for an experimental kidney cancer drug in Europe, Reuters reported.

This news comes just after a U.S. Food and Drug Administration (FDA) panel decision in early May, with a 13-to-1 vote in favor of not approving the drug immediately and of recommending an additional clinical trial before the drug tivozanib could be approved for renal cell cancer. A final decision will come after July 26.

Staff reviewers for the FDA previously emphasized that kidney cancer patients taking tivozanib did not survive longer than did patients taking Nexavar, a kidney cancer drug produced by Bayer AG and Onyx Pharmaceuticals. Some analysts reported that these results occurred possibly because the Nexavar patients had other treatments later, the Associated Press reported.

Aveo shares had lost about 55 percent of their value between April 30 and June 1, when FDA reviewers raised questions about the drug.

Astellas does not intend to fund any future studies of tivozanib in renal cell cancer, Aveo wrote in a regulatory filing on Thursday, May 30. As a partner, Astellas would have had to bear new clinical trial costs, and opted out.

"I expect (Aveo) shares to be down a little because if Astellas had decided to go ahead and pursue the [renal cell cancer] indication as well, then obviously they would have to bear half the cost of the study," RBC Capital Markets analyst Adnan Butt said.

Brian Klein, an analyst for Stifel Nicolaus, said he saw major cost cuts ahead for Aveo because of this news, which was filed with the Securities and Exchange Commission.

The regulatory filing did not indicate whether Astellas had opted to discontinue support for two other studies of the drug, for advanced colorectal and breast cancer.

Butt said he expects, on the basis of this filing, that Astellas would not pull out from the metastatic cancer trials, according to the Associated Press.

After the advisory panel vote, Aveo and Astellas had said they would work with the FDA to address the issues raised by the panel. Aveo CEO Tuan Ha-Ngoc said the company was "extremely disappointed" by the negative FDA panel vote and dismayed by the criticisms of the company's actions leveled by panel members. Given the negative panel vote, Ha-Ngoc said the FDA will "more likely reach an adverse decision on tivozanib."

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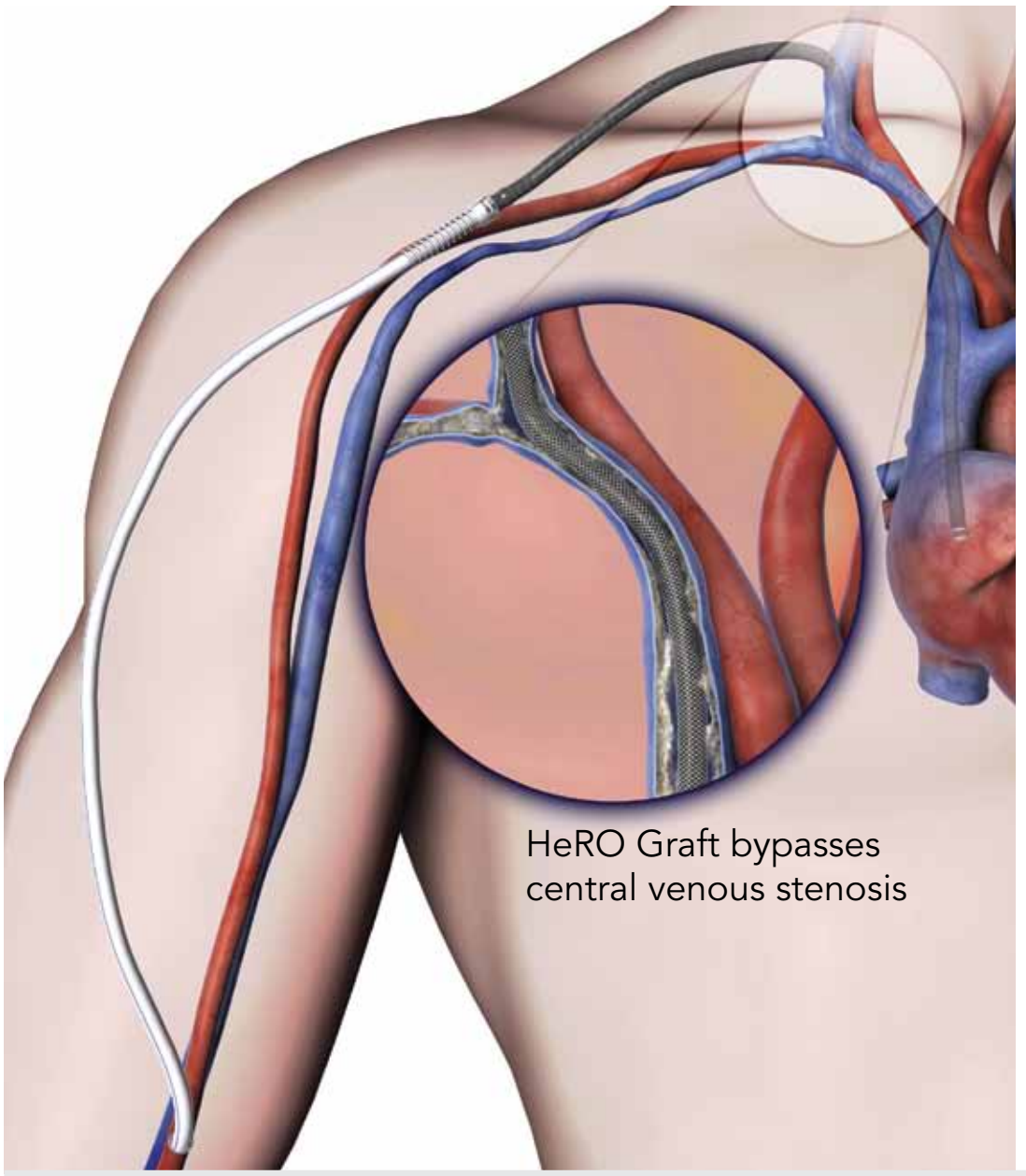

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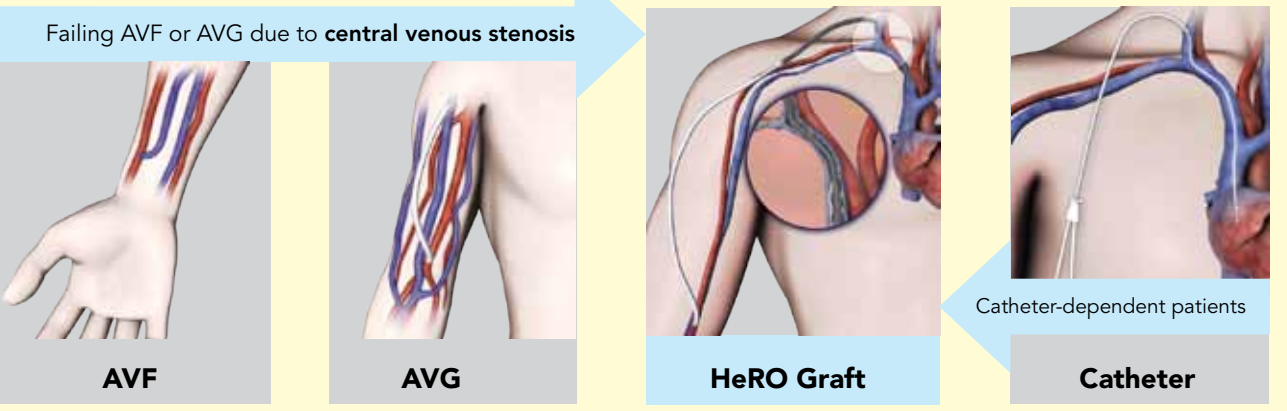

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References:
1) Katzman et al., J Vasc Surg 2009. 2) Gage et al., EJVES 2012. 3) Dageforde et al., JSR 2012.

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