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

Continued on page 3
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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 cilary base does contain a fixed pore that excludes molecules larger than 67 kDa. These researchers termed the barrier a cilary 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 cilary 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, who 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 cilary-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.”

Cytosolic Proteins

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 the leaders who 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 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 individuals with two or more races. Data do not include residents of Puerto Rico, Guam, the U.S. Virgin Islands, or the Northern Mariana Islands.


ASN Diversity Summit Participants

Jonathan Himmelfarb, MD, FASN
Sharon M. Moe, MD, FASN
Carmen A. Peralta, MD
Kalani L. Raphael, MD, MS
Sylvia E. Rosas, MD, FASN
Donald Wesson, MD, FASN
Bessie A. Young, MD, MPH

Jason Cobb, MD
Deirdra C. Crews, MD, ScM, FASN
Cynthia Delgado, MD
Keisha L. Gibson, MD, MPH
Eddie L. Greene, MD, FASN
Kevin O. Griffiths, MD, MPH, FASN
Gloria T. Hernandez, MD, FASN

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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 (Tutored 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 Glidden 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 number 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.”

The Johns Hopkins team presented to the ASN Council later this summer. Dr. Himmelfarb discussed the number of recommendations that will be presented to the ASN Council later this summer.
Kidney Health Initiative Announces Pilot Projects, Leadership

The Kidney Health Initiative (KHI), a new public-private partnership in September 2012, has made significant progress moving the partnership forward. The Board of Directors for KHI was appointed in February 2013 (Table 1). One of the Board’s first meetings has 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.

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 institutions 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

| Co-Chairs | Patrick Archdeacon, MD  
| 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  
| **Members** |  
| George R. Aronoff, MD, FACP  
| University of Louisville  
| Matthew D. Breyer, MD, FASN, Eli Lilly and Company  
| Ronald J. Falk, MD, FASN, University of North Carolina  
| Michael F. Flessner, MD, PhD, National Institute of Diabetes and Digestive and Kidney Diseases  
| Nancy M. Gallagher, RN, CNN, Nephrology Nursing Certification Commission (NNCC)  
| 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. Kligler, MD, Yale University  
| Kristine Kuus, PhD, The Binding Site  
| Celeste Castillo Lee, Vasculitis Foundation  
| Peter G. Linde, MD, FASN, Abbvie  
| Carolyn Y. Neuland, PhD, Center for Devices and Radiological Health (CDRH), FDA  
| Meda E. Pankov, MD, PhD, Centers for Disease Control (CDC)  
| Sam M. Pederson, American Association of Kidney Patients (AAKP)  
| James A. Sloand, MD, FASN, Baxter Healthcare Corporation  
| James P. Smith, MD, MS, Center for Drug Evaluation and Research (CDER), FDA  
| Kimberly A. Smith, MD, MS, Centers for Medicare & Medicaid Services (CMS)  
| Shawne Suggs-Anderson, MMSc, RD, Center for Food Safety & Applied Nutrition (CFSAN), FDA  
| **Staff Liaisons** |  
| Katlyn Leight, Staff Assistant  
| Melissa West, Project Director  

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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.

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: 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: 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, resid-
dents, and fellows prepares the next genera-
tion 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 develop-
ment awards. We also have the Paul B. Beeson award
that provides additional support to clinicians to as-
sure 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. Re-
cent 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 (GEMSSSTAR) program. This R03 is de-
signed for medical and surgical specialists who are
new to aging research. The award is contingent on
the applicant demonstrating protected time and re-
sources 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 nephrol-
ogy (http://wwwasn-online.org/foundation/career-
development.aspx) as a source of support. Other
sources can include the applicant’s institution or af-
filiated Veterans Administration hospital; a Clinical
and Translational Science Award; NIH K12 or R25
programs; specialty societies, such as the Association
of Specialty Professors or the American Geriatrics
Society; Older Americans Independence Center
Career Development Core; or other gov-
ernment, public, or private sources. The goal of the
program is to assist new faculty members in gather-
ing the data needed to successfully compete for a K
award. Both the GEMSSSTAR 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 Pro-
gram scholarships to first- and second-year medical
students, providing hands-on and didactic research
training in aging and geriatrics. We also fund train-
ing programs that reserve slots for medical students
or physicians interested in basic, clinical, and trans-
lationl 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-ca-
ter-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 pre-
care 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 Cauca-
sians. 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
each of the NIH’s initiatives is “Minority Aging and
Health Disparities.” Studies have shown that
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sians. What is the institute doing to address
health disparities in general, and disparities in
kidney disease in particular?

KN: What do you consider the greatest opportuni-
ties 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 pro-
cess and development of interventions to prevent
diseases and disability associated with growing old-
er. 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 Alz-
heimer’s Project Act (http://aspe.hhs.gov/daltcp/napa/).
This calls for a national plan for the ap-
proach to Alzheimer’s disease, and NIA/NIH leads
the research component of that plan. Aging re-
search 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 plans for the development of the
trans-NIH Geroscience Interest Group, supported by
20 of the 27 ICs. (http://signs.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 mini-
imize 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 stud-
ies and maintaining important research projects to
which we have already committed.  

Reference
1. Working Group on Health Outcomes for Old-
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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, approximately 10 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.

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 (DRHP) 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 diuretic 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 promising.
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: 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 month 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.

**Jula K. Inrig, MD, MHS, FASN, is affiliated with the Dialysis Advisory Group. Kevin Griffiths, MD, is affiliated with the Practicing Nephrologists Advisory Group.**
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1 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 the patient recovered consciousness) or where glucose levels were less than 2.2 mmol/L.

Laboratory Tests: Increases in Serum Potassium: Dose-related increases in serum potassium were observed after initation of INVOKANA™ (canagliflozin) tablets, with greater increases observed in the clinical trials and the observational study compared to the placebo-controlled trials. The observed increases were generally transient and occurred within 2-4 weeks of treatment initiation. The median increases in potassium were 0.1 mmol/L in the placebo-controlled trials, 0.4 mmol/L in the clinical trials, and 0.6 mmol/L in the observational study. In patients treated with INVOKANA™ 150 mg and INVOKANA™ 300 mg, respectively, the mean increase in potassium was 0.8 mmol/L and 1.0 mmol/L, respectively. In patients treated with INVOKANA™ 100 mg, the mean increase in potassium was 0.6 mmol/L.

Laboratory Tests: Increases in Serum Magnesium: Dose-related increases in serum magnesium were observed in patients treated with INVOKANA™ (canagliflozin) tablets. In the placebo-controlled trials, the mean change in serum magnesium was less than 0.01 mmol/L. In the clinical trials, the mean change in serum magnesium was greater than 0.01 mmol/L, with the highest mean change observed in patients treated with INVOKANA™ 300 mg, which was 0.4 mmol/L. In the observational study, the mean change in serum magnesium was less than 0.01 mmol/L.

Involvanka™ (canagliflozin) tablets

Lactation: Nursing Mothers: Caution is advised when INVOKANA™ (canagliflozin) tablets are administered to nursing mothers. The data are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from INVOKANA™ (canagliflozin), a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Use In Specific Populations

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 (2,304) 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 (14.2) in full Prescribing Information).

Drug Interactions

Use In Specific Populations

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

Geriatric Use: 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 dizziness) compared to younger patients; more prominent increase in the incidence was seen in patients who were 75 years and older (see Dosage and Administration).

Drug Interactions: Do not use INVOKANA™ (canagliflozin) tablets with insulin or sulfonylureas simultaneously. If a patient who is taking INVOKANA is switched to lisinopril, the dosage of INVOKANA™ (canagliflozin) tablets should be reduced to half the starting dose.

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Atrasentan, an oral endothelin receptor antagonists, reduces albuminuria and improves kidney function. The more these people adhered to such a diet, the more improvement was seen. 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 the diet. 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 improve albuminuria levels,” said Juan Carrero, PhD, of the Karolinska Institute in Stockholm, Sweden.

### Atrasentan with Current Optimal Therapy Reduces Albuminuria in Type 2 Nephropathy

Atrasentan, 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. From 7-day diet diaries that the men recorded, the investigators observed an 18 percent lower risk of death, for every two-point increase in the Mediterranean Diet Score, the investigators observed an 18 percent lower risk of death, 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.

### 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; healthy 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 may be mainly accounted for by individual nutrients, but low SFA [saturated fatty acid] intake rather than by the score as a whole,” he said. 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, Turkey, in May.

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### 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 m³ 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.

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...
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 1590 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 m², 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 Health 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.

(left to right) ASN Chronic Kidney Disease Advisory Group Chair Utpal 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).

(right to left) 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.

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.
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 benefits for patients infected with HIV disease benefiting 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 plan"—which defines 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.
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 SH2B3 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.


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 dose of blood transfusion and for withholding ESAs in patients with hemoglobin levels higher than 12 mg/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, 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.2013.3979].

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 60 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 36 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:e2610].

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 confounding 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 0.97 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].

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 glomerular filtration rate (eGFR) were analyzed.

The adolescents had a median eGFR of 96.8 mL/min per 1.73 m2 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 m2 decrease in eGFR.

In comparison with unexposed adolescents, the mean differences in eGFR were −0.9 mL/min per 1.73 m2 in the first tertile of serum cotinine concentration, −0.9 mL/min per 1.73 m2 in the second tertile, and −2.2 mL/min per 1.73 m2 in the third tertile. Among active smokers, the differences by tertile were 0.2, −1.9, and −2.6 mL/min per 1.73 m2, 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].
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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 $73 \times 10^9$ 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.


Ecullizumab for Atypical Hemolytic-Uremic Syndrome

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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].

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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.”

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 company documents.

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- Failing AVF or AVG due to central venous stenosis

**Treatment Algorithm**
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- AVF
- AVG
- HeRO Graft
- Catheter

**HeRO Graft Candidates**
- Catheter-dependent or approaching catheter-dependency
- Failing AVF or AVG due to central venous stenosis

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