ASN LEADING THE FIGHT AGAINST KIDNEY DISEASE

Kidney News

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Genetic Variant Linked with Kidney Failure in Women with Type 1 Diabetes But Not Men

Within the nondiabetic population, women are relatively protected from kidney failure until menopause, but this protection is reduced in diabetic women. A new study published in the *Journal of the American Society of Nephrology* now helps explain gender-specific differences in kidney failure, as well as why some diabetic women are prone to develop it.

"More than 371 million people have diabetes worldwide, and diabetes is the leading cause of end stage renal disease that requires dialysis or kidney transplant for patient survival," said first author Niina Sandholm, MSc, of Helsinki University Central Hospital and Folkhälsan Research Center, in Finland. "As gender differences exist in the development of kidney disease, our aim was to detect genetic variants that predispose diabetic patients to end stage renal disease in a gender-specific manner," she explained.

Genetic clues revealed

Despite evidence that sex influences the risk of kidney failure in patients with type 1 diabetes, no large-scale sex-specific genetic studies had been reported until now. Sandholm, along with senior author Per-Henrik Groop, MD, DMSc, and their colleagues, conducted a genome-wide association study in a cohort of 3652 patients with type 1 diabetes who participated in the Finnish Diabetic Nephropathy (FinnDiane) Study.

The FinnDiane discovery cohort included 258 women and 387 men with kidney failure. These patients were compared with those without signs of diabetic nephropa-

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CKD Prevalence Varies Widely Across European Countries; Dialysis Prevalence Skyrocketing Worldwide

By Tracy Hampton

The prevalence of stage 3 to 5 chronic kidney disease (CKD) in some elderly populations in Europe is well above 20%, according to new research. In addition, the prevalence of dialysis therapy for kidney failure is increasing much faster than population growth in most parts of the world.

The findings come from two separate studies presented at ASN Kidney Week 2013, which was held in Atlanta in November.

The European CKD Burden Consortium used standardized definitions to determine the prevalence of CKD across Europe. Katharina Brueck, MD, Vianda Stel, PhD, and Kitty Jager, MD, PhD, of the ERA-EDTA Registry in the Netherlands, initiated the analysis with a literature review to identify relevant population-based studies that could provide data on CKD prevalence.

The team has received data on prevalence from 19 studies originating from 13 countries. The crude prevalence of stages 1 to 5 CKD in individuals aged 20 years and older ranged from 4.4% in The Netherlands to 31.1% in northeast Germany. The crude stage 3 to 5 CKD prevalence for this age group ranged from 1.1% in The Netherlands to 9.9% in northeast Germany.

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Corporate Supporters

The ASN Corporate Support Program recognizes supporters year round for their generous contributions to the Society. Through this program, supporters help ASN lead the fight against kidney disease. ASN gratefully acknowledges the following companies for their contributions in 2013.

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CKD Prevalence

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In adults aged 65 to 74 years, the age and sex standardized prevalence of stage 3 to 5 CKD ranged from 4.1% in Switzerland to 25.4% in northeast Germany.

"This is the first study on international differences in the prevalence of CKD across European countries using standardized definitions based on the same GFR estimating formula, and with adjustment for general population demographics," Stel said. "Future studies should focus on the explanation for this diversity in CKD prevalence in Europe."

Another team that presented research at ASN Kidney Week 2013 looked at the trajectory of treated end stage renal disease (ESRD) rates at the global and regional level between 1990 and 2010. The effort was led by Bernadette Thomas, MD, of the University of Washington, in Seattle.

"Maintenance dialysis is an expensive form of life support," Thomas said. "Understanding the prevalence of maintenance dialysis throughout the world, and how these rates have grown within the past two decades is important information for countries to plan how to maintain providing this treatment to a rapidly growing ESRD population."

Thomas also noted that identifying regions of the world that are unable to provide maintenance dialysis treatment will indicate where greater efforts are needed to identify and treat ESRD patients.

She and her colleagues examined data from the Global Burden of Disease database, the largest existing database for global causes of illness and death. They also analyzed data from national and regional ESRD registries and performed a literature review of studies from 1990 and 2010. Data from 23 countries providing 100% dialysis access and 138 countries providing partial dialysis access were included, while data from 26 countries that lack routine access to dialysis were excluded.

The investigators found that worldwide, there has been a 165% increase in dialysis treatments for ESRD over the past two decades—a rate that has far outpaced the rate of population growth in most regions of the world.

The global prevalence of ESRD treatment with dialysis for countries with universal dialysis access increased by 134% after adjusting for population growth and aging (145% in women versus 123% in men). For countries whose populations lack universal dialysis access, adjusted prevalence increased by 102% (116% for women versus 90% for men). Five world regions did not experiencie a substantial increase in dialysis prevalence: Oceania, South Asia, central sub-Saharan Africa, Eastern Europe, and tropical Latin America.

"The prevalence of maintenance dialysis is growing rapidly, both in countries with and without the ability to provide universal access," Thomas said. "This speaks to increased disease activity. It will be difficult to continue to finance such a trajectory of growth without consequent development of transplant programs and aggressive screening and intervention programs for earlier stages of chronic kidney disease."

Something to Say?

***ASN Kidney News* accepts correspondence in response to published articles. Please submit all correspondence to kidneynews@asn-online.org**

Genetic Variant

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thy despite having a long duration of diabetes. To ensure that any genetic association with kidney failure was due to diabetes, the investigators excluded all patients with diabetes known to have end stage renal diseaes due to any nondiabetic cause.

The researchers identified a genetic variant, called rs4972593, on chromosome 2 that was linked with kidney failure in the women in the study. Additional analyses revealed that it was also linked with kidney failure in diabetic women in the United Kingdom, the United States, and Italy.

"The women with the risk variant had a nearly twofold risk of developing end stage renal disease, compared with the non-carriers," Sandholm said. "We did not find any association with end stage renal disease in any of the studied groups of men."

The genetic variant is located close to a gene—called SP3—that codes for a transcription factor that interacts with the estrogen receptor and also helps regulate kidney function. It will be interesting to see if this factor plays a role in the gender-specific protection against kidney failure seen in this study, researchers said.

Additional experiments revealed potential transcription factor–binding sites within rs4972593 and predicted eight estrogen-responsive elements within 5 kb of this locus, but the investigators stressed that a causal link cannot be made until more studies are performed.

"The identified risk variant is located between the SP3 and CDCA7 genes, and whereas the SP3 gene seems the most plausible causal gene of the region, we do not have any mechanistic information about how this variant predisposes diabetic women to end stage renal disease," said Sandholm. The CDCA7 gene encodes a transcription factor that regulates cell proliferation and is frequently overexpressed in human cancers.

Additional studies needed

In an accompanying editorial, Marcus Pezzolesi, PhD, and Andrzej Krolewski, MD, PhD, both of the Joslin Diabetes Center in Boston, commented: "In identifying evidence of an association with end stage renal disease exclusively in women, this study offers the strongest evidence to date of a sex-specific genetic factor for diabetic nephropathy." They added, however, that the findings need to be verified by additional studies.

They also stressed that a number of unanswered questions remain. For example, they asked, "Could the variant identified by Sandholm et al. purely be associated with increased survival among women with end stage renal disease rather than risk of end stage renal disease?"

"Although not addressed in this study, it remains possible that sex-specific competing risks could allow more women to survive end stage renal disease than men, Pezzolesi and Krolewski said. If true, the variant may be a consequence of its association with sex-specific survival of kidney failure rather than sex-specific risk for it, they explained.

The experts also stated that the study reflects an emerging shift in the strategy that investigators are using to search for diabetic kidney disease susceptibility genes. They believe that the genetic etiology underlying the risk of diabetic nephropathy and the factors that contribute to its development will eventually be discovered, the researchers said.

Study co-authors include Amy Jayne McKnight, PhD, Rany M. Salem, PhD, Eoin P. Brennan, PhD, Carol Forsblom, DMSc, Valma Harjutsalo, PhD, Ville-Petteri Mäkinen, DSc(Tech), Gareth J. McKay, PhD, Denise M. Sadlier, MD, Winfred W. Williams, MD, Finian Martin, Prof BSc PhD, Nicolae Mircea Panduru, MD, MSc, PhD , Lise Tarnow, MD DMSc , Jaakko Tuomilehto, Prof. MD PhD, Karl Tryggvason, MD, PhD, Gianpaolo Zerbini, MD, Mary E. Comeau, BS, Carl D. Langefeld, PhD, Catherine Godson, BSc, PhD, Joel N. Hirschhorn, MD, PhD, Alexander P. Maxwell, MD, PhD, and Jose C. Florez, MD, PhD.

Disclosures: Jose C. Florez has received consulting honoraria from Novartis, Lilly and Pfizer. Per-Henrik Groop has received lecture honorariums from Abbot, Boehringer Ingelheim, Cebix, Eli Lilly, Genzyme, Novartis, Novo Nordisk, MSD, and research grants from Eli Lilly, Roche. Per-Henrik Groop is also an advisory board member of Boehringer Ingelheim and Novartis.

The article, entitled "Chromosome 2q31.1 Associates with ESRD in Women with Type 1 Diabetes," is available online at http://jasn.asnjournals.org/, doi: 10.1681/ASN.2012111122.

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The List: Top Issues to Watch in 2014

Incorporating Supportive Care in Nephrology Research, Training, and Care

By Jean L. Holley and Sara N. Davison

Palliative care's value and intrinsic relevance to CKD care are now increasingly recognized, and nephrologists are embracing the challenges of incorporating palliative care into their research, training, and care delivery agendas. We still have a long way to go, but we anticipate a new age in clinical nephrology as we determine how best to address these issues.

Among ASN's contributions to the American Board of Internal Medicine's "Choosing Wisely" campaign (Five Things Physicians and Patients Should Question) was the statement: "Don't initiate chronic dialysis without ensuring a shared decision-making process between patients, their families, and their physicians." (1).

In short, advance care planning is needed in order to identify a patient's values and goals. Informed and shared decision-making about starting dialysis can be achieved only when the benefits and harms of dialysis are provided within the context of expected prognosis.

ASN's Choosing Wisely statement illuminates the importance of palliative care in the overall management of CKD. The statement continues: "Limited observational data suggest that survival may not differ substantially for older adults with a high burden of comorbidity who initiate chronic dialysis versus those managed conservatively"(1). Conservative management (palliative care and no dialysis) may be especially appropriate for elderly chronic kidney disease (CKD) patients with high comorbidity.

Palliative care is part of chronic disease management throughout a patient's illness and not only near the end of life. Shared decision-making, discussing prognosis, and advance care planning, along with symptom assessment and treatment, end-of-life care, and bereavement support are all aspects of palliative care in which nephrologists will increasingly engage within the realm of CKD management.

Despite the growing appreciation for the importance of palliative care, however, nephrologists are poorly prepared to participate in these aspects of CKD care. A 2003 survey of second year nephrology fellows showed that although most thought palliative care was an important part of nephrology, few felt they received training to assist them in the provision of such care (2). Ten years later, despite tremendous growth in the literature on renal palliative care and the publication of clinical practice guidelines addressing supportive care of CKD patients (3), nephrology fellows remain unprepared and poorly trained to deliver such care (4,5).

Recognizing the importance of palliative care to nephrologists, Kidney Disease: Improving Global Outcomes (KIDGO) has formed a workgroup to synthesize the literature around issues of of palliative care, including advance care planning. The workgroup will also look at prognostication; symptom assessment and management; initiating, withholding, and withdrawing dialysis; and conservative care in developed and developing countries. The ultimate aim is to develop clinical practice guidelines that will help integrate palliative care into renal care globally.

Stay tuned as the KDIGO guidelines unfold and palliative care gains increasing attention among those involved in kidney care.

Jean L Holley, MD, is affiliated with the University of Illinois, Urbana-Champaign, and with Carle Physician Group, and Sara N. Davison, MD, is affiliated with the University of Alberta and is Workgroup Chair for the KIDGO Palliative Care Initiative.

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New ABIM Maintenance of Certification Regulations Take Effect in 2014

By Kurtis Pivert

Starting in 2014, physicians will have to meet new maintenance of certification (MOC) requirements designed to continually assess their knowledge base and performance. The American Board of Internal Medicine (ABIM) has expanded the conditions for MOC to include ongoing medical education activities and a patient safety requirement, and will report whether board-certified physicians are meeting MOC requirements.

"The American Board of Medical Specialties and ABIM have concluded that completion of MOC activities every 10 years is not adequate," said Gerald Hladik, MD, FASN, of the University of North Carolina at Chapel Hill Kidney Center. ABIM will now require diplomates to earn 100 MOC Points—as well as complete a patient survey and patient safety requirement—every 5 years.

What steps should physicians take to maintain their board certification? "In order for diplomates to keep their MOC current in 2014, they must first log in to www.abim.org starting in January 2014 to enroll in MOC by March 31, 2014, to be reported as 'Meeting MOC Requirements'," said Hladik. "An MOC activity, either offered by ABIM, ASN, or another organization, must be completed by December 31, 2015."

The number of points now required to meet MOC requirements has essentially doubled, and now includes new patient safety and patient survey requirements, added Hladik. MOC points must be earned every 2 years, and a total of 100 MOC points with a mix of Self-Evaluation of Medical Knowledge and Self-Evaluation of Practice Assessment modules must be earned by December 31, 2018.

Because physicians will still need continuing medical education (CME) credits in addition to MOC Points, many educational providers, including ASN, are offering the chance to earn both for educational activities. Each ASN NephSAP exam offers up to 10 MOC Points and 8 CME credits, and the ASN Dialysis Practice Improvement Module offers up to 20 MOC Points and 20 CME credits.

ASN plans to develop additional products, including a patient survey tool in the upcoming Transplantation Nephrology Practice Improvement Module (PIM) jointly sponsored with the American Society of Transplantation. "PIMs with a patient survey will count toward patient survey requirement," Hladik said. The ABIM is currently in the process of developing patient safety modules. Diplomates must still take a secure examination every 10 years."

Diplomates can visit www.moc2014.abim.org to review the changes that took effect in January. The ABIM website (www.abim.org) will indicate the requirements necessary for individual diplomates to maintain certification. Hladik added that "when these requirements are met, ABIM will report whether or not physicians are 'Meeting MOC Requirements' on the ABIM website."

One concern raised about these changes, and other potential MOC revisions in 2015, is that they are written with the clinician in mind and may not reflect the various settings in which nephrologists and other physicians practice, including research, education, and administration. ABIM has recognized this issue, and is working toward developing modified MOC activities for physicians with limited clinical activity.

To learn more about the ABIM MOC changes and ASN's educational offerings, visit http://www.asn-online.org/education/moc/.

ESRD Program Faces Payment Freeze for 2014; Cuts on the Horizon

ASN Policy Aims to Ensure Access for Vulnerable Populations

By Rachel Shaffer

The kidney community enters 2014 on the heels of receiving some good news—and some bad news—regarding dialysis payments in the Medicare ESRD program.

First, the good news: in its November 22, 2013, final rule, the Centers for Medicare & Medicaid Services (CMS) responded to concerns raised by ASN and other stakeholders that a proposed 12% cut to dialysis payments could impede patient access to care and jeopardize the quality of care. The agency acted to delay the cuts for two years, rather than having them take effect starting this month, responding to calls from the kidney community to phase in the cuts.

In 2014 and 2015, dialysis providers will effectively see a payment freeze, as CMS set the cuts to equal exactly what the market basket update (an annual increase to account for changes in price increases) would have otherwise been. CMS has not yet decided whether it will phase in the remainder of the cuts in one year (2016) or over the course of 2016 and 2017.

Also in the good news department: CMS provided a 50% increase in payments for the home dialysis training add-on. ASN and others in the kidney community had long advocated for an increase in the training payment, which was widely perceived as undervalued, and in some cases an obstacle to starting or expanding home dialysis programs. As a result of the decision to raise the payment rates, 2014 could see more patients having access to a choice of training to dialyze at home or continuing to receive care in their dialysis centers.

The bad news is that the 12% cut is still coming. Despite concerns raised by the community regarding both the legality of the cut and its potential effect on patient care, CMS finalized the 12% reduction as originally proposed. The agency emphasized that in determining the size of the cut, it closely followed the American Taxpayer Relief Act of 2012, which specified that payment amount to reflect the Department of Health and Human Services Secretary's estimate of the change in the utilization of ESRD-related drugs and biologicals.

Cuts likely to affect vulnerable patients disproportionately

Going into 2014, concerns persist that cuts of this magnitude could result in unintended consequences for the most vulnerable patients resulting from the closure of some units, reduced staffing and facility hours, and certain quality improvement initiatives. These changes mean that patients who already face difficulty getting to dialysis may have to travel farther and face fewer choices of when to dialyze; dialysis care teams may have to contend with a higher patient-to-staff ratio; and certain benefits—such as nutritional supplements—that patients currently enjoy may be eliminated.

"Patients who rely on lifesaving dialysis in rural and inner-city environments are most likely to be at risk as a result of the 12% cut," said ASN President Sharon M. Moe, MD, FASN. "ASN is grateful that CMS delayed these cuts in the short-term. The society is committed to working with the entire kidney community and CMS in 2014 and 2015 to ensure that patients continue to receive access to the highest quality care when the cuts take effect in 2016."

Although there will be two years of flat dialysis payments, changes in practice patterns may come as early as 2014 and 2015 as providers begin to react in anticipation of the 2016 cuts.

"Increased monitoring of facility closures and patient outcomes will be crucial," said ASN Public Policy Board chair Thomas H. Hostetter, MD, FASN. "CMS already assesses many aspects of care via claims-based monitoring, and ASN has suggested a number of other important elements that the agency should track in as close to real-time as possible. We were pleased to see in the final rule that CMS is looking into the feasibility of collecting that information, which will be all the more important as 2016 approaches."

The year 2016 will also bring the addition of oral-only drugs to the bundled payment rate for dialysis care. It is unclear exactly how CMS will integrate those costs to the bundle and how those changes will interface with the slated cuts. What is clear is that the kidney community in 2014 will likely focus on developing strategies to mitigate the potentially harmful effects of the 12% cut and ensuring patients' continued access to care in 2016.

Is 2014 the Year of Renal Denervation?

By Kurtis Pivert

This year could see the introduction of renal nerve ablation for the treatment of uncontrolled refractory hypertension to the American market. Already approved for use in Europe, Canada, and Australia, the Symplicity Renal Denervation System (Medtronic) is poised to move beyond investigational status in the United States. An application could be filed depending on the results of the Symplicity 3 clinical trial, which will be released sometime after the trial's estimated completion in January. It would be the first non-pharmacologic treatment approved for treatment-resistant hypertension.

The renal sympathetic nervous system plays a large role in essential hypertension. Renal denervation—delivering radiofrequency energy through the wall of the renal artery to ablate target nerves—may interrupt the renin-angiotensin-aldosterone system cascade, and could have additional beneficial physiological effects.

In 2012, the Centers for Disease Control and Prevention estimated more than 35 million Americans had uncontrolled hypertension, and of those nearly 45 percent were currently receiving medications (1). Although resistance to three or more antihypertensive medications for hypertension is the most commonly accepted indicator of uncontrolled treatment-resistant hypertension, a good definition of treatment-resistant hypertension is lacking, said Efrain Reisin MD, FASN, Chief of the Division of Nephrology and Hypertension of the Louisiana State University Health Science Center. Other criteria, including medication compliance and sole reliance on office blood pressure levels, can complicate a diagnosis of true treatment-resistant hypertension.

The Symplicity 3 trial included 530 patients at 88 centers in the United States randomized to either baseline antihypertensives or renal denervation plus continuation of baseline antihypertensive medications. This trial will report both office and ambulatory blood pressure measurements, ensuring patients are true treatment-resistant hypertensives.

"It's a simple procedure with not too many side effects reported, but we need to wait for the results of the Symplicity 3 study to determine if the approach is safe and effective in our patient population," said Reisin. "Other very effective options for treating uncontrolled hypertension include the use of the aldosterone blockers."

Further research is needed to determine how this new procedure may affect renal function in patients with chronic kidney disease (CKD) and if it will also be useful in end stage renal disease patients, Reisin said. Results from a recent German pilot study of 15 patients with stage 3 and 4 CKD showed benefits in office and ambulatory blood pressure levels, as well as stabilization of renal function, but larger studies are needed to confirm these preliminary findings.

The Symplicity device is just one of several renal nerve ablation systems in use outside the United States, but appears to be positioned to be the first submitted for approval in the United States. At press time, St. Jude Medical announced the EnligHTN IV trial of their EnligHTN renal denervation device was being cancelled before its initiation due to the slow pace of enrollment. Patient recruitment for a sham-controlled trial (the design of the EnligHTN IV study) could be more difficult if the Symplicity device is approved this year.

Even if renal denervation is approved in 2014, it is unknown how and whether the procedure will be reimbursed by payers, a concern for both patients and physicians.

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Prospects Looking Better for NIH Funding in 2014

By Grant Olan

Congressional action on a budget deal in the final days of 2013 means that things are looking up somewhat heading into 2014. On December 10, 2013, U.S. House and Senate budget negotiators reached a deal that may reverse some federal budget cuts in 2014 and 2015. The deal raises budget caps that were established by Congress as part of its deficit reduction efforts in the Budget Control Act of 2011 (Table 1).

If the deal is approved by Congress—which as of press time looks likely—appropriations for both defense and non-defense discretionary (NDD) appropriations would increase from the caps. NDD appropriations include funding for medical research, public health, and other non–defense-related public services.

While the deal does not replace all of the budget cuts, it is a start. Under the proposal, the NDD cap for 2014 would increase to about $492 billion (up from $468 billion in 2013). If passed, the House and Senate Appropriations Committees would have discretion of which NDD programs to allocate these new dollars towards. Under that scenario, chances are favorable that funding for the National Institutes of Health (NIH), the biggest funder of medical research in the world, would be restored to 2012 levels of $30.8 billion—an increase of $1.1 billion in funding from 2013 levels. It is also possible NIH could even get a slight increase over 2012.

"This is a good deal for kidney disease patients," said ASN President Sharon M. Moe, MD, FASN. "ASN is urging Congress to pass this legislation, and I hope lawmakers will move quickly to adopt it and pass a budget that restores funding to NIH."

Advancing research is one of ASN's central missions and public policy priorities for 2014. ASN's research advocacy consists of congressional advocacy to raise awareness of and advocate for appropriations for kidney research, and advocacy within federal research agencies for support for kidney research.

ASN launches strategy for research advocacy

In 2014, ASN will implement an aggressive new research advocacy strategy. In addition to advocating for more NIH funding, ASN will ask Congress to direct the Government Accountability Office to develop a comprehensive report that assesses the adequacy of federal investments in kidney research relative to federal expenditures for kidney care. ASN plans to use the report to help bolster its new request for $1.5 billion for kidney research ($150 million over 10 years) above the current funding level.

ASN estimates based on publicly available data indicate that the annual combined total of all federal funding for kidney research is equivalent to less than 1 percent of the annual cost of kidney disease care. NIH is the largest source of federal funding for kidney research. In 2012, the agency awarded $556 million in grants, contracts, and other funding mechanisms for kidney research, which represents just 0.7 percent of the total cost of kidney care in the Medicare system.

In 2014, ASN will also double down on advocacy for more health disparity research funding. Researchers estimate that racial health disparities cost the United States $229 billion between 2003 and 2006. For instance, African Americans in the United States are on average up to four times more likely than other Americans to progress to kidney failure. NIH-supported research recently led to the exciting discovery that African Americans have mutations in the *APOL1* gene, which may explain their higher rates of kidney disease. This discovery could lead to better prevention, therapies, and potentially even a cure, but that cannot happen without additional NIH funding for health disparities research.

Moreover, ASN will engage partners in the kidney community to develop a unified advocacy message to promote the public health burden of all kidney diseases and benefits of federal investments in research. During a first-ever meeting with most of the kidney patient and professional organizations at Kidney Week 2013, the participants present agreed on the need and importance of working together and committed to joint collaborations in 2014.

"I believe ASN's thoughtful research advocacy strategy outlines a forceful approach that should improve funding for kidney research," said ASN Treasurer-Secretary and Research Advocacy Committee Chair John R. Sedor, MD, FASN. "And while we're all appreciative of the budget deal, that strategy will be more important than ever in what continues to be tough budget environment."

Table 1. Caps on discretionary budget quthority (billions)

	Defense Discretionary Spending		Non-Defense Discretionary Spending	
	2014	2015	2014	2015
Current Law	$498	$512	$469	$483
Proposed Cap	$520	$521	$492	$492

ESCOs: The Way of the Future?

By Mark Lukaszewski

To meet the ever-growing need for cost savings in the Medicare part D system, the Centers for Medicare & Medicaid Services (CMS) developed the first-ever disease-specific Accountable Care Organization (ACO) for dialysis providers. Designed to reduce duplicative services and expenditures, the ACO—which CMS titled the ESRD Seamless Care Organization (ESCO) program—would consolidate all aspects of care for patients with end stage renal disease (ESRD).

According to CMS, the initiative will identify, test, and evaluate new ways to optimize the quality of care for Medicare beneficiaries with ESRD. To do so, CMS will partner with health care providers and suppliers to test the effectiveness of a new payment- and service-delivery model with the goal of providing beneficiaries patient-centered, high-quality care resulting in improved outcomes and overall Medicare savings.

CMS originally expected between 10 to 15 unique ESCOs to participate, with representation from all dialysis provider organizations/facility types and geographic areas. However, after the first and second deadlines came and went it appeared CMS received fewer applications than the agency and the community had anticipated.

On October 25, 2013, CMS announced it would reopen the request for applications program to solicit additional participation but has not yet announced the number of applications received to date. Whether ESCOs will be the wave of the future remains to be seen.

CMS proposed rebasing reimbursements in years 4 and 5, which would effectively penalize the highest performing ESCO and could deter potential ESCO applicants. Another concern is that CMS has not identified the quality metrics the ESCO program will use—nor have they clarified how or under what criteria—to determine if the program is deemed "successful" or "unsuccessful." These uncertainties are complicated by the recent 12-percent cut to the ESRD Prospective Payment System base rate scheduled to be implemented over the next 4 years.

These outstanding questions about certain aspects of the model—such as which quality measures will be used to evaluate the program, or the state of uncertainly regarding how financially viable the shared savings model would actually be (especially in light of the proposed rebasing in years 4 and 5) remain a major concern for the success of the ESCO program, slated to be introduced on January 14, 2014.

ASN is working to ensure that if the ESCO program is implemented its focus remains on patient safety and quality of care. As of now, no further information about these updates has yet been made available, but ASN will continue to monitor developments and keep our members up-to-date on any new developments in the ESCO program as it moves forward.

Regenerative medicine

By Pascale Lane

Building new urethras and printing kidneys sounds like science fiction, but anyone who caught Anthony Atala's state-of-the-art session at Kidney Week knows that such things are closer than we think. Though still at the animal stage, building new functional glomeruli and genitourinary tract organs can be done. Someday kidneys for transplantation may be created rather than donated, although perhaps not quite in 2014.

A recent TED talk on kidney printing speaks volumes: http://www.ted.com/talks/anthony_atala_printing_a_human_kidney.html. The strides in this field are truly amazing and bear watching.

Pascale Lane, MD, is editor-in-chief of ASN Kidney News.

Journal View

Study Shows Racial Differences in Vitamin D–Binding Protein

Variations in the vitamin D–binding protein gene may help to explain differences in vitamin D levels and clinical vitamin D deficiency in black versus white individuals, according to a study in the *New England Journal of Medicine*.

The researchers analyzed data on total 25-hydroxyvitamin D, vitamin D–binding protein, parathyroid hormone, and bone mineral density in black and white adults from a United States population—based cohort study. The participants also underwent genotyping studies for the common rs7041 and rs4588 2 polymorphisms of the vitamin D–binding protein gene. The concentrations of bioavailable 25-hydroxyvitamin D were calculated in a subgroup of 1025 homozygous participants.

The black participants had a lower mean total 25-hydroxyvitamin D level: 15.6 ng/mL, compared with 25.8 ng/mL in white participants. The levels of vitamin D–binding protein were 168 and 337 µg/mL, respectively.

On adjusted analysis, the two polymorphisms accounted for close to 80 percent of the variation in vitamin D–binding protein levels and for 10 percent of the variation in total 25-hydroxyvitamin D. After genotype was accounted for, race explained less than 0.1 percent of the variation in vitamin D–binding protein. Despite their lower vitamin D levels, the black participants had a higher mean bone mineral density.

Study participants with lower total and bioavailable 25-hydroxyvitamin D levels had higher parathyroid hormone levels. However, at each level of parathyroid hormone, total 25-hydroxyvitamin D was lower among black participants. In the homozygous subgroup analysis, levels of bioavailable 25-hydroxyvitamin D were similar by race, and within categories of parathyroid hormone level.

The new results confirm that black persons have lower total 25-hydroxyvitamin D than do their white counterparts. However, because black individuals also have lower levels of vitamin D–binding protein, the levels of bioavailable 25-hydroxyvitamin D are not significantly different. The authors discuss the implications for assessing racial and ethnic differences in vitamin D levels, including the potential role of vitamin D–binding protein measurement [Powe CE, et al. Vitamin D–binding protein and vitamin D status of black Americans and white Americans. *N Engl J Med* 2013; 369:1991–2000].

Score Predicts Kidney Failure or Death in Rhabdomyolysis

A risk prediction score calculated with the use of routine admission data performs well in predicting the risk of renal replacement therapy (RRT) or mortality in patients with rhabdomyolysis, according to a study in *JAMA Internal Medicine*.

The researchers analyzed data from 2731 patients treated for rhabdomyolysis at two hospitals between 2000 and 2011. All had creatine phosphokinase levels greater than 5000 U/L within 3 days of admission. The risk prediction score was developed with the use of data from 1397 patients treated at one hospital and was validated by the use of data from 974 patients at the other hospital. The main outcome of interest was a composite of continuous RRT and in-hospital death.

Overall, 8.0 percent of patients required continuous RRT, 14.1 percent died in the hospital, and 19.0 percent met either outcome. Rates of the composite outcome were highest for patients with rhabdomyolysis associated with cardiac arrest (58.5 percent), compartment syndrome (41.2 percent), and sepsis (39.3 percent). Other independent risk factors included older age, female sex, and baseline creatinine, creatine phosphokinase, phosphate, calcium, and bicarbonate levels.

A risk score comprising these variables performed well in identifying rhabdomyolysis patients at high risk of RRT or death, with C statistics of 0.82 in the derivation cohort and 0.83 in the validation cohort. In the latter group, the composite outcome rates were 2.3 percent in patients with a risk score less than 5 versus 61.2 percent for those with a score greater than 10. For a risk score less than 5, the negative predictive value was 97.7 percent and the positive predictive value was 27.2 percent.

Patients with rhabdomyolysis are at risk of potentially life-threatening acute kidney injury. The new risk prediction score, based on readily accessible demographic, clinical, and laboratory variables, performs well in identifying patients at lower and higher risk of continuous RRT and in-hospital mortality. The authors believe their score will be most useful for triage of patients evaluated in the emergency department [McMahon GM, et al. A risk prediction score for kidney failure or mortality in rhabdomyolysis. *JAMA Intern Med* 2013; 173:1821–1827].

Evidence Questions Benefits of ESAs for Anemia in Heart Disease

Erythropoiesis-stimulating agents (ESAs) are not beneficial—and may be harmful—in the treatment of mild to moderate anemia in patients with heart disease, according to a review in the A*nnals of Internal Medicine*.

A systematic review of the literature was performed to evaluate the benefits and harms of treatments for anemia in patients with heart disease. The analysis focused on studies of blood transfusion, iron, or ESAs for adults with anemia and congestive heart failure or coronary heart disease.

On the basis of six trials and 26 observational studies, there was "low-strength" evidence of improvement in short-term mortality among patients treated with liberal transfusion protocols, compared with less aggressive protocols. The difference was not significant on meta-analysis. However, one small trial in patients with acute coronary syndrome reported lower mortality in patients treated with a liberal transfusion strategy: 1.8 versus 13.0 percent. Three trials of intravenous iron therapy provided "moderate-strength" evidence of improvements in short-term exercise tolerance and quality of life in anemic patients with heart failure.

The review identified 17 randomized trials of ESAs, most conducted in patients with heart failure. The studies provided "high-strength" evidence that ESAs did not lead to reductions in mortality, cardiovascular events, or hospitalizations. There was also "moderate-strength" evidence that ESAs did not lead to improved quality of life. The review also identified moderately strong evidence linking ESAs to serious harms, including hypertension, venous thromboembolism, and possibly mortality, in patients with congestive heart failure.

The review analyzes the growing body of evidence on strategies for correcting anemia in patients with heart disease. The data provide no consistent evidence of reduced mortality with higher transfusion thresholds, but they do suggest symptomatic improvements with intravenous iron. Further studies of both treatments are warranted.

The authors conclude: "Erythropoiesis-stimulating agents do not seem to benefit patients with mild to moderate anemia and heart disease and may be associated with serious harms." The review serves as the basis for a new American College of Physicians guideline on the treatment of anemia in patients with heart disease: http://annals.org/article.aspx?articleid=1784292 [Kansagara D, et al. Treatment of anemia in patients with heart disease: a systematic review. *Ann Intern Med* 2013; 159:746–757].

Can *APOL1* Explain Higher Risk of ESRD in Black Patients?

Increased rates of kidney disease progression among black patients—regardless of cause—are at least partly related to variants of the apolipoprotein L1 gene (APOL1), suggests a study in the *New England Journal of Medicine*.

The researchers analyzed data from 693 black patients from the African American Study of Kidney Disease and Hypertension (AASK) who had chronic kidney disease (CKD) attributed to hypertension, and 2955 white or black patients with CKD from the Chronic Renal Insufficiency Cohort (CRIC) study, about half of whom had diabetes. Both analyses compared outcomes in a "high-risk" group with two copies of high-risk *APOL1* variants versus a "low-risk" group with zero or one copy.

In the AASK data, black participants with high-risk *APOL1* status were more likely to meet a composite outcome of ESRD or doubling of serum creatinine: 58.1 percent versus 36.6 percent, hazard ratio 1.88. The association was unaffected by study interventions or baseline proteinuria.

Among CRIC participants, those with two copies of *APOL1* risk variants had a steeper decline in estimated GFR. The high-risk *APOL1* group also had a higher rate of a composite outcome of ESRD or a 50 percent reduction in estimated GFR. Among black CRIC participants, the risk of the composite outcome was 46 percent higher in the high-risk *APOL1* group than in the low-risk group. This was so regardless of the presence or absence of diabetes.

Previous research has linked *APOL-1*variants to increased rates of kidney diseases in black individuals, including ESRD in patients without diabetes. On the basis of the new study, high-risk *APOL1* genes appear to contribute to an elevated risk of ESRD and progressive CKD in black versus white patients, regardless of diabetes status. The researchers write that their study provides "direct evidence…that the *APOL1* high-risk variants are associated with increased disease progression over the long term" [Parsa A, et al. *APOL1* risk variants, race, and progression of chronic kidney disease. *N Engl J Med* 2013; 369:2183–2196].

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Which holds more promise for halting the progression of chronic kidney disease: the renin-angiotension system blockade or endothelin antagonists? Two experts weigh in.

Learning from Failure: New Therapy for Diabetic Nephropathy and Beyond?

By David M. Pollock

It took only about 5 years after the discovery of the endothelin (ET) peptide to develop potent and selective endothelin receptor antagonists (ETRAs) (7). This was about 20 years ago, and there are now two antagonists currently approved for use in pulmonary hypertension. Other targets have demonstrated tremendous promise in preclinical studies, but patent expirations and failures in several clinical studies have discouraged most of the big pharmaceutical companies from further investigation of these drugs as therapies. The failures include a wide range of disorders, including heart failure, prostate cancer, and even resistant hypertension. The latter target remains a strong possibility, but unlikely because of financial reasons.

Endothelin-1 functions through ETA receptors primarily located on vascular smooth muscle to produce the well-known vasoconstrictor effects, but perhaps more importantly as a promoter of cell growth and inflammation. In healthy conditions, these effects are held in check by ETB-dependent vasodilation and anti-inflammatory effects. Many investigators believe that the loss of ETB receptor function is as important in generating these effects as is excess ET-1 synthesis, if not more so. Physiologically, ET-1 functions as a critical regulator of sodium and water homeostasis, but not in the same manner as the renin-angiotensin system (RAS). Rather, it functions as a pronatriuretic factor mediated by both hemodynamic and renal tubular actions (2).

Since the early days of endothelin research, a wide range of animal studies have revealed that chronic kidney disease (CKD) is associated with overproduction of ET-1 (3). These models include ischemia, chemotoxins, reduced mass, immune injury, and others. More important, the administration of selective ETA or combined ETA/ETB receptor antagonists can attenuate the severity of injury and disease in these models. Nonetheless, initial drug development focused on pulmonary hypertension, heart failure, and even prostate cancer.

Little attention was paid to the promising preclinical work on endothelin in the renal field until a small biotech company, Speedel, conducted several phase 2 and phase 3 studies exploring the potential therapeutic utility in patients with stage 3 and 4 CKD with diabetic nephropathy (4). Using avosentan, a relatively little known antagonist with marginal preference for the ETA receptor over the ETB receptor, they were able to observe remarkable reductions in proteinuria on the order of 40 to 50 percent, even while more than 90 percent of those studied were already taking RAS inhibitors, diuretics, and an average of nearly five medications.

Speedel's phase 3 trial (ASCEND) had to be terminated early because of adverse events associated with drug-induced fluid retention, including congestive heart failure (5). The cause of edema is not known but is most likely mechanism-based, given that other ETRAs can also produce edema—an effect that can be reproduced in mice. The higher rate of edema in patients with CKD suggests that the kidney is involved. Another unfortunate aspect of this study is that the edema was predicted from the phase 2 trial. During that study, maximal reductions in proteinuria were observed even at the lowest dose over a dosage range of 5 to 50 mg/ day avosentan; yet fluid retention was dose dependent. For reasons that are not clear, the subsequent phase 3 trial moved forward with 25-mg and 50-mg dosing, thus maximizing the risk of fluid retention. Some anecdotal reports mentioned that the fluid issues could be managed with diuretic treatment, but adjustments in diuretic therapy were not part of the trial design, so accommodations could not be made.

So the use of ETRAs in CKD again looked like a lost cause until Abbott Laboratories (now AbbVie) recently decided to conduct a phase 2A trial with its highly selective ETA antagonist, atrasentan, in patients with diabetic nephropathy (6). They chose much lower doses (0.25 to 1.75 mg/day avosentan) and included careful management of fluids with diuretic treatment. Once again, the patients were already being treated with RAS inhibitors and a range of other standard drug therapies. Edema occurred at a much lower rate for most doses in such a manner that the 0.75-mg dose produced maximal efficacy in terms of reducing albuminuria; still, edema occurred at an identical rate as with placebo.

These promising findings led AbbVie to pursue a larger phase 2B trial (RADAR) using 0.75 and 1.25 mg/day, which showed a reduction of approximately 35 to 40 percent in albuminuria in patients with diabetic nephropathy, with no serious adverse events associated with drug-induced fluid retention (7). Currently, a phase 3 trial (SONAR), examining the effect of 0.75 mg/day atrasentan on hard renal outcomes with a planned enrollment of more than 4000 patients with diabetic nephropathy is ongoing.

One of the big lessons in the saga of ETRAs in CKD (as well as other drug development programs) is that basic pharmacology and physiologic mechanisms must remain front and center when trials are designed. A similar story developed with the use of ETRAs in resistant hypertension. Despite a large phase 3 trial and significant reductions in ambulatory blood pressure in patients taking an average of five antihypertensive drugs, a large decline in clinical blood pressure during the final week of the trial in the placebo group rendered the primary endpoint, clinical blood pressure, statistically insignificant (8). Although the vast majority of hypertension specialists insist that ambulatory blood pressure is the gold standard, this has yet to be used as a clinical endpoint by the U.S. Food and Drug Administration. In the final analysis, despite the significant problems encountered with studies involving ETRAs, there remain compelling reasons to study these agents in a variety of diseases, including CKD.

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Renin-Angiotensin System Blockade Versus Endothelin Antagonism for Halting Progression of Chronic Kidney Disease

By George Bakris

Renin-angiotensin system (RAS) blockers (e.g., angiotensin converting enzyme [ACE] inhibitors and angiotensin receptor blockers) have enjoyed a great deal of notoriety under the heading of being "renoprotective." There is no question that they can reduce very high albuminuria or macroalbuminuria (>300 mg/day) to a greater extent than other agents (1). The issue of renoprotection, however, across all stages of nephropathy is questionable and is not evidence based. Moreover, albuminuria reduction is not a proven surrogate for slowing the progression of chronic kidney disease (CKD), inasmuch as all of the data for this premise are based on retrospective or observational studies (2).

The totality of the evidence from prospective clinical trials supports the concept that RAS blockers significantly slow CKD progression compared with other agents in patients with advanced stage 3b or higher CKD who have, on average, more than 500 mg/day of albuminuria (2). This was true in the Captopril trial, Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartin trial, and Irbesartan Diabetic Nephropathy Trial involving patients with diabetes and the Angiotensin-converting-enzyme Inhibition Progresssive Renal Insufficiency, Ramipril Efficacy In Nephropathy, and Modification of Diet in Renal Disease trials, and the trial by Hou et al., involving patients with nondiabetic kidney disease (2, 3). The one exception, wherein RAS blockade slowed nephropathy progression in the absence of very high albuminuria, was the African American Study of Kidney Disease and Hypertension trial, in which most participants had stage 3b CKD and high albuminuria or microalbuminuria (4). Thus, in advanced albuminuric CKD, RAS blockade has level 1 A or B evidence, depending on the source for slowing CKD progression (5). This is not true for RAS blockers in stages 1 or 2 CKD with hypertension with or without high albuminuria or microalbuminuria, nor for individuals with normotension with or without diabetes (5). Hence, RAS blockers are an optional but not mandated antihypertensive therapy in the aforementioned patients.

Well-known markers of the perceived development of CKD, such as high albuminuria, are not accepted by regulatory authorities and are not indicative of kidney disease in diabetes, on the basis of biopsy evidence (6, 7). Moreover, reductions in high albuminuria or microalbuminuria in early nephropathy relate largely to reduction in blood pressure or other inflammatory conditions and are not consistent with arresting CKD progression, as noted when microalbuminuria returns to baseline within a month after the RAS blocker is discontinued (3). Last, RAS blockers when used in people at risk for CKD progression are clearly beneficial only when used at maximal doses, like those used in trials. In individuals without macroalbuminuria, RAS blockers are beneficial in that they lower blood pressure and may improve endothelial function, but nothing else. Therefore, it is incorrect to conclude that a patient has "renoprotection" if he or she is taking an ACE inhibitor or ARB, regardless of dose, especially if blood pressure is not controlled. Outcome trials used the highest tolerated dose of RAS blockers, with most patients getting the maximum dose.

From an evidence-based perspective, the ACE inhibitors shown to slow nephropathy progression in trials are captopril, ramipril, and benazepril (8). The most commonly used ACE inhibitor, lisinopril, has not been formally tested in clinical trials against conventional therapy to assess its effects on CKD progression. The only ARBs approved to slow CKD progression are losartan and irbesartan. Telmisartan is the only approved ARB to reduce mortality in patients who are tolerant to ACE inhibitors (9). ARBs should be started at the maximal dose, as now recommended by the U.S. Food and Drug Administration, because they do not have dose-dependent side effects.

The only evidence that supported dual RAS blockade was additional reduction in albuminuria (1). We now have conclusive evidence showing a failure of dual RAS therapy to slow CKD progression, as assessed by ALTITUDE, Veterans Administration Diabetes iN Nephropathy Study (VA NEPHRON D), and the Ongoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial (ONTARGET). All three of these trials evaluated dual ACE inhibitor/ARB therapy of CKD progression, with ALTITUDE and VA NEPHRON D powered for primary renal outcomes. All failed to show a benefit, and all showed increased risk for hyperkalemia and risk for acute kidney injury. It should be noted that the mean estimated GFR in all of these trials was well below 60 mL/min per 1.73 m^2. When the combination of valsartan and aliskiren was tested for its effect on ambulatory blood pressure changes in people with a mean estimated GFR of 84 mL/min per 1.73 m^2, it was well tolerated, with no hyperkalemia and additive blood pressure lowering (10). These data, taken together with the questionable benefit on CKD progression by lowering albuminuria, clearly indicate that it is inappropriate to use dual RAS blockade in advanced CKD. The question of aldosterone blockade in this context has not yet been answered fully. Hence, the aforementioned statement does not apply to the use of aldosterone blockade with an ACE inhibitor or ARB.

Endothelin antagonists

Endothelin receptor antagonists (ETA) have been available for almost two decades. As a class, ETAs have not made it to the forefront of antihypertensive therapy. They are efficacious for blood pressure reduction, especially in specific situations such as pulmonary hypertension and post-transplantation calcineurin inhibitor hypertension mechanistically caused by increases in endothelin (11). Their side-effect profile, however, is high, and this class has not been evaluated for its effect on CKD progression. The major side effects that lead to limited use of this class are profound sodium retention and peripheral edema; thus, they are poorly tolerated (11).

Bosetan is a nonspecific endothelin blocker approved for the treatment of pulmonary hypertension, but it is expensive and causes edema; hence, it is not commonly used.

Darusentan, a selective ETA-1 blocker, showed great promise as an antihypertensive agent, although it also had dose-dependent edema and worsening heart failure symptoms as side effects (12). Atrasentan is also a good antihypertensive agent, especially in the post-transplantation setting, but it too had dose-limiting side effects. including edema, worsening heart failure symptoms, and liver function abnormalities (13, 14). Interestingly, nonhypotensive doses of atrasentan reduce macroalbuminuria without an effect on blood pressure (14). This agent is in clinical trials to evaluate its effects as a possible "renoprotective" agent independent of blood pressure lowering. Hence, this class of agents has utility in limited circumstances. Given their dose-dependent side effects, they can be useful in only a limited number of patients with specific conditions at this time.

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Detective Nephron

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

Mr. Nice Glom enters the room along with L.O. Henle to present a case.

Nephron What do you have for me today, Henle? And we have a new medical student—the word is out that students are not interested in nephrology any more?

Henle looks at Glom.

Glom I have a 55-year-old man with a serum potassium level of 6.1 mEq/L.

Nephron Hyperkalemia! Did you repeat the serum potassium? What did the electrocardiogram (ECG) show?

Glom I don't know.

Henle I did. I actually checked the whole-blood potassium level, and it was 6.2 mEq/L. I personally took the blood sample to the arterial blood gas machine. The ECG was unremarkable: no peak T waves or wide QRS interval.

Nephron Excellent! You already ruled out pseudohyperkalemia with the measurement of whole-blood potassium. Also, remember to always obtain a 12-lead ECG with any serum potassium level greater than 6 mEq/L. Is the patient using a monitor bed?

Glom …mmm…

Henle *(interrupting Glom)* Of course! The primary team has started the treatment with insulin, dextrose, and albuterol. We will recheck his serum potassium in 1 hour.

Nephron So, what is your approach to hyperkalemia?

Henle Generally speaking, hyperkalemia can be caused by translocation or decreased renal K^+ excretion.

Glom *(curious)* Can you elaborate on translocation?

Henle Well, translocation refers to shifting of potassium out of the cells. This can result from different mechanisms. The first is from decreased activity of Na-K ATPase that occurs in patients with insulin deficiencies such as diabetes, β-blocker use, or digitalis overdose.

Nephron *(excited)* Very good! So, what is the mechanism of hyperkalemia in patients who present with diabetic ketoacidosis?

Henle Metabolic acidosis, which stimulates exchange of H^+ for K^+.

Nephron Actually, that is not true. H^+ exchange for K^+ is indeed a mechanism for hyperkalemia due to translocation, but it does not explain the hyperkalemia observed in diabetic ketoacidosis. Organic metabolic acidoses such as diabetic ketoacidosis or lactic acidosis do not cause significant hyperkalemia by this mechanism. Only inorganic metabolic acidoses do. There are two reasons why patients with diabetic ketoacidosis experience hyperkalemia: insulin deficiency and solvent drag. You have already talked about insulin deficiency. The second mechanism is solvent drag. Hyperosmolality caused by hyperglycemia pulls water out of the cells, and water carries potassium out. Actually, patients with diabetic ketoacidosis are generally depleted of total body potassium as a result of osmotic diuresis. Only when insulin is used to treat this patient is the total body potassium depletion uncovered.

Nephron Are there other mechanisms of translocation?

Henle Tissue destruction.

Glom Oh, yes! I remember that. Like in rhabdomyolysis?

Nephron Yes. Also tumor lysis syndrome. Remember: potassium is the most abundant cation in the intracellular compartment, with a concentration of 140 to 150 mEq/L.

Henle This patient does not have diabetes, nor does he have hyperglycemia. Also, his creatine phosphokinase and uric acid levels are normal.

Nephron So, it does not seem that he has a translocation, then.

Henle I don't believe so.

Nephron OK, what is the other main pathophysiologic mechanism for hyperkalemia?

Glom Decreased renal K^+ excretion.

Nephron Correct—but now, could you be more specific?

Henle Potassium first needs to be filtered. So, any reductions in GFR will cause hyperkalemia.

Nephron Exactly. Anybody with acute or chronic renal injury who is eating a diet liberal in potassium could experience hyperkalemia.

Henle His BUN level is 10 mg/dL, and his serum creatinine level is 0.8 mg/dL. So, no decline in GFR.

Nephron Now, how does the nephron handle potassium?

Henle Potassium is freely filtered, and then the proximal tubule reabsorbs about 65 percent of the filtered load. Then the thick ascending limb of the loop of Henle reabsorbs about 25 percent of the filtered load. The remaining 10 percent is delivered to the distal nephron, where—depending on the K^+ intake—it could be secreted or reabsorbed. In the case of hyperkalemia, the appropriate response is potassium secretion.

Nephron Where and how is potassium secreted?

Henle It is secreted in the cortical collecting duct.

Nephron Good! There is also some potassium secretion in the connecting tubule and the outer medullary collecting duct.

Glom I believe there is also some potassium secretion in the thick ascending limb of the loop of Henle, as well.

Nephron Potassium is technically secreted in the thick ascending limb of the loop of Henle by renal outer medullary potassium (ROMK) channels, but this serves a completely different purpose.

Glom *(surprised)* Really?

Nephron If you remember, we have these $Na^+/K^+/2Cl$ cotransporters, also known as NKCC2, in the thick ascending limb of the loop of Henle.

Henle Yes, furosemide inhibits them.

Nephron Exactly. This NKCC2 needs potassium to function.

Nephron How much sodium is filtered per day?

Glom A lot!

Henle If the normal GFR is 180 L/day, and the normal plasma sodium concentration is 140 mEq/L, then it would be 180 L/day × 140 mEq/day = 25,200 mEq/day.

Nephron Great! Now, how much of that is reabsorbed in the thick ascending limb?

Henle About 20 percent.

Nephron Great again! So that would be 20 percent of 25,200 mEq, or 5040 mEq/day.

Henle Yes, I guess.

Nephron What about for potassium?

Henle If you consider a normal plasma K^+ concentration of 4 mEq/L, then it would be 180 L/day × 4 mEq/L, or 720 mEq.

Nephron You are good at math!

Henle *(smiling)* I was an engineering major in college.

Nephron I knew it! How much of that will reach the thick ascending limb after the proximal tubule reabsorbs most of it?

Glom 65 percent of 720 mEq is about 468. Then 725 minus 486 is 257 mEq: 257 mEq!

Nephron Yes, and given that the NKCC2 has to translocate Na^+ and K^+ in a 1:1 ratio inside the thick ascending limb cells, then you will need about 5000 mEq of potassium for the NKCC2 to work. This of course, does not occur, unless …

Henle Unless potassium recycles back via the ROMK channels!

Nephron Exactly. You are very sharp today, my dear apprentice.

Henle And the K^+ recycling also creates an electrical gradient for paracellular transport of calcium and magnesium.

Nephron That is also true, but let's go back to my original question. How is potassium secreted in the distal nephron?

Henle The basolateral side of the principal cells in the cortical collecting duct have a Na^+/K^+/ATPase pump that pumps sodium out of the cell in exchange for potassium, which goes inside the cell. This will decrease the intracellular sodium concentration, which will in turn create a chemical gradient for sodium in the tubular lumen to enter the cells. First, sodium has to be delivered to the distal nephron to be able to enter the principal cells. Sodium enters the cells via the epithelial sodium channel (ENaC). When sodium enters the cell, it brings positive charges inside the cell, and this makes the inside of the cell positively charged and the tubular lumen negatively charged. This electrical gradient is responsible for potassium secretion from the cell into the lumen via the ROMK channels.

Nephron Are there any other potassium channels in the distal nephron besides ROMK that intervene in potassium secretion?

Henle I don't know.

Nephron There are other channels called BK channels or Maxi-K channels, which are flow-mediated channels. They are activated in conditions of high distal flow such as polyuria or use of diuretics.

Henle Interesting.

Nephron What is the role of aldosterone in all of this?

Henle Aldosterone is released in response to hyperkalemia and stimulates the Na^+/K^+/ATPase, ENaC, and ROMK to secrete potassium.

Nephron I am so glad you understand the physiology so well; I am sure you will be a great nephrologist. So, if anything fails in what you just described, you can expect that hyperkalemia might develop. For instance, if your distal Na^+ delivery decreases, as in severe hypovolemia, then hyperkalemia might ensue. If there is decreased activity of ENaC or ROMK caused by mutations, drugs, or lack of aldosterone, then you could expect hyperkalemia to develop. If the electrical gradient for K^+ secretion is somehow affected, then hyperkalemia will also develop. Now, let's go back to our patient. Any other significant findings?

Henle Well, he does have a mild non–anion gap metabolic acidosis. His total CO_2 is 21 mmol/L.

Nephron Interesting! Did you confirm the metabolic acidosis with an arterial blood gas?

Glom You don't have to, right?

Henle Yes, because a low total CO_2 could mean a metabolic acidosis but also a compensatory response to a chronic respiratory alkalosis. His arterial pH was 7.31.

Nephron What clinical conditions present with hyperkalemia and metabolic acidosis?

Glom Some renal tubular acidosis (RTA).

Nephron What is the urine pH?

Henle His urine pH is 6.0.

Nephron So he is unable to acidify his urine to a pH less than 5.5 in the presence of metabolic acidosis. How do you call that?

Glom A renal tubular acidosis?

Nephron Yes. Now, what renal tubular acidosis goes with hyperkalemia?

Continued on p. 14

Detective Nephron *continued*

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Henle Type 4 RTA.

Nephron Excellent. What is the problem in type 4 RTA?

Henle There is no aldosterone, and aldosterone stimulates K^+ and H^+ secretion.

Nephron Also, chronic hyperkalemia can inhibit ammoniagenesis and result in metabolic acidosis as well. Type 4 RTA can be due to hypoaldosteronism but also to aldosterone resistance. Let's start with hypoaldosteronism. What are the causes of hypoaldosteronism?

Henle Decreased synthesis of aldosterone, as in primary adrenal insufficiency. But his cortisol level is normal.

Nephron So, probably not that. Good; what else causes decreased synthesis of aldosterone?

Henle I am not sure.

Nephron Heparin. Is he getting any heparin?

Henle No, not even for prophylaxis of deep venous thrombosis.

Nephron OK, what other mechanisms of hypoaldosteronism you can think of?

Silence.

Nephron How is aldosterone produced?

Henle Everything starts with renin. Renin released from the juxtaglomerular cells transforms angiotensinogen into angiotensin I, and then the angiotensin-converting enzyme (ACE) converts angiotensin I into angiotensin II, which works in the zona glomerulosa of the adrenal gland to release aldosterone.

Nephron Again, I am impressed with your knowledge of physiology. All nephrologists have a good grasp of physiology. From what you just said, is there anything that could interfere with aldosterone release from adrenal gland?

Glom Angiotensin receptor blockers and ACE inhibitors.

Henle The patient is not taking any of those drugs. We also now have renin blockers that can do that as well, but he is not taking those either.

Nephron Certainly. Anything else that could interfere with renin?

Henle Well, I understand diabetes can cause hyporeninism, but this patient is not diabetic.

Nephron Yes. Anything else in his medical history?

Henle Nothing important. He is here for a gout flare. His primary doctors have given him indomethacin for the past 3 days.

Nephron Interesting! Can nonsteroidal anti-inflammatory drugs cause hyperkalemia?

Henle I guess. But how?

Nephron They actually decrease renin synthesis and also can decrease aldosterone release from the adrenal gland.

Glom So this could be it.

Nephron Yes. Any other RTA that goes with hyperkalemia?

Glom Not that I know of.

Nephron Well, there is a hyperkalemic variant of type 1 RTA, also known as voltage-dependent distal RTA. The problem here is that impaired sodium reabsorption via ENaC decreases the electrical gradient for H^+ secretion and K^+ secretion via the ROMK channels. But some nephrologists consider this a form of aldosterone resistance and classify it as a type 4 RTA as well.

Henle He is not taking any ENaC blockers, or any aldosterone antagonist drugs, either.

Nephron What ENaC blockers do you know?

Henle Amiloride, triamterene, and trimethoprim.

Nephron Good; also pentamidine. So, what do we need to do next?

Henle We can calculate the transtubular potassium concentration gradient (TTKG)?

Nephron Well, that would have been the right thing to do in the past. However, the Halperin group, which developed this tool, has recently discouraged its use because one of the main assumptions for the use of TTKG is that there is no significant reabsorption of osmoles downstream from the cortical collecting duct, and apparently there is a large amount of urea recycling in the inner medullary collecting duct, which aids in potassium secretion. This makes the calculation of TTKG invalid. As my good friend Dr Joel Topf posted in his pbfluids blog, "Discovered by Halperin and killed by Halperin."

Henle Can we measure renin and aldosterone levels?

Nephron That seems more appropriate. We also need to give him a low potassium diet and discontinue indomethacin.

Henle Will do.

Two days later:

Nephron *(sipping his coffee)* OK, so what happened with the patient?

Henle His renin and aldosterone levels were reduced, and his hyperkalemia has improved with the discontinuation of indomethacin. His latest serum potassium level is 4.9 mEq/L.

Nephron Great job, my apprentice. You have a great future ahead of you. Remember, besides laboratory data and clinical acumen, you need a good history and physical examination because they will never be replaced. No online tool or laboratory test is going to give you the most information as well as the patient can.

The concept of Detective Nephron was developed by Kenar D. Jhaveri, MD, associate professor of medicine at Hofstra North Shore LIJ School of Medicine and an attending nephrologist at North Shore University and Long Island Jewish Medical Center in Great Neck, NY. Special thanks to Dr. Helbert Rondon, assistant professor of medicine in the renal and electrolyte division at the University of Pittsburgh School of Medicine, writer and submitter for this case. Send correspondence regarding this section to kjhaveri@nshs.edu or kdj200@gmail.com

Industry Spotlight

New Phosphate Binder Lessens Pill Burden

Fresenius' North America unit this year will launch a drug approved in late November by the U.S. Food and Drug Administration.

Velphoro (sucroferric oxyhydroxide) received approval for controlling serum phosphorus levels in dialysis patients with chronic kidney disease.

The new drug, known previously in trials as compound PA21, is a chewable form of a phosphate binder that is iron based and free of calcium. A phase 3 study showed that Velphoro successfully controlled hyperphosphatemia with fewer pills than sevelamer carbonate (Renvela, Sanofi), which is currently used by many patients on dialysis.

Individuals on dialysis swallow on average 19 pills per day; about half of these are phosphate binder pills. By contrast, the average daily dose to control hyperphosphatemia was 3.3 Velphoro pills per day after 52 weeks. The recommended starting dose for the new medication is one tablet per meal, three times daily.

Vifor Fresenius Medical Care Renal Pharma's chief executive Charles DeLoach said his company aimed to achieve the right balance between the pills having enough pliability to keep the tablets in one piece yet soft enough to be chewed easily. Many dialysis patients have difficulty chewing tablets.

The company reported that regulatory reviews in Europe and Singapore for drug approval were expected in the first half of 2014.

Home Dialysis Matures, Offering More Options

One of the latest innovations in home dialysis is a machine that weighs less and uses less water.

Switzerland-based Debiotech SA and Singapore-based AWAK Technologies have joined forces to develop and manufacture a miniaturized home hemodialysis machine they call DialEase.

DialEase uses Debiotech's mini peritoneal dialysis equipment and a novel sorbent technology for fluid purification developed by AWAK.

The companies characterize the new system as "extremely small and convenient to use, less intrusive in a patient's life and more cost effective." In a joint release, the companies said the new system would need less fluid than conventional hemodialysis machines and would be monitored in real time from the hospital via cloud computing (network-based, remote computer services).

According to Debiotech President and CEO Frédéric Neftel, "By using the sorbent fluid purification cartridge from AWAK, we will be able to save a significant amount of fluid, simplify the entire logistics and radically reduce the size of the final system," which would contribute to cost savings.

The current model of DialEase can stand on a nightstand and weighs about 4.7 kg (10.36 pounds), the companies said in a release. A laptop weighs about 6 to 8 pounds.

Earlier in 2013, AWAK partnered with Baxter International to develop wearable dialysis technology for patients with end stage renal disease. The agreement enabled AWAK to continue the development of its investigational peritoneal dialysis–based automated wearable artificial kidney, the company said.

Financial terms for the agreement weren't disclosed, but AWAK would give Baxter exclusive global manufacturing and distribution rights for AWAK's investigational, wearable artificial kidney, a minority stake in the company, and the option to purchase additional equity.

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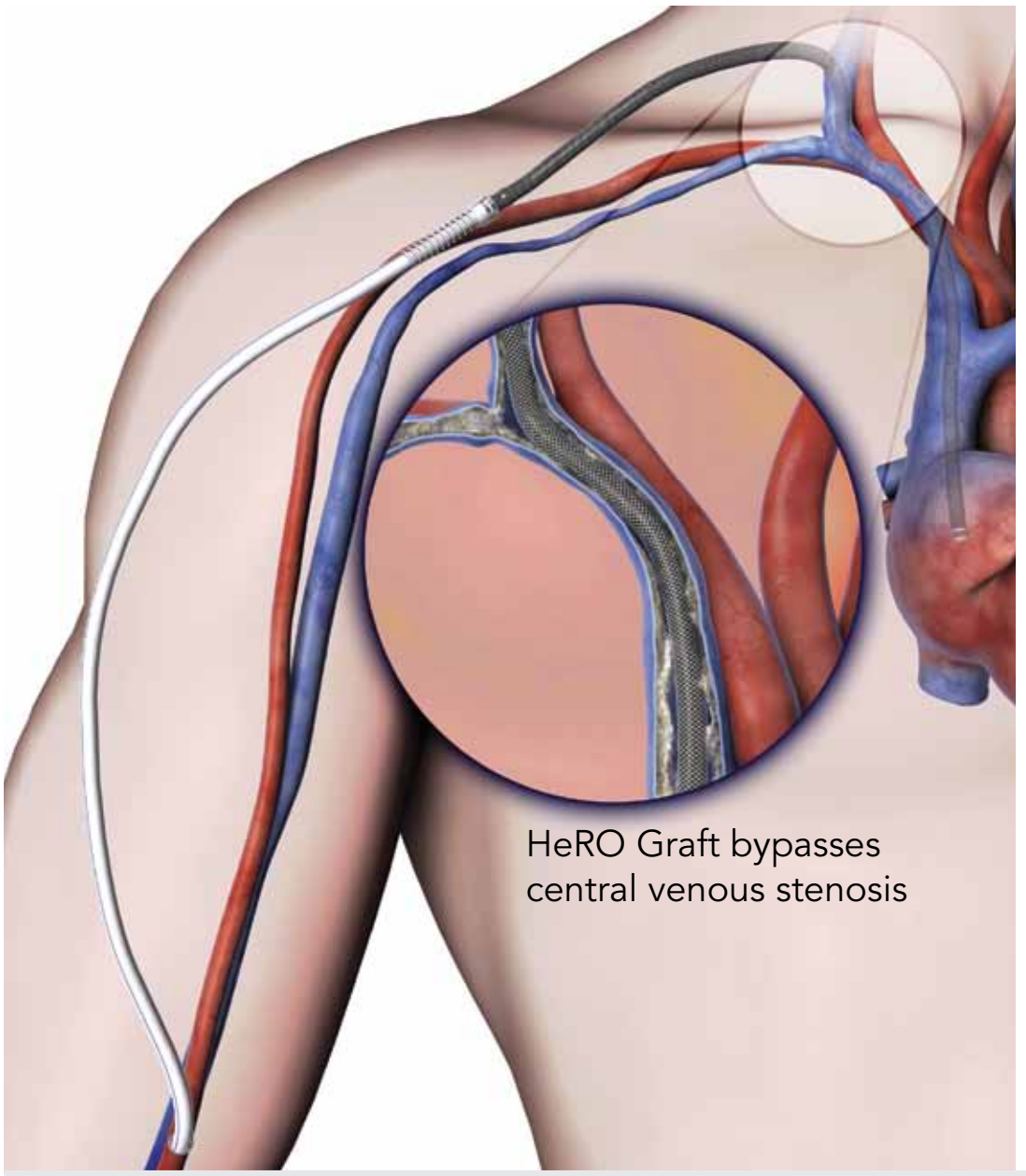

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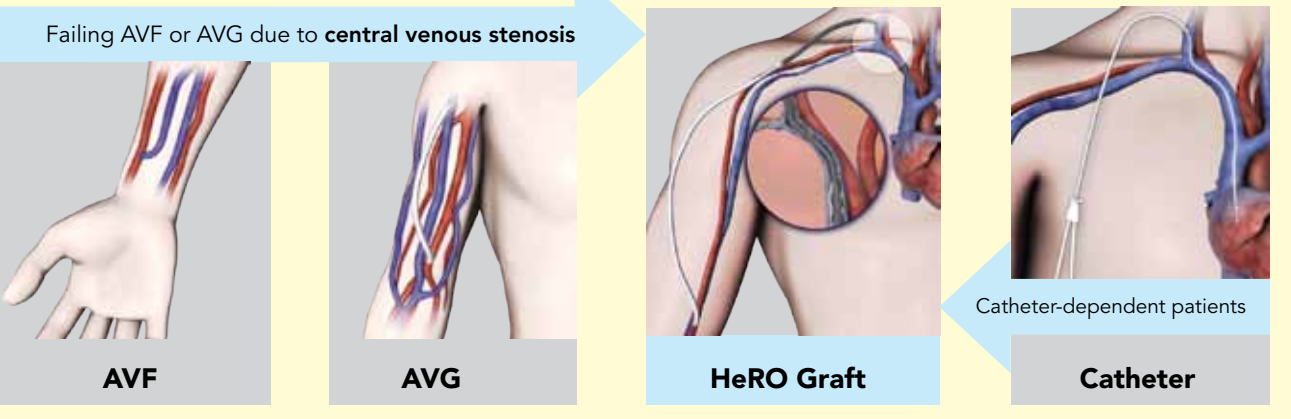

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References:
1) Katzman et al., J Vasc Surg 2009. 2) Gage et al., EJVES 2012. 3) Dageforde et al., JSR 2012.

Indications for Use: The HeRO Graft is indicated for end stage renal disease patients on hemodialysis who have exhausted all other access options. See Instructions for Use for full indication, contraindication and caution statements. Rx only.

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