ASN LEADING THE FIGHT AGAINST KIDNEY DISEASE

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Homeless CKD patients experience increased kidney failure and premature death

By Tracy Hampton

The approximately 3.5 million people who are homeless each year in the United States experience numerous barriers to obtaining appropriate and effective medical care, and they have high rates of physical illness, mental health disorders, and substance abuse.

"Prior studies suggested that risk factors for chronic kidney disease such as diabetes mellitus and hypertension might be elevated among homeless individuals, but the elusive nature of this population has limited our understanding of the long-term outcomes of chronic diseases in this population," said Yoshio Hall, MD, of the University of Washington, Seattle. "Our research attempts to address this knowledge gap and provides a rare glimpse into the characteristics and adverse health outcomes of this marginalized group."

Homelessness and health

To examine the associations between homelessness and the clinical outcomes of chronic kidney disease (CKD) among adults, Hall and his team analyzed the medical records of 15,343 adults with moderate to advanced CKD (stages 3–5) who received outpatient care from 1996 to 2005 from the Community Health Network, which along with a consortium of not-for-profit primary care clinics forms the backbone of San Francisco's healthcare safety net system and offers an array of healthcare services including primary care, specialty care, and acute care. Their results were published recently in the *Clinical Journal of the American Society of Nephrology*.

A total of 858 (6 percent) of the adults in the study were homeless. The main outcome measures of this retrospective cohort study were emergency department visits, hospitalizations, and time to ESRD or death.

"We hypothesized that in this resource-poor setting, homeless adults would experience worse morbidity and mortality, and that they would use healthcare resources far less efficiently than indigent peers with stable housing," said Hall. "We further hypothesized that the worse health outcomes among the homeless would be in part attributable to higher rates of substance use and other risk factors for death and disease progression."

The researchers found that homeless adults were younger, were dispro-

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Inside

Renal Denervation Found Safe and Effective for Chronic Kidney Disease Patients

Benefits Include Increased Hemoglobin

Renal denervation—a technique that uses radiofrequency waves to disrupt the overactive sympathetic nerves running along the arteries in the kidneys—can lower blood pressure in individuals with resistant hypertension and normal kidney function, but clinicians have worried that the procedure might not be safe for patients with compromised kidney function.

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Supreme Court Upholds Individual Mandate, Alters Medicaid Expansion

On June 28, the U.S. Supreme Court in a 5–4 decision ruled key components of the Affordable Care Act (ACA) constitutional, including the controversial individual mandate that would require nearly all Americans to obtain healthcare insurance coverage. The mandate was considered the most crucial question being considered by the court because invalidating it would have complicated other provisions of the law. The ACA is set to fully take effect in 2014.

The Court restricted the provision expanding Medicaid coverage.

ASN President Ronald J. Falk, MD, FASN, said the Court's decision will "allow more patients with kidney disease to obtain or maintain insurance coverage and access to the high-quality care they deserve to treat or slow the progression of kidney disease." Next month's *Kidney News* will feature an in-depth report on what the ruling means for the care and health of kidney disease patients and the nephrology community.

The Effects of Homelessness

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portionately male and uninsured, and had far higher rates of depression and substance abuse than adults with stable housing. Also, the large majority of homeless people in the study were destitute, reporting an annual income of less than $5000, and most were unemployed, disabled, and/or receiving public assistance. Compared with indigent adults living in stable housing, those who were homeless had a higher prevalence of mild or heavy proteinuria, as well as more advanced CKD.

The average follow-up time was 2.6 years among homeless participants and 2.7 years among housed participants. Over 57,698 person-years, 83 (10 percent) homeless adults died and 31 (4 percent) progressed to ESRD compared with 901 (6 percent) and 528 (4 percent) housed counterparts, respectively. The crude rates of ESRD or death were 1.8-fold higher among homeless adults relative to housed adults. After demographic factors, substance abuse, comorbid conditions, and laboratory variables (index kidney function, proteinuria, hemoglobin, and serum albumin concentrations) were taken into account, homeless adults had a 28 percent increased risk for the development of ESRD or death.

The investigators noted that the association of homeless status and the risk of ESRD or death differed according to substance abuse. Specifically, among individuals with a history of substance abuse, there was a trend toward a higher adjusted risk of ESRD or death among the homeless compared with those in stable housing. A link between homeless status and the risk of ESRD or death did not significantly differ by sex, race or ethnicity, the presence or absence of diabetes, or initial kidney function measures.

"This important study sheds new light on a serious problem," said Stephen Hwang, MD, who was not involved with this research. "Clinicians who take care of disadvantaged patients have long suspected that the combination of homelessness and chronic kidney disease is potentially lethal, and this study confirms that impression," he explained. Hwang's work at St. Michael's Hospital in Toronto, Canada, focuses on improving the health of people who are homeless or vulnerably housed and on deepening our understanding of housing as a social determinant of health.

The investigators also found that during follow-up, half of homeless adult patients visited the emergency department more than nine times and experienced more than five hospitalizations. Twenty-five percent made more than 20 visits to the emergency department. Most housed patients experienced one or no emergency department visits or hospitalizations.

Also, homeless adults were significantly less likely than were housed adults to have received any nephrology care, even after differences in sociodemographic factors, comorbid conditions, substance abuse, kidney function, proteinuria, hemoglobin, and serum albumin concentrations were controlled for.

Addressing unmet needs

These findings indicate that homeless adults with CKD have increased morbidity and mortality and use costly emergency care services far more frequently than do their peers who are stably housed. "Sadly, for most homeless persons, securing adequate shelter, food, and clothing often competes with regular healthcare and results in more frequent use of costly acute care services to manage chronic conditions," said Hall.

He noted that the use of these costly services might decline among homeless individuals when services such as transportation, social work, nutrition, and access to healthcare providers become available. "Nationwide concerns about high public costs incurred by homeless people have provoked various housing interventions to eliminate chronic homelessness. We feel that the degree to which interventions aimed at providing permanent, affordable housing, and other supportive services can attenuate these health inequalities warrant additional investigation, as policymakers and researchers debate where and to whom these efforts should be applied," said Hall.

"Hopefully, this study will provide an impetus to develop better strategies to help these patients, through both medical treatment and interventions to address the underlying problem of homelessness," said Hwang.

The article, entitled "Homelessness and Chronic Kidney Disease: A Cohort Study," is available online at http://cjasn.asnjournals.org/.

Renal Denervation

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New research largely puts these concerns to rest. A study recently published in the *Journal of the American Society of Nephrology* found that renal denervation not only can safely and effectively lower blood pressure in patients with chronic kidney disease (CKD) and hypertension but also may provide additional benefits, including a potential increase in hemoglobin concentration and reductions in proteinuria, brain natriuretic peptide levels, and peripheral arterial stiffness index.

Although the study's clinical trial enrolled only a small number of patients, making the results too limited to apply to patients with various forms of chronic renal failure, it provides guidance for further studies and clinical trials to properly assess the short- and long-term safety and efficacy of renal nerve ablation in CKD.

"It also emphasizes the concept that renal denervation may address crucial pathophysiologic mechanisms underlying the high cardiovascular morbidity and mortality rates in patients with chronic kidney disease and may provide a valuable tool in slowing the rate of progression of chronic kidney disease and its complications," the authors wrote.

Targeting the fight-or-flight response

Overactivity of neurons in the sympathetic nervous system, which controls the body's fight-or-flight response, is very common in patients with CKD. In addition to contributing to high blood pressure and heart problems in these patients, it can also worsen their kidney disease. Because targeting this system might provide significant benefits to individuals with kidney dysfunction, principal investigator Markus Schlaich, MD, of the Baker IDI Heart and Diabetes Institute in Melbourne, Australia, and his team designed a catheter-based renal nerve ablation trial in 15 patients with resistant hypertension and stage 3–4 CKD (mean estimated GFR 31 mL/min per 1.73 m^2).

"The main aim of this study was to prove the safety and efficacy of the procedure in the setting of chronic kidney disease, which has not been tested before," said Schlaich. Patients underwent an average of 9.9 ablation treatments, with no periprocedural or postprocedural complications.

The study participants' average blood pressure at the start of the trial was 174/91 mm Hg even though they were taking numerous antihypertensive drugs. Their ambulatory blood pressure readings dropped considerably at 1, 3, 6, and 12 months after bilateral renal denervation (–34/–14, –25/–11, –32/–15, and –33/–19 mm Hg, respectively). Also, significant reductions in rate of blood pressure increase, blood pressure power surge, and night-to-day blood pressure ratios were observed. Moreover, renal denervation diminished mean and maximum nighttime blood pressures and restored a physiologic dipping pattern.

Peripheral arterial stiffness assessed by augmentation index was significantly reduced 3 months after the procedure (51.3 percent at baseline versus 38.7 percent at follow-up). Renal denervation did not worsen patients' kidney function—as assessed by an estimation of GFR according to serum creatinine or cystatin C levels and according to plasma creatinine, cystatin C, or urea levels—indicating that it is safe even when CKD is present.

"So far, renal denervation has only been applied in patients with reasonably well kidney function; the present study provides first results indicating that it can also be performed in patients with more advanced kidney failure," said Peter Blankestijn, MD, PhD, who was not involved with the work and is a nephrologist at the University Medical Center Utrecht in the Netherlands. "This is important new information, because this treatment could be very meaningful in kidney failure patients. More studies are needed," he added. Blankestijn has researched and written about the potential of renal denervation.

Future studies

This first clinical experience with catheter-based renal nerve ablation in high-risk patients with moderate to severe kidney impairment indicates that the procedure may provide beneficial health effects beyond improved blood pressure control in patients with comorbid conditions, including resistant hypertension, diabetes, obesity, and obstructive sleep apnea.

Several interesting observations may deserve further investigation in future clinical trials. For example, the investigators noticed a tendency toward gradually increased serum hemoglobin levels in all treated patients. This could be important

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because the prevalence of anemia increases with deteriorating renal function and is related to heart complications and cerebrovascular events. Interestingly, the results of both experimental and human studies have suggested a role of renal sympathetic nerves in the regulation of erythropoiesis.

The investigators also observed a trend toward reduced urinary albumin excretion after patients underwent renal denervation, as well as a trend toward reduced plasma concentrations of circulating brain natriuretic peptide. Brain natriuretic peptide is considered an independent predictor of cardiovascular death not only in cardiorenal syndrome but also in early-stage kidney disease in the absence of heart failure.

Finally, patients in the study experienced an improvement in augmentation index. Higher augmentation index is associated with target-organ damage in patients receiving hemodialysis and with microalbuminuria in those with essential hypertension. Renal denervation may rapidly affect the peripheral vasculature through a significant reduction in arterial stiffness.

"These initial findings now open up an entirely new approach to better control blood pressure in chronic kidney disease and potentially slow down progression of the disease and reduce cardiovascular risk in these patients," Schlaich said. "Studies are now warranted to look into this in detail."

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The article, entitled "Renal Denervation in Moderate to Severe CKD," is available at http://jasn.asnjournals.org/.

ASN Glomerular Disease Advisory Group Meets with FDA

By Daniel C. Cattran

Dialogue between members of the U.S. Food and Drug Administration and ASN's Glomerular Disease Advisory Group continued at the recent National Institute of Diabetes and Digestive and Kidney Diseases–sponsored symposium *Glomerular Disease: Pathophysiology, Biomarkers, and Registries for Facilitating Translational Research*. The discussion focused on possible end points to support the approval of new treatments for glomerular disease.

Challenges associated with establishing proteinuria as a surrogate end point (a biomarker intended to substitute for a clinical efficacy end point) in drug trials for glomerular diseases were identified. Both groups agreed that future discussions should focus on the data supporting proteinuria as a surrogate within the context of a specific glomerular disease.

Patient-reported outcome measures were recognized as another important approach for establishing a drug's efficacy and an area that required further exploration and discussion. It was also agreed that a number of disease-specific and thematically-focused "white papers" should be published as a joint venture. These papers will address the next steps in defining optimal end points for the approval of drugs to treat glomerular diseases.

Daniel C. Cattran, MD, is senior scientist, division of clinical investigation and human physiology, Toronto General Research Institute, and member of the ASN Glomerular Diseases Advisory Group.

Something to Say?

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

KDIGO to Become an Independent Entity

By Kurtis Pivert

It was announced last month that Kidney Disease: Improving Global Outcomes (KDIGO) will make the transition to complete independence beginning October 1, 2012. The news came in a joint statement from KDIGO and its founding sponsor, the National Kidney Foundation (NKF). KDIGO's co-chair, Bertram Kasiske, MD, said, "the time is right for KDIGO to assume responsibility for its own guideline development processes and management."

Because of the influence of KDIGO's recommendations on nephrology practice, could the transition affect the guideline body's development of future clinical recommendations?

ASN Councilor Sharon Moe, MD, FASN, doesn't think so. "The transition won't affect KDIGO in any way other than its internal structure and personnel. It has always been an independent entity with its own board, and has contracted with NKF for management."

Based in Brussels, Belgium, KDIGO was established in 2003 to improve the care and outcomes of patients with kidney disease by "promoting coordination, collaboration, and integration of initiatives to develop and implement clinical practice guidelines," according to their mission statement. Before the formation of KDIGO, a few regional kidney practice guidelines were in place. However, the KDIGO model of "international guidelines and local implementation allows an international board to develop these guidelines, and then each country can write a commentary to adapt them for use in their regions," said Moe, who co-chaired the development of KDIGO's guideline for chronic kidney disease–mineral and bone disorder (CKD-MBD). "The evidence base from which clinical practice guidelines are generated is international literature," she said, but the "local country commentary allows for differences in practice, patient populations, and reimbursement structures."

The KDIGO approach to guideline development is exhaustive, typically lasting 1 to 2 years and involving a work group of as many as 20 experts in the field. The process begins with controversies conferences, where relevant areas of clinical nephrology with existing evidence gaps are identified. Once a guideline candidate is determined, a work group is formed, and the available literature is gathered and evaluated by an independent evidence review team, which Moe emphasized was important to the process. After the evidence has been weighed, the guidelines are drawn, are evaluated by the KDIGO board, and undergo external review before being published and disseminated. Depending on the strength of the evidence available, each practice recommendation is stratified as either level 1 ("patients should receive the recommended course of action") or level 2 (suggestions for practice, indicating that "different choices will be appropriate for different patients").

So far KDIGO has published five guidelines for patient care in transplantation, mineral and bone disorders, hepatitis C and CKD, acute kidney injury, and glomerulonephritis. Three additional guidelines—on blood pressure, anemia, and classification of CKD—await publication. In its announcement KDIGO indicated that it would start a new period of guideline development once it becomes a separate entity.

Although focused on clinical care, practice guidelines are also important for clinical research. "One of the goals of guideline development is to identify gaps in knowledge to ensure that future research focuses on these areas," Moe noted. "It is an interim process: you review the current literature, identify gaps, ensure future research examines those gaps, and then update the guidelines according to the new research—it's the life cycle of a clinical guideline."

The KDIGO recommendations have been well respected and implemented throughout the nephrology community. Because of KDIGO's focus on local implementation, it will continue to partner with NKF to help adapt KDIGO recommendations, through commentaries on regional applicability, to the practice environment in the United States. The NKF will also continue as KDIGO's educational partner, developing tools and programs to help the dissemination and adoption of KDIGO's practice recommendations.

Eculizumab Offers No Benefit in the Treatment of Hemolytic Uremic Syndrome Caused by *E. coli*, Preliminary Report Finds

When an outbreak of foodborne Shiga-toxin producing *Escherichia coli* O104:H4 (STEC) hit northern Germany beginning in May 2011, physicians had no established treatment regimen and therefore tried various therapies. By the time the outbreak ended in late July 2011, there were 52 deaths among the 3052 incidences of STEC and 733 confirmed cases of hemolytic uremic syndrome (HUS).

Within a week of the outbreak the German Society of Nephrology developed an online data collection form and registry to track cases of HUS and document the short-term effectiveness of best supportive care, therapeutic plasma exchange (TPE), and, for patients with HUS, TPE with eculizumab (TPE-Ecu). Best supportive care consisted of dialysis, mechanical ventilation, and active fluid management. Eculizumab is a monoclonal antibody that interferes with the terminal components in the activation of the complement cascade.

Jan Kielstein, MD, PhD, associate professor of medicine at the Medical School of Hannover in Germany, presented an analysis of the registry data at the 49th European Renal Association–European Dialysis and Transplant Association Congress in Paris in May. He told *Kidney News* that the data suggest that the TPE-Ecu combination does not provide any further benefit in the treatment of HUS compared to TPE alone.

Of the 631 entries from 84 centers in the STEC-HUS registry, the investigators confirmed 491 STEC-HUS cases, of which 241 underwent TPE, 193 TPE-Ecu, and 57 best supportive care.

The patients who received best supportive care alone were almost 10 years older on average (55 years) than the TPE and TPE-Ecu groups combined (45 years). Yet patients in the best supportive care group had less severe disease (including hemolysis), less need for dialysis, and a lower frequency of seizures. These patients also had lower serum creatinine at hospital discharge (1.1 mg/dL compared with 1.2 mg/dL and 1.4 mg/dL for the TPE and TPE-Ecu groups, respectively). Very few patients required dialysis at discharge, and there was no significant difference between groups.

However, mortality was significantly higher in the best supportive care group compared to the others: 10.5 percent compared with 3.7 percent and 2.6 percent in the TPE and TPE-Ecu groups, respectively.

Kielstein cautioned that one must examine the raw data from the best supportive care group, especially the mortality data, because the best supportive care group was older than the other groups "and age is an overriding risk factor for death in this patient population."

Also, of the six patients who died in the best supportive care group, two opted out of further treatment because they had advance directives, and one additional patient died from complications of insertion of the central venous catheter intended for TPE. "This very much illustrates the difficulty looking at those registry online data, and this I think is the main disadvantage from the crisis, that we don't have prospective controlled data," Kielstein said.

Further complicating interpretation of the results, disease severity triggered different intensities in treatment, so the less severely ill patients received best supportive care. The most ill patients, especially those with neurological complications, received TPE-Ecu.

While acknowledging the "scarce evidence at best" to support the use of eculizumab, Kielstein explained the rationale for its use in patients with HUS. A few preliminary studies have shown upregulation of the complement system in the active phase of HUS. "But the main triggering event to use eculizumab in these patients was, number one, the safety profile of eculizumab," he said, "number two, the fact that it was available on compassionate use [so] nobody had to pay for it, and number three, the fact that in the middle of the crisis there was a report in the *New England Journal of Medicine* (1) showing remarkable recovery of three pediatric patients that were suffering from severe neurological symptoms in the context of STEC-HUS."

From the registry data, it can't be determined if antibiotics were useful because data were lacking on the antibiotics used, their time course, and their dosages. Kielstein noted that a recent article in the *Journal of the American Medical Association* (2) showed that azithromycin can significantly decrease the shedding time of STEC from the gut, possibly prompting a rethinking of a previous recommendation not to use antibiotics in STEC-HUS lest the bacteria release more Shiga toxin as they are destroyed.

As with antibiotics, some hospitals used steroids with TPE and others did not, further complicating the retrospective analysis.

Kielstein suggested that the medical community establish systems now to collect data in a crisis situation and design a fast-track process to approve clinical trial protocols at the start of future crises since the present approval process is unable to react quickly enough.

The study had no commercial funding. Dr. Kielstein had no disclosures.

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Blood Pressure Lowering With Olmesartan No Better at Preventing Negative Outcomes in Patients on Hemodialysis

Patients receiving olmesartan fared no better in terms of outcomes or blood pressure lowering than those receiving conventional antihypertensive therapy other than angiotensin receptor blockers (ARBs) or angiotensin-converting enzyme (ACE) inhibitors in a recent study. The study looked at the effect of olmesartan in lowering blood pressure to decrease the risk of death and nonfatal cardiovascular (CV) outcomes in hypertensive hemodialysis patients.

Data indicate that hypertensive hemodialysis patients have a better prognosis compared to hemodialysis patients with normal or low blood pressure, but guidelines for treating hypertension in hemodialysis patients do not exist, said lead author Kunitoshi Iseki, MD, of the University Hospital of the Ryukyus in Nishihara, Okinawa, Japan. On the other hand, a meta-analysis showed that survival in hemodialysis patients was better if they received antihypertensive drugs, regardless of their blood pressure, suggesting possible other effects of the drugs.

The Olmesartan Clinical Trial in Okinawa Patients Under Okinawa Dialysis Study (OCTOPUS) was an open-label, prospective, randomized, controlled trial with blinded outcome assessment to determine if an ARB would lower the risk of CV disease and death among hypertensive hemodialysis patients. In an interview with *Kidney News* at the 49th European Renal Association–European Dialysis and Transplant Association Congress in Paris, Iseki described OCTOPUS and its findings.

Eligible patients had a predialysis blood pressure of 140/90 mm Hg to 200/100 mm Hg and could not have used ACE inhibitors or ARBs in the previous month. The trial's target was a predialysis blood pressure below 140/90 mm Hg.

The mean age of the patients included in the study was 60 years (range 20–79 years), and they received hemodialysis three times a week. After a 1-month period using other conventional blood pressure medications, during which resistant hypertension was confirmed, patients were randomized to conventional therapy not directed at the renin-angiotensin system (234 patients) or to olmesartan 10 mg/day (235 patients). Doses could be escalated in either group to achieve the target blood pressure.

The groups were well matched at baseline for pre-hemodialysis blood pressure, hemodialysis duration (88 months), and hemodialysis dose (Kt/V, 1.15–1.16), as well as other characteristics. The primary end points were 1) all-cause mortality; and 2) the composite of death or nonfatal CV disease, including stroke, myo-

cardial infarction, unstable angina, and heart failure requiring hospitalization.

After a median follow-up of 3.6 years, "there were no blood pressure differences between the groups," Iseki said. The blood pressure in both groups had dropped by approximately 7/2 mm Hg compared with baseline.

The olmesartan group had a nonsignificant reduction in systolic blood pressure versus the conventional therapy control group (0.9 mm Hg, p = 0.45). There was no difference in the degree of diastolic blood pressure reduction.

Among the olmesartan patients, 28.9 percent reached the primary composite end point versus 28.6 percent of patients in the control arm (hazard ratio [HR], 1.00, p = 0.99). Similarly, 16.2 percent of patients in the olmesartan group died from any cause versus 16.7 percent in the control group (HR, 0.97, p = 0.91).

Iseki concluded that blood pressure reduction with olmesartan did not alter the risk for major CV events or death among chronic hemodialysis patients with hypertension compared with other drugs to lower blood pressure. Fewer than 20 percent of patients in either treatment group reached the target blood pressure of less than 140/90 mm Hg.

He said the annual incidence of the primary composite end point (9.1 percent) and overall mortality (4.7 percent) were lower than expected. Japanese hemodialysis patients typically experience annual mortality of about 6.5 percent, Iseki noted.

A limitation of the study was that olmesartan was compared with active blood pressure-lowering therapies and not with placebo, so the absolute effect of blood pressure reduction with olmesartan could not be determined. A second and important limitation was that adherence to olmesartan and to the other antihypertensive drugs was marginal.

Phosphate-Binding Agents Regulate Serum Phosphate and Lower Mortality Risk

The use of phosphate-binding agents (PBAs) in patients on hemodialysis is associated with reduced mortality risk regardless of other factors, according to results from the large European Current Management of Secondary Hyperparathyroidism—a Multicenter Observational Study (COSMOS). The association applied to all types of PBAs except those containing aluminum, said trial chairman Jorge Cannata-Andia, MD, of the Hospital Universitario Central de Asturias in Oviedo, Spain.

The study, conducted at 220 centers across the European Union, investigated the association between treatments affecting bone metabolic parameters and clinical outcomes among patients on hemodialysis. Specifically, the researchers looked at the association between the use of a single PBA or a combination of PBAs and mortality.

COSMOS was an observational study with 3 years of follow-up that enrolled patients from a wide geographic area in Europe in numbers approximately proportional to the number of patients on hemodialysis in each country.

COSMOS essentially confirmed the relationship of phosphorus levels and mortality risk seen in previous studies, with the lowest risk of all-cause mortality occurring at a serum phosphorus level near 4.0 mg/dL. Below 3.0 mg/dL, the mortality risk doubled (hazard ratio [HR], 2.0). An elevated serum phosphorus level also conferred a higher mortality risk, increasing at a phosphorus level greater than 5.5 mg/dL. The mortality risk was about 50 percent higher (HR of about 1.5) when the serum phosphorus exceeded 6.5 mg/dL.

Similarly, for cardiovascular mortality the lowest risk was at about 4.0 mg/dL, with higher risks observed at both low and high serum phosphorus levels.

The use of PBAs reduced the risk of all-cause and cardiovascular mortality, in many cases by as much as 50 percent.

The findings held regardless of age, sex, history of diabetes or cardiovascular disease, time on hemodialysis, or baseline serum parathyroid hormone, calcium, or phosphorus levels.

The investigators developed three statistical models to study the association between mortality rates and the use of phosphate binders. The models took into account and adjusted for differences in the case mix, case mix plus therapies other than PBAs, and case mix plus other therapies plus blood chemistries.

For each model, all PBAs (except those containing aluminum) were associated with significantly lower risks of all-cause and cardiovascular mortality. A wide range of PBAs were included, encompassing those containing calcium or lanthanum, calcium and lanthanum, polyanionic gels, calcium or lanthanum plus polyanionic gels, polyanionic gels plus a lanthanum-containing PBA, a calcium plus aluminum-containing PBA, and polyanionic gels plus an aluminum-containing PBA. The greatest risk reduction (73 percent) occurred with the use of a polyanionic gel plus a lanthanum-containing PBA.

"The main message is that PBAs are ... related with a lower mortality," Cannata-Andia concluded. "We can say that this effect is from the phosphate binder and is not the effect of vitamin D or a calcium mimetic."

He emphasized that the combination of PBAs, which is a common practice, did better than agents used singly.

Cannata-Andia noted "huge differences in price" for PBAs, with the oldest and least expensive PBAs (those containing aluminum) having lesser efficacy in terms of mortality risk, and the newer and more expensive PBAs having more efficacy but also a higher cost. Still, he said it is "very reassuring" that combinations of calcium-containing and non–calcium containing PBAs "did very well."

The study was supported by Fundación Renal Iñigo Alvarez de Toledon and by Amgen. Dr. Cannata-Andia had no other disclosures.

Sevelamer Linked to Lower Cardiovascular Death Risk in Patients on Hemodialysis

In a trial comparing the phosphorus binder sevelamer with calcium-containing phosphorus binding agents (PBAs), patients starting hemodialysis who used sevelamer had a much lower risk of cardiovascular (CV) events and all-cause death over the course of the study. Antonio Bellasi, MD, of the Ospedale Sant'anna in Como, Italy, presented the results of the open-label, randomized, controlled trial in May at the 49th European Renal Association–European Dialysis and Transplant Association Congress in Paris.

The study randomly assigned incident hemodialysis patients to sevelamer (232 patients) or to calcium-containing PBAs (234 patients). The researchers followed them until study completion or until death occurred.

The study population was about half men and had a mean age of 65 years. Hypertension was present in 79 percent, CV disease in 36 percent, and diabetes in 29 percent of patients at baseline.

Bellasi explained that the trial had to be open label because the physicians would know which patients were on sevelamer "because of the impact of sevelamer on lipids." However, the investigators who analyzed the outcomes were blinded to which groups the patients were in.

Sevelamer linked to benefits on many outcome measures

After 36 months of follow-up, the patients using sevelamer had an 89 percent lower risk of CV-related mortality than the patients taking the calcium-containing PBA (relative risk [RR], 0.11, p < 0.001). There were nine CV-related deaths in the sevelamer group versus 79 in the calcium PBA group. When adjusted in a multivariate analysis for possible contributing factors, the RR remained 0.11, indicating that sevelamer use was an independent predictor of the much lowered risk.

Similarly, the sevelamer group did much better in terms of all-cause survival, with a greater than 70 percent reduction in the risk of all-cause death regardless of whether the RR was unadjusted or adjusted for various possible confounding factors. There were 28 deaths from any cause in the sevelamer group at 36 months compared with 100 deaths in the calcium-containing PBA group.

Sevelamer use was also linked to less progression of coronary artery calcification (CAC) when examined after 24 months of the study. At 12 months, half of the calcium PBA group had CAC progression whereas only one-fifth had progression in the sevelamer group (p < 0.001). At 24 months, CAC progression

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Sevelamer

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affected two-thirds of the patients on calcium-containing PBAs but slightly less than 40 percent of those taking sevelamer ($p < 0.001$).

It appeared that cardiac arrhythmias were a significant contributor to the CV deaths because sevelamer was associated with a 93 percent reduction in the risk of arrhythmias. Adjusting for other parameters yielded essentially the same result. The corrected QT interval remained fairly constant in the sevelamer group but somewhat prolonged over time for the patients assigned to a calcium-containing PBA ($p < 0.001$). Prolongation of the corrected QT interval can lead to arrhythmia.

Sevelamer did not appear to reduce the risk of death from non-CV causes, and its beneficial effect on all-cause mortality risk was most likely a result of its lowering the risk of CV mortality, which contributed to the all-cause mortality. Non-CV deaths—a secondary end point of the trial—were essentially no different at 36 months between the two groups. There were 19 deaths in the sevelamer group and 21 in the calcium-containing PBA group.

Bellasi concluded that the study lends support to the view that incident hemodialysis patients "may benefit greatly from treatment of hyperphosphatemia with use of the non–calcium containing phosphate binder sevelamer when compared to treatment with calcium-based binders." The study was fairly large and was conducted long enough to see the effects of the treatments on CV events and mortality.

However, before the results can be accepted as conclusive and applied generally, some points need to be clarified. The chairman of the session in which the results were presented, David Goldsmith, MB, BChir, consultant nephrologist at Guy's and St. Thomas' Hospital in London, told *Kidney News* that he has questions about the level of compliance with therapy in the two treatment groups, and he would like to see data on hypercalcemic episodes as well as on mortality according to the levels of serum calcium and phosphate that were actually achieved.

Dr. Bellasi has received honoraria from Genzyme, Amgen, and Sanofi, now the parent company of Genzyme. There was no commercial funding for the study. Dr. Goldsmith was not involved in the study. He has received research support from Genzyme, the maker of sevelamer, and is a consultant to Sanofi.

Dual RAS Blockade No Better Than Monotherapy to Prevent Renal Disease Progression

For type 2 diabetes patients with established nephropathy, blocking the renin-angiotensin system (RAS) with two blood pressure drugs does not add any benefit over using just one of the drugs. A combination of the ACE inhibitor lisinopril with the angiotensin receptor blocker irbesartan had similar effects to monotherapy with either drug at doses that achieved the same level of blood pressure reduction.

José Luño, MD, head of the department of nephrology at the Hospital General Universitario Gregoria Marañón, presented results of this late breaking trial at the 49th European Renal Association–European Dialysis and Transplant Association Congress in Paris in May. He said that more severe proteinuria and lower estimated glomerular filtration rate (eGFR) at baseline, as well as vitamin D deficiency, were independent predictors of progression of type 2 diabetic nephropathy.

This multicenter, open-label, four-year follow-up clinical trial ran from 2005 to 2011. After a four-week drug wash out period, 133 participants were randomly assigned in a 1:1:2 fashion to lisinopril titrated from 10 to 40 mg/day (n = 35), to irbesartan titrated from 150 to 600 mg/day (n = 28), or to lisinopril 20 mg plus irbesartan 300 mg (n = 70) to achieve equivalent blood pressure lowering in each group. Medication doses were titrated up at the first and second monthly visits. Median follow-up was 32 months, over which time blood pressure, renal function, and proteinuria were measured.

Participants were at least 35 years old, had type 2 diabetes, hypertension, and clinical proteinuria with a urinary protein-to-creatinine ratio (UPCR) of at least 300 mg/g.

Luño Luño reported that blood pressure control was similar among the three arms of the study. Although eGFR declined in each group, there were no differences in the amount of decline among the lisinopril, irbesartan, and combination therapy groups at 6, 12, or 24 months, or at the end of the study. For each group the annual rate of decline in eGFR was about 3.4 mL/min/1.73 m^2.

The composite primary endpoint of an increase of more than 50 percent in serum creatinine, progression to end stage renal disease (ESRD), or death was the same among the groups, with 29–30 in each group reaching it (hazard ratio 0.95). There was also no statistical difference among the groups in the proportion who achieved the individual components of the primary endpoint — 21–23 percent with a creatinine increase of at least 50 percent, 14–18 percent developing ESRD, and 4–7 percent dying.

"Those patients that achieved the renal endpoint — that progressed to renal disease —had at baseline higher proteinuria and lower renal function, [and] lower glomerular filtration rate," Luño said. They also had lower blood hemoglobin values at baseline ($p < .05$ for all values, comparing patients who had progression of renal disease to those who did not).

Also, vitamin D levels were lower at baseline in the patients whose renal disease progressed (12.6 ng/mL) than in the ones who did not progress (16.9 ng/mL, $p < 0.01$).

In a multivariate regression analysis adjusting for age, sex, body mass index, treatment group, and vitamin D levels, the only significant independent predictors of the primary composite outcome were the baseline proteinuria (UPCR, hazard ratio = 1.32, $p < 0.001$) and the baseline eGFR (hazard ratio = 0.96, $p = 0.03$).

Only four patients dropped out of the study because of hyperpotassemia, an important adverse effect when the RAS is blocked. Nine patients died in the study.

Luño noted that the study was limited by the relatively small sample size, and the study was not done in a double-blind fashion. There may also have been confounding effects by the use of other drugs to control blood pressure and diabetes, which was permitted according to good clinical practice, and the investigators could not evaluate these possible effects.

The trial was funded in part by Bristol-Myers Squibb of Spain.

49th European Renal Association - European Dialysis and Transplant Association Congress: No abstract (Late Breaker). Presented May 25, 2012.

Glucose-sparing Peritoneal Dialysis Regimen Shows Positive HbA1c and Lipids Results

In a study of patients with diabetes and end stage renal disease (ESRD) on peritoneal dialysis (PD), use of a low-glucose PD fluid showed beneficial effects on metabolic measures such as blood glucose control, serum cholesterol, and triglycerides compared with conventional PD solutions with higher glucose content. Joanne Bargman, MD, professor of medicine at the University of Toronto and a staff nephrologist at the Toronto General Hospital in Toronto, Ontario, Canada, presented the combined results of the IMPENDIA (Improved Metabolic Control of Physioneal, Extraneal, Nutrineal versus Dialneal only in Diabetic CAPD and APD Patients) and EDEN (Evaluation of Dianeal, Extraneal, and Nutrineal versus Dianeal Only in Diabetic CAPD Patients) trials at the 49th European Renal Association–European Dialysis and Transplant Association Congress in Paris in May.

Diabetic nephropathy accounts for 25 percent to 50 percent of new cases of ESRD in developed countries. Patients on PD or hemodialysis have similar survival rates, but overall, survival is poor. Each form of dialysis has certain adverse effects associated with it. In the case of PD, continuous glucose loading from the conventional dialysis solution may contribute to the increased cardiovascular risk that is a major cause of death in ESRD patients.

Glucose absorption makes it difficult for patients with diabetes to achieve

Continued on page 10

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WARNING: ESAs INCREASE THE RISK OF DEATH, MYOCARDIAL INFARCTION, STROKE, VENOUS THROMBOEMBOLISM, THROMBOSIS OF VASCULAR ACCESS AND TUMOR PROGRESSION OR RECURRENCE.

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- In controlled clinical trials of ESAs in patients with cancer, increased risk for death and serious adverse cardiovascular reactions was observed. These adverse reactions included myocardial infarction and stroke
- In controlled clinical trials of ESAs, ESAs increased the risk of death in patients undergoing coronary artery bypass graft surgery (CABG) and deep venous thrombosis (DVT) in patients undergoing orthopedic procedures
- In 2 trials of OMONTYS, patients with CKD not on dialysis experienced increased specific cardiovascular events

Increased mortality and/or increased risk of tumor progression or recurrence in patients with cancer: The safety and efficacy of OMONTYS have not been established for use in patients with anemia due to cancer chemotherapy. OMONTYS is not indicated in patients with cancer receiving chemotherapy.

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Glucose-sparing

Continued from page 10

their target blood glucose levels. "The sugar that's absorbed from the PD fluid is going to make their blood sugar go even higher," Bargman explained, "and that's going to affect their sugar control, how much insulin they have to use, and more downstream, will raise some types of cholesterol and fats in the blood. So every study that has looked at it has shown that patients on PD have worse levels of blood cholesterol and fats compared to hemodialysis," she said.

Patients on PD typically use four fluid bag exchanges a day containing glucose. In the IMPENDIA and EDEN trials, two of the bags were substituted with osmotic solutions not containing glucose.

These international, open-label, prospective trials randomly assigned 251 diabetic patients on PD to a glucose-sparing (GS) regimen using a combination of Physioneal (glucose), Extraneal (icodextrin), and Nutrineal (amino acids) solutions or DIANEAL (glucose), Extraneal, and Nutrineal solutions (124 patients) versus a non–glucose sparing regimen control group (NGS; 127 patients) using DIANEAL only.

At baseline, study participants incluede men or women 18 years or older with ESRD and a diagnosis of type 1 or type 2 diabetes using glycemic control medication and who were using at least one exchange of 2.5 percent or 4.25 percent dextrose per day by continuous ambulatory PD or automated PD. They had hemoglobin A1c (HbA1c) measures greater than 6.0 percent and no higher than 12.0 percent, with blood hemoglobin between 8.0 mg/dL and 13.0 mg/dL.

At 3 and 6 months, the GS group showed a significant HbA1c drop from 7.7 percent to 7.2 percent, whereas the HbA1c of the NGS control group did not change (p = 0.006). Compared to the NGS group, the patients on the GS regimen had a significant drop in their fasting triglyceride (p = 0.002), very low-density lipoprotein cholesterol (p = 0.003), and apolipoprotein B levels (p = 0.03). Apolipoprotein is a component of low-density lipoprotein cholesterol. There was also a nonsignificant trend toward lower total cholesterol levels in the GS group.

Bargman concluded that the results of these randomized, controlled trials are strong evidence that the composition of the PD fluid influences metabolic end points. She said the modest changes in HbA1c, very low-density lipoprotein cholesterol, triglycerides, and apolipoprotein B were statistically significant and were probably clinically significant as well. However, she noted the study ran for only 6 months.

She suggested that further research explore ways to perform PD with regimens containing low or no glucose. The glucose is in the PD solutions as an osmotic agent, meaning that it helps to draw water and toxins out of the body into the fluid.

Important to note, there were 10 deaths and three withdrawals for adverse effects in the GS group compared to three deaths and three withdrawals for adverse effects in the NGS group. The GS group experienced more occurrences of volume overload and hypertensive encephalopathy.

Bargman said that all the deaths and serious adverse events happened at two participating clinical sites in Chile, and the investigators are trying to determine the reasons. Nonetheless, even if the reasons can be discerned, the results from these sites must be included in the overall analysis and cannot be ignored.

GS regimens will be more expensive than NGS ones, but Bargman noted that in either case, PD is less expensive than in-center hemodialysis.

IMPENDIA: Improved Metabolic Control of Physioneal, Extraneal, Nutrineal versus Dialneal only in Diabetic CAPD and APD Patients

EDEN: Evaluation of Dianeal, Extraneal, and Nutrineal versus Dianeal Only in Diabetic CAPD Patients

Dr. Bargman is a consultant for Baxter, Amgen, and Otsuka. She is on the speakers' bureau of DaVita, Amgen, Baxter, and Otsuka. The trial was sponsored by Baxter Healthcare Corporation.

49th European Renal Association - European Dialysis and Transplant Association Congress: No abstract (Late Breaker). Presented May 25, 2012.

Overweight and Obesity Strong Risks for Renal Disease

Obesity, a major pubic health problem worldwide, is a risk factor for renal disease, operating through several mechanisms, most notably inflammatory cytokines. Speaking on the topic of obesity and chronic kidney disease, Francesca Mallamaci, MD, of the Institute of Biomedicine, Division of Nephrology in Reggio Calabria, Italy, presented evidence that inflammatory mechanisms and alterations in renal hemodynamics largely overlap.

ACE inhibition may be a good way to preserve kidney function as overweight and obese individuals have been found to be particularly sensitive to the renoprotective effects of ramipril.

In her review of the subject, Mallamaci showed that as body mass index (BMI) increases, so does the risk of chronic kidney disease (CKD). The largest study on the topic was a survey of a multiracial general population in the United States, where the prevalence of overweight and obesity is near 40 percent.

Compared with a non-overweight BMI of up to 24.9 kg/m2, CKD risk increases steadily with weight, tripling for a BMI in the range of 25.0–29.9 kg/m^2, and reaching a sevenfold higher risk once the BMI is at or above 40.0 kg/m^2.

Inflammatory cytokines, especially interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-alpha), likely

contribute to vascular dysfunction at the level of the glomerulus and cause renal damage. Procalcitonin is a relatively newly described inflammatory marker, and its concentration increases with each increasing quartile of waist circumference, "a phenomenon implicating inflammation in obesity-related CKD," Mallamaci said.

Mallamaci noted that renal plasma flow declines with increasing body weight before reaching outright obesity. Glomerular filtration rate (GFR) does not decrease concomitantly at this point, and glomerular hyperfiltration occurs in the early stages of overweight. This hyperfiltration contributes to the eventual loss of renal function.

From a post hoc analysis of results of the Ramipril Efficacy in Nephropathy (REIN) study, obesity was a strong predictor of renal events.

The more that weight increased, the more effective ramipril was in reducing proteinuria compared to placebo. It also reduced the incidence rate of ESRD more at higher BMIs.

Mallamaci proposed that ramipril exerts its renoprotective effect in the overweight/obese population by reducing glomerular efferent vasoconstriction, thereby transiently reducing the GFR, thus reducing the deleterious hyperfiltration.

She said no controlled trial testing the effect of weight loss on renal disease progression has ever been done, and she doubts one ever will be. For the future, she advocated performing randomized clinical trials specifically designed to look at possible protective effects of ACE inhibitors in preventing renal events in this patient population, but these, too, are doubtful. So she suggested further *post hoc* analysis of existing trials, as was done with REIN.

Journal View

Orders for CrCl Testing Decreased after eGFR Reporting

The introduction of estimated glomerular filtration rate (eGFR) reporting with prompts by outpatient laboratories has led to decreased physician requests for creatinine clearance (CrCl) testing in Ontario, reports *Kidney International*.

The study was designed to evaluate the 2006 introduction of eGFR reporting with prompts at outpatient laboratories in Ontario whenever a serum creatinine test was ordered. The change was implemented to improve recognition of chronic kidney disease. It also supported the 2002 Kidney Disease Outcomes/Quality Initiative (KDOQI) clinical practice guideline recommending the use of eGFR and discouraging timed urine collection for CrCl, except in specific situations. The effects of these interventions were analyzed using data on adult patients in Ontario from 1999 to 2009.

The KDOQI guideline had little or no effect on the monthly rate of CrCl collection: 42.3 versus 46.2 per 100,000 adult population. In contrast, after introduction of eGFR reporting with prompts, the rate of CrCl testing decreased from 44.6 to 34.1 per 100,000 adult population. This represented a "sudden and significant" 23.5 percent decrease over the 43-month period analyzed.

The study shows a significant reduction in the sex- and age-adjusted rate of CrCl testing after the introduction of routine eGFR reporting, whereas a clinical practice guideline alone had no significant effect. Laboratory reporting and other educational and structural changes may be more likely to achieve compliance with evidence-based guidelines [Kagoma YK, et al: Reporting of the estimated glomerular filtration rate decreased creatinine clearance testing. *Kidney Int* 2012; 81: 1245–1247].

Mixed Results on Functional Impact of Frequent Hemodialysis

Increasing hemodialysis frequency from three times to six times weekly improves subjective but not objective measures of physical functioning, reports a trial in the *Clinical Journal of the American Society of Nephrology*.

The researchers analyzed data on physical performance, health, and functioning in patients enrolled in two Frequent Hemodialysis Network (FHN) trials: 245 in the daily FHN trial and 87 in the nocturnal FHN trial. In both studies, patients were randomly assigned to frequent or conventional hemodialysis: six versus three times per week.

Consistent with other studies of hemodialysis patients, 12-month scores on the short physical performance battery (SPPB), the RAND 36-item health survey physical health composite (PHC), and the physical functioning subscale were below population norms. Patients assigned to frequent hemodialysis in the daily trial had a significant 3.4-point improvement in the PHC score, as well as a relatively large (but nonsignificant) improvement in the physical functioning subscale.

In contrast, there was no significant change in the SPPB score. None of the three measures showed a significant difference between frequent and conventional hemodialysis in the nocturnal trial.

Previous FHN trial reports have suggested beneficial effects of frequent hemodialysis, including a reduced risk of death or change in left ventricular mass. The new analysis evaluated the effects of hemodialysis frequency on important disability outcomes.

The results show significant improvement in patient-reported measures of physical health and functioning with in-center hemodialysis performed six versus three times per week. However, objective assessments of physical performance are not significantly improved. Neither type of outcome is altered for patients assigned to more frequent nocturnal hemodialysis [Hall YN, et al: Effects of six versus three times per week hemodialysis on physical performance, health, and functioning: Frequent Hemodialysis Network (FHN) randomized trials. *Clin J Am Soc Nephrol* 2012; 7: 782–794].

Pioglitazone May Increase Bladder Cancer Risk

Patients taking pioglitazone for type 2 diabetes may be at increased risk of bladder cancer, according to a study in the *British Medical Journal*.

The analysis included data on nearly 116,000 British primary care patients who started oral hypoglycemic drug treatment for type 2 diabetes from 1988 through 2009. During mean follow-up of 4.6 years, there were 470 diagnosed cases of bladder cancer: incidence rate 89.4 per 100,000 person-years. In a case-control study, 376 patients with bladder cancer diagnosed more than one year after starting treatment were matched to up to 20 controls.

Any pioglitazone exposure was associated with an increased risk of bladder cancer: rate ratio 1.83. Risk increased with both duration of treatment and total exposure to pioglitazone: rate ratio 1.99 for more than 24 months of treatment and 2.54 for a cumulative dosage greater than 28,000 mg. Patients taking rosiglitazone showed no increase in bladder cancer risk.

The study supports previous, limited data suggesting an increased incidence of bladder cancer among patients taking pioglitazone. The association appears specific to pioglitazone and appears to increase along with treatment duration and total drug exposure over time. The researchers emphasize that, although the relative risk of bladder cancer is about twice as high in patients taking pioglitazone, the absolute excess risk is low: adjusted rate difference 74 per 100,000 person years [Azoulay L, et al. The use of pioglitazone and the risk of bladder cancer in people with type 2 diabetes: nested case-control study. *BMJ* 2012; 344: e3645].

All U.S. Centers Show Racial Disparities in Living Donor Kidney Transplantation

African American patients have reduced access to living donor kidney transplantation (LDKT) at every transplant center in the United States, reports a study in *American Journal of Kidney Diseases*.

The analysis included 247,707 adults waitlisted for kidney-only transplantation from 1995 to 2007, as reported by the Scientific Registry of Transplant Recipients. Center-specific rates of LDKT attainment were estimated for African American versus non-African American patients, in models including data on a wide range of patient- and center-level characteristics.

All 275 U.S. transplant centers showed evidence of racial disparities. Center-specific adjusted odds ratios for LDKT attainment in African American patients ranged from 0.24 to 0.65. Center-level factors associated with greater disparity included higher percentages of African American and prelisted patients. Centers with higher overall rates of LDKT had lower levels of disparity.

Previous studies have reported lower rates of LDKT attainment among African American patients, but most have focused on patient-level factors. The new study, looking at center-level variations, finds that no U.S. transplant center has achieved racial parity in LDKT. The authors call for changes in transplant center policies and procedures to help narrow the racial gap in access to LDKT [Hall EC, et al: Center-level factors and racial disparities in liver donor kidney transplantation. *Am J Kidney Dis* 2012; 59: 849–857].

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Policy Update

ASN Research Advocacy Committee Chair John Sedor, MD, discusses the positive connection between research and the US economy.

Griffin P. Rodgers, MD, MACP, director, National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) said that more than 80 percent of NIH funding supports research around the country and described past NIDDK research that has led to improvements in patient care.

ASN to Congress: NIH-supported Kidney Research Drives Discovery, Best Practice, and the Economy

By Grant Olan

On Tuesday, June 19, ASN co-sponsored a congressional briefing on the importance of kidney disease research with the American Society of Pediatric Nephrology (ASPN), the American Kidney Fund (AKF), and honorary co-sponsor, the Congressional Kidney Caucus.

Congressional Kidney Caucus co-chair Rep. Tom Marino (R-PA) joined congressional staff to hear how federally funded research has transformed the lives of millions of Americans affected by kidney disease. Speakers included National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) Director Griffin P. Rodgers, MD, MACP; National Heart Lung and Blood Institute (NHLBI) Director Susan B. Shurin, MD; AKF President and CEO LaVarne Burton; and ASPN Immediate Past President H. William Schnaper, MD.

ASN Research Advocacy Committee Chair John R. Sedor, MD, moderated the panel, which attracted a standing room only crowd on Capitol Hill. Noting that costs associated with the spectrum of care provided for patients with kidney disease make up 1 percent of the entire federal budget, Dr. Sedor said there will be no cures without research.

Beyond serving as a powerful force in the war on disease, research drives U.S. economic growth. Dr. Rodgers added that more than 80 percent of NIH funding supports research around the country and described past NIDDK research that has led to improvements in patient care. Today kidney disease can be detected earlier, and NIDDK-supported research facilitated the development of new drugs to better control blood pressure, among other advances.

Dr. Shurin discussed the kidney-heart connection, pointing out that kidney and cardiovascular diseases are interrelated. She described more than 10 NHLBI-supported epidemiological studies and clinical trials related to both kidney and heart disease that are yielding promising research, including the Systolic Blood Pressure Intervention Trial (SPRINT), Chronic Kidney Disease in Children Prospective Cohort Study (CKiD), and Multi-Ethnic Study of Atherosclerosis (MESA).

Discussing the importance of research from the perspective of kidney disease patients, AKF's LaVarne Burton said investigators need NIH support that can lead to innovations and discoveries to improve patient outcomes. Ms. Burton also remarked that kidney disease can be prevented. AKF's Pair Up campaign empowers women to partner with a friend or loved one to attend free events in their communities in order to learn about their risks, get tested for kidney disease, and ask their doctors for advice. She also emphasized the need for research to drive and inform policy.

The final speaker, Dr. Schnaper, addressed the unique differences between pediatric and adult kidney disease populations. Children and adolescents suffer from a different spectrum of kidney diseases than adults and encounter problems related to the disruption of normal growth and development. In the absence of more effective treatments and cures, he said, they are doomed to a lifetime of distress and costly care.

The message is clear: NIH-funded research is important for quality care of kidney disease patients, for prevention or cure of kidney disease and for economic development. Beyond jobs lost, if NIH funding is cut, our nation could lose a whole generation of research and discoveries that could save lives and drive down healthcare costs, Dr. Shurin said.

ASN Goes to NIH

By Grant Olan

ASN President-Elect Bruce A. Molitoris, MD, FASN, and ASN Research Advocacy Committee (RAC) members (see Table 1) participated in the society's first-ever "NIH Advocacy Day" on Wednesday, June 20. The goal of NIH Advocacy Day was to advance the profile of kidney disease research at the National Institutes of Health (NIH) beyond NIDDK and encourage other institutes to dedicate resources to studying kidney disease where relevant to their mission.

NIH's 27 institutes and centers (ICs) are engaged in global health research and research training activities. Most kidney disease research is funded by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK). While ASN has had a longstanding relationship with NIDDK, other institutes also support research conducted by ASN members. ASN has had a limited relationship with other ICs in the past. RAC members met with senior staff at NIDDK and four other ICs: the Center for Scientific Review (CSR), National Institute on Aging (NIA), National Institute of Minority Health and Health Disparities (NIMHD), and National Heart, Lung and Blood Institute (NHLBI) (Table 2).

Several overarching themes emerged from the meetings: 1) grant funding opportunities are available that have not been optimally pursued by kidney community investigators; and 2) NIH needs our support in opposing further decreases in federal non-defense discretionary (NDD) spending, the portion of the federal budget that supports biomedical research.

Since the doubling of NIH's budget ended in 2002, NIH's budget has essentially been undoubled after adjusting for biomedical research inflation. As a result, research budgets have been reduced, programs have been eliminated and application success rates have fallen from 21 percent in 2010 to 18 percent in 2011.

During meetings with congressional offices on ASN Hill Day on April 26, and at the ASN–co-sponsored "Kidney Disease Research: From Concept to Cure" congressional briefing on June 19, participants stressed the importance and value of NIH-funded research, especially kidney research, and ASN has joined the NDD community in calling for a balanced approach to deficit reduction.

The society shared this information with NIH and agreed to continue its efforts to advocate against further budget cuts that do not include additional revenues.

Table 1. Research Advocacy Committee members

L. Ebony Boulware, MD
Frank C. Brosius, III, MD
Josef Coresh, MD, PhD, FASN
Harold I. Feldman, MD, FASN
Linda F. Fried, MD, FASN
T. Alp Ikizler, MD, FASN
Jordan A. Kreidberg, MD, PhD
Mary B. Leonard, MD
Kumar Sharma, MD
Michelle P. Winn, MD
John R. Sedor, MD, Chair

Table 2. NIH Advocacy Day sessions

National Heart, Lung, and Blood Institute (NHLBI)

RAC members met with NHLBI Acting Director Susan B. Shurin, MD, and five other senior staff members. NHLBI actively supports basic, clinical, and translational kidney disease research programs, and the institute's staff recognizes the major role that kidney health plays in cardiovascular disease. Institutional leaders are interested in including kidney outcomes in NHLBI-supported clinical studies, where appropriate.

National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)

Dr. Molitoris and RAC members met with NIDDK Director Griffin P. Rodgers, MD, MACP; Kidney, Urologic, and Hematologic Diseases Division Director Robert A. Star, MD; and 16 other senior staff members. ASN and NIDDK staff shared similar concerns about the declining interest of medical students in nephrology, the shrinking training pipeline, and other workforce issues. ASN and NIDDK staff also discussed the importance of diabetic nephropathy in diabetes, getting access to data from large dialysis organizations for research, the need to develop new tools for non-invasive assessment of kidney injury, and fostering more public-private partnerships to advance translation of new findings into clinical practice.

National Institute of Minority Health and Health Disparities (NIMHD)

RAC members met with NIMHD Deputy Director Joyce A. Hunter, PhD, and three other senior staff members. NIMHD staff are very aware of kidney health disparities and the recent discovery that African-American patients, but not patients of other ancestries, have mutations in a gene called APOL1, which explains up to 70 percent of the excess prevalence of kidney failure in African-Americans and provides an important insight into their higher rates of kidney disease. They encouraged more kidney applications for their existing grant opportunities, including the Centers of Excellence Program, Community Based Participatory Research Program, and Loan Repayment Program (LRP). A significant proportion of the NIMHD budget for the support of training is devoted to the LRP.

National Institute on Aging (NIA)

RAC members met with NIA Deputy Director Marie A. Bernard, MD, and four other senior staff members. NIA staff expressed interest in developing with ASN members an R13-supported meeting that addresses deleterious effects of kidney disease on aging. In addition, NIA officials will work with ASN to highlight NIA research initiatives at Kidney Week 2013. Like NIMHD, they encouraged more kidney community investigators with interests in research supported by the NIA portfolio to consider developing applications for their existing grant opportunities, including the T32 Institutional Training Grants focused on aging and kidney disease, the Paul B. Beeson Career Development Awards in Aging Research Program, K08 Mentored Clinical Scientist Development Awards, and K24 Midcareer Investigator Awards in Patient-Oriented Research.

Center for Scientific Review (CSR)

RAC members met with CSR Acting Director Richard Nakamura, PhD, and three other senior staff members. They expressed interest in ASN's help with identifying scientists with interests in kidney biology and disease to serve as study section reviewers and to give a symposium presentation at Kidney Week 2013.

Stay tuned for more information about grant funding opportunities that exist across NIH for kidney investigators, to be published in upcoming issue of *Kidney News*.

Industry Spotlight

DiaSource Opens as Small Biz Alternative

DiaSource opened virtual doors in May as a dialysis business that promises low-cost dialysis to employers who participate with DiaSource providers in its network.

The other side of the equation is that DiaSource must attract dialysis providers in an area and sign them on to participate as providers so they can serve these smaller businesses.

The employer clients are generally self-insured employers who cannot easily afford to offer dialysis treatments economically within a small employee base.

Employers access the DiaSource network of dialysis providers that have agreed to low, competitive rates. The patient's dialysis costs are covered at 100 percent, and the employer has the benefit of low, predictable costs throughout the course of treatment, according to company literature. DiaSource also offers disease management programs, screening services and education resources for members.

DiaSource's parent company already has experience in building national networks of ancillary care providers. American CareSource Holdings was the first national, publicly traded ancillary care network services company and its subsidiary, Ancillary Care Services offers DiaSource and other healthcare solutions for employers. ACS provides ancillary health care services through its network and offers alternatives to physician and hospital-based services. The ACS providers offer services in 30 categories including dialysis centers, laboratories, free-standing diagnostic imaging centers, infusion centers, and other health-care settings.

ACS conceived the DiaSource solution by analyzing the needs of self-insured employers and recognizing the need to fight high costs of dialysis. The company offered one example of how it I helping one patient in Texas, with annualized savings to the employer projected to exceed $250,000. ACS worked with The Plexus Groupe, an independent, privately owned national insurance brokerage firm, and its client, an employer group that contracted for a provider in the DiaSource network.

Bill Simpson, president and chief operating officer for ACS, commented, "The DiaSource suite of services has compelling value to self-insured employers to alleviate the financial burden of dialysis costs for their covered members. Likewise, the DiaSource solution appeals to reinsurance carriers and third-party administrators. And to our many participating dialysis providers, DiaSource makes sense from both financial and organizational perspectives."

Simpson added that ACS is pleased to partner with benefit brokers as another effective method through which to deliver dialysis cost-containment strategies into the market.

DaVita Builds Business Beyond Dialysis

DaVita's acquisition in late May of HealthCare Partners, which has 700 staff physicians and a network of 8300 independent doctors, signaled a major dedication to a new strategy, a move that gives DaVita a major foundation with an accountable care organization (ACO), a critical component solidified by the federal Patient Protection and Affordable Care Act.

The Affordable Care Act states that an ACO is an organization of health care providers that agrees to be accountable for the quality, cost, and overall care of Medicare beneficiaries who are enrolled in a traditional fee-for-service program and who are assigned to the ACO.

ACOs were named as a potential risk to revenues in DaVita's 2011 annual report, according to *American Medical News.* Rather than try to compete with organizations vying to partner for Medicare dollars in the new ACO care landscape, DaVita acquired the ACO outright. The purchase price DaVita will pay for HealthCare Partners is about $4.42 billion, according to a joint announcement.

HealthCare Partners is one of the Pioneer Accountable Care Organizations named in late 2011 by the Centers for Medicare & Medicaid Services (CMS).

HealthCare Partners' 2011 revenue was about $2.4 billion. Total care dollars managed by the company was about $3.3 billion. It had an operating income margin of 15 percent on total care dollars under management, according to the announcement.

DaVita Chairman and CEO Kent Thiry said, "DaVita currently executes on its integrated care mission with thousands of physician partners across the country for specialized kidney care services. HealthCare Partners executes on that same mission across a full and deep array of healthcare services in three geographic markets. This combination will create a unique patient- and physician-focused organization." The three major markets are the Southern California, Central Florida, and Southern Nevada areas.

American Medical News noted that this is the second time DaVita has acquired an organization outside of its core dialysis care model.

DaVita's Paladina Health LLC subsidiary on Jan. 12 acquired ModernMed, which has 30 clinics in 12 states and provides primary care to patients paying a membership fee. Terms of that deal were not disclosed.

Zack's Investment Research wrote that "ModernMed's extraordinary network of providers coupled with a history of excellent care are expected to blend well with Paladina and DaVita's long-term strategy of growth through meaningful acquisitions." Now that the unknowns of the bundling rule and of the health of capital markets have eased somewhat, more acquisitions were probable, Zack's noted. In September 2011, the company acquired competitor DSI Renal Inc.

In November 2011, DaVita's subsidiary DV Care GmbH acquired ExtraCorp in Germany to expand its dialysis services.

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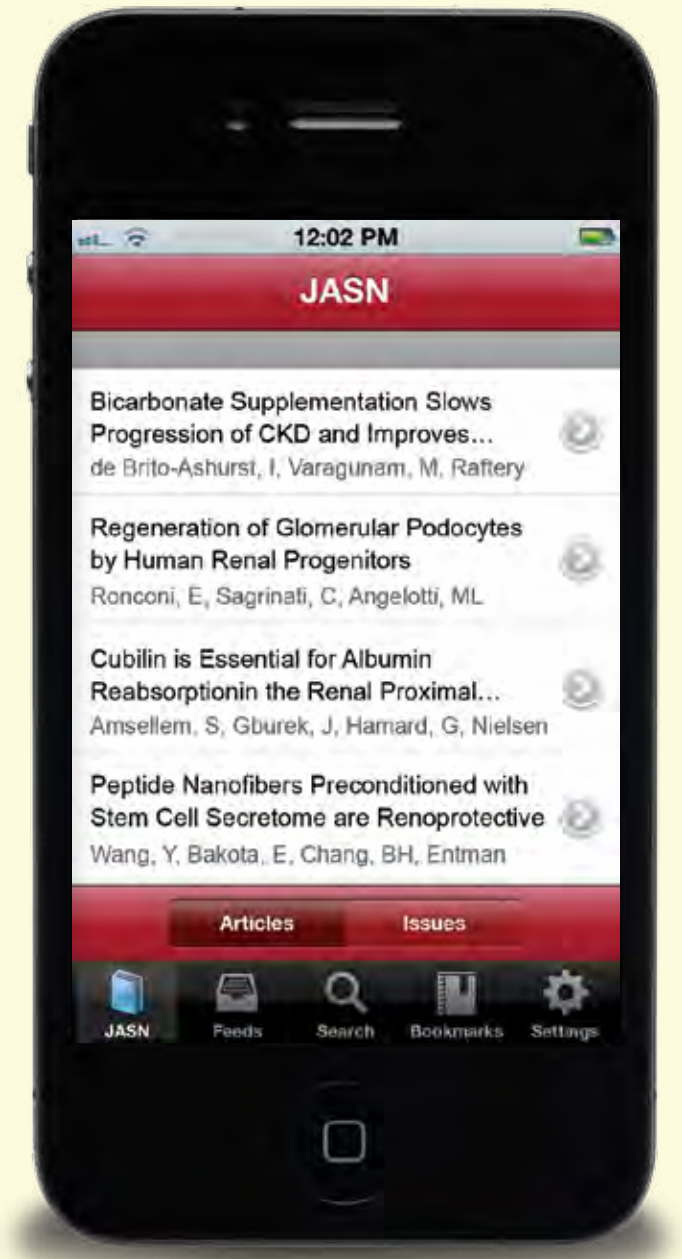

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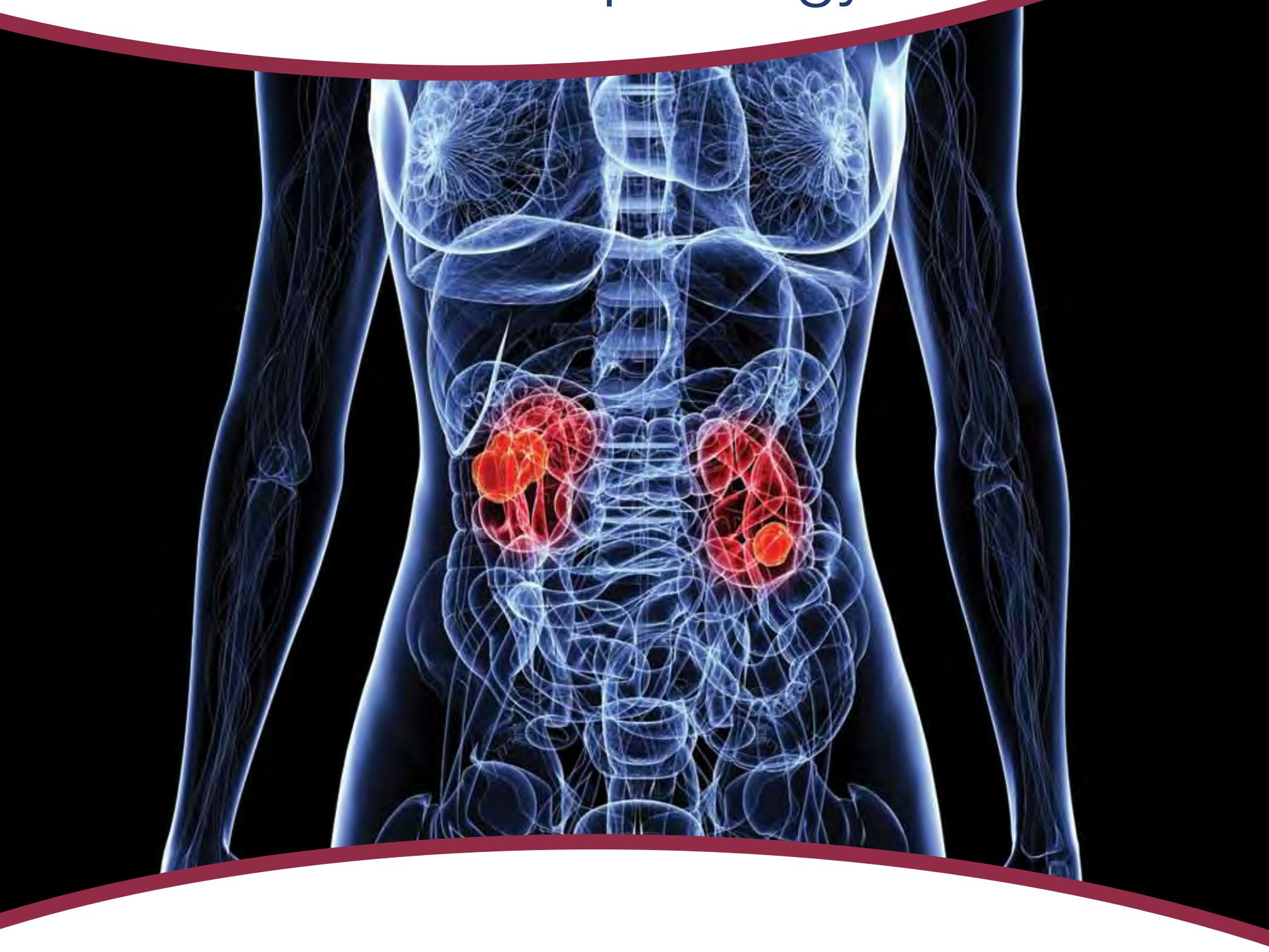

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