ASN LEADING THE FIGHT AGAINST KIDNEY DISEASE

# KidneyNews

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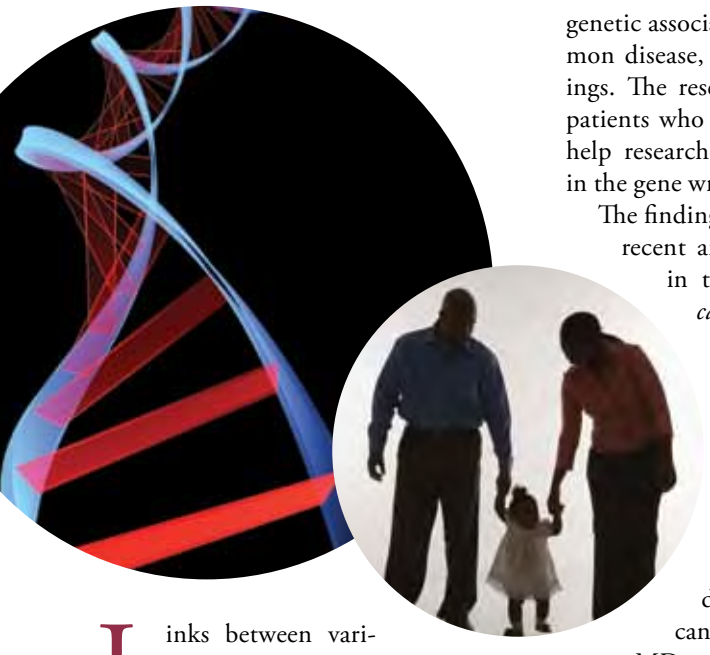
## Studies Shed Light on Link Between *APOL1* Gene Variants and Kidney Disease in African Americans

By Tracy Hampton



Links between variants in the *APOL1* gene and kidney disease in African Americans are among the strongest genetic associations reported for a common disease, according to recent findings. The research could help identify patients who need early treatment and help researchers identify how variants in the gene wreak havoc on the kidneys.

The findings were reported in several recent articles published together in the *Journal of the American Society of Nephrology (JASN)*.

"The five articles published in *JASN* launch a new era in investigating the underlying risks for developing two very common and complex kidney diseases in African Americans," said Eric G. Neilson MD, editor-in-chief of *JASN*. "Susceptibility variants such as those in the *APOL1* gene give scientists new tools for diagnosing and understanding certain diseases, and they could eventually provide new targets for drug therapy."

### APOL1, sleeping sickness, and kidney disease

Compared to European Americans, African Americans are four to five times more likely to develop kidney failure, and family members of African Americans with kidney failure have an even greater risk of developing it. This suggests that genetics may be at play.

Previous studies have found that variations in the *APOL1* gene cause up to 40 percent of kidney disease in African Americans who undergo dialysis or kidney transplantation and that *APOL1* kidney risk alleles are present only on the chromosomes of individuals of re-

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## *Bedtime Dosing of Antihypertensives Can Reduce Cardiovascular Risks for CKD Patients*

Taking at least one hypertensive medication at bedtime instead of upon waking can reduce the risk of cardiovascular events by as much as two thirds, reports Ramón C. Hermida and associates in the December Journal of the *American Society of Nephrology (JASN)*. This simple and costless approach could lead to significant improvements in outcomes for patients with high blood pressure (BP) whether or not they have chronic kidney disease (CKD) and could change how nephrologists administer antihypertensive drugs for their patients.

### Circadian rhythms and blood pressure dipping

There is a natural tendency for BP to drop during sleep. But people with high BP have a tendency to not experience this dip and may even have a rise in BP at night. These patients—nondippers and reverse dippers—tend to be at a higher risk for experiencing cardiovascular events.

Chronotherapy—using the body's

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## Inside

# *APOL1* Gene Variants

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cent African descent. The *APOL1* gene creates a protein that is a component of HDL, or good cholesterol. The protein circulates on HDL3 complexes, the densest HDL fraction, and is expressed in multiple tissue types. Researchers have wondered how variants in the *APOL1* gene contribute to kidney disease and why certain variants are so common in African Americans.

Individuals inherit two copies of the *APOL1* gene—one from each parent. It turns out that if they inherit one copy of an *APOL1* gene variant, they are protected from the parasite *Trypanosoma brucei rhodesiense* that causes African sleeping sickness, a disease transmitted by the tse-tse fly. For this reason, these variants have been preserved through evolution and are common in individuals with African ancestry. Unfortunately, when both copies of the *APOL1* gene contain a variant, a person has an increased risk of developing kidney failure.

## New insights on APOL1

In the latest *JASN* studies, researchers investigated how common *APOL1* gene variants are in individuals with and without kidney disease, examined whether African Americans with the variants need dialysis at a younger age than those without the variants, and analyzed individuals' kidney tissues to see how the protein created by the *APOL1* gene affects kidney health.

To determine how common *APOL1* gene variants are, Ali Gharavi, MD, of Columbia University College of Physicians and Surgeons, and his colleagues looked for the variants in 74 healthy African Americans and African Americans with various common kidney disorders: 44 with focal segmental glomerulosclerosis (FSGS, which is characterized by scarring of the kidneys), 21 with HIV-associated nephropathy (HIVAN, a secondary form of FSGS linked with HIV infection), and 32 with IgA nephropathy (which occurs when antibodies build up in the kidneys). The researchers found that variants in the *APOL1* gene often occurred in individuals with FSGS and HIVAN but not in those with IgA nephropathy. "This study confirms that genetic variation in the *APOL1* gene is a major risk factor for two forms of kidney disease and that the risk imparted is significant enough that *APOL1* testing may be used to determine people's risk for kidney failure," Gharavi said.

Delving deeper into the links between *APOL1* gene variants and FSGS and HIVAN, Jeffrey Kopp, MD, of the National Institutes of Health, and his team studied 271 African American cases of FSGS and HIVAN, 168 European American cases, and 939 healthy individuals. African Americans with variants in both copies of the *APOL1* gene had a significantly increased risk of developing FSGS and HIVAN. *APOL1* variants conferred 17-fold higher odds for FSGS and 29-fold higher odds for HIVAN. Among those with either FSGS or HIVAN, having two *APOL1* risk alleles could be responsible for 67 percent of cases.

Among the general population, two *APOL1* risk alleles may account for 18 percent and 35 percent of FSGS and HIVAN, respectively. Approximately 13 percent of African Americans (more than 3.5 million individuals) carry two *APOL1* gene variants, and these individuals have a 4 percent risk during their lifetime of developing FSGS; those with untreated HIV have a 50 percent risk during their lifetime of developing HIVAN. "We also found that *APOL1*-associated FSGS tended to arise at an earlier age and to progress to kidney failure more rapidly than non-*APOL1*-associated FSGS," Kopp said.

Other researchers looked to see if *APOL1* gene variants confer risks for other types of kidney disease among 2867 African Americans. Nondiabetics with two *APOL1* gene variants had a fourfold increased risk of developing chronic kidney disease over nondiabetics without the gene variants, according to findings of Martin Pollak, MD, of Beth Israel Deaconess Medical Center, and his colleagues. African Americans with zero or one *APOL1* risk allele, and African Americans with two risk alleles had microalbuminuria rates of 2.3 percent, 6.0 percent, and 16.5 percent, respectively. Rates of GFR < 60 mL/min/1.73 $m^2$ were 1.5 percent, 1.7 percent, and 6.7 percent for these same groups. APOL1 genotype was not associ-

ated with any differences in kidney disease rates for individuals with diabetes.

"Our research shows that *APOL1* variants explain the difference between the high rate of kidney disease in African Americans compared with European Americans," Pollak said.

Pollak also collaborated with Ravi Thadani, MD, of Massachusetts General Hospital, and others to examine whether African Americans with *APOL1* gene variants need dialysis to treat kidney failure at a younger age than those without the variants. Among 407 African Americans with kidney failure, individuals with two gene variants initiated chronic hemodialysis at an average age of 49.0 years, compared with 55.9 years for those with one gene variant and 61.8 years for those with no variants. "We may be able to predict when blacks with kidney disease will experience kidney failure well before it occurs," said Thadani. These results suggest that patients with two variants may benefit from early therapies to protect their kidneys.

While these association studies all provide new and valuable information, questions still remain regarding how the proteins created by the *APOL1* gene and its variants affect kidney health. To investigate, John Sedor, MD, of Case Western Reserve University, and his collaborators examined individuals' kidney tissues and found that the protein created by the *APOL1* gene resides in different regions of the kidney in patients with FSGS or HIVAN compared to individuals without kidney disease. *APOL1* in the normal human kidney was localized to the podocyte, a cell type implicated in the pathogenesis of FSGS and HIVAN, as well as in proximal tubular epithelial cells and the endothelium of small renal arteries. In FSGS and HIVAN samples, *APOL1* staining was diminished in the podocytes and proximal tubules while it was preserved in the endothelium of small renal arteries. It was also present in the vessel walls of the small renal arteries.

"Its appearance in the walls of small arteries in the kidney that occurs only in disease suggests that blood vessels may have an underappreciated role in the development and progression of these diseases," Sedor said.

## Clinical impact

Experts in the field say these latest findings will have considerable clinical impact. "These landmark articles cement the role of *APOL1* on nephropathy risk in African Americans," said Barry Freedman, MD, and Donald Bowden, PhD, of the Wake Forest School of Medicine. "Particularly novel are *APOL1* association results with chronic kidney disease in population-based samples and renal *APOL1* distribution in diseased kidney tissue."

Freedman and Bowden worked with Kopp, Pollak and others to originally demonstrate that FSGS and hypertension-attributed end stage kidney disease were associated with two independent sequence variants in the *APOL1* gene in African Americans (Genovese G et al. *Science* 2010; 329:841–845). They have since translated this groundbreaking genetic observation to clinical outcomes and potential mechanisms underlying nondiabetic kidney disease. The investigators demonstrated that kidney allograft survival is shorter in African American–donated kidneys containing two *APOL1* risk variants and that medium HDL-cholesterol subfraction concentrations are lower in African Americans with two *APOL1* risk variants.

The link between *APOL1* gene variants and kidney disease in African Americans has been one of the more exciting research developments at the intersection of nephrology, population genetics, and evolutionary medicine in recent years, said Karl Skorecki, MD, director of nephrology and molecular medicine at the Technion Faculty of Medicine in Israel. "These new *JASN* studies bring these insights closer to the benefit of the individual patient by providing genetic epidemiologic parameters that will be needed in establishing guidelines for personalized risk and preventive intervention assessments based on *APOL1* genotype," he said.

More research is needed to understand how *APOL1* variants contribute to kidney disease and what specific steps individuals with the variants should take to safeguard the health of their kidneys.

"The *APOL1*-kidney disease connection comes at a time of rapid progress in the genome-wide identification of risk loci that interact with each other and with environmental triggers and cofactors in determining kidney function in health and disease, and we all look forward to continued progress," Skorecki said.

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## Bedtime Dosing of Antihypertensives

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circadian rhythm patterns to increase the efficacy of medications—is being studied in a wide variety of diseases, including cancer, asthma, and arthritis. The cardioprotective effects of using chronotherapy to administer hypertensive medications at bedtime have been previously studied (Smolensky MH, et al. *Blood Press Monit* 2010; 15:173–180), but this was the first study to confirm the effect by using ambulatory blood pressure (AMBP) monitoring data.

"A large number of published prospective trials have reported clinically meaningful morning-evening, treatment-time differences in BP-lowering efficacy, duration of action, safety profile, and/or effects on the circadian BP pattern for different classes of hypertension medications," Hermida said.

The group previously reported that urinary albumin excretion was significantly reduced with the nighttime dosing of valsartan (Hermida RC, et al. *Hypertension* 2005; 46:960–968). Hermida called the finding "just one single example of too many similar findings for many hypertension medications."

The MAPEC [Ambulatory Blood Pressure Monitoring and Cardiovascular Events] study, from which the current report in *JASN* was derived, "was designed to test exactly what we documented, and the results were expected," Hermida said. "We were, however, surprised by the extent of the differences between groups." The MAPEC study appeared in *Chronobiology International* in 2010.

"There has been a longstanding concern about the lack of good nocturnal BP control in many patients with hypertension, including those with CKD, said Frank C. Brosius III, MD, chief of the division of nephrology at the University of Michigan and a specialist in hypertension and kidney disease. "However, albeit some evidence that nocturnal hypertension persisted in many patients, I am not aware of previous randomized controlled trials that have examined the impact of bedtime therapy on nocturnal BP control in CKD patients."

### Ambulatory blood pressure monitoring

Between 2000 and 2007, Hermida and his colleagues at the University of Vigo in Spain conducted a prospective open-label investigation with 661 patients randomly assigned to either take at least one antihypertensive medication at bedtime or take all their medications upon waking in the morning. At the beginning of the study period, both groups had similar renal and cardiac profiles.

Patients were monitored for two endpoints: 1) total cardiovascular events, including death, myocardial infarction (MI), angina pectoris, revascularization, heart failure, artery occlusion, and stroke, and 2) major cardiovascular events (cardiovascular death, MI, and stroke). This focus is important because "there have been no relatively large studies of the effect of such therapy on 'hard' cardiovascular endpoints in CKD patients," Brosius said.

The investigators were able to capture the real-time data needed to confirm the beneficial effects of bedtime dosing through the use of AMBP monitoring. Each patient wore a portable BP monitor for 48 hours before each follow-up visit, and BP measurements were recorded every 20 minutes during the day and every 30 minutes during the night. Asleep and awake periods were verified with actigraphy to ensure accurate data capture. Although previous research has confirmed the importance of nighttime BP in predicting the risk of cardiovascular events, this was based only on the AMBP data obtained at the beginning of the study, with no AMBP data captured in the follow-up period.

## Significant cardiovascular outcomes

After a median follow-up time of 5.4 years, patients in the bedtime dosing arm had experienced 35 cardiovascular events compared with 104 events in the morning dosing arm. Major cardiovascular events affected 9 of the patients in the bedtime dosing arm, compared with 26 events in the morning dosing arm. In addition to the primary endpoints of cardiovascular outcomes, patients taking at least one medication at bedtime also experienced better outcomes in reducing albumin excretion.

"These treatment-time–dependent effects on sleep-time BP control were strongly associated with lower risk of [cardiovascular disease] events," the group determined. "Indeed, the progressive reduction in the asleep BP mean from baseline was the most significant predictor of event-free survival.

"The results indicate that [cardiovascular disease] event rates in patients with hypertension can be reduced by more than 50 percent with a zero-cost strategy of administering blood pressure-lowering medications at bedtime rather than in the morning," Hermida said, adding that "differences between treatment-time groups were greater than anticipated due to some extent to the very minor number of events in the group of patients who were ingesting not just one but all medications at bedtime."

Brosius found the results "striking and provocative, but cautioned that "since this is a single-center study and because of the degree of risk reduction, these results need to be confirmed in a larger, multiinstitutional randomized controlled trial."

Hermida concurred: "The current report in *JASN* is just a subgroup analysis from the much larger MAPEC study. Fully comparable results, also derived from our much larger study, have been previously reported for subgroups of patients with diabetes (Hermida RC, et al. *Diabetes Care* 2011; 34:1270–1276), resistant hypertension (Hermida RC, et al. *Chronobiol Int* 2010; 27:1629–1651), or for the general hypertension population (Hermida RC, et al. *J Am Coll Cardiol* 2011; 58:1165–1173). These findings, however, will need further corroboration by larger studies."

Hermida and his colleagures are currently coordinating a multicenter prospective trial with the participation of primary care centers from Northwest Spain to corroborate the findings. Termed the Hygia Project, the new trial will test hypotheses similar to be those from the MAPEC study. So far the team has recruited over 9000 patients who are being followed by repeated 48-hour AMBP monitoring.

And despite the single-center scale of the current study in *JASN*, Brosius said that "since there is no known adverse consequence from nocturnal dosing of most antihypertensives I, for one, will consider more regularly prescribing these medications at bedtime, as well as in the morning."

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# Kidney Week 2011

## Renal Denervation for Control of Treatment-resistant Hypertension

Denervation of the renal nerves has the potential to dramatically reduce hypertension in medication-resistant patients. That was the message from Henry Krum, MD, PhD, professor of medicine at Monash University in Melbourne, Australia, and lead investigator of the SYMPLICITY-2 trial, which compared renal denervation to no intervention in over 150 patients. Krum spoke about the trial in a Hot Topics session at Kidney Week 2011.

"I don't need to tell this audience that hypertension is a major problem, and this problem is only going to get worse," Krum said. "The prevalence will grow to almost 50 percent in Western populations by 2025, with developing populations catching up very quickly."

About 9 percent of the population is resistant to treatment, defined as having uncontrolled blood pressure despite being on three or more antihypertensive medications.

One critical driver of hypertension is sympathetic activity involving the renal nerve. Activation from the brain to the kidney stimulates release of renin and activation of the RAAS system, retention of sodium, and reduction of renal blood flow. Feedback to the brain via renal afferents also plays a part, driving blood vessel constriction and other effects.

Renal denervation for hypertension dates back to the 1940s, but its success came with high rates of incontinence, impotence, and hypotension, due to off-target effects. Since then, precise targeting of the renal nerve has been accomplished with the "SYMPLICITY" system (Medtronic), in which a catheter is inserted into the renal artery via the femoral artery, which delivers radiofrequency energy to ablate the nerve.

The first major trial of the system, published in 2009, enrolled 57 patients with office systolic blood pressure of 160 mm Hg or greater, uncontrolled by three or more medications. In this open trial with no control group, blood pressure was reduced by 27 mm Hg systolic and 17 mm Hg diastolic, an effect maintained over the 12 months of the study.

Measures of muscle sympathetic nerve activity indicated that part of the effect was due to afferent denervation. "This opens up a new vista for treatment of renal hypertension," Krum said, since it directly implicated an important role for the afferent system.

The recently completed SYMPLICITY-2 trial supported these initial results in a controlled, but not blinded, trial comparing denervation to best medical management in 153 patients over 24 months. The mean age of patients was 57 years, with a third of them experiencing diabetes mellitus. Baseline office blood pressure was 176/17, despite that more than three-quarters of patients were on an ACE inhibitor, a calcium channel blocker, and a beta blocker.

The results mirrored those seen in the first trial, with a reduction in blood pressure of 32 mm Hg systolic and 12 mm Hg diastolic, which emerged quickly and was sustained at 12 months.

There was little to no change in the control group. Relatively few patients have reached the 24-month follow-up, but initial findings in this smaller group are equally positive, Krum said. The treatment appeared to be safe and well tolerated.

A critical question is whether there is functional (as opposed to simply anatomic) reinnervation of the nerve over the long term. "Our data suggest that is not the case at 24 months," he said.

A third trial is underway in the United States, with a placebo group undergoing a sham procedure in order to maintain a blind. "This will probably be the definitive answer in the refractory hypertension setting," Krum predicted.

Referring back to the evidence for involvement of the afferent system, he noted that sympathetic excess plays a role in many nonhypertensive disorders, including heart failure. "Many of the disorders implicated in the progression of heart failure are adrenergically mediated," including myotrophic hypertrophy, fibrosis, and renal disease itself. Sympathectomy in animal models can reduce the adverse cardiac effects of several of these disorders.

Based on that, a trial is underway to test the ability of renal denervation to reduce progression of heart failure in renal disease patients with left ventricular dysfunction. The initial aim is to demonstrate safety in this population, and to determine whether there is a physiological effect on ventricular function.

While praising the studies performed so far, Gerald DiBona, MD, emeritus professor at the University of Iowa in Iowa City, noted that too little is known about long-term reinnervation. "For me, the big issue is what about the persistence of denervation." Functional reinnervation occurs in weeks in rats, and in months in dogs. In humans, the little data there are suggest it may occur over several years. "We need to know whether the efferent renal nerves are growing back after two or three years," he said. "Is there afferent reinnervation? We have no direct data as of yet. It may be that they do not reinnervate."

## For Diabetic Dialysis Patients, Low A1C is Good, but Even Lower Isn't

Two new studies show that when it comes to hemoglobin A1c in dialysis patients, Goldilocks had it right—the best level is not too high, but not too low either. Both studies show that the lowest mortality occurred in patients with intermediate levels, ranging between 6.5 percent and 9 percent, and that dropping below that was associated with worse patient outcomes.

The guidelines for control of blood sugar in the Kidney Disease Outcomes Quality Initiative (KDOQI), dating to 2007, state that the target A1c level for people with diabetes "should be less than 7 percent, irrespective of the presence or absence of chronic kidney disease." However, according to Kamyar Kalantar-Zadeh, MD, professor of medicine and pediatrics and epidemiology at the UCLA David Geffen School of Medicine in Los Angeles, "There is no consistent evidence to support these targets for dialysis patients." Kalantar-Zadeh was lead investigator on one of the new studies.

Previous large observational studies have come to different conclusions about the effect of A1c on mortality in dialysis patients. But these studies have generally been relatively short-term, he said. To determine the long-term effect of A1c, he and his colleagues examined outcomes in over 54,000 dialysis patients with diabetes over a seven-year period.

They found that mortality from all causes followed a U-shaped curve in relation to time-averaged A1c. The lowest rate of mortality occurred when A1c was between 7 percent and 8 percent. In line with previous studies, it rose sharply above that, with the hazard ratio rising to approximately 1.4 when A1c was in the 9 percent to 10 percent range. Surprisingly, though, the hazard ratio also rose when A1c was below 7 percent, increasing gradually when the level was between 6 percent and 7 percent, and then steeply as the level dropped below 6 percent. The risk of death at an A1c level of 5 percent was higher than at levels between 9 percent and 10 percent.

The same U-shaped curve was found for mortality from cardiovascular events, again with a nadir at A1c levels between 7 percent and 8 percent, with approximately similar magnitudes of risk on either side. Kalantar-Zadeh also analyzed mortality as a function of glucose levels directly, using random glucose samples in over 50,000 patients. The lowest mortality was seen in patients with time-averaged glucose in the 150–200 mg/dL range, with the risk increasing from either more, or less, glucose.

A second study, part of the Dialysis Outcomes and Practice Pattern Study (DOPPS), reached similar conclusions, according to investigator Fritz Port, MD, of Arbor Research in Ann Arbor, Michigan. In this prospective study of over 6000 dialysis patients with diabetes from 12 countries, after fully adjusting for a range of variables affecting mortality, the lowest mortality occurred in patients with A1c levels between 7 percent and 7.9 percent.

"The desirable range for diabetic dialysis patients is 7 percent to 9 percent," Port said, "which is higher than the guidelines for the general diabetes population." To improve patient survival, he said, diabetes medications could be reduced in patients with low blood sugar, a step that may be particularly important for patients with poor nutritional status.

"I think the take-home message is that the target may need to be reconsidered in diabetic dialysis patients," Kalantar-Zadeh said, suggesting 6.5 percent to 8 percent as the appropriate range. Importantly, "the target has a lower threshold, not just an upper threshold."

"It also has practical implications," he said. "Patients do not need to be pressured all the time to achieve the same very low levels as in the general diabetes population. We may be satisfied with patients reaching the middle range."

The reason that dialysis patients differ from other diabetic patients is not clear. One reason may be that dialysis patients have adapted to moderately high glucose, reaching a new normal, and so for them, lowering glucose below 6.5 percent or 7 percent is not beneficial.

While the findings of the two studies coincide, neither was a randomized trial comparing different target glucose levels. Thus, Kalantar-Zadeh said, there is a need for controlled trials to further confirm these findings.

The findings were presented at Kidney Week 2011.

# A Lifetime of Proving Them Wrong: Robert Langer and the Development of "Bioartificial" Tissues

"They said it wouldn't work" has been a galvanizing challenge to Robert Langer, Sc.D., throughout his long and astonishingly productive career. Langer has been a pioneer in the creation of biomaterials for drug delivery, and more recently in laying the foundations for the development of engineered tissues, including those in development for treatment of renal disease. He delivered a state of the art" plenary lecture here during Kidney Week in Philadelphia.

As a young man wanting to put his chemical engineering skills to some creative use, Langer approached Judah Folkman, a cancer researcher whom Langer had heard "sometimes hired unusual people." Folkman was in the early days of seeking angiogenesis inhibitors as antitumor agents, and it fell to Langer to prospect for candidates in bovine cartilage, which is largely devoid of blood vessels. This, he said, led to long hours scraping clean the thigh bones of "most of the cows in the Northeast."

Most significantly, this early work led him to make fundamental advances in polymer chemistry, designing polymers that could hold, and equally importantly slowly release, large molecules such as proteins. The chemistry establishment was skeptical such a feat was possible. But he showed them wrong, creating polymers with high "tortuosity," full of large pores that twisted throughout the structure. He published his initial landmark results in *Nature*, in 1976. The polymer was used to deliver candidate angiogenesis inhibitors for in vivo testing. That research led, three decades later, to Nexavar and Torisel for renal cancer, and Avastin for colorectal cancer.

A different challenge was to develop polymers that would dissolve in a controlled fashion when placed in the body. Dissolvable sutures existed prior to his work, but the rate and pattern of dissolution was poorly controlled. By thinking long and hard, and experimenting relentlessly, he came up with a material that overcame these limitations. And by altering the ratio of the two subunits in the polymer, he could change the rate of dissolution, and therefore the release of anything within it, making the polymer perfect for implanted drug delivery systems.

The polymer is currently used to deliver carmustine in situ after resection of glioblastoma multiforme, killing remaining tumor cells with fewer side effects than systemic chemotherapy. The therapy was approved by the FDA in 1996, only after, as Langer told it, 15 years of grant reviewers explaining why each new advance along the way had no chance of working. The achievement was rewarding in several respects, he said. The treatment triples survival at one year, and quintuples it at two years. In addition, his many postdocs who perfected the system over the years now hold major positions in industry and academia across the country. The reviewers? Not so much, he said.

A major focus of Langer's work in recent years has been the development of biodegradable scaffolds for direct implantation in vivo, around which cells can grow. He noted that when tissue progenitor cells are injected directly into the body, "not much happens," because of the absence of the appropriate context in which to grow. But with a scaffold to provide spatial clues, cartilage cells direct their growth to take on the shape of the scaffold, which then dissolves, leaving pure animal (or human) tissue.

"We still have a good deal of work ahead of us," he cautioned, noting that strength of the new tissue is limited, making the repair of sports injuries, for instance, a still-unrealized goal. But early work indicates the potential: a remodeled ear for a soldier with a war injury, a new chest wall for a boy with a congenital deformation. A related approach is now under development for spinal cord injury repair, with preliminary results that, judging by a video of a treated rat, are nothing short of astonishing.

"It is my hope that engineering approaches such as these can play a role in nephrology," Langer concluded.

That challenge has been taken up by several researchers, including David Humes, MD, professor of internal medicine at the University of Michigan. In an interview with *Kidney News*, Langer described the development of a bioartificial kidney as "a new frontier." Of the two central functions of the kidney, dialysis handles only one: filtration clearance. The other, which combines reabsorption with metabolic and synthetic capacities, is the role of the tubule, and it is replacing the tubule to which Humes has devoted many years of research.

"The field has advanced considerably," Humes said. He spearheaded a successful phase II trial of an extracorporeal tubule cell cartridge for acute kidney disease, which cut mortality in half. But as other treatment strategies emerged, that application has become less important.

For the last several years, Humes has been developing "a compact, wearable device" that can be combined with peritoneal dialysis for end stage renal disease. The tubule cells in the device are bathed in peritoneal fluid to keep them healthy. "The concept of a fully functional, bioartificial, wearable kidney has now been conceptually formulated," he said, "and a proof of concept has been made in a large animal model." Miniaturization would allow the device to be implanted, but that remains "a number of years away."

Still further away is the replication of the tissue architecture of the kidney itself, which integrates the clearance and reabsorption functions in a compact and efficient package. "That is the ultimate challenge," he said, but one that is orders of magnitude harder than sculpting cartilage. Tubules have at least 10 segments with different functions; cells of the right type might be injected under computer control into a dissolvable matrix, Hume speculated, but would still need the appropriate vasculature and innervation. "That would be a tour de force."

"The extracorporeal systems are here already," he said, but remain in the lab, awaiting both further development and a commercial rationale that would support that development. "It is difficult to add any costly component to the system in ESRD, unless there is a cost savings that can be identified." Decreasing a patient's dependence on dialysis centers might provide the financial savings that would justify the cost of the system, he suggested.

# Podocyturia in Pregnancy Gets New Look

By Tracy Hampton

Hypertension or preeclampsia during pregnancy, while often asymptomatic, can threaten the health of women and their babies. Two Mayo Clinic studies presented at the ASN's Kidney Week 2011 provide new information related to these conditions.

Vesna Garovic, MD, and her team examined the potential of a test done mid-pregnancy to predict which women will later develop preeclampsia, a late-pregnancy disorder that is characterized by hypertension and proteinuria that affects 3 percent to 5 percent of pregnancies. Left untreated or without careful monitoring, preeclampsia can lead to serious—even fatal—complications for a pregnant woman and her baby.

The researchers previously showed that podocyturia, the shedding of live kidney cells called podocytes, is present at delivery in patients with preeclampsia. In this study, they tested whether podocyturia is predictive of later development of preeclampsia, and whether it can differentiate among normotensive pregnancies, gestational hypertension, and preeclampsia. For the analysis, urine sediments are cultured for 24 hours to select for viable cells, and podocytes are then identified on the basis of podocin staining.

Among a group of 315 patients in the study, 15 developed preeclampsia and 15 developed gestational hypertension (but not preeclampsia) during pregnancy. All of the patients who developed preeclampsia tested positive for podocyturia in mid-pregnancy (prior to 210 days gestation). None of the study participants with only hypertension tested positive, and none of 44 women with normal pregnancies tested positive.

The test is highly accurate for predicting preeclampsia, which could alert clinicians to take steps to safeguard against the condition in their patients. The test could also differentiate between later development of gestational hypertension and preeclampsia. The high accuracy of this test further supports the role of podocyte loss in the mechanism of proteinuria in preeclampsia.

"Preeclampsia is well recognized as an endothelial cell disease; however, the precise mechanism of proteinuria has remained somewhat elusive," said Michelle Hladunewich, MD, who was not involved with the research and is a clinical investigator in the divisions of nephrology, critical care, and obstetric medicine at Sunnybrook Health Sciences Center in Toronto. "Although widespread feasibility of the measurement of podocytes in the urine as a predictive marker for preeclampsia is likely limited, these novel insights into the pathophysiology of preeclampsia particularly as it relates to the cross talk between the endothelial cell and the podocyte are most interesting."

Garovic also led another study that looked at the long-term health effects of hypertensive disorders during pregnancy. Her team identified all female residents of Rochester, Minn., and the surrounding townships in Olmsted County who delivered between 1976 and 1982. The women were categorized into two groups: those with hypertensive disorders during pregnancy and those without. The investigators followed the women after they reached 40 years of age to monitor their heart and kidney health.

A total of 6051 mothers delivered between 1976 and 1982, and 607 women had hypertensive pregnancy disorders at the time while 5444 did not. Follow-up after age 40 years was available for 465 (77 percent) cases and 3898 (72 percent) controls. After the women reached age 40, women who had hypertensive disorders during pregnancy were much more likely to experience hypertension, kidney dysfunction (proteinuria, chronic kidney disease, or end stage renal disease), and strokes than women who did not have hypertensive disorders during pregnancy (51 percent vs. 31 percent, 14 percent vs. 10 percent, and 8 percent vs. 4 percent, respectively).

"Studies of the associations of hypertensive pregnancy disorders with maternal risks for future cardiovascular disease could lead to new guidelines for screening and treatment of women at risk, with the ultimate goal of improving cardiovascular health in women," Garovic said.

# Fish Oil Cuts Loss of Graft Patency and Cardiovascular Events in Dialysis Patients

For patients with a hemodialysis graft, daily fish oil substantially reduces the frequency of developing stenosis, thrombosis, and cardiovascular complications. That's the message from a large, randomized, placebo-controlled study presented at Kidney Week in November.

The results, according to lead investigator Charmaine Lok, MD, should prompt a fresh look at grafts and the potential of fish oil to improve patient outcomes in hemodialysis. Lok is associate professor of medicine at the University of Toronto and medical director of the Hemodialysis Vascular Access Program at Toronto General Hospital.

Each type of hemodialysis access has its problems, Lok noted, with stenosis and thrombosis being the major problems with grafts. These problems have led to an increasing use of fistulas, but over the past decade, she said, it has become apparent that fistulas often fail, with estimates of failure rates ranging up to 60 percent.

The reasons for stenosis are not entirely clear, although multiple factors are likely involved, including trauma during surgery or during treatment. "It has been known for a long time that fish oil has benefits in cardiovascular disease," Lok said, dating back to studies on Eskimo populations in Greenland, who have very low levels of cardiovascular disease. Fish oil reduces endothelial dysfunction through several mechanisms, including reduction of inflammatory cytokines and inhibition of endothelin-1, which constricts blood vessels.

That led Lok to wonder if fish oil might also have a beneficial effect on blood vessels elsewhere in the body, including the vessels supplying the graft. A small study in 2002 suggested that might be the case, with treatment increasing graft patency fivefold versus placebo over 12 months.

For her study, Lok recruited patients with patent grafts a week after their surgery. Patients were randomized to receive placebo or fish oil at 4 grams per day for 12 months, during which they underwent biweekly follow-up visits to assess patency, and every 3 months to monitor lipid profiles, blood pressure, and cardiovascular events. The study was conducted at 12 sites in Canada and 3 sites in the United States.

The primary outcome was the proportion of patients with loss of patency within 12 months, as evidenced by having either a thrombosis or need for an intervention to maintain graft patency. "Either you have an event or you don't—that's the most conservative endpoint," she said. Prespecified secondary outcomes included the individual rates of thrombosis or need for intervention to restore patency, the time to thrombosis, and changes in blood pressure, lipid profile, and cardiovascular medications.

The study was designed to enroll 232 patients, but, Lok said, "We had a very hard time recruiting patients, because of the push for fistulas" within the last several years. In the end, she enrolled 201 patients, of whom 101 received fish oil. Patients had a mean age of 62 years, and were well matched except for a higher proportion of congestive heart failure in the fish oil group. That imbalance increased the challenge for active treatment to show benefit, she said, but also meant that a positive result might be more meaningful.

On the primary outcome measure, 48 percent of patients in the fish oil group, and 62 percent in the placebo group, had loss of patency. The difference was just shy of statistical significance, with a p value of 0.06.

Fish oil was superior on almost all the secondary outcome measures. The rate of thrombosis or need for intervention per 1000 days was 3.43 for fish oil, versus 5.95 for placebo ($p < 0.001$). The median time to thrombosis was twice as long for patients on fish oil, and the rate of thrombosis was half, with 1.7 events per 1000 days for patients on fish oil, versus 3.4 for placebo ($p < 0.001$). The rate of any cardiovascular event in patients on fish oil was less than half that of patients on placebo. Blood pressure was reduced, as were medications. Lipid profiles were not different between the groups, perhaps, Lok said, because baseline levels were relatively low, making it difficult for treatment to have much effect.

The failure of treatment to significantly affect the primary endpoint, while providing clear superiority on many clinically important secondary ones, suggests to Lok that, in hindsight, an alternative primary endpoint may have been better. Patients who have an event may continue to use their graft, she noted, and so at that point, the more important clinical question is, "For the duration of the access, how many of these events are you going to have? From a patient and healthcare payer perspective, that is probably the more important endpoint. An intervention is extremely expensive, and inconveniencing and painful for the patient."

"Is there a role for grafts in hemodialysis? There absolutely is," Lok said. "After a decade of promoting fistulas, we are finding out there is a high failure rate. For patients who are not eligible for fistulas, grafts are a good alternative."

We were very excited about the cardiovascular outcomes," Lok said, and her group is currently pursuing a larger study in dialysis patients to formally study the effect of fish oil on these events.

# Diabetes Trials Take **Kidneys into Consideration**

Type 1 diabetics' risk of developing impaired glomerular filtration decreased 50 percent when they were given intensive diabetes therapy, according to late-breaking clinical trial results presented at Kidney Week. Other late-breaking findings pointed to the promising clinical potential of sitagliptin for patients with type 2 diabetes who have moderate or severe chronic renal insufficiency.

Diabetes and kidney dysfunction often go hand-in-hand, so researchers know that it's important to study the effects of diabetes drugs on the kidneys and to examine the safety of these drugs in patients who already have kidney disease.

In the first study, the Diabetes Control and Complications Trial (DCCT), Ian de Boer, MD, of the University of Washington, and his team looked to see if intensive diabetes therapy aimed at reducing blood sugar as close to the normal range as possible might protect type 1 diabetics' kidney function.

"Persons with type 1 diabetes are at high risk of developing kidney disease, but no interventions are proven to prevent the development of impaired glomerular filtration rate, or GFR, in this population," de Boer said.

The researchers randomly assigned 1441 individuals with type 1 diabetes to intensive diabetes therapy or to conventional diabetes therapy, aimed at preventing symptoms of high blood sugar. Patients were treated for an average of 6.5 years. Subsequently, 1375 participants were followed in the observational Epidemiology of Diabetes Interventions and Complications Study (EDIC).

Over an average of 22 years in DCCT/EDIC, intensive therapy was more effective at preserving long-term kidney function in study participants. A total of 24 participants assigned to intensive therapy and 46 assigned to conventional therapy developed impaired GFR, meaning that intensive diabetes therapy reduced patients' risk by 50 percent. Of those with impaired kidney function, 8 assigned to intensive therapy and 16 assigned to conventional therapy developed kidney failure.

Compared with conventional therapy, intensive therapy reduced mean estimated GFR by 1.7 mL/min/1.73 $m^2$ during the DCCT but slowed the rate of GFR loss and increased the mean estimated GFR by 2.5 mL/min/1.73 $m^2$ during EDIC. So small short-term reductions in GFR within the normal range were followed by long-term GFR preservation. The beneficial effect of intensive therapy on impaired GFR was fully explained by lower hemoglobin A1c and lower albumin excretion rate.

"This important study shows that loss of kidney function is potentially preventable in people with type 1 diabetes and adds to our understanding of the importance of controlling blood sugar in this population," said Marcello Tonelli MD, who moderated the late-breaking oral abstract session. Tonelli is president of the Canadian Society of Nephrology and a founding member of the Alberta Kidney Disease Network.

Another study compared the efficacy and safety of blood-sugar-lowering drugs in patients with type 2 diabetes and chronic renal insufficiency (CRI).

Previous research indicates that two of these drugs, sitagliptin and glipizide, may not cause considerable kidney damage. The agents act on different targets but generate the same result—they boost the effects of insulin, which lowers blood sugar levels.

Juan Arjona Ferreira, MD, of MSD Corp. and his colleagues conducted a 54-week study to compare the efficacy and safety of sitagliptin and glipizide in patients with type 2 diabetes and moderate or severe CRI who were not on dialysis. The researchers randomized 426 patients to receive sitagliptin or glipizide. The sitagliptin dose was 50 mg once daily for patients with moderate CRI and 25 mg once daily for patients with severe CRI. The dose was adjusted downward (from 50 to 25 mg once daily) for patients whose renal status changed from moderate to severe based on confirmed estimated GFR values. The glipizide dose was 2.5 mg once daily and could be titrated up to 10 mg twice daily. The primary efficacy endpoint was the mean change from baseline in A1C. The primary safety endpoint was the incidence of adverse events of symptomatic hypoglycemia, or dangerously low blood sugar levels.

At the end of the study, blood glucose levels dropped to a similar extent in patients in both groups. Patients receiving sitagliptin were less likely to experience hypoglycemia than patients receiving glipizide (6.2 percent vs. 17.0 percent). Also, patients who took sitagliptin tended to lose a small amount of weight, while most patients who took glipizide experienced a slight weight gain.

# Industry Spotlight

## Vytorin for CKD?

Around press time, news appeared that a drug once used to lower cholesterol was showing promise for patients with chronic kidney disease (CKD).

The drug, called Vytorin – a combination of cholesterol-lowering drugs simvastatin and ezetimibe, ran into trouble when it was discovered in trials that the drug wasn't more effective than simvastatin alone, National Public Radio reported online. Then reports surfaced through a study that suggested Vytorin raised the risk of cancer slightly, but a U.S. Food and Drug Administration analysis failed to find any increase in cancer in a new study, according to NPR.

Now a new study submitted to the FDA by Vytorin maker Merck from the SHARP (Study of Heart and Renal Protection) is presenting data that says the agency should approve a new use for the drug (http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/UCM277652.pdf) The data showed enough merit to warrant a discussion at the Nov. 2 meeting of the FDA Endocrinologic and Metabolic Drugs Advisory Committee.

This new study's data has provided the basis for Merck to receive a hearing, because Vytorin shows indications that it reduces the risk of major cardiovascular events in CKD. In particular, Vytorin, compared with placebo, significantly lowered the risk of coronary revascularization, and major atherosclerotic events, as well as the risk of ischemic stroke.

The FDA researchers who reviewed the SHARP data say that Vytorin "cut kidney disease patients' heart-related problems by 16 percent compared with placebo," CBS/AP reported. Results were different when patients were on dialysis. Dialysis patients only had a 6 percent drop in heart problems, compared with a 22 percent drop for CKD patients who weren't on dialysis.

The FDA reviewers also addressed the cancer question in their report to the advisory panel: "Risk of cancer did not increase consistently over time with longer use of ezetimibe/simvastatin, as would be expected if a drug caused cancer or promoted the growth of pre-existing cancers," they wrote.

Chronic kidney disease, which affects about 14 percent of the U.S. population, raises the risk of developing heart disease or having a stroke, Reuters noted. Patents on Vytorin and Zetia (the ezetimibe part of Vytorin) both expire in 2017.

## Turnabout Is Fair Play

DaVita, the second largest provider of dialysis services in North America, is acquiring its first operations in Europe—in Germany.

What makes the deal particularly interesting is that Germany is the headquarters of the largest provider of dialysis services and products worldwide. Fresenius Medical Care is based in Bad Homburg, Germany. Fresenius North America is well established, but DaVita is just starting to get its feet wet across the oceans.

DaVita already has expanded into Asia, providing dialysis services in Singapore and in Bangalore, India, and has an agreement to develop and operate dialysis clinics in Malaysia, according to the company web site.

"The time is right for DaVita to extend to Europe and Asia," said DaVita chairman and CEO Kent Thiry. "Our patient-centric care model is being well received on both continents."

Denver-based DaVita is taking it slowly. The *Denver Post* reports that Thiry is cautiously optimistic—and candid—about the new expansion plans. "If I was smarter, we would have started this several years ago," Thiry said. "Over the next 10 years, we intend to deliberately and thoroughly create a material global presence. … We'll make some mistakes, since we're new at it."

## Acquisition Particulars

DaVita dialysis services is now reaping the benefits of its acquisition of a rival firm, DSI Renal.

In the third quarter of 2011, DaVita reported a higher profit because of new revenue streams from its acquisition. According to Associated Press (AP), for the quarter that ended September 30, DaVita earned $135.3 million, an improvement over the $119.4 million for the same time period last year. The company's revenue increased 9.5 percent to $1.8 billion for the period.

At the close of the quarter, the company had 1777 outpatient dialysis centers serving roughly 138,000 patients. The company acquired 113 new centers with its purchase of DSI Renal and divested 28 centers to complete the acquisition.

The company reiterated its expected 2011 income guidance of between $1.1 billion and $1.2 billion.

On the downside of business, however, the company noted that it expected to get subpoenaed by federal investigators looking into payments made to the company

for dialysis services in New York State's Medicaid program. This would add to subpoenas in recent years from U.S. Justice Department staff in Missouri and Colorado and Health and Human Services officials in Texas. The New York investigation will examine payments for infusion drugs for dialysis that are covered by the state's Medicaid system, used by the poor and uninsured.

In a smaller bit of acquisition news, there is currently debate in Vermont, which is also playing out around the country, as established dialysis clinics in smaller markets sell off to larger companies that could run them more efficiently. In Vermont, the sale of five dialysis clinics to Fresenius may bring in an estimated $26 million to the state's largest hospital.

Fletcher Allen Health Care operates the clinics at a loss. Officials there say that the sale of the clinics to Fresenius Medical Care will let the Fletcher Allen hospital continue to offer a necessary service for patients in a more cost-effective way, according to Vermont Digger, a journalism web site.

Representatives of the Vermont Federation of Nurses and Health Professionals are critical of the proposed selloff. They say that the sale could worsen quality of care for patients and decrease wages for hospital workers who may staff those clinics.

Fresenius is applying for approval from the state to purchase the clinics. Vermont Digger reported that the state nurses' union is concerned about public input in the state approval process, because an act passed in the most recent legislative session eliminated the Public Oversight Commission.

In 2010, Fletcher Allen publicly announced it would sell five clinics to Bio-Medical Applications of New Hampshire, Inc., which is a subsidiary of Fresenius Medical Care North America.

# ASN Partners to Fund Research for Rare Nephrotic Syndrome Disease

The American Society of Nephrology (ASN) has partnered with The Halpin Foundation since 2007, sponsoring an annual research grant for new investigators focusing on membranous nephropathy (MN). "When we began our collaboration, there was very little funding in membranous research," says Joan Halpin, founder and president of The Halpin Foundation. "The partnership with ASN highlighted the disease and encouraged young investigators to pursue MN research."

The Halpin Foundation strongly supports collaboration in research in autoimmune, kidney, and genetic disorders. It was one of the primary sponsors of this year's Membranous Nephropathy International Conference in Bergamo, Italy, at the Mario Negri Institute (having also sponsored the conference in 2006). Mrs. Halpin also represents the foundation on the steering committee of the Nephrotic Syndrome Study Network (Neptune).

The Halpin Foundation-ASN Research Grant has sponsored a number of exciting projects, including, most recently, "Direction of anti-phospholipase A2 receptor autoantibodies in idiopathic membranous nephropathy," by Laurence H. Beck, Jr., MD, PhD. Along with David M. Salant, MD, Dr. Beck contributed to the breakthrough discovery that the soluble phospholipase A2 receptor is the elusive antigen responsible for the majority of immune-mediated membranous disease.

In 2012, ASN will begin a new partnership with The NephCure Foundation. The NephCure Foundation-ASN Research Grant, also for new investigators, will fund research focusing on focal segmental glomerulosclerosis (FSGS) or nephrotic syndrome. "NephCure is pleased to partner with ASN and strongly supports the goals of its Career Development Grants for New Investigators Program," says NephCure Research and Education Manager Marilyn Hailperin.

"With this partnership, we increase focus and funding on glomerular disease and hopefully will attract more young researchers to this area of investigation," Ms. Hailperin adds. The NephCure Foundation is the only organization committed exclusively to supporting research seeking the cause of FSGS and nephrotic syndrome, improving treatment, and finding a cure.

ASN provides more than $3 million each year for research grants. In addition to The Halpin Foundation-ASN Research Grant and The NephCure Foundation-Research Grant, the Society offers research grants for new investigators, bridge funding for established investigators, research fellowships, and stipends for medical student research. "ASN is committed to providing a robust research grants program to ensure the success of the next generation of nephrologists and kidney researchers," asserts ASN President Ronald J. Falk, MD, FASN.

The deadline to apply for The Halpin Foundation-ASN Research Grant and The NephCure Foundation-ASN Research Grant is Friday, January 27, 2012. For more information on the ASN grants program, please visit www.asn-online.org/grants_and_funding/.



## New Funding Opportunity for Fellows

Starting in July 2012, the **ASN Research Fellowship Program** will foster the training of fellows highly motivated to make contributions to the understanding of kidney biology and disease. Each ASN Research Fellowship provides $50,000 per year for up to two years.

"Together, we must support a robust cadre of young investigators who will bring enthusiasm, intelligence, and ingenuity to our scientific challenges. The future of nephrology depends on constant innovation, on helping the next generation succeed, and on our collective effort to better understand kidney disease," says ASN Past President Joseph V. Bonventre, MD, PhD, FASN.

The deadline to apply for ASN Research Fellowships is Friday, January 27, 2012, at 4 p.m. EST.

For more details, please visit the ASN Research Fellowship Program website at http://www.asn-online.org/grants_and_funding/research-fellowships-details.aspx.

ASN LEADING THE FIGHT AGAINST KIDNEY DISEASE

# ASN Membership

## Member Benefits

### Education

ASN provides member discounts for a variety of exceptional educational activities:

- **ASN Highlights 2012** summarize, critique, and integrate key Kidney Week 2011 presentations in powerful two-day courses (presented in four locations across the United States).
- **Board Review Course and Update 2012** prepares nephrologists for the ABIM initial certification and maintenance of certification examinations and provides a comprehensive update for the practicing nephrologist.
- **ASN Kidney Week 2012** remains the world's premier gathering of kidney professionals presenting advances in treatment, research, and education.

**Abstract Submission** allows members to submit and sponsor abstracts for oral and poster presentation at ASN Kidney Week.

**ASN In-Training Examination for Nephrology Fellows** helps identify gaps in training and is similar in design to the ABIM certifying examination.

**Online Geriatric Nephrology Curriculum** provides essential education in geriatric nephrology.

### Grants & Funding

ASN funds more than $3 million annually for research and travel grants.

### Membership Services

ASN supports several initiatives to enhance members' careers:

**Membership Directory**
Access ASN member contact information through a searchable online directory.

**ASN Committees and Advisory Groups**
Volunteer to serve on an ASN committee and help guide the future direction of the society.

**ASN Career Center**
Advertise jobs, review candidates, post resumes, apply for positions, and reach employers and recruiters—all through one website.

**Fellows of the American Society of Nephrology (FASN)**
Achieve FASN status and have your outstanding credentials, achievements, and scholarship recognized.

### Policy and Public Affairs

Stay informed about how current and future legislation affects nephrology and improve treatment, research, and education by volunteering to help ASN advocate on behalf of members and their patients.

### Publications and Communications

Receive all ASN publications and communications in print and online:

***Journal of the American Society of Nephrology (JASN)***
The leading kidney journal in the world.

***Clinical Journal of the American Society of Nephrology (CJASN)***
The primary resource for cutting edge clinical research in nephrology.

***Nephrology Self-Assessment Program (NephSAP)***
An essential tool for earning continuing medical education credits and maintenance of certification points.

***ASN Kidney News***
A news magazine offering exceptional coverage of current issues of interest to kidney professionals.

***ASN Kidney News Podcasts***
A bi-monthly audio program providing in-depth discussions of topics that interest and challenge the global kidney community.

***ASN Kidney Daily***
A daily email collating kidney-related news from medical journals, newspapers, and other media.

***ASN Social Media***
Connect, engage, and stay informed through the ASN Facebook, Twitter, and YouTube sites.

## Member Categories

### Active Member ($315)

An individual who holds an MD, a PhD, or the equivalent, resides in North or Central America, and fulfills at least one of the following criteria:

- Completion of research or clinical training in nephrology.
- Specialized training in nephrology during residency or other relevant postgraduate education.
- Publication of at least one peer-reviewed paper in nephrology.
- Experience as a specialist in kidney disease and related conditions.

### Corresponding Member ($315)

An individual who meets the criteria for active membership but resides outside North or Central America.

### Affliate Member ($315)

An individual in nephrology or allied fields who is not eligible for Active or Corresponding membership.

### Medical Student/Resident (FREE)

*VERIFICATION REQUIRED*

Enrolled in an accredited Internal Medicine, Pathology, or Pediatric residency, MS4 status, or enrolled in Medical-Scientist Training Program.

### Women in Neprhology (WIN) ($75)

WIN provides access to senior women in the field of nephrology who mentor more junior physicians and scientists. **Please note that WIN membership is separate from ASN membership.**

### Retired Member (FREE)

A senior member retired from clinical, research, and teaching activities who wants to receive print and online subscriptions to ASN publications.

Only **Active, Corresponding,** and **Affiliate** members may use the online membership system. To enroll in the Retired, Fellow-in-Training and Medical Student/Resident categories, please download and print the membership form from the ASN website or contact ASN Membership Director Pamela Beard at 202-640-4668 or pbeard@asn-online.org.

## Join or Renew ASN membership online at www.asn-online.org/membership/

# Policy Update

## Medicare Finalizes Changes to ESRD Quality Program, Releases Accountable Care Organization Rules

By Rachel Shaffer

The Centers for Medicare and Medicaid Services (CMS) last month released its long-awaited rule finalizing changes to the End-Stage Renal Disease Program (ESRD) payment system and the Quality Incentive Program (QIP). The final rule outlined modifications to the ESRD prospective payment system (PPS) for 2012, and it cemented adjustments—as well as major additions—to the QIP program across 2013 and 2014.

The ESRD PPS/QIP final rule came on the heels of another piece of CMS regulation that has been much anticipated by the medical community: the Accountable Care Organization (ACO) final rule, released in late October. The ASN Public Policy Board and the ASN ACO Task Force began analyzing the final rules upon their release to identify their implications for the ESRD program and the practice of nephrology.

### ESRD, PPS, and QIP final rule

Taking effect January 1, 2012, the ESRD QIP is the first-ever mandatory pay-for-performance (also known as value-based purchasing) program in the Medicare system. Having finalized the parameters for the first year of the QIP in December 2010, in this final rule the CMS finalized a key component of the second year of the program, 2013, and broad changes to 2014, the third QIP year (Table 1).

Perhaps the most controversial change to the QIP in 2013 is the decision by the CMS to eliminate the quality measure for anemia management at the low end of the hemoglobin spectrum: percentage of Medicare patients at a facility whose hemoglobin levels were greater than 12 g/dL. Many in the nephrology community, including the ASN, raised concerns that the absence of any minimal safeguards for low hemoglobin levels could be problematic for patients, potentially leading to compromised quality of life and functional status or even necessitating otherwise avoidable blood transfusions, and they stated these concerns in comments on the proposed rule. The Congressional Kidney Caucus recently expressed similar concerns about retiring the measure in a letter to the CMS on October 13, 2011.

The CMS acknowledged these concerns in the final rule but cited its own recent National Coverage Decision for ESAs for Treatment of Anemia in Adults, which concluded that the CMS could not identify a low hemoglobin target level that is safe for all patients, as part of its rationale for eliminating the measure. The CMS also noted that it conversed with the U.S. Food and Drug Administration, which agreed that retiring the measure is consistent with its recently revised label for ESAs. Consequently, in 2013 the QIP will comprise just two, equally weighted, quality measures:

- Percentage of Medicare patients with a hemoglobin level >12.0 g/dL (national performance rate = 14 percent of patients)
- Percentage of Medicare patients with a urea reduction ratio (URR) >65 percent (national performance rate = 97 percent of patients)

The CMS will also ratchet up the standards that facilities must achieve to avoid a payment reduction. In 2013, facilities must score the full possible 30 points—a change from QIP year 2012, when scoring 26 points would prevent any payment reductions. The performance year (the year from which data will be analyzed to develop scores in 2013) is 2011.

In 2014, the CMS will retain the 2012 measures and add four new measures, bringing the total to six. The one clinical measure added is a combined measure: vascular access type, examining 1) catheter reduction and 2) arteriovenous fistula use. Three of the four new measures, listed below, are reporting-only (yes/no) measures:

- Report dialysis infections to the Centers for Disease Control and Prevention NHSN Dialysis event reporting system.
- Administer ICH Consumer Assessment of Health Policy Study.
- Monitor mineral metabolism (phosphorus and calcium levels).

In the proposed rule, the CMS suggested, but did not finalize, the following three measures for 2014:

Control and Prevention NHSN Dialysis event reporting system.

- Kt/V (which would have replaced the URR measure of dialysis adequacy): The CMS noted its intention to finalize the Kt/V measures in the future once it could "ensure the validity and consistency" of Kt/V data.
- Standardized Hospitalization Ratio–Admissions (SHR): The CMS did not finalize the SHR measures because of concerns articulated by the ASN in its comment letter that the measure might not reflect hospitalizations related to ESRD care and could increase the potential for cherry-picking.
- Vascular access infections (VAI): The CMS concluded that the claims-based data the measure would be based on are not detailed enough to accurately reflect care.

The CMS finalized the bulk of its proposal to adopt a new performance scoring methodology for 2014. The performance of facilities will be determined by the higher of an "Achievement" score (worth up to 10 points) or an "Improvement" score (worth up to 9 points) for clinical measures, with a slightly different approach for the vascular access type. The benchmark to achieve full points in measures on both scales is set as the 90th percentile of all performers nationwide (a change from the proposed rule, in which the CMS proposed to set the benchmark as the mean of the top decile of all performers). More detailed information about the scoring is available on the ASN's public policy webpage (http://www.asn-online.org/policy_and_public_affairs/esrd-bundling.aspx).

### Accountable Care Organization final rule

The 696-page ACO final rule creates more generous opportunities for providers to share in savings, relaxes the EHR meaningful use criteria, and reduces the number of quality measures that ACOs must achieve from 65 to 33. And these are just some of the final rule's many changes to the ACO program compared with the original proposed rule (Table 2).

The CMS received more than 1300 comments on the proposed rule—including from ASN—most of which criticized the proposed program as being too burdensome, being too prescriptive, and offering few financial benefits for participating providers. The CMS responded to many of these concerns in the final rule.

The ASN ACO Task Force is in the

**Table 1. Evolution of the Medicare ESRD program, 2012–2014**

| Consequence Year | 2012 | 2013 | 2014 |
|---|---|---|---|
| Performance Year | 2010 | 2011 | 2012 |
| Quality measures and performance standards | • Hemodialysis adequacy (URR)<br>• Hemoglobin < 10 g/dL: 2% of patients<br>• Hemoglobin > 12 g/dL: 26% of patients | • Hemodialysis adequacy (URR)<br>• Hemoglobin > 12 g/dL: 14% of patients | • Hemoglobin > 12 g/dL<br>• Hemodialysis adequacy (URR)<br>• Vascular access type<br>• Dialysis event reporting (y/n)<br>• Patient surveys – ICD CAHPS (y/n)<br>• Mineral metabolism monitoring (y/n) |

**Abbreviations: CAHPS = Consumer Assessment of Health Policy Study; ICD = International Classification of Diseases; URR = urea reduction ratio.**

process of analyzing the potential opportunities and challenges the lengthy final rule poses for nephrology care, including assessing how nephrologists may interact with ACOs, and it will provide a detailed assessment to ASN members.

Although the final rule included important changes to the financial risks, timeline, and participatory requirements, it seems that few of the modifications addressed the nephrology-specific concerns raised by the ASN and others in the kidney community, or the specialty-specific concerns of other subspecialists. The final rule made it clear that the CMS envisions the ACO program as exclusively focused on primary care. A significant number of the potential pros and cons articulated by the ASN in its comment letter on the proposed rule remain.

Some in the kidney community had requested that the CMS allow renal-specific ACOs—a recommendation that the CMS declined to adopt. Similarly, it rejected suggestions from the cancer community for an oncology-specific ACO. In its comments, the ASN cautioned that as proposed, ACOs may not be well positioned to appropriately care for patients receiving dialysis or those who have a recent kidney transplant, recommending that these patient populations be excluded from attribution to an ACO. Of particular concern to the ASN was that some of the quality measures may not be applicable to dialysis patients and, in some cases, could actually prove harmful and unnecessarily expensive to those patients.

The CMS did not directly respond to these concerns but stated its belief that "adopting restrictions or exclusions on beneficiaries with certain conditions or utilization patterns from assignment to ACOs under the Shared Savings Program would be inappropriate." The one measure directly pertinent to kidney disease proposed by the CMS (diabetes mellitus: urine screening for microalbumin, or medical attention for nephropathy in diabetic patients) was among the 32 measures eliminated in the final rule.

Nephrologists and other specialists who wish to join an ACO can have patients attributed them and their ACO based on provision of primary care, according to the final rule. Patients will be attributed to ACOs in a stepwise fashion, first to the ACO of a primary care provider that provides the plurality (not majority) of primary care G-codes to a patient. Secondarily, a patient may be assigned to the ACO of a specialist (including a nephrologist) who provides the plurality of primary care G-codes to a patient, if that patient is not receiving primary care services from a primary care provider (whether or not affiliated with an ACO).

Another important change finalized by the CMS is that the historical benchmark expenditures against which ACO performance will be judged will be calculated to account for certain high-cost patient population categories, including ESRD and dual-eligible Medicare and Medicaid beneficiaries.

Overall, the CMS estimates that 50 to 270 organizations will form an ACO, generating $470 million in net federal savings for calendar years 2012 through 2015. Please visit the ASN public policy page for more information about ACOs and their potential effect on patients with kidney disease and on the practice of nephrology.

**Table 2. Key features of the ACO final rule**

| Feature | Detail |
|---|---|
| Providers eligible to start an ACO | • Physician practices<br>• Network of physicians<br>• Physician/hospital joint venture<br>• Hospitals employing physicians<br>• Critical Access Hospitals<br>• Federally Qualified Health Centers (added in final rule)<br>• Rural Health Clinics (added in final rule) |
| Patient attribution methodology | Patients preliminarily prospectively attributed to an ACO based on prior healthcare utilization data, with final reconciliation at the end of a performance year based on which patients the ACO actually served |
| Quality measures | 65 quality measures in five domains reduced to 33 measures in four domains |
| Evidence-based medicine | ACOs are required to develop, implement, and document use of evidence-based medicine or clinical practice guidelines and processes |
| Patient choice | ACOs must notify patients that they are receiving care from providers that participate in an ACO; however, patients are free to seek care outside the ACO from other providers |
| Electronic health records | Eliminated proposed requirement that at least 50 percent of participating physicians be certified "meaningful users" of EHR |
| Shared savings | ACOs can share cost savings (at either 50 percent or 60 percent) from the first dollar saved, rather than after reaching a 2 percent threshold as proposed |

**Abbreviations: ACO = Accountable Care Organization; EHR =electronic health record.**

# ACOs and Nephrology

By Caroline Jennette

Often compared to the health maintenance organizations (HMOs) of the past, accountable care organizations (ACOs) have taken the spotlight as a new model of health care delivery and payment under the Affordable Care Act. Mark McClellan, MD, PhD, former administrator of the Centers for Medicare & Medicaid Services and current director of the Engelberg Center for Health Care Reform, spoke about ACOs at the 2011 Kidney Week Christopher R. Blagg Endowed Lectureship in Renal Disease and Public Policy.

The main tenet of ACOs is to provide high quality (and low cost), coordinated care with payments based on the value of services versus quantity. While fee for service (FFS) payment systems can be used for ACOs, McClellan speculates that bundled payments for services will grow, especially with continuing bipartisan political support. He envisions a potential for savings through quality improvement with payments moving away from FFS and toward case coordination and case management fees driven by performance measures.

Physicians have an important role in helping design better systems of health care delivery, McClellan said. He called on nephrologists to continue to provide input, and ultimately be "bellwethers" for reforming care in other parts of the healthcare system.

The Mayo Clinic's "Re-Engineering Dialysis" or RED program uses the principals of accountable care—aligning financial incentives, collaboration between providers, flexibility in care models, and partnering with patients, said Amy Williams, MD, associate professor of medicine at Mayo Clinic. The nephrology team at Mayo is working to better understand patient needs as a way to increase patient capacity to deal with their illness and thus decrease the burden of disease.

Mark Pauly, PhD, a health economist and professor of health care management at the University of Pennsylvania, took a more pessimistic view on ACOs. He argued that health care costs are being driven by an aging population, improvements in technology, and rising wages for health care providers, not by the costs of delivering FFS care. Pauly said that successful coordinated care models (e.g., Kaiser Permanente) have been very hard to reproduce. He forecasts that ACOs will eventually convert to de facto capitation. He suggests that instead of removing FFS as the dominant system of payment, it may be possible to take a market-based approach by titrating FFS payments down until payments are truly aligned with the appropriate number of services.

Williams and Pauly spoke at the public policy forum at Kidney Week 2011.

# ASN Highlights

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ASN LEADING THE FIGHT AGAINST KIDNEY DISEASE

# Journal View

## As eGFR Goes Down, Coronary Artery Calcium Goes Up

Worsening chronic kidney disease (CKD) is linked to increasing coronary artery calcification (CAC) independently of traditional risk factors, reports a study in the *American Journal of Kidney Diseases*.

The study included a multiethnic sample of CKD patients from the Chronic Renal Insufficiency Cohort Study. All patients underwent coronary calcium scanning with calculation of the Agatston CAC score. The association between estimated GFR (eGFR) and CAC was assessed.

The results showed a strong graded association between decreased kidney function and increased CAC. On unadjusted analysis, the odds ratio for having a higher CAC score increased from 1.68 at an eGFR of 50 to 59 mL/min/1.73 $m^2$ to 2.82 at an eGFR less than 30 mL/min/1.73 $m^2$. The association was somewhat weakened on multivariate analysis but was still significant: odds ratio 1.53 at an eGFR less than 30 mL/min/1.73 $m^2$. The association was independent of traditional risk factors and albuminuria.

Coronary artery calcium is a risk factor for fatal and nonfatal cardiovascular events, but its significance in the CKD population is unclear. This cross-sectional study of CKD patients finds that lower levels of kidney function are independently associated with higher CAC scores.

The results may have important implications for the care of patients with CKD, especially in light of recent guidelines calling for vascular/valvular calcification to be considered in individualized treatment. The ongoing study will collect data on how CAC affects the rates of cardiovascular and renal events in patients with CKD. [Budoff MJ, et al. Relationship of estimated GFR and coronary artery calcification in the CRIC (Chronic Renal Insufficiency Cohort) study. *Am J Kidney Dis* 2011; 58:519–526.]

## Trial Questions the Benefits of Frequent Nocturnal Dialysis

Nocturnal home dialysis performed six nights weekly does not improve mortality or other outcomes compared with conventional hemodialysis three times weekly, concludes a trial in *Kidney International*.

In the Frequent Hemodialysis Network Nocturnal Trial, 87 patients were randomly assigned to undergo conventional hemodialysis performed three times weekly or nocturnal home dialysis performed six times weekly. Single-use high-flux dialyzers were used for all sessions.

The patients assigned to frequent nocturnal home dialysis had a mean dialysis weekly standard of 4.72 $Kt/_{Vurea}$, compared with $Kt/_{Vurea}$ in the conventional dialysis group. The average number of weekly treatments was about 75 percent higher, and the average weekly treatment time was more than twice as high.

Nevertheless, there was no significant difference in either of two coprimary outcomes: death or left ventricular mass, measured by magnetic resonance imaging; or death or SF-36 RAND Physical Health Composite. Frequent nocturnal dialysis was associated with better control of hyperphosphatemia and hypertension, with a trend toward increased vascular access interventions. Cognitive function and hospitalization were similar between groups.

Previous small studies have suggested that more frequent hemodialysis sessions, performed in the patient's home at night, might have clinical benefits. The new trial finds few significant differences in outcomes with frequent nocturnal home dialysis compared with conventional hemodialysis. The authors note some key limitations of their study, including small sample size and reduced adherence to prescribed dialysis in the group receiving frequent nocturnal dialysis. [Rocco MV, et al. The effects of frequent nocturnal home hemodialysis: the Frequent Hemodialysis Network Nocturnal Trial. *Kidney Int* 2011; 80:1080–1091.]

## Why Do Young Transplant Patients Have Poor Outcomes after Transfer to Adult Care?

The increased rate of adverse outcomes in adolescent and young adult patients transferred from pediatric to adult care appears to reflect factors other than the transfer itself, suggests a report in *BMC Nephrology*.

The researchers analyzed graft survival in three Canadian cohorts of young patients undergoing kidney transplantation at affiliated pediatric and adult hospitals from 1990 through 2009. Transplantation was performed by the same surgeons even though the two sites were geographically separate. Children are transferred from the pediatric to the adult medical team at about age 18.

Outcomes for 49 pediatric patients undergoing transplantation at the pediatric hospital were compared with outcomes for two cohorts undergoing transplantation at the adult hospital: 48 young adults 18 to less than 25; and 124 adults 25 to 35. Death-censored graft survival was assessed by a multivariate Cox model.

There was no significant difference in graft survival between the pediatric and young adult cohorts. However, survival was significantly better in the adult cohort. The three cohorts had similar rates of admitted nonadherence.

Transfer from the pediatric to the adult center occurred within a relatively narrow age window of 16.6 to 20.9 years. However, the time since transplantation varied substantially: range 0.9 to 11.0 years. Graft function at the time of transfer was also variable. Six of 18 pediatric patients had a serum creatinine greater than 180 µmol/L at transfer; all of these grafts eventually failed.

Addressing the concern that pediatric transplant patients transferred to adult centers are at increased risk for graft loss, the study's findings suggest that these poor outcomes may reflect advanced graft dysfunction rather than the transfer itself. Young transplant recipients between age 11 to 14 and age 25 are a "unique and vulnerable cohort" in need of effective and consistent management strategies, the researchers write. [Kiberd JA, et al. Kidney transplant survival in pediatric and young adults. *BMC Nephrol* 2011; 12:54.]

## How Often Should Diabetic Patients See Their Primary Care Doctor?

Making primary care visits every 2 weeks leads to faster achievement of glucose, blood pressure, and cholesterol targets in patients with diabetes, reports a study in the *Archives of Internal Medicine*.

The retrospective study included 26,496 patients with diabetes receiving primary care at two Boston hospitals between 2000 and 2009. The frequency of primary care encounters, assessed from notes in the medical records, was analyzed as a predictor of time to achievement of target levels of hemoglobin A1c, (HbA1c), blood pressure, and LDL cholesterol (LDL-C).

Primary care visits every 1 to 2 weeks were associated with shorter times to reaching all three targets compared with visits every 3 to 6 weeks. For patients not receiving insulin, the HbA1c target of less than 7.0 percent was met at a median of 4.4 months with visits every 1 to 2 weeks compared with 24.9 months for visits every 3 to 6 weeks. For patients using insulin, the medians were 10.1 versus 52.8 months.

Shorter intervals were also associated with faster achievement of a blood pressure under 130/85 mm Hg (1.3 versus 13.9 months) and LDL-C less than 100 mg/dL (5.1 versus 32.8 months). On multivariate analysis, doubling the time between visits increased the time to reaching target HbA1c by 35 percent in patients not using insulin and by 17 percent in those using insulin. Doubling the time between visits also increased the time to lowering blood pressure by 87 percent and time to lowering LDL-C by 27 percent. In general, no further reduction in time to reaching targets was achieved at intervals of less than 2 weeks.

The results suggest that more frequent primary care visits may shorten the time to achieving key clinical targets for patients with diabetes. There is a strong dose–response effect of visit frequency on all three outcomes evaluated. The effect remains significant even after treatment intensification is accounted for. [Morrison F, et al. Encounter frequency and serum glucose level, blood pressure, and cholesterol level control in patients with diabetes mellitus. *Arch Intern Med* 2011; 171:1542–1550.]

## Dialysis Is Starting Earlier, Study Finds

From the late 1990s to the late 2000s, long-term dialysis was initiated an average of nearly 150 days earlier, according to a study in the *Archives of Internal Medicine*.

Trends in the timing of initiation of long-term dialysis were assessed by use of information from the U.S. Renal Data System end stage renal disease registry. Information on estimated GFR (eGFR) at the time of the first long-term dialysis treatment was modeled for patients who started dialysis in 1997 versus those who began dialysis in 2007. Data from an integrated health care system were used to assess the predialysis eGFR slope.

Dialysis was initiated a mean of 147 days earlier in 2007 than in 1997, after differences in patient characteristics were taken into account. The difference was fairly consistent across most patient subgroups but was largest for patients 75 or older: mean 233 days. The mean eGFR before dialysis increased from 6.8 mL/min/1.73 $m^2$ for those starting dialysis in 1997 to 9.9 mL/min/1.73 $m^2$ for those starting dialysis in 2007.

As reflected by the new study, there is a trend toward starting long-term dialysis at higher rates of eGFR. The results suggest that patients in the United States are starting dialysis about 5 months earlier on average, and nearly 8 months earlier for patients 75 or older. "In the absence of strong evidence to suggest that earlier initiation of long-term dialysis is beneficial, these findings call for careful evaluation of contemporary dialysis initiation practices in the United States," the researchers write. [O'Hare AM, et al. Trends in timing of initiation of chronic dialysis in the United States. *Arch Intern Med* 2011; 171:1663–1669.]

## Survival Advantage of Black Dialysis Patients Limited to Older Adults

Compared to white patients, risk of death is lower for black dialysis patients over age 50 but higher for black patients in younger age groups, reports The Journal of the American Medical Association.

The researchers analyzed data on 1,330,007 patients with incident end-stage renal disease (ESRD) patients captured by the U.S. Renal Data System between 1995 and 2009. Multivariate age-stratified Cox proportional hazards and competing risk models were used to compare risk of death for black and white patients. Median potential follow-up was 6.7 years.

Overall mortality was lower in black patients than white patients: 57.1 percent versus 63.5 percent, adjusted hazard ratio (HR) 1.93. However, on age-stratified analysis treating kidney transplantation as a competing risk, mortality was higher for black patients in younger age groups. For those aged 18 to 30 years, mortality was 27.6 percent for black patients versus 14.2 percent for white patients: HR 1.93. This racial disparity remained significant from age 31 to 40 years, 37.4 percent versus 26.8 percent, HR 1.46; and from 41 to 50 years, 44.8 percent versus 38.0 percent, HR 1.12.

At age 51 to 60 years, the pattern reversed, with mortality of 50.9 percent for black patients and 51.5 percent for white patients: HR 0.93. This difference remained significant at older ages, with adjusted HRs of 0.87 from age 61 to 70, 0.85 from age 71 to 80, and 0.87 at age 80 and older.

Studies have consistently reported longer survival for black dialysis patients, compared to their white counterparts. The new study suggests that this survival advantage is limited to patients older than 50; in younger age groups, survival is lower for black patients than white patients. More study is needed to explore the reasons for the higher risk of death among young black patients on dialysis. [Kucirka LM, et al: Association of race and age with survival among patients undergoing dialysis. *JAMA* 2011; 171: 620–626].

## No Increase in Birth Defects with First-Trimester ACE Inhibitors

Exposure to angiotensin-converting enzyme (ACE) inhibitors during the first trimester of pregnancy does not increase the risk of congenital malformations, reports the *British Medical Journal*.

The researchers analyzed data on 465,744 mother–infant pairs in the Kaiser Permanente Northern California region between 1995 and 2008. Linked clinical and pharmacy data were used to evaluate the relationship between maternal ACE inhibitor use during the first trimester and the risk of congenital malformations in live-born offspring.

The rate of ACE inhibitor use by pregnant women dropped sharply from 0.9/1000 in the first trimester to only 0.1/1000 in the second or third trimester. The prevalence of treatment with other antihypertensive agents was 2.4/1000 and 26.5/1000, respectively.

Women who used ACE inhibitors during the first trimester had a 3.9 percent rate of congenital heart defects in their offspring compared with 1.6 percent for women without hypertension or antihypertensive medication use. No significant association extisted after adjustment for age, ethnicity, parity, and obesity. The rate of congenital heart defects among infants born to mothers using other antihypertensive drugs was 2.6 percent—not significantly different from the 2.4 percent rate for women who had hypertension but did not take antihypertensive drugs.

The ACE inhibitors have well-recognized fetal toxic effects during the second or third trimester. Addressing concerns raised by recent studies, the new results show no significant increase in congenital malformations associated with first-trimester exposure to ACE inhibitors. Any apparent increase in risk likely reflects the effects of hypertension itself rather than of antihypertensive medications. [Li DK, et al. Maternal exposure to angiotensin converting enzyme inhibitors in the first trimester and risk of malformations in offspring: a retrospective cohort study. *BMJ* 2011; 343:d5931.]



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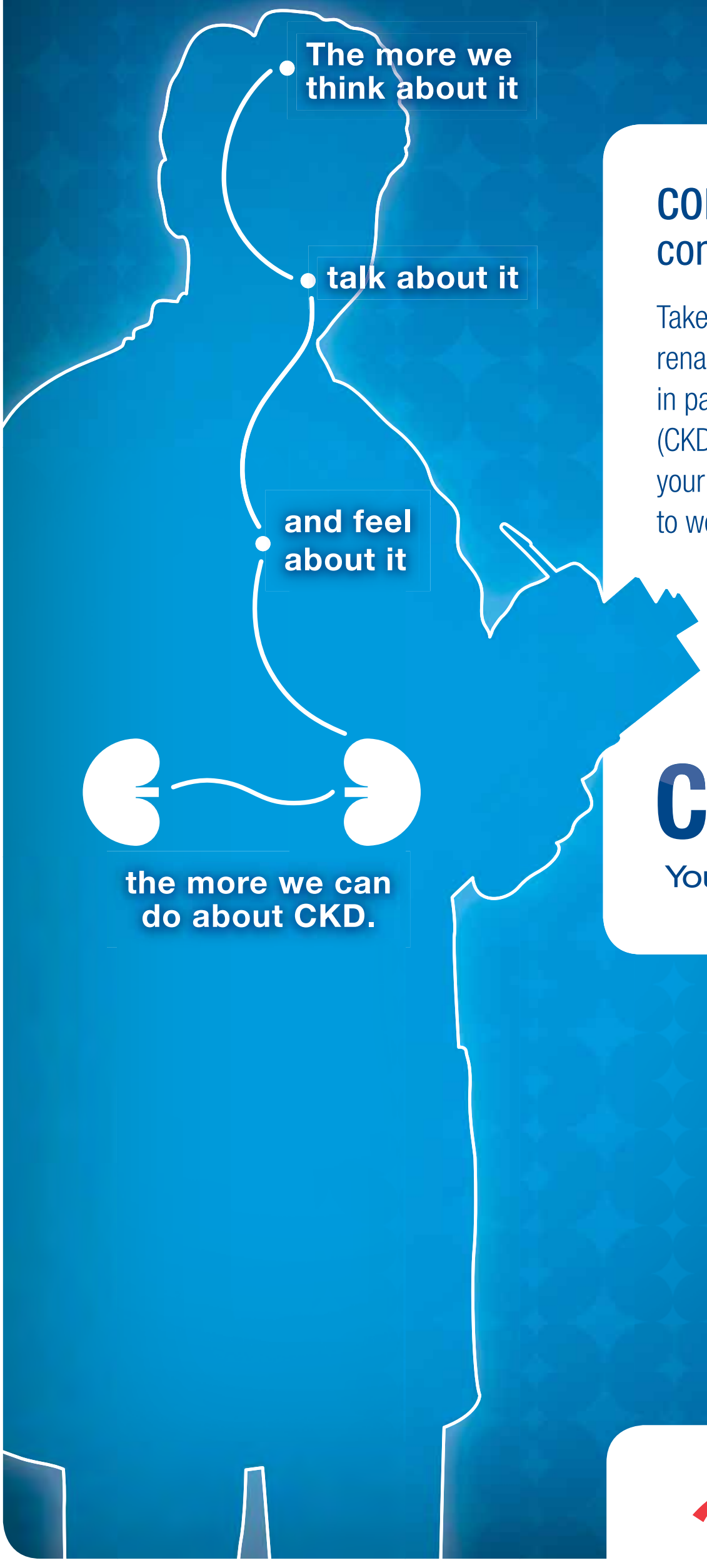


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