Safety Net Health Care Systems Can Deliver Equitable Care and Good Hypertension Outcomes

By Kurtis Pivert

Patients with CKD who rely on safety net health care systems may receive more equitable and effective care, concludes a study that compared one such system, the Community Health Network San Francisco (CHNSF), with a representative sample of the U.S. population. Delphine Tuot, MDCM, of the University of California, San Francisco, and her colleagues observed that patients with mild CKD receiving care from CHNSF demonstrated better control of hypertension among racial and ethnic minorities than a similar cohort from the National Health Examination and Nutrition Survey (NHANES) (1). Yet despite these encouraging results, Tuot also reported that African Americans have an increased risk for uncontrolled hypertension when compared to whites, even in the public health care setting. Tuot spoke at Kidney Week 2012 in San Diego.

Although the study shows the potential of systems such as CHNSF to act as front-line agents to reduce disparities of care for a population that may have higher risks for developing CKD and progression to ESRD, it also raises the question of how their success could be translated to improve hypertension control among at-risk minorities with more severe CKD.

Research has shown that racial and ethnic minorities have a higher risk for developing CKD and progressing to ESRD than whites, yet the reasons behind this are unclear. Most likely, this may be due to a combination of factors, and uncontrolled hypertension could be a major contributor to the accelerated and early rate of disease progression that these at-risk populations exhibit.

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“African Americans, with or without CKD, have a higher rate of associated conditions than Caucasians (e.g., diabetes in men and diabetes and obesity in women),” he said. They also have some congenital, behavioral, and health access factors that contribute to higher rates of uncontrolled hypertension among minorities.

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Health Reform Moves Forward

President Obama’s re-election ensures that the Patient Protection and Affordable Care Act (ACA) will continue to move forward.

The election result, following the Supreme Court decision upholding its constitutionality earlier this year, apparently removes the final obstacle to a host of provisions taking effect in just over a year—including new patient protections, marketplaces for buying insurance, and taxes and fees to pay for the law (see sidebar).

Supporters predict that Obamacare—a term coined by opponents as a pejorative but now embraced by its namesake—will grow in popularity once these provisions come into force. But the law still faces opposition and considerable uncertainty about what the next few years will bring.

The ACA’s main goal is to increase the number of Americans with health insurance coverage. According to the latest estimates from the nonpartisan Congressional Budget Office, the ACA will increase the number of people below Medicare age with health insurance coverage by 14 million in 2014 and by 29 to 30 million by 2022. That growth represents an increase from today’s 82% to 92% of the nonelderly population, but is down from estimates made before the June Supreme Court decision that upheld most of the law’s provisions, but gave states the power to opt out of the planned expansion of Medicaid.

The act’s overarching goals, if not its specifics, have been supported by a wide range of medical organizations. A greater portion of the population having insurance, which implies a greater chance for early treatment of developing conditions, should benefit patients and reduce costs, said Thomas Hosetter, MD, chair of the Planned Parenthood Federation of America’s board of directors. "The ACA is about better access to health care for those who cannot afford it and ensuring that those who receive care get the best care from qualified health professionals," Hosetter said.

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Safety Net

Continued from page 1

characteristics that increase the incidence of hypertension, including lower plasma renin activity (PRA) levels with expansion of fluid volume, and higher prevalence of salt-dependent hypertension. Other barri-
ers to controlling BP in African Americans include lack of access to medical care and poor adherence to treatment. Also, more popula-
tions of African Americans live in commu-
nities that lack safe environments for walk-
ing or exercising and less neighborhood grocery stores that may offer easy access to a fresh and healthy food supply. Because public health care delivery sys-
tems act as safety nets and deliver care for vul-
nerable populations, including minori-
ties, they have the potential to reduce dis-
patries and improve the outcomes of those who are at highest risk for kidney disease. To assess their performance in BP control, Tuot compared the prevalence and odds of uncontrolled hypertension among patients with CKD in CHNSF—an integrated health care delivery system that cares for Senegalese and other politically insured residents—with national estimates using data from NHANES.

A total of 6681 patients with CKD who received care at CHNSF between 2010 and 2012 and 3108 NHANES participants with T2DM who saw a physician between 2003 and 2010 were included in the study. Although the cohorts differed in age, racial composition, number of non-English speak-
ers, and uninsured individuals, both had similarly high rates of CKD. Prevalence of CKD was confirmed by an eGFR 15–59 mL/min/1.73 m2 or a dipstick albuminuria test result =30 mg/g, with uncontrolled hyper-
tension defined as a mean systolic BP >140 mm Hg or a mean diastolic BP >90 mm Hg. Prevalence of uncontrolled BP in the two cohorts was calculated, as well as odds ratios for uncontrolled hypertension among racial minorities as compared to whites with CKD, controlling for age, gender, insurance status, and presence of diabetes.

In mild CKD (stages 1 and 2), African Americans had higher rates of uncontrolled hypertension compared to whites. This contrasted strongly with the results from NHANES, in which odds for uncontrolled BP were 153% higher for African Americans compared to whites. In CKD stages 3 and 4, the odds for uncontrolled BP in the CHNSF were 11% higher for African Americans and 6% higher for Hispanics versus whites, compared with a 27% higher odds for blacks and 43% higher odds for those in NHANES, respec-
tively. Overall adjusted rates of uncontrolled hypertension were higher in the CHNSF cohort compared to NHANES (25.42 percent versus 21.72 percent). When strati-
ed by race, the rate of uncontrolled BP was higher for CHNSF in stage 3 and 4 CKD (28.06 percent versus 23.08 percent) but were lower for stage 1 and 2 CKD (18.00 percent versus 22.13 percent) compared to NHANES.

The results revealed that “differences in BP control among patients with CKD of different races/ethnicities were smaller in the CHNSF compared to the national av-


Health Reform

Continued from page 1

ASN’s public policy board.

“We can have some 60 percent of the pop-
culation covered, hopefully that would mean that people with chronic kidney disease could be treated earlier and more effectively, and their need for dialysis or transplantation prevented or forestalled,” Hostetter said.

One of the major ways that the ACA will improve coverage of the Medicaid eligible to include those with incomes up to 133% of the federal poverty line, for a cutoff of about $29,000 for a family of four. The Supreme Court dealt this effort a blow with its unexpected rul-
ing that states could decide whether or not they wanted to participate in the expanded program.

As of mid-November, governors of at least seven states had declared that they would not expand Medicaid (and these states generally have a higher proportion of poor and uninsured people).

States could change their positions as time went on if they didn’t like the way things were going. For instance, in 1965, according to John Poelman, senior director at Levitav Partners, a nonpartisan health care consulting group established by Mike Leavitt, a former Utah governor, Bush administration official, and head of the transition team for the Rom-

nepay campaign, Poelman said that most states implemented Medicaid within five years, but the last state, Arizona, did not do so until 1982.

Tim Jost, JD, a law professor at Wash-


Softening opposition?

Although voters in several states took sym-
bolic steps to express opposition to the law, there is evidence that opposition is softening. Alabama, Montana, and Wyo-
ming passed referenda aimed at nullifying the individual mandate to buy insurance or pay a fine. But few experts believe this can have any effect because federal law supersedes them. A similar amendment in Florida failed. Missouri passed a law that forbids the governor from setting up a health insurance exchange by executive order.

But a Kaiser Family Foundation poll taken after the election found that the prop-
portion of Americans who want to see the law repealed has dropped to a new low of 33%, the lowest number since the legisla-
tion passed and a 7% drop since August.

State exchanges

Florida Gov. Rick Scott, one of the most vocal critics of the ACA, told the Associ-
ated Press that given the election results he is willing to consider setting up a state-


Kidney care and the ACA

Kidney care is one area that illustrates the uncertainty in the essential benefit packages to be offered in policies on the exchanges. The packages will be defined mostly by each state based on their customary policies already available, but will have to meet standards for deductibles and out-of-pocket costs. Important unresolved issues include the availability of important classes of both inpatient and outpatient care, reimbursement levels for kidney transplant recipients, the interface between exchange-based insurance coverage and Medicare’s end stage renal disease program, and the treatment of living organ donors, according to Dolph Chianchiano, JD, MBA, health policy advisor to the National Kidney Foundation. Chianchiano said that federal regulators may be allowing states the latitude to design their own approaches to these issues. The National Kidney Foundation and groups like the American Medical Association have urged that the essential benefits package be modeled on Medicare Part D, which includes anti-rejection medications on its list of protected drug classes, but federal regulators have yet to give a specific response on the issue.

One way that Republican House of Representatives opponents of the law have threatened to block implementation is through the power of the purse, by withholding appropriations. How effective this tactic could be is a subject of debate, but the need to set up more federal exchanges because so many states are refusing to set up their own could require increased federal expenditures.

Michael Cannon of the libertarian Cato Institute has encouraged this approach, blogging that “Congress authorized no funds for General ‘Gallbladder’ exchanges. So Washington may not be able to impose exchanges on states at all.” Another potential area they might look to cut could be the subsidies for buying insurance.

“Restricting funding for implementation is a lever that still exists,” Leavitt Partners’ Poelman said. “But all funding of the government . . . requires both chambers to agree. The House will certainly move to restrict funding for implementing the Affordable Care Act but that will be negotiated as part of a larger funding package. When it comes down to making a final deal there will have to be compromises on both sides. It is quite likely that the administration won’t get all the money it wants to implement the law but the overall enactment won’t be halted.”

With the fiscal cliff approaching, negotiations could address almost any aspect of the budget. “The House and the Senate are going to have to get together on a whole bunch of financial issues,” said Washington and Lee’s Jost. “And the Republicans have already said they will be gunning for the Affordable Care Act through the appropriations process. Having fought this hard for the Affordable Care Act, the president is going to fight pretty hard to keep this funding there, and there aren’t a lot of places to cut [in the ACA].”

Although the election settled some questions, the coming years will still be full of uncertainty and some dislocations. Some employees may find it easier to change jobs because of the prohibition of employment based on pre-existing conditions. Those who already have coverage should be largely unaffected except for greater protections, although the possibility exists that some employers may drop coverage.

A U.S. Government Accountability Office analysis of several studies found that microsimulation studies predicted little change in employer-sponsored coverage, but surveys of employers varied widely in results. Of course, these projections come in a context in which for the past decade the share of employers offering coverage has declined and employees have been asked to pay a larger share of costs. Massachusetts has seen a small increase in employer coverage since its plan was enacted, Jost said.

Another concern is whether the health care system will be able to cope with an influx of new patients, especially with shortfalls of providers already on the horizon. A recent study in the Annals of Family Practice estimated a need for 52,000 more primary care doctors by 2025. But it said that most of these are necessitated by population growth and the aging of the population, with only 15% chalked up to the expansion of coverage from the ACA. Mehndiratta has shown creative ways of coping with the greater demand, with increased reliance on use of physician’s assistants and nurse practitioners, according to Grover of the Association of American Medical Colleges.

Research benefits

From the point of view of the kidney community, the ACA moving forward means continuity for a pair of research centers the act has already established. The Patient-Centered Outcomes Research Institute is a nonprofit with the mission of funding comparative effectiveness research—research that can be particularly difficult to fund sponsors for. ASN’s Hostetter said that nephrology is a discipline that could particularly benefit from this research. Another new agency, the Center for Medicare and Medicaid Innovation, is charged with finding new payment and delivery methods that improve quality while lowering costs. As part of this effort, Medicare has begun contracting with accountable care organizations (ACOs)—team-based efforts in which doctors and other providers coordinate care for Medicare patients. Medicare has contracted with 153 ACOs so far, but expects that 20% to double to 300 in January. ASN has weighed in with recommendations on how ACOs could provide better integrated care in kidney disease, since it is particularly suited to a team approach.

The ACA promises big changes, so the debate over it is sure to continue, but many in the kidney community say they are seeing benefits and anticipating more.

Key Milestones in Implementation of the Affordable Care Act

The Affordable Care Act is designed to increase protections for patients, increase the number of people covered by health insurance, and require more people to contribute dollars to the health-care coverage pool. Its approach is based on some trade-offs: Because more people are required to buy insurance, insurance companies can drop pre-existing conditions requirements. Because hospitals will treat fewer uninsured patients, it reduces some government payment to hospitals. In one of the most important dates in the implementation is Jan. 1, 2014, still a little more than a year away, when many provisions take effect. Although the act was passed in 2010, implementation was staged to give consumers, insurance companies, state governments, and the federal government time to adjust to the changes. Here is a summary of some of the main provisions.

Requirements already in place

The law includes a “patient’s bill of rights” that ends lifetime limits on coverage, restricts the conditions under which insurers can cancel coverage, requires plans to allow new parents to include any children under 26, and ends pre-existing condition exclusions for children under 19, among other things. It created a special insurance pool for patients with pre-existing conditions. Starting in 2010, health plans are required to cover preventive services such as mammograms and colonoscopies without charging a deductible, co-pay, or co-insurance. Starting Jan. 1, 2014, most

* eliminates pre-existing conditions exclusions: Insurance companies cannot refuse to sell coverage because of an individual’s pre-existing conditions or to exclude pre-existing conditions from coverage.
* prohibits insurance companies from charging higher premiums due to gender or health status.
* eliminates annual limits on insurance coverage.
* requires insurance to cover patients who participate in clinical trials.
* requires efficient administration by insurers: At least 85% of premium dollars collected for large employer plans and 80% for individuals and small employers must be spent on health care services and quality improvement. Any amount that doesn’t meet these goals must be rebated to consumers.

Incentives and requirements for businesses

Small businesses with fewer than 25 workers will receive tax credits for up to 50% of the premium cost, and may find coverage more easily through the exchanges. Employers with 50 or more full-time employees that do not offer coverage or offer coverage deemed inadequate will incur penalties. Employers with more than 200 employees must automatically enroll new full-time employees in coverage.

New taxes and fees

The Congressional Budget Office projects that the ACA’s net effect will be to lower the federal deficit because it includes revenues from new taxes, fees, and limits on deductions. For example, it lifts the cap on Medicare taxes paid by those with high incomes and taxes so-called unearned income under the Medicare policies. It also institutes new fees on insurers, drug makers, and medical device companies.
Congress: The Road Ahead
By Grant Olan

Voters resoundingly re-elected U.S. President Barack Obama on Election Day in November, but the balance of power in Congress remains essentially the same. Democrats gained two seats in the House of Representatives; however, Republicans will retain control by nearly 40 seats.* In the Senate, Democrats expanded their majority by two seats, but did not earn enough representation to overcome a Republican filibuster.

Because Democrats remain in control of the Senate and Republicans remain in control of the House, both parties will need to compromise to avert a “fiscal cliff” before January 2013, when automatic across-the-board cuts to federal discretionary spending would take effect (including cuts to medical research) and tax cuts would expire.

Medicare physician payments would also be reduced 26.5 percent—as mandated by the Sustainable Growth Rate formula—unless the President and Congress reach a deal.

In the days following the election, both parties have begun to indicate a greater willingness to work together to avoid the fiscal cliff. “For the purposes of forging a bipartisan agreement that begins to solve the problem,” House Speaker John Boehner (R-OH) said, “[Republicans are] willing to accept new revenue, under the right conditions.” Senate Majority Leader Harry Reid (D-NV) said, “Compromise is not a dirty word. I’m willing to negotiate any time on any issue. I’m going to do everything in my power to be conciliatory.”

Despite more conciliatory tones from both parties, the scuttlebutt is that Congress will likely push back the planned cuts to discretionary spending and extend the expiring tax cuts six months to give Democrats and Republicans more time to work out some kind of agreement.

If Congress fails to act, NIH funding will be cut by 8.2 percent, eliminating up to 2300 NIH research grants. In response to this threat, ASN has joined more than 3000 national, state, and local organizations, including other medical specialty societies and research organizations, to raise awareness of and build support for vital federal programs like medical research. For more information about how you can help, go to http://www.asn-online.org/policy/.

Other challenges for the President and Congress remain. The federal government will soon hit the “debt ceiling” again, a legal limit to how much debt the government can assume. A deal to avoid the fiscal cliff may include raising the debt ceiling. And challenges also remain for implementation of the Affordable Care Act—principally, Republican opposition to funding and meeting new deadlines for enactment of the law's provisions.

While the President and Congress work through these many issues in the coming months, ASN will be at the forefront advocating for support of promising kidney diseases research that generates jobs, stimulates the economy, improves patient health, and drives down health care costs. Visit http://www.asn-online.org/policy/ to learn how you can make a difference.

*Election outcomes of six U.S. House seats were still pending at time of publication.

113th Congress Balance of Power

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Democrats | Independents | Republicans | Republicans | Democrats

*Election outcomes of six U.S. House seats still pending at time of publication.

Help Avert Cuts to Medical Research: Join ASN in Calling for a Balanced Approach to Deficit Reduction
By Thomas H. Hostetter

ASN needs your support to protect medical research funding. It’s one of the smartest investments our country can make.

Research generates jobs, stimulates the economy, and enables life-saving medical advances. If Congress doesn’t act by January 2013, federal funding for the National Institutes of Health will be cut by 8.2 percent, eliminating up to 2300 NIH research grants.

We can’t let these cuts happen. ASN has joined more than 3000 other organizations urging Congress to adopt a balanced approach to deficit reduction that would protect medical research and other essential federal programs like education, public safety, and infrastructure.

The society needs your help, too. Tell your Congressional representatives that cuts alone will not solve our federal budget problems.

Go to http://www.asn-online.org/policy/ for all the tools to connect with you and your members of Congress, including talking points and fact sheets.

Congress won’t act unless they hear from constituents like you.

I’m going to meet with my representatives. I urge you to join me.

Thomas H. Hostetter, MD, is Chair of the ASN Public Policy Board.

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Kidney Week Session Highlights Health Care Allocation

The comprehensive care model envisioned by Vladeck would also include frank and open discussion about end-of-life care, another issue that has been part of heated debates on rationing care. Public and political discourse on providing palliative or hospice care in the place of life-sustaining procedures has often turned into talk of “death panels.” But with an increasing numbers of frail and elderly individuals starting dialysis, Vladeck said the real issue is lack of appropriate training for health care providers to discuss issues related to prognosis, death, and expectations for treatment for patients nearing the end of life.

Creating policies that better address palliative care was discussed by Manjula Kurella Tamura, MD, associate professor of nephrology at Stanford University School of Medicine. Palliative care, defined as care that relieves symptoms without a curative effect on an underlying disease or cause, is unlike hospice care in that it can be used during the entire course of the disease, not just in the last 6 months. Tamura described

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research showing that although palliative and hospice care is not cheap, it is not necessarily more expensive than regular care. Research has also shown that palliative care has been associated with increased patient and family satisfaction and improved bereavement outcomes; it has also been shown to lower costs, primarily by reducing the number of visits to the intensive care unit.

Unfortunately, ESRD patients typically receive only 3–4 days of palliative care on average, and confusion about how Medicare and hospice care work together for dialysis patients remains an issue (hospice care is not covered for dialysis patients unless their primary need for hospice is due to a different disease). There is also a scarcity of providers trained in palliative care and a need for rigorous trials to measure the effects of palliative care, especially for the dialysis population.

Tamura laid out five ways practitioners and other stakeholders can use policies to promote palliative care for this population: 1) universal screening for palliative care during transitions to care; 2) incorporating palliative care as a process measure in Medicare’s quality improvement program; 3) payment reforms, including concurrent care models and adding palliative care as an accountable care organization designation; 4) palliative care training for ESRD providers; and 5) increased funding for research into palliative care.

Like dialysis, allocation issues also abound for transplant patients. Milagros Samaniego-Picota, MD, associate professor at the University of Michigan, tried to present balanced arguments both for and against the use of financial incentives to increase donation. In the United States, the demand for organs continues to far outweigh the supply, with only a nominal increase in the number of donors in the past few years. Many states have implemented programs to help living donors through tax credits or deductions, and a national donor assistance program now exists, but direct reimbursement for the donation of organs remains illegal under the National Organ Transplant Act.

In her "for" argument, Samaniego-Picota cited an economic model used to estimate the benefits of providing reimbursement to living donors. The authors of the paper argued that the effects of reimbursement (increase in the donor pool) would outweigh the costs (possible abuse and corruption), but they included the caveat that donors should be paid upwards of $100,000 and that compensation should be included as part of the medical procedure. They suggested that signing up for living organ donation is much like joining the military and that compensation for donation is similar to a family member receiving life insurance.

To argue against compensation, Samaniego-Picota described regulated incentive programs already in place in several countries, including Iran, Israel, Pakistan, and the Philippines. Although many of these programs have shown a demonstrable increase in kidney donations, ethical and legal concerns remain. For example, although Iran’s kidney transplant wait list has been virtually eliminated, most organs come from an impoverished population more vulnerable to exploitation. In the Philippines, rules regulating the percentage of foreign recipients have been ignored, causing rampant transplant tourism. Clinical guidelines for donors in other countries are not as stringent as those in the United States, possibly leading to an increase in adverse outcomes for this already vulnerable population.

How best to use and protect living kidney donors remains a complex problem, and Samaniego-Picota’s arguments highlighted many ongoing issues in incentivizing donation.
allograft rejection despite donor specific transfection/MR1. Reconstitution experiments in Rag2-/b mice confirmed that the defect mapped with lymphocytes. Using mice that are "enucleate deficient for Arg", we showed that transplant tolerance required intact autophagy in T cells but not in B cells or dendritic cells, Verghese said. "T cells from autophagy-deficient animals proliferated more, expanded better, and died less in vivo during tolerance induction compared to wild type animals, while regulatory T cells from autophagy deficient animals functioned normally." Verghese concluded, "our findings indicate autophagy-mediated T cell death is a requisite mechanism underlying transplant tolerance. Interestingly, ... macroautophagy and microautophagy, and their main effector mechanism is to inhibit T-cell proliferation. Inhibition of mTOR is a potent inducer of autophagy and the use of rapamycin, in combination with a TCR-mediated, strong synergy and favors peripheral tol-

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**Hot Science Presentations: Push Boundaries of Kidney Knowledge**

The Hot Science session at Kidney Week 2012 covered a wide variety of both basic and clinical science, from podocyte function to genome-wide association study analyses. Here's a selection of some of the groundbreaking work that was presented in San Diego.

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**T Cell Autophagy & a Key Mechanism in Preventing Transplant Rejection**

T cell autophagy is crucial for induction of transplant tolerance, according to a study by Divya Anna Verghese, PhD, and colleagues from Mount Sinai School of Medicine. "Our study sets the stage for future work aimed at manipulating autophagy machinery in a clinical setting providing new opportunities to intervene in the allograft response," Verghese said, adding "targeting autophagy could be exploited as a means to manipulate pathogenic and/or protective immunity.

"The induction and maintenance of stable transplant tolerance involves both regulatory and deleterional mechanisms, the latter of which have been attributed to T cell apoptosis," Verghese noted. "Autophagy is responsible for the degradation of protein aggregates and damaged organelles, and while usually a pros-

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**Infections**: Dose modification is recommended if Myfortic is not tolerated. In patients receiving immunosuppressive therapy (see ADVERSE REACTIONS).

**Myophenolate mofetil**: Myophenolate mofetil is contraindicated for patients with a hypersensitivity to mycophenolic acid, mycophenolic acid or mycophenolate mofetil, or to any of its excipients.

**Toxicity**: MYCOPHENOLIC ACID: Mycophenolic acid may induce the development of lymphoma and other neoplasms. Only physicians experienced in immunosuppressors and their effects and management should be involved with patients receiving mycophenolic acid (MPA). Patients receiving Myfortic should be managed in facilities equipped with adequate long-term supportive medical care services in case of adverse events requiring hospitalization or medical intervention.

**INTERACTIONS**: The risk of increased exposure to MPA (inhibition of nucleotide synthesis).

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**Patient Information**

**Dosage and Administration**: Myfortic should be administered once daily with a meal or a non-fat beverage (milk) after 30 minutes (see CLINICAL PHARMACOLOGY).

**Contraindications**: Myfortic is contraindicated in patients with a known hypersensitivity to MPA. Myfortic is also contraindicated in patients with a platelet count below 50,000/μL and leukocyte count below 2,000/μL.

**Warnings and Precautions**: Use during pregnancy is associated with increased risks of first trimester pregnancy loss and congenital malformations. Females of reproductive potential (FPP) must be counseled about the potential risks to the fetus. For those females using Myfortic at any time during pregnancy and those who are breast feeding, they must use acceptable contraception (see PRECAUTIONS: Pregnancy Exposure Prevention and Planning).

**Indications and Usage**: Myfortic® (mycophenolic acid) delayed-release tablets are indicated for the prophylaxis of organ rejection in patients receiving allogeneic renal transplant, administered in combination with corticosteroids and calcineurin inhibitors.

**Myophenolate mofetil**: Myophenolate mofetil is contraindicated for patients with a hypersensitivity to mycophenolic acid, mycophenolic acid, or mycophenolate mofetil, or to any of its excipients. **Warnings** (see BOXED WARNING):

**Myfortic®**: Mycophenolic acid is contraindicated in patients with a hypersensitivity to mycophenolic acid, mycophenolic acid, or mycophenolate mofetil, or to any of its excipients. **Warnings** (see BOXED WARNING):

**Myophenolate mofetil**: Mycophenolic acid may induce the development of lymphoma and other neoplasms. Only physicians experienced in immunosuppressors and their effects and management should be involved with patients receiving mycophenolic acid (MPA). Patients receiving Myfortic should be managed in facilities equipped with adequate long-term supportive medical care services in case of adverse events requiring hospitalization or medical intervention.

**Interactions**: The risk of increased exposure to MPA (inhibition of nucleotide synthesis).
polynucleotides—can be differentiated in extreme versions, many patients “fall into the middle in a sort of gray zone where the fluctuations are classically inconsistent,” said Kenneth Smith, MD, PhD. The confirmation that the syndromes have different genetic underpinnings could lead to improved diagnoses and better clinical treatments for possible treatments.

Previous genome-wide association studies have successfully identified single nucleotide polymorphisms associated with several disease states, including cardiovascular disease, Parkinson disease, and Crohn disease. Presenting on behalf of the European Vasculitis Study Consortium, Smith showed the results of the first genome-wide association study in AAV that validated the genetic differences between granulomatosis with polyangiitis and microscopic polyangiitis, both of which cause kidney failure. The study included a total of 1,233 patients with AAV and 5,884 controls from the United Kingdom and a replication cohort of 1,454 patients with AAV and 1,666 controls from Europe.

Research has found that the disease causes familial clustering (similar to rheumatoid arthritis), and also observed genetic distinctions with anti- nuclear specificity—anti-protein 3 AAV and anti-myeloperoxidase AAV. The identification of the two distinct autoimmune syndromes and associated genetic differences has implications for the etiology of AAV and for future research that could lead to disease-specific pathways and therapeutic goals.

Kidney Regeneration in Zebrafish Fibrin Wnt Signaling

The Wnt signaling pathway is critical to nephron regeneration in zebrafish, according to research presented by Cara-Mei Kamei, PhD, at Kidney Week 2012. The zebrafish’s ability to restore skin, organs, and muscle without the use of stem cells has made it a model of interest for a wide range of potential therapeutic areas, including cardiovascular disease, retinopathy, and cancer. Identification of Wnt signaling involvement in kidney repair in zebrafish opens a pathway for new research into the understanding of kidney regeneration.”In contrast to mammalian kidneys, the zebrafish continuously adds new nephrons throughout its adult life,” said Kamei. Because zebrafish can repair and generate new nephrons from adult progenitor cells, she and her co-investigator, lain Drummond, PhD, of Massachusetts General Hospital wanted to determine what signaled the repair function to begin in the kidney. An in situ hybridization study revealed that adult kidney progenitor cells and differentiating cell condensates that are used to regenerate nephrons were observed to express the Wnt receptor Frizzled-9b (FZD9B) and the Wnt target Lymphoid enhancer-binding factor 1 (LEF1). Colocalization of FZD9B and LHX1-positive kidney progenitor cells also suggested Wnt signaling involvement in zebrafish nephrogenesis. Induction of acute kidney injury using gentamicin increased the number of FZD9B-positive nephron progenitors; however, when Wnt signaling was blocked after injury, the number of progenitor cells declined. An increase in FZD9B expression with activation of Wnt signaling in the absence of injury further confirmed Wnt signaling’s role in kidney regeneration. “FZD9B is a new marker for newly forming nephrons as well as single cortical cells that are candidate kidney progenitor cells,” Kamei said. Because FZD9B is expressed in the human kidney, Wnt signaling may be a target of interest in further research.

Podocyte Dysfunction and Function Are Dependent on Endophilin

Endophilin is critical to the development and maintenance of podocyte function in the kidney. This is the conclusion of Keita Soda, PhD, and co-workers from Yale University, who presented work at the Hot Science session at Kidney Week 2012. Endophilin is known to be expressed predominantly in both the basolateral and apical domains of podocytes.

Table 1: Adverse Events (%) in Controlled de novo and Maintenance Renal Studies Reported in ≥5% of Patients

<table>
<thead>
<tr>
<th></th>
<th>de novo Renal Study (N=1005)</th>
<th>Phase 3 Study (N=379)</th>
<th><em>ECLIPSE</em> Study (N=100)</th>
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</thead>
<tbody>
<tr>
<td>Arterial Hypertension</td>
<td>21%</td>
<td>21%</td>
<td>15%</td>
</tr>
<tr>
<td>Gastrointestinal Vomiting</td>
<td>10%</td>
<td>10%</td>
<td>10%</td>
</tr>
<tr>
<td>Mucosal Ulceration</td>
<td>18%</td>
<td>18%</td>
<td>15%</td>
</tr>
<tr>
<td>Upper Respiratory Infection</td>
<td>15%</td>
<td>15%</td>
<td>10%</td>
</tr>
<tr>
<td>Urinary Tract Infection</td>
<td>15%</td>
<td>15%</td>
<td>10%</td>
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</tbody>
</table>

*ECLIPSE* study: European Clinical Trial in Lupus Erythematosus in Polycystic Ovary Syndrome

*Talk given at Kidney Week 2012 by Cara M. Kamei, PhD, University of Texas Southwestern Medical Center, Dallas, TX.

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Podocyte Development

Continued from page 9

Janin 1, as well as the vital role endophilin plays in the formation and maintenance of the glomerular filtration barrier.

Expanding on their previous investigation of synaptic proteins, Soda and co-workers tried to determine the function of clathrin-coated pits that are seen in the podocyte foot processes.

They hypothesized that endophilin may play a role in podocyte function. “Endophilin interacts with CD2AP, a critical protein which when lost in mice or mutated in humans results in nephrotic syndrome,” Soda said. “Moreover, in vitro it interacts with dynamin and synaptojanin, which when also deleted in mice results in severe proteinuria. This made endophilin an attractive candidate.” Soda and colleagues used fluorescent images to demonstrate that endogenous endophilin colocalized with podocyte marker-nephrpin in glomeruli. The protein was also found in late-stage clathrin-coated pits with F-actin, dynamin, and synaptojanin 1, verifying endophilin’s role in maintaining the glomerular filtration barrier. A second experiment comparing triple knockout mice (breed lacking all three isoforms of endophilin) with wild type mice found the knockout mice had a significantly high level of proteinuria, as well as dilated tubules and accumulation of mesangial matrix in glomeruli.

When asked if the confirmation of endophilin’s role in podocyte functioning could lead to potential targets for treating nephrotic syndrome, Soda said that “stabilizing existing pathways regulated by endophilin/synaptojanin or dynamin may result in possible therapeutic interventions, but one must be cognizant as not all mechanisms of nephrotic syndrome are identical,” Soda said, concluding “further investigation and research will be required.”

Table 7: Adverse Events Reported in 3% to <20% of Patients Treated with Myfortic® in Combination with Cyclosporine and Corticosteroids

<table>
<thead>
<tr>
<th>Category</th>
<th>Myfortic® (mg/day)</th>
<th>Maintenance Study</th>
<th>Myfortic® (mg/day)</th>
<th>Maintenance Study</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Skin and Subcutaneous</strong></td>
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<tr>
<td><strong>Adverse Reaction</strong></td>
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<tr>
<td><strong>Skin Discoloration</strong></td>
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<tr>
<td><strong>Skin Necrosis</strong></td>
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<td></td>
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<tr>
<td><strong>Wound</strong></td>
<td></td>
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<td></td>
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<tr>
<td><strong>Bone</strong></td>
<td></td>
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<td></td>
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</tr>
<tr>
<td><strong>Joint Pain</strong></td>
<td></td>
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<tr>
<td><strong>Arthralgia</strong></td>
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<tr>
<td><strong>Myalgia</strong></td>
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<tr>
<td><strong>Fatigue</strong></td>
<td></td>
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<tr>
<td><strong>Mood Changes</strong></td>
<td></td>
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<tr>
<td><strong>Anxiety</strong></td>
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<tr>
<td><strong>Insomnia</strong></td>
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<td><strong>Tremors</strong></td>
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<tr>
<td><strong>Convulsion</strong></td>
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<td><strong>Psychoses</strong></td>
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Table 8: Adverse Events (%) in Controlled and Maintenance Renal Studies Reported in ≥1% of Patients

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<th>Category</th>
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<th>Maintenance Study</th>
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</thead>
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<tr>
<td><strong>Blood and Lymphatic Systems</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Anemia</strong></td>
<td></td>
<td></td>
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<tr>
<td><strong>Thrombocytopenia</strong></td>
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<td><strong>Leukopenia</strong></td>
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<td><strong>Agranulocytosis</strong></td>
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<tr>
<td><strong>Bile Acid Sequestrant</strong></td>
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<td><strong>Fatigue</strong></td>
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<tr>
<td><strong>Xerostomia</strong></td>
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<tr>
<td><strong>Nausea</strong></td>
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<tr>
<td><strong>Vomiting</strong></td>
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Table 9: Adverse Events (%) in Controlled and Maintenance Renal Studies Reported in >1% of Patients

<table>
<thead>
<tr>
<th>Category</th>
<th>Controlled Study</th>
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<tr>
<td><strong>Blood and Lymphatic Systems</strong></td>
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<td><strong>Bile Acid Sequestrant</strong></td>
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<td><strong>Fatigue</strong></td>
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<tr>
<td><strong>Vomiting</strong></td>
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Tolvaptan Trial Shows Benefit in Slowing Progression of Autosomal Dominant Polycystic Kidney Disease

A phase III clinical trial of tolvaptan for autosomal dominant polycystic kidney disease (ADPKD) demonstrated the drug slowed the rate of disease progression by almost half in the study period compared with placebo. While encouraging, the trial results presented at Kidney Week 2012 are investigative and have yet to be evaluated by the FDA. The 3-year multicenter, double-blind, placebo-controlled study (the TEMPO 3/4 Trial) found that patients with ADPKD who took tolvaptan experienced an average increase in total kidney volume of 2.8 percent per year compared with 5.51 percent for those in the placebo group (1). Given these results, how could this trial expand our understanding of ADPKD and change the investigatory approach to the fourth leading cause of ESRD?

Prior to this study, physicians caring for patients with ADPKD were limited “to treating its complications (strict blood pressure control, dietary protein restriction, drugs, and statin use for cardiovascular effects), since no treatment capable of inhibiting the development and progression of the cysts has been available,” said Vicente Torres, MD, PhD, of the Mayo Clinic and first author of the TEMPO trial. “In many patients, the growth of numerous cysts within the kidneys is accompanied by painful complications (such as bleeding into cysts or into the urinary tract, cyst infections, and passage of kidney stones), hypertrophy, and kidney failure.”

Vasopressin has been a pathway of interest to investigators in the ADPKD community, and has included research into the therapeutic use of water intake as a method to reduce vasopressin levels (2). A vasopressin V2 receptor antagonist, tolvaptan is currently indicated for hypervolemic and euvolemic hyponatremia. “Vasopressin causes production of the cyclic adenosine monophosphate (cAMP), which is thought to accelerate the progression of ADPKD by stimulating proliferation of the cells lining the cysts and fluid secretion into the cysts,” said Torres. “By blocking the production of cAMP, it would be expected that vasopressin would slow the progression of ADPKD.”

Kidney Week 2012
Renal Replacement Therapy: Cautiously Expanding the Donor Pool and Disparities in Transplant Access for Children

Two studies presented at Kidney Week 2012 offer a cross-section of the state of renal replacement therapy in the United States. The first study demonstrated that living kidney donors with prediabetes did not experience an increased risk for developing diabetes over a mean follow-up of 10 years. It indicates that the living kidney donor pool may be cautiously expanded to include prediabetic individuals, which could contribute to a reduction in the duration patients spend waiting for kidney transplants. The second study confirmed that minority children with kidney disease face disparities in access to renal replacement therapy, especially preemptive transplantation, compared to whites. Although transplantation is the preferred treatment option for children with ERD, white children were four times more likely to receive a transplant as their initial renal replacement treatment compared with black children. Both studies reflect the complex situation that patients with kidney disease encounter when selecting renal replacement options, and identify knowledge gaps for future research that could contribute to improved decision making and outcomes.

Cautiously expanding the living kidney donor pool

Potential living donors receive extensive screening before being approved for kidney donation, and a diagnosis of prediabetes (defined as impaired fasting glucose level of 100–125 mg/dL) may prevent some from donating a kidney. Current clinical guidelines lack consensus on the suitability for donation of individuals with prediabetes, which by current estimates may include as much as 35 percent of the U.S. population. To determine if the condition is truly a contraindication for donation, Sindhu Chandran, MD, of the University of California, San Francisco, and colleagues studied a single-center cohort of living kidney donors who were prediabetic at the time of donation and who agreed to a clinical follow-up after their operation (1).

Thirty-five donors who had a fasting glucose level ≥100 mg/dL at time of donation underwent a telephone interview and laboratory testing. At the time the study was conducted, the mean duration between donation and follow-up was 10.2 years (range 5.1–15.9 years). Results revealed four donors (11.4 percent) had progressed to diabetes, two of whom had progressed to diabetes within the first year. Overall, 1.1 percent of donors had progressed to diabetes at 10 years, consistent with previous studies (2). There were no apparent differences in donor characteristics between donors who did not progress to diabetes and those who did. The results from this study support current clinical guidelines for living kidney donor selection: potential donors should be evaluated for prediabetes at the time of donation and not be approved if they have a fasting glucose level ≥100 mg/dL.

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March 2–3

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• Clinical Nephrology
• End-Stage Renal Disease
• Hypertension
• Parenchymal Disorders
• Transplantation

Registration opens January 2
Visit www.asn-online.org/highlights for more information.

References

Initiated in 2007, TEMPO 3/4 trial (Tolvaptan Efficacy and Safety in Management of Polycystic Kidney Disease and Its Outcomes) involved 1445 adult patients with ADPKD from 15 countries who were randomized to receive either tolvaptan (one of three dosages as tolerated) or placebo. The study’s primary end point was reduction of total kidney volume over the course of the study. Secondary end points included the rate of decline in kidney function and time to clinical progression events, including hypertension and pain. At the end of the 3-year study, the annual increase in total kidney volume (2.8 percent per year for tolvaptan versus 5.51 percent for placebo) and the slope of renal function decline (−2.61 [mg/mL]/year for tolvaptan versus −3.81 [mg/mL]/year for placebo) were significantly reduced in the tolvaptan group (both p < 0.001). Patients taking tolvaptan also demonstrated significant reductions in risk for secondary end points including worsening kidney function (61 percent) and pain requiring increased analgesics associated with ADPKD, occurred less frequently in the patients treated with tolvaptan compared to those treated with placebo. By reducing the rate of these complications, tolvaptan may lead to an improvement in quality of life.

Yet Torres cautions that tolvaptan is not without risks. “The most common adverse effects were anticipated and related to high urine output with more frequent voiding. Unexpected liver test abnormalities were observed in approximately 5 percent of patients and led to the discontinuation of tolvaptan in 1.8 percent of the patients.” Adverse events led to a higher discontinuation rate in the tolvaptan group (25 percent) than in the placebo arm (14 percent).

“Although tolvaptan is already approved for treatment of other medical conditions, it is not approved for the treatment of ADPKD. The doses of tolvaptan used in the TEMPO trial were higher than used in previous studies of other diseases,” Torres said. “In addition, ADPKD patients are a unique patient population. Further analysis of the benefits and risks of this potential therapy will need to be performed by the sponsor (Otsuka Pharmaceuticals) and regulatory agencies. Therefore, although the results are encouraging, at the present time, patients with ADPKD should not be treated with tolvaptan outside of approved research studies.”

Terry Watnick, MD, of the University of Maryland School of Medicine and an investigator in the TEMPO trial, found the results of the trial’s primary end point very encouraging. But Watnick added that “it is still important that we control blood pressure and other cardiovascular risk factors in ADPKD patients since this population may still require renal replacement therapy. While tolvaptan may delay disease progression, it will not completely prevent or reverse established disease based on the data presented.”

There are other important questions with respect to tolvaptan that remain to be answered, Watnick said. For example she wondered if tolvaptan would be more beneficial if the drug was initiated earlier in the course of disease when patients had fewer cysts or smaller kidneys. In addition, the applicability of treatment in patients with milder disease severity, or the consequences of longer-term drug administration remain to be defined. She also pointed to a need for more basic research into the mechanisms underlying ADPKD pathogenesis. “Blocking the V2 receptor improves the disease course, but it doesn’t completely stop progression. ADPKD is a complicated disorder, and the PKD community has invested a lot in research over the past 15 years. The signaling pathways involved in cyst formation are complex, and we still don’t know everything we need to know about this disease. Blocking the V2 receptor provides one therapeutic approach, but I believe that there are likely to be others.”

Visit www.asn-online.org/highlights for more information.

References

Two studies presented at Kidney Week 2012 offer a cross-section of the state of renal replacement therapy in the United States. The first study demonstrated that living kidney donors with prediabetes did not experience an increased risk for developing diabetes over a mean follow-up of 10 years. It indicates that the living kidney donor pool may be cautiously expanded to include prediabetic individuals, which could contribute to a reduction in the duration patients spend waiting for kidney transplants. The second study confirmed that minority children with kidney disease face disparities in access to renal replacement therapy, especially preemptive transplantation, compared to whites. Although transplantation is the preferred treatment option for children with ESRD, white children were four times more likely to receive a transplant as their initial renal replacement treatment compared with black children. Both studies reflect the complex situation that patients with kidney disease encounter when selecting renal replacement options, and identify knowledge gaps for future research that could contribute to improved decision making and outcomes.

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Renal Replacement Therapy

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donors (5.7 percent) had microalbuminuria, and kidney function was well preserved in all donors (mean eGFR 68.9 mL/min/1.73 m²). In addition, 60 percent of prediabetic donors reverted to normal glycemic levels, which Chandran noted was higher than the commonly cited rate of approximately 25 percent.

“However, the reversion rate varies depending on factors such as race, family history, and obesity, and because donors are screened for these they are healthier than the average population,” Chandran said. “Also, the majority of our donors were white (75 percent) so it is perhaps not surprising.”

“Studies such as these can be controversial,” said William Harmon, MD, of Boston Children’s Hospital and Harvard Medical School, who was not involved in either study. “The major issue for living donation is that you never want to put the donor at risk for the recipient. As we’ve expanded the donor pool to include people with mild hypertension or those with a history of kidney stones, you always worry that as you expand the pool farther that we’re going to see more morbidity and mortality, which then gets to be counterproductive.” But he added the study “is good news and it will allow some other programs to say that being prediabetic is probably not a contraindication to donation.”

Although the results appear to be encouraging, what further data are needed to convince physicians to change their practice patterns and consider expanding the donor pool to include donors with prediabetes?

“This data would preferably have larger numbers of patients (to ensure major events aren’t missed); more minorities, including blacks and Hispanics because they are at higher risk; more transplant centers, to ensure that center-specific practice patterns (such as being too selective) aren’t influencing outcomes; and finally a control group,” Chandran said. “The ideal controls would be prediabetics who ended up not donating for nonmedical reasons, but because this is impracticable, the next best thing would be to compare them to similar patients with normal blood glucose who donated at the same time. We have already enrolled such controls and are working on data analysis.”

Harmon added that generating consensus for clinical guidelines to assess the risk of donor pool expansion requires studies like Chandran’s. But he pointed to a bigger problem. “The bottom line is we need more information on more donors,” he said. “Living kidney donation programs are supposed to send data at certain intervals post-transplant, yet it’s difficult to get those

Kidney Week 2012

Disparities in renal replacement options for minority children

Health care disparities have been less well documented in the U.S. pediatric population than in adults. Previous studies have shown that black children are more likely to receive hemodialysis instead of peritoneal dialysis as their initial renal replacement therapy compared with white children, yet there...
Reducing the burden of ESA administration
Consider the first once-monthly, non-EPO ESA offering less-frequent dose administration.

INDICATION AND LIMITATIONS OF USE
OMONTYS® (peginesatide) Injection is indicated for the treatment of anemia due to chronic kidney disease (CKD) in adult patients on dialysis.

OMONTYS® is not indicated and is not recommended for use in patients with CKD not on dialysis, in patients receiving treatment for cancer and whose anemia is not due to CKD, or as a substitute for red blood cell (RBC) transfusions in patients who require immediate correction of anemia. OMONTYS® has not been shown to improve symptoms, physical functioning, or health-related quality of life.

IMPORTANT SAFETY INFORMATION

WARNING: ESA increase the risk of death, myocardial infarction, stroke, venous thromboembolism, thrombosis of vascular access and tumor progression or recurrence.

Chronic Kidney Disease:
• In controlled trials, patients experienced greater risks for death, serious adverse cardiovascular reactions, and stroke when administered erythropoiesis-stimulating agents (ESAs) to target a hemoglobin level of greater than 11 g/dL.
• No trial has identified a hemoglobin target level, ESA dose, or dosing strategy that does not increase these risks.
• Use the lowest OMONTYS dose sufficient to reduce the need for red blood cell (RBC) transfusions.

Contraindications:
OMONTYS® is contraindicated in patients with uncontrolled hypertension.

Warnings and Precautions
Increased mortality, myocardial infarction, stroke, and thromboembolism:
• Using ESAs to target a hemoglobin level of greater than 11 g/dL increases the risk of serious adverse cardiovascular reactions and has not been shown to provide additional benefit. Use caution in patients with coexistent cardiovascular disease and stroke. Patients with CKD and an insufficient hemoglobin response to ESA therapy may be at even greater risk for cardiovascular reactions and mortality than other patients. A rate of hemoglobin rise of >1 g/dL over 2 weeks may contribute to these risks.
• In controlled clinical trials of ESAs in patients with cancer, increased risk for death and serious adverse cardiovascular reactions was observed. These adverse reactions included myocardial infarction and stroke.
• In controlled clinical trials of ESAs, ESAs increased the risk of death in patients undergoing coronary artery bypass graft surgery (CABG) and deep venous thrombosis (DVT) in patients undergoing orthopedic procedures.
• In 2 trials of OMONTYS, patients with CKD not on dialysis experienced increased specific cardiovascular events.

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

Hypertension: OMONTYS® is contraindicated in patients with uncontrolled hypertension. Appropriately control hypertension prior to initiation and during treatment with OMONTYS. Reduce or withhold OMONTYS if blood pressure becomes difficult to control. Advise patients of the importance of compliance with antihypertensive therapy and dietary restrictions.

Lack or loss of response to OMONTYS: For lack or loss of hemoglobin response to OMONTYS, initiate a search for causative factors. If typical causes of lack or loss of hemoglobin response are excluded, evaluate for antibodies to peginesatide. Dialysis management: Patients receiving OMONTYS may require increased anticoagulation with heparin to prevent clotting of the extracorporeal circuit during hemodialysis.

Laboratory monitoring: Evaluate transferrin saturation and serum ferritin prior to and during OMONTYS treatment. Administer supplemental iron therapy when serum ferritin is less than 100 mcg/L, or when serum transferrin saturation is less than 20%.

Adverse reactions:
The most common adverse reactions in clinical studies in patients with CKD on dialysis treated with OMONTYS® were dyspnea, diaphoresis, nausea, cough, and arteriovenous fistula site complication.

Please see accompanying Brief Summary.

References:

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have been few investigations regarding the preferred treatment for ESRD—preemptive transplantation. To determine if children experienced racial and ethnic disparities in renal replacement options and to determine the factors behind such disparities, Roshan George of Emory University School of Medicine and Children’s Healthcare of Atlanta and her co-workers examined a pediatric and adolescent cohort (<20 years of age) from the United States Renal Data System (USRDS) who initiated renal replacement therapy between January 2005 and September 2009 (2).

Of 5623 patients included in the study, 36.7% percent were white, 30.3 percent were black, and 26.4 percent were Hispanic. The results, though as expected, were stark: the percentage of black children receiving preemptive transplants was one-fourth and the percentage of Hispanic children was one-half that of white children who underwent preemptive transplantation. Hemodialysis was the renal replacement for a majority of blacks (70.8 percent) and Hispanics (60 percent) as well as whites (49.1 percent).

Yet the rates of white children initiating peritoneal dialysis (32.4 percent) or receiving preemptive transplantation (18.6 percent) were higher than in the other groups. Adjusting for demographic, clinical, and socioeconomic differences attenuated the differences in renal replacement therapy for Hispanics, yet when compared with hemodialysis, black children still had a 75 percent lower chance for preemptive transplantation than white children. Examining rates of pre-ESRD access to a nephrologist also revealed significant differences between black and Hispanic children when compared with whites.

“The study is important because typically children have safety nets in terms of prejudice and poverty,” said Harmon.

“You would hope that what’s true for adults, where socioeconomic disparities may account for differences in care, wouldn’t apply to children. Showing that these things are true in children is an important finding, and shows that we still have a way to go in terms of the transplant process.”

The results mirrored those in the incident adult population, said George, who noted that black adults are more likely to initiate therapy with hemodialysis and face delays in getting on a transplant wait list.

“It is true that there is a very big disparity between whites and blacks in terms of how soon they get on the waiting list,” Harmon said. “Until recently, physicians would place their patients on the waiting list way before they needed a transplant and keep them inactive where they could still accumulate waiting time points, whereas blacks often wouldn’t get on until after they had started dialysis, and even then there’d be a long delay in terms of giving them the opportunity to get on the transplant list.

“Some of this has been ameliorated by recent movements to not count waiting time until the patient is either on dialysis or has a GFR &lt;20 mL/min/1.73 m²,” Harmon said. “But once on the list, the time to transplant for blacks doesn’t seem to be as affected because the listing criteria are clear.”

George concluded that further research examining patient and physician perspectives when choosing renal replacement options could be helpful in resolving disparities and determining unmeasured factors that typically are not captured in most data sources.

References
Dietary habits of individuals living in poverty

Research has demonstrated that lower socioeconomic status is connected with reduced kidney function and an increased risk for progression to ESKD. To determine if dietary habits were contributing to this increased risk for CKD, Deidra Crews, MD, FASN, of the Johns Hopkins University School of Medicine, and her colleagues studied a large urban population to determine if adherence to a DASH-style diet was linked with reduced kidney disease among those living in poverty.

Crews used the Healthy Aging in Neighborhoods of Diversity Across the Lifespan (HANDLS) cohort, an intramural study of the National Institute on Aging that focuses on the influence of socioeconomic status and race on kidney disease. A total of 2058 participants from diverse backgrounds in Baltimore were included, 42 percent of whom were classified as living in poverty. The poverty group had a significantly higher number of black and uninsured individuals and tobacco users compared with the non-poverty group. Although participants were not instructed in the DASH diet, their report, via 24-hour dietary recall of intake of foods containing the macro- and micronutrients considered in DASH adherence scoring were used to assess their dietary habits.

Kidney disease was defined by reduced eGFR and/or elevated urinary albumin–creatinine ratio.

Table 2

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INDICATIONS AND USAGE

Anemia Due to Chronic Kidney Disease

OMONTYS is indicated for the treatment of anemia due to chronic kidney disease (CKD) in adult patients on dialysis.

Limitations of Use

OMONTYS is not indicated and is not recommended for use:

- In patients with CKD not on dialysis because of safety concerns in this population (see Warnings and Precautions).
- In patients requiring treatment for cancer and whose anemia is not due to CKD, because ESA has shown harm in some settings and the benefit-risk factors for OMONTYS in this setting have not been evaluated (see Warnings and Precautions).
- As a substitute for RBC transfusions in patients who require immediate correction of anemia.
- OMONTYS has not been shown to improve symptoms, physical functioning, or health-related quality of life.

CONTRAINDICATIONS

OMONTYS is contraindicated in patients with:

- Uncontrolled hypertension (see Warnings and Precautions).

WARNINGS AND PRECAUTIONS

Increased Mortality, Myocardial Infarction, Stroke, and Thromboembolism

In controlled clinical trials of other ESAs in patients with CKD comparing higher hemoglobin targets (13–14 g/dL) to lower targets (9–11 g/dL) (see Table 2), increased risk of death, myocardial infarction, stroke, and venous thromboembolic events was observed in the higher target groups. Using ESAs to target a hemoglobin level of greater than 11 g/dL increases the risk of serious adverse cardiovascular reactions and has not been shown to provide additional benefit. Use caution in patients with coincident cardiovascular disease and stroke. Patients with CKD and an insufficient hemoglobin response to ESA therapy may be at even greater risk for cardiovascular reactions and mortality than other patients. A rate of hemoglobin rise of greater than 1 g/dL over 2 weeks may contribute to these risks.

In controlled clinical trials of ESAs in patients with cancer, increased risk for death and serious adverse cardiovascular reactions was observed. These adverse reactions are a risk for patients with the presence of antibodies to pegibepatide. In the absence of antibodies to pegibepatide, following the recommended dosing schedule for management of a patient with an insufficient response to pegibepatide, there is a low likelihood ofSubscribe to OMONTYS. (Contact Affymax, Inc. 1-(855-466-6689) to request a personal consultation about the benefits of OMONTYS for your patient and how it may help improve your patient’s clinical outcomes.)

Hypertension

OMONTYS is contraindicated in patients with uncontrolled hypertension.

Increased mortality and/or increased risk of thromboembolism and/or myocardial infarction has been reported in patients treated with peginesatide. Reduce or withhold OMONTYS if blood pressure becomes difficult to control. Advise patients of the importance of compliance with antihypertensive therapy and dietary restrictions.

Lack of or Loss of Response to OMONTYS

For low or loss of hemoglobin response to OMONTYS, initiate a search for causative factors (e.g., iron deficiency, infection, inflammation, bleeding). If typical causes of lack of or loss of hemoglobin response are excluded, evaluate the patient for the presence of antibodies to pegibepatide. In the absence of antibodies to pegibepatide, following the recommended dosing schedule for management of an insufficient response to pegibepatide, there is a low likelihood ofSubscribe to OMONTYS. (Contact Affymax, Inc. 1-(855-466-6689) to request a personal consultation about the benefits of OMONTYS for your patient and how it may help improve your patient’s clinical outcomes.)

Dialysis Management

Patients may require adjustments in their dialysis prescriptions after initiation of OMONTYS. Patients receiving OMONTYS may require increased anticoagulation with heparin to prevent clotting of the extracorporeal circuit during hemodialysis.

Laboratory Monitoring

Evaluate transferrin saturation and serum ferritin prior to and during OMONTYS treatment. Administer supplemental iron therapy when serum ferritin is less than 100 μg/L, or when serum transferrin saturation is less than 20%. The majority of patients with CKD will require supplemental iron during the course

Diet and Nutrition Can Play a Pivotal Role in Improving Outcomes among Minorities and Reducing Health Disparities

Improving access to healthy foods is important to reducing health disparities and improving outcomes among lower-income individuals and minorities, at-risk populations for developing kidney disease in the United States. This was the conclusion of two new studies presented at Kidney Week 2012 that demonstrated increased intake of fruit and vegetables can ameliorate metabolic acidosis, and 2) an unhealthy diet lacking nutrients that indicate adherence to a DASH (Dietary Approaches to Stop Hypertension) diet—which is high in whole grains and fruits and vegetables—among individuals living in poverty can adversely impact their chances for developing CKD, some of whom already have an increased odds for disease progression. Both studies offer evidence that diet and nutrition present targets for reducing health disparities in individuals facing an increased risk for kidney disease.

Previous research into the effects of diet on CKD focused on limiting protein intake, most notably in the Modification of Diet in Renal Disease (MDRD) study, said Frank C. Brosius III, MD, of the University of Michigan Health System, who was not involved in either of the studies. The MDRD study, however, found no significant difference in outcomes based on diet, and despite interest in how nutrients and antioxidants impact kidney disease, “there have been no conclusive studies stating that dietary intervention leads to a statistically significant improvement in outcomes,” he said.

“This is why studies like these are exciting, because improving diet can be a low-cost high-safety intervention,” Brosius said. “The focus of this research is great, because if dietary changes can be shown to have an impact on progression of disease, particularly in those groups who are at highest risk for kidney disease, you can get the biggest bang for your buck.”
The majority in both poverty and non-poverty groups in the HANDLS cohort were found to be non-adherent to a DASH-style diet (only 4.5 percent and 6.1 percent, respectively, were adherent). Despite this, those in the poverty group fared significantly worse in levels of nutrients (cholesterol, fiber, magnesium, calcium, and potassium) and had a significantly higher rate of CKD compared with the non-poverty group (5.6 percent versus 3.8 percent).

When the entire cohort was stratified across tertiles of DASH adherence (lowest, middle, and highest) prevalence of CKD remained higher in the low and middle adherence tiers of the poverty group, but there was no statistically significant difference across the tiers in the non-poverty group. Logistic regression revealed similar findings, even after adjustment for inclusion of sociodemographic, and tobacco use variables.

Given these results, could specific factors lead to increased risk for individual in the poverty group? Crews said the reasons behind this relationship were unclear.

“The specific nutrient profiles could be the main drivers, as could additives in the foods of the poverty group (which we did not directly assess),” Crews said. It is also possible that dietary habits do not play as much of a role in CKD risk for higher income individuals because their risk is largely mitigated by access to health care, access to recreation, and less psychological stress. On the converse, dietary habits may play a bigger role in risk of CKD for poor individuals because they have so many risk ‘amplifiers’ (poor access to health care, limited access to recreation, significant stress, or discrimination), and thus when dietary habits are accessible, CKD might be lessened even in the setting of poverty.”

Brosius noted that although “it is a complex study, the results are consistent with the fact that the DASH diet tends to be more expensive, and the poverty group is more likely to be living in ‘food deserts’ where there is less access to DASH-style diets. However, those people in poverty groups who do adhere to DASH-style diets have a significantly reduced risk of CKD.” He added that a follow-up study would need to control for more than presence or absence of diabetes and hypertension, “but also having a diet rich in fat and animal proteins, in these groups, a DASH diet might be an effective preventative intervention.”

Crews is planning a tailored interventional study in a similar population, aimed at educating the participants on how to follow a DASH-style diet even with limited finances and limited access to healthy foods.

“As more evidence is revealed regarding the detrimental and costly effects of limited access to healthy foods we will see changes in policies on zoning and more incentives for full-service grocery stores opening in what are now food deserts,” Crews said. “I consider ours, and other studies of its kind, a call to action for members of the community to get involved in public policy.”

Fruits and vegetables can mitigate metabolic acidosis

Metabolic acidosis can commonly affect individuals with CKD and is associated with higher levels of angiotensin II, a pathway that powerfully promotes hypertension, a decline in renal function, and irreversible fibrosis of kidney tissue. This condition is exacerbated by a diet rich in fat and animal proteins, which generate a higher acid load than impaired kidneys can handle. Current clinical guidelines indicate alkaline thera- py for severe (<22 mM PTCO2) but not for milder (22–24 mM PTCO2) cases. To determine if patients with stage 3 CKD who suffer metabolic acidosis could also benefit from therapy, Nimrit Goraya, MD, of the Texas A&M College of Medicine and her co-workers investigated if adding fruits and vegetables (which generate a net alkaline load) or oral doses of sodium bicarbonate could reduce the decline in kidney function.

Building on their previous research, they performed a prospective trial with

Continued on page 16
Metabolic Acidosis

Continued from page 15

108 patients receiving antihypertensive medications and who were randomized to receive fruits and vegetables, oral sodium bicarbonate, or neither (control) for a period of 3 years. At the conclusion of the study, both the fruits and vegetables group and the oral bicarbonate group demonstrated significantly better outcomes in mean systolic blood pressure, urine angiotensinogen (a biomarker for angiotensin II activity), and eGFR when compared to controls. The fruits and vegetables group had a larger, but statistically significant, reduction in eGFR compared to controls. The fruits and vegetables group also had lower blood pressure than those receiving oral sodium bicarbonate. Goraya added that her group’s other studies have demonstrated the benefits of fruits and vegetables for patients with stage 4 CKD as well. Although you can’t make conclusions from a single randomized trial with a small population such as this one, the initial results look encouraging for those with mild metabolic acidosis,” said Brosius.

Goraya noted further benefits to those who received fruits and vegetables: a beneficial lifestyle change and weight loss. “They mainly received potatoes and raisins, which are relatively inexpensive, and it was easy for the participants to follow the diet and incorporate these changes.” The potato is the most alkali vegetable, and raisins, apples, and berries also have high alkali levels, she added. The study’s benefits weren’t limited to study participants because of a novel intervention mechanism: individuals received their fruits and vegetables at a local food bank and were provided enough for their entire family. In addition, “patients were followed for risk of potassium increases at serial 4 weekly intervals and no additional hyperkalemia risk was noted,” she said. Of note, the study population excluded diabetes and patients with potassium >4.6 mEq/L at baseline.

Can improved nutrition help reduce the effects of health disparities in these at-risk populations for developing CKD? Brosius says that these studies suggest that it might. “The implication of these studies, which have yet to be validated by other studies, is that the kind of diet that these studies recommend—high in fruits and vegetables and lower in animal protein and fat and lower in sodium—will in the long run have a significant impact on the outcome of patients who are at highest risk and live in poverty situations, and will mitigate some of that risk.”

Brosius cautions that physicians need to be aware of potassium levels, to ensure they don’t become elevated in patients with CKD, especially. “These are high-potassium diets and that’s the only risk associated with them, although it is a relatively modest one. These studies suggest that nutrition could possibly help in ameliorating the disparities in health care that individuals in poverty face,” which he concludes is “potentially a very positive low-cost intervention that may help long-term outcomes.”

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Medical Professionalism in the New Millennium: A Physician Charter. Translated into 12 languages, the "Physician Charter" has been endorsed by more than 130 organizations worldwide, including ASN, during the past decade.

The medical profession faces a proliferation of technology, fluctuating market forces, health care delivery challenges, and globalization, the Physician Charter observed 10 years ago. “As a result, physicians find it increasingly difficult to meet their responsibilities to patients and society,” stated the charter. “In these circumstances, reaffirming the fundamental and universal principles and values of medical professionalism, which remain ideals to be pursued by all physicians, becomes all the more important.”

As a guide to help physicians understand their professional responsibilities to individual patients and society as a whole, the charter focuses on three fundamental principles:

- Privacy of Patient Welfare. “The principle is based on a dedication to serving the interest of the patient. Altruism contributes to the trust that is central to the physician-patient relationship. Market forces, societal pressures, and administrative exigencies must not compromise this principle.”
- Patient Autonomy. “Physicians must have respect for patient autonomy. Physicians must be honest with their patients and empower them to make informed decisions about their treatment. Patients’ decisions about their care must be paramount, as long as those decisions are in keeping with ethical practice and do not lead to demands for inappropriate care.”
- Social Justice. “The medical profession must promote justice in the health care system, including the fair distribution of health care resources. Physicians should work actively to eliminate discrimination in health care, whether based on race, gender, socioeconomic status, ethnicity, religion, or any other social category.”

“For the past 10 years, the Physician Charter has provided a framework for ensuring the personal commitment of physicians to their patients as well as our collective effort to improve health care and benefit society,” said Donald E. Wesson, MD, FASN, who chairs the ABIM Foundation Board of Trustees. “Together, medical professionals, including nephrologists, and society must clearly understand the principles and responsibilities of medical professionalism,” added Dr. Wesson, who also serves as ASN Secretary-Treasurer. More than any external incentives or disincentives, according to Dr. Wesson, “actions driven by values internal to physicians, outlined in the Physician Charter, will help us successfully navigate through the crises facing modern medicine to improved and maintained health of the public that we have the privilege to serve.”

Commitment to medical professionalism

The Physician Charter articulates 10 professional commitments of physicians and health care professionals, including improving access to high quality health care, advocating for a just and cost-effective distribution of finite resources, and maintaining trust by managing conflicts of interest. The charter also includes a “commitment to professional competence” that states: “Physicians must be committed to lifelong learning and be responsible for maintaining the medical knowledge and clinical and team skills necessary for the provision of quality care.”

“ASN contributes to this commitment to professional competence by helping ABIM develop practice improvement modules, offering the Board Review Course and Update, producing the Nephrology Self-Assessment Program (NephSSAP), and providing opportunities for continuing education credits to physicians and other health professionals,” said ASN President Bruce A. Molitoris, MD, FASN. “Helping nephrologists maintain professional competence is core to ASN’s mission.”

Dr. Wesson noted that several of the challenges to medical professionalism the Physician Charter identified still remain present 10 years later: “We need to address growing disparities among the legitimate needs of patients, bolster available resources to meet those needs, harness the power of market forces to transform health care systems, and help physicians maintain their traditional commitment to the primacy of patients’ interests.”

Since 1999, the ABIM Foundation has been “working towards improving health care through the advancement of medical professionalism.” To accomplish this goal, the foundation promotes “organizational and policy forces to advance professional values and behaviors,” learns from international comparisons, engages physicians in advancing care, and supports new competencies to improve quality.

What is your reaction to “Medical Professionalism in the New Millennium: A Physician Charter”? How is the Physician Charter still relevant today? How do you teach medical students, residents, fellows, and other trainees about professionalism? If you could provide one suggestion for strengthening the charter on its 10th anniversary, what would you recommend? Please email your feedback about the charter to communications@asn-online.org. Thank you.

For example, the ABIM Foundation partnered with Consumer Reports and nine specialty societies, including ASN, on April 4, 2012, to launch the “Choosing Wisely Campaign.” Each society identified “Five Things Physicians and Patients Should Question” to help initiate conversations between physicians and patients about the actual need for many frequently ordered tests or treatments.

ASN’s contribution to the “Choosing Wisely Campaign” is available at http://www.asn-online.org/policy/choosing-wisely/. More than 20 societies are scheduled to join the campaign in 2013.

To learn more about “Medical Professionalism in the New Millennium: A Physician Charter” or the ABIM Foundation, please visit http://www.abimfoundation.org/.

Your membership matters.

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- Discounts on ASN’s live educational and distance learning programs
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Visit www.asn-online.org/membership for more information.
Medicare Announces Changes to ESRD Program for 2013 and Beyond

By Rachel Shaffer

In 2011, the U.S. Food and Drug Administration changed the erythropoietin stimulating agent (ESA) label, removing the recommended hemoglobin level of 10–12 g/dL, stating it could not identify a minimum safe target. CMS followed suit by eliminating a QIP measure ensuring a minimum hemoglobin level of 10 g/dL. Since then, many in the nephrology community have been concerned about potential for compromised patient access to ESA therapy or increased transfusions to treat anemia.

CMS acknowledged these concerns in its November ruling. While it recognized that there has been a slight but noticeable increase in transfusion rates since FDA and PPS modifications, the agency noted that any possible associations between the changes “are not yet known.” CMS explained that it is “working through our ESRD QIP monitoring and evaluation program to further assess the effects of the ESRD PPS.” Moreover, CMS finalized its proposal to implement an Anemia Management Reporting Measure, requiring facilities to report ESA dosage (if applicable) and hemoglobin/hematocrit values on at least one monthly claim. Similar to the mineral metabolism metabolism measure for 2015 and beyond.

Mineral Metabolism Reporting Requirements for Payment Year 2014

One of the key ASN recommendations that CMS adopted in the final rule was that facilities should exclude patients who received fewer than seven dialysis sessions in a month from QIP data reporting for the mineral metabolism measure that month. CMS originally proposed that data from patients receiving just two sessions should be included in QIP data reporting, but ultimately concurred with ASN and other commenters—that treating a patient twice may not provide enough time to ensure or assess) high-quality patient outcomes.

Similarly, CMS responded to concerns that requiring facilities to obtain and report data for patients who received dialysis treatments in other environments may be overly burdensome and not accurately reflect patient care provided in the facility. In the final rule, CMS stated that it recognizes “it may be difficult for facilities to coordinate with hospitals and other care providers in order to obtain lab values” and would not require reporting for those patients.

Home Dialysis

ASN urged CMS to ensure, to the extent possible, that all QIP measures include patients who dialyze via peritoneal dialysis or home hemodialysis (HHHD). The society specifically recommended expanding the existing National Health Safety Network infection reporting measure to PD and HHHD patients. While CMS did not implement the recommendation, it stated that it “will take these suggestions into consideration during future measure development and rulemaking.” Notably, CMS did integrate a peritoneal dialysis measure into the composite dialysis adequacy measure for the QIP in 2015.

ASN will continue to advocate for equitable, evidence-based QIP measures that apply to patients who dialyze at home.

Additions and Changes to QIP Measures for 2015

CMS finalized that, parallel to previous years, it will use all of calendar year (CY) 2013 as the performance period for payment year (PY) 2015. In 2015, CMS will continue to use five of the six QIP measures from PY 2014, but made changes to two measures and added four new ones:

- Clinical Measure for Dialysis Adequacy, a composite of three measures:
  - Hemodialysis Adequacy Minimum Delivered Dose (NQF #0249)
  - Peritoneal Dialysis Adequacy Delivered Dose Above Minimum (NQF #0318)
  - Minimum spKt/V for Pediatric Hemodialysis Patients (NQF #1423)

- Anemia Management Reporting Measure

In 2011, the U.S. Food and Drug Administration changed the erythropoietin stimulating agent (ESA) label, removing the recommended hemoglobin level of 10–12 g/dL, stating it could not identify a minimum safe target. CMS followed suit by eliminating a QIP measure ensuring a minimum hemoglobin level of 10 g/dL. Since then, many in the nephrology community have been concerned about potential for compromised patient access to ESA therapy or increased transfusions to treat anemia.

In the coming months, ASN will be working with CMS and the greater kidney community to ensure that subsequent additions to the QIP are appropriate and evidence-based, and critically important, to ensure that the impending addition of oral-only drugs to the PPS bundle is fair and maintains patient access.

Read more about ASN’s comments to CMS about the ESRD program online at www.asn-online.org/policy, and stay tuned to Kidney News in 2013.

Innovators Place Unveiled at Kidney Week 2012

Among the new features introduced at Kidney Week 2012 in San Diego was Innovators Place: a dedicated space to exhibit medical technologies not yet approved by the U.S. Food and Drug Administration (FDA). Inaugural exhibitors were selected by an ASN committee based on a set of criteria including the technology’s relevance to curing kidney disease and the exhibitor’s educational value for Kidney Week attendees.

The exhibitors—mostly U.S. and European start-up companies, as well as nonprofit academic labs—presented innovations ranging from a benchtop instrument for early detection of severe acute kidney injury (AKI) to a compression device to reduce postdialysis clotting time. For most participants, Innovators Place provided an opportunity to secure potential partners and investors.

One exception was Sempurus Biosciences, which was acquired 5 months before Kidney Week 2012 by Telzefex, Inc., and whose vascular access catheter received 501(k) clearance from the FDA 2 weeks after the meeting. Designed to reduce thrombus accumulation inside and outside the device, the catheter was exhibited at Innovators Place to generate awareness of the new technology, according to a Sempurus Biosciences representative. Based on biomaterial discoveries by Robert Langer, ScD, of the Massachusetts Institute of Technology, the catheter received European market clearance in July 2012.

Other exhibitors presented innovations that are in the early stages of development. Joris Rotmans, MD, PhD, from the Leiden University Medical Center (LUMC) in the Netherlands
said that he and his colleagues are searching for a commercial partner for the joint preclinical and clinical development of the Dutch group’s new technique for generating in vivo tissue-engineered blood vessels for hemodialysis vascular access. He noted the technique was developed at LUMC labs as part of the DialysisX consortium, a research collaboration with the University of Twente in the Netherlands, the Dutch Kidney Foundation, and the Swiss biotech firm Xeltis.

Also searching for partners is the French nephrologist Mokhtar Chawki, MD, founder of the Nephrokit company, which he said that he and his fellow nephrologists designed the sustained low-efficiency dialysis (SLED)-RCA technology to provide 100 percent-effective RCA with automated delivery using integrated intravenous pumps and optical blood and dialyzer effluent sensing. It can be adapted to most commercial renal replacement therapy devices with a customized RCA protocol and dialysis machine data interface program, Szamosfalvi said. In over 50,000 hours of clinical use, the technology prevented systematic citrate accumulation in patients with severe liver failure, and predictive-calcium infusion dosing maintains normal systematic ionized calcium levels, according to the display material.

Another Innovators Place participant was FAST BioMedical, whose co-founders include ASN President Bruce A. Molitoris, MD, FASN, of Indiana University. The Indianapolis medical device company has developed a small, durable bedside device to accurately measure GFR in approximately 40 minutes, based on technology licensed from Indiana University, said co-founder and president James Strickland. Over 30 clinical trials of FAST (Filtration Assessment and Surveillance Technology) have been conducted in Europe, Strickland said.

Argutus Medical of Dublin, Ireland, likely demonstrated the most professional marketing display at Innovators Place, where visitors learned about Re-naStar, a new point of care test bench-top device for early detection of AKI in critical care requiring 100 mL of patient urine. Argutus Medical also provided scientific information about the development and use of biomarkers for AKI detection.

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### Industry Spotlight

#### Trials for Best Ways to Treat Non-Dialysis–Dependent CKD

The search for effective treatments for non-dialysis–dependent chronic kidney disease (NDD-CKD) is gaining renewed interest. In the United States, more than one and a half million people suffering from stages 3 to 5 non-dialysis dependent NDD-CKD have iron deficiency anemia, but no oral iron supplements have yet been approved by the FDA for use for the condition. Likewise, no FDA-approved phosphate binders exist for use in NDD-CKD.

The federal government issued a request for application (RFA) for CKD clinical trials that closed on Nov. 21. That RFA sought pilot studies that optimize critical elements of a full-scale, randomized controlled trial design in return for U01 grant funding. The National Institute of Diabetes and Digestive and Kidney Diseases noted in its RFA that studies to date have looked at treatments and effects in small groups of patients, and that many questions remain regarding optimal dosing and drugs’ ability to reach appropriate patient outcomes.

One new NDD-CKD study that builds on earlier work was announced in early November, Keryx Biopharmaceuticals said that it had started a phase 2 study of its drug Zerenex (ferric citrate) for the treatment of patients with stage 3 to stage 5 non-dialysis dependent chronic kidney disease. Zerenex is a ferric iron–based phosphate binder drug candidate for managing serum phosphorus and iron deficiency in anemic patients with NDD-CKD.

Several studies have shown that higher serum phosphorus concentrations may be associated with increased mortality and morbidity in CKD.

The phase 2 study will be a multicenter, randomized, safety and efficacy clinical trial designed to compare the ability of Zerenex to manage serum phosphorus and iron deficiency versus placebo in anemic patients. Eligible patients will be randomized in similar groups to receive either Zerenex or placebo for a 12-week treatment period.

The primary endpoints of the study are designed to demonstrate changes in ferritin, transferrin saturation (the ratio of serum iron and total iron-binding capacity), and serum phosphorus levels over the 12-week treatment period.

The study plans to randomize about 150 patients from about 15 sites in the United States. Patient enrollment should take about six months, and Keryx expects the study to wrap up in mid-2013.

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### Journal View

#### Age Interacts with Kidney Measures on Mortality Risk

Although effects on relative versus absolute risk differ, low estimated glomerular filtration rate (eGFR) and high albuminuria are linked to increased mortality in all age groups, reports a study in The Journal of the American Medical Association.

The meta-analysis examined whether age modified the associations of eGFR and albuminuria with clinical outcomes. The investigators pooled individual-level data on more than 2 million members of Chronic Kidney Disease Prognosis Consortium (CKD-PC) cohorts. The data included 33 non-kidney disease cohorts (general population or people at high vascular disease risk) and 13 CKD cohorts. Clinical associations with eGFR and albuminuria were examined across age groups, with adjustment for other risks.

In non-CKD cohorts, individuals with lower eGFR and higher albuminuria were at higher risk of death and end stage renal disease (ESRD). At an eGFR of 45 mL/min/1.73 m² (versus 80 mL/min/1.73 m²), the adjusted hazard ratio for death decreased with age: from 3.50 for people aged 18 to 54 years, to 2.21 at 55 to 64 years, 1.59 for 65 to 74 years, and 1.35 at 75 years or older. In contrast, absolute risk increased with age: excess deaths per 1000 person-years were 9.0, 12.2, 13.3, and 27.2, respectively.

The absolute risk of death associated with higher levels of albuminuria also increased with age. At an albumin-creatinine ratio of 300 mg/g (versus 10 mg/g), excess mortality per 1000 person years was 7.5 at 18 to 54 years, 12.2 per 1000 at 55 to 64 years, 22.7 per 1000 at 65 to 74 years, and 34.3 per 1000 at age 75 or older.

The CKD cohorts showed no age-related decrease in the adjusted relative hazards of mortality. For all cohorts, the relative risks of ESRD and the absolute risk differences associated with both kidney markers were similar across age groups. It has been suggested that the CKD classification system should be revised to include a combination of eGFR and albuminuria levels. Before this is done, it is important to understand how age affects the clinical risks associated with these measures.

This meta-analysis finds that low eGFR and high albuminuria affect mortality risk in all age groups, across a wide range of populations. At older ages, the relative risk is lower but the absolute risk differences are higher. The researchers call for “a common definition and staging of CKD based on eGFR and albuminuria for all age groups” [Hallan SI, et al: Age and association of kidney measures with mortality and end-stage renal disease. JAMA. 2012; doi:10.1001/jama.2012.16817].
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