ASN LEADING THE FIGHT AGAINST KIDNEY DISEASE

KidneyNews

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Stem Cells Created from Adult Kidney Cells May Help Combat Disease

By Tracy Hampton

Researchers have genetically reprogrammed adult human kidney cells to become induced pluripotent stem (iPS) cells—a feat that may help in the study of kidney diseases and the development of novel therapies to treat them.

The findings could help millions of people with kidney disease, many of whom experience progression to end stage renal disease, which has only two treatment options: long-term dialysis or kidney transplantation. Effective alternatives are urgently needed for these patients, given the poor quality of life associated with dialysis and the increasing organ transplant waiting lists.

The study "Generation of induced pluripotent stem cells from human kidney mesangial cells" appears in the July issue of the *Journal of the American Society of Nephrology*.

"This research is the stepping stone for the development of iPS cells from patients with kidney disease, particularly genetic kidney disease, which has an extraordinary potential for new drug discovery and personalized medicine," said senior author Sharon Ricardo, PhD, of Monash University in Clayton, Victoria, Australia. "It will enable researchers to understand kidney disease in a way they have never been able to before."

Reprogramming kidney cells

Researchers have recently succeeded in reprogramming certain somatic cells to produce iPS cells. For example, pluripotent cells can be derived from mouse and human fibroblasts by the induced expression of four transcription factors (OCT4, SOX2, KLF4, and c-Myc), and iPS cell lines

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Recommendations Target Prevention of HIV Transmission to Transplant Recipients

By Tracy Hampton

In 2009, a kidney transplant recipient in New York City received a kidney that was far from ideal—it carried HIV.

The Centers for Disease Control and Prevention (CDC) recently released the details of a public health investigation into the case, which revealed the first confirmed case of HIV transmission through organ transplantation from a living donor reported since 1989 and the first such transmission documented in the United States since laboratory screening for HIV infection became available in 1985. The CDC's recent *Morbidity and Mortality Weekly Report* offers recommendations to help prevent such a serious event from occurring in the future (http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6010a1.htm?s_cid=mm6010a1_w).

"The recent acquisition of HIV through living donor kidney transplantation is extremely unfortunate, both for the specific recipient, and perhaps for public confidence in organ transplant safety more broadly," said University of

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Stem Cells

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can be generated from patients with certain genetic disorders.

In the current study, investigators questioned whether terminally differentiated kidney cells could be reprogrammed to pluripotency so that the resulting stem cells could differentiate into all three germ layers.

To answer this, Ricardo and her colleagues used normal human mesangial cells to derive iPS cell lines via genetic programming that consisted of transfection of 293FT cells with retroviral vectors containing the genes *OCT3/4, SOX2, KLF4*, and *c-Myc*. After several days, mesangial cells were reseeded on mouse embryonic fibroblast feeders. From 5 × 104 normal human mesangial cells, an average of 40 iPS colonies was observed. Numerous in vitro tests demonstrated that the kidney-derived iPS (kiPS) cells resembled human embryonic stem cell–like colonies in morphology and gene expression. For example, they were alkaline phosphatase positive; expressed OCT3/4, TRA-1-60, and TRA-1-81 proteins; and showed downregulation of mesangial cell markers. The kiPS cells expressed genes analogous to embryonic stem cells and showed silencing of the retroviral transgenes by the fourth passage of differentiation. In addition, the kiPS cells formed embryoid bodies and expressed markers of all three germ layers.

To test the cells' pluripotency in vivo, three immunodeficient mice were injected with kiPS colonies. Encapsulated cystic teratomas formed in all mice and showed differentiated tissues from all three germ layers.

"Our study for the first time provides proof-of-concept for the direct nuclear reprogramming of adult human mesangial cells to generate kiPS cells," the authors wrote.

Implications for the clinic

Patient-derived iPS cell lines generated by reprogramming somatic cells could have considerable importance in the clinic. "Induced pluripotent cells hold tremendous promise for stem cell and regenerative medicine," said Benjamin Humphreys, MD, who is codirector of the Harvard Stem Cell Institute's Kidney Group and was not involved with the research. "Since iPS cells appear to retain some molecular memory of their tissue of origin, this demonstration that kidney mesangial cells can be reprogrammed to pluripotency is an important step forward in developing this technology for disease modeling, toxicity testing, and ultimately cell therapy for patients suffering from kidney disease."

Ricardo noted that through the study of an individual patient's iPS cell line, researchers may be able to optimize that patient's preventive and therapeutic care.

Others in the field are interested to see what advances come next. "This article shows that the renal field, like many others, is embracing the possibility that iPS cell generation may act as a source of stem cells for eventual use in the repair of kidney disease," said Melissa Little, PhD, of the University of Queensland in St. Lucia, Queensland, Australia. "It should also be possible to make such cells from patients with genetic diseases such as polycystic kidney disease and potentially use them as tools to better understand such diseases," she added.

Paola Romagnani, MD, of the University of Florence in Italy, noted that the research may also advance drug development. "Mesangial cell–derived iPS cells may be helpful for screening of novel pharmacological compounds for treatment of these renal disorders," he said.

The study shows that human kidney biopsy specimens are a viable starting source for the generation of iPS cells," Little said, but "what this does not address is how to take these cells and then regenerate useful renal cells for treatment." To date, no one has developed a way of directing the differentiation of such cells into a kidney cell type.

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Prevention of HIV

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Pennsylvania School of Medicine's Scott Halpern, MD, PhD. "However, this extremely rare event provides both an opportunity for clinicians and transplant programs to revisit their practices and a useful reminder for clinicians and the public alike that no form of organ transplantation can ever be risk-free." Halpern has published numerous articles on ethical issues related to transplantation.

Public investigation

The public health investigation was initiated after the test results for both the recipient and the donor were positive for HIV approximately one year after the transplant. During the investigation, the donor and recipient, as well as the recipient's transplant coordinator, nephrologist, and HIV physician, and the donor's primary care physician and transplant nephrologist, were interviewed. Medical records were also reviewed. The donor reported unprotected sex with one male partner during the year before the transplant, including the time between his initial evaluation and organ recovery.

HIV nucleic acid testing on donor leukocytes collected 57 days before the transplant yielded negative results; however, DNA sequences for three HIV genes (envelope gp41, polymerase, and group-specific antigen p17) were detected from donor leukocytes collected 11 days before the transplant. Recipient serum collected 11 days before the transplant was nonreactive for HIV-1 RNA by Aptima (Gen-Probe), but serum collected 12 days after the transplant was reactive.

HIV DNA sequences from donor and recipient peripheral blood lymphocytes collected on day 404 were analyzed together with HIV DNA obtained from the donor's frozen leukocyte specimen collected 11 days before the transplant. The gp41, polymerase, and p17 sequences from the donor and recipient were nearly identical, suggesting that the two viruses are highly related.

When to screen

In this particular case, the donor was screened by enzymeimmunoassay 10 weeks before organ procurement but was not rescreened closer to the date of transplant surgery. According to the CDC, because individuals may acquire infections after such an initial evaluation, repeat testing is needed before organs are recovered from living donors.

Transplant centers should screen living donors for HIV as close to the time of organ recovery and transplantation as possible, but no longer than seven days before organ donation, using sensitive tests (such as serology and nucleic acid testing) for both chronic and acute infection.

As officials work to prevent transplantation of organs infected with HIV, they question whether it should be legal to transplant organs from donors who test positive for the virus to others who test positive.

Unlike in the late 1980s, now many individuals infected with HIV are living long lives and are developing conditions such as kidney disease. Also in contrast to the beginning of the AIDS epidemic, today's infected individuals are considered healthy enough to receive transplants.

Because transplant wait lists are so long, some experts are calling for a repeal of the National Organ Transplant Act, which was passed more than two decades ago and bans transplants from HIV-positive donors to HIV-positive recipients. Others are concerned about the ethical implications of making such a change though. Because HIV-positive recipients now have comparable outcomes following transplantation to HIV-negative recipients, "suggesting that HIV-positive recipients should get potentially substandard organs from HIV-positive donors is tantamount to suggesting that HIV-infected patients do not merit equitable access to higher-quality organs," said the University of Pennsylvania School of Medicine's Scott Halpern, MD, PhD. "I see no clear reason for drawing this dichotomy when similar restrictions are not placed on the donors from whom patients with hepatitis C may receive organs."

Halpern participated in an expert panel that oversaw the development of a new guideline, soon be issued by the Centers for Disease Control and Prevention (CDC), that includes recommendations on research into the risks and benefits of the use of organs from HIV-positive donors. The guideline also highlights new measures to prevent unexpected transmissions of infectious diseases from donors to recipients. "The draft *Public Health Service Guideline for Reducing Transmission of HIV, HBV, and HCV through Solid Organ Transplantation* currently is in Health and Human Services clearance," said Matthew Kuehnert, MD, the director of the CDC's Office of Blood, Organ and Other Tissue Safety. It is being published to replace the 1994 guideline and is being issued to improve transplant patient safety and outcomes through recommendations to organ procurement organizations and transplant centers, Kuehnert said.

fections. Nucleic acid testing can detect HIV infection before antibodies develop and are detectable by serology.

The window between the time of HIV infection and the time of development of detectable HIV-specific antibodies ranges from three to eight weeks, whereas with nucleic acid testing, the window is estimated to be eight to 10 days. Currently, the combination of HIV nucleic acid testing and serology is used to screen all donors who give blood or tissue; however, nucleic acid testing is not consistently used for screening organ donors.

The CDC recommends that all living donors be informed about modes of transmission and risk factors for HIV infection and counseled to avoid behaviors that would place them at risk for acquiring HIV infection before organ recovery. Individuals with a history of previous high-risk behaviors—such as high-risk sexual activity or use of injection drugs—that are identified during evaluation should receive individualized counseling and should be advised about specific strategies for avoiding risky behaviors. In addition, all transplant candidates should be informed during the evaluation process that despite donor screening, they have a very small risk of acquiring HIV or other infections as a result of transplantation.

"From a public health perspective, the goal is to enact policies that reduce the probability of disease transmission through organ transplantation without further restricting an already scarce organ supply," Halpern said. "The current CDC recommendations seem likely to toe that line appropriately, but follow-up will be needed to ensure that the new recommendations do not have unintended consequences such as unnecessarily delaying transplantations."

In 2009, the Living Donor Committee of the Organ Procurement and Transplantation Network (OPTN) and the United Network for Organ Sharing (UNOS) developed a voluntary guidance document for transplant programs regarding the medical evaluation of potential living donors. The document recommends that HIV testing be performed, but it does not identify the type of testing or the timing of the test.

"There is as yet no absolute testing requirement for living donors," said Connie Davis, MD, who is chair of the committee. "However, UNOS, in cooperation with transplant practitioner societies, is preparing recommendations for the medical evaluation and consent for living donors based upon current scientific knowledge and they should be ready in the next few months. This is part of the OPTN's new mandate to establish national policy for living donation in addition to that already accomplished for deceased donation.

"Optimizing safety will be a focus of the development of this document. We recognize the unique needs and circumstances involved in living donation and must act to maintain the health and safety of donors and recipients alike." Davis said.

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Industry Spotlight

Kidney Cancer News

Pfizer Inc. announced in June that it had asked European Union regulators to approve axitinib as a treatment for advanced kidney cancer.

According to Bloomberg *Businessweek*, Pfizer is seeking to market the drug to patients who have not had good results with other therapies for advanced kidney cancer. Many pharmaceutical business analysts are calling axitinib one of Pfizer's top drug candidates.

Designed to be taken orally, the candidate drug works by blocking receptors that influence cancer in several ways. The drug works to affect tumor growth, blood vessel growth, and cancer spread (metastasis).

In May, Pfizer said that axitinib met its primary goal in a late-stage clinical trial of 723 patients, inasmuch as patients who were treated with axitinib survived longer without disease progression than did patients who were treated with Nexavar, a different cancer drug manufactured by Bayer Pharmaceuticals and Onyx Pharmaceuticals. A report in Bloomberg News said that the group taking axitinib lived a median time of 6.7 months before their tumors grew, compared with 4.7 months for patients who received Nexavar. The data were presented at the American Society for Clinical Oncology annual meeting. The company said that it is working with other regulatory agencies on filings for approval of axitinib in other regions. It is also running other clinical trials of the drug in cases of kidney cancer and liver cancer.

The New York drugmaker said that about 210,000 people worldwide are diagnosed with advanced renal cell carcinoma every year, just under half—102,000 individuals—die of the disease, and about 20 percent of patients survive at least 5 years.

Another kidney cancer study of axitinib shows progress in preventing tumor growth, and a new gene is emerging as a candidate for therapy against the disease.

At a conference on nuclear medicine and imaging, a group from Radboud University Nijmegen Medical Centre in the Netherlands announced the results of a radioimmunotherapy agent, Lu-177-cG250, that may become another treatment option. A study of 20 patients showed that the compound works by locating the antigen associated with renal cell cancer and targets tissues with this antigen. It kills cancer cells while leaving healthy tissue intact. Each patient received a maximum of three doses, and at the 12-week posttreatment mark, the radioimmunotherapy had stabilized the cancer in 14 of 20 patients. The researchers found that the average decrease in tumor growth went from 28.5 percent growth in size before radioimmunotherapy to just 4.1 percent in the 3 months after the patients' first treatment, reported Asia News International.

In the early phases of discovery is a gene that may play a role in kidney cancer and may help patients who do not respond to current therapies, reported Ivanhoe Newswire, a broadcasting service. Oregon Health & Science University (OHSU) Knight Cancer Institute researchers found a gene that may be the key to helping patients whose kidney cancer is unresponsive to current therapies. This discovery could also provide a "toolkit" to identify patients who most likely could benefit from drugs that block this gene from causing cancer cells to grow.

Published in the June 1 edition of *Science Translational Medicine*, the study identified a gene, Src, that helps certain kidney cancers grow. The investigators found the gene using a mass spectrometry approach that showed the Src pathway was activated, suggesting that it had a role in the growth of cancer cells. They then assessed the role of Src in tumor tissues from patients with renal cancer.

"We found that patients with tumors expressing high levels of Src had worse survival rates than those patients whose tumors had weak expression of Src," said George Thomas, MD, senior author of the study and an OHSU surgical pathologist. "This suggested to us that Src played a role in kidney cancer and that it was a therapeutic target worth exploring."

Affymax Moves for Approval

Affymax, a company based in Palo Alto, CA, and its partner, Takeda Pharmaceuticals of Osaka, Japan, are making a bid for U.S. Food and Drug Administration (FDA) approval of the drug peginesatide, used to treat anemia in patients with advanced chronic kidney disease.

The companies have submitted a new drug application to the FDA. The drug is a synthetic PEGylated peptidic compound that binds to and activates the erythropoietin receptor. It acts like an erythropoiesis-stimulating agent.

This move won't come without a fight, however. Johnson & Johnson may block that bid with a patent suit to protect its interests.

The Affymax drug was studied in patients with chronic kidney failure who were not receiving dialysis. Although the drug met its goals in that study, the side effects were more severe for patients who were not receiving dialysis.

According to Forbes magazine, the companies face a potential challenge from a relative giant, Johnson & Johnson, whose drug Procrit, another type of erythropoietin drug, is used to treat anemia in patients who are receiving dialysis for kidney failure or who are being treated for cancer. In October, an arbitrator ruled that Johnson & Johnson was the owner of a group of patents on those drugs.

Affymax said that it thinks the patent is invalid and doesn't apply to Procrit or peginesatide. Nevertheless, the ruling could allow the sole owner, Johnson & Johnson, to sue Affymax for patent infringement. If Affymax asks a federal court to overturn the decision, this could apply to current patents and applications in the United States, Canada, Australia, Japan, and Europe.

ASN News

JASN's Impact Factor Hits New High

On June 26, 2011, Thomson Reuters released new impact factor calculations for their 2010 Journal Citation Reports. The impact factor is an average composite measure of the frequency with which articles from a peer-reviewed journal are cited over a given two-year period; the 2010 impact factor, reported in 2011, reflects papers cited in 2008 and 2009 divided by the total number of papers published over that time. The *Journal of the American Society of Nephrology (JASN)* retained its ranking as the top journal in nephrology with a 2010 impact factor of 8.288, up from 7.111 in 2007. *JASN*'s impact factor has risen quickly under the leadership of its current editorial team.

Editor-in-chief Eric G. Neilson, MD, FASN, shared with *ASN Kidney News* his view of the value of this measure of journal performance. "Impact factor provides an easy way to rank order those journals publishing citable material over a discrete period of time. *JASN* has the good fortune of having a wonderful pool of authors submitting their best work to a superb group of associate editors who pick great papers relevant to nephrology that happily get cited more often."

We asked Dr. Neilson what he tells young authors about choosing a journal to submit their manuscript to. "Before submitting a manuscript, they should read carefully through a group of journals to evaluate the quality of their published work and to get a sense of the selection criteria that might apply. The higher a journal's impact factor, the more competitive and widely read it is likely to be. One should always strive to publish in the best journal you can."

What does Dr. Neilson look for in a manuscript? He encourages authors to tell a compelling story, to try and fit their work into a larger theme, and to provide data that well supports a novel message. No doubt many more will try to do just that as *JASN* continues its impressive rise.

Social Media and Health Care: Moving Medicine Forward ▶▶▶

By Jennifer Young

Social media provide powerful, game-changing tools for health care providers and patients

In a series of videos produced by the American Society of Nephrology, a physician and a social media expert discuss how physicians, researchers, and patients can use current social media tools to benefit their patients, themselves, and their organizations.

Victor Montori, MD, and Lee Aase, of the Mayo Clinic Center for Social Media, discuss these new communication tools. In the first video, "Social Media for Patients and Physicians," Montori, medical director at the Mayo Clinic Center for Social Media, explains how social media allow organizations to communicate directly with patients and to participate in "unmediated" conversations. It gives us a "bigger ear on the world," he said, "and provides a good channel for patients to give feedback."

Many physicians find it difficult to see the benefit of social media, Montori says. They don't have much time to spare. But social media can be a time saver. He describes how following people of interest on Twitter helps "crowdsource" his own web browsing. The people he follows send him interesting content and links. "It makes my time online *more* efficient."

Lee Aase, manager of syndication and social media at the Mayo Clinic Center for Social Media, discusses organizational uses of social media. The Social Media Health Network helps health care organizations around the world share how they use these new tools, create a master database of patient support groups, and establish new ways to help researchers connect. This network also improves global health literacy, he says. Currently, more than 70 health care organizations around the world belong to the network (www.socialmedia.mayoclinic.org/network).

Social media also provide direct patient benefits. Research results and the most effective therapies can be disseminated more quickly, and patients learn more about managing their health. For example, Aase noted, a mainstream media story might spend 90 seconds describing a condition, but a patient care organization might produce a 10-minute YouTube video on the same topic. "We are reaching a very targeted audience: people who watch these videos have *searched* for that information."

Patients not only share their stories but help spread valuable information to others. "Content that is developed in one place can be shared throughout the world," says Aase. Health care organizations can produce content that helps teach the public how to make sense of scientific studies. The public can then spread this information, improving overall health literacy. The clinic's Center for Social Media hosts this information on its recently launched Social Media Health Network. The center also maintains a database of online patient support groups on the network, so newly diagnosed patients can easily find discussions on their conditions. Many of these social media efforts will improve the work of health care professionals and the lives of the patients they care for.

The links to the Youtube videos are as follows:

Part 1 http://bit.ly/hDJycD

Part 2 http://bit.ly/isz3CN

Part 3 http://bit.ly/l1SlW6

Prevent Kidney Disease to Lower High Level of Cardiovascular Risk

By Daniel M. Keller

With the incidence and prevalence of cardiovascular disease (CVD) increasing worldwide and its connection to chronic kidney disease (CKD), the new president of the European Renal Association – European Dialysis and Transplant Association outlined in a news conference at the association's 48th Congress in Prague several steps by which physicians can help to alleviate the personal and economic burdens of CVD. CVD is responsible for about 10 percent of all illness and 30 percent of all deaths in the world.

Raymond Vanholder, MD, PhD, professor of medicine at the University of Ghent and clinical head of the nephrology division of the Ghent University Hospital in Belgium, said the most prominent risk factors for CVD are type 2 diabetes, hypertension, hypercholesterolemia, smoking, and overweight. Among other negative outcomes, obesity often leads to hypertension and disturbances in blood glucose and lipid metabolism. Besides poor diet, other unhealthy lifestyle factors such as physical inactivity, stress, alcohol consumption, and smoking increase the risk of CVD.

While the connection between CKD and CVD has been recognized only fairly recently, Vanholder made the point that it is significant and unmistakable. Even minor renal dysfunction confers a significantly greater risk of CVD, and a published community-based population study (Go AS et al. *N Engl J Med.* 2004; 351:1296–1305) on more than one million people with a mean age of 52 years has shown an independent association between a rising glomerular filtration rate (GFR) and mortality, cardiovascular events, and hospitalizations.

At the extreme end of the spectrum—people with end-stage renal disease on hemodialysis – the mortality risk may be hundreds-fold higher compared to the general public. Vanholder showed data that patients on dialysis aged 25 to 34 years have 375-fold higher risk of death compared with their healthy counterparts. The elevated risk compared to the general population decreases for older groups but is still significant. "Even for people 75 to 84 years old, which is people who have not much to go anymore, even there the mortality risk is five times higher in the patients on hemodialysis," Vanholder showed.

For people who started on dialysis as children, their coronary artery calcification scores, a marker of atherosclerosis, remained fairly low until age 20 years but then increased exponentially. By age 30, "they show a calcification pattern that is worse than in normal people of age 80 or 90," he said. (See Goodman WG et al. *N Engl J Med*. 2000; 342(20):1478–83). For patients who underwent follow-up measurements, their calcification scores nearly doubled over a mean period of 20 months.

Next he showed that the age-adjusted risk of death from any cause is directly related to the GFR. With a GFR of 60 mL/min/1.73 m^2 or greater, the risk of death was 0.76/100 person-years. At a GFR of 45–59, essentially a loss of at least half one's kidney function, the rate rose to 1.08/100 person-years. But as the GFR dropped below 45, the death rates rose precipitously, and with a GFR below 15, the death rate was 14.14/100 person-years.

Vanholder noted that dialysis is begun with a GFR below 15, so the increased risk of death persists for years even before dialysis is initiated. His own work has shown that mortality risk begins to increase as the GFR drops below 75 mL/min/1.73 m^2.

"The big problem is that these people do not feel bad… and some people appear [at the nephrologist] only at the moment they need dialysis," he said. "So screening is really something which is very necessary." Estimates are that at least 10 percent of the global population has a GFR of 60 mL/min/1.73 m^2 or below. Most will die before they ever reach the stage of dialysis.

What to do

Vanholder said there needs to be better recognition of the association between CKD and CVD among the general population, politicians, and especially among physicians. Screening allows earlier referral to nephrologists and the potential to slow the progression of CKD.

Albuminuria is an early indicator of CKD, and so is the serum creatinine level. In the Heart Outcomes and Prevention Evaluation (HOPE) trial (Mann JF et al. *Ann Intern Med*. 2001; 134:629-–636) of patients with pre-existing vascular disease or diabetes plus an additional risk factor, at a serum creatinine level of 1.40 mg/dL there was a 40 percent higher cardiovascular risk. This level "is not much, [and] many doctors would even consider this number as a normal number," Vanholder noted. For comparison, he said male sex, often seen as a significant risk for CVD, raised the risk by only 2 percent.

Many preventive interventions are inexpensive or free. Smoking decreases kidney function, so smoking cessation is a cheap (and even money-saving) beneficial lifestyle change. Vanholder called salt "very toxic for the kidneys," so salt restriction, both on a per-patient and population basis, is highly recommended. Additional inexpensive measures are correction of body mass index, exercise, treatment of hypertension, and use of aspirin to treat blood hypercoagulability.

More expensive but effective interventions apply to diabetes, dyslipidemia, and anemia. Specific to the nephrologist are treatment of volume status, maintenance of nutritional status, and calcium/phosphate metabolism.

Vanholder said the best use of resources is to focus on the groups at highest potential risk. Some that are generally addressed are people with diabetes, hypertension, a family history of renal disease, previous renal damage or risks for it, and proteinuria. "What is perhaps more important are the ones we do not necessarily think of," he emphasized. These include smoking, infectious diseases such as hepatitis B or C and HIV, age above 60 years, and CVD, "and most of all, obesity or what we call the metabolic syndrome," he said. "I think the most important thing is that medical doctors have to be aware that these are the risk factors, and they have to check the kidney function attentively in those people, and from the moment there is an alarm sign, they have even more even reasons to try to convince these people to be careful.

"The earlier you start, the better. With most of these measures you cannot return the whole picture [of kidney function], but at least you can stabilize it and prevent the kidney function from going down further, and very much in parallel with this, the cardiovascular system will also be better protected."

Nighttime drugs

Greater Cardiovascular Risk Reduction With Antihypertensives at Bedtime Than in Morning

One simple, no-cost change appears to lower cardiovascular (CV) risk among patients with resistant hypertension. By taking their antihypertensive medications at bedtime instead of in the morning, patients in a Spanish trial significantly reduced their cardiovascular risk.

Researchers have known that sleep-time blood pressure (BP) better predicts CV risk than does either the awake or 24-hour BP means. However, all previous studies relied on a single baseline ambulatory blood pressure monitoring (ABPM) profile on each participant at the beginning of the study. Thus, they could not detect changes in the pattern or level of BP if they occurred.

Reporting at the 48th Congress of the European Renal Association—European Dialysis and Transplant Association in Prague, lead investigator Ramón Hermida, PhD, director of the laboratory of bioengineering and chronobiology at the University of Vigo in Vigo, Spain, told *ASN Kidney News* that his study tested the hypothesis that bedtime dosing of at least one blood pressure medication would more effectively reduce CV disease (CVD) risk than would conventional morning dosing of all of a patient's antihypertensive medications. He pointed out that bedtime dosing is a cost-effective and simple strategy to achieve adequate asleep BP reductions and to re-establish a normal 24-hour pattern of BP reduction at night ("dipping pattern") if it is missing.

Hermida reported the results of a substudy of a larger study of people with hypertension, which was prospective, randomized, and open-label. In the substudy, 776 participants with resistant hypertension had a mean age of 61.6 years, an approximately equal number of men and women, and were randomly assigned to take all their prescribed BP medications upon awaken-

ing or at least one of them at bedtime. At the physician's discretion, additional antihypertensive medication could be added as required, but no nighttime medication was allowed in the morning, meaning that any one drug could not be taken at both times. For controls, who took all BP medication in the morning, any additional BP medications also had to be taken in the morning.

At baseline, BP was measured at 20 min intervals during waking hours and at 30 min intervals at night. A wrist actigraph recorded periods of daytime activity and noctural sleep. These measurements were performed annually, or quarterly if treatment adjustments were necessary. Patients were followed for a median of 5.4 years.

Lower risk of CV events with bedtime dosing

The group of patients assigned to take at least one medication at bedtime had significantly better BP control during sleep, with a greater reduction in the asleep BP mean and the asleep BP declines constituting a more normal dipping pattern when compared to patients taking all their BP drugs in the morning.

When several characteristics of the ABPM were applied in a Cox regression model, only the decrease in sleeping BP was an independent predictor significantly associated with survival. Neither the daytime BP mean nor the morning surge in BP were predictors of survival. The nighttime dosing group had a 62 percent lower relative risk of total CV events compared to the morning group (relative risk 0.38, $p<0.001$). Their relative risk of major CV events, consisting of CVD death, myocardial infarction, or ischemic or hemorrhagic stroke, was 0.35 ($p=0.002$).

Referring to the BP study as a whole and not just the results in resistant hypertension, Hermida said that bedtime dosing was associated with greater reductions than morning dosing in the risk of all the individual endpoints of CV mortality, myocardial infarction, development of heart failure, or stroke. These results were true for the study population as a whole as well as when patients with diabetes or CKD were analyzed separately. "These two groups are relevant because they are characterized with a significantly higher cardiovascular risk as compared to the general population," he said.

Survival advantage with nighttime dosing

At 8 years of follow-up, the group taking at least one BP medication at bedtime had an event-free survival of about 81 percent compared to approximately 64 percent for the group taking all medications in the morning ($p<0.001$). For every 5 mm Hg decrease in sleep time systolic or diastolic mean BP, there was an 11 percent decrease in the relative risk of a CVD event.

Antihypertensive drugs are normally recommended once a day without specifying a time of day. Surveys in Spain have shown that more than 80 percent of all patients with hypertension take all their BP drugs in a single morning dose. Hermida said there is no clinical rationale for this practice, and in fact, his results argue against it. "From the point of view of cardiovascular risk reduction and renal protection what we found is that most if not all of the hypertensive medications perform much better when ingested in the evening," he concluded.

"Blood pressure level is not the only significant cardiovascular risk factor. However, it has been basically the only therapeutic goal from the point of view of hypertension treatment so far," he said. "Controlling nighttime blood pressure needs to be considered as a therapeutic target for cardiovascular risk reduction."

The main study results were published last year in *Chronobiology International* (2010; 27(8):1629–1651). A substudy of patients with type 2 diabetes was recently published in *Diabetes Care* (2011; 34:1270–1276).

Bardoxolone Reverses Kidney Function Decline in CKD Out to One Year

By Daniel M. Keller

Patients with advanced chronic kidney disease (CKD) and type 2 diabetes who took bardoxolone, a first-in-class oral antioxidant inflammation modulator, continued to show improvements in their estimated glomerular filtration rates (eGFR) at 52 weeks, mirroring results at 24 weeks that were presented at least year's American Society of Nephrology meeting in Denver.

Speaking at the 48th Congress of the European Renal Association – European Dialysis and Transplant Association (ERA-EDTA) in Prague, David Warnock, MD, professor of medicine at the University of Alabama at Birmingham, told the congress that these latest results suggest that the drug may be useful for treating CKD, although larger confirmatory trials are still needed. The findings were published online by the *New England Journal of Medicine* on June 24.

The phase 2b, randomized, double-blind, placebo-controlled Bardoxolone Methyl Treatment: Renal Function in CKD/Type 2 Diabetes (BEAM) trial (NCT00811889) assigned 227 adults with type 2 diabetes and an eGFR of 20–45 mL/min/1.73 m^2 equally to 1of 4 groups: bardoxolone at a dose of 25 mg, 75 mg, or 150 mg once daily, or to placebo. All patients received the standard of care of a renin-angiotensin-aldosterone system blocker unless they could not tolerate them. The primary endpoint was the change in eGFR from baseline with bardoxolone compared to placebo at 24 weeks, and the secondary endpoint of the change at 52 weeks was reported at the ERA-EDTA meeting.

Baseline variables for the four treatment groups were similar: a mean age of 67 years, a time from diabetes diagnosis of approximately 18 years, and a body mass index of 35.0–36.3 kg/m^2. The mean eGFR was 32.4 ± 6.9 mL/min/1.73 m^2. Blood glucose levels and blood pressure were generally well controlled.

Durable improvements in eGFR at 52 weeks

The eGFR increased within four weeks of starting bardoxolone, reached a peak at 12 weeks, and was relatively stable through 52 weeks, Warnock showed. At 24 weeks, the eGFRs in all the bardoxolone groups were significantly higher than in the placebo arm ($p<0.001$). At 52 weeks, the changes in eGFR continued to be superior to placebo, which showed no significant changes from baseline at either time point. The 52-week increases in eGFR were 5.8, 10.5, and 9.3 mL/min/1.73 m^2 for the 25 mg, 75 mg, and 150 mg doses, respectively ($p \le 0.002$ vs. placebo).

At 24 weeks 13 percent of patients in the placebo arm had a reduction in eGFR of at least 25 percent, whereas only 2 percent in the combined bardoxolone groups lost that amount of kidney function ($p=0.05$).

Even four weeks after the drug was stopped, the bardoxolone groups still showed increases in eGFR although at a lower level than when they were on the drug. Warnock noted that the persistent effect, especially in patients with the greatest increases in eGFR, suggests that the drug did not merely act by causing hyperfiltration and did not appear to cause any kidney injury over the 52 weeks of the trial. Blood urea nitrogen, serum phosphorus, uric acid, and magnesium decreased at both time points in the bardoxolone groups compared with placebo.

The majority of adverse events occurred in the first 24 weeks and were generally mild and dose related. Muscle spasm was the most common one, with hypomagnesemia, mild increases in aminotransferase levels, and gastrointestinal effects occurring less frequently.

Warnock told *ASN Kidney News* that the study was successful in achieving its primary goal of demonstrating a dose of bardoxolone for future trials and that the adverse events observed were acceptable when bardoxolone was added to the current standard of care therapy.

There remains some concern among nephrologists that increasing the GFR may have some negative consequences since previous studies have suggested that a decrease in GFR may slow the progression of kidney disease in the long term. Further studies will need to assess the effects of the drug in a larger population, including patients with CKD but who do not have diabetes.

Reata Pharmaceuticals and Abbott are starting the Bardoxolone methyl EvAluation in patients with Chronic kidney disease and type 2 diabetes: the Occurrence of renal eveNts (BEACON) trial, a 1600-patient multinational study to assess the impact of bardoxolone methyl on the time to the important clinical endpoints of cardiovascular death or time to progression to dialysis.

For more information, see the Q and A in *Kidney News'* dynamic edition.

RAVE trial

Short Course Rituximab Gives Long-lasting Results in ANCA Vasculitis

By Daniel M. Keller

A single 4-week course of rituximab was as effective as 18 months of standard therapy with daily oral cyclophosphamide (CyP) and azathioprine (AZA) for induction of remission and maintenance therapy of severe anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV). The number, rate, and severity of adverse events was similar between the treatment groups, Cees Kallenberg, MD, PhD, professor of clinical immunology at University Medical Center Groningen in Groningen, Netherlands, reported at the 48th Congress of the European Renal Association-European Dialysis and Transplant Association in Prague in June. Rituximab is a monoclonal antibody directed against B lymphocytes.

AAV, an autoimmune disease, affects small blood vessels in multiple organ sites. It can attack the capillaries of the glomeruli, and glomerulonephritis is common in patients with AAV. Left untreated, AAV has a very poor prognosis.

The Rituximab in ANCA-Associated Vasculitis (RAVE) trial tested whether rituximab would be as effective as cyclophosphamide to induce remission of severe AAV. The primary endpoint in the trial was complete remission at 6 months, as measured by a Birmingham vasculitis activity score specific for Wegener's granulomatosis (BVAS/WG) of 0 and no need for corticosteroids. (WG is one form of AAV.)

Eligible patients had active or severe AAV—either WG or microscopic polyangiitis. The trial design specified that at least half of the participants were to have WG, with a BVAS/WG score of 3 or greater, require cyclophosphamide, and be ANCA-positive at screening. All patients were followed for at least 18 months.

All 200 trial participants initially received 1 to 3 grams of methylprednisolone and were then randomly assigned to a rituximab group or to a CyP/AZA group. The rituximab group received rituximab infusions once weekly for 4 weeks, followed by CyP-placebo for 6 months and AZA-placebo for 12 more months.

The other group took oral CyP daily for 3 to 6 months and rituximab-placebo infusions. For those patients who achieved remission, CyP was replaced by AZA between months 3 and 6 and continued for the remainder of the 18 months. All patients in both groups received daily prednisone, which was tapered over 5.5 months.

If the assigned induction therapy failed, patients were crossed-over to the other treatment. Or if remission was lost for patients while they were taking AZA maintenance therapy, they then received rituximab in an open-label fashion. Analysis of results was on an intention-to-treat basis, meaning participants' results were analyzed according to the original treatment group to which they were assigned.

The groups were well matched at baseline: two-thirds of the patients were positive for antibodies against proteinase 3 (PR3), one-third for antibodies against myeloperoxidase (MPO), one-quarter had microscopic polyangiitis, and three-quarters had WG. The rituximab (n=99) and CyP/AZA (n=98) groups had similar BVAS/WG scores (5.6–5.7) and scores on the physical and mental components of the SF-36 questionnaire, which profiles functional health and well-being.

Rituximab induced complete remissions at least as well as CyP/AZA

"B cells were undetectable after 2 infusions of rituximab and stayed undetectable during 6 months," Kallenberg reported. CyP was also effective in reducing B cell counts out to 6 months. Results were the same for patients with either the MPO or PR3 form of ANCA.

At 6 months, "the primary endpoint was reached, which means that rituximab is not inferior to cyclophosphamide for induction of remission," Kallenberg told the conference attendees. By that time, 64 percent of patients on rituximab and 53 percent receiving CyP had achieved remission (p=0.089).

The proportion of newly diagnosed patients experiencing a remission was about the same in the 2 groups (60 to 65 percent), but for patients with a severe disease flare, rituximab administration was associated with more responses (67 vs. 42 percent; p=0.013). MPO-ANCA patients did as well with either treatment, but for PR3-ANCA, more patients responded in the rituximab group (65 vs. 48 percent; p=0.04).

Short course rituximab effective for 18 months

At 12 and 18 months, fewer patients remained in each treatment arm, but overall, patients continued to respond to the therapies, and there was no significant difference in the proportions of remissions. At 18 months, the rituximab group had 39 out of 47 patients still in remission, compared to 32 out of 38 patients in the CyP/AZA group.

Similarly, the groups did not differ in the number of severe or limited disease flares at either time point. Most treatment failures were because of disease flare or the need for prednisone, usually for conditions other than AAV.

Flares were associated with the return of detectable B cells. Of the 76 patients randomized to rituximab who had achieved complete remission, 16 flares occurred after 6 months and were treated with open-label rituximab. "All these 16 severe flares occurred in the presence of detectable peripheral blood B lymphocytes," Kallenberg reported.

Adverse events or serious adverse events occurred about equally in the 2 arms, with 2 deaths in each treatment group. Eighteen of 99 rituximab patients developed grade 3 infections, compared to 16 of 98 CyP/AZA patients.

Kallenberg summarized the trial results, saying that both treatments were associated with similar rates of complete remissions at 12 and 18 months, the times to complete remission and to first disease flare were similar, as were the rates of severe and limited flares. Severe flares rarely occurred in the absence of B cells. He concluded, "One course of 4 weekly infusions of rituximab without any maintenance treatments is as effective as 18 months treatment of standard therapy with daily oral cyclophosphamide followed by azathioprine."

An important issue for the future will be to identify patients who will do best on rituximab as either front-line or rescue treatment, given the expense of the drug. And while the adverse event profile of the RAVE trial looks good, there is still some concern about the potential for infectious complications when rituximab is used.

Policy Update

FDA Abandons ESA Target Range, Lowers Dosing Recommendations

By Rachel Shaffer

The U.S. Food and Drug Administration (FDA) recently recommended more conservative dosing guidelines for erythropoiesis-stimulating agents (ESAs) used to treat anemia in patients with chronic kidney disease (CKD), for both patients receiving dialysis and those not receiving dialysis. Before the FDA's announcement on June 24, 2011, product labels for ESAs recommended dosing to achieve and maintain hemoglobin levels within the target range of 10–12 g/dL in patients with CKD.

The modified guidelines remove the concept of a target hemoglobin range and instead now recommend that "Physicians and their patients with chronic kidney disease should weigh the possible benefits of using ESAs to decrease the need for red blood cell transfusions against the increased risks for serious adverse cardiovascular events. For each patient, individualize dosing and use the lowest dose of ESA sufficient to reduce the need for transfusion."

For patients with the anemia of CKD who are not receiving dialysis, the FDA now recommends that physicians consider starting ESA treatment only when the hemoglobin level is less than 10 g/dL and when certain other considerations apply, and that if the hemoglobin level exceeds 10 g/dL, the dosage of ESA should be reduced or interrupted.

The FDA also now recommends that for patients with the anemia of CKD who are receiving dialysis, physicians begin ESA treatment when the hemoglobin level is less than 10 g/dL. If the hemoglobin level approaches or exceeds 11 g/dL, the dosage of ESA should be reduced or interrupted.

"Health care practitioners should carefully consider when to begin treatment with an ESA and actively monitor dosing in patients with chronic kidney disease, keeping in mind the increased risk for serious cardiovascular events, and should talk to their patients about these potential risks," said John Jenkins, MD, director of the office of new drugs in the FDA's Center for Drug Evaluation and Research. "The goal is to individualize therapy and use the lowest ESA dose possible to reduce the need for red blood cell transfusions."

The FDA cited data from clinical trials, including TREAT (Trial to Reduce Cardiovascular Events with Aranesp Therapy), as the basis for guideline changes, stating that "TREAT showed using ESAs to target a hemoglobin level of greater than 11 g/dL increased the risk of serious adverse cardiovascular events, such as heart attack and stroke, and provided no additional benefit to patients." The use of ESAs to treat anemia in patients with CKD was most recently discussed at the Cardiovascular and Renal Drugs Advisory Committee meeting in October 2010. ASN public policy board member Wolfgang Winkelmayer, MD, ScD, FASN, presented testimony on behalf of the society at that meeting.

Besides changing the labels and recommendations for ESAs, the FDA is also requiring Amgen, the manufacturer of Epogen, to conduct at least two new clinical trials of its product. One trial should identify the optimal ESA dosage and schedule strategy in patients with CKD who are receiving dialysis, and the other should determine whether a fixed dosage strategy different from what the currently approved label recommends can further reduce exposure to ESA while preserving the benefit of reducing transfusion use in patients with CKD who are not receiving dialysis.

"Though the long-term effects of the new FDA recommendations are as of yet unclear, I see some potential pros and cons," said ASN public policy board chair Thomas Hostetter, MD. "I think it's heartening that the FDA has so emphasized individualizing patient care. Yet, as always, we remain deeply concerned about protecting patients' access to ESAs in order avoid blood transfusions and maintain a high quality of life."

Caring for Those Who Serve: A Brief History of Veterans Affairs Research

By Daniel Kochis

Throughout its history, the government of the United States has traditionally expanded services to veterans after the outbreak of a major conflict. Whereas individual states initially carried the majority of the burden of caring for wounded soldiers, the federal government has gradually expanded its responsibility in this arena. During the Revolutionary War, disabled soldiers received pensions from the Continental Congress (although Congress did not have money to provide for many of them); however, hospital medical care was the responsibility of an individual soldier's home state. During the Civil War, some states began to establish centers specifically designed to care for the large number of wounded soldiers returning home from the battlefield. In 1865, the National Home for Disabled Soldiers was founded by Congress to care for wounded Union soldiers (Confederate soldiers were not eligible for federal benefits until 1958).

It was not until World War I that the federal government began to formally administer a full benefits system for veterans, and it initially did so through three agencies scattered among a few different federal cabinet departments. In 1930, the activities of these agencies were combined to form the Veterans Administration. Throughout the next 50 years, each major conflict the United States engaged in resulted in an expansion of benefits for veterans after the war. Increasing federal responsibility for the care of wounded veterans led in 1989 to the creation of the Department of Veterans Affairs, a cabinet-level agency, which continues to expand today with the influx of new veterans from the wars in Iraq and Afghanistan. Swelled by these recent conflicts, and by the baby boomer generation cohort of veterans who are now advancing in age and increasingly consuming medical care, the VA system has greatly expanded to become a significant provider of medical care in the nation (Table 1).

The VA's office of research and development is today one of this government's health care research entities, along with the National Institutes of Health (NIH) and the Agency for Healthcare Research and Quality. However, the relationship between the VA and the NIH remains collaborative rather than competitive, inasmuch as the NIH is the most prominent source of additional funding for VA investigators.

In addition to NIH funds, the VA Research and Development Program received $590 million in congressional appropriations in 2011, with 90 percent of the funds going to support investigator-initiated research (1). VA hospitals are an idea forum for conducting research projects because the VA system has leading researchers on staff and the physical facilities to conduct long-term research projects. Of the 153 medical centers in the VA system, 116 have the capacity to conduct research.

Knowledge about the causes and treatment of kidney disease has greatly benefited from research performed at the Department of Veterans Affairs facilities. Annually, 7500 articles based on VA-sponsored research are published (1), many of which have an effect on the causes and progression of kidney disease. In 1970, one such published study was the VA Cooperative Study on Hypertension, which demonstrated the effectiveness of drug treatment in controlling blood pressure (1). Reducing hypertension, a major risk factor for kidney disease, through medication has undoubtedly reduced the number of Americans with kidney disease in the past 40 years. Clinical trials are currently under way to determine the efficacy of an automated wearable artificial kidney that was developed by researchers at the VA Research and Development Program. The device could hold significant hope for dialysis patients because it would allow additional freedom of movement by eliminating the need for stationary dialysis machines by some patients.

In recognition of the past, present, and future contributions of the VA Research and Development Program to kidney disease research, the ASN made certain to include representatives from the VA research program in the recently formed ASN Research Advocacy Committee (RAC). Linda F. Fried MD, FASN, a member of the RAC and an associate professor of medicine and epidemiology in the VA health care system in Pittsburgh, sums up the VA program's contribution: "The VA has become a major research partner in studying the causes of and treatment for kidney disease. I have no doubt VA researchers will play a pivotal role in the next major breakthrough for patients suffering from the disease."

Reference

1. VA Research and Development Program, State of VA Research 2011.

Table 1. Veterans Affairs at a glance in 2011

153	medical centers
350	outpatient centers
126	nursing homes
35	domiciliaries

Policy Update

CMS Proposes Changes to ESRD PPS, Significant Expansion of Quality Improvement Program

By Rachel Shaffer

The Centers for Medicare and Medicaid Services (CMS) outlined proposed changes to the End-Stage Renal Disease Prospective Payment System (ESRD PPS) and the ESRD Quality Incentive Program (QIP) in a proposed rule on Friday, July 1, 2011. The ASN Public Policy Board and ASN staff are analyzing the proposed rule and will provide feedback to CMS on behalf of the society's members.

The proposed rule suggests some important modifications to the Medicare ESRD program. Unlike previous instances of rule making, CMS addressed both the ESRD PPS and the QIP in the same July 1 proposed rule. If the proposed rule were finalized, the QIP would be subject to the broadest changes in 2013 and 2014, with some key modifications applied to the ESRD PPS beginning in 2012.

Proposed changes to the ESRD PPS in 2012

CMS proposed to set the base rate, adjusted for budget neutrality and wage index, at $234.02 for 2012. Overall, the agency projects that the changes contained in the proposed rule will result in an increase in payments to providers of ESRD care of $200 million, or 1.8 percent, in 2012 compared with payments in 2011. However, it also estimates that QIP changes will reduce payments by $47.2 million in 2013 and $14 million in 2014.

The ASN and other stakeholders in the nephrology community have urged CMS to address a 3.1 percent payment reduction that was calculated on the basis of a flawed estimate. CMS recently updated its calculations and, in an interim final rule, stated that it would eliminate the payment reduction. In the proposed rule, CMS noted that it would respond to related comments in the final rule. In its comments, ASN will commend the agency for rectifying the error.

CMS also clarified eligibility for qualification as a low-volume facility, as well as proposed provisions that would allow providers to prescribe vancomycin for conditions unrelated to dialysis service and receive reimbursement. The agency stated that changes related to the categories of comorbidities, and diagnoses within these categories that are eligible for payment adjustments, will be addressed through subregulatory guidance.

Proposed changes to the QIP in 2013

CMS issued the proposed rule on the heels of a crucial June 24, 2011, notice from the U.S. Food and Drug Administration (FDA) that recommended changes to the package insert and dosing guidelines for erythropoiesis-stimulating agents (ESAs). The new modifications eliminate the concept of a target hemoglobin range, and they encourage care providers to initiate ESA treatment for dialysis patients only when the hemoglobin level is less than 10 g/dL (exact amount unspecified) and to reduce or interrupt the dose of ESA if the hemoglobin level approaches or exceeds 11 g/dL. (See FDA article in this issue of *ASN Kidney News*.)

In accordance with the new FDA recommendation, CMS proposes to eliminate the anemia management measure on the percentage of Medicare patients with an average hemoglobin level less than 10 g/dL. Besides the desire to remain consistent with the FDA, CMS also cites its own recent National Coverage Determination final decision memorandum for ESAs for treatment of anemia in adults with CKD including patients receiving dialysis and patients not receiving dialysis, which could not identify a specific hemoglobin target level that is safe for all patients.

Retiring the "percentage of patients with average hemoglobin level less than 10 g/dL" quality measure leaves just two measures in place for 2013: percentage of patients with average hemoglobin level greater than 12 g/dL, and with average urea reduction ratio (URR) greater than 65 percent. CMS proposes to give the two remaining measures equal weight when calculating the performance scores of facilities. The agency proposes using data on these quality measures from 2011 to determine payments in 2013.

This proposal is consistent with CMS's previous approach to QIP payment reductions. Payment reductions are applied 2 years after the care is provided, with CMS using the year in between to calculate facilities' scores (Figure 1). On the basis of 2009 Dialysis Facility Compare data, CMS has maintained the original national performance rate (96 percent) for the URR measure but reduces the percentage of patients who must have hemoglobin levels less than 12 g/dL from 26 percent to 16 percent.

If the rule is finalized as written, the proposed rule would maintain the ability of dialysis facilities to be judged against the lesser (more lenient) of two performance standards in 2013: either its own performance on the measures during 2007, or the average national performance rate on the measures in 2009 (which CMS notes is the most recent year for which data are available). As determined at the program's inception, facilities must score between 26 and 30 of a total possible 30 points to be eligible for a full payment in 2013. In 2014, however, CMS proposed that standards for this score and several other elements of the QIP will become more stringent.

Proposed changes to the QIP in 2014

CMS is upping the ante for the QIP in 2014. The agency proposes a major increase in the number of quality measures, jumping from two measures in 2013 to eight measures in 2014. The agency put forth suggestions to implement both clinical and "structural"—or reporting—measures, based largely on metrics endorsed by the National Quality Forum (NQF). The five clinical measures (Table 1) will be based on patient data, whereas facilities will report "yes" or "no" responses to structural/reporting measures. Notably, CMS proposes retiring the URR measure, replacing it with a modality-specific threshold that examines Kt/V levels. CMS cites its belief that the kidney community has embraced the Kt/V measure as a better measure of dialysis adequacy than URR and explains that care providers have been asked to report Kt/V on all claims since July 2010.

CMS notes that phosphorus and calcium monitoring is an important part of care and that whereas the NQF has endorsed monitoring measures (#0261 and #0255), a consensus on specific target ranges does yet not exist within the nephrology community. As such, CMS proposes that facilities attest that they monitor these levels via CROWNWeb and in future years anticipates adding at least one mineral metabolism clinical measure on top of, or as a replacement for, the proposed reporting measure.

Performance standards for anemia management, dialysis adequacy, and vascular access infection measures against which facilities will be judged were not specified in the proposed rule, but CMS stated its intention to determine them using data collected between July 1, 2010, and June 30, 2011. In the proposed rule, CMS outlines a new, more rigorous scoring method for 2014. It would eliminate the "special rule," which currently compares care providers' quality data against the less stringent of two standards: their own performance on the measures during 2007, or the average national performance rate on the measures in 2009.

In 2014, CMS proposes to score care providers on the basis of achievement or improvement of the clinical measures, using whichever score is highest. The achievement score would be based on whether a care provider's data collected during the performance period falls within one standard deviation below the national performance rate. The improvement score would be based on comparison of a provider's data collected during the performance period versus its own performance during the baseline period and the national performance rate. CMS also proposes to increase the number of points that facilities must earn to receive full reimbursement from 30 points to an estimated 60 points.

The agency names several quality measures it may develop in future years, including the following:

- serum calcium concentration
- serum phosphorus concentration
- assessment of iron stores
- in-center hemodialysis Consumer Assessment of Health Care Providers and Systems survey results
- clinical mineral metabolism measure
- fluid weight management
- pediatric quality measures

Table 2 illustrates the high-level changes that CMS is proposing to roll out over the next three years. Although certain aspects of this proposed evolution are likely to change during the course of rule making, the table encapsulates CMS's vision to intensify the scope and rigor of the QIP program.

Key proposed changes to the QIP

1. Eliminate the minimum anemia management measure of 10 g/dL in 2013
2. Replace Urea Reduction Ratio with Kt/V as the standard for the dialysis adequacy measure in 2014
3. Add three more new clinical quality measures and three new structural/reporting measures in 2014

In the coming weeks, ASN will release detailed analyses to help the kidney community understand how medical practice and patient care could be affected by these potential changes. CMS is accepting public comments regarding the proposed rule, which are due August 30, 2011.

Figure 1. Timeline of Performance Period and Payment Year 2013

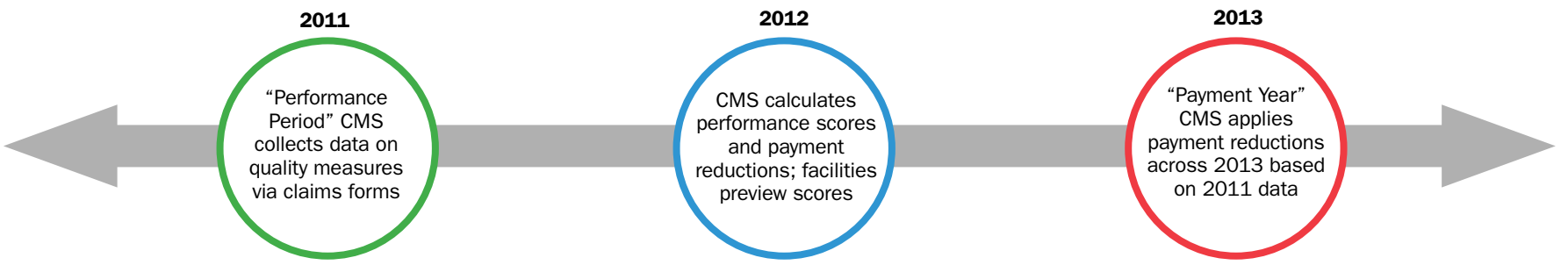

Table 1. Proposed 2014 Clinical and Structural Quality Measures

Type	Measure	NQF Endorsement?
Clinical	1. Percentage of Medicare patients with a hemoglobin > 12 g/dL	
	2. Percentage of Medicare dialysis patients (PD, HD, and HHD) meeting the modality-specific threshold: • Percentage of adult Medicare patients on hemodialysis for 6 months or more and dialyzing three times a week whose average delivered dose of hemodialysis was a Kt/V of at least 1.2 during the proposed performance period; or • Percentage of adult Medicare patients on peritoneal dialysis whose average delivered dose was a weekly Kt/V of at least 1.7 during the proposed performance period.	Yes - #0250 and #0321
	3. Vascular access (these two percentages will be calculated separately and later combined into one): • Percentage of a provider's/facility's Medicare hemodialysis patients using an autogenous AV fistula with two needles during the last HD treatment of the month; and • Percentage of a provider's/facility's Medicare hemodialysis patients who have an intravenous catheter in place for 90 days or longer prior to the last hemodialysis session.	Yes - #0257 and #0256
	4. Vascular access infection: Number of months in which a monthly hemodialysis claim reports a dialysis access-related infection using HCPCS modifier V8	—
	5. Standardized Hospitalization Ratio-Admissions: Number of ESRD Medicare patient actual admissions versus expected hospitalizations adjusted for the provider's/facility's Medicare patient case mix.	Undergoing review for endorsement by NQF in July 2011
Structural	6. National Healthcare Safety Network (NHSN) Dialysis Event Reporting: Reports dialysis infection events to the Centers for Disease Control and Prevention (CDC)	—
	7. Patient Experience of Care Survey Usage: Surveys patients using in-center hemodialysis (ICH) consumer assessment of healthcare providers and systems (CAHPS) to learn about their experience of care	ICH CAHPS Survey is endorsed - #0258
	8. Mineral Metabolism Reporting: Monitors patients for abnormalities in phosphorus and calcium levels.	—

Table 2. Proposed Evolution of the QIP, 2012–2014.

	Payment Year		
QIP Program Element	**2012**	**2013**	**2014**
Year data collected in:	2010	2011	2012
Quality measures and performance standards	• Hemodialysis adequacy (URR > or = 65%: 96% of patients) • Hemoglobin < 10 g/dL: 2% of patients • Hemoglobin >12 g/dL: 26% of patients	• Hemodialysis adequacy (URR > or = 65%: 96% of patients) • Hemoglobin >12 g/dL: 16% of patients	• Anemia management* • Modality-specific dialysis adequacy • Vascular access • Vascular access infection • Standardized hospitalization ratio • Dialysis event reporting (y/n)** • Patient surveys – ICD CAHPS (y/n) • Mineral metabolism monitoring (y/n)
Minimum Hgb Level	10 g/dL	none	none
"Special rule"?	Yes	Yes	Improvement or Achievement
Measure weighting	50% Hemoglobin < 10 g/dL; 25% to others	50%-50%	90% clinical measures, equal weight – 10% structural/reporting measures
Performance score for full payment	26–30	30	30

* CMS proposes to determine performance standards based on national data collected between July 1, 2010 and June 30, 2011 for the first 5 measures listed.
**CMS proposes that facilities will attest on a yes/no basis whether or not they have complied with the last 3 "structural/reporting" measures listed.

Journal View

Higher Risk of Acute Urinary Retention with Inhaled Anticholinergics for Chronic Obstructive Pulmonary Disease

For men with chronic obstructive pulmonary disease (COPD), inhaled anticholinergic therapy may lead to an increased risk of acute urinary retention, suggests a study in the *Archives of Internal Medicine*.

The nested case–control study included 9432 male and 1806 female patients with COPD who were treated for acute urinary retention between 2003 and 2009. The patients, aged 60 years or older, were identified from Ontario health databases. Each case patient was matched with up to five control individuals. Associations with inhaled anticholinergic use, based on prescription records, were assessed.

Compared with control individuals, patients with acute urinary retention had higher rates of prostate disease, neurologic disease, and urinary incontinence. Among men, those who had recently started inhaled anticholinergic therapy were at increased risk of acute urinary retention: 42 percent higher on adjusted analysis. For anticholinergic-exposed men with evidence of benign prostatic hyperplasia, the increase in risk was 81 percent. The risk of acute urinary retention was increased for men who used either short- or long-acting inhaled anticholinergics. For women with COPD, anticholinergic use was not significantly associated with acute urinary retention.

The population-based study adds to recent evidence suggesting an increased risk of acute urinary retention in men with COPD taking inhaled anticholinergics. Patients treated with both short- and long-acting inhaled anticholinergics and those with benign prostatic hyperplasia appear to be at highest risk. Patients with COPD and their physicians should be aware of this association and the possible preventive and treatment interventions [Stephenson A, et al. Inhaled anticholinergic drug therapy and the risk of acute urinary retention in chronic obstructive pulmonary disease: a population-based study. *Arch Intern Med* 2011; 171:914–920].

Alemtuzumab Induction May Lower Acute Rejection Rate

In low-risk patients undergoing kidney transplantation, induction with alemtuzumab reduces the risk of acute rejection during the first year, reports a trial in *The New England Journal of Medicine*.

The multicenter randomize trial included 474 patients undergoing live-donor or deceased-donor kidney transplantation. On the basis of repeat transplantation, panel-reactive antibodies of 20 percent or higher, or black race, the patients were stratified as being at high risk (139 patients) or low risk (335 patients) for acute rejection. They were then assigned to antibody induction with a single 30-mg intravenous dose of alemtuzumab or to conventional induction therapy consisting of rabbit antithymocyte globulin 6 mg/kg over 4 days (high-risk patients) or basiliximab 40 mg over 4 days (low-risk patients).

All patients received tacrolimus plus mycophenolate mofetil and early steroid withdrawal with a 5-day glucocorticoid taper. Biopsy-confirmed acute rejection rates were assessed at 6 and 12 months.

For all patients, the 6-month acute rejection rate was 3 percent with alemtuzumab versus 15 percent with conventional induction therapy. The 1-year rates were 5 percent versus 17 percent. The difference was significant only for low-risk patients: with alemtuzumab, the acute rejection rate was 2 percent versus 18 percent at 6 months and 3 percent versus 20 percent at 12 months.

The beneficial effect on rejection rate persisted through 3 years: 10 percent with alemtuzumab versus 22 percent with basiliximab. Adverse events were similar between the two induction strategies.

The study is one of the first to compare the outcomes of antibody induction regimens allowing early glucocorticoid withdrawal. Among patients at low immunologic risk, alemtuzumab seems to reduce the acute rejection rate in comparison with conventional induction therapy. The study found no significant differences in patient or allograft survival [Hanaway MJ, et al. Alemtuzumab induction in renal transplantation. *N Engl J Med* 2011; 364:1909–1919].

Single-Dose Erythropoietin Doesn't Reduce Myocardial Infarct Size

For patients with ST-elevation myocardial infarction (STEMI) undergoing reperfusion, an intravenous bolus of epoetin-α does not reduce infarct size, according to a study in the *Journal of the American Medical Association*.

The randomized controlled trial included 222 patients who underwent successful primary or rescue reperfusion with percutaneous coronary intervention after STEMI. After an initial dose-escalation phase, patients were randomly assigned to receive a single 60,000-U intravenous dose of epoetin-α or saline placebo within 4 hours after reperfusion. Infarct size was measured by use of cardiac magnetic resonance during the first week and again at 12 weeks after treatment.

Neither scan showed a significant difference in infarct size between groups: approximately 15 percent of left ventricular mass at 2–6 days after percutaneous coronary intervention and 10 percent at 12 weeks. Among patients aged 70 years or older, epoetin alfa was associated with a larger infarct size at the first assessment: 20 percent of left ventricular mass, compared with 12 percent in the placebo group. A composite of adverse events—death, myocardial infarction, stroke, or stent thrombosis—occurred in 4 percent of the epoetin-α group versus none of the placebo group.

Erythropoietin has shown cardioprotective effects in preclinical models of myocardial ischemia and ischemia reperfusion. However, this phase 2 clinical trial found no reduction in infarct size for STEMI patients receiving single-dose epoetin-α after successful reperfusion. The study also raises concerns about the safety of erythropoietin treatment after STEMI [Najjar SS, et al. Intravenous erythropoietin in patients with ST-segment elevation myocardial infarction. *JAMA* 2011; 305:1863–1872].

Predialysis Pathways Increase Arteriovenous Fistula Placement before Hemodialysis

Formal predialysis pathways, including estimated GFR (eGFR) thresholds, are associated with higher rates of timely arteriovenous fistula (AVF) placement, reports a study in the *American Journal of Kidney Diseases*.

The study sought to identify barriers to and enablers of AVF placement among 319 incident hemodialysis patients at nine nephrology centers in Australia and New Zealand. Thirty-nine percent of the patients had an AVF in place at the time they started hemodialysis.

Barriers to timely AVF placement included absence of formal patient referral policies, longer wait times for surgical evaluation and access placement, and lack of a central database for patient tracking and management. The eGFR values at surgical referral and AVF placement were lower than expected: the median threshold was 7 mL/min/1.73 m^2 for both. The median wait time for AVF creation was only 3.7 weeks.

Patients whose first assessment by a nephrologist was less than 12 months before the start of hemodialysis were much more likely to start dialysis with a catheter. Nephrology centers with higher rates of timely AVF placement were more likely to have a formalized predialysis pathway and a centralized patient database, along with lower nephrologist- and surgeon-to-patient ratios.

Contrary to guidelines, most hemodialysis patients do not have an AVF in place when they start hemodialysis. This qualitative/quantitative study suggests that centers with formalized predialysis pathways that incorporate patient education and eGFR thresholds for access placement achieve higher rates of timely AVF creation. The study is limited by a relative lack of data on patient-based barriers [Lopez-Vargas PA, et al. Barriers to timely arteriovenous fistula creation: a study of providers and patients. *Am J Kidney Dis* 2011; 79:873–882].

Severity of Acute Kidney Injury Predicts Risk of Incident Chronic Kidney Disease

More acute kidney injury (AKI)—especially requiring dialysis—is a strong and independent predictor of progression to stage 4 chronic kidney disease (CKD), reports a study in *Kidney International*.

Department of Veterans Affairs Healthcare System data were used to identify 5351 patients who had a primary diagnosis consistent with AKI. Of these, 728 developed stage 4 CKD after hospitalization. An exploratory analysis evaluated three multivariate models to predict progression to stage 4 CKD. The predictive value of the models was then confirmed in a validation stage that included 11,589 patients hospitalized for myocardial infarction or pneumonia during the same period—all with RIFLE codes R, I, or F plus complete data for all predictor variables.

All three multivariate models were significant, with c statistics of 0.82, 0.81, and 0.77. All models showed good predictive accuracy in the validation stage, with c statistics of 0.81–0.82. Factors associated with poor long-term renal outcomes included advanced age, low serum albumin, presence of diabetes, and severity of AKI, based on either RIFLE score or mean serum creatinine levels during hospitalization.

Patients who required dialysis during their episode of AKI and subsequently recovered were at particularly high risk of progressing to stage 4 CKD. In the validation phase, patients who required renal replacement therapy had a 500-fold increase in likelihood of progression to CKD.

Severity of AKI, among other factors, predicts the risk of progression to CKD in an incident AKI population. Patients who require dialysis and then recover seem to be at particularly high risk, requiring follow-up after hospital discharge. The researchers call for further study to refine the risk equations and evaluate potential interventions [Chawla LS, et al. The severity of acute kidney injury predicts progression to chronic kidney disease. *Kidney Int* 2011; 79:1361–1369].

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- Fundamentals of Renal Pathology
- Glomerulonephritis Update: Diagnosis and Therapy 2011
- Kidney Transplantation for the General Nephrologist
- Maintenance Dialysis: Principles, Practical Aspects, and Case-Based Workshops
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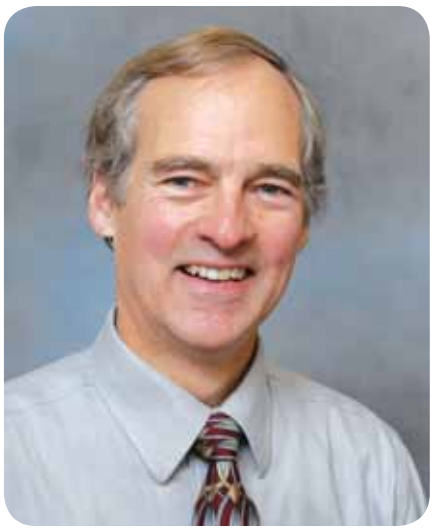
Practice Pointers

In this month's issue, ASN Kidney News editorial board member Edgar Lerma interviewed Bertram L. Kasiske, director of nephrology at Hennepin County Medical Center in Minneapolis.

Dyslipidemias in Chronic Kidney Disease



Bertram L. Kasiske

Please characterize the typical lipid profile of patients with chronic kidney disease. Please describe its unique features compared with that of the general population.

As kidney function declines, there is a tendency for triglycerides to increase and HDL cholesterol to decline. Declining kidney function is not associated with increased levels of LDL cholesterol per se. However, patients can certainly have elevated levels of LDL cholesterol independently of the level of kidney function. In addition, many of the treatments we use for glomerulonephritis can also adversely affect lipid levels. In particular, corticosteroids and cyclosporine increase the levels of total and LDL cholesterol.

What about the patient receiving renal replacement therapy? Is there any difference based on their modality of dialysis, e.g., hemodialysis versus peritoneal dialysis?

Patients treated with maintenance hemodialysis (HD) tend to have lipid profiles that qualitatively resemble those of patients with stage III or IV chronic kidney disease (CKD). That is, they frequently have high triglycerides and low HDL cholesterol levels. Total and LDL cholesterol are often normal or even low in HD patients. Patients treated with maintenance peritoneal dialysis tend to have both increased triglycerides and low HDL cholesterol, but unlike HD patients, they often have elevated LDL cholesterol as well.

What about the posttransplant patient?

Kidney transplant patients typically take one or more immunosuppressive medications that can cause dyslipidemias. These include corticosteroids, cyclosporine, and mammalian target of rapamycin, also known as proliferation signal inhibitors. As a result, a typical kidney transplant recipient has high total and LDL cholesterol, and often increased triglycerides as well. Despite the fact that kidney function is often decreased, HDL cholesterol levels are usually normal. This may be due to the use of corticosteroids, which tend to raise HDL levels, although increased HDL cholesterol from corticosteroids may not reduce the risk of cardiovascular disease.

Is there any known association between proteinuria and dyslipidemia?

Yes. Patients with nephrotic-range proteinuria—that is, total urine protein excretion greater than 3.0 g/24 h—often have increased total and LDL cholesterol as well as elevated triglycerides. The greater the amount of urine protein excretion, the more likely these lipoprotein abnormalities will be present.

Is there any correlation between lipid control and progression of renal disease?

Dyslipidemias have been associated with progression of CKD in observational studies. In addition, post hoc subgroup analyses of randomized controlled lipid-lowering trials in the general population have examined whether CKD patients in these trials experienced slower progression of CKD with treatment. At least some of these studies have shown a reduced rate of decline in estimated GFR in patients treated with statins compared with placebo.

The Study of Heart and Renal Protection (SHARP) compared ezetimibe plus simvastatin versus placebo in over 9000 patients with CKD and included CKD progression as a secondary endpoint. The primary endpoint in SHARP, major adverse cardiac events, was significantly reduced in the treatment group. Prespecified CKD endpoints were end stage renal disease (ESRD), ESRD or death, and ESRD or a doubling of baseline serum creatinine, and at randomization there were 6247 patients not receiving dialysis. Of these, 36 percent had stage III, 43 percent stage IV, and 20 percent stage V CKD. During follow-up, 2141 (34 percent) of these patients reached ESRD. Thus, the study population of SHARP tended to have advanced CKD. Unfortunately, treatment did not significantly reduce the rate of CKD progression in SHARP, possibly because CKD was more advanced in the SHARP patients than in other statin trials that found reduced rates of CKD association with statin treatment.

The bottom line is that it is still uncertain whether treatment of dyslipidemia reduces the rate of CKD progression. However, the results of the SHARP trial indicate that many, if not most, patients with CKD should be treated to prevent coronary heart disease.

Please define reverse epidemiology in the context of dyslipidemias and CKD. What are your thoughts about this concept?

Retrospective observational studies of patients with advanced CKD, especially studies of patients treated with HD, have reported that patients with low cholesterol levels have higher mortality than do patients with higher cholesterol levels. The same observation has been reported for blood pressure and body mass index. It is unlikely that low cholesterol levels cause a higher mortality rate. Rather, it is more likely that patients with low cholesterol already have advanced disease, and possibly malnutrition with inflammation, which causes both a higher mortality and lower cholesterol.

This phenomenon has been called reverse epidemiology because the disease causes the alterations in risk factors, rather than the alterations in risk factors causing disease. The bottom line is that we need randomized controlled trials in advanced CKD populations to determine whether the benefits of treating traditional cardiovascular disease risk factors outweigh the harms.

Are there any guidelines regarding screening and monitoring for dyslipidemia in patients with various stages of CKD?

Kidney Disease Improving Quality Outcomes (KDOQI) published guidelines for the management of dyslipidemia in CKD in the *American Journal of Kidney Diseases* in April 2003. However, these guidelines were written before the results of some major clinical trials were published, including the Assessment of Lescol in Renal Transplantation, Die Deutsche Diabetes Dialyse Studie (4D), the Study to Evaluate the Use of Rosuvastatin in Subjects on Regular Hemodialysis: An Assessment of Survival and Cardiovascular Events (AURORA), and the SHARP study.

The KDOQI guidelines state that they would need updating in three years, especially because publication of these major trials was pending. The Kidney Disease Improving Global Outcomes organization is planning to develop updated guidelines when the results of the SHARP study are available. In the meantime, there are really no up-to-date evidence-based guidelines that address the screening and monitoring of dyslipidemia in patients with CKD.

Please summarize what we can conclude from the lipid landmark trials, namely 4D, AURORA, and SHARP?

Unlike the SHARP study, the 4D and AURORA studies failed to show a reduction in cardiac events. It is most likely that the 4D and AURORA studies did not have adequate statistical power to demonstrate that lowering LDL cholesterol reduced atherosclerotic coronary artery disease events.

In the 4D trial, 20 mg of atorvastatin daily in HD patients with type 2 diabetes resulted in a nonsignificant 8 percent reduction in cardiac death, nonfatal myocardial infarction, or stroke. In the AURORA trial, 10 mg of rosuvastatin daily in HD patients resulted in a nonsignificant 4 percent reduction in cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke. Both the 4D and AURORA study endpoints likely included many cardiovascular deaths that were not caused by atherosclerotic coronary heart disease and thus could not be expected to be reduced by lowering LDL cholesterol.

In contrast to the 4D and AURORA studies, the primary endpoint in the SHARP study was nonfatal myocardial infarction, coronary death, nonhemorrhagic stroke, or any revascularization procedure. This endpoint was designed to exclude non–coronary heart disease deaths. In addition, the SHARP study, which included about two thirds CKD patients not receiving dialysis, was much larger than both the 4D and AURORA trials put together. Thus, the reduction in the primary endpoint with ezetimibe plus simvastatin in SHARP was likely the result of adequate statistical power. A meta-analysis of the results of 4D, AURORA, and dialysis patients in SHARP is planned and will help us better understand the differences in these important trials.

On the basis of the above trials, should we use statin therapy in CKD patients? Does the stage of CKD have any bearing on the initiation of statin therapy?

Reducing LDL cholesterol is beneficial in patients at any stage of CKD, and statins are the safest and most effective for reduc-

ing LDL cholesterol in CKD. Risk of coronary heart disease should be the major determinant of who should receive reduction of LDL cholesterol with statin therapy. To the extent that the risk for coronary heart disease increases with the stage of CKD, the absolute risk reduction and benefit from a statin may also increase as the stage of CKD increases. Studies are needed to determine whether the stage of CKD and proteinuria should be used in equations to determine the risk of coronary heart disease, along with other traditional risk factors.

Consideration also needs to be given to whether the level of LDL cholesterol should be used in the decision to initiate a statin, or whether LDL cholesterol should be used only in the overall determination of coronary heart disease risk. Studies— including the SHARP study—have shown that high-risk patients benefit from statin therapy at any level of LDL cholesterol, and therefore any patient with a high enough level of coronary heart disease risk should receive a statin, regardless of LDL cholesterol level.

In clinical trials, statins have had a remarkable safety record at any level of GFR, as well as in dialysis and transplant patients. This was true for atorvastatin in the 4D and AURORA trials among dialysis patients, for fluvastatin in kidney transplant recipients at different levels of kidney function, and in the SHARP study with ezetimibe and ezetimibe plus simvastatin in combination.

Are all statins created equal?

There are no comparison trials showing that any statin is better than any other for preventing coronary heart disease events beyond the differences in their ability to lower LDL cholesterol. The lower the reduction of LDL cholesterol, the lower the risk of coronary heart disease has been. Of course, any statin should be used only at doses proved to be safe.

How about fibrates? Please comment on the use of combination statin and fibrate therapy in CKD patients.

Studies in the general population have shown that fibrates are not as effective as statins in lowering LDL cholesterol and reducing coronary heart disease events. Therefore, statins should be considered to be first-line agents for the reduction of LDL cholesterol. Combining simvastatin with ezetimibe was shown to be safe and effective in the SHARP trial. Otherwise, combining a statin with a lipid-lowering agent other than ezetimibe should probably be used only if additional trial evidence showing safety and efficacy becomes available in the future.

There are no trials of fibrate, used either alone or in combination with other lipid-lowering drugs in patients with CKD, showing that fibrates are safe and effective for reducing coronary heart disease events. The safety of fibrates is a major concern, given that blood levels of most fibrates increase in patients with low levels of kidney function and especially in patients receiving dialysis. Therefore, if fibrates are used in patients with CKD, the dose of the fibrate should be adjusted according to the level of kidney function. Blood levels of gemfibrozil appear to be less affected by reduced kidney function than are blood levels of other fibrates, but all fibrates should be used cautiously if at all in patients with advanced CKD. Given the lack of data on efficacy and concerns about safety, I would generally avoid combining statins with fibrates in patients with CKD.

If a CKD patient is intolerant of statin/fibrate therapy, what alternative choices are available, and how effective are they in this population?

The only large randomized controlled trial examining the safety and efficacy of LDL cholesterol reduction in CKD with an agent other than a statin is the SHARP trial. In the SHARP trial, the combination of ezetimibe 10 mg with simvastatin 20 mg was compared with simvastatin 20 mg alone and placebo for 1 year. During this first year, the incidence of adverse events was similar in patients receiving ezetimibe plus simvastatin compared with simvastatin alone and compared with placebo. The levels of LDL cholesterol at 1 year were (mean ± SE) 1 ± 1 mg/dL in the placebo group, –29 ± 3 mg/dL with simvastatin alone, and –42 ± 2 mg/dL in the ezetimibe plus simvastatin group. Thus, as expected, the combination of ezetimibe with simvastatin appeared to result in a greater reduction in LDL cholesterol than did simvastatin alone. Thereafter, patients taking simvastatin alone were randomly reallocated to either ezetimibe plus simvastatin or placebo, and thus there was no comparison between ezetimibe plus simvastatin versus simvastatin alone with regard to impact on coronary heart disease events. Similarly, no patients received ezetimibe alone, although if the ezetimibe plus simvastatin combination was safe compared with simvastatin alone and compared with placebo, then it is probably safe to assume that ezetimibe alone is probably also safe in patients with CKD.

What practice pointers would you like to give our readers?

Many, if not most, patients with CKD are at increased risk for coronary heart disease and should be taking a statin. Although some patients may develop myopathies, the incidence of this and other adverse effects attributed to statins in CKD patients has not been different in comparison with placebo.

The greatest barrier to reducing coronary heart disease events with a statin is not an adverse effect of a statin, but patient nonadherence to statin therapy. Therefore, strongly encourage patients to adhere to statin therapy, perhaps try a different statin if they think they are having adverse effects from a particular statin, or consider using the "statin-sparing" combination of ezetimibe 10 mg with simvastatin 20 mg. Patients generally need considerable education and encouragement to take medication to prevent complications that they may have not yet experienced.

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