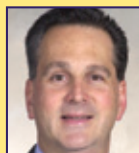


Reducing Cardiovascular Events in Patients With Chronic Kidney Disease: New Strategies for Primary Care

An Educational Monograph Based on an Expert Roundtable Discussion



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Target Audience

This activity is for osteopathic physicians and other healthcare professionals who care for people with lipid disorders and/or CKD.

Statement of Need

Chronic kidney disease (CKD) is a growing health burden in the United States, with estimates of nearly 20 million affected. More than 10% of the US population has some form of CKD. Although many CKD patients will develop renal failure, most will die of cardiovascular disease (CVD) before dialysis becomes necessary. National guidelines have identified dyslipidemia, and elevated levels of low-density lipoprotein cholesterol (LDL-C) in particular, as a key risk factor for CVD risk modification in the general population. Patients with CKD are at higher risk for CVD than patients in the general population. Many patients are unable to achieve the lipid goals established in the clinical guidelines through lifestyle changes alone and, for these patients, guidelines advise pharmacologic therapy. One potentially modifiable risk factor for CVD in patients with CKD is dyslipidemia. Until recently, it has been unclear if the use of LDL-lowering therapies in CKD patients reduces the risk of cardiovascular events in this patient population.

Educational Objectives

At the conclusion of this activity, participants should be able to demonstrate improved ability to:

- Describe the link between dyslipidemia and increased CVD risk in patients with CKD
- Explain the impact of lipid lowering on primary or secondary prevention of cardiovascular events in patients with CKD
- Cite the available clinical evidence on the effect of lipid-lowering agents on major vascular events in patients with CKD
- Outline evidence-based lipid management strategies for patients with CKD

Faculty

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Carman A. Ciervo, DO, Faculty, reports no financial interest/relationship relating to the topic of this activity.

Peter A. McCullough, MD, MPH, Faculty, reports no financial interest/relationship relating to the topic of this activity.

Kelly Anne Spratt, DO, Faculty, reports no financial interest/relationship relating to the topic of this activity.

Keith Engelke, PhD, Writer, reports no financial interest/relationship relating to the topic of this activity.

Steve Casebeer, MBA, Planner, reports no financial interest/relationship relating to the topic of this activity.

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Monograph

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Disclaimer

Participants have an implied responsibility to use the newly acquired information to enhance patient outcomes and their own professional development. The information presented in this activity is not meant to serve as a guideline for patient management. Any procedures, medications, or other courses of diagnosis or treatment discussed or suggested in this activity should not be used by clinicians without evaluation of their patient's conditions and possible contraindications on dangers in use, review of any applicable manufacturer's product information, and comparison with recommendations of other authorities.

Background

Chronic kidney disease (CKD) is associated with premature mortality, decreased quality of life, and increased healthcare expenditures.¹ Untreated CKD can result in poor outcomes including renal failure, the need for dialysis or kidney transplantation, increased risk for cardiovascular disease, and/or death.^{1,2} As illustrated in *Figure 1*, CKD is a common condition that is currently estimated to affect more than 26 million (greater than 16% of) Americans adults,^{3,4} and its prevalence continues to rise.^{4,5} Despite the increasing number of adults at risk for CKD, patient and provider awareness of CKD is alarmingly low (*Figure 2*).^{4,6,7} Important risk factors for CKD include cardiovascular disease, diabetes, hypertension, smoking, and obesity,^{1,2} all of which are commonly managed in the primary care setting.

CKD is defined by the presence of kidney damage or a glomerular filtration rate (GFR) less than 60 mL/min/1.73 m² for at least 3 months, irrespective of cause.⁸ Abnormalities in the serum and urine are early markers of kidney disease.⁹ Proteinuria is the earliest marker of kidney damage and occurs with cardio-metabolic disease (eg, hypertension, diabetes) and glomerular diseases; thus, it is the most commonly used indicator of kidney damage in adults.^{8,10} GFR is difficult to measure directly, but it can be estimated easily on the basis of serum creatinine level, and patient age, sex, and race.

CKD has many causes and the prognosis for a patient with CKD is dependent on the underlying pathology, rate of disease progression, and presence of comorbid conditions. Regardless of the cause of CKD, in the majority of patients its presence can be detected with either of 2 simple tests: (a) a urine test for the detection of albuminuria/proteinuria and (b) a blood test to estimate the GFR.^{8,10} These 2 tests facilitate detection of CKD by all physicians, including primary care physicians, by allowing for identification of CKD without first identifying its cause.

Although CKD screening costs relatively little and is easy to implement, CKD remains undetected in many patients until the onset of symptomatic kidney failure.⁹ However, not all CKD patients will develop renal failure; most will die of cardiovascular disease before dialysis becomes necessary (*Figures 3, 4*).² In fact, the prevalence of CKD is higher in individuals with cardiovascular disease

than in those without it.² Patients with CKD have significant pro-atherogenic lipid abnormalities that are treatable with readily available therapies. However, many primary care physicians remain reluctant to treat these patients aggressively, citing concerns about safety or lack of evidence suggesting clinical benefit when using drugs in this population.

As the prevalence of CKD increases, primary care physicians must be equipped to care for patients with this condition. Obesity-related cardio-metabolic diseases such as dyslipidemia,

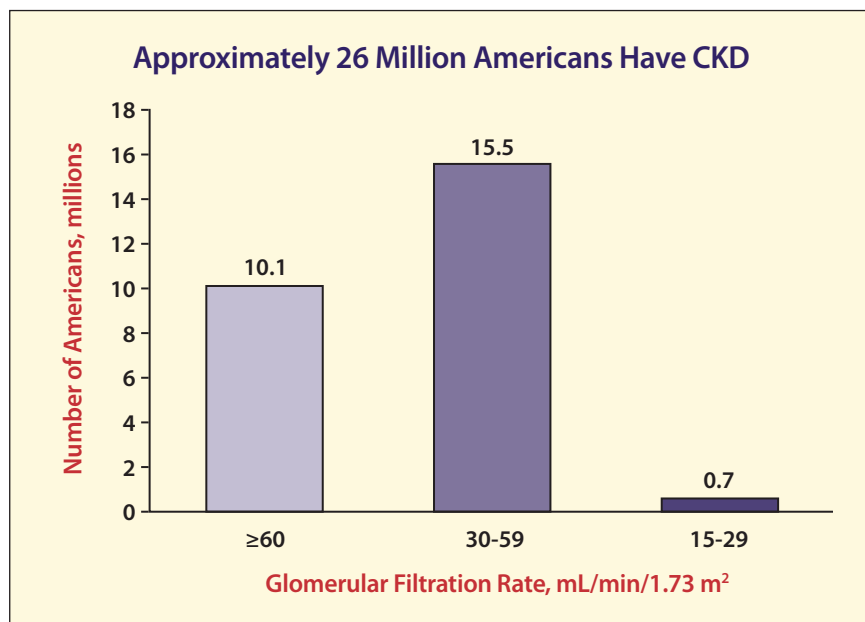


Figure 1. Number of Americans who have CKD. **Source:** Coresh J, Selvin E, Stevens LA, et al. Prevalence of chronic kidney disease in the United States. *JAMA*. 2007;298(17):2038-2047.

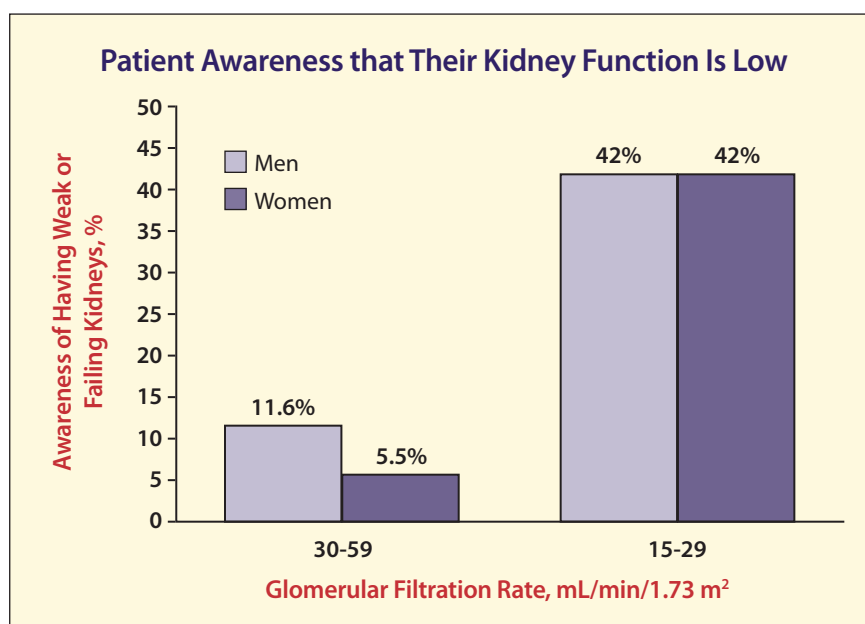


Figure 2. Patient awareness of low kidney function. **Source:** Coresh J, Selvin E, Stevens LA, et al. Prevalence of chronic kidney disease in the United States. *JAMA*. 2007;298(17):2038-2047.

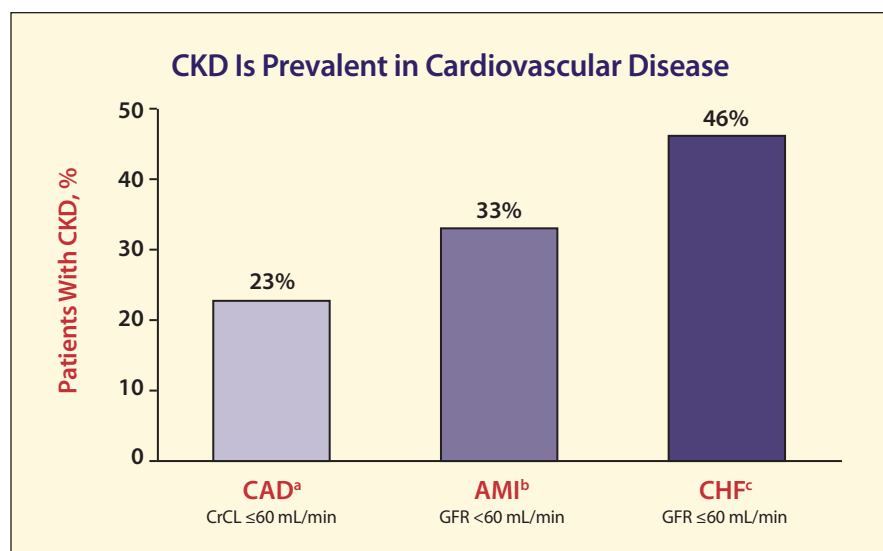


Figure 3. Prevalence of CKD in cardiovascular disease. **Abbreviations:** AMI, acute myocardial infarction; CAD, coronary artery disease; CHF, congestive heart failure; CrCL, creatinine clearance; GFR, glomerular filtration rate. **Sources:** (a) Anavekar NS, McMurray JJ, Velazquez EJ, et al. Relation between renal dysfunction and cardiovascular outcomes after myocardial infarction. *N Engl J Med.* 2004;351:1285-1295. (b) Ix JH, Shlipak MG, Liu HH, Schiller NB, Whooley MA. Association between renal insufficiency and inducible ischemia in patients with coronary artery disease: the heart and soul study. *J Am Soc Nephrol.* 2003;14:3233-3238. (c) Shlipak MG, Smith GL, Rathore SS, Massie BM, Krumholz HM. Renal function, digoxin therapy, and heart failure outcomes: evidence from the digoxin intervention group trial. *J Am Soc Nephrol.* 2004;15:2195-2203.

staged, primary care physicians should take steps to slow disease progression by implementing strict blood pressure and tight glycemic control, by reducing the degree of proteinuria, and by encouraging smoking cessation.¹¹ Dyslipidemia and other cardiovascular risk factors should also be aggressively managed. In addition, appropriate education is needed for this patient population and should be provided by the primary care physician responsible for delivering care.

Results of a recently published survey indicate that although primary care physicians are aware of blood pressure treatment goals in patients with CKD,¹² there is a need to improve CKD knowledge about other aspects of the disease.^{6,7} This CME activity entitled *Reducing Cardiovascular Events in Patients With Chronic Kidney Disease: New Strategies for Primary Care* is designed to provide expert guidance on optimal strategies for patients with CKD, as well as perspective on relevant recent clinical research.

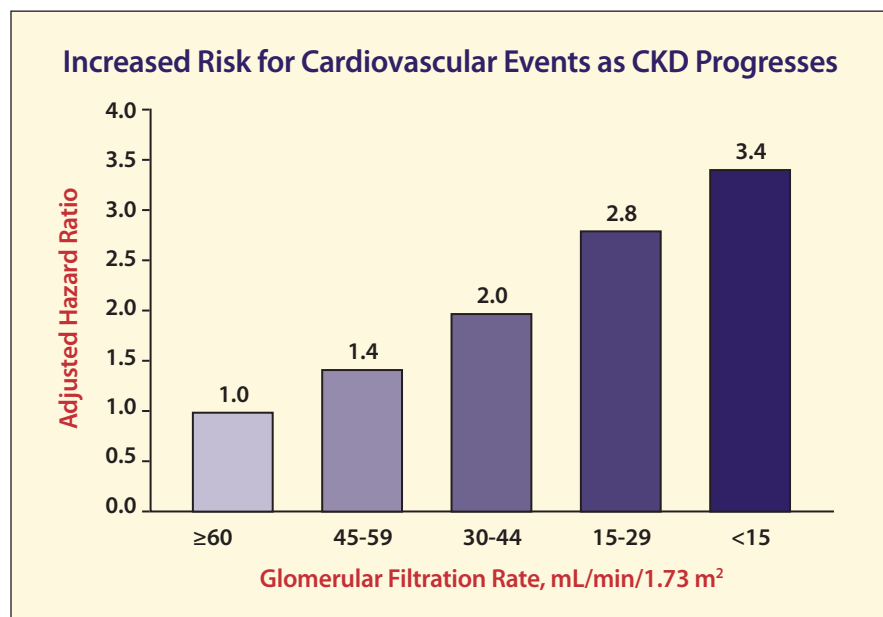


Figure 4. Risk of cardiovascular events associated with CKD progression. **Source:** Go AS, Chertow GM, Fan D, McCulloch CE, Hsu CY. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. *N Engl J Med.* 2004;351(13):1296-1305.

hypertension, and diabetes, which are commonly addressed in the office setting, are the largest contributors to CKD; therefore, the National Kidney Foundation recommends that these patients be screened for signs of renal damage via measurement of the GFR and assessment for the presence of proteinuria.⁸ Once a diagnosis of CKD is established and the disease is appropriately

Faculty Introduction

Moderator: My name is Keith Engelke, PhD, and I'd like to welcome you to our roundtable discussion entitled *Reducing Cardiovascular Events in Patients With Chronic Kidney Disease: New Strategies for Primary Care*. I am joined by Carman Ciervo, DO, senior vice president of clinical integration at Kennedy University Hospital and clinical professor in the Department of Family Medicine at the University of Medicine and Dentistry of New Jersey School of Osteopathic Medicine; Peter McCullough, MD, MPH, consultant cardiologist and chief academic and scientific officer with the St. John Providence Health System in Novi, Michigan; and Kelly Anne Spratt, DO, clinical associate professor of medicine at the University of Pennsylvania School of Medicine and a physician within the Philadelphia Heart Institute of the University of Pennsylvania Presbyterian Medical Center.

I am pleased to be a part of such a distinguished group of scientists and clinicians. Thank you to each of the faculty for your willingness to participate in this discussion.

Case Study

Moderator: *I'd like to start our discussion with a case study. Here's a brief overview of the patient:*

- 76-year-old white woman; long-time patient; in your office for a routine physical examination
- No current complaints, appears healthy, has a relatively active lifestyle
- Medical history
 - Positive for long-standing hypertension (high blood pressure), mild dyslipidemia, and osteoarthritis
 - Nonsmoker
 - Height of 63 inches; weight of 123 lb; body mass index, 21.8 kg/m²
 - Negative findings for diabetes, heart disease, atherosclerosis, and obesity
- Blood pressure of 148/84 mm Hg
- Lipid levels:
 - Total cholesterol: 202 mg/dL
 - Low-density lipoprotein cholesterol (LDL-C): 107 mg/dL
 - High-density lipoprotein cholesterol (HDL-C): 49 mg/dL
 - Triglycerides: 153 mg/dL
- Fasting blood glucose level of 107 mg/dL
 - Hemoglobin A_{1c} level of 5.8%
- Framingham Risk Score of 9%
- Creatinine level of 1.7 mg/dL
- Urine albumin-to-creatinine ratio of 213 mg/g

Moderator: *What appear to be this patient's primary medical challenges?*

Dr. Ciervo: From a primary care physician's perspective, she has elevated blood pressure, and I certainly have concerns about her creatinine level.

Dr. Spratt: Considering she doesn't have any complaints, many clinicians might conclude this patient really doesn't have any medical problems. However, as a cardiologist, I see the creatinine level as her most important issue.

Dr. McCullough: I think that the principle issue here is the awareness of CKD in the community. It's been shown in a variety of studies that in a case with data like these, fewer than 10% of patients or physicians would actually recognize this patient as having CKD.⁷ Patients don't come into the office and say they have kidney disease. So at this point in time, a lack of awareness about kidney disease by both patients and physicians is the real challenge.

Moderator: *What disease risk factors are present?*

Dr. Ciervo: She has hyperlipidemia based on her medical history. She also has osteoarthritis, although I would want more information from the patient to see whether it interferes with her activities of daily living.

Dr. Spratt: Her cholesterol level is mildly abnormal, but most primary care physicians would be hard pressed to say that she has a compelling indication for getting her LDL-C level to a target between 70 and 100 mg/dL. It appears as if her blood pressure is above goal. She also has a very mildly elevated fasting blood glucose level.

Moderator: *Define chronic kidney disease.*

Dr. McCullough: Prior to 2001, we really didn't have a definition of CKD—terms like “chronic renal insufficiency” and “chronic renal failure” were used. However, through a variety of efforts, in 2001 the National Kidney Foundation developed a definition that basically states CKD is either the presence of structural kidney disease or markers of kidney damage.

In the case of the patient we are discussing, we don't have data indicating structural problems with her kidneys, but we do have evidence of kidney damage as suggested by an elevated urine albumin-to-creatinine ratio (ACR) and possibly a reduced GFR. So the current definition of CKD is a urine ACR of greater than 30 mg/g and an estimated GFR less than 60 mL/min/1.73 m².

Moderator: *How does acute renal failure differ from chronic renal failure?*

Dr. Spratt: By definition, an acute condition progresses very rapidly. There is usually a precipitating event—that is, either contrast material-induced nephropathy or acute hypotension causing acute renal failure. Dehydration in the elderly is a very common cause of acute renal failure; several drugs, too, such as angiotensin-converting enzyme (ACE) inhibitors or other nephrotoxic drugs, could precipitate acute renal failure.

In general, in many instances acute renal failure is at least partially reversible.

Chronic kidney disease is the slow, progressive downward decline of GFR, usually occurring over a period of years. It often is seen in patients with at least one of the following conditions: diabetes, hypertension, or atherosclerotic disease.

Dr. McCullough: Two major definitions of acute kidney injury go under the acronyms AKIN (Acute Kidney Injury Network) and RIFLE (Risk of renal dysfunction, Injury to the kidney, Failure of kidney function, Loss of kidney function, and End-stage kidney disease).

I think what the primary care physician needs to know is that both definitions now are reconciled and that a rise in the creatinine level of ≥ 0.3 mg/dL within a 48-hour window is the definition of acute kidney injury. If the creatinine level remains elevated for 90 days or longer, then the condition is considered CKD.

For example, in a circumstance in which there has been acute kidney injury and the creatinine level goes from 1 to 2 mg/dL and the GFR goes from 60 to 30 mL/min/1.73 m², according to these definitions we would not give that patient a diagnosis of CKD until we hit the 90-day mark.

Moderator: *What role does CKD play in chronic renal failure?*

Dr. McCullough: It is very much a precursor. It's possible that in unusual cases of severe trauma or muscle damage, someone could go from totally normal renal function to complete renal failure requiring renal replacement therapy. However, in the majority of cases patients progress through stages of CKD; so the issue of CKD progression is a critical one for the primary care physician to understand.

Of all the clinical features in this case, the patient has 2 indicators of more rapidly progressive CKD compared to more slowly progressing CKD: (a) her blood pressure is elevated and (b) she has an elevated albumin-to-creatinine ratio. The albumin-to-creatinine ratio is not only a marker of rapid disease progression, but the presence of albumin in the urine is now considered pathogenic.

As the endothelium and glomeruli are progressively damaged and the glomeruli leak more and more albumin into the urinary space, the proximal tubule cells work overtime trying to reabsorb the albumin. This heightened activity turns on several gene programs, activates oxidative stress within these cells, and basically causes a dropout of nephrons.

So it is clear that albuminuria is definitely something that the primary care doctor would want to pay attention to and understand that this is a patient who very easily could be on dialysis within a few years.

Moderator: *What are common risk factors for CKD?*

Dr. Ciervo: Long-term use of nonsteroidal anti-inflammatory drug (NSAID) therapy for her osteoarthritis—either prescribed or over the counter—can be a risk factor and exacerbate any existing kidney damage. Also, underlying vascular disease, a history of renal calculi, or other obstructive uropathies can place her at increased risk for CKD.

Dr. Spratt: I agree with Dr. Ciervo's comment about NSAIDs. Recently, another paper was published on increased cardiovascular risk associated with long-term NSAID use.¹³ NSAIDs are a big challenge because many patients don't think over-the-counter NSAIDs, like aspirin and ibuprofen, are unsafe. I would rarely encourage—or prescribe—any type of NSAID or cyclooxygenase-2, or COX-2, inhibitor to this patient, and yet she may be taking them on her own.

Dr. McCullough: Both type 1 and type 2 diabetes are strong contributors to CKD and to progression on to dialysis. It is unclear whether, and to what degree, metabolic syndrome is associated with CKD, but it appears obesity may put an individual at increased risk. Other risk factors for primary care physicians to ask their patients about include prior and current smoking and a family history of CKD—particularly any first-degree family members who ended up on dialysis.

Moderator: *How can you determine if this patient is at risk for CKD?*

Dr. McCullough: As we discussed earlier, all position papers in cardiology, nephrology, and primary care encourage the use of GFR and ACR to determine if a patient has CKD. So a random spot urine-to-albumin and creatinine ratio of greater than 30 mg/g and an estimated GFR less than 60 mL/min/1.73 m² indicate that a patient has CKD.

Calculation of the GFR

Moderator: *What is this patient's GFR?*

Dr. Spratt: Taking into account this patient's age (76 years), race (white), sex (female), and creatinine level (1.7 mg/dL), this patient has a GFR of approximately 29 mL/min/1.73 m².

Moderator: *How is the GFR calculated?*

Dr. McCullough: The 4-variable equation—serum creatinine level, age, sex, and race—called the Modification of Diet in Renal Disease, or MDRD, equation, is commonly used to calculate the estimated GFR.

To provide some perspective, beginning in 2001 there was a campaign by the American College of Pathology to have all laboratories report the GFR. Most laboratories already measured creatinine and also had the other 3 variables—age, sex, and race—so the GFR was easy to calculate. However, some laboratories don't have access to all the data feeds and use only the creatinine level to estimate the GFR—which is not ideal but, generally speaking, is a reasonable approximation.

What the primary care physician can take away from this is that it is important to be aware of the data used to calculate the GFR. In the best of all worlds the GFR on the laboratory report is based on your patient's 4 variables, but sometimes it's a bit different depending on the data provided to the lab.

One more important note: over the next year or so many laboratories will adopt a modified version of the MDRD equation called the Chronic Kidney Disease Epidemiology Collaboration, or CKD-EPI, equation. The CKD-EPI equation is slightly more accurate, but both equations should be used and in my view, checked at least annually. If the GFR is found to be abnormal, the patient should be followed up with more frequently.

Dr. Spratt: We can also help busy primary care physicians by letting them know that the GFR can be estimated quickly by using a simple calculator. Most practices have adopted an EMR system that can be used to quickly generate a bona fide GFR.

Generating a GFR right in the office with the patient present is very helpful because it allows the physician to stage the CKD immediately and have a real-time conversation with the patient about his or her current status.

Dr. Ciervo: The GFR should be viewed as another vital sign. Having an EMR that can calculate GFR and instantly stage a patient's condition is great. However, for those without EMR systems the GFR can be quickly determined using a simple calculator—many can be found online.

Moderator: *Going back to Dr. McCullough's point about calculating the GFR using as many variables as possible, how reliable is creatinine level alone as an indicator of GFR?*

Dr. Spratt: I think it's deceptive. You could have someone who is quite young with a creatinine level of 1.7 mg/dL and someone who is quite old with the same value, but each value means very different things. Many healthcare providers might not have thought twice about a creatinine level of 1.7 mg/dL in our case study, but having a GFR helps you realize that this patient is in stage 4 kidney disease—and having that information really helps you focus. As was said earlier, the most important thing we can do here is increase awareness—it's too easy to look right past the creatinine level of 1.7 mg/dL in this patient.

Moderator: *Why is it important to consider a patient's age when calculating GFR and CKD risk?*

Dr. Spratt: Age is one of the most important of the 4 variables. If your patient is a very petite, elderly, white female, a creatinine level of 1.7 mg/dL represents a marked decrease in GFR.

Dr. Ciervo: A younger person has more muscle mass than this older lady, so you would be less inclined to worry about a creatinine level of 1.7 mg/dL. However, in an older person this creatinine level is a marker of her kidney damage.

will soon be available in the United States; it is a measurement of neutrophil gelatinase-associated lipocalin, or NGAL. NGAL levels increase rapidly following acute kidney injury, but are also elevated chronically in patients with CKD. I think both cystatin C and NGAL will improve our ability to diagnose CKD.

Moderator: *What about renal ultrasonography?*

Dr. Ciervo: Renal ultrasonography plays a role in the initial work-up of both acute and chronic kidney disease. It can be used to rule out the presence or absence of a number of renal pathologic conditions. More advanced imaging techniques are also used—magnetic resonance imaging with or without contrast material, Doppler ultrasonography, and positron emission tomography. The latter can be used with a variety of tracers that give us information on not only renal filtration function but also on ongoing kidney damage.

CKD Staging and Prognosis

Moderator: *How would you stage this patient's CKD?*

Dr. Ciervo: A GFR of 29 mL/min/1.73 m² puts the patient at stage 4 CKD.

Moderator: *What does the GFR tell you of this patient's current status and prognosis?*

Dr. McCullough: This patient has a deceptively poor prognosis. There may be a 30% to 50% chance that she ends up on dialysis within 5 years. For someone this age, it's actually more likely that she will die rather than end up on dialysis.

“The published data suggest CKD is not inherently stable—the disease is very active. The rates of hospitalization are very high and the rates of complications with medications—medication adverse effects and medication interactions—are also elevated.”

– Dr. McCullough

Moderator: *What new diagnostics are available to assess a patient for the presence of CKD?*

Dr. McCullough: There's a laboratory diagnostic test, which was recently approved by the Food and Drug Administration, called cystatin C that's now available nationwide; according to the literature, it is a better indicator of GFR than serum creatinine level. The test is an immunoassay, so it requires a different type of methodology and it's more expensive. For that reason, it will most likely be used as a confirmatory test or in particular circumstances where physicians believe the creatinine-based calculation is potentially deceptive.

A new diagnostic test is now available in Europe, and I think it

Dr. Ciervo: I agree with Dr. McCullough's point—this patient has deceptively significant CKD, particularly since the case describes her as “apparently healthy with no current complaints.” I could see my colleagues looking at this case and saying, “Well, the patient feels good and her creatinine level is 1.7 mg/dL, but let's watch her for another 3 months.”

As was pointed out by Dr. Spratt, this patient's blood pressure and lipid levels are modestly elevated, but as a primary care physician, the thing that captured my attention was her creatinine level.

Dr. Spratt: I think her benign appearance is what makes this case so interesting. I think it's easy to get lulled into a sense of security

when an older patient reports she is feeling pretty good and her blood pressure and lipid levels are only up a little.

CKD Treatment Guidelines

Moderator: *What is the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (KDOQI) and what information do the KDOQI guidelines provide?*

Dr. McCullough: KDOQI was the original guideline infrastructure assembled by the National Kidney Foundation. It initially addressed a variety of activities that were very specific to nephrologists in the care of dialysis patients. Starting in 2001, KDOQI focused on developing the nomenclature for CKD and establishing the basis for CKD severity staging.⁸ Recently, KDOQI turned the responsibility for guideline development over to a global organization called the Kidney Disease International Global Outcomes Group (KDIGO).

Moderator: *How would you prioritize your approach to treating this patient's conditions?*

Dr. Ciervo: Her CKD is actually what stands out the most, and I would unfortunately have to have the uncomfortable conversation about what her elevated creatinine level means. I would also address her elevated blood pressure and lipid levels. In addition, she's over the age of 55 and she's postmenopausal—both of which increase her risk for cardiovascular disease. Considering she has no complaints and a relatively active lifestyle, I would not do anything with her osteoarthritis at this point.

Dr. Spratt: I agree. I think that her CKD is what stands out. It's easy to look at the blood pressure and say, "that's the issue," but as this case shows us CKD can be deceptive and easy to miss. Now, the question becomes how are you going to approach her CKD—being more intensive in terms of treating her hypertension or more intensive in treating her lipids?

Dr. McCullough: A prioritization scheme in my view is to achieve better blood pressure control to reduce the progression of CKD; better lipid control to reduce the risks of myocardial infarction, stroke, and coronary revascularization; then global treatment and protection of the patient with CKD to reduce the risks of end-stage renal disease, going on dialysis, or death.

Moderator: *What is your rationale for prioritizing treatment in this way?*

Dr. McCullough: The published data suggest CKD is not inherently stable—the disease is very active. The rates of hospitalization are very high and the rates of complications with medications—medication adverse effects and medication interactions—are also elevated.

First and foremost to me, this would be a patient that I would see once a month, even though at first glance she may look like someone who could be seen every 3 or 6 months. There is a relationship between the frequency of office visits and the control

of risk factors.

Dr. Spratt: This patient cannot have her CKD treated or her progression prevented until we recognize and diagnose it, so it's critical that we identify it as a problem. We do not want to lose an opportunity to retard progression of her disease. Certainly, this patient who has a creatinine level of 1.7 mg/dL today could easily have a creatinine level of 1.9 or 2.0 mg/dL by next year.

Moderator: *Why is it important to identify and treat CKD in the primary care setting?*

Dr. Ciervo: Identifying and addressing these issues in a primary care setting before the disease progresses can have a favorable impact on overall longevity, morbidity, and mortality.

Dr. Spratt: I don't think monitoring a patient's GFR is any different than watching someone's glucose level go from 115 mg/dL to 120 mg/dL to 128 mg/dL to 135 mg/dL and up and realizing in retrospect that all along the way there were several points at which you could have turned things around. In diabetes, the average duration before a diagnosis is 7 years; I'd hate to lose the same amount of time in our CKD patients.

Dr. McCullough: It is really important that the patient and family understand the benefits of restricting sodium in the diet.

Patients need to understand any delay in treatment can place them at increased risk for additional kidney damage and may limit therapeutic options due to kidney disease–related contraindications. For instance, let's say this patient develops dysmetabolic syndrome and a physician wants to prescribe metformin. Well, that's contraindicated in this patient. Another example is that if this patient is given aspirin or other antiplatelet agents, the patient will be at a much higher risk for bleeding. We can go on and on.

Moderator: *How does age influence decisions on how to treat this patient's multiple conditions?*

Dr. Ciervo: I would treat her blood pressure to the level recommended in the JNC 7, which is the 7th report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. In addition, because there is evidence that an age-related loss of sympathetic response occurs, I would check her blood pressure while she is sitting, standing, walking, and doing a few other maneuvers. I might not be as aggressive about lowering her blood pressure until I was sure that lowering her blood pressure was not going to cause orthostasis; I do not want the patient to fall and fracture a hip, develop subsequent pneumonia or deep venous thrombosis, and develop the associated morbidity and potential mortality from those disease processes.

Dr. Spratt: I agree—I would want to make sure her blood pressure was adequately treated in order to retard hypertension-related kidney damage and possibly prevent her from needing dialysis. An article published in the *New England Journal of Medicine* in 2009 reported that most people who begin dialysis when they are in their

80s do not have good outcomes, either in terms of quality of life or mortality.¹⁴

Moderator: *Thinking about her dyslipidemia, would you worry as much if she were 85 or 86 years old?*

Dr. Spratt: We don't have a lot of robust studies in an octogenarian population. The PROSPER (Prospective Study of Pravastatin in the Elderly at Risk) trial¹⁵ comes to mind, but there's not a lot of data on patients who are in their 80s.

Considering that this patient is very active, enjoying life, and physiologically not 85 years old—she's more like 65 years old—then you might be more aggressive. In most situations with a patient who is both chronologically and physiologically 85 years old, aggressive cardiovascular risk reduction can lead to problems with polypharmacy rather than actual benefit.

Dr. Ciervo: I agree with Dr. Spratt; the risk associated with polypharmacy in an 85- or 86-year-old person may be higher than the risk of not treating her at all. As a result, I may be less inclined to be as aggressive when managing her cholesterol.

Dr. McCullough: I would just add that in my view, the single greatest clinical question is, "Does the primary care physician think the patient could be a candidate for renal transplantation?" If the answer is yes, as is typically the case with a younger person, an early referral to the nephrologist is worthwhile. But in the elderly, even though patients can receive a transplant after age 70, for a patient in her upper 70s heading for 80 renal transplantation is not a consideration.

"Reducing CKD mortality and slowing the progression of kidney damage might be possible, but from an overall standpoint I think the most important issue is reducing risk for cardiovascular disease and stroke. In this population, 1 of every 2 people is going to have cardiovascular disease or stroke. Elderly patients are not afraid of dying from a heart attack; they're afraid of having a stroke and not dying. If we can reduce the risk of stroke by 25%, then we've made an impact in the leading cause of death and disability in this population."

– Dr. Spratt

Having said that, I think of all the other things we're talking about—blood pressure control, lipid control, proper patient counseling—they all apply equally across the age spectrum if you take the transplant issue off the table.

Dr. Ciervo: I think from the standpoint of a primary care physician, that's a really helpful point because it's a good barometer for us to use as primary care physicians when we're looking at these patients. If we have a 65-year-old patient and he or she is going to be a potential transplant candidate at age 70, we're going to take that into consideration when we make treatment decisions. But

if we have an 80-year-old patient, we're going to take a different perspective, and the insight you just provided is invaluable.

Slowing CKD Progression and Reducing Risk for Cardiovascular Disease: Hypertension

Moderator: *How would you manage this patient's hypertension and what is the goal of treatment?*

Dr. Spratt: Reducing CKD mortality and slowing the progression of kidney damage might be possible, but from an overall standpoint I think the most important issue is reducing risk for cardiovascular disease and stroke. In this population, 1 of every 2 people is going to have cardiovascular disease or stroke. Elderly patients are not afraid of dying of a heart attack; they're afraid of having a stroke and not dying. If we can reduce the risk of stroke by 25%, then we've made an impact in the leading cause of death and disability in this population.

Dr. Ciervo: I agree with Dr. Spratt. I would want to take a look at the CKD in the context of her overall cardiovascular disease risk and address it collectively.

Dr. McCullough: The published studies, when taken together, suggest better control of blood pressure and less progression of kidney disease; the results come on a regression line. However, in clinical trials that have targeted one blood pressure target versus another, the relationship between blood pressure control and reduced progression of CKD really hasn't manifested.

For instance, in the AASK, or African American Study of Kidney Disease and Hypertension trial,¹⁶ patients with CKD treated with a more intensive blood pressure target didn't fare any better than those with a less intensive blood pressure target. I agree with the comments, however, that we treat blood pressure the best we can; if the patient had lower blood pressure, there may be less progression of CKD.

As Dr. Spratt stated, the high ground is in reducing stroke and cardiovascular events. There are 2 cardiovascular events that are

blood pressure—responsive in the randomized trials: one is stroke—and clearly blood pressure control will reduce the risk of stroke in this patient—and the other is the development of heart failure.

In a recent meta-analysis of all the randomized blood pressure clinical trials, there were 4 possible outcomes: cardiovascular death, acute myocardial infarction, heart failure, and stroke. Both heart failure and stroke can be reduced up to 50 percent with blood pressure control, but there's relatively little impact on myocardial infarction or cardiovascular death.¹⁷

Dr. Spratt: In blood pressure clinical trials with large subgroups of older patients—the SHEP (Systolic Hypertension in the Elderly Program) study,¹⁸ the SystEur (Systolic Hypertension in Europe) study,¹⁹ and even the ACCORD (Action to Control Cardiovascular Risk in Diabetes) study²⁰—blood pressure reduction was associated with a significantly lower risk of stroke. So it makes sense that in elderly patients, blood pressure should be more tightly controlled.

Moderator: *What is the target blood pressure for this patient? Is “lower” better?*

Dr. Spratt: For a typical elderly patient, 140/90 mm Hg would be acceptable. For patients with CKD, however, I would probably aim for 130/80 mm Hg.

Dr. McCullough: I agree with 130/80 mm Hg. The only caveat is if the patient's proteinuria progresses—typically by greater than 2 g/d—then the recommendations are for systolic blood pressure to be less than 120 mm Hg. For the patient in our case scenario, according to the JNC 7 and KDIGO the goal would be less than 130/80 mm Hg.

Moderator: *Has treatment to achieve lower than usual blood pressure targets in elderly CKD patients proven to improve outcomes?*

Dr. McCullough: No, not in a prospective, randomized trial. It's all based on regression and associative data.

Moderator: *What are the risks associated with a lower than usual blood pressure target in the elderly patient?*

Dr. Spratt: Most of the trials have shown increased adverse events, in terms of both hypotension and hyperkalemia. So the lower you go, the greater the risk of adverse events.

Moderator: *Does the available data adequately describe and quantify the safety of lower than usual blood pressure targets in patients over 75 years of age? In patients over 85 years of age?*

Dr. McCullough: It's difficult to extrapolate the current data to elderly populations. In the placebo-controlled, prospective trials that recruited elderly patients, such as SHEP¹⁸ and SYST-EUR,¹⁹ the blood pressure targets were not very low, so it's difficult to infer.

As stated by my colleagues, the more aggressively we lower blood pressure, particularly in populations with coronary artery or

cerebrovascular disease, the higher the rate of adverse events. This relationship has been demonstrated in the ON-TARGET (Ongoing Telmisartan Alone and in Combination With Ramipril Global Endpoint Trial)²¹ and INVEST (International Verapamil SR Trandolapril Study)²² trials.

So one of the big things that I want the primary care physicians to understand is that for patients who have established coronary heart disease or cerebrovascular disease, we want blood pressure control, but we can't overdo it. We really do want to be cautious; we must be aware that there may be both cardiac and cerebrovascular events, greater rates of dizziness and falling, and possibly other complications.

Moderator: *What therapeutic choices are supported by the JNC 7 for this patient?*

Dr. Spratt: For this patient who has evidence of proteinuria, the JNC 7 would suggest an ACE inhibitor or an angiotensin receptor blocker (ARB) as first-line therapy.

Dr. McCullough: Dr. Spratt's recommendation is concordant with the KDOQI guidelines for blood pressure, but I should note that KDOQI does make a distinction between diabetic and nondiabetic kidney disease. A patient who is diabetic clearly has a stronger mandate for an ACE or an ARB as first-line therapy. In someone without diabetes, therapy can be a bit more stylized, although I do agree that if you integrate other clinical trial data—for instance, the HOPE (Heart Outcomes Prevention Evaluation) trial²³ and others designed to elicit cardiovascular risk reduction—the data in general favor an ACE inhibitor or an ARB as first-line therapy.

Dr. Ciervo: I would suggest that most primary care physicians are aware to use an ACE inhibitor or ARB in patients with proteinuria, regardless of whether they do or do not have diabetes.

Moderator: *How would you manage this patient's osteoarthritis?*

Dr. Ciervo: If the patient has no complaints I certainly would not use palliative or palliation-type treatment, but if she started complaining of pain I would stay away from NSAIDs and consider other agents such as acetaminophen or maybe an agent like tramadol. Topical patches or topical gels may also be appropriate. I would also encourage aquatic therapy as a form of physical therapy.

Dr. Spratt: I agree with Dr. Ciervo; I would absolutely not recommend or prescribe an NSAID, and I would tell her to avoid everything that may contain ibuprofen or naprosyn-like ingredients. I would also caution her to be careful of any cough or cold remedy that has an NSAID component.

I think that educating the patient is very important here. The patient in our case is not complaining, so we do not need to worry about pain management. If her condition progresses, my first-line therapy would be acetaminophen, followed by tramadol, and followed, if necessary, by narcotics.

Slowing CKD Progression and Reducing Risk of Cardiovascular Disease: Dyslipidemia

Moderator: *What is the rationale for treating dyslipidemia in a patient with CKD?*

Dr. Ciervo: For me, it would be the fact that she has probably had underlying dyslipidemia for some period of time. There's enough evidence to convince me to use a statin to stabilize any plaques she may have. I'm looking at it not so much as to achieve a low-density lipoprotein (LDL) goal, but more to stabilize her plaque and reduce her risk of having a cardiac event.

Dr. Spratt: She has 2 risk factors: age and hypertension. Her Framingham Risk Score is about 9%, which isn't too high. She gets a lot of points for being 76 years old and she gets points for having hypertension. She's not a smoker, does not have diabetes, and her high-density lipoprotein (HDL) and LDL levels are relatively low.

Dr. Ciervo: How about the fact that she's a postmenopausal female, even though it's not a major risk factor?

Dr. Spratt: It should be considered, when assessing her risk, that postmenopausal status is not part of the Framingham Risk Score. Framingham Risk scoring does consider age and sex but not specifically menopause; this becomes important in a young woman who may have premature menopause or have undergone a hysterectomy.

Moderator: *What impact does the presence of CKD have on your decision to treat this patient's lipid levels?*

Dr. McCullough: It's important for physicians to recognize that the CKD state alters lipoprotein metabolism. There is a reduction in the action of lipoprotein lipase, so the triglycerides begin to rise. Then there's an impairment of reverse cholesterol transport; apoprotein AI is much less effective in picking up the cholesterol and bringing it back to the liver. As a result, the HDL level is low.

For that reason, there are more small, dense LDL particles. And so for this patient, the LDL particle composition itself is actually more clinically valuable than the reported LDL value, and our conventional risk-scoring schemes do not recognize these nuances. We should just realize the patient has the dyslipidemia of CKD, which in and of itself is pathogenic and in my view is a "call to treatment."

Moderator: *Summarize some of the key trials—4D, AURORA, ALERT—with regard to lipid therapy in patients with CKD.*

Dr. McCullough: There have been many randomized trials of lipid lowering in the general population. Within those studies, there are subgroups of individuals who have CKD. Looking back, all of those studies were supportive of the idea that lipid-lowering therapy provided a benefit.²⁴

One randomized trial—the ALERT (Assessment of Lescol in

Renal Transplantation) trial²⁵—was conducted in renal transplant recipients treated with statins. Results of this trial were equivocal on the initial analysis, but on longer-term follow-up the benefit of lipid lowering in these patients was clearly statistically significant.²⁶

After publication of the ALERT study results, 2 additional trials were conducted to investigate the impact of lipid lowering on cardiovascular risk reduction in dialysis patients—the 4D (Deutsche Diabetes Dialyse Studie)²⁷ and AURORA (A Study to Evaluate the Use of Rosuvastatin in Subjects on Regular Hemodialysis: An Assessment of Survival and Cardiovascular Events)²⁸ trials. Neither of these 2 trials showed any overall reduction of cardiovascular risk with lipid lowering.

After completing trials in the general population and in patients with more severe CKD—transplant recipients and dialysis patients—it became evident that we had a data gap; there were no data for patients with an estimated GFR of 30 down to patients receiving dialysis. As a result, the entire medical community—nephrology, cardiology, primary care—was very much in a state of confusion regarding whether or not there was any benefit in altering lipid levels in patients with CKD.

Dr. Spratt: I agree. Physicians have been confused about how aggressive to get in terms of lipid levels in these CKD patients.

Dr. Ciervo: From a primary care perspective, there's a need for data that tell us who we should treat. We deal with a multitude of disease processes each day, and the more clarity that we can achieve about a particular issue, the more effectively we can treat it.

Moderator: *Do current KDOQI and/or ATP III guidelines address the treatment of dyslipidemia in patients with CKD?*

Dr. Spratt: ATP III guidelines don't address it at all; there's no separate category for patients with CKD. Certainly risk factors such as diabetes and hypertension influence your treatment decisions, but ATP III guidelines do not contain recommendations specifically for CKD patients.

Dr. McCullough: The KDOQI version of the lipid guidelines basically says to follow the ATP III recommendations. KDOQI/KDIGO is planning to release a revised set of lipid recommendations that will have a lot of information included from the SHARP (Study of Heart and Renal Protection) study.²⁹

Moderator: *What would be your choice for first-line therapy for the 76-year-old patient in the case?*

Dr. Ciervo: For the reasons that I had mentioned earlier about plaque stabilization, I probably would go with a statin therapy.

Dr. Spratt: There is only 1 drug class that has been shown time and time again to reduce cardiovascular risk, and that is the statins.

Dr. McCullough: For this patient with CKD and an estimated GFR below 30, the only clinical trial data that apply are from the SHARP²⁹ study, which used the combination product containing 20 mg of simvastatin and 10 mg of ezetimibe. Patients

receiving this combination had a positive outcome for the overall primary endpoint and, in particular, on the nonfatal endpoints of myocardial infarction, stroke, and revascularization.

Remember that the dyslipidemia in a patient with CKD is different than that in the general population. It's sufficiently unclear if any other approach to therapy would hit the mark. Lipid metabolism is complex; it's a problem of lipoprotein lipase, we believe, as well as a problem with reverse cholesterol transport, on which we wouldn't necessarily expect that statins or ezetimibe would have a major impact, but in fact, they did.

Moderator: *How do you minimize statin dose-related side effects, particularly in a patient requiring more aggressive lipid lowering?*

Dr. McCullough: Well, there are some theoretical approaches to minimizing these side effects that involve the use of cholesterol uptake inhibitors, which block the uptake of dietary cholesterol. We know that if intestinal absorption of cholesterol is blocked, there is an upregulation of LDL receptors in addition to a reduction of cholesterol synthesis, which results in better disposal of cholesterol.

Another benefit of using a cholesterol absorption inhibitor is that if the inhibitor is combined with a statin, for the same amount of LDL lowering you could use a lower dose of statin. The biggest advantage of this approach is that some statin side effects are clearly dose-related—particularly elevation of liver function tests and myalgias, or muscle aches.

Dr. Ciervo: From a primary care standpoint, that information is very helpful. When you increase the statin dose beyond a certain point, side effects, such as myalgias, become a much bigger issue, and most of my patients just do not tolerate muscle aches.

“[The SHARP] study provides justification for treating lipids in our patients who have more advanced CKD—even patients receiving dialysis. There aren't enough nephrologists to take care of all of these individuals, so very often these patients are coming back to us as their primary care provider.”

– Dr. Ciervo

Dr. Spratt: I'd like to highlight a couple points. First, I use the rule of 6—that is, for every doubling of the statin dose, you get approximately an additional 6% reduction in LDL. In other words, the initial dose provides the greatest LDL reduction. A reduction of only 6% may not be worth the potential side effects. Just recently, there was an FDA warning about a higher risk of myopathy with high-dose statin therapy. I think the ability to use statins at a lower dose to minimize the risk of myopathy is important.

Dr. McCullough: Fortunately, our understanding of statins and statin myopathy is increasing. It's now known that what causes

statin myopathies is a buildup of the statin concentration in the blood. It appears that statin breakdown products, possibly statin alcohols, are directly toxic to myocytes. It has been suggested that individuals with impaired statin clearance—possibly due to drug interactions with cytochrome P450 enzymes, glucuronidation, or a genetic polymorphism of the organic anion transporter 1—may be at highest risk for myopathy. In fact, 15% of the population may have a loss-of-function mutation in that transporter. Therefore, it's possible that 15% of our patients truly have biologically real statin myalgias. As we give higher doses or more potent statins, the myalgias would become more apparent.³⁰

Now, the good news from the SHARP study is that the rate of statin myalgias were not higher in the simvastatin and ezetimibe groups, but only the 20-mg dose of simvastatin was used in the study, which indicates that the trial excluded patients who may have had serious drug interactions. But unlike other statin trials, this trial accepted statin-naïve patients. Other trials have actually excluded patients with prior myalgias, and that way the investigators reduce the potential for high myalgia rates. The SHARP study, I think, is very much a real-world experiment of what happens when you treat patients with this specific drug at this specific dose.

Dr. Spratt: There's been an increasing amount of evidence to suggest that very high doses of statins are not necessarily beneficial except in the patient with acute coronary syndrome.

Dr. McCullough: I would completely agree with that. High-dose statin therapy has been compared with low-dose statin therapy in a variety of settings, and it's really only in the setting of acute coronary syndrome where there's probably a differential effect.

Lowering LDL-Cholesterol in a Wide Range of Patients With CKD: The SHARP Study

Moderator: *Describe the purpose, design, and endpoints of the Study of Heart and Renal Protection (SHARP) study.*

Dr. McCullough: The purpose of the SHARP study was to evaluate the safety and efficacy of LDL cholesterol reduction with a combination product containing simvastatin (20 mg) and ezetimibe in patients with CKD, both in the pre-dialysis phase and in the dialysis phase of kidney disease. The primary

objective was to reduce major vascular events defined as non-fatal myocardial infarction or cardiac death, non-fatal or fatal stroke, or revascularization.

Moderator: *Describe the characteristics of patients enrolled in the trial.*

Dr. McCullough: Overall, more than 9000 patients were randomized into two groups—4560 received simvastatin plus ezetimibe and 4620 received a placebo. There were 3023 patients on dialysis at the start of the trial and 6247 who were not. All patients were naïve to statins, so they had never been on statins in the past.

The mean age at baseline was 62 years, 15% had a prior history of vascular disease, 23% had diabetes, 63% were men, 13% had a background history of smoking, and systolic blood pressure was 139 mmHg. Baseline LDL was 107 mg/dL and the mean estimated GFR of those not on dialysis was 26.6 mL/min/1.73 m².

Moderator: *What was the primary finding of the trial?*

Dr. McCullough: The SHARP study demonstrated a 17% risk reduction in the primary endpoint, which was collectively called a major atherosclerotic event.

Major atherosclerotic events were subdivided into coronary events, which were nonfatal myocardial infarction and coronary heart disease death; non-hemorrhagic stroke, which was divided into ischemic or stroke of unknown type; and revascularization procedures, including coronary revascularization and noncoronary revascularization procedures. These events were tabulated, and the time to the first event in any 1 of those categories was measured.

Moderator: *What is the significance of the SHARP study?*

Dr. Spratt: Results of the SHARP study are very helpful because they provide data on a very common patient—it's a patient we all routinely see.

Dr. Ciervo: This study provides justification for treating lipids in our patients who have more advanced CKD—even patients receiving dialysis. There aren't enough nephrologists to take care of all of these individuals, so very often these patients are coming back to us as their primary care provider.

Moderator: *Outside of therapeutic interventions, what other steps can be taken to improve outcomes for patients with CKD?*

Dr. Ciervo: Educating primary care physicians about lipid management in CKD patients is important. Patients need to be educated, as well. Very often it's the patient who is bringing materials in to the physician now and discussing them in a bilateral conversation.

Dr. McCullough: I think one of the best suggestions is to take the creatinine level and estimated GFR and feature them on an EMR dashboard. GFR influences so many issues—drug selection, surgical evaluation, radiology—and it influences so

much in medicine across all disciplines. I think it ought to be on a dashboard and really visible. Doing this would probably be the single greatest thing that would help improve awareness of the importance of CKD, at least on the on the physician's side.

Dr. Ciervo: Many EMRs are set up to evaluate risk factors for you and generate a pop-up that says, "Have you considered..." or "Have you checked..." or "Have you thought about checking the GFR and the impact of the drugs that you're going to prescribe?" You can build evidence-based guidelines into the platform.

Dr. McCullough: EMRs can also be used as a surveillance system; the device would actually track the creatinine levels and estimated GFR in a population. When the EMR begins to note patients making progress or abnormal developments occurring, the EMR could notify the primary care physician and prompt a nephrology consultation. The devices actually start interceding. You can actually use them as surveillance systems.

Summary

Moderator: *What are the key take-home messages regarding the treatment of CKD in primary care?*

Dr. Ciervo: To me, it's about raising awareness, instituting regular follow-up, and recognizing the importance of monitoring the creatinine level and the GFR. We don't want a patient to get to stage 4 before we intervene; we should be making the necessary modifications at stage 1 or stage 2.

We also need to recognize the importance of treating comorbidities such as hypertension and dyslipidemia. The SHARP study provides us with additional evidence that addressing lipid levels can make a difference, even in patients who are receiving dialysis.

We all need to have easy and ready access to patient data; EMRs are great for this. For those physicians who are not yet using EMRs, documenting the GFR and creatinine level in the patient chart and following up at least annually are critical.

Dr. McCullough: I think awareness actually is the biggest step on both the provider and patient sides. Like I mentioned earlier, we have data—both on the physician and on the patient sides—that less than 10% would recognize that this patient has kidney disease.^{6,7,12} In comparison, recognition by both the physician and the patient is on the order of 80% to 90% for hypertension, 80% to 90% for diabetes, and 100% for cancer.

As a medical community, we have not communicated this appropriately. CKD is almost a background laboratory phenomenon that physicians tend to minimize and probably never mention to the patients. And patients never think to ask about it; they just assume everything is okay.

Once we start to make some inroads on awareness, we will need a major campaign with the messages that the dyslipidemia of CKD, just like CKD itself, is deceptive. It's a deceptive risk that looks like a pretty mild, bland type of dyslipidemia that doesn't warrant

treatment, but now the clinical trials clearly show that it does.

Dr. Spratt: Before the publication of the SHARP study, this patient may not have been referred for lipid therapy. Such patients don't possess a high Framingham Risk Score, which indicates that they don't meet a high secondary endpoint, such as diabetes or coronary artery disease, so there was no other reason, prior to the release of the SHARP trial, to actively treat lipid levels in the CKD patient.

Patients with CKD, along with patients who have diabetes or coronary artery disease, have a cardiovascular disease–like risk equivalent. One of our key messages is that this group of patients requires the same aggressive risk-factor modification that we pursue with diabetes patients and patients with multiple risk factors.

Dr. Ciervo: The message to primary care physicians, like myself, is that there is now significant evidence that appropriate treatment of blood pressure and cholesterol will favorably impact CKD.

Dr. Spratt: In addition, an important message of the SHARP study is to treat dyslipidemia—not necessarily just to slow the progression of CKD but to reduce the risk of cardiovascular events. Again, this is 1 more reason to put this person in a high-risk cardiovascular monitoring situation.

Moderator: *I'd like to thank our faculty—Dr. Carman Ciervo, Dr. Kelly Anne Spratt, and Dr. Peter McCullough—for an enlightening and interesting discussion. Many patients and physicians will benefit from your insights and expertise. Thank you all.*

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CKD Monograph Post-Test

The purpose of this quiz is to provide a convenient means for osteopathic physicians to assess their understanding of the scientific content in the monograph that accompanied the August 2011 issue of *JAOA—The Journal of the American Osteopathic Association*.

To apply for 2.0 hours of Category 1-B continuing medical education (CME) credit, AOA members may take this quiz online at <http://www.osteopathic.org/quiz> by August 31, 2012. Quizzes that are completed online will be graded and credited to members' CME activity reports.

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American Osteopathic Association
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CME credit will be applied to the following CME cycle: 2010-2012.

1. Chronic kidney disease (CKD) is estimated to affect approximately how many American adults?

- ☐ (a) 2 million
- ☐ (b) 10 million
- ☐ (c) 26 million
- ☐ (d) 38 million

2. Regardless of its origin, in the majority of patients, the presence of CKD can be detected via:

- ☐ (a) A urine test for the detection of albuminuria/proteinuria
- ☐ (b) A blood test to estimate the glomerular filtration rate (GFR)
- ☐ (c) Either a OR b
- ☐ (d) Neither a NOR b

3. The current definition of CKD is a urine albumin-to-creatinine ratio (ACR) of greater than 30 mg/g OR an estimated GFR less than 60 mL/min/1.73 m².

- ☐ (a) True
- ☐ (b) False

4. All of the following are risk factors for CKD EXCEPT:

- ☐ (a) Vascular disease
- ☐ (b) Acetaminophen use
- ☐ (c) Type 2 diabetes
- ☐ (d) Prior or current smoking

5. The 4-variable Modification of Diet in Renal Disease (MDRD) equation that is commonly used to estimate GFR takes into account which of the following factors?

- ☐ (a) Age, blood pressure, sex, and serum creatinine level
- ☐ (b) Age, blood pressure, cholesterol level, and race
- ☐ (c) Age, cholesterol level, fasting blood glucose level, and sex
- ☐ (d) Age, sex, race, and serum creatinine level

6. The greatest clinical consideration to take into consideration during the initial primary care encounter with a patient with advanced CKD is:

- ☐ (a) Fasting blood glucose level
- ☐ (b) Serum creatinine level
- ☐ (c) Candidacy for renal transplant
- ☐ (d) Framingham Risk Score

7. In randomized clinical trials, which cardiovascular event(s) can be reduced up to 50% with blood pressure control?

- ☐ (a) Cardiovascular death
- ☐ (b) Acute myocardial infarction (MI)
- ☐ (c) Cardiovascular death and MI
- ☐ (d) Incidence of stroke and development of heart failure

8. The _____ aggressively a patient's blood pressure is lowered, particularly in populations with coronary artery or cerebrovascular disease, the _____ the rate of adverse events.

- ☐ (a) More, higher
- ☐ (b) Less, higher
- ☐ (c) No correlation has been found

9. In the SHARP study, the use of what lipid-lowering therapy in patients with CKD showed a reduction in major vascular events.

- ☐ (a) Statin in combination with ezetimibe
- ☐ (b) Nonsteroidal anti-inflammatory drug (NSAID)
- ☐ (c) Sulfonylurea
- ☐ (d) Thiazolidinedione

10. For every doubling of a statin dose, the patient sees approximately what percentage reduction in low-density lipoprotein cholesterol?

- ☐ (a) 1%
- ☐ (b) 6%
- ☐ (c) 10%
- ☐ (d) 16%

11. The most important factors in the diagnosis and treatment of patients with CKD in the primary care setting include which of the following?

- ☐ (a) Awareness of factors that contribute to CKD
- ☐ (b) Instituting regular follow-up for the patient with or at risk for CKD
- ☐ (c) Monitoring the patient's creatinine level and GFR
- ☐ (d) All of the above

