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Practical Steps to Improve Outcomes for Patients with Chronic Kidney Disease (CKD): A Whole Patient Approach

An Educational Monograph Based on an Expert Roundtable Discussion

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Target Audience

This activity is for osteopathic physicians and other health care professionals who care for people with chronic kidney disease (CKD).

Statement of Need

There are several important practice gaps that contribute to less than optimal outcomes for patients with chronic kidney disease (CKD). These include a lack of awareness of the early stages of CKD among primary care physicians and implementation of treatment strategies that reduce or eliminate comorbid risk factors. Practitioners need to recognize that patients may have more than one long-term condition and that cardiovascular disease (CVD) and CKD commonly occur together. Once CKD is recognized, a proven treatment approach should be taken to intensify the therapeutic response to reduce the risk of cardiovascular events with these patients. If osteopathic physicians improve their competence to recognize and appropriately treat patients with CKD and their concurrent risk factors, then practice gaps can be overcome and enhanced outcomes will be achieved. This whole patient approach is in line with the osteopathic philosophy of patient care.

Educational Objectives

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

- Evaluate screening techniques and assessment methods used to identify patients with CKD at risk for the development of CVD
- Assess recent clinical evidence on the effect of lipid-lowering therapy to reduce risk of premature CVD in patients with CKD
- Apply evidence-based treatment strategies to reduce cardiovascular events in patients with CKD

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Monograph

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Abstract

Chronic kidney disease (CKD) is a common disorder with an increasing prevalence. Early diagnosis based on presence of proteinuria or reduced estimated glomerular filtration rate permits early intervention to reduce the risks of premature cardiovascular disease, kidney failure, and death. CKD screening efforts should target high-risk groups, including the elderly and those with risk factors such as diabetes, hypertension, dyslipidemia, or a family history of CKD. Effective treatments are available to slow the progression of CKD, minimize cardiovascular risk, and reduce mortality. Treatment of high blood pressure is recommended for all hypertensive patients with or at risk for CKD, and glycemic control can help prevent or slow glomerular damage in individuals with diabetes. Recent evidence suggests that lipid-lowering therapy with a statin in combination with a cholesterol absorption inhibitor is beneficial for most patients with CKD at high cardiovascular risk. Treatment outcomes in CKD may be enhanced by implementation of models of care that facilitate early identification and diagnosis of patients at risk for progression to later stages of CKD, global risk reduction, routine follow-up, and patient education.

Background

Chronic kidney disease (CKD) affects an estimated 26 million American adults and is associated with increased risk of cardiovascular disease (CVD), kidney failure, and other complications.[1] An aging population combined with a rising prevalence of diabetes and hypertension suggests that the prevalence of CKD will increase in the coming years (Figure 1). A diagnosis of CKD carries a 3-fold higher risk of death. Therefore, clinical risk factors should be routinely assessed during regular physician encounters and periodically thereafter. Effective treatment strategies include interventions proven to slow disease progression and minimize excess cardiovascular risk.

Definition of CKD

CKD is defined as a sustained reduction in the glomerular filtration rate (GFR) or evidence of structural or functional abnormalities of the kidneys.[2] Signs of kidney damage include proteinuria and other markers such as persistent glomerulonephritis or structural damage from polycystic kidney disease.

Individuals at Risk for CKD

It is recommended that all individuals in high-risk groups, including the elderly and those with diabetes, hypertension, or a family history of kidney disease, undergo screening to determine whether they are at increased risk for developing CKD.[2] Demographically, the prevalence of CKD is higher in persons older than 60 years (39.4%) compared with those aged 40–59 years (12.6%) or 20–39 years (8.5%). The prevalence of CKD is also higher among persons with less than a high school education (22.1%) compared with persons with at least a high school education (15.7%) and is greater among the non-Hispanic African-American population (15.6%), the non-Hispanic white population (14.5%), and other ethnicities (13.1%). As illustrated in Figure 2, the prevalence of CKD is higher in individuals with clinical manifestations of conditions such as diabetes, CVD, and hypertension.[3]

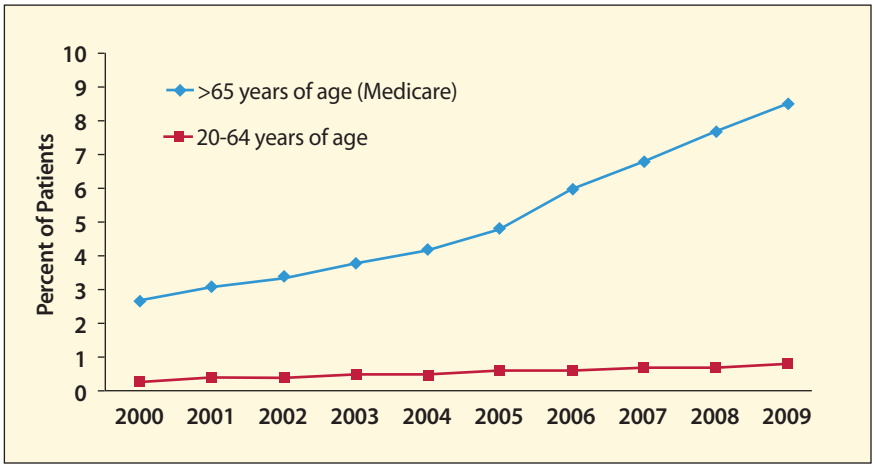
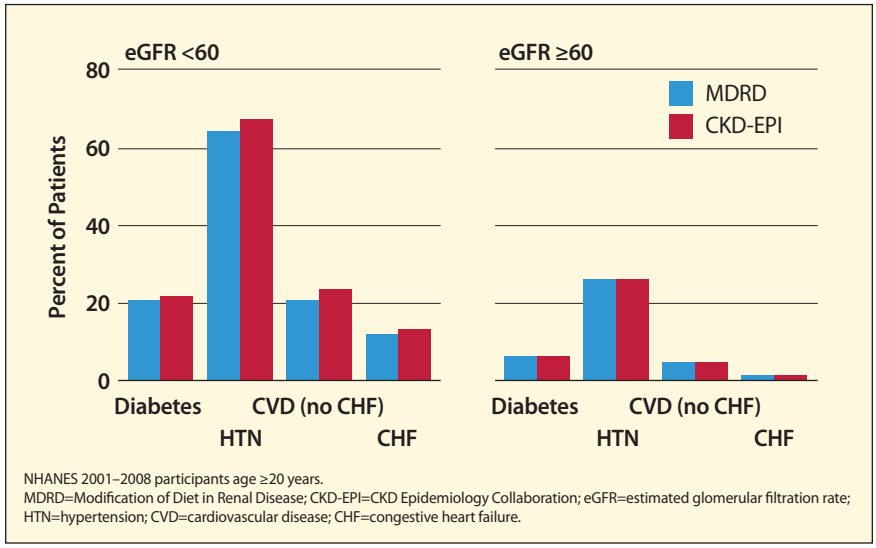


Figure 1. The prevalence of CKD is rising, particularly in the Medicare (≥65 year old) population. **Source:** USRDS 2011. ADR. http://www.usrds.org/atlas.aspx. Accessed June 22, 2012.



NHANES 2001–2008 participants age ≥20 years.
MDRD=Modification of Diet in Renal Disease; CKD-EPI=CKD Epidemiology Collaboration; eGFR=estimated glomerular filtration rate; HTN=hypertension; CVD=cardiovascular disease; CHF=congestive heart failure.

Figure 2. Prevalence of comorbidity in NHANES 2001–2008 participants, by risk factor, estimated GFR, and method used to estimate GFR. **Source:** USRDS 2011. ADR. http://www.usrds.org/atlas.aspx. Accessed June 22, 2012.

Diagnosis

CKD is diagnosed when either the urinary albumin-creatinine ratio is >30 mg/g or the GFR, as measured by the Modification of Diet in Renal Diseases (MDRD) Study equation, is <60 mL/min/1.73 m^2 on at least 2 different occasions over 3 or more months.[2] These 2 simple tests facilitate diagnosis of CKD by all clinicians, irrespective of the etiology. Once the diagnosis is confirmed, a 5-stage CKD classification system is used to facilitate patient management (Table 1).[4] The severity of CKD is based mainly on GFR (Table 1), although the risk of complications at a given rate is modified substantially by the amount of proteinuria.

Once the diagnosis has been established, goals include staging the disease and evaluating comorbid conditions. Because CKD carries a 3-fold higher risk of death, clinical risk factors underlying the disease should be routinely assessed. Individuals at increased risk for CKD should be tested for kidney damage and have their GFR evaluated more frequently. In addition, aggressive risk factor reduction should be conducted in individuals at increased risk for CKD even when CKD is not clinically apparent.

Cardiovascular Risk Reduction

CVD is the most common cause of premature death in the CKD population; regardless of age, race, gender, or presence of diabetes, individuals with CKD have a 10-20 times greater risk of cardiac death than those without CKD (Figure 3).[3] The risk of death, cardiovascular events, and hospitalization increases in a graded fashion as the GFR decreases to less than 60 mL/min/1.73 m^2.[5] Similarly, following myocardial infarction, the risk of death or an additional cardiovascular event increases as kidney function declines,[6] with risk increasing more than 3-fold when the GFR is less than 45 mL/min/1.73 m^2.[7] As a result, the majority of patients with CKD die of CVD before dialysis becomes necessary.[8-10] CVD in this population is attributable to CKD-associated pathology as well as well-known CVD risk factors such as diabetes, hypertension, and dyslipidemia. In patients with advanced CKD, nontraditional or novel risk factors such as inflammation, oxidative stress, vascular calcification, a tendency for thrombogenesis, and anemia appear to confer additional risk. Therefore, risk factor assessment is essential.

Table 1. Stages of CKD.

Stage	Characteristics	Estimated GFR (mL/min/1.73 m2)
1	Kidney damage with normal or ↑ GFR	≥ 90
2	Kidney damage with mild ↓ GFR	60 - 89
3	Moderate ↓ GFR	30 - 59
4	Severe ↓ GFR	15 - 29
5	Kidney failure/ESRD	< 15 (or dialysis)

ESRD=end stage renal disease.

Source: Reprinted with permission from National Kidney Foundation. *Am J Kid Dis.* 2002;39(2 suppl):S1-S266.

Global risk reduction is crucial for improving outcomes in patients with CKD. Targeted interventions include blood pressure control in hypertensive patients with angiotensin-converting enzyme inhibitors or angiotensin receptor blockers and glycemic control in patients with diabetes.[2] Due to the disproportionately high CVD burden in later stages of CKD, it is also essential to treat dyslipidemia.[2] In addition to targeted interventions, all patients with CKD should be encouraged to undertake therapeutic lifestyle changes, including smoking cessation, weight loss, reduced alcohol consumption, increased physical activity, and dietary modifications. Most adults with CKD should follow a modified Dietary Approaches to Stop Hypertension (DASH) diet as part of a comprehensive strategy to lower blood pressure and reduce CVD risk.[2]

Hypertension

Hypertension is both a cause and a consequence of CKD, and CVD in turn can contribute to the progression of renal failure.[11] Therefore, it is essential to meet established blood pressure goals to slow the progression of CKD as well as to limit the development and worsening of CVD. In addition to restricting sodium intake, all antihypertensive agents can be used to lower blood pressure in CKD unless contraindicated in the particular patient. In fact, multidrug regimens will be necessary in most patients with CKD to achieve therapeutic goals.[2]

Diabetes

Diabetes accounts for the largest percentage of patients with CKD that has progressed to end-stage renal disease.[3] Tight glycemic control can minimize development or progression of nephropathy in patients with diabetes[2,12,13]; therefore, achieving glycemic control is an essential component of the comprehensive care of these patients. CVD is the primary cause of mortality in patients with type 2 diabetes, and this risk is magnified with concomitant CKD.[14] A multifactorial approach to managing hyperglycemia, hypertension, and dyslipidemia can minimize macrovascular complications. Global risk factor reduction would also augment the benefit to the nephrons or kidneys, which are associated with tight glycemic control. Patients with type 2 diabetes often require multiple drugs to attain glycemic control. Although no single oral agent appears superior to another in ability to reduce nephropathy, metformin should be used in overweight patients with type 2 diabetes because it can reduce macrovascular complications in this population.[15] Caution is warranted when treating patients with diabetes and CKD because use of metformin has been associated with life-threatening lactic acidosis; therefore, it is contraindicated in any patients with elevated serum creatinine levels (≥1.4 mg/dL in women; ≥1.5 mg/dL in men) or an estimated GFR <60 mL/min.

Dyslipidemia

Dyslipidemia confers a substantial risk for CVD in patients with CKD with and without diabetes. CKD appears to disrupt normal lipoprotein metabolism,

resulting in depressed high-density lipoprotein cholesterol (HDL-C) and increased triglyceride-rich lipoprotein levels.[16] Evaluation of dyslipidemia is recommended on presentation with CKD. Evaluation should also take place 2 to 3 months after initiation of or change in treatment (eg, diet, lipid-lowering agents) or other change in status that may affect lipid levels and then yearly thereafter.[2] Patients with dyslipidemia should also be assessed for renal dysfunction, especially microalbuminuria. Patients with diabetes and CKD should be recognized as being at particularly high risk for adverse CVD outcomes and eligible for treatment regardless of baseline low-density lipoprotein cholesterol (LDL-C) level.

Overall, statins have the strongest evidence-based association with reduced CVD risk.[17] Meta-analyses of randomized trials have shown that statin therapy reduces the incidence of major coronary events (ie, nonfatal myocardial infarction or coronary revascularization), ischemic stroke, and coronary heart disease mortality by about one-fifth for every 39-mg/dL reduction in LDL-C level.[18,19] Although patients with CKD have typically been excluded from the large randomized trials of statins, post-hoc subgroup analyses have demonstrated benefits associated with statin use in patients with mild to moderate CKD. These studies have consistently shown reductions in major adverse cardiac events with statin therapy.[20-22]

The Study of Heart and Renal Protection (SHARP study) was the first large-scale, long-term, placebo-controlled trial of statins for primary prevention of CVD in patients with advanced CKD.[23] This study directly addressed past concerns with statin therapy in CKD and provides substantial evidence of benefits for lipid lowering in this population. The SHARP study enrolled 9270 patients with CKD (3023 on dialysis at study entry) and randomly assigned them to receive simvastatin 20 mg daily plus ezetimibe 10 mg daily or placebo. Patients were followed up for a median of 4.9 years. The primary end point was major atherosclerotic events, including death due to coronary disease, myocardial infarction, nonhemorrhagic stroke, or the need for revascularization. The end point was refined during the study to exclude noncoronary cardiac death and hemorrhagic stroke.

Treatment with the combination of simvastatin plus ezetimibe was associated with an average reduction in LDL-C of 15.3 mg/dL and a 17% reduction in major atherosclerotic events (rate ratio, 0.83; 95% confidence interval, 0.74–0.94; $P = .0021$; Figure 4). The largest contribution to the primary end point was reduction in coronary revascularization. No difference in adverse outcomes was identified (specifically cancer and myopathy). The clinical implication of the SHARP study is that the combination of low-dose simvastatin (20 mg) and ezetimibe (10 mg) is safe and effective, even in patients with advanced CKD. Moreover, if high doses are avoided, statins can be used safely to reduce CVD risk in patients with CKD.

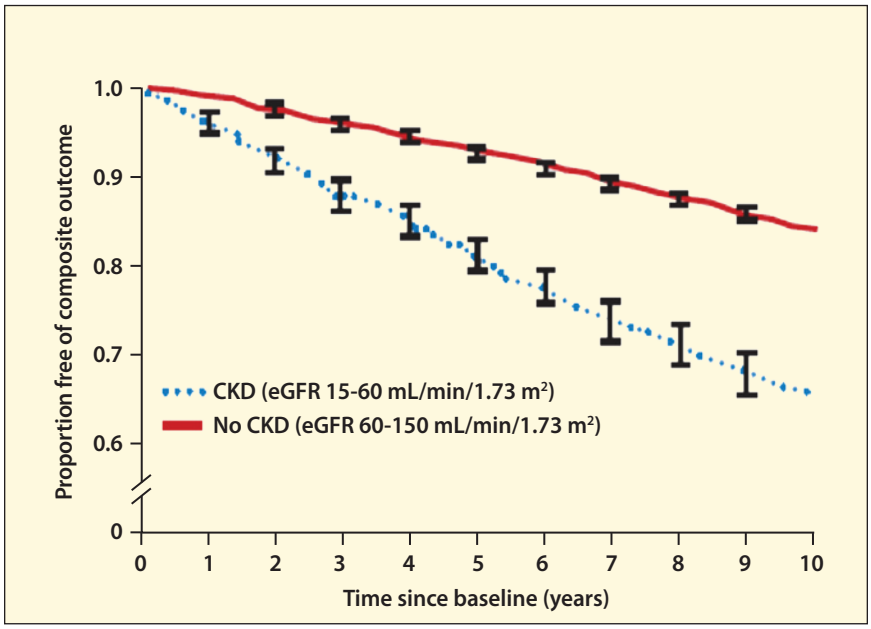


Figure 3. Presence of CKD increases the probability of experiencing a cardiovascular event, including myocardial infarction, stroke, heart failure, or cardiovascular death. **Source:** Reprinted with permission from Weiner DE, et al. *J Am Soc Nephrol.* 2004;15(5):1307-1315.

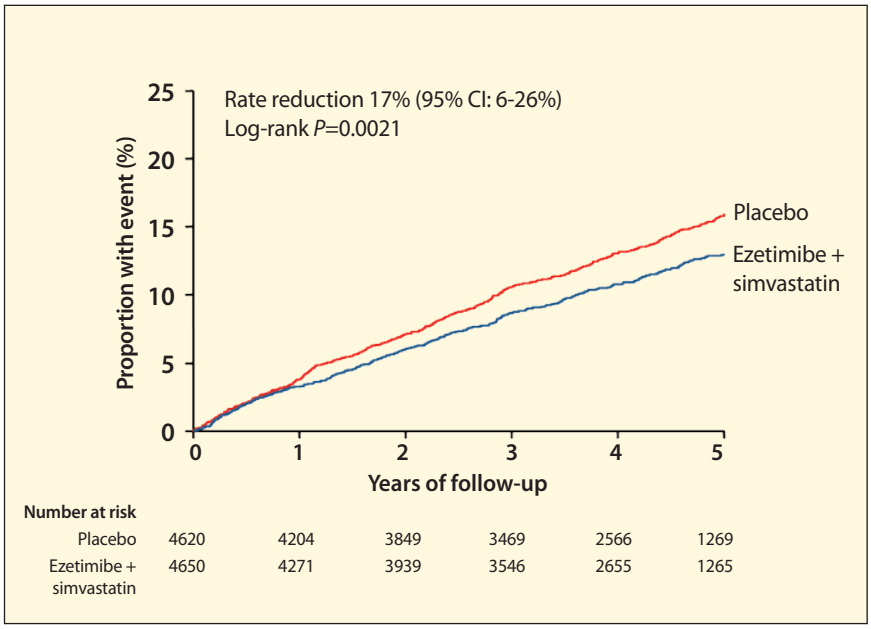


Figure 4. In the SHARP study, there was a 17% reduction in major atherosclerotic events in patients randomized to the group that received a combination of simvastatin (20 mg every day) and ezetimibe (10 mg every day). **Source:** Reprinted with permission from Baigent C, et al. *Lancet.* 2011;377(9784):2181-92.

Improving CKD Outcomes in Primary Care

Primary care providers play a critical role in both recognition and management of CVD risk in CKD. Although referral to a nephrologist is appropriate for patients with more complicated or advanced CKD, primary care physicians should feel comfortable making the initial diagnosis and providing appropriate initial and ongoing care to these patients. Interventions to manage diabetes, hypertension, and dyslipidemia should be initiated early and clear treatment goals established. Patients should be scheduled for regular follow-up visits to measure progress toward the treatment goal and to adjust therapy if necessary.[2]

Regular clinician-patient interaction, patient education, and strong clinician-patient relationships serve to improve therapeutic outcomes. Physicians and other providers need to be sensitive to the influence of culture on health and health care because this often influences treatment outcomes. Use of a multidisciplinary team approach can improve care delivery. For example, a patient-centered medical home provides a setting that facilitates partnerships between individual patients and their physicians and other providers with the goal of integrating care across all conditions and health care settings.[24]

Summary

The number of patients with CKD is expected to increase in the coming years; thus, primary care physicians must be equipped to care for this unique patient population.

Regardless of the underlying etiology of the CKD, the primary care physician can have a significant impact in slowing disease progression. Patients with CKD require evaluation, treatment, and control of primary care conditions such as diabetes, hypertension, and dyslipidemia to reduce kidney damage. All patients with CKD are at significantly increased risk for cardiovascular events; therefore, additional cardiovascular risk factors such as dyslipidemia should be managed aggressively. Delivery of care can be improved through the use of integrative care models that facilitate the coordination of care across the health care spectrum.

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Faculty Introduction

Moderator: My name is Keith Engelke, PhD, and I'd like to welcome you to the roundtable discussion titled *Practical Steps to Improve Outcomes for Patients with Chronic Kidney Disease: A Whole Patient Approach*. I am joined by Carman A. Ciervo, DO, clinical professor in the Department of Family Medicine at University of Medicine and Dentistry of New Jersey School of Osteopathic Medicine; senior vice president for clinical integration at the Kennedy Health System, and a member of the Board of Governors for the American College of Osteopathic Family Physicians. I am also joined by Michael H. Davidson, MD, clinical professor and director of preventative cardiology at the The University of Chicago Medicine, and Matthew R. Weir, MD, professor of medicine at the University of Maryland School of Medicine and attending physician and director of the Division of Nephrology in the Department of Medicine at the University of Maryland Medical Center.

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

Case Study 1

Moderator: *Let's begin our discussion with a case study.*

Mr. Jackson is a 58-year-old African-American man with a history of hypertension and hypercholesterolemia. His social history includes smoking 10 cigarettes a day for 30 years, moderate alcohol intake, and a relatively sedentary lifestyle. He has a family history of hypertension and end-stage renal disease. Currently Mr. Jackson is not taking any medications. He is 71" tall and weighs 248 lb, and his body mass index is 34.6 kg/m^2. His resting blood pressure is 148/92 mm Hg, total cholesterol level is 209 mg/dL, LDL-C level is 112 mg/dL, and HDL-C level is 39 mg/dL. His blood glucose level is 157 mg/dL, hemoglobin A_{1c} is 9.3%, creatinine clearance is 2.4 mg/dL, and GFR is 34 mL/min.

Moderator: *What appear to be Mr. Jackson's primary medical problems?*

Dr. Ciervo: This gentleman presents with significant risk factors for both renal disease and heart disease. He is hypertensive, his cholesterol level is high, he is a long-term smoker, his hemoglobin A_{1c} is elevated, and he has a family history of diabetes. I am also concerned about his GFR because it is very low, even adjusted for an African-American man. In short, all 4 disease processes—hypertension, dyslipidemia, diabetes, and CKD—are very concerning and appear to be untreated.

Dr. Weir: At 58 years of age, Mr. Jackson is nearly eligible for Medicare. Statistically speaking, looking at the Medicare data, this gentleman is 5 times as likely to die of a stroke or a heart attack as he is to reach dialysis. His risk of CVD is substantial, even relative to his risk of kidney disease progression, and his primary medical problem is dying of a stroke or a heart attack. Mr. Jackson requires interventions to reduce his global risk for CVD, and he should be started immediately on cardiovascular risk-reducing therapies.

Dr. Davidson: I would add that we often tend to think of risk factors in silos and only pay attention to the ones we consider severe. When viewed in isolation, each of Mr. Jackson's risk factors appears moderate and therefore may not set off the same alarm as if he presented with severe hypertension or severe hypercholesterolemia. However, when you look at the combination of risk factors, the alarm should go off because cumulatively they put this patient at an extremely high risk of cardiovascular events.

Moderator: *We'll come back to the cardiovascular issues in a moment, but let's focus on CKD for the next few minutes. Dr. Weir, can you give us a definition of CKD?*

Dr. Weir: The National Kidney Foundation (NKF) definition uses epidemiological data to stage CKD into 5 categories based on glomerular filtration. The traditional threshold for defining CKD is an estimated GFR less than 60 mL/min.[1] There is clear evidence that there is a rise in the incidence of cardiovascular events as the GFR drops below this point, and the curve gets even steeper below 45 mL/min. There is evidence that proteinuria, which is not in the staging system, also plays an important role in not only the prediction of CVD but also progression of CKD. There are also structural forms of kidney disease.

There has been some discussion about whether the NKF definition is too dogmatic in the sense that we have many older patients with age-related reductions in filtration capability who do not have proteinuria or substantial hypertension and yet they are labeled as having CKD. A modified staging system that subdivides stage 3 CKD into 2 groups has been proposed to avoid misclassification of CKD in aging populations. The proposed modification would stage patients with a GFR between 30 and 45 mL/min as stage 3B and those with a GFR between 45 and 59 mL/min as stage 3A.[2] This schema has yet to be incorporated into the standard of care.

Perhaps the most important take-home message for primary care physicians regarding the definition of CKD has to do with what the GFR represents relative to the overall health of the vasculature. We know that CKD is a biomeasure of vascular disease burden in the body. With the heart and the brain, we do not have an objective measure of vascular disease burden until the patient starts manifesting symptoms such as angina or transient ischemic attacks or has an event such as sudden cardiac death or stroke. With the kidney, we have an objective opportunity to look at the loss of glomerular filtration surface area as a biomeasure of vascular disease risk. We have a similar

opportunity if the patient has protein in the urine because the higher the proteinuria, the greater the risk. It is not an all-or-nothing phenomena; it is a graded and continuous relationship between both the loss of GFR and increased risk and elevated protein level in the urine and increased risk.

has a family member with kidney disease. Overall, diabetes is probably the biggest cause of kidney disease in westernized countries, but there are forms of immunological kidney disease as well as disease caused by toxins and acute kidney injury. Blood pressure also plays a role, probably not as a generator

"Perhaps the most important take-home message for primary care physicians is that the GFR is an indicator of the overall health of the vasculature. The loss of glomerular filtration surface is a biomeasure of vascular disease risk."

– Dr. Weir

It is important to emphasize that there is the competing hazard of cardiovascular and kidney disease events in patients with reduced GFR and/or increased protein level in the urine, and this influences how populations in clinical trials respond to various interventions. For example, clinical trials designed to evaluate interventions to slow the progression of kidney disease should include patients more likely to have kidney disease events than heart disease events. Patients with more substantial reductions in kidney function or more protein in the urine are more likely to progress to a kidney end point despite the fact that they are at high risk for cardiovascular end points. From an opposite standpoint, if you want to examine the likelihood of developing cardiovascular events in a kidney disease population, examine patients with lower levels of protein in the urine, preferably microalbuminuria, and lesser reductions in GFR.

I think this is the real opportunity in clinical practice because we can use the kidney as the biomeasure of vascular disease burden in the body and then hopefully more appropriately initiate known cardiovascular risk-reducing therapies. The key-take home message is to take advantage of the kidneys as a measure of risk for stroke and heart attack.

Dr. Ciervo: This is really important information. I'm not sure there is a full understanding in primary care about how the kidney can be used to evaluate the overall health of the vasculature.

Moderator: *Thanks, Dr. Weir, for your insight on the role of the kidney as an indicator of overall vascular health. Returning to our case, what factors play into the risk of CKD in any given population?*

Dr. Weir: Everybody who has risk factors for CKD, including hypertension, diabetes, and evidence of protein or albumin in the urine, needs to be carefully screened. In terms of demographics, age is certainly an important risk factor, as is being of African-American heritage, particularly if a patient

of kidney disease, but as a propagator of disease progression. Traditional risk factors such as blood glucose level and possibly cholesterol level may also play a propagating role. We also continue to learn about nontraditional risk factors that lead to the progression of CVD in patients with kidney disease, such as albuminuria, fibroblast growth factor 23, parathyroid hormone, anemia, and uremic solutes, that may lead to systemic inflammation.

The bottom line is that the cause of kidney disease is probably easier to identify than progression factors. There is more and more interest in the fact that progressive kidney disease is an inflammatory condition. In the future, it is likely that therapeutic strategies will target inflammatory processes in the kidney.

Moderator: *Dr. Ciervo, as a primary care physician seeing a patient like Mr. Jackson for the first time, what are the first steps you might take to manage his condition?*

Dr. Ciervo: It's important to be realistic about what can be accomplished in the first few visits with a patient who presents with multiple risk factors. During the first visit, I would target his blood pressure and discuss lifestyle modifications with him, including dietary changes that may have a beneficial impact on his blood pressure and diabetes. I need to keep in mind that his elevated creatinine level and reduced GFR are going to influence the choice of drugs I can prescribe for his blood pressure; I want to lower his pressure but also want to preserve the remaining kidney function. In subsequent visits, I would strongly consider initiating therapy to lower his blood glucose and cholesterol levels to augment any lifestyle modifications he has been able to implement.

Moderator: *At what point would you, as a primary care physician, potentially refer a patient like Mr. Jackson to a specialist?*

Dr. Ciervo: As I mentioned a moment ago, if this patient came into my office, I would immediately initiate treatment to lower his blood pressure and consider medical management of his cholesterol and blood glucose levels. However, this patient may need dialysis, so to me, this is clearly a patient who should be referred to a nephrologist or a kidney specialist, at least according to the standard of care in my geographic area.

Moderator: *Dr. Weir, how is a diagnosis of CKD made?*

Dr. Weir: In a broad clinical sense, it can be made using a serum creatinine and a creatinine-based estimating formula. A diagnosis of CKD can also be made with a spot urine albumin or protein-to-creatinine ratio or with a renal ultrasound demonstrating structural abnormalities of the kidney.

Moderator: *Is there an ideal point when a patient would be considered for an evaluation for CKD?*

Dr. Weir: As I mentioned earlier, everybody who has risk factors for CKD, meaning age, hypertension, and diabetes, or obviously evidence of protein or albumin in the urine, needs to be very carefully screened.

Dr. Ciervo: I would add that because of this patient's family history of hypertension and end-stage renal disease, he is at risk even though he is relatively young.

Moderator: *From the laboratory report, we know that Mr. Jackson has a GFR of 34 mL/min; therefore, according to the NKF, he has CKD. What is his CKD stage?*

Dr. Weir: He would be staged as CKD stage 3 but, depending on the amount of protein in his urine, his overall risk could be substantially more than what his estimated GFR suggests. As I mentioned earlier, there is increasing interest in including the amount of protein or albumin in the urine as part of our staging efforts.

Moderator: *Do current CKD treatment guidelines exist?*

Dr. Weir: The NKF Kidney Disease Outcomes Quality Initiative (KDOQI) has provided evidence-based clinical practice guidelines for CKD since 1997, with the most recent version published in 2002.[3] The Kidney Disease Improving Global Outcomes (KDIGO) Foundation is in the process of developing an updated treatment guideline that is expected to be available in the near future.[4] KDIGO also made public the proceedings from a "controversies" conference, which introduced the concept that albumin should be considered a risk factor for both heart disease and kidney disease progression in patients with CKD.[2]

Moderator: *Dr. Ciervo, how commonly are the guidelines used to direct the treatment of a patient such as Mr. Jackson in the primary care setting?*

Dr. Ciervo: Primary care physicians are familiar with the traditional 1 through 5 staging scheme for CKD, but to be honest, I just learned about CKD-A and CKD-B from Dr. Weir. In addition, primary care physicians understand the importance of treating the underlying disease processes and are familiar with the importance of using therapy that targets the renin-angiotensin system to control blood pressure in these patients.

Moderator: *Dr. Weir, just as an aside, should we expect to see the CKD-A and CKD-B nomenclature in future treatment guidelines?*

Dr. Weir: I wish I could give you an answer to that, but I really don't know.

Moderator: *How would you treat this patient to modify his risk factors and control the progression of his CKD?*

"Everyone who has hypertension, diabetes, and evidence of protein in their urine should be screened for CKD."

– Dr. Weir

Dr. Weir: This patient has diabetes, so he has a very high risk for CVD. We know from the Heart Protection Study[5] that there is no threshold of benefit for lipid lowering in patients with diabetes, so the treatment target should be at least a 30-40% reduction in LDL-C from baseline. In addition, I think he is sufficiently at risk to benefit from antiplatelet therapy with a low dose of aspirin.

He is also a candidate for better blood pressure control. With regard to blood pressure, there are absolutely no clinical trial data in humans with diabetic kidney disease that have looked at 2 levels of blood pressure to determine the most appropriate target. There are data in nondiabetic patients with kidney disease indicating that there does not appear to be any benefit of lowering systolic blood pressure to less than 140 mm Hg, except for patients who have more than 1 g of protein in their urine on a daily basis. We do not have the data to support a target of 130 mm Hg in diabetic patients even if they have

more than 1 g of protein in their urine, but secondary analyses of results of both the Irbesartan Diabetic Nephropathy Trial (IDNT)[6] and the Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL) Study[7] suggest this may be appropriate. My personal practice is to target below 130 mm Hg. Regardless, I think the next edition of the Joint National Committee Guidelines will take a very conservative look at the data and probably recommend treating to a target systolic pressure of 140 mm Hg in patients with diabetes, regardless of whether there is proteinuria or not.

Dr. Davidson: I agree with Dr. Weir. I think the more complicated issue for the primary care physician is how to manage a patient with stage 3 CKD who has a low GFR. The patient we have been discussing in our case has diabetes, dyslipidemia, hypertension, and an elevated creatinine level, and he smokes. The question becomes, what is the best treatment option? What type of drug should be used in a patient with so many risk factors?

Dr. Weir: This is a great question. I think it is fair for us to say that in this patient with a reduced GFR and diabetes, a drug that blocks the renin-angiotensin system is the preferred initial therapy, either an angiotensin-converting enzyme (ACE) inhibitor or an angiotensin receptor blocker (ARB). In type 2 diabetes, there are more data supporting the use of an ARB, but in type 1 diabetes, the preponderance of the data support the use of an ACE inhibitor. Frankly, based on my evaluation of the literature, level C evidence would say that they are interchangeable. Further, I would use the fully approved dose for lowering blood pressure.

In addition, it is important to recognize that the majority of patients would probably require 2 or 3 drugs to get to a systolic goal of 140 mm Hg or even 130 mm Hg, but currently we do not have sufficient data to say with certainty what option would provide the next best choice. In general, diuretics and calcium channel blockers are probably the best second and third choices and are somewhat interchangeable in these patients. For patients with prior evidence of myocardial infarction, systolic heart failure, or angina pectoris, I would also add beta-blockers.

Dr. Ciervo: I agree with Dr. Weir's approach to treatment. Certainly from a purist standpoint, I would start with an ACE inhibitor; however, in my clinical experience, lowering diastolic blood pressure to within a range of 80 to 85 mm Hg in African-American patients is very difficult using ACE inhibitor monotherapy, so I often have to add a calcium channel blocker as a second-line agent. Dr. Weir, do you have any caveats about what drugs to select as second- or third-line drug choices in African-American patients?

Dr. Weir: Race or ethnicity does not alter my decision to use a thiazide or a calcium channel blocker, because I don't believe there is any evidence in the literature or in my clinical experience indicating that there is a preferable strategy in one direction or the other.

Dr. Davidson: I would like to broaden our discussion a bit and comment that the patient in our case is physically inactive and overweight, has moderate alcohol intake, and is probably consuming a lot of sodium. As Dr. Ciervo indicated earlier, this patient would benefit tremendously from lifestyle changes. I would invest time in reviewing the DASH[8] diet and developing an exercise and weight loss program for him. I also would evaluate him for sleep apnea to make sure we consider all of the factors that could be affecting his blood pressure.

Dr. Weir: I think the point about sleep apnea is excellent, but it has been my experience that the only individuals in whom weight loss really made a clinical difference were those who underwent bariatric surgery.

Moderator: *How might an electronic medical record (EMR) system be helpful in screening and identifying risk factors in a patient such as Mr. Jackson?*

Dr. Ciervo: EMRs are very helpful in supporting care delivery at the point of service. As a primary care physician, you only have a short time to work with each patient, so you have to prioritize your efforts. Most EMR platforms are programmed with all the current treatment guidelines and normative data. After entering the patient data, the EMR assists physicians by flagging the medical issues that need our attention and prompting us to ask the patient a question or to follow up on an issue. For example, in our case, the EMR would most likely flag blood pressure, cholesterol level, blood glucose level, creatinine clearance, and GFR, indicating these are all areas where this patient falls outside of accepted healthy ranges.

The EMR can also risk stratify patients based on any number of criteria, including the Framingham criteria, CKD stage, body mass index, blood glucose level, and the like. In addition, many EMRs are loaded with the approved treatment algorithm used by the health plan to identify drug therapies for each medical issue. With all these data available at the point of care, we can focus our energies on the patient. When the patient returns for a follow-up visit, the EMR provides a spreadsheet that tracks changes in the laboratory values; I find this to be particularly helpful in my discussion with my patients about their progress on therapy.

Dr. Davidson: Our EMR came online just a few weeks ago. I find one of the greatest benefits of the EMR is the ability to better track patients who only visit the clinic every once in a while or who are being treated by other physicians in our health care system. This is a helpful feature because it increases physician awareness of all the medical issues for which the patient is being treated and provides access to the patient's laboratory data.

Case Study 2

Moderator: *Let's move on to our next patient, Mrs. Santiago.*

Mrs. Santiago is a 68-year-old Mexican-American woman. She has not seen a physician in more than a year, but she continues to refill the prescriptions she received the last time she saw her physician. Her current symptoms include stiffness and pain in her wrists and fingers as well as frequent headaches. She has a 30-year history of type 2 diabetes, hypertension, dyslipidemia, and osteoarthritis. She is a nonsmoker and a social drinker. She has a family history of paternal diabetes, end-stage renal disease/dialysis, and heart disease (her father died at age 61 years). Laboratory data include a body mass index of 33 kg/m^2, hemoglobin A_{1c} of 8.3%, blood pressure of 139/79 mm Hg, total cholesterol level of 195 mg/dL, LDL-C level of 91 mg/dL, HDL-C level of 38 mg/dL, triglyceride level of 169 mg/dL, creatinine level of 1.7 mg/dL, albumin level of 3.9 mg/dL, and GFR of 30 mL/min. Current medications include metformin, hydrochlorothiazide, amlodipine, and over-the-counter nonsteroidal anti-inflammatory drugs (NSAIDs).

Dr. Ciervo, what do you consider to be her primary medical issues?

Dr. Ciervo: Again, this is not an easy patient; she has long-standing type 2 diabetes and increased blood pressure as well as a positive family history for kidney disease and heart disease. In addition, her cholesterol and creatinine levels are elevated. I want to be very aggressive in controlling her blood pressure as well as her cholesterol levels. I would want to double check her GFR to determine if she should even be on metformin. I would also need to quantitate her consumption of over-the-counter NSAIDs. Is she taking 2 ibuprofen tablets twice a day or is she taking 4 pills every few hours? This is important because NSAIDs can impact kidney function as well as have an effect on blood pressure.

Dr. Davidson: As a preventative cardiologist and lipidologist, I see this patient as a train wreck waiting to happen. Because she has so many issues, I would take a global approach and utilize interventions that provide risk reduction via several mechanisms. For example, I would initially focus on initiating lifestyle modifications to help her begin to control her body weight, cholesterol level, hypertension, and diabetes. Even a modest reduction of dietary carbohydrates may make a big difference because her triglyceride levels are high, her HDL-C level is low, and she is overweight. One of my recommendations is to begin a low-carbohydrate diet for a few weeks and see how she responds to it. Because her history suggests that she does not follow up with her physician regularly, I would make sure my office contacts her regularly so we can evaluate how she is progressing with her dietary changes. I would also initiate pharmacologic therapy to begin to reduce her cardiovascular risk.

Dr. Weir: Like the first patient, Mrs. Santiago has a series of medical problems: obesity, poorly controlled diabetes, blood pressure, although reasonably well controlled, and dyslipidemia. Some may view her LDL-C level as acceptable at 91 mg/dL, but as I mentioned earlier, it's not where you start, it's where you finish. Therefore, she needs a 30-40% reduction in LDL-C level, so she should be on a statin. With regard to her kidney function, her GFR is low.

As Dr. Ciervo stated, it is critical to evaluate her use of over-the-counter NSAIDs. Long-term use of NSAIDs can have a substantial influence on glomerular filtration in a patient like this. More to the point, given her age, she is most likely already salt sensitive, so the use of NSAIDs will tend to raise her blood pressure. She may not even need some of the antihypertensive medication if she stops the NSAIDs.

Dr. Davidson: Dr. Weir, what about the metformin? With a creatinine level of 1.7 mg/dL, would you stop the metformin?

Dr. Weir: Good question. There is some debate about the lactic acidosis GFR cutoff point in patients treated with metformin (either 40 or 50 mL/min), so before tackling that issue, I would want to stop her NSAID use and see how that affects the GFR. Without NSAIDs, her GFR might be 45 or 50 mL/min. Once I know her GFR after discontinuation of the NSAIDs, I would reevaluate the safety of metformin.

I have one other point about her current diuretic. Some might question the effectiveness of a hydrochlorothiazide in a patient with a GFR of 30 mL/min. If you look at the literature, it may be better than expected for lowering blood pressure in this patient—not for diuresis, but for lowering blood pressure. However, not everyone agrees with this.

Moderator: *Mrs. Santiago's GFR is 30 mL/min, which corresponds to CKD stage 3, correct?*

Dr. Weir: Correct.

Moderator: *Let's step back from the patient for a moment and review the pathology associated with CKD and CVD. Dr. Weir, you alluded to this in your earlier comments. What does the literature tell us in terms of the primary cause of mortality in patients who have CKD?*

Dr. Weir: In a patient like this who has numerous risk factors and reduced GFR, she is 5 times as likely to die of a heart attack or a stroke as she is to reach end-stage renal disease. That would be especially true if she had lower levels of protein in her urine. My major focus would be preventing stroke and heart attack in this patient.

Moderator: *Dr. Davidson, can you identify the mechanism that predisposes patients with CKD to an increased risk of CVD?*

Dr. Davidson: It is very multifactorial. The risk factors

underlying the development of CKD are often the same as those that lead to CVD, namely, hypertension, diabetes, and dyslipidemia.

The level of LDL-C for the patient in this case is not very high at 91 mg/dL; however, she does have high triglyceride levels and a low HDL-C level, both of which place her at high risk for CVD. The pattern of dyslipidemia in CKD is unique in that these patients have a large number of small dense LDL particles, elevated C-reactive protein (CRP) level, and increased levels of inflammatory cytokines, all of which are associated with increased cardiovascular risk. In addition, there is evidence that elevated levels of uremia and creatinine commonly seen in patients with CKD may promote atherosclerosis.

Moderator: *Dr. Davidson, you indicated that the pattern of dyslipidemia in these particular patients is highly atherogenic. This patient has a relatively low LDL-C level of 91 mg/dL, but her HDL-C level is also low. What are some of the other patterns that you see in these patients?*

Dr. Davidson: According to the ATP III guidelines, an LDL-C level of 91 mg/dL would be acceptable for most patients. However, in patients with CKD, relatively "good" levels of LDL-C can be deceiving. If we look more closely, we frequently find that patients with CKD have a high number of small dense LDL particles and an elevated apolipoprotein B level. If we determined the lipid profile using a technique that counts the number of lipid particles in the sample, it is highly likely the levels of the highly atherogenic small dense LDL particles and apolipoprotein B would be elevated, and the presence of high levels of these particles is predictive of increased risk of cardiovascular events.

Moderator: *Dr. Ciervo, from your perspective, what is the level of sensitivity in the primary care community regarding the more subtle changes in the lipid profile that Dr. Davidson just described?*

Dr. Ciervo: I would say that the level of awareness among my primary care colleagues of the need for a more comprehensive lipid analysis in these patients is fairly high. There is also awareness that elevated levels of proinflammatory markers such as CRP place patients at higher risk.

Dr. Weir: Dr. Ciervo, you raise a good point about CRP. How would knowledge of the CRP level change your management of this particular patient?

Dr. Ciervo: It would not change it at all because we already know that this patient is at high risk. I think we all agree that this is a patient for whom we have to pull the trigger when it comes to lipid therapy. My point about CRP has more to do with an awareness at the primary care level that elevated inflammatory markers are associated with higher risk in this type of patient.

Moderator: *Let's discuss the treatment of dyslipidemia in this patient. Dr. Weir, what does the clinical trial evidence suggest regarding the benefit of lipid lowering in patients with CKD?*

Dr. Weir: The available evidence is strongly suggestive that lipid lowering in CKD does make a difference. Until recently, we had to rely on meta-analyses, ad hoc analyses, and subgroup analyses of patients with reduced GFR enrolled in larger trials. For example, in the Pravastatin Pooling Project, treatment with a statin reduced the absolute risk for a combined cardiovascular end point in patients with CKD.[9] There was also evidence in the ALERT Trial[10] in kidney transplant recipients[11] and in patients with reduced GFR enrolled in the 4S trial that was very suggestive that lipid reduction improved cardiovascular outcomes in these patients.[11] Many of these findings were confirmed with the recently published Study of Heart and Renal Protection (SHARP) study, which was a randomized, placebo-controlled, multicenter study that focused exclusively on describing the benefits of lipid modification therapy on cardiovascular outcomes in patients with CKD as well as those on dialysis. In the SHARP study, patients received either placebo or a daily combination regimen of simvastatin 20 mg and ezetimibe 10 mg. The primary outcome was all-cause cardiovascular events over time.[12]

Moderator: *Let's take a closer look at the SHARP study. Dr. Davidson, can you provide us a little more detail on the study design and patients who were enrolled in the trial?*

Dr. Davidson: Sure. The objective of the SHARP study was to assess whether treatment with cholesterol-lowering medication, in this case a combination of ezetimibe and simvastatin, could reduce the risk of atherosclerotic and/or vascular events in patients with advanced CKD compared with placebo.

Eligibility criteria included elevated creatinine level on 2 occasions—men with a level greater than 1.7 mg/dL and women with a level greater than 1.5 mg/dL—or on either hemodialysis or peritoneal dialysis. Patients had to be 40 years of age or older, and none had a history of previous coronary disease, myocardial infarction, or revascularization. A total of 9270 patients were randomized to one of three groups: 1) simvastatin 20 mg plus ezetimibe 10 mg daily, 2) simvastatin 20 mg daily, and 3) placebo. Patients initially allocated to simvastatin alone were then re-randomized to simvastatin 20 mg plus ezetimibe 10 mg daily after 1 year. At baseline, 63% of enrolled patients were men. The mean age was 62 years, blood pressure was 139/79 mm Hg, body mass index was 27 kg/m^2, 13% were smokers, 15% had vascular disease, and 23% had diabetes. The nondialysis patients had a mean GFR of 27 mL/min, and 80% had albuminuria. The mean follow-up was 4.9 years. At the end of the study, there were almost 5000 patients per arm followed up for 4.9 years.[12]

Moderator: *Dr. Weir, what were the findings of the SHARP study?*

Dr. Weir: Importantly, the SHARP study demonstrated that, compared with placebo, treatment with simvastatin/ezetimibe resulted in a 17% reduction in major atherosclerotic events. There were significant reductions in nonhemorrhagic stroke and arterial revascularization procedures in patients receiving combined therapy. In addition, fewer patients receiving the combination had a nonfatal myocardial infarction or died from coronary heart disease, although this difference was not significant. Subgroup analysis indicated that the reduction in cardiovascular risk was no different for patients on dialysis versus those who were not.

still warrants debate is regarding patients on dialysis. The trend toward risk reduction in these patients was favorable, but the data were insufficient to make a definitive statement about the benefit of lipid lowering.

As clinicians, we have to appreciate that patients on dialysis are different from patients with CKD. They are not the same and should not be considered as such. In reality, they have many more problems related to sudden death and systolic heart failure than the traditional nondialysis patient with CKD, which may explain why there is less power in them to see the reduction in atherosclerotic events with lipid-lowering therapy.

"In CKD, relatively 'good' levels of LDL can be deceiving. Patients with CKD often have elevated levels of highly atherogenic small dense LDL and apolipoprotein. Increased levels of these particles are predictive of increased risk of cardiovascular events."

– Dr. Davidson

What was remarkable about the SHARP study was that whether all cardiovascular events were included or just atherosclerotic events, there was consistent evidence that reducing LDL-C levels with the combination of simvastatin and ezetimibe resulted in fewer overall cardiovascular events. In my mind, the results of the SHARP study were absolutely no surprise whatsoever—it is how I have been practicing medicine for many years. It is nice to finally have the data in hand to support the use of lipid-lowering therapy for our patients with CKD with a high global risk for CVD.

Moderator: *Dr. Ciervo, what do the findings of the SHARP study mean for the treatment of patients with CKD in your clinic?*

Dr. Ciervo: Primary care physicians already know that we have to lower the global risk of CVD in our patients with CKD. The SHARP study drives home this point by reiterating the need to assess and treat the patient's global risk and not be lulled into inaction by numbers that fall into a "normal" range on the laboratory report. The SHARP study confirms that an opportunity exists to reduce the risk of future events by aggressively treating these patients with a lipid-lowering agent.

Moderator: *Dr. Weir, from your perspective as a nephrologist, what do the findings of the SHARP study mean for the treatment of patients with CKD?*

Dr. Weir: As I've stated already, this trial did not come as a great surprise. I believe the results are now certainly well incorporated into routine practice in the nephrology community. However, the one issue that remains unsettled and

Moderator: *Taking the discussion of the SHARP study back to the patient in our case, how would you approach the treatment of her dyslipidemia?*

Dr. Davidson: The patient in our case should absolutely be on lipid therapy, preferably statin-based therapy. Although an LDL-C level of 91 mg/dL looks good on the surface, as we stated earlier, when we take a closer look, she has a ton of bad LDL particles, a lot of apolipoprotein B, and high triglyceride levels. Despite a seemingly good LDL-C level, she needs aggressive lipid therapy.

If we use an evidence-based approach, the SHARP study demonstrated that treatment with the combination of a statin and ezetimibe resulted in a 17% reduction in major cardiovascular events. Although the degree of risk reduction is in line with the results of other outcome trials that looked at LDL-C lowering in high-risk patient populations, there are a couple of unique findings of the SHARP study that should be highlighted. One is the trend for benefit in patients on dialysis; this has not been shown in earlier trials. The other is in the safety of the statin-ezetimibe combination. An important issue to consider when using a statin-based regimen is how best to avoid statin-related side effects, particularly dose-related adverse events in patients requiring aggressive treatment. Because most statins are metabolized to at least some degree in the kidney, we have to be careful when using high doses of these agents in patients with CKD.

We also have to be careful about drug interactions. It is highly likely that patients like the one in our case study are going

to be taking several drugs—calcium channel blockers, ACE inhibitors, diuretics, maybe metformin or other diabetes drugs—many of which are metabolized in the kidney, specifically by the cytochrome P450 3A4 pathway. My goal in these patients is to avoid using a high-dose statin because I am really concerned about drug interactions.

What was nice about the SHARP study was not only did we see that treatment with the combination of simvastatin 20 mg and ezetimibe 10 mg was associated with a significant reduction in cardiovascular events, we also saw that the regimen was safe and well tolerated with a low incidence of statin-related side effects—especially rhabdomyolysis—in this high-risk population. The dose of simvastatin 20 mg and ezetimibe 10 mg provided a significant reduction in LDL-C level that was safe for the patient with renal impairment.

In the case of our patient, assuming the drug was reimbursed by her insurance provider, I would consider using the treatment regimen described in the SHARP study because I think a low-dose statin alone is not going to modify her lipids sufficiently to reduce her risk of CVD.

Moderator: *Dr. Weir, any additional thoughts?*

Dr. Weir: Even if this patient did not have diabetes and just presented with a GFR of 30 mL/min, she would meet the criteria for lipid-lowering therapy, regardless of the level of LDL-C. Again, the emphasis here is that we need to abandon thresholds and adopt more appropriate algorithms based on the data. There is a continuous relationship between LDL-C level and events, and in high-risk patients, lower is indeed better. As I stated earlier, the data tell us that we need to treat to an LDL-C level that is at least 30-40% below the level at the start of therapy.

Moderator: *Dr. Davidson, do the current lipid guidelines reflect the need for lipid lowering in patients with CKD? Do they identify patients with CKD as a subgroup of patients needing aggressive therapy?*

Dr. Davidson: Not yet, although I think that will change because there is now clear evidence that these patients are at increased risk and a large clinical trial has shown a benefit. I would suspect that based on the accumulating evidence, patients with CKD will be identified as a high-risk population that warrants treatment, much like how patients with diabetes are identified as a high-risk group.

I'd like to echo Dr. Weir's comments about treating patients only based on an LDL-C threshold. Basing treatment decisions purely on a threshold is a disservice to our patients. The clinical trial evidence supports a new approach; the decision to treat should be based on the overall risk, not simply the LDL-C level. This is an example where the LDL-C level looks okay, but the risk is extremely high and treatment is absolutely indicated. Fortunately, the guidelines are moving in the direction of matching treatment to the level of risk. Future guidelines will most likely identify the patient in our case as "high risk" despite her "normal" LDL-C level and recommend aggressive risk reduction therapy.

Moderator: *Thanks, Dr. Davidson. Your comments and those of your colleagues fall nicely within today's theme of treating the whole patient to reduce global risk. Let's move on to a discussion about improving outcomes for patients with CKD at risk for CVD. Dr. Ciervo, what steps can be taken to improve the outcomes for patients with CKD who have dyslipidemia?*

Dr. Ciervo: Following evidence-based treatment guidelines, whether they are level A, B, or C guidelines, can improve care across the board. Obviously, level A guidelines are ideal, but unfortunately we don't have that for all of medicine.

"The SHARP study drives home the point that primary care physicians need to assess and treat the patient's global risk and not be lulled into inaction by lipid numbers that fall into a 'normal' range on the laboratory report."

– Dr. Ciervo

As we discussed earlier, the EMR also provides an opportunity to improve outcomes. Most current EMR platforms provide patient data as well as guidelines, algorithms, risk stratification schemes, and the like right at the point of care. Many also have prompts to remind the physician to ask the patient questions specific to the issue being addressed. Having immediate access to these data provides us the opportunity to query the patient panel and identify individuals who are at risk for various disease processes. It also provides recommendations on evidence-based treatment strategies.

Moderator: *Dr. Weir, from your perspective, what can be done to improve the outcomes for these patients?*

Dr. Weir: Given the data from the Heart Protection Study and the SHARP study, there is a strong argument to abandon the threshold-based algorithm for treating dyslipidemia in these patients. It may be advisable to treat those at high risk for atherosclerotic events regardless of the initial LDL-C level and to treat with a potent dose of a statin alone or in combination with a second-line drug, such as ezetimibe, to get at least a 40% reduction in LDL-C level, or at least to ATP III LDL goal levels.

Dr. Ciervo: Identification of treatment targets, efforts to improve adherence, and patient education can be applied to the treatment of our patients with CKD. It is very important that we sit down with the patient and talk about the risks associated with the disease. I find that patients get motivated when they understand the changes that are occurring as a result of their treatment; I actually show them their data on the EMR because this can provide some positive reinforcement.

"The decison to treat should be based on overall risk—hypertension, diabetes, glucose—and not simply the LDL-C level."

– Dr. Davidson

Whether these patients need a goal lower than 70 mg/dL is not clear. However, based on the available information on cardiovascular risk from these patients and the data from the SHARP study, a goal of 70 mg/dL may be reasonable. Based on evidence that patients with CKD often have multiple risk factors for CVD, it is reasonable to consider reduced GFR or proteinuria as a CVD risk equivalent. Finally, in my view, the literature supports the conclusion that the milder the degree of renal insufficiency, the more likely an individual will respond to treatments that have shown benefit in the general population. With a large study like SHARP, we now have the data to indicate that this is also the case in people with more advanced CKD.

Moderator: *Dr. Davidson, your thoughts?*

Dr. Davidson: When the results of the SHARP study were first presented, there was a standing ovation at the end of the talk because the audience had never before seen anything lower cardiovascular risk in this patient population. We should not underestimate the role of lipid therapy in reducing the overall cardiovascular risk in these patients, but there is more work to be done. As mentioned, there are all the lifestyle issues that need to be addressed. There are also compliance issues and all the issues related to whether a patient continues to receive follow-up care so the treatment plan can be adjusted as the disease evolves. I think we need to focus on all the different risk factors and intervene in as many ways as possible to reduce risk.

Moderator: *Thinking about the treatment of other chronic disease states such as diabetes—identification of treatment targets, interventions to improve adherence, and so on—what lessons can be learned and applied to the care of patients with CKD and high overall risk for CVD?*

As Dr. Davidson said, it is also important to teach our patients about the benefit of lifestyle modifications, that even small changes in diet, exercise, and salt and alcohol intake can be additive in a very positive way. Studies have shown in primary care that if you just introduce a topic with a patient during the course of a visit and follow up with that patient at least 4 times per year, there is a good likelihood that you will have an impact on that patient as far as behavior. Having these discussions is critical.

Moderator: *Dr. Davidson, regarding lifestyle modification, what lessons can be applied to the management of patients with CKD?*

Dr. Davidson: Diet therapy and lifestyle changes can be quite effective in patients such as the one in our case, particularly when combined with effective drug therapy. One thing I've learned is that we have to take into consideration cultural differences between our patients. Some patients are very reluctant to initiate drug therapy; it takes a lot of education and convincing before they are willing to try it. It is very important to have the patient buy into the treatment plan to have a chance of making it work.

Dr. Ciervo: I agree that our treatment plans have to be culturally sensitive. For example, very often my Hispanic patients defer implementation of a treatment plan until they have had a chance to speak with someone in the home who is considered an authority or resource as to whether the prescribed treatment is appropriate. Very often that individual will accompany the patient to the office visit, but sometimes they don't, so you have to be aware that this person exists and needs to be included in the decision-making process. More frequently than not I will ask the patient, "Is there anyone else you would like me to talk with about the treatment regimen so they understand that it is safe and effective?"

Moderator: *From our discussion, patients with CKD who have multiple risk factors may benefit from treatment in a patient-centered medical home. Any thoughts on that, Dr. Ciervo?*

Dr. Ciervo: Absolutely. Our offices are now level 3 patient-centered medical homes. This is a wonderful opportunity for our patients because within the same office, we have health coaches, ambulatory navigators, and the opportunity for patients to participate in group office visits. It's not just you as the clinician impacting this patient; there is an entire team of health care professionals. Physician assistants, nurse practitioners, and even certified medical assistants interact with patients about their disease process and routinely follow up regarding education, adherence, side effects, need for additional care, coordinating home care visits, and referring them to specialty clinics such as a diabetes control center. All of this plays an important role in building trust, garnering compliance, and nudging patients toward taking ownership of their health.

Moderator: *We're running out of time, so let's take a moment to go around the table and summarize some of the key takeaways from this afternoon's discussion. Dr. Davidson, would you like to start?*

Dr. Davidson: One key message is that we have to do a better job identifying patients with CKD who are at high risk and then implement appropriate therapy to reduce that risk. Another key takeaway is that we should not base our treatment on an LDL-C threshold. The SHARP study tells us that regardless of the baseline LDL-C level, the CKD population is at high risk for cardiovascular events and will benefit from lipid modification with a combination of simvastatin 20 mg and ezetimibe 10 mg. The SHARP study also demonstrated that this combination is safe in these patients.

Dr. Weir: I would reiterate the point that people with CKD need global cardiovascular risk reduction across the board: blood pressure, cholesterol, glucose, and antiplatelet therapy. We as physicians need to take advantage of the fact that the kidneys can serve as a biomeasure of vascular disease burden in the body. We need to appreciate that in the Medicare-eligible population, a patient with diabetes and CKD is 5 times as likely to die as to reach dialysis. For that reason, we need to pay attention to all known cardiovascular risk-reducing therapies but also appreciate that there may be other nontraditional risk factors that we need to recognize and perhaps treat.

Dr. Ciervo: As both Drs. Weir and Davidson stated, it is critical that we increase awareness of the association between CKD and CVD if we are going to have an impact on outcomes in this population. Early identification of these patients is very important. We now have evidence that treatment with lipid-lowering agents can have a beneficial effect on cardiovascular outcomes in individuals with CKD. With the implementation of EMR systems that allow us to track patients and the rapidly maturing concept of patient-centered medical homes, patient management will not come from a single physician but from a multidisciplinary health care team responsible for delivering high-quality care. However, the primary care provider will always play a crucial role in identifying patients who require intervention and initiating treatments designed to reduce their global risk.

Moderator: *Thanks to Dr. Ciervo and to our other faculty, Dr. Davidson and Dr. Weir, for participating in this discussion. On behalf of my colleagues, thanks again for your time and the excellent discussion.*

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CKD Monograph Post-Test

The purpose of this post-test is to provide a convenient means for osteopathic physicians to assess their understanding of the scientific content in the monograph that accompanied the September 2012 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 post-test online at http://www.osteopathic.org/quiz by September 30, 2013. Post-tests that are completed online will be graded and credited to members' CME activity reports.

Alternatively, osteopathic physicians can complete the post-test below and fax it to the following number by September 30, 2013:

American Osteopathic Association
Attention: ROME Southeast
Fax (312) 202-8224

AOA No. _____

Full Name _____

CME credit will be applied to the following CME cycle: 2012-2014.

1. The risk of death, cardiovascular events, and hospitalization in patients with CKD increases in a graded fashion as the GFR decreases to less than _____ mL/min/1.73 m^2.
- ☐ A. 45
- ☐ B. 60
- ☐ C. 75
- ☐ D. 90

2. Which of the following oral medications is recommended for use in overweight patients with type 2 diabetes because it has been shown to reduce macrovascular complications in this patient population?
- ☐ A. Glipizide
- ☐ B. Glyburide
- ☐ C. Metformin
- ☐ D. Rosiglitazone

3. Patients should be evaluated for _____ upon presenting with CKD and 2 to 3 months after initiation of or change in treatment.
- ☐ A. Diabetes
- ☐ B. Dyslipidemia
- ☐ C. Hypertension
- ☐ D. Kidney failure

4. If high doses are avoided, which of the following classes of medications can be used safely to reduce CVD risk in patients with CKD?
- ☐ A. Bile acid sequestrants
- ☐ B. Fibrates
- ☐ C. Phytosterols
- ☐ D. Statins

5. What plays an important role in not only the prediction of cardiovascular disease but also progression of CKD?
- ☐ A. Albuminuria
- ☐ B. Creatinine clearance
- ☐ C. HbA1c
- ☐ D. Proteinuria

6. Which of the following assessments can be used to confirm a diagnosis of CKD?
- ☐ A. Protein-to-creatinine ratio
- ☐ B. Renal ultrasonography
- ☐ C. Spot urine albumin test
- ☐ D. All of the above

7. In patients with diabetes and CKD, the treatment target should be at least a _____ reduction in LDL-C level from baseline.
- ☐ A. 10-20%
- ☐ B. 20-30%
- ☐ C. 30-40%
- ☐ D. 40-50%

8. According to the panelists, a drug from which of the following classes is most appropriate to initially treat a patient with a reduced GFR and diabetes to modify the risk factors and control the progression of CKD?
- ☐ A. Angiotensin-converting enzyme inhibitors
- ☐ B. Calcium channel blockers
- ☐ C. Diuretics
- ☐ D. Thiazides

9. According to the panelists, use of _____ should be evaluated in patients with CKD because it can have an impact on GFR and blood pressure.
- ☐ A. Acetaminophen
- ☐ B. Aspirin
- ☐ C. COX-2 inhibitors
- ☐ D. Nonsteroidal anti-inflammatory drugs

10. The pattern of dyslipidemia in patients with CKD is unique because they have increased levels of _____, which is associated with increased cardiovascular risk.
- ☐ A. Small dense LDL particles
- ☐ B. C-reactive protein
- ☐ C. Inflammatory cytokines
- ☐ D. All of the above

11. In the SHARP study, the combination of simvastatin and _____ reduced LDL-C levels in patients with advanced CKD and resulted in fewer overall cardiovascular events.
- ☐ A. Cholestyramine
- ☐ B. Ezetimibe
- ☐ C. Gemfibrozil
- ☐ D. Niacin

12. According to the panelists, clinical trial evidence shows that the decision to initiate lipid-lowering therapy in patients with CKD for risk reduction should be based on _____.
- ☐ A. GFR
- ☐ B. LDL-C level
- ☐ C. Overall risk
- ☐ D. Stage of CKD

OVER →

Evaluation

Please rate your level of agreement by circling the appropriate rating:

1 = Strongly Disagree	2 = Disagree	3 = Neutral	4 = Agree	5 = Strongly Agree

Learning Objectives	After participating in this activity, I am now better able to:
Evaluate screening techniques and assessment methods used to identify patients with CKD at risk for the development of CVD	1 2 3 4 5
Assess recent clinical evidence on the effect of lipid-lowering therapy to reduce risk of premature CVD in patients with CKD	1 2 3 4 5
Apply evidence-based treatment strategies to reduce cardiovascular events in patients with CKD	1 2 3 4 5

Based upon your participation in this activity, choose the statement(s) that apply:

☐ I gained new strategies/skills/information that I can apply to my area of practice.
☐ I plan to implement new strategies/skills/information into my practice.
☐ I need more information before I can implement new strategies/skills/information into my practice behavior.
☐ This activity will not change my practice, as my current practice is consistent with the information presented.
☐ This activity will not change my practice, as I do not agree with the information presented.

What strategies/changes do you plan to implement into your practice?

_____

_____

How confident are you that you will be able to make this change?

☐ Very confident ☐ Somewhat confident ☐ Unsure ☐ Not very confident

What barriers do you see to making a change in your practice?

_____

_____

Please rate your level of agreement by circling the appropriate rating:

1 = Strongly Disagree	2 = Disagree	3 = Neutral	4 = Agree	5 = Strongly Agree

The content presentation:

Enhanced my current knowledge base	1 2 3 4 5
Addressed my most pressing questions	1 2 3 4 5
Promoted improvements or quality in health care	1 2 3 4 5
Was scientifically rigorous and evidence-based	1 2 3 4 5
Avoided commercial bias or influence (Provide details of any perceived bias in the comments section below.)	1 2 3 4 5
Provided appropriate and effective opportunities for active learning (e.g., case studies, discussion, Q &A, etc)	1 2 3 4 5
My opportunity for learning assessment was appropriate to the activity	1 2 3 4 5

Would you be willing to participate in a post-activity follow-up survey? ☐ Yes ☐ No

Please list any clinical issues/problems within your scope of practice you would like to see addressed in future educational activities:

_____

_____

_____

Practical Steps to Improve Outcomes for Patients with Chronic Kidney Disease (CKD):

A Whole Patient Approach

This activity is jointly sponsored by the American Osteopathic Association, Georgia Osteopathic Medical Society, North Carolina Osteopathic Medical Association, South Carolina Osteopathic Medical Society, and Impact Education, LLC.

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