For several decades, the healthcare needs of the American public have been shifting from predominantly acute, episodic therapy to long-term treatment of chronic conditions. Considered together, chronic conditions now make up the leading cause of illness, disability, and death in the United States. Chronic conditions affect nearly half the population in the United States, accounting for the majority of resources applied to healthcare. Chronic kidney disease (CKD) is an example of a chronic condition that is more common than is generally realized.

Many physicians and their patients remain unaware of the diversity of clinical characteristics of renal disease. To date, the primary focus of research and treatment regarding this illness has been on end-stage renal disease (ESRD), which is the most visible clinical consequence of CKD. By comparison, CKD in its earlier stages often shows no symptoms and has received scant attention.

Data from the United States Renal Data System (USRDS) indicate that, in 2005, the US population with prevalent ESRD (N=452,957) consisted of 324,862 (72%) patients receiving dialysis treatment and 128,131 (28%) with a functioning renal transplant. Yet, individuals with ESRD represent only a small portion of total diagnosed CKD cases. Most CKD cases involve illnesses in earlier, milder stages. A recent analysis using data from the Third National Health and Nutrition Examination Survey indicates that the number of people in the United States with moderate-stage CKD (7.6 million) is approximately 20 times greater than the number of individuals with severe-stage CKD (400,000).

Chronic Kidney Disease and Cardiovascular Events

As chronic kidney disease progresses, it often leads to serious cardiovascular events. In fact, patients with CKD are more likely to die of cardiovascular disease (CVD) than to progress to kidney failure. The risk of subsequent cardiovascular events is much higher among patients with ESRD than among individuals with normal renal function. After stratification for age, race, and gender, mortality from CVD is 10 to 20 times higher in patients undergoing dialysis for renal disease than it is among the general US population (Figure 1). Chronic kidney disease is thus a great multiplier of patients’ CVD risk.

This increased risk was clearly demonstrated in a recent analysis by the Valsartan in Acute Myocardial Infarction Trial (VALIANT), which examined the relationship between CKD and cardiovascular outcomes in patients who had experienced acute myocardial infarction. This randomized controlled trial demonstrated that even mild renal insufficiency is a major risk factor for adverse cardiovascular events. The increased risk demonstrated in the analysis was progressive, beginning with an estimated glomerular filtration rate (GFR) of less than 81 mL per minute per 1.73 m² of body surface area. Each 10-unit decrease in GFR was associated with a 10% increase in the relative risk of death or in nonfatal cardiovascular complications. In addition, the incidence of cardiovascular events in the patients was far greater than the incidence of adverse renal events, confirming CKD as a potent, independent risk factor for cardiovascular events.

Another study, supported by the National Institute of Diabetes and Digestive and Kidney Diseases, highlighted how important CKD is to public health. This study, which observed more than 1.1 million ambulatory adults from the Kaiser Permanente Renal Registry, revealed a graded association between estimated GFR and cardiovascular events (Figure 2), hospitalization, and risk of death.

Editor’s note: The Initiative on Chronic Kidney Disease Committee of the American Society of Nephrology has developed a CKD symposium for the nonnephrologist. This symposium is scheduled to be held in 2006 at the American College of Osteopathic Family Physicians’ 43rd Annual Convention and Exhibition in Grapevine, Tex, on March 22–26, and at the American College of Osteopathic Internists’ 2006 Annual Convention and Scientific Sessions in Phoenix, Ariz (October 18–22).
Uniform Definition Aids Diagnosis of Chronic Kidney Disease

We need to move from a healthcare system of reacting to acute events to a system of anticipating the needs of our patients, especially in regard to CKD. Early detection of CKD is important not only to halt the progression of early-stage renal disease to ESRD, but also to prevent morbidity and mortality from CVD. In the past, it was not uncommon to see patients with serum creatinine levels of 1.5 to 2.5 mg per deciliter and erroneously assume that they had relatively preserved renal function. Frequently overlooked in these diagnoses, however, were such important variables as age, sex, race, and body mass index. Estimated GFR provides an alternative to serum creatinine, and it is a much more reliable indicator of the level of kidney function.

The equation developed in the Modification of Diet in Renal Disease (MDRD) Study provides a useful approximation of GFR. Calculators for quickly running the complex MDRD equation are available on a number of Web sites (eg, http://www.kidney.org/professionals/kdoqi/gfr_calculator.cfm), aiding in the diagnosis of CKD.

The publication in 2002 of the National Kidney Foundation’s Kidney Disease Outcomes Quality Initiative (K/DOQI) clinical practice guidelines for CKD has also facilitated the identification and classification of CKD. The K/DOQI guidelines define CKD as persistent kidney damage and/or a GFR of less than 60 mL per minute per 1.73 m² of body surface area for at least 3 months. Kidney damage may be confirmed by renal biopsy or by markers of damage, including abnormal blood tests, urine tests, or imaging studies. Based on the degree of decrease in GFR, the K/DOQI guidelines classify CKD into five stages of development, with higher numbers (and lower GFR values) representing increasingly severe clinical conditions (Figure 3). Based on the K/DOQI definition of CKD, it has become apparent that this disease is more prevalent than previously recognized. Approximately 11% of the adult population in the United States has CKD, and the prevalence rate increases to about 25% for individuals older than 70 years. It can be assumed that any older patient with a serum creatinine level of greater than 1 mg per deciliter also has a GFR of less than 60 mL per minute per 1.73 m² of body surface area. Thus, that patient would have, by definition, CKD. In addition to age, hypertension and diabetes are other important predictors of CKD.

Factors that suggest increased risk of progression of CKD to ESRD include anemia, chronic use of nephrotoxins (eg, analgesics), congenitally low nephron numbers (as in low-birth-weight infants), diabetes mellitus, hyperlipidemia, hypertension, low GFR, obesity, proteinuria, and smoking. These factors need to be identified and managed aggressively in all patients with CKD in order to slow the spread of CKD/ESRD and CVD.

With a uniform and widely accepted definition and classification of CKD, physicians can easily screen patients for CKD by measuring serum creatinine, using the MDRD equation to calculate an estimated GFR, and obtaining a ratio of urinary total protein to creatinine. Many laboratories and hospitals are now offering tests for estimating GFR values, along with tests for serum creatinine concentrations, as part of their screening programs. The National Kidney Disease Education Program has developed a format for setting up such a screening program in hospitals that currently do not have one. This information is available on the following Web pages:

- http://www.nkdep.nih.gov/resources/laboratory_reporting.htm

Figure 1. Annual cardiovascular mortality (death as a result of arrhythmias, atherosclerotic heart disease, cardiac arrest, cardiomyopathy, myocardial infarction, or pulmonary edema) in the US general population compared with patients with end-stage renal disease who were treated with dialysis, by age, sex, and racial group. (Adapted from Foley RN, Parfrey PS, Sarnak MJ. Clinical epidemiology of cardiovascular disease in chronic renal disease [review]. Am J Kidney Dis. 1998;32(5 suppl 3):S112–S119. Copyright © 1998, with permission from the National Kidney Foundation.)
sued in all patients with CKD. Chronic kidney disease should not be regarded as simply a risk factor for CVD, but also as an indication to develop a global risk-management strategy for patients. Such a strategy would begin with strict blood pressure control (\(110/80\) mm Hg), lipid control (low-density lipoprotein \(100\) mg/dL), diabetic control (hemoglobin A1c \(7\)%), and management of the stress and depression common in these patients.9

Furthermore, evidence increasingly supports the need for earlier intervention to reduce acidosis, anemia, and hyperparathyroidism with calcium/phosphorus abnormalities. These abnormalities are now recognized when GFR falls to less than 60 mL per minute per 1.73 m\(^2\) of body-surface area for at least 3 months. To reduce morbidity and mortality, nutrition must be addressed as patients progress through the stages of CKD.

Patients in stages 2 to 3 of CKD development (Figure 3) may be referred to nephrologists, who could make adjustments in therapeutic interventions to take into account such nontraditional risk factors as acidosis, anemia, hyperparathyroidism, and vitamin D deficiency. Nephrologists could also assist patients in optimizing control of blood pressure. Given the large number of patients with either stage 2 or stage 3 CKD—as well as the limited number of nephrologists in the United States—referrals of patients to nephrologists will require close working relationships between primary care providers and the nephrology community.

**Therapeutic Interventions for Chronic Kidney Disease**

The therapeutic intervention that has demonstrated the greatest benefit in slowing the progression of CKD, both in patients with and without diabetes mellitus, is the use of medications targeting the renin-angiotensin-aldosterone system: angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs).10-13 Unfortunately, these medications are not widely used. According to Nissenson et al,14 only about one third of patients with CKD are prescribed ACE inhibitors.

The therapeutic goal of ACE inhibitor/ARB therapy is to slow the rate of GFR decline to less than 2 mL per minute per year and to reduce proteinuria measurements to less than 0.5 gram per day. This goal mandates that physicians closely track estimated GFR and proteinuria in all patients with CKD, titrating the ACE inhibitor/ARB therapy to achieve the desired outcomes. A review by Weir15 of clinical trials with ARBs—used for either cardiovascular or renal end points—suggests that the maximum positive effect of this therapy is achieved with the highest recommended doses. This conclusion should be considered when trying to preserve renal function and prevent cardiovascular events in patients.

In addition to specific renal therapy, adjunctive therapy for cardiovascular protection needs to be aggressively pur-
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A nephrologist might recommend a clinical action plan for the optimal care of a patient. Alternatively, the patient’s primary care provider might use Internet-based resources to develop his or her own therapeutic plan. An example of such a resource is the Kidney Learning System Web site, established by the National Kidney Foundation: http://www.kidney.org/professionals/kdoqi/cap/index.htm. For a patient with relatively uncomplicated stage 2 or stage 3 CKD, most of the clinical monitoring and therapeutic adjustments will be the responsibility of that patient’s primary care physician. However, for a patient with late stage 3 or stage 4 CKD, a nephrologist will need to assume a more prominent role in that individual’s care.

A patient with stage 2 CKD should be educated to take special care of his or her nondominant arm—such as by avoiding phlebotomy incisions or intravenous access placement—in order to preserve the veins for the possible need of surgically created arteriovenous fistulae. This type of intervention could significantly reduce the need for arteriovenous grafts and tunneled catheters, both of which are associated with increased morbidity and mortality.\textsuperscript{14,17} The K/DOQI\textsuperscript{16,17} has established clinical practice guidelines regarding vascular access for hemodialysis.

Finally, nephrologists should begin to educate their patients who have stage 3 or stage 4 CKD about modalities for treating ESRD. Such modalities include hemodialysis, peritoneal dialysis, and kidney transplantation.\textsuperscript{18}

Conclusion

Chronic kidney disease should be considered a cardiovascular risk equivalent. It is imperative not only to aggressively employ therapeutic interventions to slow the progression of CKD, but also to identify those patients with the greatest need for aggressive CVD risk-factor reduction.

References


