A Scientific Statement from the American Heart Association in 2003 (1) focused attention on the observation that cardiovascular mortality in patients with chronic kidney disease (CKD) treated by either dialysis or transplantation is markedly higher than in the general population stratified by age, race, and gender. This formalized report updated a concept that was perhaps first enunciated by Shulman et al. (2) in 1989, which was based on data from the Hypertension Detection and Follow-up Program (HDFP). The HDFP was a community-based, randomized, controlled trial of two antihypertensive treatment strategies that was conducted with 10,940 participants between 1975 and 1980. It was relatively unique among hypertensive clinical trials because it was the first to include data on serum creatinine values. These data helped to establish two important observations. First, the incidence of CKD in adults with mainly stage 1 to 2 hypertension was low at approximately 1.4% over 5 yr. Second, 8-yr all-cause mortality risk increased in a stepwise manner according to serum creatinine values. These data demonstrated that increased mortality risk begins at the earliest stages of CKD. Death before dialysis is a common outcome in CKD; it should not be surprising that cardiovascular death rather than ESRD and that this enhanced risk is prevalent at all stages of CKD and (2) to rebalance interest in traditional interventions at earlier stages as potentially more effective than late-stage, nontraditional interventions.

It is axiomatic that patients with CKD are inherently different from patients without CKD. It is less firmly and less widely appreciated that the major threat to patients with CKD is cardiovascular death rather than ESRD and that this enhanced risk begins at the earliest stages of CKD. Death before dialysis is a common outcome in CKD; it should not be surprising that death rates are high after starting dialysis.

Patients with CKD have traditional as well as nontraditional cardiovascular risk factors, and their responses to medical and surgical treatments may also be atypical or nontraditional. The purposes of this review are (1) to provide recent, representative data that reinforce the observation that increased cardiovascular risk is prevalent at all stages of CKD and (2) to rebalance interest in traditional interventions at earlier stages as potentially more effective than late-stage, nontraditional interventions.

CKD as a Concept

The nosology of nephrology has shifted from focus on specific etiologic (and to most physicians, esoteric) diseases such as type 2 membranoproliferative glomerulonephritis to more enveloping, less intimidating designations that transcend etiology. This shift has its greatest value in epidemiology and public health policy. The two major terms are ESRD, which technically means treatment with dialysis or kidney transplantation but in more common parlance refers to dialysis, and CKD. By definition (3), CKD is based on documentation of kidney damage sustained over at least 3 months. There are five stages (Table 1) based on ranges of GFR measured directly or estimated mathematically from serum creatinine values. This is an evolving science in which there is imperfect validation of creatinine-based estimates of GFR versus more direct measurements, especially for serum creatinine values near the upper range of normal (4,5). Specifically, the prevalence of stage 2 CKD tends to be overestimated significantly. Nevertheless, within this and other limitations, the concept of CKD is a useful although oversimplified means of assessing degrees of reduced GFR as a marker or risk factor for adverse clinical outcomes.

CKD as a Risk Factor for Premature Mortality

In addition to the earlier and underappreciated data from HDFP, two recent, large studies of managed care populations demonstrate that death is a more common outcome than ESRD in patients with CKD. An analysis of outcomes of 27,998 patients between 1996 and 2001 showed that 5-yr mortality rates for CKD stages 2, 3, and 4 were 19.5, 24.3, and 45.7%, respectively, whereas the frequencies of renal replacement therapy were much lower at 1.1, 1.3, and 19.9%, respectively (6). Congestive heart failure, coronary artery disease, and diabetes were more prevalent in those who died. One obvious interpretation of these observations is that these are the disease processes that warrant primary therapeutic focus rather than progression of CKD itself.

A similar study analyzed outcomes of 1,120,295 adults who were enrolled in Kaiser Permanente of Northern California (7). Their average age was 52 yr, 55% were women, and 51% were white. As shown in Figure 1, on the basis of a median follow-up of 2.84 yr, age-standardized rates for all-cause mortality and for cardiovascular events followed a stepwise progression according to reductions in GFR with major step-ups at GFR <45 ml/min, which is mid-stage 3. During the follow-up period,
only 0.28% of patients started dialysis and 0.03% underwent kidney transplantation.

Collectively, these data extend the observations of HDFP that patients with CKD have increased rates of all-cause mortality and cardiovascular events that are demonstrable at all stages and that progress with advancing CKD. This increased risk develops well before ESRD. The data also show a strikingly higher frequency of nonrenal over renal outcomes.

**CKD as a Modifier of Secondary Outcomes**

In addition to being a risk factor for primary cardiovascular events, the presence of CKD adversely affects outcomes after a cardiovascular event. The Valsartan in Acute Myocardial Infarction Trial (8) examined the relative effects of captopril, valsartan, or both in 14,527 patients who sustained an acute myocardial infarction complicated by congestive heart failure, left ventricular dysfunction, or both. The study excluded patients with initial serum creatinine values of 2.5 mg/dl or greater. The 3-yr event rates for death and for a composite of cardiovascular end points were increased for patients with GFR values consistent with CKD stages 2 and 3. Relative to patients with estimated GFR >75 ml/min, the adjusted hazard ratios and confidence intervals for death were 1.14 (1.02 to 1.27), 1.38 (1.24 to 1.54), and 1.70 (1.50 to 1.93) for those with GFR 60 to 74.9, 45 to 59.9, and <45 ml/min, respectively. Thus, progressive stages of CKD adversely affect outcomes after an acute myocardial infarction.

With regard to surgical treatments, there is general agreement that patients who have coronary heart disease (CHD) and CKD who warrant intervention do better with coronary artery bypass surgery than with percutaneous coronary angioplasty (9). In this regard, among 3608 patients who were enrolled in the Bypass Angioplasty Revascularization Investigation (10) that compared bypass with angioplasty, there were 76 with CKD. These showed significantly increased 7-yr relative risk ratios of 2.2 for all-cause mortality and 2.8 for cardiac mortality as compared with those without CKD. The risk associated with CKD was comparable to and additive to the risk associated with diabetes.

**How Is CKD an Added Risk Factor for Cardiovascular Disease?**

Although not all cardiovascular disease derives from CHD, ischemic heart disease was the most common single entity identified in HDFP (2) and is presumably the major cardiovascular factor in the two managed care epidemiologic studies cited above (6,7). Although a comprehensive review of CHD is beyond the limits of space and the author’s qualifications, a brief summary of current concepts is useful as a frame of reference. Coronary occlusion and its complications result from the combined effects of chronic accumulation of a lipid-core atheromatous plaque, inflammation, and coagulation, with stabilization or destabilization over time that may lead to plaque consolidation or rupture with acute thrombosis. This concept transcends simple luminoiny and portrays a more dynamically active process that expresses many opportunities for aggravation and intervention. Clinically, we identify modifiable and nonmodifiable risk factors and project their roles. The risk pyramid for patients with CKD (Figure 2) includes (1) traditional risks, most of which are more prevalent in patients with
CKD than in the general population; (2) common, nontraditional risks that may be more frequent or more intense in CKD; (3) uncommon, nontraditional risks that are largely unique to CKD, such as azotemia, chronic anemia, and disordered potassium and divalent ion metabolism, and treatment-related factors associated with dialysis or transplantation; and (4) unknown factors. The connotation of the pyramidal arrangement of these factors is two-fold: First, that risks accumulate as CKD progresses and, second, that an intervention aimed at a single risk factor at one level may be thwarted by the cumulative risks at other levels.

Lipid accumulation and inflammation are two major factors associated with acute coronary events. Measurements of LDL cholesterol and ultrasensitive C-reactive protein serve as their respective biomarkers and independently predict risk (11). In this regard, two selective observations serve as representative examples of how patients with CKD differ from others in their cardiovascular vulnerability. First, CRP as a marker of inflammation is increased in patients with CKD and is a potent predictor of their cardiovascular mortality (12). The meaning of CRP in this context is not fully understood, but it remains as a distinguishing feature of patients with CKD. Second, the 4-D Study (13) showed that atorvastatin, a potent statin with demonstrated cardiovascular benefits in patients with hypercholesterolemia (14), hypertension (15), diabetes (16), and CHD (17), reduced LDL cholesterol by >40% but showed no cardiovascular benefit in a randomized, placebo-controlled trial of a 20-mg dose administered to 619 patients who had diabetes and were on hemodialysis and followed for a median duration of 4 yr. This is an important and enlightening therapeutic failure. One interpretation is that the most advanced stage of CKD characterized by the need for dialysis poses cumulative cardiovascular risks that overall are refractory to the traditional treatment of a traditional risk factor. In essence, the failure of the 4-D Study to show benefits of an intervention notable for broad success in other high-risk disease states may indicate that later interventions require greater interventions. Alternatively, there may be statin-insensitive risk factors that are unique to advanced CKD or to hemodialysis and that may or may not apply with equal intensity at earlier stages of CKD. These and other alternatives need to be addressed through clinical trials.

Nontraditional Interventions and Nontraditional Risk Factors

Most current interest in the major nontraditional risk factor for increased all-cause mortality in patients who are on hemodialysis focuses on hyperphosphatemia and related derangements in serum calcium and parathyroid levels. Epidemiologic studies show that hyperphosphatemia >6.5 mg/dl is associated with increased risk for any-cause mortality in patients who are on hemodialysis (18). It is not clear whether hyperphosphatemia in this context is causally related to increased mortality or serves simply as a marker. The significance of disordered calcium, phosphate, vitamin D, and parathyroid hormone metabolism to cardiovascular mortality is and should remain controversial (19). Currently, divalent ion metabolism receives intense and expensive attention that is disproportionate to evidence-based medicine and heavily promoted by the pharmaceutical and dialysis industries. The correct balance between therapeutic efforts that are aimed at both traditional and nontraditional risk factors awaits the results of appropriate, comprehensive clinical trials.

Conclusion

The concept of CKD is a useful oversimplification that facilitates the assessment of degrees of overall renal impairment in the context of renal and nonrenal events. On the basis of this concept, compelling epidemiologic observations demonstrate that CKD is an independent risk factor for cardiovascular disease and for all-cause mortality and that these risks escalate as CKD progresses. CKD also adversely affects the outcomes of medical and surgical interventions related to CHD. CKD is arguably not a modifiable risk factor but should be included in global risk assessment with potency comparable to diabetes. We do not know the ingredients in CKD that constitute threat or the interventions that might reduce them. Reducing the risk for cardiovascular disease and death in patients with CKD at stages 2 to 4 requires comprehensive, open-minded approaches to both traditional and nontraditional factors and support of appropriate clinical trials that will eventually provide answers.

References


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