Chapter 12: Cardiovascular Disease in the Elderly With Kidney Disease

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Heart disease constitutes the leading cause of death in the United States. Age is an important, albeit nonmodifiable, risk factor for cardiovascular disease in the general population, as well as in patients with chronic kidney disease (CKD). The prevalence of chronic ischemic heart disease in men and women ≥65 yr of age in the United States in 1995 was 83 per 1000 men and 90 per 1000 women. Among those ≥75 years of age, the prevalences were 217 per 1000 for men and 129 per 1000 for women. Increasing evidence has accumulated that elderly individuals with cardiovascular disease can benefit greatly from several aspects of secondary prevention.[1]

Kidney disease has been shown to be an important determinant of cardiovascular disease,[2,3] and patients with CKD should be regarded a "highest risk" group for cardiovascular disease, irrespective of levels of traditional cardiovascular disease (CVD) risk factors (http://www.kidney.org/professionals/kdoqi/guidelines_ckd/p7_risk_g15.htm). Furthermore, several cardiovascular risk factors are increasingly prevalent with declining kidney function.[4] Interestingly, the Framingham Risk Score is only poorly predictive for CVD in patients with CKD, and standard factors only account for a small proportion of the observed risk in these patients.[5] Finally, older age is an important determinant of kidney function (as indicated by its representation in the Modification of Diet in Renal Disease (MDRD) estimation equation for GFR[6]). It has been estimated that more than a third of US individuals over age 70 have CKD Stages 3 to 5 and the prevalence is increasing over time.[7] One can postulate that the older individual with CKD is at the highest risk of CVD, and even more so if additional comorbid conditions including diabetes (DM), hypertension, obesity, and other vascular disease are present. Indeed, among adults over age 67, 2-yr cardiovascular mortality was 10% for those without diagnosed CKD or diabetes but 30% for those with CKD and 32% for those with both CKD and diabetes.[8]

Ample information is available on the epidemiology of cardiovascular disease in older individuals and its relationship with kidney function, including key prospective studies in elderly individuals such as the Cardiovascular Health Study. In a prospective study of traditional and novel cardiovascular risk factors, diabetes, hypertension, smoking, low physical activity, left ventricular hypertension, and nonuse of alcohol were all predictors of subsequent cardiovascular mortality, whereas high-density lipoprotein (HDL)-cholesterol, low-density lipoprotein (LDL)-cholesterol, triglycerides, and obesity were not associated with such risk.[9] None of the novel cardiovascular risk factors that were tested were independently associated with cardiovascular mortality, including C-reactive protein and anemia among others. Of note, homocysteine and phosphorus were not evaluated in that study, and the other negative associations need to be interpreted in light of the relatively low power of this study. Table 1 provides a list of established and novel cardiovascular risk factors in patients with CKD.

In contrast, little evidence has been generated on the efficacy and safety of standard curative or preventive cardiovascular interventions in patients with CKD. Most landmark trials have explicitly excluded patients with CKD,[10,11] and similarly, older subjects were also barred from participation in most of these trials. These two independent phenomena jointly explain the particular evidence vacuum for the population of older adults with CKD.

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Table 1. Cardiovascular risk factors in CKD (established or proposed, selection)

Traditional Risk Factors	Novel Risk Factors, Some CKD-related
Older age	Decreased kidney function
Male gender	Proteinuria
White race	Renin-angiotensin-system activity
Higher blood pressure	Extracellular fluid overload
Higher LDL-cholesterol	Higher phosphorus concentration
Lower HDL-cholesterol	Hyperparathyroidism
Diabetes mellitus/impaired glucose tolerance	Vitamin D deficiency
Tobacco use	Dyslipidemia
Physical inactivity	Anemia
Menopause	Malnutrition
Psychosocial stress	Inflammation
Family history of cardiovascular disease	Oxidative stress
	Infection
	Higher homocysteine
	Thrombogenic factors

Modified and updated from Sarnak and Levey.[35]

The fundamental question is whether evidence can be extrapolated to older patients with CKD from trials that effectively excluded those patients or contained only few such patients? Or should we require that specific trials be conducted in this relatively small segment of the population? Alternatively, should we require that prespecified and sufficiently powered tests for interaction of drug efficacy with age and kidney function be planned and conducted? Although it would be desirable to inform more evidence-based practice in geriatric nephrology, it is unlikely that such information will become available on a larger scale anytime soon. Only recently, studies were conducted, at the very least, that specifically focused on the older population.[12] Additional top-level evidence has been made available from *post hoc* analyses of individual or pooled data from randomized trials. The vast majority of the evidence on cardiovascular risk interventions in older patients with CKD, however, has come from retrospective pharmaco-epidemiologic studies, often with serious methodological limitations. The following aims to provide evidence on a selected number of cardiovascular risk factors and interventions in elderly patients with CKD: lipid disorders and lipid-lowering therapy, C-reactive protein and inflammation, homocysteine, as well as hyperphosphatemia and use of phosphate binders. Other risk factors are covered in other chapters of this curriculum, notably diabetes and proteinuria, hypertension, and anemia.

CARDIOVASCULAR RISK FACTORS IN CKD

Traditional Risk Factors

Lipids.

Although HDL-cholesterol, LDL-cholesterol, and triglycerides were not associated with cardiovascular mortality in the Cardiovascular Heath Study, the wide confidence limits of these estimates are compatible with substantial risk increases associated with these factors. In the general population, hyperlipidemia is clearly accepted as an important cardiovascular risk factor, and medical treatment, predominantly with statins, is well established for both primary and secondary cardiovascular prevention. Cardiovascular prevention with statins has also been studied in a trial dedicated to the older population. In the PROspective Study of Pravastatin in the Elderly at Risk (PROSPER) trial, patients aged between 70 and 82 yr were enrolled and compared with placebo. Treatment with 40 mg of pravastatin per day conferred a 15% reduction in the risk of the primary combined cardiovascular endpoint (fatal or nonfatal myocardial infarction or stroke) and a 19% reduction in the secondary endpoint of fatal or nonfatal myocardial infarction. These risk reductions were found to be in line with those found in trials of younger patients. In a *post hoc* analysis of data from three pravastatin trials, it was found that statins were also efficacious in reducing cardiovascular outcomes in patients with CKD Stage 3.[13] The mean age in this study was 65.7 yr. Although an interaction test with age was not conducted in this analysis, it is probably safe to assume that lipid-lowering treatment using statins is also efficacious in older patients with CKD. The optimal dose of specific agents or any preferred lipid targets, however, is not clearly established. Statins were also efficacious in reducing cardiovascular events in kidney transplant patients.[14] Whether statins are also efficacious in patients on hemodialysis is unclear. At the very least, chronic dialysis patients with diabetes did not benefit from statin treatment in a large randomized trial.[15] Further evidence can be expected in the near future when the results from the large Study of Heart and Renal Protection (SHARP) trial will be released.

Smoking and Physical Activity.

Smoking is a strong cardiovascular risk factor in the elderly, and smoking cessation reduces overall morbidity and mortality rates in patients with myocardial infarction (MI) and coronary artery bypass graft surgery, including those older than 70 yr.[16,17] Furthermore, smoking is a risk factor for progression of kidney disease. Although specific studies of smoking cessation

in elderly patients with CKD or ESRD are lacking, smoking cessation counseling seems to be a prudent approach in this population. Similarly, physical activity has been shown to be associated with CVD in older adults with CKD,[9] but trials supporting specific interventions are not available in that population.

Novel Risk Factors

C-Reactive Protein.

C-reactive protein (CRP) is an acute-phase protein and has evolved as a major cardiovascular risk factor in the general population and in other subpopulations. CRP is higher, on average, in older individuals, and some studies have also shown that CRP concentrations tend to be higher in patients with CKD. In a study of patients with CKD Stages 3 and 4 enrolled in the MDRD study, CRP was positively associated with mortality from any cause. Elevated concentrations of this marker were also independently associated with a doubling in cardiovascular mortality.[18] Similarly, CRP was associated with mortality in kidney transplant recipients.[19] Most recently, therapeutic approaches to lowering CRP and to reduce cardiovascular mortality through it have become available. The recently published Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) enrolled patients with normal lipid concentrations and no history of cardiovascular disease, but elevated CRP concentrations.[20] Rosuvastatin 40 mg lowered CRP concentrations by 37% and reduced the risk of a composite cardiovascular endpoint by 44%. Although one half of the enrolled patients were older than 66 yr, <25% of patients had an estimated GFR <60 ml/min per 1.73 m^2. Thus, the applicability of these results to older patients with CKD is uncertain, but subsequent subgroup analysis by kidney function can certainly be expected.

Homocysteine.

Homocysteine is a sulfur-containing amino acid that occupies an important role in 1-carbon metabolism and nucleotide synthesis. Both age and reduced kidney function are important determinants of total homocysteine plasma concentrations. Elevated homocysteine, in turn, has been shown to be a powerful cardiovascular risk factor in the general population, as well as in the elderly and in patients with diabetes. In kidney disease, this association is less clear: an association with mortality has been shown in kidney transplant recipients[21] but was absent in patients enrolled in the MDRD study, although the confidence intervals in this study were rather wide.[22] It is well established that high-dose vitamin therapy with folic acid, pyridoxine (vitamin B_6), and/or cyanocobalamin (vitamin B_{12}) can reduce plasma homocysteine concentrations quite significantly, especially in patients with kidney disease. Several large randomized trials were conducted, and their results were expected with great enthusiasm and hope. The findings, however, were sobering. The majority of these trials showed no beneficial effect on cardiovascular outcomes.[23] Thus, therapeutic lowering of homocysteine using vitamin therapy cannot be recommended.

Phosphorus.

Serum phosphate has evolved as a recent risk factor for all-cause and cardiovascular mortality and morbidity. The prevalence of hyperphosphatemia increases with decreasing kidney function. It is an important therapeutic goal to maintain a normal phosphorus concentration and a normal calcium-phosphate product, but dietary measures are often insufficient to achieve these goals. Phosphate binders have become important tools to maintain phosphate control in patients with ESRD but are also used in patients with CKD who are not on dialysis. An ongoing debate has focused on the preferred choice of phosphate binder and calcium-containing binders have been associated with an increased risk of vascular and valvular calcification in dialysis patients. The largest randomized trial of calcium-containing phosphate binders *versus* sevelamer, a calcium-free binder, showed no differences in the prespecified endpoint of all-cause or cardiovascular mortality.[24] An interaction with age was found, however, in that, among patients older than 65 yr, sevelamer conferred a significant reduction in mortality. Because these results arose from subgroup analyses with the possibility of a false-positive result from multiple testing, these findings need to be interpreted with caution.

DIAGNOSIS OF ACUTE CORONARY SYNDROMES

One important issue with coronary artery disease in older patients with CKD is the fact that it is harder to diagnose than in younger patients free from CKD. Noninvasive tests seem to have different sensitivities and specificities in patients with CKD than in the general population. For example, ST-elevation myocardial infarction is considerably less likely in patients with CKD compared with patients without it.[25] Patients with CKD are less likely to present with arm, shoulder, or chest pain or pressure, or with diaphoresis, but more likely complain of cough or dyspnea.[26] Standard laboratory markers such as creatine kinase and its myocardial subfraction and troponins are frequently and intermittently elevated in patients with kidney disease.[27–29] Thus, diagnosing acute coronary syndromes in older patients with CKD can be challenging at times and further research on improved diagnostic tests or algorithms in this subgroup of patients is warranted.

USE OF ACUTE AND CHRONIC CARDIOVASCULAR INTERVENTIONS

Numerous studies have shown that older individuals are less likely to receive recommended medications, both in cardiovascular disease and in other diseases and disorders. Such treatment bias has sometimes been termed "Ageism." Similarly, Chertow has coined the term "Renalism" based on the obser-

vation that patients with kidney disease also were less likely to receive standard therapies compared with others without kidney disease but of similar age. Again, at the intersection of Ageism and Renalism, older individuals with kidney disease are least likely to receive recommended interventions and treatments. For cardiovascular disease, this has been observed for acute coronary interventions as well as for chronic treatments for secondary prevention including statins, β-blockers, aspirin, and inhibitors of the rennin-angiotensin system[25,30–33] (see Wetmore and Shireman for a comprehensive review of this literature.[34]). It is unclear on what basis such discrimination occurs: the lack of available evidence in this specific population group? Perceived futility in a population of assumed low benefit in light of the naturally shortened lifespan? Cost-effectiveness considerations in that older patients with CKD may not live long enough to reap the benefits from chronic preventive treatment? Presence of multiple comorbid conditions that may diffuse focus on cardiovascular care? Probably all of the above contribute. Further research is necessary to provide the evidence needed and focused integrative curricula such as this geriatric nephrology effort are necessary to improve the care and outcomes of this very vulnerable population of older patients with CKD.

TAKE HOME POINTS

- Most established cardiovascular risk factors are also predictive in older patients with CKD
- Sparse information is available on the efficacy of interventions in older patients with CKD
- The best evidence is available for secondary cardiovascular prevention with statins, although the optimal lipid targets are not known
- BP and diabetes control also seem to confer benefit in older patients with CKD
- Most of the evidence is from observational studies, with associations that do not necessarily reflect causal relationships
- Underuse of curative and preventive therapies is prevalent in older patients with CKD

DISCLOSURES

None.

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REVIEW QUESTIONS: CARDIOVASCULAR DISEASE IN THE ELDERLY WITH KIDNEY DISEASE

1. What individuals have frequently been excluded from participation in large cardiovascular efficacy trials?
   a. Older individuals
   b. Patients with advanced kidney disease or on dialysis
   c. Both
   d. Neither

2. The efficacy of statins in the secondary prevention of cardiovascular events has been shown in which populations?
   a. Patients with mild to moderate chronic kidney disease
   b. Patients on hemodialysis
   c. Older individuals
   d. All of the above

3. Most cardiovascular risk factors in the general population appear to be also operational in older patients with chronic kidney disease
   a. True
   b. False
   c. Uncertain. While several cardiovascular risk factors have been confirmed in older patients with CKD, others were not probably because of limited statistical power