

Clinical Nephrology 2019 : Renal insufficiency as a predictor of cardiovascular outcomes and mortality in elderly individuals

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Objectives This study was designed to evaluate the relationship between elevated creatinine levels and cardiovascular events.

Background End-stage renal disease is associated with high cardiovascular morbidity and mortality. The association of mild to moderate renal insufficiency with cardiovascular outcomes remains unclear.

Methods We analyzed data from the Cardiovascular Health Study, a prospective population-based study of subjects, aged >65 years, who had a serum creatinine measured at baseline (n = 5,808) and were followed for a median of 7.3 years. Proportional hazards models were used to examine the association of creatinine to all-cause mortality and incident cardiovascular mortality and morbidity. Renal insufficiency was defined as a creatinine level ≥ 1.5 mg/dl in men or ≥ 1.3 mg/dl in women.

Results An elevated creatinine level was present in 648 (11.2%) participants. Subjects with elevated creatinine had higher overall (76.7 vs. 29.5/1,000 years, $p < 0.001$) and cardiovascular (35.8 vs. 13.0/1,000 years, $p < 0.001$) mortality than those with normal creatinine levels. They were more likely to develop cardiovascular disease (54.0 vs. 31.8/1,000 years, $p < 0.001$), stroke (21.1 vs. 11.9/1,000 years, $p < 0.001$), congestive heart failure (38.7 vs. 17/1,000 years, $p < 0.001$), and symptomatic peripheral vascular disease (10.6 vs. 3.5/1,000 years, $p < 0.001$). After adjusting for cardiovascular risk factors and subclinical disease measures, elevated creatinine remained a significant predictor of all-cause and cardiovascular mortality, total cardiovascular disease (CVD), claudication, and congestive heart failure (CHF). A linear increase in risk was observed with increasing creatinine.

Conclusions Elevated creatinine levels are common in older adults and are associated with increased risk of mortality, CVD, and CHF. The increased risk is apparent early in renal disease.

Individuals with end-stage renal disease have a cardiovascular mortality rate that is 10 to 20 times greater than that in the general population. However, whether milder degrees of renal insufficiency are an independent predictor of cardiovascular outcomes is unclear. In several prospective studies, renal insufficiency, as documented by elevated creatinine levels, has been associated with an increased risk of cardiovascular events and mortality. In other studies, however, elevated creatinine was no longer an independent predictor after adjustment for other risk factors. Renal insufficiency is associated with a high prevalence of traditional cardiovascular risk factors, which may explain the association with cardiovascular events. Renal insufficiency may also amplify the severity of these risk factors, thus promoting cardiovascular risk. In addition, renal insufficiency is associated with higher levels of novel risk factors, such as C-reactive protein (CRP), homocysteine, asymmetric dimethylarginine, and fibrinogen.

The prevalence of renal dysfunction rises with age, particularly after age 70. The elderly also have the highest incidence of cardiac events and thus would experience the greatest burden from both cardiovascular disease (CVD) and renal disease. The Cardiovascular Health Study (CHS) is a population-based, longitudinal study of CVD and stroke in men and women aged >65 years. Previous analyses of CHS have found elevated creatinine levels to be among the predictors of total mortality and congestive heart failure (CHF). This report investigates in depth the association of

elevated creatinine with cardiovascular events and mortality.

Results: The number of participants in CHS who had elevated creatinine was 648 (11.2%) at baseline, as defined by a serum creatinine ≥ 1.3 mg/dl for women and ≥ 1.5 mg/dl for men. The mean serum creatinine was 1.2 ± 0.4 mg/dl (range 0.6 to 10.0) in men and 0.9 ± 0.3 mg/dl (range 0.4 to 7.3) in women. The characteristics of those with and without an elevated creatinine are summarized in Table 1. Those with an elevated creatinine were older, more likely to smoke, and had higher levels of inflammatory and prothrombotic markers. Low-density lipoprotein cholesterol levels in both groups were similar, but participants with elevated creatinine had higher triglycerides and lower HDL levels. Those with elevated creatinine had a higher prevalence at baseline of clinical and subclinical CVD; 278 (42.9%) of people with an elevated creatinine had prevalent disease at baseline compared with 1,200 (23.2%) of people without ($p < 0.0001$). The prevalence of subclinical disease was 446 (68.8%) among individuals with elevated creatinine levels versus 2,260 (43.8%) of those without elevated creatinine ($p < 0.001$).

Discussion: We found that elderly individuals with mildly elevated serum creatinine levels had a greater incidence of cardiovascular events and mortality compared with other elderly individuals with normal creatinine levels. The value of elevated creatinine levels in predicting the development of CHF, CVD morbidity and mortality, and all-cause mortality remained after adjustment for many cardiovascular risk factors and subclinical disease measures. That the increased risk of death began at low creatinine levels in our study is noteworthy, as the values are near or below the normal value for many laboratories. Many physicians and patients may not, therefore, recognize the increased risk associated with mildly elevated creatinine.

Conclusions: More than 10% of our cohort had elevated serum creatinine levels, defined as ≥ 1.5 mg/dl in men or ≥ 1.3 mg/dl in women. As there is an increased risk of CVD in individuals with an elevated creatinine, this implies that an elevated creatinine, defined this way, may have a substantial attributable risk for CVD and mortality in the elderly population. As the population ages, the prevalence of renal insufficiency and CVD may also grow. That elevated creatinine is associated with a high prevalence of cardiac risk factors suggests that attention to risk factor reduction may impact the high risk of CVD. A recent Canadian study suggests that cardiac risk factors are inadequately addressed in patients with renal insufficiency (43). In that study, 35% of those with renal insufficiency and established CVD had a blood pressure $>140/90$ mm Hg; 45% were receiving aspirin, 50% were receiving beta-blockers and only 50% of those with hyperlipidemia were on statins. There is a lack of research on prevention of CVD in individuals with renal insufficiency. The National Cholesterol Education Program (NCEP) Adult Treatment Panel III recommended that diabetes be considered a coronary heart disease equivalent (44). In a similar fashion, the National Kidney Foundation Task Force on Cardiovascular Disease recommended that patients with chronic kidney disease be considered in the highest risk group for cardiovascular events (45). Although this recommendation was not adopted by NCEP, our study supports this recommendation.

In summary, our study found that mildly elevated creatinine levels are predictive of cardiovascular morbidity and mortality. Elevated creatinine was associated with a high prevalence of cardiac risk factors. Further studies aimed at risk reduction of traditional and novel risk factors in those with renal insufficiency are needed in order to have an impact in this high-risk population.