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Kidney Disease 2015: Cardiovascular Mortality Risk in Chronic Kidney Disease

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Context Elderly persons with chronic kidney disease have substantial risk for cardiovascular mortality, but the relative importance of traditional and novel risk factors is unknown.

Objective: To compare traditional and novel risk factors as predictors of cardiovascular mortality.

Design, Setting, and Patients A total of 5808 community-dwelling persons aged 65 years or older living in 4 communities in the United States participated in the Cardiovascular Health Study cohort. Participants were initially recruited from 1989 to June 1990; an additional 687 black participants were recruited in 1992-1993. The average length of follow-up in this longitudinal study was 8.6 years.

Main Outcome Measures Cardiovascular mortality among those with and without chronic kidney disease. Chronic kidney disease was defined as an estimated glomerular filtration rate of less than 60 mL/min per 1.73 m2.

Results: Among the participants, 1249 (22%) had chronic kidney disease at baseline. The cardiovascular mortality risk rate was 32 deaths/1000 person-years among those with chronic kidney disease vs 16/1000 person-years among those without it. In multivariate analyses, diabetes, systolic hypertension, smoking, low physical activity, nonuse of alcohol, and left ventricular hypertrophy were predictors of cardiovascular mortality in persons with chronic kidney disease (all P values <.05). Among the novel risk factors, only log C-reactive protein (P = .05) and log interleukin 6 (P<.001) were associated with the outcome as linear predictors. Traditional risk factors were associated with the largest absolute increases in risks for cardiovascular deaths among persons with chronic kidney disease: for left ventricular hypertrophy, there were 25 deaths per 1000 person-years; current smoking, 20 per 1000 person-years; physical inactivity, 15 per 1000 person-years; systolic hypertension, 14 per 1000 person-years; diabetes, 14 per 1000 person-years; and nonuse of alcohol, 11 per 1000 person-years vs 5 deaths per 1000 person-years for those with increased C-reactive protein and 5 per 1000 person-years for those with increased interleukin 6 levels. A receiver operating characteristic analysis found that traditional risk factors had an area under the curve of 0.73 (95% confidence interval, 0.70-0.77) among those with chronic kidney disease. Adding novel risk factors only increased the area under the curve to 0.74 (95% confidence interval, 0.71-0.78; P for difference = .15).

Conclusions: Traditional cardiovascular risk factors had larger associations with cardiovascular mortality than novel risk factors in elderly persons with chronic kidney disease. Future research should investigate whether aggressive lifestyle intervention in patients with chronic kidney disease can reduce their substantial cardiovascular risk.

The National Kidney Foundation, American Heart Association, and the Seventh Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure have classified the presence of chronic kidney disease as a cardiovascular risk factor.1-3 Chronic kidney disease is associated with substantially increased risk for cardiovascular disease morbidity and mortality, independent of traditional cardiovascular risk factors such as diabetes, hypertension, lipoprotein levels, and tobacco use.1,4-6 In addition, certain novel cardiovascular risk factors are more prevalent in persons with chronic kidney disease, including elevated inflammatory and prothrombotic factors (C-reactive protein [CRP], fibrinogen, interleukin 6 [IL-6], and factor VIII), and lipoprotein(a)

Note: The work is Submitted from International Conference on Kidney Disease and Disadvantages March 2015, Spain Italy

(Lp[a]), and decreased hemoglobin levels. These novel risk factors have been discussed as potential mechanisms for the elevated cardiovascular risk of chronickidney disease,7-9 but few studies have evaluated their association with cardiovascular events in persons with chronic kidney disease or compared the strength of association of traditional and novel cardiovascular risk factors. Though the National Institutes of Health and the National Kidney Foundation have prioritized the reduction of cardiovascular disease burden in persons with chronic kidney disease, prevention efforts will first require an in-depth understanding of the determinants of cardiovascular risk in persons with chronic kidney disease.10

In the Cardiovascular Health Study (CHS), a well-characterized cohort of elderly persons with a high prevalence of chronic kidney disease, we compared the association of traditional and novel risk factors with cardiovascular mortality among subgroups of participants with and without chronic kidney disease at baseline. In addition, we estimated the absolute risk associated with each candidate risk factor and constructed receiver operating characteristic (ROC) curves to estimate the aggregate predictive utility of traditional and novel risk factors.

Methods

Subjects and Design

The CHS is a prospective cohort study of risk factors for cardiovascular disease in elderly men and women. The study recruited eligible persons who resided in the households of individuals identified from an age-stratified random sample from Medicare eligibility lists in Forsyth County, North Carolina; Sacramento County, California; Washington County, Maryland; and Pittsburgh, Pa. Household members and spouses of the person being recruited were also invited to participate in the CHS if they met the following inclusion criteria: (1) at least 65 years, (2) not institutionalized, (3) expected to remain in the current community for 3 years or longer, (4) not under active treatment for cancer, and (5) gave written informed consent without requiring a proxy respondent at entry. Among those who met the eligibility requirements and were invited to participate, 57% were enrolled. The initial 5201 participants (original cohort) were enrolled from 1989 to June 1990; an additional 687 black participants (African-American cohort) were recruited and enrolled in 1992-1993. Race was self-reported in 5 categories: white, black, American Indian/American Native, Asian/Pacific Islander, other. A separate question addressed Hispanic heritage. Race was subsequently collapsed into white, black, and other because the nonwhite or nonblack proportion was very small. The baseline examination for each cohort included a medical history, physical examination, laboratory testing, and assessments of cardiovascular disease status. The study design, quality-control procedures, laboratory methods, and blood pressure measurement procedures have been published previously.

Results: At study entry, 1249 (22%) participants had chronic kidney disease, defined by an estimated GFR of less than 60 mL/min per 1.73 m2. Participants with chronic kidney disease were on average 3 years older; were more likely to be men and white; were less likely to have more than a high school education; and had a greater prevalence of cardiovascular disease than those without chronic kidney disease (Table 1). Those with chronic kidney disease also had higher levels of triglycerides and lower HDL cholesterol levels. Participants with chronic kidney disease used less alcohol, were less physically active, and had a greater prevalence of LVH. Among the novel risk factors,mean levels of CRP, fibrinogen, IL-6, factor VIIIc, and Lp(a) were higher and hemoglobin was lower among those with than among those without chronic kidney disease.