Kidney Disease as a Risk Factor for Recurrent Cardiovascular Disease and Mortality

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• ***Background:*** **Chronic kidney disease (CKD) is highly prevalent in the United States and is an independent risk factor for adverse cardiovascular disease (CVD) and all-cause mortality outcomes in patients with acute coronary syndromes. Few studies have evaluated the effect of CKD on cardiovascular events in a diverse community-based population with underlying CVD.** ***Methods:*** **Data for subjects with preexisting CVD were pooled from 4 publicly available, community-based, longitudinal studies: Atherosclerosis Risk in Communities, Cardiovascular Health Study, Framingham Heart Study, and Framingham Offspring Study. CKD was defined as an estimated glomerular filtration rate less than 60 mL/min/1.73 m^2 (<1 mL/s/1.73 m^2). The primary study outcome was a composite of myocardial infarction (MI), fatal coronary heart disease (CHD), stroke, and all-cause mortality. The secondary outcome included only MI and fatal CHD.** ***Results:*** **A total of 4,278 subjects satisfied inclusion criteria, and 759 subjects (17.7%) had CKD. Mean follow-up was 86 months. The primary and secondary outcomes were observed in 1,703 (39.8%) and 857 subjects (20.0%), respectively. Incidence rates for the primary and secondary outcomes were greater in persons with CKD compared with those without CKD (62.5% versus 34.9% and 30.6% versus 17.8%, respectively). Adjusted hazard ratios for the primary and secondary outcomes were 1.35 (95% confidence interval [CI], 1.21 to 1.52) and 1.32 (95% CI, 1.12 to 1.55), respectively.** ***Conclusion:*** **The presence of CKD in a community-based population with preexisting CVD is associated with an increased risk for recurrent CVD outcomes. This increased risk persists after adjustment for traditional CVD risk factors.** ***Am J Kidney Dis*** **44:198-206.**

INDEX WORDS: Kidney; chronic kidney disease (CKD); cardiovascular disease (CVD); outcomes; myocardial infarction (MI).

CHRONIC KIDNEY DISEASE (CKD) is a major public health problem in the United States.[1] Given the aging population and increasing incidence of diabetes and hypertension, the prevalence of CKD is projected to increase dramatically, with the number of patients with kidney failure treated by dialysis nearly doubling during the next decade.[2]

It is well appreciated that patients on dialysis therapy are at increased risk for adverse cardiovascular disease (CVD) outcomes.[3] However, the increased risk for CVD likely begins before the development of kidney failure.[4,5] Recent studies of subjects with a history of acute myocardial infarction (MI),[6-10] acute coronary syndromes,[10,11] and revascularization procedures[12-14] have shown that the presence of CKD is an independent predictor of subsequent CVD events and mortality. These studies primarily examined the risk for adverse outcomes in patients visiting the emergency department or admitted to the hospital with unstable coronary syndromes, potentially limiting their generalizability.

Few studies have examined the relationship between CKD and recurrence of CVD in a generalizable community-based population with long-term follow-up. In the current study, we pooled data from subjects with preexisting CVD from several large community-based cohorts to evaluate whether CKD, quantified by estimated glomerular filtration rate (GFR), is a risk factor for recurrence of adverse cardiovascular events.

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Received February 6, 2004; accepted in revised form April 14, 2004.

Supported in part by grants no. K23 02904, T32DK007777, and RO1DK53689 from the National Institute of Diabetes and Digestive and Kidney Diseases; and Amgen Inc, Thousand Oaks, CA.

The Atherosclerosis Risk in Communities Study, Cardiovascular Health Study, and the Framingham Heart and Framingham Offspring studies are conducted and supported by the National Heart, Lung and Blood Institute in collaboration with the individual study investigators. This manuscript was not prepared in collaboration with the study investigators and does not necessarily reflect the opinions or views of the study investigators or the National Heart, Lung and Blood Institute.

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0272-6386/04/4402-0004$30.00/0

doi:10.1053/j.ajkd.2004.04.024

METHODS

Study Design

This study is a post hoc analysis of pooled subject-level data from subgroups of subjects with preexisting CVD from 4 community-based longitudinal public-use data sets to ascertain the relationship between baseline level of kidney function and risk for development of recurrent CVD events.

Study Population

Information from the following cohort studies was used: Atherosclerosis Risk in Communities (ARIC) Study, the Cardiovascular Health Study (CHS), the Framingham Heart Study (FHS), and the Framingham Offspring Study (Offspring).[15-18]

ARIC enrolled 15,792 participants aged 45 to 64 years between 1987 and 1989 from 4 communities, while CHS enrolled 5,201 subjects 65 years and older between 1989 and 1990, also from 4 communities. CHS recruited an additional 687 African Americans in 1992 and 1993. The FHS began in 1948 with 5,209 residents of Framingham, MA, aged 28 to 62 years, and Offspring recruited 5,124 of the children and spouses of children of FHS participants in 1971. Serum creatinine levels were assessed at baseline in ARIC and CHS, at the fifteenth biennial examination (1977 to 1979; n = 2,632) in FHS, and at the second examination (1979 to 1983; n = 3,863) in Offspring; these examinations are considered the baseline period for our analyses. Details of recruitment and procedures for all studies have been described elsewhere.[15-18]

Ascertainment of Level of Kidney Function

In the ARIC study, baseline serum creatinine levels were assessed in 15,582 subjects (99%) by using the modified kinetic Jaffé method (alkaline picrate). Serum creatinine levels in CHS were assessed by means of the Kodak Ektachem 700 Analyzer (Eastman Kodak Corp, Rochester, NY), a colorimetric method, in 5,716 subjects (97%). Creatinine levels were assessed in the FHS and Offspring cohorts by using either an autoanalyzer technique or the creatinine imodohydrolase assay in 2,536 (96%) and 3,703 subjects (96%), respectively.

Kidney function was quantified by using estimated GFR derived from the 4-variable Modification of Diet in Renal Disease (MDRD) study equation[19]:

$$\text{GFR} = 186.3 \times (\text{serum creatinine}^{-1.154}) \times (\text{age}^{-0.203}) \times 1.212 \text{ (if African American)} \times 0.742 \text{ (if female)}$$

Serum creatinine is measured in milligrams per deciliter; age, in years; and GFR, in milliliters per minute per 1.73 m^2.

The MDRD Study equations for estimating GFR were derived by comparing GFR assessed by clearance of iothalamate by the kidney with demographic characteristics and laboratory values.[20] Serum creatinine assays in the MDRD Study were performed at the Cleveland Clinic Foundation. Because serum creatinine assays vary across laboratories, use of the MDRD Study equation in these analyses requires calibration of serum creatinine assays from each study laboratory with the Cleveland Clinic. We calibrated the study laboratories indirectly by using data from the Third National Health and Nutrition Examination Survey (NHANES III). Serum specimens from a subset of individuals from NHANES III were assayed previously at the Cleveland Clinic laboratory.[21] Because both NHANES III and the studies used for these analyses were designed as population samples, we assumed that the mean serum creatinine level in each study for individuals of a given age range, race, and sex should be similar to those of NHANES III. We fitted a linear regression in which serum creatinine was the dependent variable and study terms age, sex, and race were the covariates in the model. The β coefficient of the study term indicated the magnitude of the difference between serum creatinine levels in the individual studies compared with NHANES III. Calibration was accomplished by subtracting the study-specific β coefficients from the measured serum creatinine levels for each study. This calibration model showed that serum creatinine values were 0.24 mg/dL (21.2 μmol/L) greater in ARIC, 0.11 mg/dL (9.7 μmol/L) greater in CHS, 0.04 mg/dL (3.5 μmol/L) greater in the CHS African-American cohort, 0.22 mg/dL (19.5 μmol/L) greater in FHS, and 0.32 mg/dL (28.3 μmol/L) greater in Offspring than among NHANES III participants. Similar calibration corrections have been made by the CHS investigators to pool the 2 CHS cohorts, and by the Framingham investigators, to pool data from the FHS and Offspring studies.[22]

GFR subsequently was dichotomized based on the Kidney Disease Outcomes and Quality Initiative guidelines.[1] Subjects were classified as having CKD if their GFR values were less than 60 mL/min/1.73 m^2. Subjects with a GFR less than 15 mL/min/1.73 m^2 were excluded from the study to avoid confounding by imminent dialysis therapy.

Baseline Variables

Baseline characteristics included demographics (age, sex, race, and education level), lifestyle (smoking and alcohol intake), medical history (baseline CVD, diabetes mellitus, and hypertension), medication use (antihypertensive agents, lipid-lowering agents, and diabetes medications), physical examination findings (body mass index, systolic and diastolic blood pressure), left ventricular hypertrophy (LVH) by electrocardiogram; and laboratory variables (total cholesterol, high-density lipoprotein [HDL] cholesterol, creatinine, and glucose).

Race is defined as white or African American. The Framingham cohorts were assumed to be entirely white.[23] Level of education was dichotomized according to high school graduation status. Cigarette smoking and alcohol use were dichotomized as current users and nonusers. Diabetes is defined as present when individuals reported the use of insulin or oral hypoglycemic medications or had a fasting glucose level of 126 mg/dL or greater ($\geq$7.0 mmol/L). Although fasting state was unknown at visit 15 of the FHS, we maintained glucose level at 126 mg/dL or greater ($\geq$7.0 mmol/L) as defining diabetes for this study. Hypertension is defined as a systolic blood pressure of 140 mm Hg or greater, diastolic blood pressure of 90 mm Hg or greater, or use of an antihypertensive medication at baseline. Body mass index was calculated using the formula weight (kg)/height^2 (m), and LVH is defined by electrocardiographic criteria.

Baseline CVD included a history of MI, angina, stroke, transient ischemic attack, and intermittent claudication, de-

fined by consensus committees for the respective studies. In addition, baseline CVD included a history of congestive heart failure in CHS, FHS, and Offspring (not ascertained in ARIC) and a history of angioplasty or coronary bypass procedures in ARIC and CHS (not available in the Framingham cohorts). Methods used for collection of baseline data and CVD events by each of these studies are described elsewhere.[15-18]

Study Sample

We excluded data for 575 subjects who had information missing on age, race, sex, or creatinine level or were of nonwhite/non–African-American race; 36 subjects with a GFR less than 15 mL/min/1.73 m^2; 93 subjects who did not provide permission to release data; 3 subjects without follow-up data; and 556 subjects with missing data on the presence of baseline CVD. Of the remaining 26,912 subjects, the 4,278 subjects with preexisting CVD were selected for the present analysis. In this study sample, 231 subjects (5.4%) were missing single data points, such as systolic blood pressure or total cholesterol level; for these subjects, single inputation was performed based on age-, sex-, and race-stratified means. Final regression models are based on the imputed results.

Follow-Up Time and Outcomes

Because only the Framingham cohorts had more than 10 years of follow-up data, we censored all subjects at 10 years so that follow-up times would be similar in the pooled cohort. The primary study outcome was a composite end point of MI and fatal coronary heart disease (CHD), stroke, or all-cause mortality. MI is defined by the occurrence of both clinically recognized and silent infarctions. Silent MI was ascertained either at scheduled follow-up visits or by interim electrocardiogram performed for other clinical indications. The main secondary outcome included the individual analysis of MI/fatal CHD. We additionally investigated stroke and all-cause mortality as other secondary outcomes.

Analysis and Statistical Methods

Chi-square tests and analysis of variance were used to compare baseline data between subjects with and without CKD. Kaplan-Meier survival analysis was used to estimate the nonparametric survival distribution among study participants by CKD status. Log-rank test was used to examine the significance of differences in long-term outcomes between respective comparison groups. Cox proportional hazards regression was used to examine differences in the principal study outcomes between the respective comparison groups while adjusting for various covariates. All models included traditional CVD risk factors described in the Framingham population; namely, age, sex, smoking status, total cholesterol level, HDL cholesterol level, diabetes mellitus, and history of hypertension. Additional candidate covariates included race, LVH, alcohol use, body mass index, and education status; these variables were retained in our regression model if P was less than 0.05 in the multivariate model. A term for each study was included in the models. Nonlinear relationships between covariates and outcomes were tested by including squared terms in models and retaining them when significant ($P < 0.05$). We also tested for interactions between CKD and the major CVD risk factors and demographic characteristics. The main effect of the original study terms was tested for significance by using the Wald statistic with 3 *df*.

A sensitivity analysis was performed comparing the model with imputed data for missing data on covariates with the model without imputed data. To account for the absence of fasting glucose levels in the FHS, we reanalyzed the data using 2 alternate definitions of diabetes for the FHS cohort: (1) serum glucose level of 200 mg/dL or greater (≥11.1 mmol/L) or the use of antihyperglycemic medications at visit 15, or (2) serum glucose level of 200 mg/dL or greater (≥11.1 mmol/L) or the use of antihyperglycemic medications at any time, including or before visit 15.[24] Furthermore, because heart failure may influence adverse outcomes independent of atherosclerosis, an additional analysis was performed after excluding subjects whose only CVD history was heart failure. A final sensitivity analysis examined the impact of additional adjustment for coronary angioplasty or bypass grafting in ARIC and CHS.

Evaluation of the secondary outcomes of MI/fatal CHD, as well as stroke and all-cause mortality outcomes, was performed using covariates that were significant in the fully adjusted model for the composite outcome. Data were analyzed using SAS, version 8.2 (SAS Institute, Cary, NC), and plots were generated using Splus, version 6.1 (Insightful Corp, Seattle, WA).

RESULTS

Baseline Characteristics

Baseline characteristics of the 4,278 subjects with previous CVD are listed in Tables 1 and 2. Subjects with CKD comprised 17.7% of the population and had a mean GFR of 49.6 mL/min/1.73 m^2 (0.83 mL/s/1.73 m^2), whereas subjects without CKD had a mean GFR of 90.2 mL/min/1.73 m^2 (1.50 mL/s/1.73 m^2). Subjects with CKD were significantly older and more likely to have a history of diabetes and hypertension. A greater percentage of subjects with CKD were administered antihypertensive and hypoglycemic agents.

Outcomes

Average duration of follow-up was 86 months for the pooled database; mean follow-up for ARIC was 96 months; for CHS, 72 months; for FHS, 89 months; and for Offspring, 111 months.

The composite outcome occurred in 1,703 subjects (39.8%). There were 857 MI/fatal CHD events (20.0%), 424 strokes (9.9%), and 1,202 deaths (28.1%). Compared with subjects without CKD, a significantly greater percentage of subjects with CKD reached each of the study outcomes (Table 3).

Among the 759 subjects with CKD, 62.5%

Table 1. Baseline Characteristics of the Study Population With Baseline CVD by Original Study

Variables	ARIC (n = 2,102)	CHS (n = 1,435)	FHS (n = 586)	Offspring (N = 155)	Total (n = 4,278)
Demographics (%)					
Mean age (y)	55.7	74.4	71.3	54.1	64.1
Men	48.1	54.2	49.8	69.7	51.2
Black	22.6	16.4	0	0	16.6
High school graduates	67.3	66.0	55.5	77.4	65.6
Lifestyle (%)					
Smoking	30.2	11.2	25.3	43.2	23.6
Alcohol	47.9	46.6	51.7	71.0	48.8
Medical history (%)					
Diabetes mellitus	17.9	23.6	19.6	9.0	19.7
Hypertension	60.1	83.3	64.7	54.2	68.3
Medication use (%)					
Antihypertensive	54.0	72.1	42.5	30.3	57.6
Lipid-lowering	5.9	8.6	3.8	4.5	6.5
Hypoglycemic	11.3	14.6	10.1	4.5	12.0
Physical characteristics					
Body mass index (kg/m^2)	28.4	26.7	26.8	29.4	27.6
Systolic blood pressure (mm Hg)	122.8	137.3	139.1	133.5	130.3
Diastolic blood pressure (mm Hg)	72.5	69.4	75.1	82.3	72.2
LVH	5.7	9.1	5.3	1.3	6.6
Laboratory values					
Serum creatinine (mg/dL)	0.89	1.06	0.97	0.90	0.96
Estimated GFR (mL/min/1.73 m^2)	90.4	72.7	79.3	92.9	83.0
Total cholesterol (mg/dL)	219.0	208.1	226.1	256.0	217.7
HDL cholesterol (mg/dL)	47.8	49.8	44.9	41.2	47.8

NOTE. To convert serum creatinine in mg/dL to μmol/L, multiply by 88.4; GFR in mL/min/1.73 m^2 to mL/s/1.73 m^2, multiply by 0.01667; HDL and total cholesterol in mg/dL to mmol/L, multiply by 0.0259.

experienced an event; among the 3,519 subjects who did not have CKD, 34.9% experienced an event. Unadjusted analysis showed a hazard ratio (HR) of 2.26 (95% confidence interval [CI], 2.03 to 2.52; Fig 1). In the fully adjusted analysis, the hazard was significantly increased in subjects with CKD compared with those without CKD (HR, 1.35; 95% CI, 1.21 to 1.52; Fig 2). This increased risk was seen in men and women and in whites and African Americans. The presence of CKD yielded a similar increase in hazard to that seen for diabetes, hypertension, and LVH (Table 4). Terms for the individual studies were not statistically significant (Wald statistic, $P = 0.36$). Interaction terms between CKD and major CVD risk factors and demographic characteristics also were not statistically significant.

Secondary Outcomes

Subjects with CKD were more likely to have an MI/fatal CHD event (30.6% versus 17.8%). Unadjusted analysis showed an HR of 2.09 (95% CI, 1.80 to 2.43) for MI/fatal CHD in subjects with CKD (Fig 1). The fully adjusted HR was significantly greater for patients with CKD (HR, 1.32; 95% CI, 1.12 to 1.55). Subjects with CKD also were more likely to develop a stroke (HR, 1.30; 95% CI, 1.04 to 1.63) and experience all-cause mortality (HR, 1.56; 95% CI, 1.37 to 1.78) in adjusted analyses (Table 4; Fig 2).

Sensitivity Analyses

Results using the imputed and nonimputed models were not significantly different. The relationship between CKD and recurrent CVD did not significantly change using several different definitions of diabetes in the FHS cohort (data not shown).

Ninety-eight subjects had a history of heart failure without other manifestations of CVD; after excluding these subjects, 4,180 subjects met inclusion criteria. In these subjects, the adjusted HR associated with CKD was essentially unchanged for both the primary and secondary outcomes.

Table 2. Baseline Characteristics and Outcomes of Subjects With and Without CKD

Variables	CKD (n = 759)	Non-CKD (n = 3,519)
Demographics (%)		
Age (y)*	72.4 ± 9.0	62.2 ± 10.4
Men	49.9	51.5
Black*	10.1	18.0
High school graduate	62.5	66.2
Lifestyle (%)		
Smoking*	13.7	25.8
Alcohol†	43.6	50.0
Medical history (%)		
Diabetes†	24.2	18.7
Hypertension*	84.3	64.8
Medication use (%)		
Antihypertensive*	72.7	54.4
Lipid-lowering	7.1	6.3
Diabetes*	15.9	11.1
Physical examination		
Body mass index (kg/m^2)	27.1 ± 4.8	27.8 ± 5.3
Systolic blood pressure (mm Hg)	137.7 ± 24.5	128.7 ± 21.9
Diastolic blood pressure (mm Hg)	71.6 ± 12.5	72.3 ± 11.7
LVH (%)*	10.0	5.9
Laboratory values		
Creatinine* (mg/dL)	1.39 ± 0.40	0.86 ± 0.19
GFR* (mL/min/1.73 m^2)	49.6 ± 9.4	90.2 ± 20.7
Total cholesterol (mg/dL)	217.5 ± 46.0	217.7 ± 43.6
HDL cholesterol‡ (mg/dL)	46.6 ± 14.9	48.1 ± 15.9
Outcomes (%)		
Composite*	62.5	34.9
Cardiac*	30.6	17.8
Stroke*	15.9	8.6
Mortality*	51.1	23.1

NOTE. Values expressed as percent or mean ± SD. To convert serum creatinine in mg/dL to μmol/L, multiply by 88.4; GFR in mL/min/1.73 m^2 to mL/s/1.73 m^2, multiply by 0.01667; HDL and total cholesterol in mg/dL to mmol/L, multiply by 0.0259.

*$P < 0.001$.

†$P < 0.01$.

‡$P < 0.05$.

In ARIC, 302 subjects underwent either coronary angioplasty or bypass grafting procedures before study enrollment, and of these, 6.6% had CKD. In CHS, 298 subjects underwent either of these procedures before study enrollment and 32.2% had CKD. Only 15 subjects (0.35% of the study population) qualified as having baseline CVD based on previous coronary procedures alone. The HR associated with CKD did not change after additional adjustment for coronary procedures in ARIC and CHS and was similar to that seen in the entire pooled cohort (data not shown).

DISCUSSION

In the current study, the presence of CKD was associated with an increased risk for recurrent CVD outcomes, stroke and all-cause mortality; this association remained after adjustment for traditional CVD risk factors. The results of this study add to the current state of knowledge because it is one of only a few studies to evaluate the association of CKD with risk for recurrent CVD in stable outpatients and the only study of which we are aware that evaluated the association of CKD with recurrent CVD in a community-based population recruited into observational studies, rather than controlled trials. It therefore is more generalizable to patients in the community.

Several possible causes may explain the association between kidney function and recurrent CVD. (1) Both kidney disease and CVD may be sequelae of atherosclerosis, such that the pres-

Table 3. Adverse Event Rates for Subjects With and Without CKD

Outcomes	CKD	Non-CKD
Primary composite		
Follow-up (y)	4,091	23,639
Events	474	1,229
Rate/100 person-y	11.6	5.2
MI/fatal CHD		
Follow-up (y)	4,325	24,382
Events	232	625
Rate/100 person-y	5.4	2.6
Stroke		
Follow-up (y)	4,337	24,939
Events	121	303
Rate/100 person-y	2.8	1.2
All-cause mortality		
Follow-up (y)	4,609	25,811
Events	388	814
Rate/100 person-y	8.4	3.2

ence of kidney disease identifies patients with a greater burden of systemic vascular disease caused by the magnitude and severity of such traditional CVD risk factors as hypertension and diabetes. (2) Patients with kidney disease may have an acceleration of CVD such that recurrent CVD develops earlier in patients with CKD. (3) Kidney disease itself may create a milieu for increased cardiovascular progression through nontraditional factors. (4) CVD itself, through mechanisms including atherosclerosis and heart failure, may cause kidney disease. (5) Patients with kidney disease may receive less aggressive therapy for vascular disease and risk-factor modification.

Evidence exists for all these possibilities, and the most likely explanation is that the increased risk for outcomes in patients with CKD is multifactorial in nature. In NHANES III data, patients with CKD were more likely to have hypertension, had greater mean blood pressures, and were less likely to have achieved blood pressure goals with hypertensive therapy.[25] Overall, patients with CKD have a greater prevalence of traditional CVD risk factors than the general population.[26]

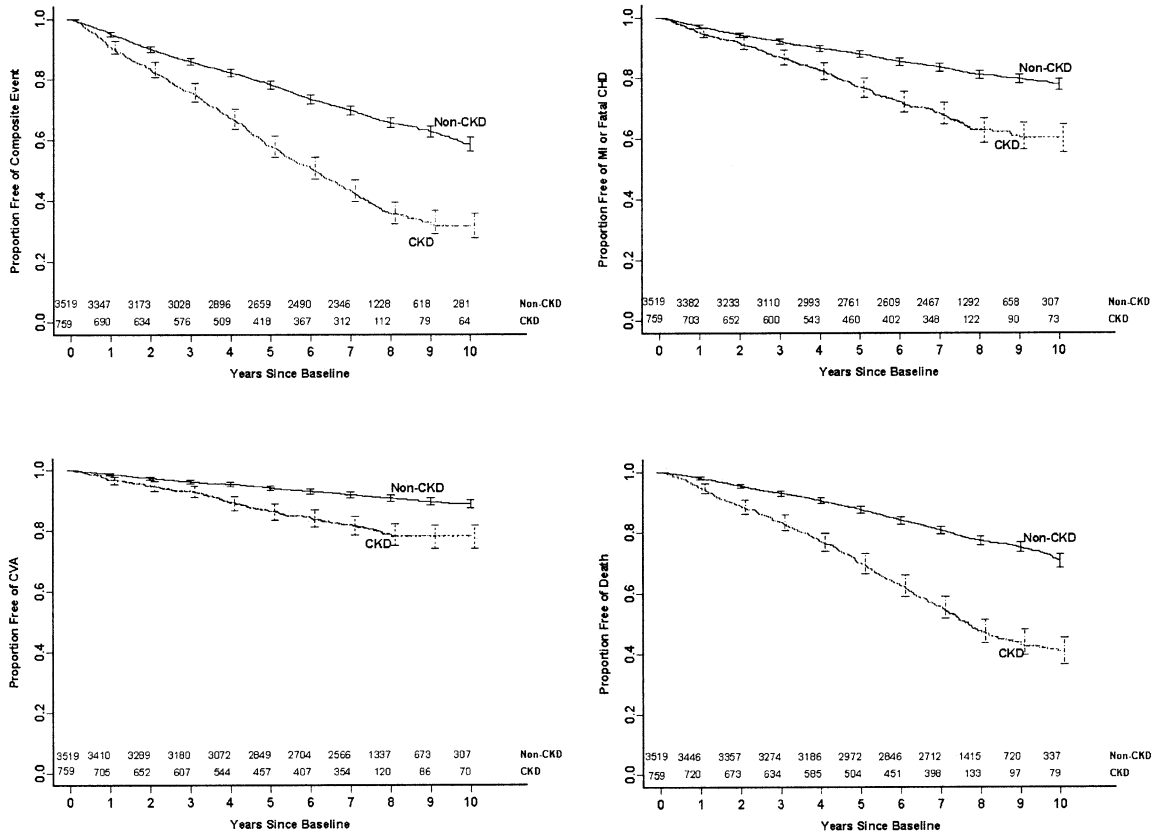

Fig 1. Kaplan-Meier curves delineating the differing effect of the presence versus absence of CKD on study outcomes. Vertical bars at each year represent 95% CIs.

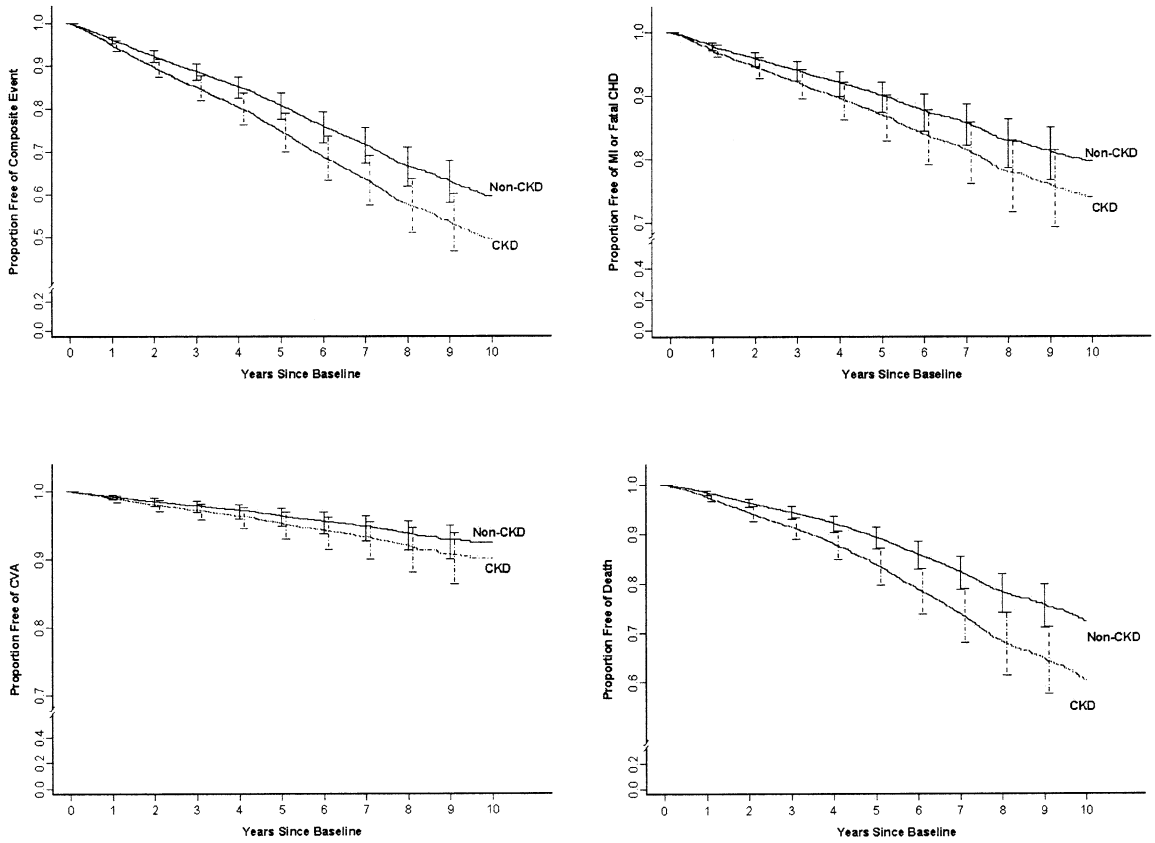

Fig 2. Graphical representation of the differing effects of the presence versus absence of CKD on study outcomes in multivariate fully adjusted analysis. Vertical bars at each year represent 95% CIs.

Patients with CKD also have a high prevalence of such nontraditional risk factors as hyperhomocysteinemia, inflammation, and oxidative stress, which may contribute to the progression of atherosclerosis.[27] Other comorbid conditions, such as anemia, particularly in conjunction with hypertension, may promote the development of LVH, a known CVD risk factor.[5] Finally, recent studies have shown that patients with CKD who present to the hospital with acute MI may be less likely to undergo both revascularization procedures, as well as be administered known effective cardiac medications, including aspirin and β-blockers.[7,9] This difference in treatment pattern may be caused by therapeutic nihilism and could potentially manifest as worse outcomes for patients with CKD.[28]

Several studies have examined the role of CKD in patients with known acute coronary syndromes. In patients referred for angiography and percutaneous interventions, subjects with CKD were more likely to have significant coronary artery disease[13] and have worse in-hospital and posthospitalization outcomes after revascularization.[12,14] Other studies of cardiac care unit admissions[6,9,10] and admissions for acute MI[7,8,29] also have shown excess short-term and long-term mortality in patients with CKD. Importantly, many of these studies used serum creatinine level at the time of initial hospital presentation to define level of kidney function; therefore, hemodynamic instability may have limited extrapolation of creatinine levels to a stable assessment of kidney function.

A post hoc analysis of data from the Heart and Estrogen/Progestin Replacement Study (HERS) noted that elevated creatinine level was an independent risk factor for recurrent adverse CVD outcomes in postmenopausal women randomly assigned to the administration of hormone replacement therapy or placebo.[30] Similarly, in the Heart Outcomes and Prevention Evaluation (HOPE) study, CKD, defined as serum creatinine level greater than 1.4 mg/dL ($>$124 μmol/L) or

Table 4. HRs and CIs for the Study Outcomes in Multivariate Analysis

	Primary Composite*	MI/Fatal CHD	Stroke	All-Cause Mortality
CKD	1.35 (1.21-1.52)	1.32 (1.12-1.55)	1.30 (1.04-1.63)	1.56 (1.37-1.78)
Age	1.68 (1.55-1.83)	1.42 (1.26-1.60)	1.40 (1.19-1.66)	1.99 (1.80-2.20)
Female sex	0.59 (0.53-0.66)	0.44 (0.37-0.52)	0.75 (0.60-0.94)	0.58 (0.51-0.67)
Black race	1.11 (0.96-1.30)	0.87 (0.69-1.09)	1.39 (1.05-1.85)	1.22 (1.01-1.47)
History of diabetes	1.42 (1.27-1.60)	1.51 (1.29-1.76)	1.50 (1.20-1.88)	1.62 (1.42-1.84)
History of hypertension	1.40 (1.23-1.59)	1.75 (1.45-2.11)	1.23 (0.94-1.61)	1.25 (1.08-1.46)
LVH	1.35 (1.13-1.60)	1.45 (1.15-1.84)	1.44 (1.05-1.97)	1.33 (1.10-1.62)
Systolic blood pressure	1.04 (1.02-1.07)	1.01 (0.98-1.05)	1.12 (1.07-1.17)	1.04 (1.02-1.07)
Body mass index	0.97 (0.95-0.99)	0.99 (0.96-1.03)	0.96 (0.92-1.01)	0.96 (0.93-0.99)
Total cholesterol	1.02 (1.00-1.04)	1.08 (1.05-1.12)	1.05 (1.00-1.10)	0.98 (0.95-1.01)
HDL cholesterol	0.72 (0.63-0.82)	0.67 (0.55-0.82)	0.78 (0.59-1.04)	0.74 (0.64-0.86)
HDL cholesterol (squared)	1.02 (1.01-1.04)	1.03 (1.01-1.04)	1.02 (0.99-1.04)	1.02 (1.01-1.04)
Current smoking	1.54 (1.36-1.73)	1.49 (1.26-1.76)	1.32 (1.03-1.69)	1.60 (1.39-1.84)
Current alcohol use	0.81 (0.73-0.90)	0.74 (0.64-0.86)	0.84 (0.69-1.03)	0.79 (0.70-0.89)
High school graduate	0.82 (0.74-0.91)	0.83 (0.72-0.95)	0.89 (0.72-1.09)	0.85 (0.75-0.95)

NOTE. The HR for age reflects risk associated with a 10-year increase; systolic blood pressure, a 10–mm Hg increase; HDL cholesterol, a 10-mg/dL increase; body mass index, a 2-unit increase; and total cholesterol, a 20-mg/dL increase. Terms for studies were included in the multivariate models, but were not significant and are not presented here. Medication use and diastolic blood pressure were not statistically significant and were not included in final models.

*The primary outcome was a composite of MI, fatal CHD, stroke, or all-cause mortality.

estimated creatinine clearance less than 65 mL/min (<1.1 mL/s) in adults 55 years and older, was associated with increased risk for adverse CVD outcomes, including a composite of MI/fatal CHD and stroke.[31] HRs in these secondary analyses of randomized trials were very similar to those observed in our study. The current study builds on the findings from the HOPE study and the HERS in that we assessed patients who were not involved in a clinical trial, increasing the applicability to medical care in the general population.

A major strength of our study is that it assesses the importance of kidney function in a generalizable adult US population. The original studies all recruited ambulatory patients, and serum creatinine levels used to estimate GFR in these patients are more likely to represent true kidney function than those assessed during an acute MI or acute hospitalization. Additionally, there was rigid ascertainment of cardiovascular events in each of the original studies, with adjudication committees reviewing all possible CVD outcomes. To best estimate the true level of kidney function, we also use GFR estimating equations using calibrated creatinine values, rather than serum creatinine values alone.

Our study also has several limitations. First, there are slight differences in the definitions for preexisting CVD in the various studies. Second, serum creatinine level used to define CKD was assessed at only a single visit. This may lead to misclassification of patients with CKD, but would not likely bias the conclusions. Furthermore, given that patients were free of acute illnesses at the time of enrollment, creatinine level is more likely a reflection of stable level of kidney function. Third, we were unable to adjust for certain preexisting conditions, including reduced systolic function and coronary revascularization procedures in the primary analyses, because these data were not available in all studies. Fourth, we were unable to assess for differences across the studies related to period effects, including differences in diagnostic and therapeutic modalities. Finally, we cannot account for the impact that several newer therapies, such as statins and renin-angiotensin-aldosterone system blockade, may have had on CVD outcomes because the initiation of the 4 studies predated extensive use of these now commonly prescribed medications. However, even without this information, our study adjusts for most history, physical examination, and laboratory items that are evaluated in a routine patient visit, making the results applicable to clinical practice.

In summary, the presence of CKD is an independent risk factor for recurrence of adverse CVD events in a community-based population. CKD is a CVD risk factor of importance similar

to several major traditional risk factors, including hypertension, diabetes, and LVH. Aggressive treatment of CVD and modifiable cardiovascular risk factors should be instituted in this population.

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