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The Association Between Kidney Disease and Cardiovascular Risk in a Multiethnic Cohort:

Findings From the Northern Manhattan Study (NOMAS)

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Abstract

Background and Purpose—The objective of this study was to determine the relationship between chronic kidney disease (CKD), race–ethnicity, and vascular outcomes.

Methods—A prospective, multiracial cohort of 3298 stroke-free subjects with 6.5 years of mean follow-up time for vascular outcomes (stroke, myocardial infarction, vascular death) was used. Kidney function was estimated using serum creatinine and Cockcroft-Gault formula. Cox proportional hazards models were fitted to evaluate the relationship between kidney function and vascular outcomes.

Results—In multivariate analysis, Cockcroft-Gault formula between 15 and 59 mL/min was associated with a significant 43% increased stroke risk in the overall cohort. Blacks with Cockcroft-Gault formula between 15 and 59 mL/min had significantly increased risk of both stroke (hazard ratio, 2.65; 95% CI, 1.47 to 4.77) and combined vascular outcomes (hazard ratio, 1.59; 95% CI, 1.10–2.92).

Conclusion—Chronic kidney disease is a significant risk factor for stroke and combined vascular events, especially in blacks.

Keywords

cardiac; chronic kidney disease; epidemiology; outcome; risk factors; stroke

Over the next decade, the worldwide epidemic of chronic kidney disease (CKD) will result in a continued increase in the number of individuals with decreased kidney function,1 a doubling in the number of patients with end-stage renal disease2 and a subsequent increase in morbidity and mortality related to CKD complications. Increased risk of cardiovascular disease (CVD) and CVD-related mortality is an important complication of CKD. As kidney

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Disclosures
None.

function decreases, CVD risk increases exponentially; in the setting of other risk factors for CVD (ie, hypertension or diabetes), CKD confers a higher CVD risk than that in those patients without CKD.3 Although substantial investigations have been conducted on the relationship between CKD and CVD risk, it remains unclear if an independent association with stroke exists. Most investigations have included stroke as part of an aggregate cardiovascular end point, and studies that have evaluated stroke as a separate outcome have been conflicting.4,5

CVD epidemiology also differs by race–ethnicity;[6,7] however, this relationship has not been completely elucidated in populations with CKD. In this regard, studies have noted that in patients with CKD, paradoxical relationships exist between CVD risk factors, race, and survival. Investigations of cardiovascular outcomes in Hispanics with CKD have demonstrated lower overall cardiovascular risk compared to non-Hispanics, although stroke risk was not independently investigated.[8] Likewise, although blacks with CKD are known to have an increased risk of cardiovascular events compared to whites with CKD, the association for stroke is unclear.[4,9] Therefore, it is particularly important to further investigate and identify race-specific risk and risk factors for stroke to promote more effective race-specific CVD risk reduction.

In this study, we used the multiethnic composition of the Northern Manhattan Study (NOMAS) to investigate the association between CKD and incident stroke and cardiovascular events, as well as the possible influences of race–ethnicity in modulating any such relationship.

Materials and Methods

Cohort

The NOMAS is a prospective population-based study designed to document the incidence of stroke, identify novel risk factors, and investigate stroke prognosis in a multiethnic urban community (63% Hispanic, 20% black, and 15% white). The methods of subject recruitment and enrollment into NOMAS have been described elsewhere.[10] In brief, community participants were eligible if they: (1) never had stroke diagnosed; (2) were age 40 years or older; and (3) resided for at least 3 months in a household with a telephone in Northern Manhattan. Between 1993 and 2001, 3298 subjects were enrolled All subjects were followed-up annually by telephone starting in 1998 to gather information regarding incident cardiovascular events.10

Assessment of Kidney Function

Subjects were eligible for this investigation if they had laboratory data to assess kidney function, had a creatinine clearance (CCl) >15 mL/min, and were not using renal replacement therapy (dialysis or kidney transplant). Kidney function was determined by both serum creatinine (Scr) and CCl derived from the Cockcroft-Gault formula[11]:

Cockcroft-Gault CCl=(140–age)/(Scr)×(weight/72)×(0.85 for women).

CKD was defined as CCl between 15 and 59 mL/min.

Statistical Analyses

Statistical analyses were conducted on SAS 8.2 software (SAS Institute, Cary, NC). The Student *t* test or ANOVA were used to analyze continuous data, and χ^2 test was used for categorical data. Univariate and multivariate Cox models were used to evaluate the association between kidney function and incident stroke (ischemic and hemorrhagic) and combined vascular events (stroke, MI, and vascular death). Confounding variables in

multivariate analysis included age, gender, race–ethnicity, education, hypertension, serum LDL levels, diabetes, history of cardiac disease, cigarette smoking, and moderate alcohol consumption.

Results

The NOMAS cohort included 3298 subjects. Baseline Scr levels were available for 3037 subjects; 23 subjects with a CCl <15 mL/min were excluded, bringing the cohort to 3014 subjects. Mean follow-up time was 6.5 years; mean age was 69 years; and most participants were women (63%). The group consisted of 52% Hispanics, 25% blacks, and 21% whites, and >32% had CKD. Table 1 describes the distribution of covariates by race–ethnicity. Hispanics had the lowest prevalence of kidney dysfunction. Hispanics and blacks had the highest prevalence of hypertension and diabetes, whereas whites had the highest prevalence of heart disease. The Figure shows the prevalence of CKD stratified by both race–ethnicity and age. Older Hispanics had significantly less CKD than age-stratified peers, and CKD prevalence in blacks notably exceeded that of other race–ethnic groups in the sixth decade.

There were 177 ischemic strokes, 24 intracerebral hemorrhages, 179 MI, and 285 vascular deaths documented. Hazard ratios for the association between CKD and incident stroke and combined vascular outcomes are summarized in Table 2. For the combined cohort in multivariate hazard analysis, Scr had a significant relationship with combined outcomes, as did CCl (15 to 59 mL/min for stroke). Inclusion of confounders attenuated the association between CKD and all outcomes for Hispanics and whites. For blacks, Scr and CCl remained significant predictors of incident stroke and combined cardiovascular events after adjustment. We did not find a significant interaction between race–ethnicity and CKD for either outcome.

Discussion

We found that in a multiethnic cohort, CKD maintained a robust association with CVD, even after adjustment for multiple risk factors causally related to both CKD and CVD. We also demonstrated that prevalence rates of CKD are not equivalent across different race-ethnic groups.

Differences in CVD-related morbidity and mortality among race–ethnic groups are of particular interest to this investigation. In multivariate analysis, blacks with CKD had a 2.65-fold increased risk of incident stroke and a 59% increased risk of incident vascular events, the former being a novel finding. The elevated burden of CVD in blacks compared to whites has been attributed to increased cardiovascular risk factor clustering in conjunction with their undertreatment.[12] The addition of CVD risk factors to multivariate models did attenuate the association between CKD and combined CVD outcomes for blacks, suggesting a substantial burden of disease could be averted with better CVD risk factor control in this population. However, multivariate adjustment did not attenuate the relationship between CKD and stroke in blacks, suggesting a robust relationship with causal mechanisms that require further elucidation. It is also noteworthy that after multivariate adjustment, the increased association between CKD and risk of stroke and cardiovascular events for Hispanics was no longer significant. Other studies have demonstrated a lower risk of cardiovascular events compared to that of whites with CKD.[8] However, those Hispanic populations were of different genetic admixture than predominantly Caribbean-Hispanics enrolled in our study.

This study has several limitations. NOMAS did not measure proteinuria, both a marker of CKD and a known risk factor for CVD, which may have resulted in an underestimation of

the association between CKD and CVD. Furthermore, CKD classification was based on a single Scr measurement; thus, we were unable to assess the impact of changing kidney function on outcomes. Last, this study was not designed to measure the association between CKD and cardiovascular outcomes, and it may have been underpowered to determine the modulating effect of CKD on CVD risk across the three race–ethnic groups.

Despite these limitations, our data demonstrate the impact of CKD on CVD risk in an inner city population that is unique from other community-based cohorts with respect to race–ethnic composition, socioeconomic status, and access to medical care. This study is the first to our knowledge to measure CKD prevalence rates and to evaluate the association of CKD with CVD in the Caribbean-Hispanic community. Finally, our study clearly demonstrates that CKD is an independent risk for incident stroke and combined vascular events in blacks.

Conclusions

In a multiethnic, prospective, cohort study, we demonstrated that Caribbean-Hispanics had the lowest prevalence of CKD, that kidney dysfunction was associated with incident stroke and vascular events, and that CKD was an independent risk factor for incident stroke and vascular events in blacks. This has significant public health implications, especially in blacks, given the expected increase in CKD incidence and prevalence over the next decade.[1,2] Further investigations are needed to determine the mechanisms by which CKD modulates stroke risk in this population. Until specific treatments are available that lower stroke risk in patients with CKD, aggressive control of traditional risk factors for stroke and CVD are recommended.

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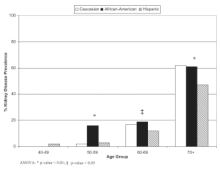

Figure.
Prevalence of kidney disease in the NOMAS cohort stratified by race-ethnicity and age.

Table 1

Baseline Characteristics of Cohort by Race

	White (n=639)	Black (n=740)	Hispanic (n=1566)	*P*
Events				
Stroke, N (%)	43 (6.7)	68 (9.2)	89 (5.7)	<0.001
Combined vascular, N	142 (22.2)	176 (23.8)	191 (12.1)	<0.001
Age, yr (SD)	74 (10)	72 (10)	66 (9)	<0.001
				<0.001
Female, N (%)	369 (58)	500 (68)	980 (63)	
Male, N (%)	270 (42)	240 (32)	586 (37)	
Medical history				
Any heart disease, N (%)	204 (32)	168 (23)	321 (21)	<0.001
Hypertension, N (%)	417 (65)	586 (79)	1167 (75)	<0.001
Diabetes, N (%)	93 (15)	183 (25)	371 (24)	<0.001
Behavioral				
Former smoker, N (%)	280 (44)	269 (36)	543 (35)	<0.001
Current smoker, N (%)	74 (12)	165 (22)	229 (15)	<0.001
Moderate alcohol consumption, N (%)	275 (43)	234 (32)	456 (29)	<0.001
Completed high school, N (%)	526 (82)	469 (63)	354 (23)	<0.001
SBP, mm Hg, mean (SD)	141 (20)	147 (21)	144 (21)	<0.001
DBP, mm Hg, mean (SD)	79 (11)	84 (12)	84 (11)	<0.001
LDL, mg/dL, mean (SD)	132 (35)	126 (37)	130 (36)	<0.023
Kidney function parameters				
Prevalence of CCI 15–59 mL/min, N (%)	291 (46)	319 (43)	335 (21)	<0.001
Creatinine, mg/dL, mean (SD)	1.0 (0.3)	1.0 (0.3)	0.9 (0.3)	<0.001
Creatinine clearance, mL/min, mean (SD)	68 (30)	69 (27)	80 (27)	<0.001

Table 2

Hazard Ratio for Outcomes in Patients in the Both Univariate and Multivariate Models

	Univariate Models			
	Hazard Ratio (95% Cl) Serum Creatinine (per mg/dL)	***P***	**Hazard Ratio (95% Cl) CCI (15–59 mL/min)**	***P***
Stroke				
All	1.87 (1.45–2.43)	<0.001	1.95 (1.48–2.57)	<0.001
Caucasian	2.17 (0.82–5.70)	<0.117	1.56 (0.85–2.85)	<0.148
Hispanic	1.78 (1.26–2.53)	<0.001	1.65 (1.05–2.60)	<0.030
Black	1.81 (1.06–3.11)	0.031	2.55 (1.56–4.18)	<0.001
All vascular events				
All	1.93 (1.65–2.25)	<0.001	2.36 (1.99–2.81)	<0.001
White	2.84 (1.73–4.67)	<0.001	1.96 (1.40–2.75)	<0.001
Hispanic	1.75 (1.36–2.24)	<0.001	2.08 (1.54–2.79)	<0.001
Black	1.88 (1.35–2.61)	<0.001	2.35 (1.74–3.19)	<0.001
	Multivariate Models*			
	Hazard Ratio (95% Cl) Serum Creatinine (per mg/dL)	*P*	Hazard Ratio (95% Cl) CCI (15–59 mL/min)	*P*
Stroke				
All	1.38 (0.94–2.02)	<0.098	1.43 (1.02–2.02)	<0.040
White	0.91 (0.24–3.40)	<0.888	1.08 (0.50–2.34)	<0.847
Hispanic	1.33 (0.81–2.19)	<0.264	0.93 (0.54–1.60)	<0.803
Black	1.58 (0.85–2.95)	<0.150	2.65 (1.47–4.77)	<0.001
All vascular events				
All	1.34 (1.06–1.76)	<0.015	1.20 (0.97–1.50)	<0.098
White	1.55 (0.80–3.01)	<0.195	1.12 (0.73–1.72)	<0.595
Hispanic	1.24 (0.85–1.82)	<0.269	0.93 (0.65–1.33)	<0.686
Black	1.51 (1.00–2.27)	<0.051	1.59 (1.10–2.92)	<0.014

*Adjusted for age, gender, education, hypertension, LDL cholesterol, diabetes, prevalent cardiac disease, smoking, and alcohol consumption.