Lowest Systolic Blood Pressure Is Associated with Stroke in Stages 3 to 4 Chronic Kidney Disease

Daniel E. Weiner,* Hocine Tighiouart,† Andrew S. Levey,* Essam Elsayed,* John L. Griffith,† Deeb N. Salem,‡ and Mark J. Sarnak*

*Division of Nephrology, †Department of Clinical Care Research, and ‡Division of Cardiology, Tufts-New England Medical Center, Boston, Massachusetts

Hypertension is a risk factor for stroke in the general population, whereas in hemodialysis patients, higher systolic BP (SBP) may be protective. Therefore, this study evaluated the relationship between SBP and stroke in individuals with and without chronic kidney disease (CKD) to assess whether this altered relationship exists in earlier stages of CKD. A secondary evaluation of two community-based, longitudinal, limited-access data sets was performed: Atherosclerosis Risk in Communities and Cardiovascular Health Study. CKD was defined as estimated GFR <60 ml/min per 1.73 m^2. The primary study outcome was definite or probable incident stroke. We used Cox proportional hazards models to assess the relationship between CKD and stroke, focusing on the role of SBP. Among 20,358 individuals studied, 1549 (7.6%) had CKD. During a median duration of 111 mo, 1029 (5.1%) individuals had a stroke. CKD and elevated SBP both independently predicted incident stroke (hazard ratio [HR] 1.22 [95% confidence interval [CI]1.02 to 1.44] and HR 1.18 [95% CI 1.14 to 1.21] per 10-mmHg rise, respectively). Individuals with CKD had a J-shaped relationship with stroke outcomes such that those with SBP <120 mmHg were at significantly increased risk compared with individuals with CKD and SBP 120 to 129 mmHg (HR 2.51; 95% CI 1.30 to 4.87); risk increased for BP >130 mmHg in CKD. This J shape was not seen in individuals without CKD. CKD and elevated SBP are independent risk factors for incident stroke. In CKD, individuals with the lowest BP are at increased risk for stroke. This pattern is not seen in the general population.

J Am Soc Nephrol 18: 960–966, 2007. doi: 10.1681/ASN.2006080858

Chronic kidney disease (CKD) is an important public health problem in the United States, especially in the elderly. It is estimated that 20 million Americans have CKD, and, with the aging of the US population as well as the increasing incidence of diabetes and hypertension, the prevalence of CKD will increase (1).

Hypertension, notably elevated systolic BP (SBP), is a risk factor for stroke in the general population. In addition, hypertension is a major component of CKD, both as a cause and a result of impaired kidney function. Furthermore, chronic hypertension may represent an important causal pathway between kidney disease and increased cardiovascular disease outcomes in CKD, including stroke (2). However, many factors that increase cardiovascular disease risk in the general population seem to be either protective or associated with an altered risk factor pattern in dialysis patients (3–6). This phenomenon remains poorly understood, and few investigations have evaluated its presence in earlier stages of CKD.

Stroke is the third leading cause of mortality in the United States and is defined as a rapid onset central neurologic deficit that either lasts more than 24 h or results in death (7). Although stroke and stroke risk factors have not been studied extensively in CKD, there are numerous investigations of BP and stroke in the general population. Although several studies have shown a J-shaped relationship with small increases in stroke risk at the lowest SBP, most have demonstrated reduced stroke risk even at the lowest BP, such that every 10-mmHg lower SBP is associated with a one-third lower risk for stroke in the elderly (8). Both elevated SBP and diastolic BP (DBP) seem to be predictive of stroke in the general population, although SBP is considered the better measure (8,9). To evaluate these potentially conflicting trends, we used patient-level data from a pooled data set of community-based studies to investigate stroke risk factors, focusing on the relationship between SBP and stroke outcomes in individuals with CKD.

Materials and Methods

Study Design

We performed a secondary evaluation of two community-based, longitudinal, limited-access data sets: Atherosclerosis Risk in Communities Study (ARIC) and Cardiovascular Health Study (CHS). These studies were designed to have similar data ascertainment, and pooling these population-based studies allows for evaluation of a diverse group

Received August 14, 2006. Accepted December 28, 2006.

Published online ahead of print. Publication date available at www.jasn.org.

The ARIC Study and CHS are conducted and supported by the National Heart, Lung, and Blood Institute (NHLBI) 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 NHLBI.

Address correspondence to: Dr. Daniel E. Weiner, Division of Nephrology, Box 391, Tufts-New England Medical Center, Boston, MA 02111. Phone: 617-636-5070; Fax: 617-636-2369; E-mail: dweiner@tufts-nemc.org

ISSN: 1046-6673/1803-0960

of individuals in a wide age range while increasing the number of patients with CKD.

Study Population

Between 1987 and 1989, ARIC enrolled 15,792 participants aged 45 to 64 yr from four communities. CHS is a population-based study of 5201 patients who were 65 yr and older and randomly selected from Medicare eligibility files during 1989 and 1990 also from four communities. CHS recruited an additional 687 black patients in 1992 and 1993 (10,11).

Ascertainment of Level of Kidney Function

We quantified kidney function using GFR estimated with the four-variable Modification of Diet in Renal Disease (MDRD) study equation, after calibrating the ARIC and CHS laboratories indirectly using Third National Health and Nutrition Examination Survey (NHANES III) data (12–15). CKD was defined as estimated GFR <60 ml/min per 1.73 m^2 (1). Patients with stage 5 CKD (GFR <15 ml/min per 1.73 m^2) were excluded.

Baseline Variables

Baseline characteristics included demographics (age, gender, race, and education level), lifestyle (smoking and alcohol), medical history (baseline coronary disease, diabetes, and stroke), physical findings (SBP and left ventricular hypertrophy), and laboratory variables (total cholesterol, HDL cholesterol, creatinine, albumin, and hemoglobin). Methods that were used for baseline data collection by each of these studies have been previously described (10,11). BP in CHS was measured in the right arm of seated participants after a 5-min rest using a random-zero sphygmomanometer; the first and second readings were averaged. ARIC investigators averaged the second and third measurements with a random-zero sphygmomanometer. Left ventricular hypertrophy was defined using resting 12-lead electrocardiogram based on voltage criteria and characteristic S-T segment or T-wave changes (16).

Race was defined as white or black. Education level was dichotomized by high school graduation status. Cigarette smoking and alcohol use were dichotomized as current users and nonusers. Diabetes was defined by use of insulin or oral hypoglycemic medications or fasting glucose ≥126 mg/dl. Hypertension was defined by SBP ≥140 mmHg, DBP ≥90 mmHg, or use of antihypertensive medications.

Baseline coronary heart disease included a history of both recognized and silent myocardial infarction and angioplasty and coronary bypass procedures. Baseline stroke was defined by consensus committees in each study on the basis of patient report and confirmation from appropriate medical records (10,11).

Study Sample

We excluded 434 (2.0%) patients for missing GFR or GFR <15 ml/min per 1.73 m^2. An additional 874 (4.1%) individuals with either history of stroke or missing stroke status at baseline were excluded from further analyses as were 14 individuals with missing SBP, yielding a final cohort of 20,358 individuals.

Outcomes

The primary study outcome was definite or probable incident stroke. In ARIC, a consensus committee defined stroke as sudden or rapid onset of neurologic symptoms that lasted for >24 h or led to death in the absence of evidence of a nonstroke cause (17,18). In CHS, the Cerebrovascular Adjudication Committee was composed of study neurologists from each of the four study sites, a neuroradiologist from the MRI Reading Center, and an internist or neurologist who represented the Coordinating Center. On the basis of patient data, including medical records, physicians' outpatient records, death certificates, obituaries, and the Health Care Financing Administration health care utilization database for hospitalizations as well as neuroimaging studies in 86% of possible strokes, the adjudication committee decided whether a transient ischemic attack, nonfatal stroke, or fatal stroke had occurred and assigned a stroke subtype (19).

Statistical Analyses

The goal of our analysis was to determine the relationship between baseline SBP and incident stroke in individuals with and without CKD. First, we tested the effects of CKD and SBP in (*1*) univariate models, (*2*) parsimonious models that included only terms for CKD and linear SBP, and (*3*) fully adjusted Cox proportional hazards models. Then we stratified SBP into five predetermined, clinically relevant strata (<120, 120 to 129, 130 to 139, 140 to 159, and ≥160 mmHg) and performed three analyses: (*1*) Risk associated with SBP groups in individuals with CKD and in individuals without CKD using parsimonious Cox proportional hazards models that contained terms only for BP groups, (*2*) risk associated with SBP groups in individuals with CKD and in individuals without CKD in fully adjusted multivariable models, and (*3*) risk associated with SBP groups first in the parsimonious and then in the fully adjusted model using dummy variables for BP groups by CKD status to conceptualize the risk associated with hypertension in those with and without CKD within a single model. Fully adjusted models were fitted using potential clinically significant predictors of incident stroke listed in the Baseline Variables section. A term for study of origin (CHS *versus* ARIC) was forced into all fully adjusted models. The proportional hazards assumption was satisfied.

Sensitivity Analyses

Subgroup analyses examined whether the results were affected by baseline use of antihypertensive medications, baseline coronary heart disease, and study of origin. We also examined models using only ischemic stroke as an outcome (we lacked sufficient events to examine hemorrhagic stoke separately). Last, we examined the impact of atrial fibrillation on outcomes by adjusting for atrial fibrillation exclusively in the CHS cohort, because patient-level atrial fibrillation data were not available in the ARIC limited-access data set. Data were analyzed using SAS Version 9.1 (SAS Institute, Cary, NC).

Results

Among the 20,358 individuals studied, mean age was 59.2 ± 10.2 yr, and 1549 (7.6%) had CKD (Table 1). Mean SBP at baseline was 125.3 ± 20.7 mmHg; 9359 (46.0%) individuals had hypertension, and, of these, 6990 (34.3%) were on antihypertensive medications. Individuals with CKD were more likely to be on antihypertensive medications than those without CKD, and antihypertensive medication use increased as SBP increased (Table 2). During a median duration of 111 mo, 1029 (5.1%) individuals had a stroke. There were 875 (4.3%) ischemic strokes and 129 (0.6%) hemorrhagic strokes (Table 3), with the remainder of uncertain cause.

In univariate analysis, each 10-mmHg rise in SBP was associated with a 35% increased risk for stroke (hazard ratio [HR] 1.35 [95% confidence interval (CI) 1.31 to 1.38]), and individuals with CKD had more than three times the risk for stroke of those without CKD (HR 3.23 [95% CI 2.76 to 3.78]). In parsimonious multivariable models that included terms for only CKD and SBP, both factors were associated with incident stroke (HR_{CKD} 2.38 [95% CI 2.01 to 2.77] and HR_{SBP} 1.32 [95% CI 1.29 to 1.35]

Table 1. Baseline demographics and study outcomes stratified by kidney disease status[a]

Characteristic	CKD (n = 1549; 7.6%)	Non-CKD (n = 18,809; 92.4%)
Demographics		
age (yr)	70.2 ± 10.3	58.3 ± 9.7
black race	214 (13.8%)	4589 (24.4%)
female gender	883 (57.0%)	10,490 (55.8%)
high school graduate	1072 (69.4%)	14,183 (75.6%)
CHS cohort	1137 (73.4%)	4306 (22.9%)
Medical history		
diabetes	278 (17.9%)	2159 (11.5%)
hypertension	1139 (73.5%)	8220 (43.7%)
coronary disease	226 (14.6%)	968 (5.2%)
hypertension medication	947 (61.1%)	6043 (32.1%)
cigarette use	214 (13.8%)	4338 (23.1%)
alcohol use	732 (47.4%)	10,379 (55.4%)
Physical findings		
SBP (mmHg)	135.2 ± 23.7	124.5 ± 20.3
DBP (mmHg)	71.5 ± 12.0	73.1 ± 11.4
BMI (kg/m^2)	27.2 ± 4.6	27.3 ± 5.1
LVH	92 (6.2%)	445 (2.4%)
Laboratory results		
serum creatinine (mg/dl)	1.3 ± 0.4	0.8 ± 0.2
eGFR (ml/min per 1.73 m^2)	51.2 ± 8.4	92.2 ± 19.2
serum albumin (g/dl)	3.9 ± 0.3	3.9 ± 0.3
non-HDL cholesterol (mg/dl)	163.9 ± 44.1	161.2 ± 42.9
hemoglobin (g/dl)	13.8 ± 1.6	13.9 ± 1.4
Outcomes		
all-cause stroke	191 (12.3%)	838 (4.5%)
ischemic stroke	163 (10.5%)	712 (3.8%)
hemorrhagic stroke	22 (1.4%)	107 (0.6%)
follow-up time (mo)	105.6 (59.6)	111.1 (22.1)
stroke rate[b]	16.1	5.0

[a]Categorical variables are presented as n (%) and continuous variables as mean ± SD except follow-up time, which is median (interquartile range). Because of missing data, not all rows add to 20,358. All P values were statistically significant ($P < 0.05$) except female gender and BMI. BMI, body mass index; CHD, Cardiovascular Health Study; CKD, chronic kidney disease; DBP, diastolic BP; eGFR, estimated GFR; LVH, left ventricular hypertrophy; SBP, systolic BP.
[b]Stroke rate refers to incident strokes per 1000 person-years.

Table 2. Individuals using antihypertensive medications by CKD status and BP group[a]

CKD Status	SBP (mmHg; n [%])				
	<120	120 to 129	130 to 139	140 to 159	≥160
CKD	209 (50.2)	173 (62.7)	151 (59.9)	246 (66.3)	168 (71.8)
Non-CKD	1876 (22.0)	1214 (32.2)	1104 (41.0)	1232 (45.1)	617 (56.0)

[a]$P < 0.0001$ for all within–BP group comparisons.

per 10-mmHg rise). In fully adjusted models, both CKD and SBP were independent risk factors for stroke (HR 1.22 [95% CI 1.02 to 1.44] and HR 1.18 [95% CI 1.14 to 1.21] per 10-mmHg rise, respectively).

When BP groups were used in unadjusted subgroup analyses, individuals without CKD had a more linear relationship between SBP and incident stroke, whereas individuals with CKD had a J-shaped relationship such that there was a trend to increased risk for stroke (HR 1.59 [95% CI 0.85 to 2.96]) when comparing individuals with SBP <120 mmHg with the reference group (SBP between 120 and 129 mmHg). When a term for age was added to this model, the association between the

Table 3. Stroke events by CKD status and BP group[a]

Parameter	SBP Group (mmHg)					Total
	<120	120 to 129	130 to 139	140 to 159	≥160	
CKD	$n = 416$	$n = 276$	$n = 252$	$n = 371$	$n = 234$	$n = 1549$
strokes per 1000 person-years	10.0	6.3	13.7	22.4	35.9	15.1
events (*n*)						
total	34	14	28	60	55	191 (12.3%)
ischemic	27	13	26	50	47	163 (10.5%)
hemorrhagic	4	1	2	8	7	22 (1.4%)
Non-CKD	$n = 8518$	$n = 3776$	$n = 2694$	$n = 2729$	$n = 1102$	$n = 18,809$
strokes per 1000 person-years	2.3	4.1	6.4	9.6	17.2	5.0
events (*n*)						
total	174	138	153	224	149	838 (4.5%)
ischemic	143	116	136	196	121	712 (3.8%)
hemorrhagic	27	18	18	23	21	107 (0.6%)

[a]Hemorrhagic and ischemic stroke events may not equal the total number of strokes because 42 strokes ($n = 10$ for CKD) were not able to be classified definitively as ischemic or hemorrhagic and 17 ($n = 4$ for CKD) individuals had both ischemic and hemorrhagic strokes at disparate follow-up times.

lowest BP group in individuals with CKD and incident stroke reached statistical significance when compared with individuals with CKD in the reference group (HR 2.03 [95% CI 1.09 to 3.78]). In fully adjusted subgroup analyses of only individuals with CKD, the J shape persisted, such that individuals who had CKD and SBP <120 mmHg were at significantly increased risk for incident stroke compared with individuals with CKD in the reference group (HR 2.26 [95% CI 1.16 to 4.41]). In models that examined the entire population, individuals with CKD and SBP <120 mmHg remained at significantly increased risk for incident stroke when compared with individuals with CKD in the reference group (HR 2.51 [95% CI 1.30,4.87]; Figure 1).

Sensitivity Analyses

In multivariable analysis of individuals with CKD, those who were in the lowest SBP group and using antihypertensive medications had significantly increased risk for incident stroke (HR 2.62 [95% CI 1.22 to 5.66]) compared with the reference group of individuals with CKD and SBP 120 to 129 mmHg. Among the 602 individuals who had CKD and were not on antihypertensive medications, there were only 58 incident strokes. In these individuals, there was no statistically significant increased risk for incident stroke for those with CKD in the lowest BP group as compared with the reference group (HR 2.26 [95% CI 0.61 to 8.39]). Notably, in individuals without CKD, risk for stroke progressively increased in each BP group regardless of baseline antihypertensive medication use.

Among individuals without baseline coronary heart disease, those with CKD and SBP <120 mmHg remained at significantly increased risk for incident stroke when compared with individuals with CKD and SBP of 120 to 129 mmHg in fully adjusted models (HR 2.25 [95% CI 1.10 to 4.59]). A similar trend was seen for individuals with baseline coronary heart disease, CKD, and SBP <120 mmHg (HR 5.30 [95% CI 0.67 to 42.0]).

Models that examined individuals stratified by study showed similar patterns of increased risk in individuals with CKD in the lowest BP group, although this achieved statistical significance only in the CHS subgroup (HR 2.54 [95% CI 1.18 to 5.47] and HR 1.70 [95% CI 0.46 to 6.29] for individuals with CKD in the lowest BP group compared with individuals with CKD in the reference BP group in CHS and ARIC, respectively).

Models that examined only ischemic stroke also had similar relationships to those just described (data not shown). In addition, in a model that included a term for atrial fibrillation in the CHS cohort, HR that were associated with BP groups were similar to those that were seen in the full model (data not shown).

Discussion

In this study, we found that hypertension was an independent risk factor for incident stroke in individuals with and without CKD; however, individuals who had CKD and were in the lowest BP group were also at increased risk for incident stroke when compared with those with SBP of 120 to 129 mmHg, whereas for individuals without CKD, risk for stroke was increased as SBP rose at all BP levels. These differences may reflect imbalances in BP therapy in individuals with and without CKD, differences in overall cardiovascular disease burden, and/or undiagnosed systolic dysfunction in CKD.

Hypertension is an important risk factor for cardiovascular and cerebrovascular disease. In the general population, the risk for stroke doubles with each incremental rise of 20/10 mmHg above a baseline BP of 115/75 mmHg (8). At elevated BP, this relationship also holds true for individuals with CKD; however, at the lowest SBP, the relationship between risk factors and outcomes in patients with CKD seems to be different from that seen in the general population. A similar but more marked pattern of increased survival associated with higher BP, higher cholesterol, and higher body mass index has been described in

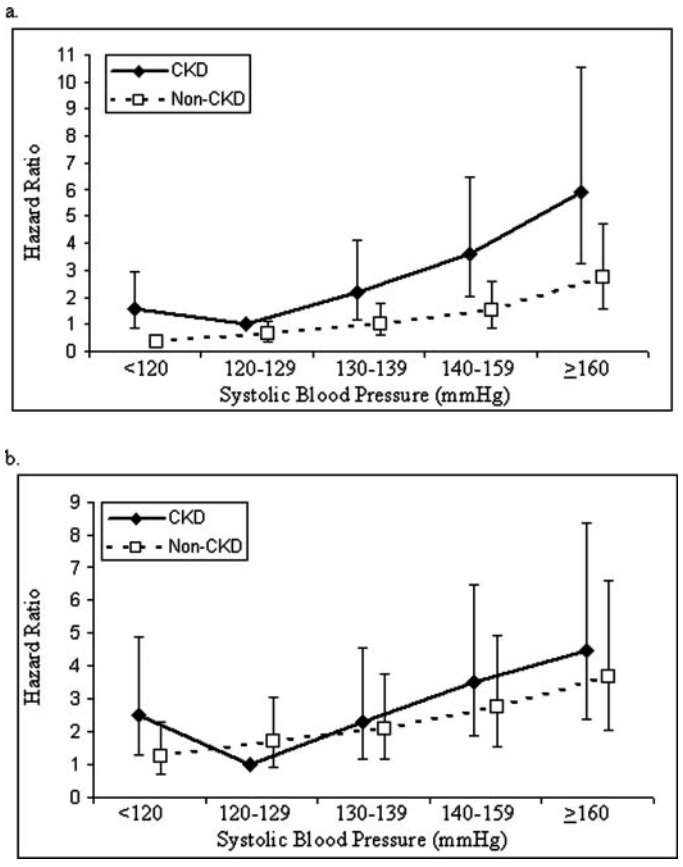

Figure 1. The hazard of incident stroke associated with systolic BP (SBP) and chronic kidney disease (CKD) using an unadjusted model that contained dummy variables for CKD and BP groups (A) and a fully adjusted model that contained dummy variables for CKD and BP groups (B; model adjusted for age, race, gender, history of diabetes, history of coronary disease, left ventricular hypertrophy, use of antihypertensive medication, education status, smoking status, serum albumin, non-HDL cholesterol, hemoglobin, and study of origin). Reference group is individuals with CKD and SBP 120 to 129 mmHg.

the dialysis population, using the term "reverse epidemiology" (3–6,20,21). Rather than reflecting different pathophysiology, it may be that these altered relationships are due to confounding from other comorbid conditions, including cardiomyopathy and malnutrition, such that BP and cholesterol levels decrease as patients become progressively more infirm (20). In these cases, lower BP could seem harmful but actually be a proxy for poor health status and overall cardiovascular disease burden. Therefore, reduced BP may indicate individuals at higher risk, rather than being a cause of stroke.

For incident stroke events, this study suggests that this altered relationship is not unique to dialysis but rather begins in earlier stages of CKD. One possibility is that changes in BP that occur during earlier stages of CKD preface overt development of heart disease and systemic vascular disease, thereby accounting for the altered risk relationship that was seen in this study. For better understanding of this relationship, studies that examine changes in BP levels and therapy as kidney disease and associated conditions progress will be necessary.

Several studies have specifically examined kidney disease as a risk factor for stroke. Most recently, a secondary analysis of the Bezafibrate Infarction Prevention Trial demonstrated that CKD is an independent risk factor for stroke (22). Manolio *et al.* (23) used baseline data from CHS with 3.5 yr of follow-up and found an increased risk for stroke (HR 1.77 [95% CI 1.08 to 2.91]) with serum creatinine levels ≥1.5 mg/dl; however, this study did not specifically focus on CKD. Wannamethee *et al.* (24) examined a cohort of men in the British Regional Heart Study and found a significantly increased risk for stroke in individuals with the highest 10% of serum creatinine levels (relative risk 1.6 [95% CI 1.1 to 2.1]). In the ARIC Study, individuals with reduced creatinine clearance and anemia were at increased risk for stroke. However, this analysis did not focus on the role of hypertension (25). Our study confirms these previous findings and expands on their generalizability, because few studies have specifically examined the relationship between BP and incident stroke in a population-based CKD cohort.

This study has several weaknesses. We do not have data on proteinuria and therefore are unable to include this factor in our analysis. We also do not have data on atrial fibrillation in ARIC; however, a previous article by ARIC investigators (17) stated that fewer than 30 individuals had atrial fibrillation at baseline in ARIC and only two of these developed a stroke in 12 yr of follow-up. Therefore, we do not believe that this would have a significant impact on our results. Second, in univariate analysis, there was only a trend to increased risk for stroke in individuals with CKD in the lowest BP category compared with those with CKD and SBP of 120 to 129 mmHg. However, once age was added to these models, a statistically significant difference was seen. We believe that the multivariable model more accurately represents truth, because any assessment of the interrelationship among SBP, stroke, and kidney disease would be incomplete if age were not accounted for. There may be inherent study differences between CHS and ARIC, as indicated by the absence of a statistically significant increased risk for stroke events for individuals who had CKD and were in the lowest SBP group that originated in ARIC; however, there was a trend toward increased risk in the ARIC cohort, and pooling of these cohorts allows for improved power to examine other subgroups. Furthermore, we evaluated only baseline SBP and antihypertensive medication use; this may not capture important information that is reflected in changes in antihypertensive regimens during the follow-up period. In addition, both SBP and CKD are categorized by baseline values. Although these individuals are clinically stable at enrollment, misclassification may have resulted; however, this would most likely bias results to the null and therefore would be more concerning if our investigation were negative. Finally, this study is most applicable to stage 3 CKD, and relationships may be different in individuals with more advanced kidney disease.

It is interesting that we found that in all analyses, the use of antihypertensive medications was associated with an increased risk for stroke, although we lacked power in individuals who had CKD and were not on antihypertensive medications to demonstrate more than a weak trend. Although individuals

with the lowest BP and CKD were less likely to be on antihypertensive medications than other individuals with CKD, nearly half of individuals with CKD and lower BP were on antihypertensive medications. Given the finding of increased stroke risk among individuals who had CKD and SBP <120 mmHg and were on antihypertensive medications, it is possible that this increased risk results from overly aggressive BP treatment; however, the study design cannot adequately support a causal relationship, and it is equally likely that medication use reflects an indication bias, identifying individuals with a greater lifetime cardiovascular disease burden and therefore higher stroke risk.

This study also has several strengths. It uses a population-based, multiracial cohort that likely is generalizable to the US population. In addition, there is thorough event ascertainment because these studies were designed to detect cardiovascular events, including stroke. Finally, we have a substantial number of individuals with CKD and stroke events, allowing us to power adequately multivariable analyses that examined risk factors for stroke outcomes.

Conclusion

The presence of CKD and elevated SBP both are independent risk factors for incident stroke. However, in individuals with CKD, SBP has an altered relationship, such that individuals with the lowest BP are actually at increased stroke risk, whereas individuals with SBP >120 mmHg still remain at increased risk. This pattern is not seen in the general population and may be secondary to increased severity of comorbid conditions in individuals with CKD.

Acknowledgments

This study was supported by NIH NIDDK grants R21 DK068310, K23 DK71636, and T32 DK007777 and Amgen (Thousand Oaks, CA). Study sponsors were not involved in data analysis or interpretation of findings.

This work was presented in abstract form at the annual meeting of the American Society of Nephrology; November 14 through 19, 2006; San Diego, CA.

Disclosures

None.

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