Serum potassium level and dietary potassium intake as risk factors for stroke

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Abstract—*Background:* Numerous studies have found that low potassium intake and low serum potassium are associated with increased stroke mortality, but data regarding stroke incidence have been limited. Serum potassium levels, dietary potassium intake, and diuretic use in relation to risk for stroke in a prospectively studied cohort were investigated. *Methods:* The study comprised 5,600 men and women older than 65 years who were free of stroke at enrollment. Baseline data included serum potassium level, dietary potassium intake, and diuretic use. Participants were followed for 4 to 8 years, and the incidence and types of strokes were recorded. Low serum potassium was defined as less than 4.1 mEq/L, and low potassium intake as less than 2.4 g/d. *Results:* Among diuretic users, there was an increased risk for stroke associated with lower serum potassium (relative risk [RR]: 2.5, $p < 0.0001$). Among individuals not taking diuretics, there was an increased risk for stroke associated with low dietary potassium intake (RR: 1.5, $p < 0.005$). The small number of diuretic users with lower serum potassium and atrial fibrillation had a 10-fold greater risk for stroke compared with those with higher serum potassium and normal sinus rhythm. *Conclusions:* A lower serum potassium level in diuretic users, and low potassium intake in those not taking diuretics were associated with increased stroke incidence among older individuals. Lower serum potassium was associated with a particularly high risk for stroke in the small number of diuretic users with atrial fibrillation. Further study is required to determine if modification of these factors would prevent strokes.

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Numerous studies have implicated low potassium intake and low serum potassium concentration as risk factors for stroke mortality.[1-6] One of the most compelling of these was a 12-year prospective series of more than 800 individuals, in which those in the lowest tertile of potassium intake had substantially higher stroke mortality.[1] However, data regarding the occurrence of stroke in relation to dietary potassium intake and serum potassium level are limited.[7-9] Although the widespread use of diuretics and other antihypertensive medications clearly has been associated with a reduction in stroke risk,[10-17] one concern has been that serum potassium levels may be depressed by their use and that this may alter stroke risk. In one provocative study of U.S. males, potassium supplementation was associated with a lower incidence of stroke among patients taking diuretics,[7] but there has not been a systematic evaluation of the risk for stroke in diuretic users with low serum potassium or with low dietary potassium intake.

The large database of the Cardiovascular Health Study (CHS) allowed us to examine the relationships between the incidence of strokes and both potassium intake and serum potassium levels among older individuals taking, and not taking, diuretics.

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Patients and methods. *Patients.* The CHS is a prospective, multicenter database of 5,888 men and women 65 years of age or older. Participants were selected randomly

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Table 1 *Relative risk (RR) for stroke for serum and dietary potassium treated as continuous variables*

Potassium	RR* (95% CI)	*p* Value	*p* Value for interaction
Serum K (total cohort)			
Nondiuretic User	1.01 (0.88–1.15)	NS	
Diuretic User	1.38 (1.20–1.59)	<0.0001	<0.005
Dietary K (original cohort)			
Nondiuretic User	1.18 (1.04–1.33)	<0.01	<0.005
Diuretic User	0.89 (0.77–1.03)	NS	

These Cox models include age, sex, history of diabetes, hypertension, coronary artery disease, congestive heart failure, atrial fibrillation, systolic blood pressure, serum creatinine, potassium supplement use, and serum potassium in the dietary potassium model.

* Relative risks are for a one standard deviation *decrease* (0.38 mEq/L for serum K and 1.15 g/d for dietary K).

from households on Medicare eligibility lists in four U.S. communities: Forsyth County, NC; Sacramento County, CA; Washington County, MD; and Allegheny County, PA. From 1989 to 1990, 5,201 subjects (referred to as the "original cohort") were recruited and examined, and an additional 687 minority individuals, primarily blacks, were added from 1992 to 1993.[18] Details of the study design and its objectives have been published.[19]

As a part of the initial enrollment testing, a medical history and physical examination were obtained, documenting age, sex, race, and history of hypertension, diabetes, coronary artery disease, and congestive heart failure. Each of these medical conditions was determined by questioning and examining the participants and by reviewing their medical records. Information on medications, including diuretic and potassium supplement use, was obtained by a thorough medication inventory, in which the participants were asked to bring to the clinic all medications they were taking.[20] This method of collecting medication data has been shown to be more reliable than direct questioning and is sensitive for the cardiovascular drugs of interest.[21] Dietary potassium intake was determined by a commonly used food frequency questionnaire developed by the National Cancer Institute from the original cohort only.[22-24] The questionnaire was administered at a single point in time on enrollment in the study, in a two-step, partly self-administered fashion. In quality-control experiments, this method of administration was found to be of similar reliability to other food frequency questionnaires. Baseline testing included a fasting blood sugar, potassium, and creatinine levels, an EKG, echocardiogram, and carotid ultrasound studies. Atrial fibrillation was determined from the baseline EKG.

Methods. Incident strokes were ascertained by questions at annual clinic visits and interim telephone interviews every 6 months during which participants were questioned regarding hospitalizations or other acute events. The patient and family were interviewed regarding the details of the stroke onset. The occurrence of an event that potentially may have been a stroke led to a review of hospital records, including admission and discharge notes, results of pertinent tests, and cerebral imaging studies. A panel of neurologists, blinded to CHS entry data, verified the occurrence of stroke and determined its type (atherothrombotic, cardioembolic, lacunar, hemorrhagic, or unclassifiable) based on review of this information and, if the data were unclear, reviewed the case with the patient's physician. The algorithms used for classifying strokes in the study have been described in detail.[25,26] To be categorized as a stroke, the neurologic deficit had to persist for 24 hours, or if less than 24 hours, a lesion appropriate to the clinical deficit must have been detected on brain imaging studies. Transient ischemic attacks were classified separately and not included in the current analysis. Follow-up was complete for 98% of the cohort as of 1996, with a median duration of 7.3 years (maximum 8.0 years) for the original cohort and 4.2 years (maximum 4.6 years) for the minority cohort.

Statistical analysis. Statistical analyses were performed using the SPSS/Windows statistical package (version 8.0, SPSS, Chicago, IL). Cox proportional hazards regression was used to estimate hazard ratios (referred to as relative risks [RR] throughout) for incident stroke. Initial exploratory analyses were done to determine the shape of the hazard ratio function for both serum and dietary potassium. A linear model was initially fit and this fit was compared with a model using quintiles of the potassium variables. If the quintile model showed clear nonlinearity of the risks, this was further explored by breaking the distribution into 20 equal frequency intervals, to determine an optimal cut-point for characterizing the risk associated with potassium levels. Only the final results of this process are displayed in tables 1 and 2.. Based on these analyses, a cut-point of 4.0 mEq/L (the lowest two quintiles) was chosen for serum potassium and a cut-point of 2.34 g/d (the lowest quintile) was chosen for dietary potassium (see tables 2 and 3). In addition, we examined the stroke–potassium association stratified on both a history of hypertension and the use of diuretics. Only the use of diuretics appeared to modify the stroke–potassium association, so the data stratified on a history of hypertension are not presented here.

Adjustment was made in all models for potential confounding factors that were found to be predictors of stroke selected by forward selection in the model involving all strokes and all participants from among the variables (additional material related to this article can be found on the *Neurology* Web site. Go to www.neurology.org and scroll down the Table of Contents for this issue to find the title link for this article). These potential confounding factors were the following: age, sex, race, history of hypertension, diabetes, coronary artery disease, congestive heart failure, atrial fibrillation, and systolic and diastolic blood pressure. Other factors for which adjustment was considered included serum creatinine level, diuretic use, angiotensin-converting enzyme (ACE) inhibitor use, beta blocker use, calcium channel blocker use, and use of potassium supplements. Only those variables found to be significant predictors in the model involving all strokes and all participants were forced into the models for subsets of the sample or specific stroke subtypes. Both baseline serum potassium level and baseline dietary potassium intake level were included in all analyses except those that included the mi-

Table 2 *Relationship of serum potassium levels in quintiles to stroke risk by diuretic use (total cohort)*

	Quintiles of serum potassium in mEq/L					
Diuretic use	2.6–3.8	3.81–4.0	4.01–4.2	4.21–4.4	4.41–5.8	*p* Value
Nonusers of diuretics, n = 3,974,* RR† (95% CI)	1.07 (0.68–1.69)	0.94 (0.63–1.4)	1.07 (0.77–1.49)	1.10 (0.8–1.53)	1.0 (referent)	0.96
Users of diuretics, n = 1,566,* RR† (95% CI)	2.37 (1.33–4.23)	2.21 (1.21–4.03)	0.77 (0.37–1.59)	1.06 (0.53–2.14)	1.0 (referent)	<0.0001

* Participants with missing values on any covariate were excluded (64 from nonuser and 32 from user group). n = number of participants.

† These Cox models included age, sex, history of diabetes, hypertension, coronary artery disease, congestive heart failure, atrial fibrillation, systolic blood pressure, serum creatinine, and use of potassium supplements. Sixty participants were not included in the analysis because they had one or more missing values of the variables included in the model.

RR = relative risk.

nority cohort for which the dietary potassium was not available. All two-way interactions of the potassium variables and the other predictors of stroke risk were examined. When significant interactions were found, separate analyses stratified by the interacting variable were done. Separate Cox model regressions were performed using the various stroke subtypes as the endpoint. In all analyses, death and stroke from a subtype not being used as the endpoint in the analysis were treated as censoring events. Because these analyses were exploratory in nature, all *p* values and confidence intervals should be interpreted accordingly.

Results. We excluded from the analysis 198 participants from the original cohort and 49 participants from the minority cohort who had a history of stroke before entry into the study. Also excluded were 41 participants who had no measurement of either serum or dietary potassium. There remained 5,600 subjects for analysis who were free of stroke on entry (supplementary data related to this article can be found on the *Neurology* Web site). The mean age was 72.8 years, women comprised 58% of the 5,600 participants, and 15% were black. The mean baseline serum potassium level was 4.2 mmol/L and the mean dietary potassium intake was 3.3 g/d at entry. During the period of observation, 473 strokes occurred, 404 of which were ischemic, 50 hemorrhagic (including both subarachnoid and intraparenchymal), and 19 not clearly classifiable (i.e., no MRI or CT data obtained, usually because of early death).

A description of the patients and their characteristics are listed in the supplementary data (go to www.neurology.org and scroll down the Table of Contents to find the title link for this article). The mean systolic and diastolic blood pressures, creatinine level, frequency of atrial fibrillation, congestive heart failure, coronary disease, and diabetes were similar between those with lower and those with higher serum potassium levels and between those with lower and those with higher dietary potassium intake. Of participants taking diuretics, 84% had a history of hypertension and 10% had a history of congestive heart failure. Not surprisingly, a history of hypertension, potassium supplementation, or diuretic use was more common in those with lower serum potassium than in those with higher serum potassium, but similar in those with lower and those with higher dietary potassium.

In Cox proportional hazards models, including both serum and dietary potassium as continuous variables in the original cohort, stroke risk was associated with lower serum potassium only in participants on diuretics and was associated with low dietary potassium only in those not on

Table 3 *Relationship of dietary potassium levels in quintiles to stroke risk by diuretic use (original cohort)*

	Quintiles of dietary potassium in g/d					
Diuretic use	≤2.34	2.35–2.92	2.93–3.47	3.48–4.16	≥4.17	*p* Value
Nonusers of diuretics, n = 3,595, RR* (95% CI)	1.76 (1.21–2.57)	1.22 (0.81–1.83)	1.11 (0.73–1.67)	1.37 (0.93–2.04)	1.0 referent	<0.025
Users of diuretics, n = 1,339, RR* (95% CI)	0.87 (0.54–1.40)	0.66 (0.40–1.11)	0.66 (0.40–1.10)	1.09 (0.69–1.73)	1.0 referent	NS

Twenty-six participants were missing either the diuretic status or dietary potassium information, and 27 of the nondiuretic users and 15 of the diuretic users had missing data for one or more of the risk factors. These participants were excluded from the analyses in this table.

* These Cox models include age, sex, history of diabetes, hypertension, coronary artery disease, congestive heart failure, atrial fibrillation, systolic blood pressure, serum creatinine, serum potassium, and potassium supplement use.

RR = relative risk.

Table 4 *Relative risks (RR) of stroke for serum potassium ≤4.0 mEq/L compared with serum potassium >4.0 mEq/L among users and nonusers of various diuretics*

Diuretic use	No. of strokes	Total no. of participants	% of participants with serum potassium levels ≤4.0 mEq/L	RR* (95% CI)	*p* Value
All diuretic users	177	1566	59.6%	2.5 (1.7–3.5)	<0.0001
Loop	42	369	38.6%	2.4 (1.2–4.7)	<0.001
HCTZ	84	709	71.9%	3.1 (1.7–5.8)	<0.0005
K+-sparing	51	489	57.5%	2.0 (1.1–3.7)	<0.05
Any diuretic without potassium supplement	130	1210	60.6%	3.2 (2.1–5.0)	<0.005
Any diuretic with potassium supplement	47	357	56.3%	1.4 (0.8–2.6)	NS
Nonusers of diuretics	289	3974	25.6%	0.9 (0.7–1.2)	NS

Five participants were missing diuretic status and two were missing the type of diuretic. Thirty-five of the nondiuretic users and 20 of the diuretic users had missing data for one or more of the risk factors. These participants were excluded from the analyses in this table. Among these excluded participants, there were four nonusers and three users of diuretics who had a stroke. Relative risks were adjusted for age, sex, history of hypertension, diabetes, coronary artery disease, congestive heart failure, systolic blood pressure, atrial fibrillation, serum creatinine level, and use of potassium supplements.

* The referent group for each row in the table is the participants in the subgroup specified for that row with serum potassium >4.0 mEq/L.

diuretics. For each SD decrease in serum potassium in a diuretic user, there was a 38% increase in the RR for stroke. For each SD decrease in dietary potassium in a nondiuretic user, there was an 18% increase in the RR for stroke. Significant interactions of both potassium measures with diuretic use were found ($p < 0.005$ for both interactions; see table 1). Because of these findings, all additional analyses are shown in stratified form by diuretic use.

Diuretics and potassium supplementation. In table 2, the association of stroke with the quintile of serum potassium level is stratified for diuretic use. Among diuretic users only, both of the lowest two quintiles of serum potassium were associated with an increased risk for stroke (RR: 2.37 and 2.21, $p < 0.0001$).

The proportion of participants with lower serum potassium was, as expected, much higher in users of diuretics (use determined at baseline evaluation) than in those not taking diuretics (59.6% compared with 25.6%; table 4). There was considerable variability in the proportion of participants with lower serum potassium among the various classes of diuretics, with the highest number having a lower serum potassium in those taking thiazide diuretics (71.9%), the lowest proportion in those taking loop diuretics (38.6%), and an intermediate number among those taking potassium-sparing diuretics (57.5%). However, there was little difference in the proportions with lower serum potassium between those taking (56.3%) or not taking (60.6%) potassium supplements with the diuretics. This was tested in the Cox model by testing the significance of the potassium supplementation variable interaction with low serum potassium among diuretic users. The coefficient for this interaction was not significantly different from zero. Adjustment for diuretic dose did not change the relationship of serum potassium with stroke risk. Serum potassium less than or equal to 4.0 mEq/L was associated with an increased RR for stroke for those participants on diuretic therapy (RR: 2.5, 95% CI: 1.7 to 3.5, $p < 0.0001$; see table 4). This RR for stroke associated with lower serum potassium was found in those on hydrochlorothiazide (3.1), loop diuretics (2.4), and potassium-sparing diuretics (2.0). The overall RR for stroke associated with lower serum potassium for the group on diuretics without a potassium supplement was 3.2, compared with 1.4 in those receiving a potassium supplement (difference not significant). As alluded to above, among those not taking diuretics, there was no increased risk for stroke associated with lower serum potassium.

Stroke subtypes. As shown in table 5, low serum potassium level was associated with an increased risk for stroke in the total cohort (including both users and nonusers of diuretics; RR: 1.3, $p < 0.005$) and in the subset of diuretic users (RR: 2.5, $p < 0.0001$), but not among those who did not take diuretics. Among diuretic users, the risk for stroke associated with lower serum potassium was elevated for both atherothrombotic (RR: 2.5, 95% CI: 1.5 to 4.2, $p < 0.001$) and embolic types (RR: 2.3, 95% CI: 1.2 to 4.5, $p < 0.01$). The RR for lacunar strokes (RR: 2.5, 95% CI: 0.9 to 6.8,) and for hemorrhagic strokes (RR: 2.5, 95% CI: 0.6 to 9.5) were similar in magnitude to those for the other stroke subtypes, but were not significant, perhaps because of the smaller number of individuals in these groups.

Atrial fibrillation. As expected, among all participants, regardless of serum potassium level or diuretic use, atrial fibrillation was associated with an increased RR for stroke (RR: 2.3, 95% CI: 1.5 to 3.4, $p < 0.0001$) compared with those in sinus rhythm. However, among diuretic users, there was an interaction ($p < 0.05$) between atrial fibrillation and lower serum potassium levels on stroke risk. Specifically, diuretic users with both atrial fibrillation and serum potassium less than or equal to 4.0 mEq/L were nearly 10 times more likely to have a stroke (95% CI: 4.7 to 20.0, $p < 0.0001$) than diuretic users who had neither atrial fibrillation nor a lower serum potassium (table 6); however, the number of subjects involved was small. Among diuretic users with atrial fibrillation and serum potassium greater than 4.0 mEq/L, there was no enhanced risk for stroke compared with diuretic users with a normal

Table 5 *Relative risks (RR) of each stroke subtype with a serum potassium ≤4.0 mEq/L compared with serum potassium >4.0 mEq/L among users and nonusers of diuretics (total cohort)*

Diuretic use	No. of strokes	No. of participants	RR* (95% CI)	*p* Value
Total cohort	466	5,540	1.3 (1.1–1.6)	<0.005
Users of diuretics				
All strokes	177	1,566	2.5 (1.7–3.5)	<0.0001
Atherothrombotic	85		2.5 (1.5–4.2)	<0.001
Embolic	51		2.3 (1.2–4.5)	<0.01
Lacunar	22		2.5 (0.9–6.8)	0.085
Hemorrhagic	13		2.5 (0.6–9.5)	NS
Nonusers of diuretics				
All strokes	289	3,974	0.9 (0.7–1.2)	NS
Atherothrombotic	132		0.9 (0.6–1.4)	NS
Embolic	77		0.9 (0.5–1.5)	NS
Lacunar	31		1.1 (0.5–2.5)	NS
Hemorrhagic	36		1.2 (0.6–2.6)	NS

Five participants were missing diuretic status, and 35 of the nondiuretic users and 20 of the diuretic users had missing data for one or more of the risk factors. These participants were excluded from the analyses in this table. Of those excluded, there were four nonusers and three users of diuretics who had a stroke of known type. There were 19 strokes of unknown type, 13 in the nonusers, and 6 in the users of diuretics.

* The referent group for each section of the table (users and nonusers of diuretics) is the participants in that section with serum potassium >4.0 mEq/L. Relative risks for the particular stroke subtype are adjusted for age, sex, and risk factors as in table 3.

sinus rhythm and normal serum potassium (RR: 1.5, 95% CI: 0.6 to 3.9).

Dietary potassium. In table 3, the association of stroke with quintile of dietary potassium intake level is stratified for diuretic use. Among nonusers of diuretics only, the lowest quintile of potassium intake (i.e., less than or equal to 2.34 g/d) was associated with an increased risk for stroke (RR: 1.76, 95% CI: 1.21 to 2.57, $p < 0.025$) when compared with the referent group with potassium intake greater than or equal to 4.17 g/d.

Data from the entire original cohort demonstrated that a baseline dietary potassium intake less than or equal to 2.34 g/d, when compared with intake greater than this level, was associated with a slightly increased RR for stroke of 1.3 (95% CI: 1.0 to 1.6, $p < 0.05$) (supplementary data related to this article can be found on the *Neurology* Web site. Go to www.neurology.org and scroll down the Table of Contents to find the title link for this article). However, an increased RR for stroke was observed only in those participants who did not take diuretics (RR: 1.5, 95% CI: 1.1 to 2.0, $p < 0.005$). This risk was significant for embolic strokes (RR: 2.0, 95% CI: 1.2 to 3.3), and nearly significant for atherothrombotic strokes (RR: 1.5, 95% CI: 1.0 to 2.3), but not for other stroke subtypes.

Discussion. These results indicate that serum potassium less than or equal to 4.0 mEq/L on entry to the study was associated with an increased risk for stroke among diuretic users older than 65 years. Those individuals not taking diuretics had a greater risk for stroke if they had low dietary potassium intake, but not in relation to lower serum potassium level. This study includes women in the observation that low dietary potassium may be a risk factor for stroke, and confirms a prior study regarding stroke risk and potassium intake in men.[7,8]

Several studies have implicated low dietary potassium intake as a risk factor for stroke mortality. In a 12-year prospective study of more than 800 individuals, those in the lowest tertile of potassium intake were at highest risk for stroke mortality, independent of several other dietary variables.[1] Furthermore, a survey by the WHO demonstrated that low urinary potassium, which was considered to reflect low dietary potassium intake, was associated with increased stroke mortality.[2] In another multicenter cohort, stroke mortality was higher in those with an elevated ratio of dietary sodium to potassium.[3] Stroke mortality was diminished among participants who had changed their diet to replace sodium with potassium in one small Japanese trial.[4] Similarly, low potassium intake was associated with an increased number of fatal thromboembolic strokes among males in the Honolulu Heart Program.[5]

There are only two large prospective studies that relate the intake of potassium to the incidence of stroke. The first, limited to males, found a lower stroke incidence in hypertensive patients who ingested an estimated 4.3 g/d or more of potassium, compared with those who ingested 2.4 g/d or less.[7] The second study, limited to females, suggested that low potassium intake was associated with increased stroke incidence, but the RR did not reach statistical significance.[8]

Another approach to this relationship was studied in 400 consecutive patients with stroke whose electrolyte levels were measured within 2 hours of arrival to the hospital. Lower initial serum potassium levels were associated with increased stroke mortality.[6] The Systolic Hypertension in the Elderly (SHEP) study indicated that low serum potassium was associated with increased stroke incidence.[9]

In our series, the increased risk for stroke with a low to low normal serum potassium was slightly less apparent in individuals taking potassium-sparing diuretics compared with other types of diuretic, but the differences were not significant. Perhaps this was related to the similar proportions of participants with lower serum potassium between both groups of diuretic users. Unlike a previous study that found a lower stroke rate, we found a small but insignificantly lower stroke rate among diuretic users who took potassium supplements.[7] Possible explanations for the lack of benefit associated with potassium supplementation include use of potassium supplements in those with the lowest serum potassium (indication bias), an intrinsic biologic phenomenon related to lower serum potassium, poor compliance, or inadequate doses of potassium supplements. Our study was limited by having only one serum potassium

Table 6 *Relative risks (RR) for stroke among diuretic users as a function of atrial fibrillation and serum potassium (total cohort)*

Atrial fibrillation	Serum potassium ≤4.0 mEq/L	No. of strokes	No. of participants	RR (95% CI)	*p* Value
No	No	43	595	1.0 (Reference)	
Yes	No	5	40	1.5 (0.6–3.9)	NS
No	Yes	120	908	2.2 (1.5–3.2)	<0.0001
Yes	Yes	10	24	9.7 (4.7–20.0)	<0.0001

Relative risks are adjusted for age, sex, and risk factors as in table 4.

determination at entry, by estimating dietary potassium intake, and by an inability to ensure diuretic and potassium supplement use during the entire investigation. However, the large number of participants may offer insights into these relationships. Furthermore, these limiting factors would likely lead to an underestimation of the risk for stroke associated with repeated measurements of serum levels and dietary intake.

The apparent deleterious role of lower potassium did not appear to be mediated by changes in blood pressure.[27] Although lower serum potassium in elderly diuretic users was associated with an increased incidence of strokes in general, there was no significant association with the lacunar and hemorrhagic stroke subtypes, the subtypes more typically derived from the effects of chronic hypertension.[28,29] Similarly, low dietary potassium in those not taking diuretics was associated with an increased incidence of embolic strokes only. All analyses were adjusted for the putative risk for stroke associated with elevation of systolic blood pressure, thus diminishing its potential confounding effect. Although we only have single baseline measurements of potassium and blood pressure, our study does not support the notion that hypertension can explain the association between lower potassium and stroke risk. This agrees with previous human and animal studies that have shown an independent effect of potassium on stroke mortality risk.[1,30] For example, stroke-prone spontaneously hypertensive rats placed on high potassium diets had a lower stroke mortality compared with those on a normal potassium diet, independent of the blood pressure–lowering effect of potassium.[30] In one human cohort study, there was a 40% reduction in the risk for stroke per 10-mmol increase in daily intake of potassium, and this effect was independent of the effect of either systolic or diastolic blood pressure, suggesting that potassium may have a protective effect against stroke that was not mediated through blood pressure.[31] The finding in another study that high intake of potassium was associated with lower stroke-associated mortality was also independent of blood pressure levels.[1] In the SHEP trial, serum hypokalemia was not associated with a higher blood pressure, yet it was associated with a higher risk for stroke; therefore, they concluded that the higher risk for stroke could not be explained by differences in blood pressure.[9]

Variations in dietary potassium intake can be associated with variations in sodium or other dietary intake. We did some preliminary analyses that did not show any significant associations between specific food groups or food items and stroke risk. Similar to another study, there was no association between sodium intake and risk for stroke.[7] As a possible explanation for this lack of association, the other study suggests the difficulty in measuring sodium intake accurately and that there are few individuals with very low or high intake.[7]

It was not possible to determine if low to low normal serum potassium or low dietary potassium intake had a direct causal relationship to increased stroke risk. Diuretics, for example, can alter other serum electrolyte levels, such as magnesium, that may play a role in cerebral protection from stroke. There have been a number of suggested mechanisms for the protective effect of higher potassium diet on the aforementioned stroke-prone spontaneously hypertensive rats, including protection against oxidative stress to the endothelium, reduced endothelial permeability and dysfunction, and reduced macrophage adherence to the vascular wall.[32-34] Potassium also has been demonstrated to inhibit vascular smooth muscle proliferation in canine coronary arteries and high potassium diets may reduce cholesterol deposition in the aortas of rats, but all of these potential protective mechanisms are speculative.[35,36] It is not clear why low potassium intake only affected the risk for stroke in those individuals not taking diuretics and low serum potassium level only affected the risk for stroke in those individuals who were taking diuretics. One possible explanation for this revolves around the major effect that diuretic use can have on body stores of potassium. In those individuals taking diuretics, the serum potassium may reflect the effect of the diuretic on the amount of potassium in the tissues of the body. This effect may make the amount of potassium ingested in the diet inconsequential. However, in those not taking diuretics, the intake of potassium may provide a better reflection of body stores of potassium than the amount found in the blood stream. Supporting this is that the correlation in both diuretic users and nonusers between serum potassium and potassium intake is close to zero. It is not unusual to have a poor correlation between serum levels and intakes of nu-

trients because nutrients are stored in varying amounts in different body compartments.

An unexpected finding of our study was that lower serum potassium combined with atrial fibrillation was associated with a 10-fold increased stroke risk among diuretic users older than 65 years. Although the number of subjects involved was small, this marked difference is intriguing enough to warrant an attempt at corroboration by either further prospective studies or reexamination of prior cohorts.

It is important to note that we are neither implying, nor does our data support, any excess risk for stroke associated with the use of diuretics. The question can be raised, however, as to whether diuretics would be even more effective if potassium levels were maintained at normal levels. A randomized trial of diuretic use with and without intensive monitoring and supplementation of potassium might be desirable to address this issue. If potassium supplementation or potassium-sparing diuretic use alters the risk for stroke occurrence, consideration might be given to the use of potassium-sparing diuretics or to aggressive potassium supplementation when a diuretic is indicated. In older adults not taking a diuretic, our data also tentatively suggest a benefit relating to stroke risk with increased potassium intake.

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