

Mild Hypokalemia and Supraventricular Ectopy Increases the Risk of Stroke in Community-Dwelling Subjects

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Background and Purpose—Stroke is independently associated with the common conditions of hypokalemia and supraventricular ectopy, and we hypothesize that the combination of excessive supraventricular ectopic activity and hypokalemia has a synergistic impact on the prognosis in terms of stroke in the general population.

Methods—Subjects (55–75 years old) from the Copenhagen Holter Study cohort (N=671) with no history of atrial fibrillation or stroke were studied—including baseline values of potassium and ambulatory 48-hour Holter monitoring. Excessive supraventricular ectopic activity is defined as ≥ 30 premature atrial complexes per hour or any episodes of runs of ≥ 20 . Hypokalemia was defined as plasma-potassium ≤ 3.6 mmol/L. The primary end point was ischemic stroke. Cox models were used.

Results—Hypokalemia was mild (mean, 3.4 mmol/L; range, 2.7–3.6). Hypokalemic subjects were older (67.0 ± 6.94 versus 64.0 ± 6.66 years; $P < 0.0001$) and more hypertensive (165.1 ± 26.1 versus 154.6 ± 23.5 mm Hg; $P < 0.0001$). Median follow-up time was 14.4 years (Q1–Q3, 9.4–14.7 years). The incidence of stroke was significantly higher in the hypokalemic group (hazard ratio, 1.84; 95% confidence interval, 1.04–3.28) after covariate adjustments, as well as in a competing risk analysis with death (hazard ratio, 1.51; 95% confidence interval, 1.12–2.04). Excessive supraventricular ectopic activity was also associated with stroke (hazard ratio, 2.23; 95% confidence interval, 1.33–3.76). The combination of hypokalemia and excessive supraventricular ectopic activity increased the risk of events synergistically. Stroke rate was 93 per 1000 patient-year ($P < 0.0001$) in this group (n=17) compared with 6.9 (n=480); 11 (n=81), and 13 (n=93) per 1000 patient-year in the groups without the combination.

Conclusions—The combination of hypokalemia and excessive supraventricular ectopy carries a poor prognosis in terms of stroke. (*Stroke*. 2017;48:537-543. DOI: 10.1161/STROKEAHA.116.015439.)

Key Words: epidemiology ■ hypokalemia ■ premature atrial contractions ■ RAAS ■ stroke

Stroke is one of the leading causes of functional impairment worldwide with an incidence of 85 and 143 cases per 100 000 person-years, respectively, in the United Kingdom and the United States in 2010.¹ Almost 30% of stroke cases are diagnosed with atrial fibrillation; however, the actual burden of arrhythmia seems higher as many of the silent paroxysmal forms are undiagnosed.² Excessive supraventricular ectopic activity (ESVEA) has been shown to increase the risk of atrial fibrillation.³ Recent data show that ESVEA increase the risk of ischemic stroke beyond incident atrial fibrillation.^{4,5} This has increased the focus on the clinical handling of patients in terms of primary and secondary stroke prophylaxis.

Hypokalemia has several deleterious cardiovascular effects, including facilitation or inducing of cardiac arrhythmias.⁶ One of the suggested mechanisms is prolongation of the repolarization phase of the myocardial action potential

because of a reduced repolarizing outward potassium current.^{7,8} Prolongation of the repolarization phase can cause early after-depolarizations, which potentially could lead to arrhythmia. Recent data have shown a significant association between long-QT interval and atrial fibrillation,⁹ and studies have suggested hypokalemia, along with polypharmacy,^{10,11} as a concurrent factor in the development of atrial fibrillation, long-QT interval, and torsade de pointes ventricular tachycardia.⁷ Furthermore, hypokalemia can induce or aggravate diastolic dysfunction, with atrial dilatation and atrial fibrillation as a consequence.¹²

Mild hypokalemia is a common finding and is generally not considered harmful in a clinical setting, and it may occur as a primary condition or secondary to many medications, such as diuretics and laxatives.^{6,13} Both hypokalemia and ESVEA are independently associated with increased risk of stroke, and both conditions are relatively common in the general

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population; however, the combination of hypokalemia and ESVEA in relation to stroke and death has not been explored.

We hypothesize that the combination of ESVEA and mild hypokalemia has a synergistic impact on the prognosis in terms of stroke and death in the general population.

Methods

Data from the Copenhagen Holter Study were analyzed. The Copenhagen Holter Study is one of the largest Holter studies in randomly selected subjects. It was launched in 1998 and inclusion stopped in 2000. The details of the study protocol and selection procedures have been published previously.¹⁴ In brief, within 2 well-defined postal regions in the city of Copenhagen, all men aged 55 years and all men and women aged 60, 65, 70, and 75 years (n=2969) were contacted with a questionnaire about medical history, cardiovascular risk factors, and use of medication. All subjects with >1 risk factor and 60% of randomly selected subjects with 0 to 1 risk factors were invited to a physician-based questionnaire, physical examination, laboratory testing, ECG, and 48-hour Holter monitoring. Blood pressure and resting heart rate were measured with the patients in a recumbent position after at least 10 minutes of rest. Subjects with current or past cardiac disease, atrial fibrillation, stroke, cancer, or other life-threatening conditions were excluded. The study includes ≤48 hours of successful Holter monitoring in 678 subjects.¹⁴ The quality of the Holter monitoring has been described in detail previously,¹⁵ and the interobserver variability of Holter variables, including ectopic beats, shows κ values of 0.91 to 0.94. The range of technically acceptable recording and analysis times was 17.2 to 49.2 hours. The median value was 44.1 hours, and first and third quartiles (Q1–Q3) were 41.4 to 45.5 hours. More than 98% of the subjects had >24 hours of recording. Diabetes mellitus was defined as already diagnosed diabetes mellitus or fasting plasma glucose of ≥ 7 mmol/L.

Two classes of supraventricular arrhythmias were investigated: (1) premature atrial contractions (PACs) and (2) runs of ≥ 3 PACs. The verification of PAC was based on 3 criteria: prematurity, postcontraction pause, and morphology. The coupling interval to the preceding QRS complex had to be $\leq 70\%$ of the mean R-R interval of basic rhythm before the event. QRS complexes had a length of <0.11 seconds unless aberration was assumed. The postcontraction pause had to be noncompensatory. ESVEA was defined as ≥ 30 PACs per hour or any episode of runs of ≥ 20 PACs.⁴ Premature ventricular complexes ≥ 30 /hour were defined as excessive ventricular ectopic activity.¹⁶

Hypokalemia

Plasma-potassium (p-potassium) was studied in quintiles, and the lowest quintile (2.7–3.6 mmol/L) was defined as hypokalemia. To evaluate whether the prognostic burden was carried by the lower end of potassium, the hypokalemia was also studied in 2 subgroups in sensitivity analyses (2.7–3.4 and 3.5–3.6). The 2 subgroups were similar in terms of risk of stroke (see sensitivity analysis in the Results section).

Laboratory Testing

Laboratory testing was conducted between 7:00 AM and 10:00 AM after overnight fasting. Standard analyses, including p-potassium and other electrolytes, were immediately performed on a Hitachi 7170 automated analyzer. For future analyses, the separated plasma and serum were stored at -70°C . NT pro-BNP (N-terminal pro-B-type natriuretic peptide) was measured by electrochemiluminescence technique using Elecsys 2010 provided by Roche (Basel, Switzerland).

Follow-Up and End Points

Total stroke and all-cause mortality were evaluated as end points. In Denmark, all deaths, hospital admissions, and discharges are reported to national central registries within 2 weeks. Data on stroke, death, and atrial fibrillation were obtained from these registries, and data were confirmed manually in patient files afterward. Discharge letters

from hospital admissions and, in necessary cases, patient files were reviewed manually. Follow-up was 100% in all groups. The diagnosis of stroke was based on a history of neurological deficits and was verified with computed tomography or magnetic resonance scanning of the cerebrum. Only verified ischemic strokes were accepted for this study. Diagnosis of incident atrial fibrillation was verified with documentation in the form of ECG, telemetry, or both from patient records. All medications were registered at baseline, and no participants were treated with anticoagulants.

Ethics

Written informed consent was obtained from all study subjects. The Regional Ethical Committee approved the study, and the Helsinki Declaration was complied with.

Statistical Analysis

Statistical analyses were made with the use of the SAS statistical software program (SAS Enterprise, version 7.11; SAS Institute Inc, Cary, NC). For normally distributed variables, mean and standard deviation are presented; otherwise, median value and quartiles (Q1–Q3) are presented.

Univariate associations between potassium and other baseline parameters were evaluated by Spearman's correlation, Kruskal–Wallis, Wilcoxon rank-sum, or *t* test as appropriate. Two-tailed tests of significance are reported, and *P* values <0.05 are considered statistically significant. Regression analyses (logistic or linear) were performed to evaluate the covariate-adjusted associations between variable of interest. Event-free survival in groups of interest was evaluated by the method of Kaplan–Meier, and the differences were compared by means of the log-rank test. Cox proportional hazard models were used to evaluate the covariate-adjusted associations with events. The assumption of proportional hazards was assessed by visual judgment of the log-minus-log survival plots. Covariates were entered as continuous variables when possible. The assumption of linearity for a continuous variable was checked by entering the transformed variable in addition to the variable of interest.

The following variables of potential prognostic importance were evaluated in the Cox models: age, sex, smoking, serum cholesterol, systolic arterial blood pressure, and diabetes mellitus. In multivariable Cox models (full models), we included 1 covariate for every 10 events from the list with the mentioned sequence. The addition of any further covariate was only accepted if it did not change the main results significantly in any direction. These procedures were used to avoid possible overfitting. In forward and backward elimination procedures, *P*<0.05 was used as a criterion to enter and stay in the model. Subdistribution hazards were used in Cox regression competing risk analysis models, with death and atrial fibrillation as competing events, respectively.

Potassium did not meet the linearity assumption and was studied in quintiles and then dichotomized at lower quintiles according to visual judgment of the event rates in quintiles.

Results

Baseline Data

From 678 subjects in the original population study, 671 had a valid p-potassium and were included. Mean and median value for p-potassium was 3.9 mmol/L (Q1, 3.7 mmol/L; Q3, 4.1 mmol/L; range, 2.7–5.4). Table 1 shows baseline characteristics of the study population; hypokalemic subjects (mean, 3.4 mmol/L; range, 2.7–3.6) were significantly older, had higher systolic and diastolic blood pressure, and were more likely to use diuretics, β -blockers, and aspirin, as well as a higher NT-pro-BNP, although the levels of the latter were low in both groups. There were no differences in smoking habits, sex, diabetes mellitus incidence, or body mass index.

Table 1. Baseline Characteristics of the Study Population in 2 Groups

	Normokalemia (n=561)	Hypokalemia (n=110)	P Value
Age, y	64.0±6.7	67.0±6.9	<0.0001
Female sex, n (%)	225 (40%)	52 (47%)	0.16
Body mass index, kg/m ²	26.3±4.3	25.6±3.9	0.19
Systolic BP, mm Hg	154.6±23.5	165.1±26.1	<0.0001
Diastolic BP, mm Hg	90.5±10.9	93.0±11.1	0.03
Current smoker, n (%)	262 (47%)	49 (45%)	0.68
Diabetes mellitus, n (%)	61 (11%)	14 (13%)	0.62
Low-level physical activity, n (%)	136 (24%)	37 (34%)	0.043
Creatinine, mmol/L	92.5±18.7	93.4±21.1	0.67
Sodium, mmol/L	140.9±2.4	140.6±3.0	0.29
Total cholesterol, mmol/L	6.1±1.1	6.0±1.00	0.89
NT-proBNP, pmol/L (range)	6.6 (3.5–12.9)	9.0 (4.5–18.2)	0.006
CHA ₂ DS ₂ VASc (mean)	1.5	2.1	<0.0001
Aspirin use, n (%)	75 (13%)	27 (25%)	0.003
β-Blocker use, n (%)	22 (3.9%)	12 (11%)	0.002
Diuretic use, n (%)	67 (12%)	53 (48%)	<0.001
ACE inhibitor use, n (%)	25 (4.5%)	7 (6.4%)	0.46

Baseline characteristics of hypokalemic vs normokalemic study subjects. Values are presented as mean±SD and number (%). ACE indicates angiotensin-converting enzyme; BP, blood pressure; CHA₂DS₂VASc, congestive heart failure, hypertension, age ≥75 y, diabetes mellitus, previous stroke or transient ischemic attack, vascular disease, age 65 to 74 y, female sex; and NT-proBNP, N-terminal pro-B-type natriuretic peptide.

Totally, 98 subjects (14.6%) had ESVEA, 81 subjects with normokalemia (14.4%) and 17 subjects with hypokalemia (15.4%; *P*=0.79).

Follow-Up and End Points

Median follow-up time for all subjects was 14.4 years (Q1–Q3, 9.4–14.7 years): 12.4 years (Q1–Q3, 5.1–14.7 years) in the hypokalemic group and 14.5 years (Q1–Q3, 10.3–14.7 years) in the normokalemic group, respectively. During this follow-up period, a total of 72 strokes and 254 all-cause deaths were detected, including 20 strokes and 58 all-cause deaths in subjects with hypokalemia (*n*=110). The rate of stroke was 17.8 per 1000 patient-year in patients with hypokalemia versus 7.6 per 1000 patient-year in patients with normokalemia (*n*=561; *P*=0.0006). In a Cox model, hypokalemia was associated with increased risk of stroke after adjustments for sex and age (hazard ratio [HR], 2.09; 95% confidence interval [CI], 1.25–3.50) and after adjustments for additional conventional risk factors (HR, 1.94; 95% CI, 1.13–3.32) and also further adjustments for diuretics and CHA₂DS₂VASc score (HR, 1.84; 95% CI, 1.04–3.28). The same significant associations were seen for the combined end point of death and stroke (Table 2). In a competing risk analysis, death as a competing event did not change the

Table 2. Cox Regression Models Showing the Hazard Ratio of Stroke and Death or Stroke in Relation to Hypokalemia

	Stroke (HR, 95% CI)	Time at Risk (Person-Years)	Death or Stroke (HR, 95% CI)
Model 1	2.07 (1.22–3.50); <i>P</i> =0.007	7950	1.60 (1.20–2.14); <i>P</i> =0.001
Model 2	1.74 (1.01–3.02); <i>P</i> =0.047	7865	1.42 (1.06–1.92); <i>P</i> =0.019
Model 3	1.88 (1.05–3.38); <i>P</i> =0.034	7799	1.40 (1.02–1.92); <i>P</i> =0.040

Model 1 is adjusted for age and sex. Model 2 is adjusted for additional stroke risk factors (age, sex, smoking, total cholesterol, NT-proBNP, diabetes mellitus, body mass index, the level of physical activity and systolic blood pressure). Model 3 is adjusted for model 2+adjustment for diuretics and CHA₂DS₂VASc score. CHA₂DS₂VASc indicates congestive heart failure, hypertension, age ≥75 y, diabetes mellitus, previous stroke or transient ischemic attack, vascular disease, age 65 to 74 y, female sex; CI, confidence interval; HR, hazard ratio; and NT-proBNP, N-terminal pro-B-type natriuretic peptide.

hypokalemic association with stroke (HR, 1.51; 95% CI, 1.12–2.04). Incidences of atrial fibrillation were seen in 9 hypokalemic and 68 normokalemic patients (8.2% versus 12.1%; *P*=0.33).

The rate of stroke was 21.7 per 1000 patient-year in patients with ESVEA (*n*=99) versus 7.4 per 1000 patient-year in patients without ESVEA (*n*=579; *P*<0.0001). In a sex- and age-adjusted Cox model, ESVEA remained associated with increased risk of stroke (HR, 2.23; 95% CI, 1.33–3.76). The increased risk remained significant after additional adjustments for additional risk factors, including CHA₂DS₂VASc score (HR, 2.07; 95% CI, 1.21–3.54).

Synergism Between Ambulatory Arrhythmias and Hypokalemia in Relation to Event Rates

The combination of hypokalemia and ESVEA increased the risk of events synergistically. Stroke rate was 93 per 1000 patient-year (*n*=17) in this group compared with 6.9 per 1000 patient-year (*n*=480) in the group with no hypokalemia and no ESVEA, 11 per 1000 patient-year (*n*=81) in patients with no hypokalemia but with ESVEA, and 13 per 1000 patient-year (*n*=93) in the group with hypokalemia but with no ESVEA (*P*<0.0001; Figure 1 and Table 3; Table I in the [online-only Data Supplement](#) shows baseline characteristics in the 4 groups). Kaplan–Meier survival analysis showed the same worse prognosis in terms of stroke with the combination of mild hypokalemia and ESVEA (Figure 2). The likelihood ratio test for statistical interaction between hypokalemia and ESVEA was highly significant (*P*<0.0001). The combination of excessive ventricular ectopic activity and hypokalemia was not associated with a worse prognosis, in terms of stroke, than hypokalemia alone.

Diuretics

The incidence of stroke was 18.5% and 17.5% (*P*=0.88) in hypokalemic groups with and without the use of diuretics and 13.4% and 8.7% (*P*=0.21) in normokalemic groups, respectively. Adjustment for diuretic use in Cox models did not change the significance of association between end points

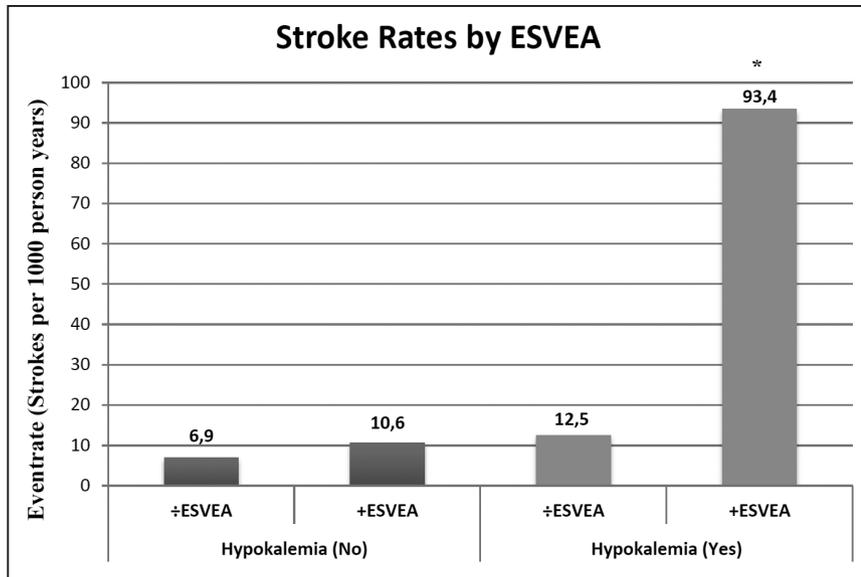


Figure 1. Events per 1000 patient-year in subjects with hypokalemia, ESVEA, or both as compared with controls. ESVEA indicates excessive supraventricular ectopic activity; and hypokalemia, plasma-potassium 2.7 to 3.6 mmol/L. *Significance ($P < 0.0001$).

and hypokalemia. Excluding diuretics users from the analyses did not change the main results significantly because the HRs remained unchanged or increased in the respective models with mild changes in the CI (Table II in the [online-only Data Supplement](#)).

Sensitivity Analyses

Because a p-potassium level of 3.6 is usually considered normal, we assessed the event rates in 2 hypokalemic subgroups in a sensitivity analysis; p-potassium (2.7–3.4) and (3.5–3.6). Subjects in the latter group had a stroke rate of 62.5 events per 1000 patient-year, thus, comparable with the whole hypokalemic group, which has substantially increased event rates (Figure 3) compared with the normokalemic group.

Discussion

The major finding of this study is that the combination of mild hypokalemia and ESVEA increases the risk of stroke synergistically even after adjustment for risk factors,

including CHA_2DS_2VASc score. Thus, event rates in subjects with ESVEA and accompanying hypokalemia were almost 14× greater compared with the event rates seen when no ESVEA or hypokalemia were present.

According to this study and previous studies, hypokalemia seems to be independently associated with a worse prognostic outcome in terms of cardiovascular-related events,^{6,17–19} and data from the present study suggest that mild hypokalemia interacts with excessive supraventricular ectopy to increase the risk of stroke significantly. Earlier studies has shown ESVEA as a predictor of atrial fibrillation and stroke.^{4,20–22} The Rotterdam Study²³ data suggest that hypokalemia could facilitate the transition to atrial fibrillation in these subjects and, thereby, increase the rate of stroke and death. Although the rate of incident atrial fibrillation in our study was not increased in the hypokalemic group, the rate of undetected paroxysmal atrial fibrillation could have been increased. Hypokalemia could facilitate the transition to paroxysmal atrial fibrillation in subjects with ESVEA and, thereby, increase the risk of stroke in this group. A recent publication

Table 3. Event Rates in Normokalemic and Hypokalemic Subjects, Respectively, With and Without Excessive Supraventricular Ectopic Activity

	n	Stroke, n	Time at Risk, (Person-Years)	Strokes/1000 Person-Years (95% CI)	Hazard Ratio* (95% CI)
Normokalemia					
–ESVEA	480	41	5943	6.9 (5.1–9.4)	Reference
+ESVEA	81	11	1040	10.6 (5.9–19.1)	1.69 (0.85–3.37)
Hypokalemia					
–ESVEA	93	11	877	12.5 (6.9–22.6)	1.36 (0.65–2.85)
+ESVEA	17	9	96	93.4† (48.6–179.5)	9.92† (4.12–23.9)
Total	671	72	7956		

Subjects with normokalemia and without ESVEA is reference group in the Cox model. Time at risk column refers to stroke rate estimates. CI indicates confidence interval; and ESVEA, excessive supraventricular ectopic activity.

*Multivariate adjusted Cox model (adjusted covariates equal to model 3 in Table 2).

† $P < 0.0001$.

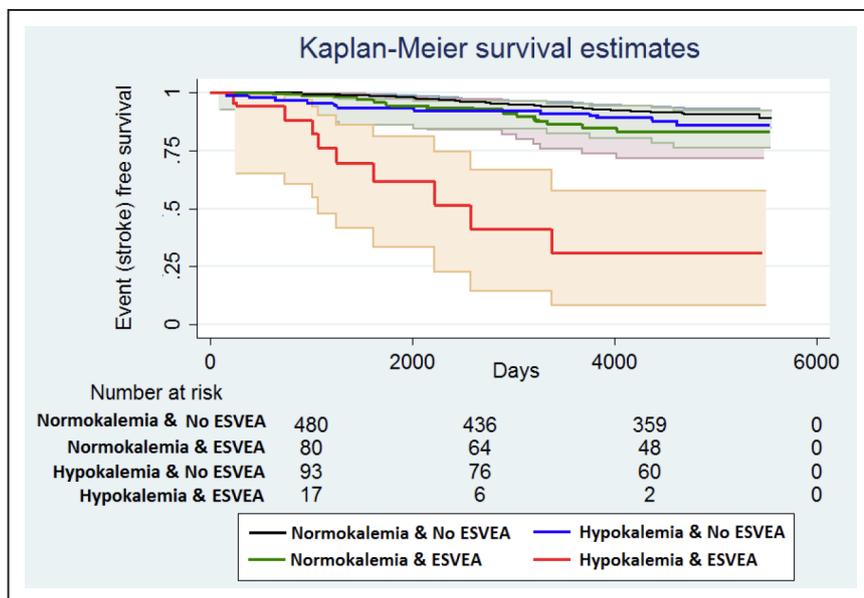


Figure 2. Kaplan–Meier plot. Event (stroke)-free survival in normokalemic (range 3.7–5.4 mmol/L) and hypokalemic (range 2.7–3.6 mmol/L) subjects with and without ESVEA, including confidence limits. Log-rank $P < 0.0001$ for the hypokalemic subgroup with ESVEA compared with the other groups. ESVEA indicates excessive supraventricular ectopic activity.

from the Copenhagen Holter Study showed that ESVEA was associated with ischemic stroke, and the association seemed to reach beyond incidences of atrial fibrillation⁵; however, it was suggested that undetected runs of atrial fibrillation may be the link between the 2 conditions.

Even though mild hypokalemia seems innocent, it may be a marker of increased activity in the renin–angiotension–aldosterone system (RAAS) and could potentiate the detrimental effects of other risk factors. The possible hypokalemia-induced increased stroke risk seen in our present study supports that hypothesis. In a recent study, mild hypokalemia was found to be associated to increased risk of mortality in a hypertensive population,²⁴ and these data are consistent with our previous findings in the Copenhagen Holter Study cohort.¹⁹ Even though our study population had hypertensive blood pressure values at baseline, adjustments for systolic blood pressure did not change significance in terms of end points in neither the previous nor the present study. Therefore, it seems likely

that the effect of the possible RAAS activation exceeds an increased blood pressure level.

The linkage between RAAS and stroke was already suggested in 1986 by Brown and Brown,²⁵ and several later studies showed beneficial effects of an increased dietary intake of potassium in terms of a reduced stroke risk.^{26,27} One of the mechanisms proposed to be responsible could be suppression of the RAAS system secondary to a higher p-potassium level. New studies have elaborated on the hypothesis because the neuronal damage seen in stroke patients could be associated with increased activity of the angiotensin receptor subtype 1 in the brain-specific RAAS system, whereas the expression of the angiotensin receptor subtype 2 in contrast seems to exert neuroprotective effects.^{28–30} An overactive RAAS system—with hypokalemia as a possible pseudo marker—could, therefore, as a consequence potentiate subclinical strokes, resulting in more extensive neurological damage, worse symptoms, and subsidiarily more pronounced neurological deficits. The synergistic effect of mild hypokalemia and ESVEA could be a

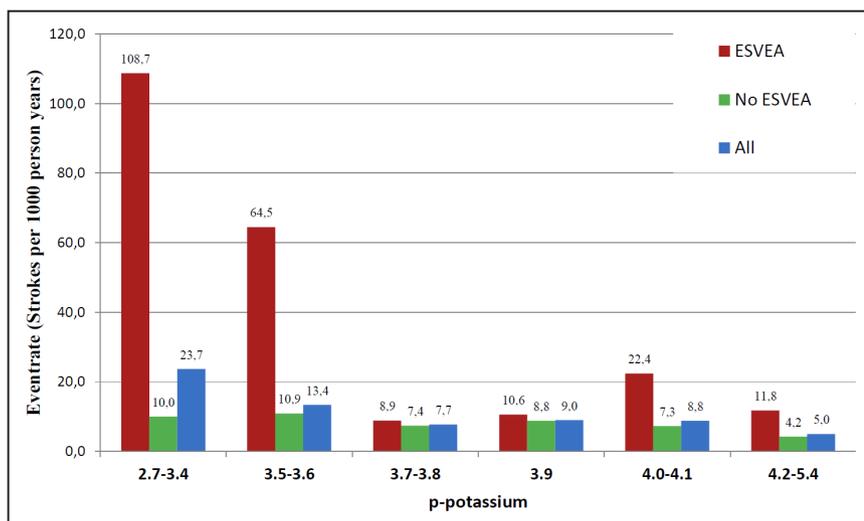


Figure 3. Stroke rates (events per 1000 person-years) by potassium level—including the 2 hypokalemic subgroups—in subjects with or without ESVEA. ESVEA indicates excessive supraventricular ectopic activity; and p-potassium, plasma-potassium.

possible explanation of the substantially increased stroke risk seen in our study.

As angiotensin receptor blockers specifically inhibit the angiotensin receptor subtype I and enhances expression of the angiotensin receptor subtype 2, mild hypokalemic subjects in risk of stroke could be the target for angiotensin receptor blocker treatment. None of the subjects in this study were treated with an angiotensin receptor blocker at baseline.

Perspectives

The prognostic impact of PAC in ambulatory Holter recordings is uncertain, and studies are sparse. The present study adds some knowledge to the prognostic impact of excessive PAC (ESVEA) in mild hypokalemic subjects. We argue that early identification and risk management of hypokalemic patients, who are at higher risk of stroke, may improve the prognosis in terms of lower incidence of stroke and cardiac arrhythmias, including atrial fibrillation. This is, however, hypothetical and should be tested in randomized clinical trials. Even though ESVEA is identified as an independent risk factor for atrial fibrillation and stroke, the majority of these patients do not develop end points in our 14-year follow-up study. Thus, methods are needed to identify subjects at risk, and we argue that p-potassium could be considered in the risk stratification.

To our knowledge, this is the first study to show the possible prognostic impact of hypokalemia in subjects with increased atrial ectopic activity.

Limitations

Because blood samples are only obtained once, the data reflects transient values of p-potassium. However, p-potassium is a key ion in the body with many regulatory mechanisms securing a steady blood concentration and low individual variations over time. All analyses were done immediately after blood sampling to minimize the risk of false values.

Even though adjustments have been made for conventional risk factors, there may still be residual confounding that contributes to the presence of the demonstrated associations. In terms of recruitment, a selection bias cannot be excluded because not all eligible subjects were able to or willing to participate.

Although the total number of hypokalemic subjects with ESVEA was not high in the total population (17 subjects, 2.5% of the total population), event rates remained high enough with good statistical margins of significance, indicating a considerable statistical robustness.

Conclusions

The combination of mild hypokalemia and excessive supraventricular ectopy increases the risk of stroke in middle-aged and elderly subjects synergistically.

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Disclosures

None.

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Mild Hypokalemia and Supraventricular Ectopy Increases the Risk of Stroke in Community-Dwelling Subjects

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Supplemental material

Supplemental table I:

	Normokalemia		Hypokalemia		P-value
	+ ESVEA (n = 81)	- ESVEA (n = 480)	+ ESVEA (n = 17)	- ESVEA (n = 93)	
Age (Years)	66.9 (±6.2)	63.5 (±6.6)	70.3 (±6.0)	66.3 (±7.0)	<0.0001
Female sex, n (%)	28 (35%)	197 (41%)	6 (35%)	46 (49%)	0.23
Body Mass Index (kg/m ²)	27.5 (±5.4)	26.8 (±4.2)	24.7 (±3.5)	26.5 (±4.0)	0.12
Systolic BP (mmHg)	161.3 (±26.1)	153.5 (±22.9)	166.8 (±24.9)	164.8 (±26.5)	<0.0001
Diastolic BP (mmHg)	91.8 (±10.4)	90.3 (±11.0)	94.1 (±8.2)	92.8 (±11.6)	0.10
Current Smoker, n (%)	34 (42%)	228 (48%)	13 (76%)	36 (39%)	0.03
Diabetes Mellitus, n (%)	11 (14%)	50 (10%)	1 (6%)	13 (14%)	0.58
Low-level physical activity, n (%)	19 (23%)	120 (25%)	8 (47%)	29 (31%)	0.11
Creatinine (mmol/L)	95.3 (±16.3)	92.1 (±19.0)	97.9 (±21.2)	92.6 (±21.1)	0.34
Sodium (mmol/L)	140.9 (±2.4)	140.9 (±2.5)	140.8 (±1.9)	140.5 (±3.1)	0.73
Total Cholesterol (mmol/L)	5.8 (±1.0)	6.1 (±1.1)	6.0 (±1.0)	6.0 (±1.0)	0.15
NT-proBNP (pmol/l)	26.1 (±42.8)	14.2 (±52.6)	36.6 (±51.2)	19.8 (±38.8)	0.07
CHA ₂ DS ₂ -VASc (mean, range):	1.9 (0-4)	1.5 (0-5)	2.3 (0-4)	2.1 (0-5)	<0.0001
Aspirin use, n (%)	15 (19%)	60 (13%)	7 (41%)	20 (22%)	0.002
β-Blocker use, n (%)	3 (4%)	19 (4%)	1 (6%)	11 (12%)	0.02
Diuretic use, n (%)	16 (20%)	51 (11%)	9 (53%)	44 (47%)	<0.0001
ACE Inhibitor use, n (%)	4 (5%)	21 (4%)	1 (6%)	6 (6%)	0.85

Supplemental table I: Baseline characteristics of normo- or hypokalemic groups stratified on excessive supraventricular ectopic activity (ESVEA) status. Values are presented as mean ± SD and number (%). BP = Blood pressure. ACE = Angiotensin Converting Enzyme, CRP = C-Reactive-Peptide. CHA₂DS₂-VASc = congestive heart failure, hypertension, age 75 years or older, diabetes mellitus, previous stroke or transient ischemic attack, vascular disease, age 65 to 74 years, female sex.

Supplemental table II:

	<u>Stroke</u> (Hazard Ratio, 95% confidence Interval)	Time At Risk (person-years)	<u>Death or stroke</u> (Hazard ratio, 95% confidence interval)
Model 1	2.05 (1.02-4.09) P = 0.043	6651	1.57 (1.08-2.28) P = 0.020
Model 2	1.94 (0.94-4.00) P = 0.073	6567	1.46 (0.98-2.16) P = 0.062
Model 3	2.32 (1.12-4.77) P = 0.023	6506	1.49 (1.00-2.23) P = 0.051

Supplemental table II: Cox Regression Models showing the Hazard Ratio of Stroke and Death or Stroke in Relation to Hypokalemia after exclusion of diuretic users. *Model 1:* Age and sex adjusted. *Model 2:* Adjusted for additional stroke risk factors (age, sex, smoking, total cholesterol, NT-proBNP, diabetes, body mass index, the level of physical activity and systolic blood pressure). *Model 3:* Model 2 + adjustment for CHA₂DS₂VASc-score.