Plasma Vitamin C Modifies the Association Between Hypertension and Risk of Stroke

S. Kurl, MD; T.P. Tuomainen, MD; J.A. Laukkanen, MD; K. Nyyssönen, PhD; T. Lakka, MD, PhD; J. Sivenius, MD, PhD; J.T. Salonen, MD, PhD, MscPH

**Background and Purpose**—There are no prospective studies to determine whether plasma vitamin C modifies the risk of stroke among hypertensive and overweight individuals. We sought to examine whether plasma vitamin C modifies the association between overweight and hypertension and the risk of stroke in middle-aged men from eastern Finland.

**Methods**—We conducted a 10.4-year prospective population-based cohort study of 2419 randomly selected middle-aged men (42 to 60 years) with no history of stroke at baseline examination. A total of 120 men developed a stroke, of which 96 were ischemic and 24 hemorrhagic strokes.

**Results**—Men with the lowest levels of plasma vitamin C (<28.4 μmol/L, lowest quarter) had a 2.4-fold (95% CI, 1.4 to 4.3; *P*=0.002) risk of any stroke compared with men with highest levels of plasma vitamin C (>64.96 μmol/L, highest quarter) after adjustment for age and examination months. An additional adjustment for body mass index, systolic blood pressure, smoking, alcohol consumption, serum total cholesterol, diabetes, and exercise-induced myocardial ischemia attenuated the association marginally (relative risk, 2.1; 95% CI, 1.2 to 3.8; *P*=0.01). Adjustment for prevalent coronary heart disease and atrial fibrillation did not attenuate the association any further. Furthermore, hypertensive men with the lowest vitamin C levels (<28.4 μmol/L) had a 2.6-fold risk (95% CI, 1.52 to 4.48; *P*<0.001), and overweight men (≥25 kg/m²) with low plasma vitamin C had a 2.7-fold risk (95% CI, 1.48 to 4.90; *P*=0.001) for any stroke after adjustment for age, examination months, and other risk factors.

**Conclusions**—Low plasma vitamin C was associated with increased risk of stroke, especially among hypertensive and overweight men. (*Stroke. 2002;33:1568-1573.)*

**Key Words:** ascorbic acid ■ hypertension ■ obesity ■ preventive medicine ■ risk ■ stroke

Previous studies have shown that oxidation of LDL is involved in atherogenesis and increases the progression of atherosclerosis.¹ ³ Experimental studies have demonstrated that atherogenesis can be slowed by antioxidants.¹ ⁴ Some population studies have suggested that increased consumption of fruits and vegetables decreases the risk of atherosclerotic cardiovascular diseases (CVD), including cerebrovascular strokes.⁵-⁹ whereas ¹ study did not confirm this association.¹⁰ These findings led to a great interest in the role of antioxidative vitamins in CVD, including cerebrovascular strokes.

Low plasma vitamin C concentration has been related to increased progression of carotid atherosclerosis¹¹ and increased risk of acute myocardial infarction.¹² Additionally, supplementation of both vitamin C and vitamin E decelerated the progression of atherosclerosis among male smokers in a large Finnish randomized trial.¹³ Few studies have shown an association between plasma vitamin C levels and the risk of stroke, although plasma vitamin C may be a better indicator of the availability of vitamin C as an antioxidant in the body than dietary intake. Some prospective studies have demonstrated that low serum or plasma ascorbic acid has been associated with increased incidence of stroke¹⁴ and mortality from stroke.⁷ ¹⁵

We investigated the association of plasma vitamin C with the risk of stroke in eastern Finnish middle-aged men with no history of stroke. Furthermore, we studied whether plasma vitamin C modifies the association between blood pressure and body weight and the risk of stroke.

**Subjects and Methods**

**Subjects**

Subjects were participants in the Kuopio Ischemic Heart Disease Risk Factor Study, designed to investigate risk factors for CVD, atherosclerosis, and related outcomes in a population-based sample of men in eastern Finland.⁶lin The study group is a representative random sample of men who lived in the town of Kuopio or its surrounding rural communities and were aged 42, 48, 54, or 60 years at baseline examination between March 1984 and December 1989.
Of 3235 eligible men, 2682 (83%) participated in the study. Men with history of stroke (n = 69) or missing values (n = 193) of covariates were excluded. Complete data on plasma vitamin C level were available for 2419 men.

**Plasma Vitamin C**

Fasting blood samples were obtained from subjects. The sample was drawn in the morning between 7 and 10 AM with the use of Vacutest VT-050 HL heparin tubes. The plasma was separated within 30 minutes by centrifuging at 20°C for 10 minutes and was stabilized with metaphosphoric acid. The stabilized samples were stored at −80°C. Plasma ascorbate concentrations were determined by a chromatographic method in deep-frozen samples. The coefficient of variation between batches for 12 batches was 7.2%.17

**Assessment of Covariates**

The lifelong exposure to smoking was estimated as the product of the number of years spent smoking and the number of tobacco products smoked daily at the time of examination. The serum total cholesterol was measured enzymatically.18–20 Myocardial ischemia during exercise ECG was coded manually by 1 cardiologist. The criteria for myocardial ischemia during the exercise test were ischemic ECG changes, defined as horizontal or downsloping ST depression ≥1.0 mm at 80 ms after J point. The consumption of alcohol in the previous 12 months was assessed with the Nordic Alcohol Consumption Inventory. Alcohol consumption was calculated as grams of absolute alcohol per week. Body mass index (BMI) was computed as the ratio of weight in kilograms to the square of height in meters. Resting blood pressure was measured by an experienced nurse using a random-zero sphygmomanometer. The mean of 2 systolic blood pressure (SBP) values while the subject was sitting was used in these analyses. Diabetes was defined as either previous diagnosis of diabetes mellitus or fasting blood glucose concentration >6.7 mmol/L. Left ventricle hypertrophy (LVH) was assessed according to resting ECG voltage.21

**Ascertainment of Strokes**

Incident strokes between 1984 and 1992 were ascertained through the FINMONICA stroke register.22 Information on stroke incidence between 1993 and December 31, 1998, was obtained by computerized linkage to the Finnish national hospital discharge registry and death certificate registers. Diagnostic information was collected from hospitals and classified by 1 neurologist (J.S.) with diagnostic criteria identical to the FINMONICA criteria. The sources of information on stroke were hospital documents, death certificates, autopsy reports, and medicolegal reports. The diagnosis of stroke was based on sudden onset of clinical signs or focal or global disturbance of cerebral function lasting >24 hours (except in the case of sudden death or if interrupted by surgical intervention) with no apparent cause other than a vascular origin. Each suspected stroke was classified into (1) an ischemic stroke (ICD-9 codes 430 to 439 and International Classification of Diseases, 10th Revision [ICD-10] codes I60 to I63 and G45 to G46) was classified into (1) a definite stroke, (2) no stroke, or (3) unclassifiable events. The FINMONICA stroke register data were annually rechecked with the data obtained from the computerized national hospital discharge and death registers. Definite strokes and unclassifiable events were included in the group of any stroke. Each definite stroke was classified into (1) an ischemic stroke (ICD-9 codes 432 to 434, ICD-10 code I63) or (2) a hemorrhagic stroke (ICD-9 codes 430 to 431, ICD-10 codes I60 to I61). If the subject had multiple nonfatal strokes during the follow-up, the first stroke was considered the end point. The average follow-up time was 10.4 years (range, 0.3 to 13.4 years). A total of 120 first strokes occurred, of which 96 were ischemic strokes.

**Statistical Analysis**

The association of plasma vitamin C with the risk of stroke was analyzed with the use of Cox proportional hazards models. Covariates were selected by entering smoking, serum total cholesterol, diabetes, BMI, alcohol consumption, fasting blood glucose, serum LDL cholesterol, exercise-induced myocardial ischemia, and LVH as possible risk factors for stroke into age- and examination-months–adjusted stepwise Cox models, with a value of P < 0.05 as a selection criterion. Two different sets of covariates were used in subsequent forced Cox models: (1) age and examination months and (2) age, examination months, BMI, smoking, alcohol consumption, SBP, serum total cholesterol, diabetes, exercise-induced myocardial ischemia, atrial fibrillation, and prevalent CHD at baseline. Relative hazards adjusted for risk factors were estimated as antilogarithms of coefficients from multivariate models. Their CIs were estimated under the assumption of asymptotic normality of the estimates. All tests for statistical significance were 2-sided. In the interaction analysis between vitamin C, hypertension, and BMI, (1) plasma vitamin C level was categorized as low and moderate to high according to lowest quartile (28.4 μmol/L); (2) blood pressure level was categorized as hypertension (SBP >140 mm Hg, diastolic blood pressure [DBP] >90 mm Hg, or current use of antihypertensive medication), and normotension (SBP <140 mm Hg, DBP <90 mm Hg, and no medication for blood pressure); and (3) BMI was divided as ≥25 kg/m² (overweight) and <25 kg/m² (normal weight). Statistical analyses were performed with the use of SPSS versions 9.0 and 10.0 software for Windows.

### Results

**Baseline Characteristics**

Plasma vitamin C concentration ranged from 1.7 to 265 μmol/L, with a mean of 47 μmol/L. The distributions of other characteristics are presented in Table 1.

### Strongest Risk Factors for Stroke

In a stepwise Cox model, statistically significant predictors for any stroke were plasma vitamin C, SBP, fasting blood glucose, and exercise-induced myocardial ischemia (Table 2). With an increase of 1 SD in plasma vitamin C (28.4 μmol/L), the risk for any stroke decreased by 26%. A 1-SD increase in resting SBP (17 mm Hg) was associated with a 33% increase in the risk for any stroke; a 1-SD increase in fasting blood glucose level (1.2 mmol/L) amounted to 17% increased risk for any stroke; and the presence of exercise-induced myocardial ischemia was associated with a 19% increase in the risk for any stroke.

<table>
<thead>
<tr>
<th>TABLE 1. Baseline Characteristics of Study Population</th>
<th>Mean (SD)</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma Vitamin C, μmol/L</td>
<td>47.56 (28.4)</td>
<td>1.7–265</td>
</tr>
<tr>
<td>Age, y</td>
<td>53.1 (5.1)</td>
<td>42.0–61.3</td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td>134 (17.1)</td>
<td>87–221</td>
</tr>
<tr>
<td>Exercise-induced myocardial ischemia, %</td>
<td>34.4</td>
<td></td>
</tr>
<tr>
<td>Diabetes, %</td>
<td>5.3</td>
<td></td>
</tr>
<tr>
<td>Serum total cholesterol, mmol/L</td>
<td>5.9 (1.1)</td>
<td>2.6–14.4</td>
</tr>
<tr>
<td>Cigarette smoking, pack-years*</td>
<td>8.7 (17.1)</td>
<td>0.0–174.3</td>
</tr>
<tr>
<td>Alcohol consumption, g/wk</td>
<td>77 (138)</td>
<td>0–2853</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>26.9 (3.6)</td>
<td>17.1–48.6</td>
</tr>
<tr>
<td>Fasting blood glucose, mmol/L</td>
<td>4.8 (1.2)</td>
<td>3.2–28.7</td>
</tr>
<tr>
<td>LVH, %</td>
<td>1.5</td>
<td></td>
</tr>
</tbody>
</table>

*Pack-years denotes lifelong exposure to smoking, estimated as the product of the number of years spent smoking and the number of tobacco products smoked daily at the time of examination.
In an age- and examination months-adjusted stepwise Cox model for ischemic stroke, SBP (P=0.001), BMI (P=0.007), plasma vitamin C (P=0.02), exercise-induced myocardial ischemia (P=0.02), and LVH (P=0.04) were the strongest risk factors. The single most significant predictor for hemorrhagic stroke was plasma vitamin C (P<0.001). With a 1-SD (28.4 μmol/L) increase in plasma vitamin C, the risk for ischemic stroke decreased by 26%, and the risk for hemorrhagic stroke decreased by 47%. A 1-SD (17 mm Hg) increase in SBP was associated with a 33% increase in the risk for ischemic stroke. A 1-SD (3.6 kg/m²) increase in BMI was associated with an increase of 31% in the risk for ischemic stroke.

Plasma vitamin C concentration in quartiles was inversely associated with the risk of ischemic stroke (P=0.03 for linear trend across the quartiles) and hemorrhagic stroke (P=0.007 for linear trend across the quartiles) after adjustment for age and examination months. After further adjustment for other risk factors, the linear trend across the quartiles of vitamin C and ischemic stroke was not statistically significant (P=0.10), whereas the linear trend across the quartiles of vitamin C and hemorrhagic stroke remained significant (P=0.02).

### Interaction Between Plasma Vitamin C and Hypertension and Risk for Stroke

The interaction term between plasma vitamin C and blood pressure, when included into the Cox model with other covariates, was statistically significant (P=0.03). Hypertensive men with the lowest vitamin C levels had a 2.61-fold (95% CI, 1.52 to 4.48; P<0.001) risk for any stroke and a 1.96-fold (95% CI, 1.06 to 3.63; P=0.03) risk for ischemic stroke compared with normotensive men with moderate to high vitamin C levels (≥28.4 μmol/L) after adjustment for age, examination months, and other risk factors (Figure 2). The greatest increase in the risk of stroke was observed among hypertensive men with low and moderate to high vitamin C, and therefore low vitamin C was associated with a 1.85-fold (95% CI, 1.20 to 2.84; P=0.005) risk for any stroke compared with moderate to high vitamin C levels after adjustment for age, examination months, and other risk factors in these men. In a subsample of 620 men with low vitamin C (<28.4 μmol/L, lowest quarter), hypertension (blood pressure >140/90 mm Hg) was related to a 5.41-fold (95% CI, 2.12 to 13.80; P<0.001) risk of stroke after adjustment for age and examination months. In another subsample of 1905 men with plasma vitamin C ≥28.4 μmol/L, hypertensive men had a 1.64-fold (95% CI, 1.01 to 2.66; P=0.04) risk for any stroke. The respective association remained statistically significant (RR=4.87; 95% CI, 1.86 to 12.7; P=0.001) among men with low vitamin C, whereas hypertension was not statistically associated among men with plasma vitamin C ≥28.4 μmol/L after adjustment for other risk factors.

### Interaction Between Plasma Vitamin C and BMI and Risk for Stroke

The age- and examination months-adjusted RRs for any stroke in various combinations of plasma vitamin C level and

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### TABLE 2. Strongest Risk Factors for Any Stroke (n=120) in 2419 Men With No History of Stroke at Baseline

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>RR (95% CI)*</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma Vitamin C (per 28.4 μmol/L)</td>
<td>0.74 (0.61–0.91)</td>
<td>0.004</td>
</tr>
<tr>
<td>SBP (per 17 mm Hg)</td>
<td>1.33 (1.14–1.55)</td>
<td>0.0002</td>
</tr>
<tr>
<td>Fasting blood glucose (per 1.2 mmol/L)</td>
<td>1.17 (1.04–1.33)</td>
<td>0.009</td>
</tr>
<tr>
<td>Exercise-induced myocardial ischemia</td>
<td>1.19 (1.01–1.42)</td>
<td>0.04</td>
</tr>
</tbody>
</table>

*Adjusted for age and examination months. RRs for continuous variables are presented per 1-SD increase in value.

### TABLE 3. Risk for Stroke in 2419 Men With No History of Stroke at Baseline According to Quartiles of Plasma Vitamin C

<table>
<thead>
<tr>
<th>Quartiles of Vitamin C</th>
<th>RR (95% CI)*</th>
<th>P</th>
<th>RR (95% CI)†</th>
<th>P</th>
<th>No. of Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;64.96 μmol/L (n=623)</td>
<td>1.00 (reference)</td>
<td>1.00 (reference)</td>
<td>16 (2.6%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>48.14–64.96 μmol/L (n=600)</td>
<td>1.61 (0.86–2.99)</td>
<td>0.14</td>
<td>1.47 (0.79–2.75)</td>
<td>0.23</td>
<td>26 (4.3%)</td>
</tr>
<tr>
<td>28.4–47.56 μmol/L (n=599)</td>
<td>2.02 (1.12–3.67)</td>
<td>0.02</td>
<td>1.76 (0.96–3.20)</td>
<td>0.06</td>
<td>34 (5.7%)</td>
</tr>
<tr>
<td>≤28.4 μmol/L (n=597)</td>
<td>2.44 (1.37–4.34)</td>
<td>0.002</td>
<td>2.10 (1.17–3.80)</td>
<td>0.01</td>
<td>44 (7.4%)</td>
</tr>
</tbody>
</table>

*Adjusted for age and examination months.
†Adjusted for age, examination months, BMI, smoking, alcohol consumption, SBP at rest, serum total cholesterol, diabetes, and myocardial ischemia during exercise.

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BMI in men with moderate to high plasma vitamin C and normal weight (<25 kg/m²), as a reference group, are presented in Figure 3. The greatest difference in the risk for stroke was observed among normal-weight men with moderate to high vitamin C and overweight men with low vitamin C. In these analyses, overweight men (≥25 kg/m²) with low plasma vitamin C had a 2.69-fold (95% CI, 1.48 to 4.90; P=0.001) risk for any stroke and a 2.30-fold (95% CI, 1.16 to 4.53; P=0.02) risk for ischemic stroke compared with normal-weight men with moderate to high levels of plasma vitamin C. After adjustment for other risk factors except for BMI, the RR was 2.04 (95% CI, 1.10 to 3.77; P=0.002) for any stroke, whereas this association was not statistically significant for ischemic stroke (RR=1.74; 95% CI, 0.87 to 3.50; P=0.12). Additionally, in these Cox models overweight men with low plasma vitamin C had a 1.57-fold (95% CI, 1.03 to 2.39; P=0.04) risk for any stroke compared with overweight men who had moderate to high plasma vitamin C after adjustment for age and examination months.

Discussion
This prospective follow-up study shows that low plasma vitamin C concentration was associated with an increased risk of stroke in a representative population-based sample of middle-aged men from eastern Finland. Low plasma vitamin C increases the risk for any stroke among hypertensive and overweight men. On the basis of our study, it seems that hypertension appeared to elevate the risk of stroke, especially in men with low plasma vitamin C levels.

The association between plasma vitamin C and the risk of stroke has been evaluated in few studies. In a recent prospective study, an inverse association between serum vitamin C and the risk of any, ischemic, and hemorrhagic stroke was observed.
observed after potential confounders were taken into account. In this study, \textsuperscript{14} serum vitamin C was associated with the risk of any stroke among women but not with ischemic or hemorrhagic strokes. Furthermore, 2 other cohort studies reported an inverse relation between vitamin C concentration and mortality from stroke. \textsuperscript{7,15} In a follow-up study of elderly persons, both the lowest vitamin C intake and plasma vitamin C were related to an increased mortality from stroke. \textsuperscript{7} Additionally, a prospective population study \textsuperscript{15} found that low plasma concentration of vitamin C was associated with a markedly increased risk of death from stroke.

Ascorbate is an effective antioxidant in human plasma and important in the prevention of atherosclerosis progression. \textsuperscript{23} It is known that vitamin C inhibits the oxidation of LDLs in vitro\textsuperscript{24–26} and thus probably also in vivo. Ascorbic acid is the first antioxidant to be exhausted during the process of lipid peroxidation in plasma, and detectable lipid peroxidation begins only after all of ascorbate has been completely exhausted. \textsuperscript{24} Previous studies have suggested that ascorbate can inhibit the initiation\textsuperscript{25,26} and propagation of lipid peroxidation, even though it is not lipid soluble. \textsuperscript{27} Furthermore, ascorbate is a physiological antioxidant that helps to regenerate reduced antioxidative tocopherol from the tocopheroxyl radical. \textsuperscript{25,26} An additional possible mechanism through which ascorbate may reduce the risk of CVD is the promotion of endothelial prostacyclin, which decreases vascular tone and reduces platelet. \textsuperscript{4}

In this study we observed that hypertensive men with low plasma vitamin C have an increased risk for cerebrovascular strokes, emphasizing the interaction between vitamin C and blood pressure. This is supported by our previous findings that show an association between low plasma vitamin C and elevated blood pressure. \textsuperscript{28} This clinical trial showed a beneficial effect of antioxidant supplementation on blood pressure. Additionally, we previously observed that increase in plasma ascorbic acid concentration correlated strongly with reduction in blood pressure. \textsuperscript{29} There is some evidence for a role of oxidative stress in the etiology of hypertension. \textsuperscript{30} However, the results regarding the effect of vitamin C on blood pressure are sparse and not convincing. Another possible effect of vitamin C is that it enhances endothelial function as nitric oxide inactivation by oxygen free radicals contributes to the dysfunction of endothelium in essential hypertension commonly due to overweight. \textsuperscript{31} The endothelial dysfunction can be improved by antioxidant vitamin C, thereby reducing the risk of stroke, especially among hypertensive and overweight individuals. \textsuperscript{32} Thus, vitamin C decreases blood pressure, which may partly explain the association between fruit and vegetable intake and mortality from stroke and CVD. \textsuperscript{5,6,8} Lastly, the Dietary Approaches to Stop Hypertension (DASH) study demonstrates that a diet rich in fruits, vegetables, low-fat dairy products, fiber, and minerals (calcium, potassium, and magnesium) produces a potent antihypertensive effect. \textsuperscript{33}

The main strength of our study is that the results are based on a representative population-based sample of men. Second, there were no losses to follow-up. Furthermore, the diagnostic information was validated by the practices and criteria used in the FINMONICA stroke register. Finally, plasma vitamin C concentrations were determined after a freezing time of several days; plasma vitamin C may be the most accurate marker of vitamin C availability in the body.

An important problem in population-based cohort studies is the confounding between nutrient intake and the incidence of stroke. For example, people taking vitamin supplements or eating fruits and vegetables rich in vitamin C may be more health conscious than those who do not. High intake of vitamin C may be also a marker of a diet enriched by fruits and vegetables, including low intake of foods that contain sodium and fat. \textsuperscript{33} Therefore, it is possible that vitamin C alone was not responsible for the results presented in the present study. It is difficult to associate any 1 mineral or vitamin with reduction in blood pressure or stroke incidence because an appropriate metabolic balance of vitamins is recommended and because of the strong correlations among vitamin and mineral intake when diets enriched in fruits and vegetables are consumed. In fact, the evidence reviewed indicates that although vitamin C apparently has a marked effect, other vitamins and minerals may potentially contribute to blood pressure and stroke reduction. \textsuperscript{33,34}

Furthermore, we previously reported that the plasma ascorbate has seasonal variations, and the average concentration falls considerably during winter in eastern Finnish men. \textsuperscript{35} This variability is probably random among subjects. Thus, this may attenuate the observed associations. Furthermore, we adjusted for examination months to avoid seasonal differences in the intake of vitamin C. Another possible limitation is that our study was based only on an eastern Finnish male population. In addition, plasma vitamin C levels were measured only at the baseline examination. It would be more ideal to measure plasma vitamin C over a period of time to study whether the changes in vitamin C would predict the risk of stroke.

In conclusion, this prospective study from eastern Finland suggests that low vitamin C concentration is a risk factor for future stroke. Our study shows that hypertensive and overweight men are the specific risk groups with an increased risk of stroke if plasma vitamin C level is low. These findings provide rationale for clinical trials that test the efficacy of vitamin C supplements in the prevention of strokes among hypertensive and obese men.

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References


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