Different Risk Factors for Different Stroke Subtypes
Association of Blood Pressure, Cholesterol, and Antioxidants

Jaana M. Leppälä, MD; Jarmo Virtamo, MD; Rainer Fogelholm, MD; Demetrius Albanes, MD; Olli P. Heinonen, MD

Background and Purpose—Blood pressure is an important risk factor for stroke, but the roles of serum total and HDL cholesterol, α-tocopherol, and β-carotene are poorly established. We studied these factors in relation to stroke subtypes.

Methods—Male smokers (n=28519) aged 50 to 69 years without a history of stroke participated in the Alpha-Tocopherol, Beta-Carotene Cancer Prevention (ATBC) Study, a controlled trial to test the effect of α-tocopherol and β-carotene supplementation on cancer. From 1985 to 1993, a total of 1057 men suffered from primary stroke: 85 had subarachnoid hemorrhage; 112, intracerebral hemorrhage; 807, cerebral infarction; and 53, unspecified stroke.

Results—Systolic blood pressure ≥160 mmHg increased the risk of all stroke subtypes 2.5 to 4-fold. Serum total cholesterol was inversely associated with the risk of intracerebral hemorrhage, whereas the risk of cerebral infarction was raised at concentrations ≥7.0 mmol/L. The risks of subarachnoid hemorrhage and cerebral infarction were lowered with serum HDL cholesterol levels ≥0.85 mmol/L. Pretrial high serum α-tocopherol decreased the risk of intracerebral hemorrhage by half and cerebral infarction by one third, whereas high serum β-carotene doubled the risk of subarachnoid hemorrhage and decreased that of cerebral infarction by one fifth.

Conclusions—The risk factor profiles of stroke subtypes differ, reflecting different etiopathology. Because reducing atherosclerotic diseases, including ischemic stroke, by lowering high serum cholesterol is one of the main targets in public health care, further studies are needed to distinguish subjects with risk of hemorrhagic stroke. The performance of antioxidants needs confirmation from clinical trials. (Stroke. 1999;30:2535-2540.)

Key Words: antioxidants ■ blood pressure ■ cerebral infarction ■ cholesterol ■ intracerebral hemorrhage ■ subarachnoid hemorrhage

High blood pressure is the most important of the known risk factors for all stroke subtypes.1-5 Cigarette smoking is also a well-known risk factor for subarachnoid hemorrhage4 and cerebral infarction,1,2,5,6 but the association with intracerebral hemorrhage is not clear-cut.2,3,6-9 The relations between serum total and HDL cholesterol and stroke risk are not clear, yet there is mounting evidence that serum total cholesterol concentration is inversely associated with the risk of intracerebral hemorrhage, whereas the risk of cerebral infarction was raised at concentrations ≥7.0 mmol/L. The risks of subarachnoid hemorrhage and cerebral infarction were lowered with serum HDL cholesterol levels ≥0.85 mmol/L. Pretrial high serum α-tocopherol decreased the risk of intracerebral hemorrhage by half and cerebral infarction by one third, whereas high serum β-carotene doubled the risk of subarachnoid hemorrhage and decreased that of cerebral infarction by one fifth.

The aim of the present study was to evaluate the association of systolic and diastolic blood pressure, serum total and HDL cholesterol, serum α-tocopherol and β-carotene, and cigarette smoking (measured at the beginning of follow-up) with the risks of subarachnoid and intracerebral hemorrhage and cerebral infarction in middle-aged male smokers.

Subjects and Methods
The present study was carried out within the Alpha-Tocopherol, Beta-Carotene Cancer Prevention (ATBC) Study, a randomized, double-blind, placebo-controlled, primary-prevention trial to test the hypothesis that α-tocopherol and β-carotene supplements reduce the incidence of lung and other cancers.22,23 Of the 29133 smokers (≥5 cigarettes per day) aged 50 to 69 years who were recruited to the ATBC Study from 1985 to 1988 from the total male population of southwestern Finland (n=290,406), 28519 were included in the present study. Excluded from the study were 614 men who had reported previous stroke. The median length of follow-up was 6.0 years. The study was approved by the institutional review boards of the National Public Health Institute, Helsinki, Finland, and the National Cancer Institute, Bethesda, Md. All participants gave written informed consent, and their safety was monitored by an outside committee.
At baseline, the participants completed a questionnaire about their general background, smoking, and medical history, including a question about physician-diagnosed stroke. Blood pressure levels were assessed by nurses who were trained to obtain standardized and coherent measurements. Height and weight were measured, and body mass index was calculated as weight divided by height squared. Serum total and HDL cholesterol levels were determined enzymatically (CHOD-PAP method, Boehringer-Mannheim). HDL cholesterol was measured after precipitation of VLDL and LDL cholesterol with dextran sulfate and magnesium chloride. Serum α-tocopherol and β-carotene were determined by high-performance liquid chromatography. Alcohol consumption during the previous year was assessed with a detailed dietary history questionnaire.25

The end points were incident subarachnoid and intracerebral hemorrhage and cerebral infarction. Strokes were identified by record linkage to the National Hospital Discharge Register and the National Register of Causes of Death, which used 2 editions of the International Classification of Diseases (ICD): up to the end of 1986, the 8th edition (ICD-8) was used; thereafter, the 9th edition (ICD-9) was used.26,27 ICD codes 430 to 434 and 436 were included in the present study, but ICD-8 codes 431.01 and 431.91 and ICD-9 code 432 denoting subdural hematoma and ICD-9 codes 4330X, 4339X, and 4340X representing steming occlusion or stenosis of a precerebral or cerebral artery without infarction were excluded. In a reviewed sample, the diagnoses of subarachnoid and intracerebral hemorrhage and cerebral infarction proved correct by strict preset criteria in 79%, 82%, and 90% of the discharge diagnoses and in 95%, 91%, and 92% of the causes of death.28 Of men with stroke, 77% had been examined with computed tomography, 4% had been examined with MRI, 17% had been examined with angiography, 7% had had brain surgery, 7% were examined at autopsy, and 14% had clinical evaluation only.

Baseline systolic and diastolic blood pressures were divided into 3 categories: $\geq 139$, 140 to 159, and $\geq 160$ mm Hg and $< 89$, 90 to 99, and $\geq 100$ mm Hg for systolic and diastolic, respectively. Serum total cholesterol was categorized as $< 4.9$, 5.0 to 5.9, 6.0 to 6.9, and $\geq 7.0$ mmol/L, and HDL cholesterol was categorized as $< 0.84$, 0.85 to 1.14, 1.15 to 1.44, and $\geq 1.45$ mmol/L. Smoking was determined as the number of cigarettes smoked per day, and men were divided into 3 groups (5 to 15, 16 to 20, and $\geq 21$ cigarettes per day). Serum α-tocopherol and β-carotene were divided into quartiles. Information on diabetes and heart disease (coronary heart disease, myocardial infarction, valvular disease, arrhythmia, cardiac enlargement, and congestive heart failure) was based on medical history reported before the follow-up. The level of education was categorized as primary school (7 years), secondary school (7 to 12 years), and university or other higher education (>$12$ years). Leisure-time physical activity was categorized as sedentary or active (strenuous exercise at least once a week).

When calculating person-years for incidence rates, the follow-up ended at any stroke end point of interest, at death, or at April 30, 1993, the end of follow-up. Crude incidence rates were calculated per 10 000 person-years. Relative risks were computed by using Cox proportional hazards models adjusted for age, systolic blood pressure, body mass index, serum total and HDL cholesterol, diabetes, previous heart disease, alcohol consumption, number of cigarettes smoked per day, education, physical activity, and serum α-tocopherol and β-carotene levels (Table 1). Baseline values of blood pressure were missing for 5 men; weight or height, for 17 men; serum total cholesterol, for 33 men; serum HDL cholesterol, for 37 men; and serum α-tocopherol and β-carotene, for 27 men. Men with a missing value for the specific variable under study were excluded from respective multivariate analyses, whereas missing values of covariates were replaced with group-specific mean values. When the effect of a specific variable was examined, the examined variable was categorized, but the covariates were in their continuous forms in the models. When risk factor profiles were compared, variables were in their continuous forms in the models, their effects were evaluated concurrently, and men with missing values were all excluded. All analyses were repeated in the trial placebo group only. Because the findings were similar, only the results based on the total study population are reported in detail.

### Results

A total of 1057 men with no history of stroke suffered from incident stroke during the follow-up: 85 men had subarachnoid hemorrhage, 112 had intracerebral hemorrhage, 807 men had cerebral infarction, and 53 men had unspecified stroke. Table 1 shows the baseline characteristics by outcome.

**Subarachnoid Hemorrhage**

There was a steady increase of adjusted relative risk with increasing systolic and diastolic blood pressure, and serum HDL cholesterol levels $\geq 0.85$ mmol/L seemed to decrease and smoking $\geq 16$ cigarettes per day seemed to increase the risk (Table 2). Serum β-carotene levels $\geq 0.26$ mg/L increased the adjusted relative risk (Table 3).

**Intracerebral Hemorrhage**

The risk of intracerebral hemorrhage increased with increasing systolic and diastolic blood pressures (Table 2). The adjusted relative risk decreased unvaryingly to 0.20 at serum total cholesterol levels $\geq 7.0$ mmol/L compared with the lowest levels ($< 5.0$ mmol/L). An interesting finding was that the adjusted relative risk dropped to $\approx 0.50$ in all 3 upper serum α-tocopherol quartiles compared with the lowest quartile ($< 9.8$ mg/L) (Table 3).

**Cerebral Infarction**

The adjusted relative risk of cerebral infarction was increased with increasing systolic and diastolic blood pressures (Table 2). A marginally increased risk associated with serum total cholesterol was evident in only the highest concentrations ($\geq 7.0$ mmol/L), but the decrease in the risk with increasing serum HDL cholesterol was already evident in concentrations $\geq 0.85$ mmol/L. The higher the levels of both serum α-tocopherol and β-carotene, the smaller was the adjusted relative risk, being statistically significant at the highest levels ($\geq 13.6$ mg/L and $\geq 0.26$ mg/L, respectively) (Table 3).

### Risk Factor Profiles in Comparison

The multivariate adjusted risk factor profile of subarachnoid hemorrhage had little in common with those of intracerebral hemorrhage and cerebral infarction, whereas the latter ones resembled each other. High systolic and diastolic blood pressure increased the risk of all stroke subtypes. Only smoking increased and serum HDL cholesterol decreased the risk of subarachnoid hemorrhage. High serum total cholesterol seemed to decrease the risk of intracerebral hemorrhage but to increase the risk of cerebral infarction. By contrast, low serum HDL cholesterol increased the risk of cerebral infarction but not of intracerebral hemorrhage. In addition, age significantly increased the risks of both intracerebral hemorrhage and cerebral infarction. Diabetes and heart disease marginally increased the risk of intracerebral hemorrhage and significantly increased the risk of cerebral infarction. On the other hand, physical activity marginally decreased the risk of intracerebral hemorrhage and significantly decreased the risk of cerebral infarction. Body mass index had no effect on any...
type of stroke. The main findings remained unchanged when evaluated in the trial placebo group only.

Discussion

The advantages of the present study are manifold. This study was population-based, and the number of participants was large. The accuracy of stroke diagnoses was good. The diagnostic practice of stroke remained apparently stable during the follow-up, even though the ICD coding system changed in the beginning of follow-up. The main findings remained unchanged when examined in the trial placebo group only, indicating that controlling the trial supplement by mathematical modeling in the total study group was successful. Risk factors for different stroke subtypes have also been evaluated in the MRFIT Study1 but only for fatal strokes, and follow-up for that study started in the 1970s, when computed tomography was not yet diagnostic practice.

The risks of all subtypes of stroke increased with increasing systolic and diastolic blood pressures, which is in accord with the literature.1-5 Similar to earlier studies,7,8,10,11 a trend of inverse association was found between serum total cholesterol and the risk of subarachnoid hemorrhage. The inverse association of serum total cholesterol with the risk of intracerebral hemorrhage was significant despite the relatively high upper limit of the lowest quartile (4.9 mmol/L); in other studies, the highest incidences have been observed in lower concentrations (<4.14 mmol/L).11 The risk of cerebral infarction was increased in men with serum cholesterol at least 7.0 mmol/L, a level similar to that reported by others.7,10,12 Serum HDL cholesterol was inversely associated with the risks of subarachnoid hemorrhage and cerebral infarction but not with the risk of intracerebral hemorrhage; there appeared to be a threshold for the lowered risks at ≥0.85 mmol/L for subarachnoid hemorrhage and cerebral infarction. Woo et al29 reported decreased odds ratios for all strokes combined at serum HDL cholesterol levels ≥0.97 mmol/L. In their study, subarachnoid hemorrhages were excluded, 21% of the strokes were intracerebral hemorrhages and 79% were ischemic events, and lipid concentrations were measured after the stroke occurred.

All men in the present study were cigarette smokers; nonsmoking controls were not available. Nevertheless, the number of cigarettes smoked increased the risk of subarachnoid hemorrhage but not the risk of intracerebral hemorrhage and cerebral infarction. This emphasizes the importance of smoking as a risk factor for subarachnoid hemorrhage and its comparatively lesser role in the other stroke subtypes, even though the apparent weak association of cigarette smoking with the latter ones relates to the study design and lack of variability in smoking exposure among the participants. Similar findings have been reported in other studies.2,3,5,9,30,31

Subarachnoid hemorrhage is commonly caused by rupture of an arterial aneurysm. An aneurysm may be due to a congenital defect in the wall of an artery or, more probably,
to an acquired lesion related to degenerative changes of the vessel wall later in life. Hypertension alone or in connection with atherosclerosis, combined with hemodynamic action and natural weak points in the cerebral vessel wall, is thought to be important in causing the degenerative changes. It is still unclear how the effect of smoking is mediated in subarachnoid hemorrhage and what roles the hemodynamic and rheological changes caused by smoking play in the pathogenesis, but the increased serum proteolytic activity of cigarette smokers may be one explanation.

The etiopathology of intracerebral hemorrhage is poorly understood. The most popular current theory of "microaneurysms" has been challenged lately, and it has been postulated that fibrinoid necrosis of small arteries and arterioles

### TABLE 2. Crude Incidence per 10 000 Person-Years and Adjusted Relative Risk (95% CI) of Stroke Subtypes by Systolic and Diastolic Blood Pressure, Serum Total and HDL Cholesterol, and Smoking at Beginning of Follow-Up

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Subarachnoid Hemorrhage</th>
<th>Intracerebral Hemorrhage</th>
<th>Cerebral Infarction</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>I</td>
<td>RR (95% CI)</td>
</tr>
<tr>
<td><strong>Systolic blood pressure</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤139 mm Hg</td>
<td>21</td>
<td>2.7</td>
<td>1.00 ...</td>
</tr>
<tr>
<td>140–159 mm Hg</td>
<td>36</td>
<td>6.5</td>
<td>2.57 (1.49–4.44)</td>
</tr>
<tr>
<td>≥160 mm Hg</td>
<td>28</td>
<td>9.4</td>
<td>3.86 (2.14–6.94)</td>
</tr>
<tr>
<td><strong>Diastolic blood pressure</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤89 mm Hg</td>
<td>30</td>
<td>3.3</td>
<td>1.00 ...</td>
</tr>
<tr>
<td>90–99 mm Hg</td>
<td>30</td>
<td>6.0</td>
<td>1.89 (1.13–3.16)</td>
</tr>
<tr>
<td>≥100 mm Hg</td>
<td>25</td>
<td>11.1</td>
<td>3.54 (2.04–6.17)</td>
</tr>
<tr>
<td><strong>Serum total cholesterol</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤4.9 mmol/L</td>
<td>12</td>
<td>5.7</td>
<td>1.00 ...</td>
</tr>
<tr>
<td>5.0–5.9 mmol/L</td>
<td>35</td>
<td>7.0</td>
<td>1.20 (0.62–2.32)</td>
</tr>
<tr>
<td>6.0–6.9 mmol/L</td>
<td>19</td>
<td>3.6</td>
<td>0.60 (0.29–1.24)</td>
</tr>
<tr>
<td>≥7.0 mmol/L</td>
<td>19</td>
<td>4.8</td>
<td>0.78 (0.38–1.62)</td>
</tr>
<tr>
<td><strong>Serum HDL cholesterol</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤0.84 mmol/L</td>
<td>14</td>
<td>8.3</td>
<td>1.00 ...</td>
</tr>
<tr>
<td>0.85–1.14 mmol/L</td>
<td>29</td>
<td>4.4</td>
<td>0.50 (0.26–0.95)</td>
</tr>
<tr>
<td>1.15–1.44 mmol/L</td>
<td>33</td>
<td>6.5</td>
<td>0.69 (0.36–1.33)</td>
</tr>
<tr>
<td>≥1.45 mmol/L</td>
<td>9</td>
<td>2.9</td>
<td>0.26 (0.11–0.62)</td>
</tr>
<tr>
<td><strong>Smoking</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5–15 cigarettes/d</td>
<td>20</td>
<td>3.7</td>
<td>1.00 ...</td>
</tr>
<tr>
<td>16–20 cigarettes/d</td>
<td>31</td>
<td>5.6</td>
<td>1.42 (0.81–2.51)</td>
</tr>
<tr>
<td>≥21 cigarettes/d</td>
<td>34</td>
<td>6.2</td>
<td>1.55 (0.87–2.74)</td>
</tr>
</tbody>
</table>

N indicates number of incident strokes; I, incidence per 10,000 person-years; and RR, relative risk adjusted for age, body mass index, systolic blood pressure, serum total and HDL cholesterol, smoking, alcohol consumption, diabetes, heart disease, education, physical activity, and α-tocopherol and β-carotene supplementation.

### TABLE 3. Crude Incidence per 10 000 Person-Years and Adjusted Relative Risk (95% CI) of Stroke Subtypes by Serum α-Tocopherol and β-Carotene at Beginning of Follow-Up

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Subarachnoid Hemorrhage</th>
<th>Intracerebral Hemorrhage</th>
<th>Cerebral Infarction</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>I</td>
<td>RR (95% CI)</td>
</tr>
<tr>
<td><strong>Serum α-tocopherol</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤9.7 mg/L</td>
<td>24</td>
<td>5.9</td>
<td>1.00 ...</td>
</tr>
<tr>
<td>9.8–11.4 mg/L</td>
<td>25</td>
<td>6.2</td>
<td>1.15 (0.64–2.06)</td>
</tr>
<tr>
<td>11.5–13.5 mg/L</td>
<td>13</td>
<td>3.1</td>
<td>0.61 (0.29–1.27)</td>
</tr>
<tr>
<td>≥13.6 mg/L</td>
<td>23</td>
<td>5.6</td>
<td>1.10 (0.53–2.31)</td>
</tr>
<tr>
<td><strong>Serum β-carotene</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤0.10 mg/L</td>
<td>19</td>
<td>4.7</td>
<td>1.00 ...</td>
</tr>
<tr>
<td>0.11–0.16 mg/L</td>
<td>22</td>
<td>5.5</td>
<td>1.47 (0.78–2.75)</td>
</tr>
<tr>
<td>0.17–0.25 mg/L</td>
<td>17</td>
<td>4.1</td>
<td>1.25 (0.63–2.49)</td>
</tr>
<tr>
<td>≥0.26 mg/L</td>
<td>27</td>
<td>6.3</td>
<td>2.30 (1.20–4.40)</td>
</tr>
</tbody>
</table>

RR was adjusted for age, body mass index, systolic blood pressure, serum total and HDL cholesterol, smoking, alcohol consumption, diabetes, heart disease, education, physical activity, and α-tocopherol and β-carotene supplementation.
caused by hypertension might lead directly to cerebral hemorrhage. The etiopathology of cerebral infarction is better understood, and its causes can be grossly divided into thrombosis and embolism or large artery and lacunar disease, both associated with atherosclerosis.35,36

Hypertension seems to be the most important determinant in both intracerebral hemorrhage and cerebral infarction and is known to lead to atherosclerosis, with predilection for precerebral and large cerebral arteries.37 On the other hand, the small intraparenchymal cerebral arteries develop hyaline degeneration and fibrinoid necroses associated with lacunar infarcts and hemorrhages; however, the body of evidence is much weaker for this explanation than for the association between hypertension and atherosclerosis.38

The only risk factors examined in the present study that had opposite effects on the risks of intracerebral hemorrhage and cerebral infarction were serum total and HDL cholesterol levels. The harmful effect of high serum total cholesterol and the protective effect of high serum HDL cholesterol on the risk of cerebral infarction were in accord with the general concepts of atherosclerosis. It has been postulated that low serum cholesterol levels could cause weakening of the endothelium of small intracerebral arteries, which, in connection with hypertension, could lead to hemorrhagic stroke.39 Because intracerebral hemorrhage and cerebral infarction appear to share the risk factors for stroke, there must be some yet-unknown mechanism (which may well be connected to lipid metabolism) that determines whether the degenerative process leads to intracerebral hemorrhage or cerebral infarction.

The protective effect of both serum \( \alpha \)-tocopherol and \( \beta \)-carotene on the risk of cerebral infarction is consistent with previous studies.20,21,40 The possible beneficial effect of \( \alpha \)-tocopherol and \( \beta \)-carotene on both intracerebral hemorrhage and cerebral infarction could be mediated by their antioxidant actions in preventing atherosclerosis. On the other hand, the effect of \( \alpha \)-tocopherol could also be mediated by its antiplatelet and anticoagulant actions,16–19 which would prevent the thrombotic consequences of atherosclerosis. \( \alpha \)-Tocopherol supplementation increased the risk of subarachnoid hemorrhage and decreased the risk of cerebral infarction, whereas \( \beta \)-carotene supplementation increased the risk of intracerebral hemorrhage in our controlled trial.41 There may be a limited physiological range within which compounds such as \( \alpha \)-tocopherol and \( \beta \)-carotene act benefically, with lower or higher concentrations bringing no additional benefit and possibly even being harmful. In epidemiological studies, serum \( \alpha \)-tocopherol and \( \beta \)-carotene may also be markers of lifestyles relevant to stroke risks.

Overall, the risk factor profiles differed among the stroke subtypes, and the risk profile of intracerebral hemorrhage resembled that of cerebral infarction more than that of subarachnoid hemorrhage. On the other hand, the risk profile of all strokes combined reflected, for the most part, the heavy weight of cerebral infarction with the largest incidence. This implies that studies ignoring stroke subtyping might give misleading weights for various risk factors and might not detect true associations. Given that the etiopathology differs in each stroke subtype, it is important that future studies of stroke classify events properly by subtypes.

In conclusion, elevated blood pressure increases the risk of all subtypes of stroke. By contrast, the associations of serum total and HDL cholesterol are different for different strokes. Reducing the burden of atherosclerotic cardiovascular diseases, including cerebral infarction, by lowering high cholesterol is one of the main targets in public health care. Further study is needed to distinguish subjects who benefit from lowering cholesterol without risk of hemorrhagic stroke. The different associations of serum \( \alpha \)-tocopherol and \( \beta \)-carotene with the risks of stroke subtypes call for further research to clarify their potential role in stroke prevention. Subarachnoid and intracerebral hemorrhage and cerebral infarction are separate entities, each having an individual risk factor profile. In studies involving the epidemiology of stroke, subtypes of stroke must be dealt with separately.

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References


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