Use of Aspirin, Epistaxis, and Untreated Hypertension as Risk Factors for Primary Intracerebral Hemorrhage in Middle-Aged and Elderly People

Pertti Saloheimo, MD; Seppo Juvela, MD, PhD; Matti Hillbom, MD, PhD

Background and Purpose—The incidence of primary intracerebral hemorrhage (ICH) increases exponentially with age, but the risk factors are not well known. We investigated lifestyle factors, previous diseases, and medications as risk factors for ICH in middle-aged and elderly people.

Methods—We compared 98 consecutive patients with primary ICH between 36 and 90 years of age with 206 community-based control subjects matched for age and sex. Odds ratios (ORs) and 95% confidence intervals (CIs) after adjustment for possible confounding variables were calculated by logistic regression.

Results—The independent risk factors for ICH were untreated hypertension (OR, 6.95; 95% CI, 3.06 to 15.8), previous ischemic stroke (OR, 3.83; 95% CI, 1.70 to 8.63), epilepsy (OR, 13.8; 95% CI, 2.49 to 76.6), recent strenuous physical exertion (OR, 3.97; 95% CI, 1.95 to 8.10), and a history of epistaxis (OR, 2.92; 95% CI, 1.28 to 6.62). In men, treated hypertension (OR, 2.67; 95% CI, 1.03 to 6.93) was also a significant risk factor. Patients with a history of epistaxis who had used nonsteroidal anti-inflammatory drugs, especially aspirin in high doses, had an increased risk for ICH (adjusted OR of epistaxis, 2.75; 95% CI, 1.11 to 6.81; adjusted OR of aspirin use, 14.7; 95% CI, 2.03 to 106). In addition, there was a significant (P<0.01) positive interaction between the history of epistaxis and the use of aspirin on the risk for ICH.

Conclusions—Epistaxis is a risk factor for ICH in middle-aged and elderly people, both independently and combined with the use of aspirin. Other independent risk factors are untreated hypertension, previous ischemic stroke, epilepsy, and recent strenuous physical exertion. Epistaxis may be a warning sign of an increased risk for ICH in subjects using aspirin. (Stroke. 2001;32:399-404.)

Key Words: aspirin ■ exercise ■ hypertension ■ intracerebral hemorrhage ■ risk factors

To influence the annual incidence (26 to 60 per 100 000) of intracerebral hemorrhage (ICH), it is important to recognize all the modifiable risk factors for this serious subtype of stroke, which carries a case fatality rate of ≈50%. Arterial hypertension is the best documented treatable risk factor for ICH. The other known modifiable risk factors include drug abuse and the use of anticoagulants, as well as the use of platelet inhibitors, such as aspirin.

Although many studies have suggested that the use of aspirin may predispose to spontaneous ICH, the significance of aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs) as an identifiable risk factor for ICH has remained unclear. Furthermore, we do not know whether the risk is associated with some other risk factors of ICH, such as the patient’s age, hypertension, and heavy drinking of alcohol, and how the dose of the drug influences the risk.

This study was designed to identify the role of lifestyle factors, previous diseases, and medication as risk factors and exceptionally strenuous physical exertion as a triggering factor for primary ICH in middle-aged and elderly people. In addition, the independent roles of several factors not studied before as risk factors for ICH were investigated.

Subjects and Methods

From January 1993 to September 1995, a total of 98 consecutive patients (56 men, 42 women; age, 36 to 90 years) with spontaneous ICH were admitted to the Department of Neurology, Oulu University Hospital. ICH was verified by head computed tomography (CT) on admission in all cases. We excluded patients who had a brain tumor, saccular arterial aneurysm, arteriovenous malformation, head trauma, or epileptic seizure concomitant to ICH (to exclude traumatic ICH).

Two hundred six control subjects, matched for age (±3 years) and sex, were randomly drawn from population register of the catchment area of Oulu University Hospital. The study protocol was approved by the ethics committee of the hospital, and informed consent was obtained before the subjects were interviewed. Data and permission for the study were given by a relative if the patient was too ill to cooperate.

Received July 7, 2000; final revision received October 24, 2000; accepted October 24, 2000.

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The patients and control subjects were always interviewed by the same person (P.S.). For those ICH patients who were confused, unconscious, or dysphasic or who died soon after admission, family members were interviewed. Patients and/or their relatives were personally interviewed, but the control subjects were interviewed over telephone. Control subjects were interviewed on days of the week matched with the bleeding days of the patients. Information was gathered by use of a structured questionnaire including items on the use of medicines, events preceding the onset of stroke, previous diseases, lifestyle factors, exact time of disease onset, and height and weight of the subjects. Previous hospital records were available for all ICH patients and 166 (81%) of the control subjects. All available hospital records were reviewed to check diseases, medication, and blood pressure histories.

The subjects were considered hypertensive if their blood pressure readings preceding the index stroke had repeatedly exceeded 160/95 mm Hg or if they were taking antihypertensive medication. Those without antihypertensive medication but with repeatedly measured blood pressures exceeding 160/95 mm Hg were classified as patients or control subjects having untreated hypertension. Untreated hypertensives also included patients or control subjects who had terminated their medication for blood pressure without supervision. Body mass index, calculated as weight divided by height squared, was used as the index of relative weight. Patients were recorded to have diabetes mellitus if they used oral hypoglycemic agents or insulin. Previous hemorrhagic strokes (ICH and subarachnoid hemorrhage) and ischemic strokes were recorded. Cardiac disease included myocardial infarction, coronary artery disease, heart failure, and atrial fibrillation. Migraine in the patient’s earlier history was defined according to classification of the International Headache Society.14 Patients were recorded to have epilepsy if they used antiepileptic medication. Patients were positive for a history of epistaxis if they had had >1 episode of nosebleed during the preceding 5 years or if they had visited an outpatient clinic of otorhinolaryngology or had been hospitalized because of epistaxis.

Recent drinking of alcohol was estimated by asking the patients and control subjects how many drinks of alcohol (standard drink = 12 g of ethanol) they had consumed during the week preceding the week preceding the onset of the first symptoms of stroke or, in the case of a control subject, during the week preceding the interview. Because it is well known that patients tend to underestimate their recent alcohol consumption, relatives were also interviewed about the patients’ recent consumption of alcohol. The larger amount, reported by either the patient or the relative, was used in the analysis. To identify problem drinking, patients were also interviewed with the short GAGE questionnaire. (Have you ever felt you should cut down on your drinking? Have people annoyed you by criticizing your drinking? Have you ever felt bad or guilty about your drinking? Have you ever had a drink first thing in the morning to steady your nerves and to get rid of a hangover?)15-17 Recent heavy drinkers were subjects whose alcohol intake had exceeded 300 g of ethanol during the week preceding the index stroke or the interview. Former heavy drinkers included subjects whose recent mean weekly alcohol intake had regularly exceeded 300 g of ethanol or who were classified as problem drinkers because of ≥2 positive answers to the 4 questions of the short GAGE questionnaire but reported no alcohol intake during the week preceding the index admission or interview.

Smokers were categorized into current cigarette smokers and nonsmokers. The latter included former regular cigarette smokers who had quit ≥1 year ago. The use of all kinds of medicines, including NSAIDs purchased over the counter, during the preceding week before admission for the index stroke or the interview was recorded. Drug abuse was also inquired, but our series did not include illicit drug abusers.

Patients were asked whether they had engaged in exceptionally strenuous physical exertion (eg, pushing a car from snow, lifting a heavy weight, heavy household cleaning work, or other physical exertion that greatly exceeds the subject’s usual level of daily physical activity) within 24 hours before the onset of the index stroke. Likewise, control subjects were asked about exceptional physical exertion within 24 hours before the interview. Patients and control subjects were also asked if they had had an infection with fever during the preceding week before the onset of the stroke or before the interview.

Data were analyzed with biomedical data package statistical programs (1993 version by BMDP Statistical Software Inc). Categorical variables were compared by use of Fisher’s exact 2-tailed test or the Pearson $\chi^2$ test. Univariate and multivariate odds ratios (ORs) with 95% confidence intervals (CIs) were calculated by logistic regression (maximum likelihood method). Stepwise logistic regression ($P<0.1$ for entry limit and $P>0.15$ for removal limit) was used to test the significant independent risk factors for ICH. A 2-tailed value of $P<0.05$ was considered statistically significant.

### Results

The baseline characteristics and health habits of the patients and control subjects are shown in Table 1. Treated hypertension was equally common in both groups. However, untreated hypertension was much more common in the ICH patients than in the control subjects (OR, 5.28; 95% CI, 2.55 to 10.9). The occurrence of cardiac disease, diabetes mellitus, and migraine was not significantly different between the groups. Univariate analysis showed the other significant risk factors for ICH to be epilepsy (OR, 9.27; 95% CI, 1.92 to 44.8), previous hemorrhagic stroke (OR, 18.4; 95% CI, 2.25 to 151),

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Cases</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects, n</td>
<td>98</td>
<td>206</td>
</tr>
<tr>
<td>Men, n (%)</td>
<td>56 (57)</td>
<td>121 (59)</td>
</tr>
<tr>
<td>Mean ± SD age, y</td>
<td>65 ± 11</td>
<td>66 ± 11</td>
</tr>
<tr>
<td>Mean ± SD BMI, kg/m²</td>
<td>28 ± 6</td>
<td>27 ± 4</td>
</tr>
<tr>
<td>Previous diseases, n %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension treated</td>
<td>41 (42)</td>
<td>85 (41)</td>
</tr>
<tr>
<td>Hypertension untreated</td>
<td>27 (28)</td>
<td>18 (9)</td>
</tr>
<tr>
<td>Cardiac disease</td>
<td>30 (31)</td>
<td>70 (34)</td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>21 (21)</td>
<td>19 (9)</td>
</tr>
<tr>
<td>Hemorrhagic stroke</td>
<td>8 (8)</td>
<td>1 (0.5)</td>
</tr>
<tr>
<td>Epistaxis</td>
<td>21 (21)</td>
<td>17 (8)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>10 (10)</td>
<td>17 (8)</td>
</tr>
<tr>
<td>Migraine</td>
<td>9 (9)</td>
<td>16 (8)</td>
</tr>
<tr>
<td>Epilepsy</td>
<td>8 (8)†</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Recent infection</td>
<td>5 (5)</td>
<td>5 (2)</td>
</tr>
<tr>
<td>Lifestyle factors, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recent physical exertion</td>
<td>29 (29)</td>
<td>25 (12)</td>
</tr>
<tr>
<td>Recent heavy drinking</td>
<td>7 (8)*</td>
<td>4 (2)</td>
</tr>
<tr>
<td>Former heavy drinking</td>
<td>8/89 (9)</td>
<td>23/206 (11)</td>
</tr>
<tr>
<td>Current smoking</td>
<td>13 (13)</td>
<td>33 (16)</td>
</tr>
<tr>
<td>Former smoking</td>
<td>31 (32)</td>
<td>84 (41)</td>
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<tr>
<td>Medication, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ASA/NSAID</td>
<td>52 (53)</td>
<td>101 (49)</td>
</tr>
<tr>
<td>ASA</td>
<td>38 (39)</td>
<td>71 (34)</td>
</tr>
<tr>
<td>Dipyridamole</td>
<td>7 (7)*</td>
<td>3 (1.5)</td>
</tr>
<tr>
<td>Warfarin</td>
<td>6 (6)</td>
<td>5 (2)</td>
</tr>
<tr>
<td>Sympathomimetics</td>
<td>5 (5)</td>
<td>16 (8)</td>
</tr>
</tbody>
</table>

BMI indicates body mass index; ASA, acetylsalicylic acid. *$P<0.05$; †$P<0.01$. |
previous ischemic stroke (OR, 2.68; 95% CI, 1.36 to 5.29), and a history of epilepsy (OR, 3.20; 95% CI, 1.59 to 6.42). Of the lifestyle factors, recent heavy drinking of alcohol (OR, 4.11; 95% CI, 1.17 to 14.5) and recent strenuous physical exertion (OR, 3.28; 95% CI, 1.79 to 6.03) were significant risk factors for ICH, whereas former heavy drinking of alcohol and current smoking were not. Dipyridamole medication was significantly (OR, 5.08; 95% CI, 1.28 to 20.2) and warfarin medication was nonsignificantly more frequent among the patients than the control subjects.

In stepwise logistic regression, untreated hypertension (P<0.001), recent strenuous physical exertion (P<0.001), a history of ischemic stroke (P<0.01), epilepsy (P<0.01), and a history of epistaxis (P<0.05) were significant risk factors for ICH. In addition, recent heavy drinking (OR, 3.43; 95% CI, 0.88 to 13.5) and treated hypertension (OR, 1.67; 95% CI, 0.86 to 3.22) tended to associate with the occurrence of ICH, whereas a history of hemorrhagic stroke, recent infection, and recent use of dipyridamole did not. Accordingly, we included all the significant risk factors listed above, together with treated hypertension and recent heavy drinking of alcohol, in a multivariate analysis. In this analysis, all the significant risk factors mentioned above remained significant after adjustment for each other, age, and sex (Table 2). When the subjects with anticoagulant treatment were omitted from the model and the subjects using NSAIDs remained, the history of epistaxis still was a significant risk factor for ICH (OR, 2.62; 95% CI, 1.14 to 6.01). This suggests that the use of anticoagulants did not influence the epistaxis-associated risk for ICH.

The use of NSAIDs was significantly associated with the history of epistaxis (P<0.05). When a logistic model that included the use of NSAIDs, history of epistaxis, their interaction, recent heavy drinking of alcohol, hypertension, ischemic stroke, epilepsy, physical exertion, age, and sex was constructed, it appeared that the history of epistaxis (adjusted OR, 3.10; 95% CI, 1.29 to 7.46), use of NSAIDs (OR, 4.00; 95% CI, 1.02 to 15.6), and their interaction (OR, 1.75; 95% CI, 1.05 to 2.92) were all significant (P<0.05) risk factors for ICH. The interaction seemed to relate to aspirin use, because most of our patients (73%) who had used NSAIDs had been taking aspirin. Of the 38 aspirin users, 31 had been taking a relatively high dose of aspirin, i.e., >1225 mg/wk, a dose that has been reported to increase the risk for ICH.13 Accordingly, in a similar model including aspirin instead of NSAIDs, a history of epistaxis (OR, 2.75; 95% CI, 1.11 to 6.81; P<0.05), use of aspirin (OR, 14.7; 95% CI, 2.03 to 106; P<0.01), and their interaction (OR, 16.9; 95% CI, 2.48 to 114; P<0.01) were found to be significant independent risk factors as well.

Because a history of ischemic stroke may be associated with the occurrence of epilepsy, we tested whether the significance of epilepsy as an independent risk factor for ICH remained when the subjects with history of ischemic stroke were omitted. The analysis showed that epilepsy still was a significant risk factor for ICH (P<0.01). Recent heavy drinking did not show any association with a history of epistaxis, epilepsy, or untreated hypertension. Nor did we observe any statistically significant interaction between hypertension and a history of epistaxis or between hypertension and previous ischemic stroke.

When men and women were analyzed separately, treated and untreated hypertension, previous ischemic stroke, recent strenuous physical exertion, and a history of epistaxis were significant risk factors for ICH in men, whereas epilepsy did not reach statistical significance (Table 3). In women, untreated hypertension, epilepsy, and recent strenuous physical exertion were significant risk factors. Recent heavy drinking did not reach statistical significance as a risk factor in men (OR, 3.22; 95% CI, 0.70 to 14.9; P<0.05). Because none of the control women were recent heavy drinkers, we could not perform a similar analysis for women. The interactions between the history of nosebleeds and use of NSAIDs or aspirin did not reach statistical significance, probably because of the small number of subjects in the subgroups classified by sex.

### Discussion

We found a history of epistaxis to be an independent risk factor for ICH. This is a new finding. Patients who had had nosebleeds during the 5 years preceding the index stroke had a significantly increased risk for ICH independent of the other investigated risk factors. Use of anticoagulants was not found to influence the risk, but in the patients with a history of epistaxis, recent use of aspirin seemed to increase the risk for ICH. In fact, the history of epistaxis and use of aspirin constituted a potential and new risk factor combination,
whereas the use of aspirin itself in low doses may not be a significant risk factor.

Acute strenuous physical exertion was significantly associated with the onset of ICH. This was another new finding. Acute exercise may trigger ICH through a sudden increase in blood pressure. It is well known that acute physical exercise raises systolic blood pressure, and it has been shown that exercise-induced blood pressure responses are greater in old than young people. Because elderly people seldom engage in regular physical exercise, acute strenuous physical exertion may powerfully increase their systolic blood pressure.

A history of ischemic stroke was a significant and independent risk factor for ICH. This was also a finding not previously reported, although it is well known that ischemic lacunar infarctions and deep ICHs are both complications of small-vessel disease caused by hypertension. Untreated hypertension was a significant risk factor for primary ICH in both men and women. In men but not in women, even treated hypertension was a significant risk factor. The latter observation may have been due to the poorer compliance of men in using antihypertensive medication. Unfortunately, we did not systematically obtain information on the last blood pressure recordings preceding the index stroke of our subjects. If we had known the blood pressure values of our subjects for the week preceding the index stroke, we could have separated a group of inadequately treated hypertensives, and thus, treated hypertension had perhaps lost its significance as a risk factor in men.

We found epilepsy to be a risk factor for ICH in women but not in men. We did not find any specific reason for this. The finding could be a spurious one, because the number of epileptics in our series was small. When the subjects with a history of ischemic stroke were omitted, the remaining 3 subjects with epilepsy were all women. Cavernous malformation, which is a rare cause of ICH, could not be excluded as a common cause for both epilepsy and ICH in these women, because no head magnetic resonance imaging (MRI) or intracranial angiography was done.

Bias may have resulted from the different techniques used to interview the patients and control subjects. The patients or their relatives were personally interviewed; control subjects themselves for the interview by, for example, reducing their alcohol consumption.

Telephone interview has been found to be a reliable procedure for obtaining information of drinking habits, functional capacity, and quality of life. Unfortunately, we did not interview family members of the control subjects. However, Nelson et al have found a good correlation between alcohol consumption data obtained from control subjects and their proxies. The alcohol data we obtained from our patients and their proxies did not differ from each other.

Recall bias is also possible, because the patients or their relatives may have been better able to remember, for example, previous bleedings than the healthy control subjects. Patients with a previous stroke could be a special group prone to recall bias. We tried to minimize this type of bias by having the interviews conducted according to a structured protocol by the same person and by carefully reviewing the previous hospital records of all the subjects. Previous hospital records were available for 81% of the control subjects, which strengthens the reliability of our results. Bias resulting from exclusion of patients not hospitalized is unlikely because sudden deaths are infrequent in primary ICH. Attention to careful interviewing of all the subjects is a strength of our study.

There has been considerable uncertainty as to whether the intake of aspirin increases the risk for ICH. Although this problem has been investigated in a large number of clinical trials on aspirin treatment, CT has not been systematically used to verify the type of stroke. In the Swedish Aspirin Low-Dose Trial (SALT), in which CT or necropsy was carried out in 98% of the patients with stroke, there was an excess of hemorrhagic strokes and a significant increase in the risk of fatal hemorrhagic strokes among the aspirin (75 mg/d) users. However, Thrift et al found no increase in risk among those who took low doses of aspirin (<1225 mg/wk) or other NSAIDs. In our own previous study, we observed a tendency of NSAIDs to increase the risk for ICH in people of working age.

The cerebral arteries of patients with a history of ischemic stroke may be more prone to rupture than those of patients with other manifestations of atherosclerotic disease. Kwa et al studied local cerebral hemosiderin deposits, which are signs of old ICHs, on MRI scans of patients with ischemic stroke, myocardial infarction, and peripheral arterial disease. They found hemosiderin deposits more frequently in patients with ischemic stroke (26%) than in patients with myocardial infarction (4%). These findings might explain the association between previous ischemic stroke and ICH in our study. Ischemic stroke may be a real independent risk factor for ICH or a proxy of another risk factor, which was not included in our model.

Former studies have focused on the effects of regular physical activity on the risk for stroke rather than the effects of acute strenuous physical exertion. Moreover, the subtypes of stroke have been inaccurately differentiated in these studies. Physical exertion has not previously been found to increase the risk for ICH. However, a U-shaped relation between stroke incidence and the degree of physical activity has been observed. Moderate physical activity was protective against stroke compared with light physical activity, but more strenuous physical activity was less protective. Nakayama et al observed that heavy physical activity increased the risk for all strokes in middle-aged and elderly men, whereas avoidance of physical exercise increased the risk for ICH in women.

The alcohol-associated risk for ICH observed in several previous studies was not significant in this series of middle-aged and elderly people, although recent heavy drinking of alcohol almost reached statistical significance as a risk factor for ICH in men. It is well known that heavy drinking increases untimely deaths, and elderly people are seldom heavy drinkers. In our previous study, recent heavy drinking of alcohol was a significant independent risk factor for ICH in people of working age. In that study, the alcohol-associated
risk for ICH was not explained by chronic hypertension, anticoagulant treatment, or use of NSAIDs.

We believe that our finding of epistaxis as a risk factor for ICH has clinical significance. Subjects prone to ICH may show epistaxis as a sign of impaired hemostasis or a coagulation disorder. Epistaxis may also result from nasal abnormalities, and the major risk factors for epistaxis are hypertension, use of aspirin, and alcohol abuse. Impaired platelet function related to use of NSAIDs has been observed in patients with idiopathic epistaxis. Alcohol is also known to impair the hemostatic mechanism. We did not observe any association between the history of epistaxis and recent heavy drinking of alcohol, but there were only a few recent heavy drinkers in our series. Aging may involve an increased risk for epistaxis, because the nasal mucosa becomes atrophic and its physiological activity less proficient. A sudden rise of blood pressure in the systemic circulation exposes the capillaries to high pressure, which may precipitate both epistaxis and ICH. Preexisting damage either in the capillaries of the nasal mucosa or in the small penetrating cerebral arteries could determine whether the bleeding occurs as an epistaxis or ICH. The use of drugs inhibiting the hemostatic mechanism, such as aspirin, could predispose for more profuse bleeding. Accordingly, patients with a history of nosebleeds should perhaps be advised to other analgesics but not aspirin. Lower doses of aspirin should be recommended as prophylaxis of atherosclerotic diseases, particularly for people with uncontrolled hypertension or other known risk factors for ICH.

Hypertension is the most important risk factor for ICH. In general, about half of the cases are considered to be caused by hypertension. Therefore, adequate control of hypertension is probably the most important prophylaxis of ICH. Klungel et al reported that about a quarter of all incident strokes among hypertensives were attributable to undertreatment of hypertension. Hsiang et al observed that only 20% of the hypertensive subjects stricken by ICH had been compliant with their antihypertensive medication, and Thrift et al reported that the risk for ICH associated with hypertension was significantly greater among hypertensive subjects who had ceased taking medications with and without supervision.

In conclusion, untreated hypertension was found to be the main modifiable risk factor for ICH in middle-aged and elderly people. This finding points out the need for more careful control in the treatment of hypertension. Use of aspirin appeared to be a significant risk factor for ICH in subjects with a history of epistaxis. Patients with a history of epistaxis should avoid using high doses of aspirin for prophylaxis of atherosclerotic diseases and should instead use other kinds of analgesics.

Acknowledgment
This study was supported in part by the Oulu Medical Foundation and the Maire Taponen Foundation (P.S.).

References
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Stroke. 2001;32:399-404
doi: 10.1161/01.STR.32.2.399
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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