Risk of Intracerebral Hemorrhage in Patients With Arterial Versus Cardiac Origin of Cerebral Ischemia on Aspirin or Placebo
Analysis of Individual Patient Data From 9 Trials

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Background and Purpose—Patients who are anticoagulated after cerebral ischemia have a 19-fold-higher risk of intracerebral hemorrhage (ICH) if they had an arterial rather than a cardiac source. To determine whether this excess risk of ICH was due to the underlying disease (cerebral ischemia of arterial versus cardiac origin) or whether it depended on the antithrombotic regimen, we studied the risk of ICH in arterial versus cardiac origin of cerebral ischemia in patients who received aspirin or no antithrombotic drugs.

Methods—Individual patient data of patients who received aspirin or placebo after cerebral ischemia were obtained from 9 clinical trials. Presence of atrial fibrillation was considered evidence of a cardiac source. Otherwise, events were considered of arterial origin. Cox proportional-hazards modeling was used for univariate and multivariate analyses.

Results—Fifty-four ICHs occurred in 16,625 patient-years in the aspirin-treated patients, and 7 ICHs occurred in 4,317 patient-years in those on placebo. After multivariate adjustment for age, sex, current smoking, history of hypertension and diabetes, and aspirin dose (aspirin-treated patients only), the hazard ratio for ICH in patients with an arterial versus a cardiac source was 0.74 (95% confidence interval, 0.30 to 1.82) for aspirin-treated patients and 4.34 (95% confidence interval, 0.35 to 54) for placebo-randomized patients.

Conclusions—Our findings do not confirm the previous finding of an excess risk of ICH in patients with cerebral ischemia of arterial origin. Therefore, it seems that having cerebral ischemia of arterial origin by itself is not associated with an increased risk of ICH, but only in combination with high-intensity anticoagulation. (Stroke. 2004;35:710-714.)

Key Words: cerebral ischemia ■ intracerebral hemorrhage ■ secondary prevention

An earlier study indicated that patients with previous cerebral ischemia of arterial origin who subsequently received high-intensity oral anticoagulation (international normalized ratio [INR], 3.0 to 4.5) have a higher risk of intracerebral hemorrhage (ICH) than those with previous cerebral ischemia of cardiac origin.1 This study directly compared patients from the Stroke Prevention in Reversible Ischemia Trial (SPIRIT),2 who had a presumed arterial origin of their cerebral ischemia, and the European Atrial Fibrillation Trial (EAFT),3 who had a presumed cardiac origin of their cerebral ischemia.3 Anticoagulated patients with an arterial origin had an incidence of ICH of 3.7% per year. In contrast, the rate of ICH in anticoagulated patients with a cardiac origin was lower, 0.39% per year. After adjustment for important potential confounders such as sex, age, history of hypertension, leukoaraiosis, intensity of anticoagulation (mean INR), and standard deviation of the mean INR, the risk of ICH was 19 times higher (hazard ratio [HR], 19.0; 95% confidence interval [CI], 2.4 to 150) among patients with an arterial origin than among those with a cardiac origin for their cerebral ischemia.1

These findings are possibly explained by increased fragility of small cerebral arteries in patients with cerebral ischemia of arterial origin. This assumption is supported by results of the SPIRIT trial in which there was a positive association between the presence of white matter lesions on CT and the risk of ICH.2 There also was a positive trend for severity of leukoaraiosis and the risk of ICH in SPIRIT.3 If this finding is independent of treatment, one would expect to find a similar association between source of cerebral ischemia and risk of subsequent ICH.
in patients who received aspirin and in patients who received no antithrombotics at all. Such a finding would confirm that having cerebral ischemia of arterial origin increases the risk of ICH independently of treatment.

Preliminary analyses show that the incidence of ICH in patients who received aspirin was 0.39% per year in SPIRIT, which is not unexpectedly high in itself, but compared with the incidence of ICH of 0.21% per year in EAFT, there may be an increased risk (HR, 2.4; 95% CI, 3.2 to 18). This possibly suggests a similar association between arterial versus cardiac origin of cerebral ischemia and the risk of ICH that is independent of treatment but of a lower magnitude. However, the number of patients in SPIRIT and EAFT who received aspirin was small. We therefore obtained individual patient data from as many trials as feasible in patients with previous cerebral ischemia who received aspirin or no antithrombotics to study whether patients who received aspirin or were randomized to placebo after cerebral ischemia of arterial origin had a higher risk of ICH than patients with cerebral ischemia of cardiac origin.

Determining whether this excess risk also applies to patients on aspirin or patients who received no antithrombotic treatment (patients randomized to placebo) is important because it stresses the value of identifying the source of cerebral ischemia and could have implications for future antithrombotic treatment.

Methods
This study used individual patient data from 9 randomized clinical trials in patients with previous cerebral ischemia who received aspirin or were randomized to placebo. Patients who did not have atrial fibrillation were classified as having cerebral ischemia of arterial origin. Patients with atrial fibrillation at the time of cerebral ischemia were classified as having a cardiac origin. Because patients were screened by a neurologist before they were randomized in the trials in patients with atrial fibrillation, in general, patients with a carotid stenosis of >70% were not randomized; therefore, patients with atrial fibrillation were randomized only if the treating neurologist considered a cardiac cause the most likely on the basis of all the evidence collected.

Patients With Cerebral Ischemia of Arterial Origin
Data of patients with cerebral ischemia of arterial origin were obtained from 3 studies, 2 coordinated at the University Medical Center Utrecht (the Netherlands) and 1 in the United Kingdom. The Dutch TIA Trial (DTT) was a double-blind clinical trial in which patients with a history of transient ischemic attacks or nondisabling stroke (Rankin grade ≤3) were randomized to aspirin 30 or 283 mg/d and to atenolol 50 mg or placebo. The SPIRIT trial was a double-blind clinical trial in similar patients who were randomized to aspirin 30 mg/d or oral anticoagulation (INR, 3.0 to 4.5). The United Kingdom TIA Aspirin Trial (UK TIA) randomized patients with a transient ischemic attack or minor ischemic stroke to long-term “blind” treatment with aspirin 600 mg twice daily, aspirin 300 mg once daily, or placebo.

The DTT contributed 3131, the SPIRIT trial contributed 665, and the UK TIA trial contributed 1597 aspirin-treated patients with ischemia of presumed arterial origin. The UK TIA trial contributed 802 patients with ischemia of presumed arterial origin who received no antithrombotics (randomized to placebo).

Patients With Cerebral Ischemia of Cardiac Origin
Individual patient data of patients with nonvalvular atrial fibrillation were attained from 7 clinical trials. The European Atrial Fibrillation Trial (EAFT) enrolled patients with constant or intermittent atrial fibrillation and a recent transient ischemic attack or minor ischemic stroke. Patients were randomized to open anticoagulation or double-blind treatment with either aspirin 300 mg/d or placebo. Patients who were not eligible for anticoagulants were randomized to double-blind treatment with 300 mg aspirin or placebo. The Stroke Prevention in Atrial Fibrillation (SPAF) I study randomized patients with constant or intermittent atrial fibrillation to open-label warfarin or to double-blind treatment with aspirin 325 mg/d or placebo if they were eligible for anticoagulants and to double-blind aspirin 325 mg/d or placebo if they were not eligible. The SPAF II study randomized patients with constant or intermittent atrial fibrillation to warfarin (prothrombin time ratio, 1.3 to 1.8; INR, 2.0 to 4.5) or aspirin 325 mg/d for prevention of ischemic stroke and systemic embolism (primary events). Some patients in SPAF I who were randomized to warfarin or aspirin continued on their initially assigned treatment in SPAF II. Some patients in SPAF I who were randomized to placebo or aspirin (anticoagulation-ineligible group only) were rerandomized to receive

<table>
<thead>
<tr>
<th>TABLE 1. Baseline Characteristics and Risk of ICH in Patients After Cerebral Ischemia of Arterial Versus Cardiac Origin Who Received Aspirin</th>
<th>Aspirin</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arterial</td>
<td>Cardiac</td>
<td>Arterial</td>
</tr>
<tr>
<td>n</td>
<td>5393</td>
<td>521</td>
</tr>
<tr>
<td>Mean age (SD), y</td>
<td>63.4 (9.9)</td>
<td>75.2 (8.0)</td>
</tr>
<tr>
<td>Mean systolic blood pressure (SD), mm Hg</td>
<td>156 (26)</td>
<td>148 (21)</td>
</tr>
<tr>
<td>Mean diastolic blood pressure (SD), mm Hg</td>
<td>90 (13)</td>
<td>85 (11)</td>
</tr>
<tr>
<td>Men, n (%)</td>
<td>3636 (68)</td>
<td>322 (62)</td>
</tr>
<tr>
<td>Current smoking, n (%)</td>
<td>2550 (47)</td>
<td>103 (20)</td>
</tr>
<tr>
<td>History of angina, n (%)</td>
<td>602 (11)</td>
<td>67 (13)</td>
</tr>
<tr>
<td>History of myocardial infarction, n (%)</td>
<td>521 (10)</td>
<td>58 (11)</td>
</tr>
<tr>
<td>History of hypertension, n (%)</td>
<td>2045 (38)</td>
<td>246 (47)</td>
</tr>
<tr>
<td>History of diabetes, n (%)</td>
<td>393 (7)</td>
<td>67 (13)</td>
</tr>
<tr>
<td>Dose of aspirin ≥283 mg/d, n (%)</td>
<td>3173 (59)</td>
<td>501 (96)</td>
</tr>
<tr>
<td>Mean follow-up (SD), y</td>
<td>2.9 (1.6)</td>
<td>2.3 (1.3)</td>
</tr>
<tr>
<td>ICH, n (%)</td>
<td>47 (0.9)</td>
<td>7 (1.3)</td>
</tr>
<tr>
<td>Incidence %/(n/y)</td>
<td>0.31 (47/15406)</td>
<td>0.57 (7/1219)</td>
</tr>
</tbody>
</table>
warfarin or aspirin 325 mg. By linking between SPAF I and SPAF II data sets, we ensured that patient observation on aspirin was not double counted. The Atrial Fibrillation, Aspirin and Anticoagulant Therapy Study (AFASAK I) randomized outpatients with chronic nonrheumatic atrial fibrillation to anticoagulation with open-label warfarin and in a double-blind way to aspirin 75 mg once daily or placebo. The AFASAK II study, a randomized, single-center, primary prevention trial, randomized patients with atrial fibrillation to fixed-dose warfarin 1.25 mg/d, a combination of warfarin 1.25 mg and aspirin 300 mg daily, aspirin 300 mg/d, or conventional warfarin therapy (INR, 2.0 to 3.0). The Primary Prevention of Arterial Thromboembolism in Nonrheumatic Atrial Fibrillation (PATAF) study randomized nonrheumatic atrial fibrillation patients in a primary care setting to low-intensity anticoagulation, regular-intensity anticoagulation therapies, or aspirin 150 mg/d. The UK TIA trial did not focus on patients with cardiac origin of cerebral ischemia; nevertheless, 49 patients of the UK TIA trial presented previous cerebral ischemia; AFASAK II, 13; EAFT, 404; SPAF I, 21; SPAF II, 29; PATAF, 3; and UK TIA, 34 patients. We avoided double counting of patients who continued from SPAF I into SPAF II. The EAFT contributed 376, SPAF I contributed 41, AFASAK I contributed 21, and UK TIA trial contributed 15 patients with cerebral ischemia of presumed arterial origin who received no antithrombotics.

Outcome Event
The primary outcome was ICH. We took the classifications used by the original studies, which categorized a stroke as an ICH if a patient had a sudden focal deficit accompanied by hemorrhage on brain imaging or at autopsy.

Baseline Characteristics
The following patient characteristics were recorded in all trials: age, sex, history of hypertension, history of angina, history of diabetes, history of myocardial infarction, current smoking, and systolic and diastolic blood pressures. The variables were taken as defined in the original studies. Data on these characteristics were collected in a way similar to that used in the trials. Dose of aspirin was dichotomized at 283 mg/d (the approximate median of the aspirin dose distribution), above which patients were classified as having received high-dose aspirin and below which patients were classified as having received low-dose aspirin.

Statistical Analyses
Cox proportional-hazard modeling was used to measure the association between origin of cerebral ischemia and the risk of ICH. The randomization date was the start of observation. Patients were followed up until they had an ICH or died of another cause or until the study ended. Cox models adjusted for differences in baseline characteristics between patients with cerebral ischemia of cardiac origin and those with an arterial source.

First, we adjusted for 1 variable at a time to assess its influence on the crude relationship between origin of cerebral ischemia and ICH (bivariate analyses). In addition to adjustment for age and sex, we eventually adjusted simultaneously for those characteristics that changed the crude HR by >5% in the bivariate analyses in 1 of the 2 models. The strength of the relationship was expressed as an HR—to be interpreted as a relative risk—with corresponding 95% CIs to describe its precision.

We chose to perform separate analyses for patients who received aspirin and patients who received placebo because we did not expect a linear relationship between aspirin dose (ranging from 0 [placebo] to 1200 mg/d) and risk of ICH. To assess the influence of aspirin dose, we used a dichotomy of the dose (at 283 mg/d) rather than all different dose categories separately to limit the number of degrees of freedom used in the regression model.

It was not feasible to adjust for source of study because most trials studied only patients with cerebral ischemia of arterial origin or only patients with cerebral ischemia of cardiac origin. Therefore, to study the effect of the different trials from which patients originated, we compared the maximum likelihood estimate (MLE) of the model with origin of cerebral ischemia and risk of ICH with that of the model with origin of trial and risk of ICH. If there is no statistically significant difference between these 2 models, then there is no confounding influence of origin of study.

Results
Overall, patients with cerebral ischemia of arterial origin (aspirin, n = 5393; placebo, n = 802) were ~13 years younger than patients with cerebral ischemia of cardiac origin (aspirin, n = 522; placebo, n = 453) (Table 1). Patients with an arterial origin of cerebral ischemia were more often current smokers (aspirin, 47%; placebo, 52%) than patients with cerebral ischemia of cardiac origin (aspirin, 20%; placebo, 18%) and were less likely to have a history of hypertension (aspirin, 38% versus 47%; placebo, 27% versus 49%).

![Figure 1. Cumulative proportion of ICH: arterial vs cardiac origin of cerebral ischemia (CI).](http://stroke.ahajournals.org/)

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**Figure 1.** Cumulative proportion of ICH: arterial vs cardiac origin of cerebral ischemia (CI).
When we compared the model with origin of cerebral ischemia and ICH (aspirin: model  $\chi^2$, 873.4; placebo: model $\chi^2$, 84.3) with the model with origin of trial and ICH (aspirin: model $\chi^2$, 868.2; placebo: model $\chi^2$, 84.2), there was no statistically significant difference between these 2 models ($P>0.10$) in the data of patients on aspirin and on placebo; therefore, we assumed that there was no confounding influence of origin of trial.

The unadjusted annual risk of ICH was 0.31% in patients with an arterial source who received aspirin and 0.18% in patients who received placebo; the unadjusted annual risk was 0.57% in those with a cardiac origin who received aspirin and 0.10% in those who received placebo. Kaplan-Meier curves show that the rate of ICH was fairly constant in both groups (Figure 1).

The corresponding crude HR for the risk of ICH in patients with arterial versus cardiac origin of cerebral ischemia was 0.52 (95% CI, 0.23 to 1.15) for patients who received aspirin and 1.29 (95% CI, 0.14 to 11.6) for patients randomized to placebo. In bivariate analyses (Table 2), the crude HR changed >5% in aspirin-treated patients after adjustment for age and systolic and diastolic blood pressures and in patients randomized to placebo after adjustment for age, current smoking, and history of hypertension and diabetes. Because of the close association between actual blood pressure and history of hypertension, we decided to adjust for history of hypertension only in the final model. In the final multivariate models, we adjusted for age, sex, current smoking, history of hypertension, history of diabetes, and dose of aspirin (only in aspirin-treated patients); the resulting HR was 0.74 (95% CI, 0.30 to 1.82) for patients treated with aspirin and 4.34 (95% CI, 0.35 to 54) for patients randomized to placebo when patients with cerebral ischemia of arterial origin were compared with patients with cerebral ischemia of cardiac origin (Figure 2). These results were not statistically significantly different ($P=0.33$). The HR for ICH for the aspirin and placebo groups combined was 0.99 (95% CI, 0.43 to 2.25), which differs ($P=0.02$) from the previous finding in anticoagulated patients (HR, 19; 95% CI, 2.4 to 150).

**Discussion**

This study does not confirm that patients with arterial origin of cerebral ischemia who receive aspirin have an increased risk of ICH (aspirin: HR, 0.74; 95% CI, 0.30 to 1.82; placebo: HR, 4.34; 95% CI, 0.35 to 54) compared with patients with cardiac origin of cerebral ischemia.

We collected individual patient data from 9 trials. We are aware of the methodological problems that can occur when data from different studies are combined. However, the incidence of ICH is low, so individual patient data gave us the opportunity to study origin of cerebral ischemia and risk of ICH. The advantage is that such data allow calculation of adjusted HRs to minimize the confounding that results from differences in baseline characteristics between the 2 groups. However, we could adjust only for those characteristics on which information was available in all trials. For example, we could not adjust for the presence of leukoaraiosis on CT or MRI, which was identified as an important predictor of ICH in SPIRIT. Moreover, the definition of baseline characteristics may have been slightly different between trials. It is not likely that the relatively small number of subjects in the group with cardiac origin of cerebral ischemia (aspirin, n=522; placebo, n=453) can be increased by adding other studies because nowadays patients with cerebral ischemia of cardiac origin receive anticoagulation.

When we compared the results of our study in patients who received aspirin (HR, 0.74; 95% CI, 0.30 to 1.82) and patients randomized to placebo (HR, 4.34; 95% CI, 0.35 to 54) with those in patients who received oral anticoagulants (HR, 19; 95% CI, 2.4 to 150) (Figure 2), the CI of the finding in...
patients who received anticoagulants overlaps the CI of the finding in patients randomized to placebo but not the CI of the finding in patients who received placebo, indicating a statistically significant difference between these 2 findings.

The primary aim of our study was to obtain more insight into the origin of ICH according to source of cerebral ischemia and type of antithrombotic agent. Therefore, our findings should be viewed primarily from a pathophysiological perspective. With regard to the results of our study, one might speculate that it takes 2 factors to cause intracerebral bleeding in patients with an arterial source of cerebral ischemia: anticoagulant treatment with a sufficiently high intensity and fragile, small cerebral arteries. With aspirin, the threshold for a clinically overt ICH may not be reached.

In conclusion, this study does not confirm the previous finding in patients who received high-intensity anticoagulation (INR, 3.0 to 4.5). This suggests that arterial origin of cerebral ischemia does not in itself increase the risk of ICH, but only in combination with anticoagulants. For future research, it is important to pay more attention to relevant subgroups of patients, eg, those with hypertension, who may be at increased risk of ICH from antithrombotic treatment, even when this therapy consists of antiplatelet agents.

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References

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