Predictors for Recurrent Primary Intracerebral Hemorrhage
A Retrospective Population-Based Study

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Background and Purpose—Underlying comorbidities, previous strokes, and medication may increase the risk for primary intracerebral hemorrhage (PICH) and its recurrence. The aim of this study was to determine the independent predictors for recurrent PICH.

Methods—We identified 961 subjects with first-ever PICH from 1993 to 2008 among the population of Northern Ostrobothnia, Finland. Hospital and death records were reviewed and data on drug use were obtained from the national register of prescribed medicines. Kaplan–Meier survival curves and Cox proportional hazards models were used to demonstrate predictors for recurrence of PICH.

Results—Total follow-up time of the 961 patients was 3481 person-years. During the follow-up time, 58 subjects had altogether 68 recurrent PICHs. The annual average incidence of first recurrence was 1.67%. Cumulative 5- and 10-year incidence rates were 9.6% and 14.2%, respectively. In univariable analysis, history of ischemic stroke, diabetes mellitus, and aspirin use were associated with a higher recurrence rate. In multivariable analysis, only previous ischemic stroke (adjusted hazard ratio, 2.22; 95% confidence interval, 1.22–4.05; \(P=0.009\)) independently predicted PICH recurrence. Diabetes mellitus tended to increase (adjusted hazard ratio, 2.38; 95% confidence interval, 0.98–5.80; \(P=0.056\)), whereas treated hypertension tended to decrease (0.45, 0.20–1.01; \(P=0.054\)) the risk for fatal recurrent PICH.

Conclusions—Previous ischemic stroke independent of confounding factors may increase the risk for PICH recurrence. (Stroke. 2013;44:XXX-XXX.)

Key Words: epidemiology ■ intracerebral hemorrhage ■ recurrent ■ risk factor
had 58 subjects with recurrent PICHs and 622 subjects with a first-ever PICH without a recurrence who were still alive 1 month after the initial bleed. Data of these subjects were used to determine variables predicting PICH recurrence. Information regarding reasons for a hospital visit, blood pressure histories, and the use of medications was extracted from hospital charts. Subjects were considered to be hypertensive if their blood pressure readings preceding the index stroke had repeatedly exceeded 160/90 mm Hg in accordance with the World Health Organization/International Society of Hypertension statement, or if they used antihypertensive medication. Patients were recorded as having diabetes mellitus if they used oral hypoglycemic agents or insulin. Data on the use of anticoagulants, antiplatelet agents, and serotonin reuptake inhibitors were also obtained from the national register of prescribed medicine maintained by the Social Insurance Institution of Finland. Such data include information on all purchases of drugs by individuals linked to personal social security numbers. However, the use of aspirin and nonsteroidal anti-inflammatory drugs were extracted only from hospital records because they were available without prescription in Finland. SSRIs were categorized into groups of high (fluoxetine, paroxetine, and sertraline) and intermediate (citalopram, escitalopram, and fluvoxamine) affinity to serotonin transporters. Mirtazapine and mianserin were grouped as noradrenergic serotonin reuptake inhibitors (NSSRI).

The patient’s clinical condition on admission was assessed using the Glasgow Coma Scale score. Computed tomography scans were analyzed, and the locations and volumes of hematomas were measured by experienced neuroradiologists blinded to the case histories of the patients. Methods used for volume measurements have been described previously. In 9 cases, data on initial hematoma volumes were missing. Secondary structural abnormalities were searched and excluded with repeated brain imaging (computed tomography/magnetic resonance imaging) and angiographic imaging. Sixteen subjects (2.4%) remained without any follow-up investigations.

Data were analyzed with the SPSS for Windows (release 17.0;2.2.2009, SPSS Inc). Categorical variables were compared by Fisher exact 2-tailed test and the Pearson’s r test. Spearman rank correlation coefficients (r), t tests, or Mann–Whitney U test were used for comparisons of continuous variables. For life-table analysis and the Cox proportional hazards regression model, each patient was followed to recurrent ICH, to death from a cause other than recurrent ICH, or to the last contact. Average annual incidence of recurrent ICH was calculated by number of events of first recurrence divided by number of person-years of follow-up. Cumulative rates of recurrent PICH were estimated by the Kaplan–Meier product-limit method, and the curves of the different groups were compared by the log-rank test. Cox proportional hazards model was performed to determine hazard ratios and 95% confidence intervals of variables, which may predict recurrent PICH. The following variables known at the beginning of follow-up were first tested in univariable analysis: sex, age, diabetes mellitus, untreated hypertension, treated hypertension, aspirin use, anticoagulation, SSRI or NSSRI use, previous ischemic stroke, interaction between aspirin use and previous ischemic stroke, interaction between aspirin use and diabetes mellitus, lobar location of PICH, Glasgow Coma Scale score, and volume of hematoma. The final model included significant predictors obtained in univariable analysis, as well as sex and age. The test for significance was based on changes in log (partial) likelihood. A 2-tailed P value of <0.05 was considered to be statistically significant.

**Results**

Demographic and clinical characteristics of the 680 subjects who survived for at least 1 month after the index bleed are shown in Table 1. The subjects’ admission Glasgow Coma Scale scores were lower and hematoma volumes larger at recurrence than at the time of the first bleed (P<0.001 and P=0.003, respectively). Lobar location (in cortical or subcortical white matter of cerebrum) was not more frequent among recurrent bleeds than among first-ever bleeds. Among the 58 subjects who had a recurrence, there was significant heterogeneity (P=0.046) according to the treatment of hypertension. At the time of the first-ever bleed, untreated hypertension was more frequent than at the time of recurrent bleeds. At the time of the recurrence, those diagnosed with hypertension, all except 3, had adequate antihypertensive treatment. Significant differences were not observed in the use of any drugs. None of the subjects with recurrence were on warfarin at the time of the recurrence.

Data on the use of drugs after the index stroke were available either until death of the subject or until the end of 2008. Table 2 shows drug use after the first recurrent PICHs among subjects with recurrence and drug use after the index bleed among those without a recurrence. Subjects with a recurrence had used significantly (P=0.026) more often high-affinity SSRIs than those without a recurrence. They had also used aspirin and NSSRIs more often and these drugs in combination, but these differences were not statistically significant. However, subjects without a recurrence had used nonsignificantly more frequently intermediate-affinity SSRIs.

Locations of first PICHs among subjects having a recurrence were as follows: ganglionic (putamen, thalamus, and caudate nucleus) in 28 patients (48.3%), lobar in 19 (32.8%), cerebellar in 9 (15.5%), and brain stem in 2 (3.4%). The most frequent patterns for recurrence were ganglionic–ganglionic (n=24; 41.4%) and lobar–lobar (n=13; 24.1%). Aspirin users were nonsignificantly more frequent among those with a lobar PICH than among those with a ganglionic PICH (57.9% vs 39.3% for first-ever ICH and 61.1% vs 42.9% for first recurrence). We identified 58 subjects with recurrent PICHs, and they had altogether 68 recurrence events. Three of the subjects had 3 recurrent bleeds and 4 others had 2 recurrences. The mean follow-up time per patient was 3.62 years (range, 0–16 years; median, 1.82 years). A total follow-up time was 3481 person-years. The annual average incidence of first recurrence was 1.67%. At 5 years, the cumulative incidence of recurrence was 9.6% (95% confidence interval, 6.9–12.3), and at 10 years, it was 14.2% (10.3–18.1). Figure 1 demonstrates the cumulative rate of recurrent PICH. The incidence of recurrent PICH was rather constant by time until 12 years after the initial bleed. The average annual recurrence rate was higher in those with previous ischemic stroke than in those without (3.52% vs 1.35%; 18 events/511 person-years vs 40 events/2970 person-years). Diabetics also had higher average annual recurrence rate than those without diabetes mellitus (3.34% vs 1.47%; 12 events/359 years vs 46 events/3122 years) as well as aspirin users compared with nonusers (2.54% vs 1.34%; 24 events/946 years vs 34 events/2533 years).

The cumulative rate of PICH recurrence was higher in those with a history of ischemic stroke than in those without such history: 19.8% versus 7.5% at 5 years and 28.3% versus 12.4% at 10 years (Figure 2A). Previous transient ischemic attack alone did not yield a similar effect (data not shown). The cumulative rate of PICH recurrence was also higher in diabetics than in nondiabetic patients (Figure 2B), as well as in aspirin users compared with nonusers (Figure 2C).
Crude and adjusted hazard ratios of risk factors for PICH recurrence are shown in Table 3. Only previous ischemic stroke significantly and independent of confounding factors predicted recurrence. Inclusion of SSRIs to the final model (Table 3) showed that the use of SSRIs did not increase the risk for recurrent bleeding (adjusted hazard ratio, 1.76; 95% confidence interval, 0.62–4.99).

Finally, we searched predictors for fatal recurrence. After adjustment of other variables shown in the multivariable model in Table 3 and history of hypertension, we found that diabetes mellitus (2.38; 0.98–5.80; \(P=0.056\)) tended to increase, whereas treated hypertension tended to decrease (0.45; 0.20–1.01; \(P=0.054\)) the risk for fatal recurrent PICH.

### Discussion

We found previous ischemic stroke to independently predict recurrence of PICH. In univariable analysis, diabetes mellitus and aspirin use were also associated with elevated recurrence rate. Diabetes mellitus may increase the risk for recurrent PICH, whereas treatment of hypertension may reduce it, but our material was too small to prove significant associations. Patients with lobar PICH were not significantly more likely to have recurrent PICH than those with basal ganglionic PICH.

Although subjects with a history of ischemic stroke may carry an increased risk for hemorrhagic stroke,\(^{19,20}\) only 1 previous study of PICH recurrence included previous TIA or brain infarction in multivariable analysis.\(^{4}\) In that study, lobar location was the only significant predictor for recurrent bleed, a finding confirmed by several other investigations.\(^ {3,5,8,10,21}\)

In our population-based material, lobar location of index PICH did not significantly predict recurrent bleeding, but lobar PICH comprised only about one third of all PICHs. Previous investigations included selected patient populations, which may explain why lobar location and older age, but not ischemic stroke, were observed as significant predictors. Our findings are based on follow-up of a defined population and can more easily be generalized to all ICH patients.

Previous brain infarction enhanced the risk for recurrent PICH irrespective of concomitant use of aspirin, although about half of the subjects with previous ischemic stroke used aspirin. A previous study found no excess risk of PICH recurrence among subjects using aspirin.\(^{3}\) We believe that benefic of aspirin use probably overweigh the risks caused by it. Our findings suggest that, in the absence of cerebral amyloid angiopathy, aspirin could safely be used after PICH if needed to prevent ischemic events.

Poorly controlled hypertension may contribute to the increased risk of PICH recurrence.\(^{22}\) Patients with previous lacunar ischemic stroke or diabetes mellitus may have more fragile deep cerebral arteries than subjects without these comorbidities. Furthermore, blood pressure may be more labile and poorly controlled by treatment among diabetics because of concomitant neuropathy.\(^ {23}\)

We did not observe any significant risk for PICH recurrence attributable to the use of SSRI and NSSRI drugs, although antidepressants were frequently used during rehabilitation after the
strokes. However, our study was underpowered in issues such as SSRI use. SSRIs inhibit the serotonin reuptake transporter (5-HTT), leading to depletion of serotonin in platelets and impaired platelet aggregation and inhibition of platelet plug formation.24 The most potent inhibitors of 5-HTT are high-affinity SSRIs (paroxetine, sertraline, and fluoxetine).25,26 NSSRI drugs exert less 5-HTT inhibition than intermediate-affinity SSRIs.27

In a large cohort study, the use of SSRIs was significantly associated with incident hemorrhagic stroke.13 This was confirmed by a large case–control study.12 However, several other case–control studies have not observed increased risk for hemorrhagic stroke to be associated with SSRI use.25,26–30

We did not observe SSRIs combine with aspirin to associate with an increased risk of recurrent bleeding. However, few patients used combined treatments. One subject had used aspirin together with a high-affinity SSRI just before a fatal recurrent bleed. One study observed that combined use of aspirin and SSRI drugs (as well as clopidogrel) increased the risk for bleeding (gastrointestinal+intracranial+other).14 However, another study reported that hemorrhagic stroke risk conferred by warfarin or aspirin was not potentiated by use of SSRIs.30 Considering how a combined treatment will influence the occurrence of PICH, one should note that such a treatment may contribute more to the growth of the bleed than to its onset. Accordingly, it may be worth studying whether a combined treatment will increase the risk for fatal PICH.

Our finding that diabetes mellitus may increase and treatment of hypertension may decrease the risk for fatal recurrent PICH is supported by our previous observation, in which increased blood pressure values on admission and diabetes mellitus increased the risk for early death after initial PICH.31 Thus, risk factors for death after initial and recurrent bleeding may be similar.

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**Figure 1.** Kaplan–Meier curve showing cumulative rate of recurrent primary intracerebral hemorrhage for all patients.

**Figure 2.** Kaplan–Meier curves showing (A) a significant (P=0.001) difference in cumulative rates of recurrent primary intracerebral hemorrhage (PICH) among subjects with and without previous brain infarction, (B) a significant (P=0.026) difference in cumulative rates of recurrent PICH among subjects with and without diabetes mellitus (curve of those with diabetes mellitus is the lower one), and (C) a significant (P=0.021) difference in cumulative rates of recurrent PICH according to previous aspirin use.
In our study, the annual incidence of recurrent ICH was 1.67%, which is slightly higher than that (1.2/100 per year) reported by Hanger et al., but comparable to that of a previous Finnish population-based study. Recent studies have reported annual incidences varying from 2.1 to 3.7. The longer the total observation time, the lower will be the calculated annual average incidence, suggesting that the incidence rate will decrease by time. It is worth noticing that white people usually show lower incidence rates than Asian people.

The major strength of our study is the population-based case ascertainment, which should exclude selection bias. We ruled out 281 subjects because they died within 30 days after the index stroke and 21 subjects having intracranial bleed before 1993 to get as reliable a cohort as possible. We were able to determine accurate figures for cumulative incidence attributable to a long follow-up period. We also took into account as many of the well-known risk factors for ICH as possible and adjusted our analyses for those factors. We used a double-check method for drug exposure. We obtained purchase data on drug use from the national register of prescribed medicine and also checked drug use from hospital charts. Finally, we included only verified cases of PICH.

There are some limitations in our study. First, because aspirin is available without prescription in our country, we could only extract regular aspirin use from hospital charts but not record occasional aspirin use. Second, although antihypertensive medication was recorded, we were not able to assess subjects’ compliance with medication. Therefore, our study may underestimate the role of poorly treated hypertension. Third, only bleeding events leading either to death or to hospitalization were recorded. However, subjects with even minor strokes are currently admitted to our hospital if they have clear clinical signs and symptoms.

In conclusion, our findings suggest that ischemic stroke is the major risk factor for recurrent PICH in an unselected population. Diabetes mellitus may increase and treatments of hypertension reduce the risk for fatal recurrent PICH. We observed that subjects placed on SSRI/NSSRI drugs or aspirin were not at increased risk for recurrent PICH. However, further studies with larger materials are needed before concluding that combined use of antidepressants with warfarin or antiplatelet drugs is harmless with regard to occurrence of PICH and PICH recurrence.

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Disclosures
None.

References
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