Pretreatment With Antiplatelet Agents Is Not Independently Associated With Unfavorable Outcome in Intracerebral Hemorrhage

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Background and Purpose—This study investigated the effect of preexisting antiplatelet therapy on mortality and functional outcome in patients with intracerebral hemorrhage (ICH).

Methods—Our analysis was based on a large, country-wide stroke registry in Germany. All parameters relevant to this analysis, including age, prehospital status (according to the modified Rankin Scale, mRS), International Classification of Diseases–based diagnosis, and pretreatment with antiplatelet agents or oral anticoagulants, were recorded prospectively. Main outcome measures were in-hospital mortality rate and functional status at hospital discharge (mRS).

Results—Over a 2-year period, 1691 patients with ICH (ICD-10: I61) were documented (48% female; mean age, 72±12 years). At symptom onset, 26% were taking antiplatelet agents, and 12% were taking oral anticoagulants. By univariate logistic regression, pretreatment with antiplatelet drugs or anticoagulants was found to be a significant predictor of in-hospital mortality (odds ratio [OR], 1.42; \( P = 0.008 \) OR, 1.53; \( P < 0.001 \)) and of an unfavorable functional outcome (defined as mRS >2 or death; OR, 1.33; \( P = 0.039 \); OR, 1.51; \( P < 0.001 \)). However, after adjustment for age and prehospital status, antiplatelet pretreatment was no longer an independent risk factor of in-hospital death (OR, 1.12; \( P = 0.490 \)) or unfavorable functional outcome (OR, 0.97; \( P = 0.830 \)), whereas the influence of pretreatment with oral anticoagulants remained significant (OR, 1.45; \( P < 0.001 \); OR, 1.42; \( P = 0.009 \)).

Conclusions—In contrast to oral anticoagulants, pretreatment with antiplatelet agents is not an independent risk factor of mortality and unfavorable outcome in patients with ICH. (Stroke. 2006;37:2165-2167.)

Key Words: antiplatelet agents ■ cerebral hemorrhage ■ outcome

Patients who experience an intracerebral hemorrhage (ICH) while taking oral anticoagulants tend to have larger hematomas and a worse prognosis compared with patients who are not on anticoagulation therapy. Recent investigations suggested that pretreatment with antiplatelet agents could also be associated with hematoma expansion, an increased mortality rate, and a poor functional outcome. However, those studies were hampered by relatively small numbers of patients, making it difficult to control for the effects of potential confounders. For instance, patients taking antiplatelet drugs were shown to be significantly older and to have a worse prehospital status than those without such medication.

Subjects and Methods

Our analysis was based on a large, country-wide prospective stroke registry in Germany, provided by the Arbeitsgruppe Schlaganfall Hessen (for details, see www.gqhnet.de). At present, >100 hospitals participate in enrolling patients with a final diagnosis of transient ischemic attack (ICD-10: G45), cerebral infarction (ICD-10: I63), or ICH (ICD-10: I61) into this standardized and computerized registry. All parameters relevant to this analysis, including age, sex, vascular risk factors, and prehospital status (according to the modified Rankin Scale [mRS], determined at hospital admission and based on all available information provided by the patient and/or relatives) and pretreatment with antiplatelet drugs or oral anticoagulation were recorded prospectively. Main outcome measures were in-hospital mortality rate and functional status at hospital discharge quantified by the mRS.

We did not obtain ethics board approval because the registry is a country-wide quality assurance measure based on state law, wherein all inpatients are documented anonymously. Informed consent is not required before enrollment in the registry.

We used \( t \) tests and \( \chi^2 \) statistics to compare baseline variables (age, prehospital mRS) between patients with and without antithrombotic pretreatment. Univariate and multivariate logistic regression analyses were used to determine the influence of antithrombotic therapy on mortality rate and functional outcome.

Results

Between January 2003 and December 2004, 1691 patients with a final diagnosis of ICH were documented (48% female;
mean age, 72±12 years, see the Table). At the time of stroke onset, 441 patients (26%) were on antiplatelet therapy, and 208 (12%) were receiving oral anticoagulation. Compared with patients without any antithrombotic pretreatment, patients using antiplatelet therapy were significantly older (70±14 versus 75±10 years, \(P=0.001\), \(t\) test) and had a significantly worse prehospital status (mRS >1, 18% versus 38%, \(P<0.001\), \(\chi^2\)). The corresponding findings for patients without antithrombotic pretreatment compared with patients on oral anticoagulation were similar (70±14 versus 75±7 years, \(P<0.001\); 18% versus 30%, \(P=0.001\)).

In-hospital mortality rates were 21% for patients without antithrombotic pretreatment, 27% for patients using antiplatelet agents, and 38% for patients on oral anticoagulation. The corresponding values for patients having an unfavorable functional outcome (defined as mRS >2 or death) at hospital discharge were 75%, 80%, and 87%, respectively.

By univariate logistic-regression analysis, pretreatment with antiplatelet agents or oral anticoagulation was found to be a significant predictor of in-hospital mortality (odds ratio [OR], 1.42; \(P=0.008\); OR, 1.53; \(P<0.001\)) and of an unfavorable functional outcome (OR, 1.33; \(P=0.039\); OR, 1.51; \(P<0.001\)). However, after adjustment for age and prehospital mRS, pretreatment with antiplatelet agents was no longer an independent predictor of in-hospital death (OR, 1.12; \(P=0.490\)) or unfavorable functional outcome (OR, 0.97; \(P=0.830\)), whereas the influence of treatment with oral anticoagulants still remained significant (OR, 1.45; \(P<0.001\); OR, 1.42; \(P=0.009\); see the Figure).

**Discussion**

Our study does not support the hypothesis that pretreatment with antiplatelet agents is an independent risk factor for a higher in-hospital mortality rate and an unfavorable outcome in patients with ICH. After adjusting for age and prehospital status, 2 main confounders, no significant effect on outcome independently attributable to pretreatment with antiplatelet drugs could be detected.

In accordance with previous investigations, our analysis revealed that patients on antiplatelet therapy or oral anticoagulation were older and had a worse prehospital status compared with patients without any antithrombotic treatment.\(^4\,5\) Our study also confirmed that patients who experienced an ICH while taking oral anticoagulants (mostly phenprocoumon in our cohort) had a significantly worse prognosis compared with patients without pretreatment, independent of age and prehospital functional status.\(^1\,2\) However, the same did not apply to patients taking antiplatelet agents.

Recently, 2 retrospective studies reported results that are apparently contradictory to our data.\(^4\,5\) Both studies sug-

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### Baseline Characteristics, Clinical Variables, and Risk Factors for 1691 Patients With ICH

<table>
<thead>
<tr>
<th>Pretreatment</th>
<th>None</th>
<th>Antiplatelet Agents</th>
<th>Anticoagulants</th>
</tr>
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<tbody>
<tr>
<td>Age, y</td>
<td>70±14</td>
<td>75±10</td>
<td>75±7</td>
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<tr>
<td>Female sex, %</td>
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<td>49</td>
<td>43</td>
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<tr>
<td>Premorbid mRS &gt;1, %</td>
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<tr>
<td>mRS at admission &gt;2, %</td>
<td>83</td>
<td>88</td>
<td>84</td>
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<tr>
<td>In-hospital mortality, %</td>
<td>21</td>
<td>27</td>
<td>38</td>
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<tr>
<td>Unfavorable outcome, %*</td>
<td>75</td>
<td>80</td>
<td>87</td>
</tr>
<tr>
<td>Arterial hypertension, %</td>
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<td>Hypercholesterolemia, %</td>
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<tr>
<td>Diagnosis: I61.0 (deep), %</td>
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<td>35</td>
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<td>Diagnosis: I61.2–I61.9, %</td>
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</table>

*Unfavorable outcome was defined as an mRS >2 or death.

### Influence of preexisting antiplatelet therapy and oral anticoagulation on in-hospital mortality and unfavorable functional outcome (defined as mRS >2 or death) in 1691 patients with ICH. A higher OR indicates a higher risk for having the defined outcome at hospital discharge in relation to patients without antithrombotic treatment.
gested that previous antiplatelet therapy contributed to an unfavorable outcome in ICH. However, closer analysis of the demographic data of those studies reveals a substantial difference between patients with and without antiplatelet pretreatment in the rate of previous ischemic cerebrovascular events (54% versus 7% and 43% versus 9%, respectively). Ischemic strokes often lead to relevant functional impairment, and it is therefore likely that patients taking antiplatelet drugs had a worse prehospital status. This hypothesis is supported by our analysis showing that 38% of patients on antiplatelet agents had a prehospital mRS >1 compared with only 18% of patients without pretreatment (P<0.001). Because a reduced prehospital status is a known predictor of an unfavorable prognosis, adjustment for this confounder seems to be essential for determining any independent effect of antiplatelet pretreatment on mortality and functional outcome. In our opinion, both the study by Toyoda et al and that by Saloheimo et al did not sufficiently control for prehospital status. In view of other negative studies, their results remain questionable.

Surrogate markers of clinical deterioration (eg, hematoma enlargement) may still be significantly different between patients with and without antiplatelet pretreatment, as suggested by the study of Toyoda et al. However, considering our data, the influence on the overall prognosis seems to be marginal. In contrast to patients on oral anticoagulation, those on antiplatelet drugs did not show larger hematomas at hospital admission compared with patients without pretreatment. This further strengthens the hypothesis that factors other than antiplatelet therapy may worsen mortality and functional outcome.

In summary, our data do not support an independent effect of previous antiplatelet therapy on mortality and functional outcome in patients with acute ICH and thus, do not justify aggressive measures to revert the effect of antiplatelet agents in the acute setting.

Disclosures

None.

References

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