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Background and Purpose—The results of the Sarpogrelate-Aspirin Comparative Clinical Study for Efficacy and Safety in Secondary Prevention of Cerebral Infarction (S-ACCESS), a randomized double-blind study of sarpogrelate (selective 5-HT2A receptor antagonist) versus aspirin in 1510 Japanese patients, have been reported. But S-ACCESS failed to demonstrate noninferiority of sarpogrelate to aspirin for preventing the recurrence of cerebral infarction. Here we compare the characteristics of sarpogrelate and aspirin in various subgroups.

Methods—Subgroups were predefined from patients’ baseline characteristics. Hazard ratio (HR) and 95% confidence interval (CI) for sarpogrelate versus aspirin were calculated for primary (cerebral infarction) and secondary (serious vascular events) end points. Interactions between treatment effects and subgroup variables were examined by post hoc analysis.

Results—No significant difference in outcome between sarpogrelate and aspirin was found across multiple predefined subgroups. In post hoc analysis, a qualitative treatment interaction with diabetes mellitus was detected (P = 0.166 for recurrence of cerebral infarction; P = 0.098 for serious vascular events). HR for the recurrence of cerebral infarction with sarpogrelate versus that with aspirin was 0.87 (95% CI: 0.48 to 1.60) in diabetic patients and 1.51 (95% CI: 0.98 to 2.31) in nondiabetic patients. For serious vascular events, the corresponding HRs were 0.73 (95% CI: 0.42 to 1.25) and 1.28 (95% CI: 0.89 to 1.83).

Conclusions—No specific baseline characteristic resulting in a significant difference between the effects of sarpogrelate and aspirin was identified. Aspirin was superior in most subgroups, except diabetics. Sarpogrelate may be a useful treatment option for Japanese patients with diabetes. (Stroke. 2009;40:2862-2865.)

Key Words: cerebrovascular diseases/stroke ■ clinical studies ■ secondary prevention ■ antiplatelets ■ diabetes mellitus

Aspirin is a first-line agent for secondary prevention of cerebral infarction, but is insufficiently effective in specific populations, such as patients who are postoperative or smokers, or who have diabetes, hyperlipidemia, or unstable angina.1

Sarpogrelate is an antiplatelet agent having a selective antagonistic effect on 5-HT2A receptors. The Sarpogrelate-Aspirin Comparative Clinical Study for Efficacy and Safety in Secondary Prevention of Cerebral Infarction (S-ACCESS), a randomized double-blind study in 1510 Japanese patients, failed to demonstrate noninferiority of sarpogrelate to aspirin for preventing the recurrence of cerebral infarction. However, the incidence of bleeding events was significantly lower with sarpogrelate than with aspirin.2

Because aspirin has some significant disadvantages, it seemed worthwhile to evaluate sarpogrelate, which has pleiotropic actions, not only antiplatelet activity.3 Here, to examine the characteristic effects of sarpogrelate compared with aspirin, we analyzed S-ACCESS subgroups predefined according to patients’ baseline characteristics. We also assessed the consistency of the treatment effects by examining interactions.

Methods
The study design of S-ACCESS has been reported.2 Briefly, patients with cerebral infarction were randomly assigned to receive sarpogrelate (100 mg × TID, group S) or aspirin (81 mg/d, group A) on a double-blind basis. Mean duration of follow-up was 1.59 years (SD 0.88, maximum 3.37 years). The primary end point was recurrence of cerebral infarction. Clusters of serious vascular events (stroke, acute coronary syndrome, or vascular event–related death) were selected as secondary end points.

Analyses of predefined subgroups based on baseline characteristics (age, sex, presence or absence of complications [hypertension, dyslipidemia, and diabetes mellitus], first episode versus recurrence, and type of cerebral infarction) were performed for the primary and secondary end points of S-ACCESS. The complications were judged...
by the investigators. To assess whether the treatment effects differ among subgroup, treatment interaction for baseline characteristics was examined by post hoc analysis.

**Statistical Analysis**

Hazard ratio (HR) and its 95% confidence interval (CI) in group S versus group A were calculated, and the log-rank test was performed, using a 2-tailed significance level of 5%. Interaction was evaluated by a test of homogeneity across strata based on the log-rank test, using a 2-tailed significance level of 20%. All analyses were conducted with SAS version 9.1 software (SAS Institute).

**Results**

In S-ACCESS, 1510 patients were randomly assigned to either group S or group A; the 2 groups were well matched.²

HR and 95% CI of primary and secondary outcomes are shown in the Table. No significant difference was found between groups in any subgroup. Although in most populations the hazard of group S was higher than that of group A, in diabetics the hazard was reversed for both primary and secondary end points.

The interaction test detected heterogeneity of treatment effects only in the subgroup with diabetes mellitus (\(P = 0.166\) for recurrence of cerebral infarction; \(P = 0.098\) for occurrence of serious vascular events; Table). The Figure shows the event rates of each treatment in diabetic and nondiabetic patients. HR for the recurrence of cerebral infarction with sarpogrelate versus aspirin was 0.87 (95% CI: 0.48 to 1.60) in diabetic patients and 1.51 (95% CI: 0.98 to 2.31) in nondiabetic patients. For serious vascular events, the corresponding HRs were 0.73 (95% CI: 0.42 to 1.25) and 1.28 (95% CI: 0.89 to 1.83). A qualitative interaction was observed between groups in any subgroup. Although in most populations the hazard of group S was higher than that of group A, in diabetics the hazard was reversed for both primary and secondary end points.

### Table. Subgroup Analysis for Cerebral Infarction and Serious Vascular Events (Stroke, ACS, or Vascular Event-Related Death)

<table>
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<th>Subgroup</th>
<th>Cerebral Infarction</th>
<th></th>
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<th>Hazard (%)</th>
<th>Hazard Ratio (95% CI)</th>
<th>(P^*)</th>
<th>Serious Vascular Event</th>
<th></th>
<th></th>
<th>Hazard (%)</th>
<th>Hazard Ratio (95% CI)</th>
<th>(P^*)</th>
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<td>Age, y</td>
<td>Sarpogrelate</td>
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<td></td>
<td>Aspirin</td>
<td>Interaction (treatment/age 65)</td>
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<td>&lt;65</td>
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<td>2.89</td>
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<td>5.57</td>
<td>4.83</td>
<td>1.15 (0.67–1.98)</td>
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<td>≥65</td>
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<td>6.36</td>
<td>1.25 (0.84–1.87)</td>
<td>0.259</td>
<td>9.13</td>
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<td>Lacunar</td>
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*Log-rank test.
†Interaction between treatment and NINDS classification (atherothrombotic or lacunar).
ACS indicates acute coronary syndrome; NINDS, National Institute of Neurological Disorders and Stroke.

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treatment effect and diabetes mellitus. With regard to bleeding complication, the event rates in diabetic patients were 25/199 (12.6%) in group S and 34/222 (15.3%) in group A (P = 0.50), whereas those in non-diabetic patients were 64/551 (11.6%) and 97/535 (18.1%), respectively (P < 0.01). A total of 21 intracerebral hemorrhages occurred; for diabetic patients 1 in group S and 2 in group A, and for non-diabetic patients, 8 and 10, respectively.

Discussion

This subgroup analysis of S-ACCESS did not identify any statistically significant difference between the effects of sarpogrelate and aspirin, though sarpogrelate tended to be inferior to aspirin, except in diabetics. Although the American Diabetes Association recommends aspirin for primary and secondary prevention in type 2 diabetic patients with cardiovascular risk factors, aspirin did not reduce primary cardiovascular events in Japanese diabetics. The treatment effect of aspirin may vary between diabetic and non-diabetic patients. Our results are thus consistent with clinical studies.

Our results reveal a unique feature of sarpogrelate: its hazard in diabetic patients is at as low a level as in non-diabetic patients. This finding may be attributable to the protective effect of sarpogrelate against vascular endothelial dysfunction. In addition, sarpogrelate was associated with fewer bleeding complications than aspirin even in diabetic patients in this study. Bleeding complication, including intracerebral hemorrhage, during antithrombotic therapy might be more common in Japanese than in Western patients. Given that sarpogrelate prevented secondary vascular events specifically in diabetic patients, this drug could have a role in the clinical arsenal, at least for Japanese patients.

There are limitations in our interaction analysis. First, the treatment heterogeneity for diabetes mellitus was found by post hoc analysis. Second, the finding that the effects of the 2 drugs differed between diabetic and non-diabetic patients does not necessarily mean that sarpogrelate has higher efficacy than aspirin in diabetic patients because the difference between the two drugs in diabetics was not statistically significant.

In conclusion, no specific subgroup showing a statistically significant difference between the effects of sarpogrelate and aspirin was identified. Aspirin was superior for most sub-groups of patients, except diabetics. Sarpogrelate may be a useful treatment option for Japanese patients with diabetes.

Appendix

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Disclosures

None.

References

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