Sarpogrelate-Aspirin Comparative Clinical Study for Efficacy and Safety in Secondary Prevention of Cerebral Infarction (S-ACCESS)

A Randomized, Double-Blind, Aspirin-Controlled Trial

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Background and Purpose—The antiplatelet agent sarpogrelate is a selective inhibitor of 5-hydroxytryptamine receptors. The purpose of this study was to compare the efficacy and safety of sarpogrelate with those of aspirin in Japanese ischemic stroke patients.

Methods—In total, 1510 patients with recent cerebral infarction (1 week to 6 months after onset) were randomly assigned to receive either sarpogrelate (100 mg TID) or aspirin (81 mg/d). Mean follow-up period was 1.59 years. The primary efficacy 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. The aim of the primary efficacy analysis was to demonstrate the noninferiority of sarpogrelate with respect to aspirin, with the criterion that the upper limit of the 95% CI of the hazard ratio (sarpogrelate vs aspirin) for recurrence of cerebral infarction should not exceed 1.33.

Results—Cerebral infarction recurred in 72 patients (6.09%/y) in the sarpogrelate group and in 58 (4.86%/y) in the aspirin group (hazard ratio = 1.25; 95% CI, 0.89 to 1.77; P = 0.19). A serious vascular event occurred in 90 (7.61%/y) and in 85 (7.12%/y) patients, respectively (hazard ratio = 1.07; 95% CI, 0.80 to 1.44; P = 0.65). The overall incidences of bleeding events were 89 (11.9%) and 131 (17.3%), respectively (P < 0.01).

Conclusions—Sarpogrelate was not noninferior to aspirin for prevention of recurrence of cerebral infarction. Bleeding events were significantly fewer with sarpogrelate than aspirin. The effect of aspirin in Japanese patients was similar to that in Western studies. (Stroke. 2008;39:1827-1833.)

Key Words: cerebrovascular diseases/stroke ■ clinical studies ■ secondary prevention ■ antiplatelet agents

Atherothrombotic vascular diseases are the leading causes of morbidity and mortality throughout the world.1 Vascular risk factor control and antiplatelet therapy are of proven value for secondary prevention of recurrence in these patients.2 Although many randomized trials and meta-analyses have yielded reliable evidence of the value of antiplatelet therapy in atherothrombotic vascular disease,3–8 the number needed to treat with aspirin, thienopyridine derivatives, etc, to prevent 1 vascular accident in patients with a history of stroke or transient ischemic attack (TIA) was found to be rather high.3,4 Furthermore, these antiplatelet agents have the potential to cause bleeding.9,10

The antiplatelet agent sarpogrelate, (±)-2-(dimethylamino)-1-[[o-(m-methoxyphenethyl)phenoxy]methyl]ethyl hydrogen succinate hydrochloride, has been used for years to treat patients with peripheral arterial disease in Japan,11 China, and the Republic of Korea. It works as a selective 5-hydroxytryptamine (5-HT) receptor antagonist, inhibiting responses to 5-HT medi-
ated by 5-HT₂A receptors, including platelet aggregation and vasoconstriction. Sarpogrelate was found to prevent thrombus formation in experimental models, and a clinical pharmacologic study has shown that it inhibits platelet aggregation in patients with ischemic stroke.

The Sarpogrelate-Aspirin Comparative Clinical study for Efficacy and Safety in Secondary prevention of cerebral infarction (S-ACCESS) trial was designed to evaluate and compare the efficacy and safety of sarpogrelate with those of aspirin for prevention of recurrence in patients with recent ischemic stroke. Although aspirin is widely used throughout the world for primary and secondary prevention of atherosclerosis, several reports indicate that the incidence of intracerebral hemorrhage in Japan is higher than in Western countries, and Japanese patients treated with aspirin may be at greater risk of bleeding.

The use of aspirin for secondary stroke prevention was approved by the Japanese Ministry of Health, Labor and Welfare in 2000, although clinical evidence of its efficacy and safety specifically in Japanese patients is still limited. Therefore, an additional purpose of this study was to obtain information about the efficacy and safety of aspirin in a rather large series of Japanese patients.

Methods

Patients

Between April 2001 and November 2003, we enrolled patients with recent cerebral infarction, based on the National Institute of Neurological Disorders and Stroke classification, at 113 institutes in Japan. The patients provided written, informed consent, and the study was approved by the ethics review board at each institution in accordance with the Helsinki Declaration.

Inclusion Criteria

Patients ≥20 years were eligible for inclusion if they had had a symptomatic cerebral infarction in the previous 1 week to 6 months and met the following criteria: focal signs that had lasted ≥24 hours; infarction-related focal lesion compatible with their signs and symptoms defined by computed tomography or magnetic resonance imaging; systolic blood pressure <180 mm Hg; and diastolic blood pressure <110 mm Hg.

Exclusion Criteria

Patients were excluded from enrollment if any of the following criteria were met: cardioembolic stroke; modified Rankin Scale (mRS) score of 4 or more; previous or scheduled vascular surgery for cerebral infarction; history of intracranial hemorrhage, systemic bleeding, or other history of bleeding diathesis or coagulopathy; severe complications such as cardiac, renal, hepatic, and blood disorders; treatment for malignancy within the past 5 years; pregnancy, possible pregnancy, or nursing mothers; history of sarpogrelate and aspirin sensitivity; current peptic ulceration; enrollment ≤3 months in any other clinical trial; judgment by investigators to be unsuitable for the study.

Procedures

Patients were randomly assigned to receive sarpogrelate (100 mg TID, group S) or aspirin (81 mg/d, group A), according to an allocation table that was generated by random numbers by a person who was not part of this study. The assigned treatments were unknown to both the investigators and patients. A double-dummy design was used to maintain blinding with aspirin-matched placebo (once daily) or sarpogrelate-matched placebo (three times daily). The trial was started on the day of the first medication and continued to September 2004. Patients were evaluated at 4-week intervals throughout the study by stroke specialists. We evaluated the occurrence of cerebral infarction, intracerebral hemorrhage, subarachnoid hemorrhage, undetermined stroke, TIA, acute coronary syndrome (myocardial infarction/unstable angina), other vascular-related events, or sudden death. All outcome events were reported to the Efficacy End Point Committee, which assessed the appropriateness of the clinical judgment; any differences of opinion were resolved by discussion.

Patients were to be followed up until the end of the study period, except for the exclusions set forth in the protocol; ie, patients who experienced cerebral infarction, intracerebral hemorrhage, subarachnoid hemorrhage, or undetermined stroke; patients with persistent hypertension lasting longer than 3 months (systolic blood pressure
The primary end point was the first recurrence of cerebral infarction. Various combinations of vascular event outcomes were selected for analysis as secondary end points. Safety-related events, judged to be related to administration of the study drug by investigators, were followed up for an additional month after the study period. Bleeding events were defined as hemorrhage based on the Special Search Category of the Medical Dictionary for Regulatory Activities, version 6.0.

The aim of this study was to establish the noninferiority of sarpogrelate with respect to aspirin according to a predefined margin (Δ) for the difference in rates of the primary event; ie, the upper limit of the 95% CI of the hazard ratio (HR) for recurrence of cerebral infarction in group S versus group A should not exceed 1.33.

### Statistical Analysis

The primary efficacy analysis was performed according to the intention-to-treat principle, except for patients who did not receive medication at all or who did not meet the aforementioned inclusion criteria. The sample size and the criterion for noninferiority of sarpogrelate with respect to aspirin were established on the following bases.

We estimated that the relative risk reduction (RR) of sarpogrelate compared with placebo for secondary prevention of cerebral infarction would be 30%, based on unpublished data from 278 TIA patients. Furthermore, according to the Antiplatelet Trialists’ Collaboration meta-analyses, aspirin showed a 25% odds reduction for serious vascular events.3 The analyses of the Cilostazol Stroke Prevention Study (CSPS) performed in Japan,20,21 which is likely for ethical reasons to be the last trial of an antiplatelet agent against placebo, indicated that annual recurrence rates for cerebral infarction in Japanese subjects in the placebo group were 5.25% for lacunar infarction and 10.58% for atherothrombotic infarction. If the risks of occurrence of these 2 clinical categories in our patients are assumed to be equal (1:1) and the annual recurrence rates are the same as in the CSPS, the putative annual event rate for placebo-treated patients would have been ≈8.0% in the present study. Therefore, we considered that the expected annual event rates for cerebral infarction would be 5.5% in group S and 6.0% in group A, compared with the expected rate of 8.0% for placebo, if it had been included.

The criterion for noninferiority in the primary efficacy analysis was defined in terms of the 95% CI of the HR in the 2 groups on the

### Table 2. Incidences of Each Category of Vascular Events and All Deaths

<table>
<thead>
<tr>
<th>Category</th>
<th>No. With Events*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Group S (n=747)</td>
</tr>
<tr>
<td>Vascular events</td>
<td></td>
</tr>
<tr>
<td>Cerebral infarction</td>
<td>72</td>
</tr>
<tr>
<td>TIA</td>
<td>19</td>
</tr>
<tr>
<td>Intracerebral hemorrhage</td>
<td>7</td>
</tr>
<tr>
<td>Subarachnoid hemorrhage</td>
<td>0</td>
</tr>
<tr>
<td>Undetermined stroke</td>
<td>0</td>
</tr>
<tr>
<td>ACS</td>
<td>11</td>
</tr>
<tr>
<td>Other vascular events</td>
<td>1</td>
</tr>
<tr>
<td>Sudden vascular death except stroke† and ACS</td>
<td>3</td>
</tr>
<tr>
<td>All death‡</td>
<td>16</td>
</tr>
<tr>
<td>Vascular death‡</td>
<td>7</td>
</tr>
<tr>
<td>Nonvascular death</td>
<td>9</td>
</tr>
</tbody>
</table>

ACS indicates acute coronary syndrome.
*Only the first occurrence of an event was counted.
†Stroke comprises cerebral infarction, intracerebral hemorrhage, subarachnoid hemorrhage or undetermined stroke.
‡Category includes sudden vascular death.
following bases. From a statistical perspective, the maximum acceptable margin ($\Delta$) for the difference in rates of the primary event should be no larger than the upper limit of the 2-sided 95% CI of the standard treatment effect relative to placebo. We can calculate this as follows: $rac{1}{\frac{1}{2}(1 - RR)/100} = rac{1}{1/(1 - 0.25)} = 1/0.75 = 1.33$, where RR is the risk reduction in percent of aspirin versus placebo, which is taken to be 25%, based on meta-analyses of the Antiplatelet Trialists’ Collaboration. Thus, the noninferiority criterion was defined as the case that the value of the upper limit of the 95% CI of the HR for recurrence of cerebral infarction between group S and group A is not more than 1.33. We had planned to enroll 1500 patients with a follow-up period of 2.25 years, and our study should have 80% power to detect noninferiority as defined in this way.

The Kaplan-Meier method was used to estimate incidence over time, and the log-rank test was used to compare curves. The safety analyses were based on the treated population, including all randomized patients who received at least 1 dose of the study medication. Statistical comparisons of safety data were made using the $\chi^2$ test. All analyses were conducted with SAS version 8.2 software (SAS Institute, Cary, NC).

Results

Figure 1 shows the trial profile. A total of 1510 patients were randomly allocated to either group S ($n=752$) or group A ($n=758$). Mean duration of follow-up was 1.59 years (maximum, 3.37 years). The 2 groups were well matched with respect to baseline characteristics, age, male-female ratio, coexisting risk factors, type of cerebral infarction, and mRS score at randomization (Table 1).

Efficacy End Point

The incidence of vascular events and the results of the primary and secondary outcomes (clusters A through F) are shown in Tables 2 and 3, respectively. Symptomatic cerebral infarction developed in 72 patients in group S during 1182.7 patient-years and in 58 patients in group A during 1194.2 patient-years. The event rate was 6.09%/y with sarpogrelate and 4.86%/y with aspirin; the HR was 1.25 (95% CI, 0.89 to 1.77); the upper limit of 95% CI of the HR thus exceeded 1.33.

By subtype of prior ischemic stroke, in patients with atherothrombotic infarction, the event rates were 7.31%/y in group S and 5.96%/y in group A (HR = 1.23; 95% CI, 0.70 to 2.16). In those with lacunar infarction, the event rates were 5.95%/y in group S and 4.53%/y in group A (HR = 1.14; 95% CI, 0.84 to 1.57). A serious vascular event (cluster E) occurred in 90 patients (7.61%/y) in group S and in 85 patients (7.12%/y) in group A (HR = 1.07; 95% CI, 0.80 to 1.44; $P = 0.65$).

Kaplan-Meier plots (Figures 2A and 2B) suggested no statistically significant differences in cumulative risk over time between the groups ($P = 0.19$ for recurrence of cerebral infarction, $P = 0.65$ for a serious vascular event).

Safety-Related Events

During the trial, 712 (94.9%) patients in group S and 691 (91.3%) in group A reported at least 1 adverse event...
A total of 27 deaths occurred during follow-up; 16 in group S and 11 in group A. Twelve fatal vascular events occurred; 7 in group S (4 due to stroke and 3 due to sudden death of unknown origin) and 6 in group A (1 due to stroke, 1 due to myocardial infarction, 2 due to dissection of the aorta, and 2 due to sudden death).

**Discussion**

A clinical pharmacologic study with ischemic stroke patients has evaluated the dose-response relation of sarpogrelate by measuring the inhibitory effect on platelet aggregation after medication, and the recommended clinical dosage was concluded to be 100 mg TID, which was the dosage that we used.

Although the incidence of atherothrombotic infarction is increasing and that of lacunar infarction is decreasing in Japan, the ratio of patients with lacunar infarction to patients with atherothrombotic infarction was 2.1 in the present study, as shown in Table 1. This is probably partially due to the fact that we excluded patients with severe disability (mRS 4 or more) in the trial. According to a population-based cohort study, the annual recurrence rate for stroke after first-ever cerebral infarction in Japanese subjects was higher than in other populations, being \( \approx 10\% / y \) in the first 2 years; the recurrence rates at 1 year were 7.2% (95% CI, 3.1% to 11.2%) after lacunar infarction and 14.8% (95% CI, 4.5% to 25.0%) after atherothrombotic infarction, which are much higher than the results of the CSPS. On the basis of the annual event rates of patients in each clinical category in the CSPS, we recalculated the putative annual event rate for placebo-treated patients as 7.03% by using this ratio of 2:1 for lacunar and atherothrombotic infarction (see the Statistical Analysis section). Thus, the putative annual event rate of recurrence of cerebral infarction for untreated Japanese patients may be in the range of 7% to 10%. This uncertainty makes it difficult to assess the magnitude of the RR reduction of sarpogrelate, based on the annual event rate in group S (6.09%) observed in this study. Further work will be needed to determine the potency of sarpogrelate for secondary prevention of ischemic stroke.

Although the primary end point in this study was recurrence of cerebral infarction, antiplatelet therapy acts systemically, and patients with cerebrovascular disease are at high risk for developing cardiovascular and other vascular events. Indeed, in a recent meta-analysis of antiplatelet therapy, the primary measure of outcome was a serious vascular event (ie, nonfatal myocardial infarction, nonfatal stroke, or vascular event–related death). Therefore, it might be better to evaluate efficacy on a systemic basis, ie, by taking systemic vascular events as the primary events, as in our study. The corresponding category in our study was cluster E, and sarpogrelate showed an effect comparable to that of aspirin in the Kaplan-Meier plots for event-free rates of serious vascular events (Figure 2B).

5-HT is released from circulating platelets at sites of atherosclerotic vascular lesions, and it contributes to platelet aggregation and vasoconstriction via 5-HT2A receptors. It has been reported that plasma 5-HT concentrations are higher in patients with atherosclerotic cardiovascular disease, and there is clinical evidence that high 5-HT levels are associated...
with the occurrence of cardiac events. Thus, 5-HT may play a key role in the progression of atherosclerosis.

Several studies have suggested that aspirin increases the risk of hemorrhagic stroke, and it is generally accepted that antiplatelet agents should be used with caution in patients with a high risk of bleeding. Sarpogrelate was associated with fewer bleeding complications than aspirin, and intracerebral hemorrhage was seen in 9 patients (1.2%) in group S (1 occurred at 27 days and 1 at 32 days after discontinuation of the study drug) and in 12 (1.6%) patients in group A. The possibility that the reduced rate of hemorrhagic complications seen in group S might simply reflect the lower efficacy of sarpogrelate cannot be ruled out completely. However, although this study failed to demonstrate noninferiority of sarpogrelate with respect to aspirin for prevention of recurrence cerebral infarction, sarpogrelate and aspirin showed similar effectiveness for prevention of serious vascular events. Therefore, we consider that the reduced rate of hemorrhage seen with sarpogrelate may be a consequence of the different mechanisms of action of the 2 agents: sarpogrelate reversibly inhibits responses to 5-HT mediated by 5-HT2A receptors, whereas aspirin irreversibly inactivates cyclooxygenase activity for the lifespan of a platelet.

In conclusion, this is the first randomized, double-blind, aspirin-controlled trial of sarpogrelate. The results indicate that aspirin should remain the first-line treatment to prevent recurrence of serious vascular events. However, although sarpogrelate did not meet the predefined criterion for noninferiority with respect to aspirin in our setting, it was associated with significantly fewer bleeding complications than aspirin. Further studies appear to be required to determine the clinical value of sarpogrelate for prevention of stroke.

Disclosures

Mitsubishi Tanabe Pharma Corp was the main source of funding for this study and provided the study medication. The sponsor cooperated in the work of the steering committee: study design, data collection, and statistical analysis. The corresponding author had full access to all data in the study and has final responsibility for all publications arising from the study. Kazuoki Kondo, MD, serves on a medical advisory board to Mitsubishi Tanabe Pharma Corp. All other authors reported no conflicts of interest.

References


Table 4. Adverse Event Summary

<table>
<thead>
<tr>
<th></th>
<th>Group S (n=750)</th>
<th>Group A (n=757)</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adverse events</td>
<td>712</td>
<td>691</td>
<td>0.0070</td>
</tr>
<tr>
<td>Drug-related adverse events</td>
<td>259</td>
<td>279</td>
<td>0.3750</td>
</tr>
<tr>
<td>Bleeding events</td>
<td>89</td>
<td>131</td>
<td>0.0035</td>
</tr>
<tr>
<td>Drug-related bleeding events</td>
<td>60</td>
<td>103</td>
<td>0.0006</td>
</tr>
<tr>
<td>Frequent events (excluding end points)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>255</td>
<td>261</td>
<td>0.8876</td>
</tr>
<tr>
<td>Headache</td>
<td>71</td>
<td>70</td>
<td>0.9538</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>61</td>
<td>63</td>
<td>0.9683</td>
</tr>
<tr>
<td>Dizziness and vertigo</td>
<td>58</td>
<td>59</td>
<td>1.0000</td>
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<tr>
<td>Blood pressure increase</td>
<td>55</td>
<td>55</td>
<td>1.0000</td>
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<tr>
<td>Constipation</td>
<td>54</td>
<td>53</td>
<td>0.1064</td>
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<tr>
<td>Back pain</td>
<td>51</td>
<td>54</td>
<td>0.8784</td>
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<tr>
<td>Upper respiratory infection</td>
<td>50</td>
<td>45</td>
<td>0.6378</td>
</tr>
<tr>
<td>Contusion</td>
<td>48</td>
<td>43</td>
<td>0.6324</td>
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<tr>
<td>Cough</td>
<td>44</td>
<td>42</td>
<td>0.8765</td>
</tr>
<tr>
<td>Hypertension</td>
<td>39</td>
<td>36</td>
<td>0.7809</td>
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<tr>
<td>Skin rash</td>
<td>36</td>
<td>39</td>
<td>0.8449</td>
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<tr>
<td>Pain in extremity</td>
<td>28</td>
<td>39</td>
<td>0.2259</td>
</tr>
<tr>
<td>Nasal bleeding</td>
<td>19</td>
<td>40</td>
<td>0.0088</td>
</tr>
<tr>
<td>Subcutaneous hemorrhage</td>
<td>11</td>
<td>38</td>
<td>0.0002</td>
</tr>
</tbody>
</table>

*χ² test.


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