Dear Sir,

Aspirin, commonly used worldwide as an antiplatelet agent, inhibits the production of thromboxane A2 by blocking cyclooxygenase (1). A recent meta-analysis also concluded that in a population at high risk for occlusive vascular events, antiplatelet therapy reduced the combined endpoint of serious vascular events by a fourth, non-fatal myocardial infarction by a third, non-fatal stroke by a fourth, and vascular mortality by a sixth (2).

However, many patients who take aspirin for secondary prevention have further vascular events, implying the possibility that aspirin treatment is not necessarily associated with in vivo platelet inactivation (3). Also, the relevance of its inhibitory effects on plasma PAI-1 levels is not clearly understood (4–7). In the present study, we demonstrated that elevation of the plasma PAI-1 level was elicited by additional aspirin treatment to ischemic patients already undergoing treatment with antiplatelet agents.

In this study, we initially performed the measurement of plasma PAI-1 levels and platelet aggregation induced by collagen in 23 patients without anti-platelet treatment (9 men and 14 women; mean age 65 years; age range 39–88 years) who attended regular health check-ups between July 2004 and August 2005, and in whom ischemic stroke was diagnosed. Also, none of them experienced acute events. The patients were treated with 100 mg of aspirin daily, for one week. Informed consent was obtained from all participants. For the PAI-1 assay, a latex photometric immunoassay kit (Mitsubishi Chemical Co., Japan) for total PAI-1 within a dynamic measurement range (0–270 ng/ml) that can detect all forms of PAI-1 without the influence of conformational changes was used (8, 9). Also, we used the LPIA-A700 (Mitsubishi Chemical Co., Japan), a fully automated quantitative latex photometric immunoassay instrument, to measure PAI-1. Platelet aggregation induced by collagen (Arkay Factory Inc., Japan) was determined using Hematracer 801 (MC Medical, Japan), where percent platelet aggregation was expressed as the maximal percentage change in light transmission relative to that of platelet-poor plasma. Collagen was used at a concentration of 1.7 µg/ml. Results are shown as the mean ± SD. Statistical evaluation was performed using Wilcoxon’s signed-rank test to compare two paired groups, and P<0.05 was considered significant.

The plasma PAI-1 levels at one week post-aspirin treatment (14.1 ± 6.6 ng/ml) were significantly decreased compared to levels before aspirin treatment (20.9 ± 8.0 ng/ml, P<0.0001), and platelet aggregation in these patients was also significantly reduced (before, 78.0 ± 6.5%; after, 48.0 ± 16.4%; P<0.0001). These results suggest that low-dose aspirin treatment is basically effective for both reduction of plasma PAI-1 levels and ex vivo platelet aggregation, consistent with previous observations (1, 7). However, it remains to be clarified whether the addition of aspirin to the treatment regimen in patients already being treated with antiplatelet drugs, including aspirin, is effective for reducing plasma PAI-1 levels.

We then performed another study in 20 consecutive patients (15 men and 5 women; mean age 61 years; age range 35–83 years) who had suffered ischemic strokes and had already been undergoing treatment with antiplatelet agents for over a month. The patients were treated with 100 mg of aspirin daily for one week in addition to the already prescribed antiplatelet agents, including aspirin. As a control, we used 46 patients with ischemic stroke (38 men and 8 women; mean age 69 years; age range 36–90 years) who were not treated with any other agents, only the already prescribed antiplatelet agents.

There was a significant difference in plasma PAI-1 levels between before (14.3 ± 5.0 ng/ml) and after the additional aspirin treatment (26.8 ± 11.6 ng/ml), representing a 1.9-fold increase in plasma PAI-1 levels after additional aspirin treatment (Table 1). In contrast, platelet aggregation after the additional aspirin treatment was significantly inhibited compared with before aspirin treatment, indicating that the addition of aspirin is effective in inhibiting ex vivo thromboxane A2 production in platelets (1). Furthermore, we confirmed that the elevation of plasma PAI-1 levels observed after the additional aspirin treatment was absent in the control group.

The origin of the elevated plasma PAI-1 levels detected in this study is unknown, but release from activated platelets is possibly involved, because only 10% of circulating PAI-1 is in

### Table 1: Changes in plasma plasminogen activator inhibitor-1 (PAI-1) levels and platelet aggregation after additional aspirin treatment.

<table>
<thead>
<tr>
<th>Additional treatment</th>
<th>PAI-1 (ng/ml)</th>
<th>Platelet aggregation (%)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Before</td>
<td>After</td>
</tr>
<tr>
<td>Aspirin 100mg daily for 7 days (n=20)</td>
<td>14.3 ± 5.0</td>
<td>26.8 ± 11.6</td>
</tr>
<tr>
<td>No treatment (control) (n=46)</td>
<td>20.9 ± 9.9</td>
<td>16.4 ± 8.5</td>
</tr>
</tbody>
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Data are expressed as mean±SD. †P<0.05, ‡P<0.01, §P<0.0001 vs. before treatment.
the plasma and the remaining PAI-1 is stored in platelet α-granules, which is released by the activation of platelets (10, 11). However, only a small proportion of PAI-1 released from activated platelets is functionally active (12). Therefore, it is uncertain whether the increased PAI-1 levels are related to the resistance of thrombolysis.

In summary, our findings suggest that a daily 100 mg dose of aspirin for one week in patients not undergoing antiplatelet treatment effectively reduces plasma PAI-1 levels, but the addition of the same dose of aspirin for one week to the regimens of patients already undergoing antiplatelet treatment triggers the elevation of plasma PAI-1 levels.

References