Dual Antithrombotic Therapy Increases Severe Bleeding Events in Patients With Stroke and Cardiovascular Disease
A Prospective, Multicenter, Observational Study

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Background and Purpose—We sought to determine the incidence and severity of bleeding events in patients with stroke and cardiovascular diseases who were taking oral antithrombotic agents in Japan, where the incidence of hemorrhagic stroke is higher than in Western countries.

Methods—A prospective, multicenter, observational study was conducted; 4009 patients who were taking oral antithrombotic agents for stroke and cardiovascular diseases were enrolled. The patients were classified into 4 groups according to their antithrombotic treatment: the single antiplatelet agent group (47.2%); the dual antiplatelet agent group (8.7%); the warfarin group (32.4%); and the warfarin plus antiplatelet agent group (11.7%). The primary end point was life-threatening or major bleeding according to the MATCH trial definition.

Results—During a median follow-up of 19 months, there were 57 life-threatening and 51 major bleeding events, including 31 intracranial hemorrhages. The annual incidence of the primary end point was 1.21% in the single antiplatelet agent group, 2.00% in the dual antiplatelet agent group, 2.06% in the warfarin group, and 3.56% in the warfarin plus antiplatelet agent group (P<0.001). After adjustment for baseline characteristics, adding an antiplatelet agent to warfarin increased the risk of the primary end point (relative risk=1.76; 95% CI, 1.05 to 2.95), and adding another antiplatelet agent to single antiplatelet agent therapy increased the secondary end point of any bleeding, including minor events (relative risk=1.37; 95% CI, 1.07 to 1.76).

Conclusions—The incidence of bleeding events during antithrombotic therapy in Japan was similar to that reported for Western countries, although the trials used different study designs. Dual antithrombotic therapy was independently related to an increased risk of bleeding events. (Stroke. 2008;39:1740-1745.)

Key Words: antiplatelet therapy ■ aspirin ■ anticoagulation ■ warfarin ■ intracerebral hemorrhage

Owing to the increase in the number of patients with thrombotic diseases worldwide, antithrombotic therapy is often chosen to treat high vascular risk patients. The use of antithrombotic agents increased after several clinical trials demonstrated that antithrombotic therapy successfully prevented vascular disease.1 To more effectively prevent thrombotic events, a combination of dual antiplatelet agents that inhibit platelet aggregation through different modes of action or a combination of antiplatelet and anticoagulant agents is sometimes used. However, bleeding complications are common during antithrombotic therapy, especially when multiple antithrombotic agents are taken. The Management of ATherothrombosis with Clopidogrel in High-risk patients with recent transient ischemic attack or ischemic stroke study (MATCH)2 showed that dual antiplatelet agent therapy was not superior to single antiplatelet agent therapy in the prevention of thrombotic events for cerebrovascular patients, whereas the rate of bleeding events was higher with dual than with single antiplatelet therapy. The Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization Manage-
ment and Avoidance study (CHARISMA)\(^3\) showed that dual antiplatelet therapy was superior to single antiplatelet therapy in patients with vascular disease, but not asymptomatic patients, and raised questions about the efficacy of dual therapy for the primary prevention of atherothrombotic events. Dual antiplatelet therapy in CHARISMA did not result in an increase of severe bleeding, but moderate bleeding was higher. When aspirin is given in addition to warfarin, the risk of bleeding events also increases.\(^4,5\)

Asian ethnic origin is a possible risk factor for intracranial hemorrhage (ICH).\(^4\) The Japanese population is known to have a high incidence of ICH; the incidence in the Hisayama study\(^6\) (130/100 000 person-years in men and 70/100 000 person-years in women) and the Shibata study\(^7\) (61/100 000 person-years) was >5 times higher than the incidence in Western countries (7 to 12 per 100 000 person-years).\(^8\) The difference in the incidence between Japanese and Western populations is in part due to the high prevalences of small-artery cerebrovascular lesions and hypertension due to high salt intake, especially among the elderly Japanese population. It is likely that bleeding complications, including ICH, during antithrombotic therapy might also be more common in Japanese than in Western patients. Single-center studies done in our institutes support this concern; <5% of ICH patients were taking antiplatelet agents between 1985 and 1994,\(^9\) but 23% of ICH patients were taking antiplatelet agents between 1999 and 2005.\(^10\)

Therefore, to determine the incidence and severity of bleeding complications in patients with stroke and cardiovascular diseases treated with oral antithrombotic therapy in Japan, a prospective, multicenter, observational study was conducted.

Patients and Methods
The Bleeding with Antithrombotic Therapy (BAT) Study was conducted between October 2003 and March 2006 at 19 stroke and cardiovascular centers in Japan (supplemental Appendix, available online at http://stroke.ahajournals.org). The medical ethics review boards of the participating institutes approved the study protocol, and all patients provided written, informed consent.

Patients were eligible to enroll in the study if they were taking oral antiplatelet agents or warfarin as outpatients or if they began taking them as inpatients for cerebrovascular or cardiovascular diseases. Consecutive patients were primarily enrolled. On the basis of the antithrombotic regimen that they were taking at the time of enrollment, the patients were divided into 4 groups: a single antiplatelet agent (single AP) group; a dual antiplatelet agent (dual AP) group; a warfarin (W) group; and a warfarin plus an antiplatelet agent (W+AP) group. The patients’ comorbidities included ischemic and hemorrhagic stroke, heart disease (including atrial fibrillation), neoplasms, and liver cirrhosis. Cardiovascular risk factors included hypertension, diabetes mellitus, hypercholesterolemia, hypcholesterolemia (serum total cholesterol <130 mg/dL on enrollment), current or previous smoking habit, and alcohol consumption ≥2 drinks per day. Systolic and diastolic blood pressures on enrollment were also documented. Follow-up evaluations were normally performed every month. At each contact, the occurrence of possible outcome events was recorded according to the unified questionnaires.

The primary end point was the first occurrence of a life-threatening or major bleeding event. Secondary end points were any bleeding event, including minor bleeding events, vascular events, or death from any cause except fatal bleeding. Bleeding events were classified according to the MATCH trial definition.\(^2\) In brief, life-threatening bleeding was defined as any fatal bleeding event; a drop in hemoglobin of ≥50 g/L; hemorrhagic shock; symptomatic ICH; or transfusion of ≥4 U of red blood cells. Major bleeding was defined as significantly disabling, severe intracranial bleeding or transfusion of ≤3 U of red blood cells. Secondary hemorrhagic transformation of a symptomatic ischemic stroke was not regarded as a bleeding event. For each patient, the most severe bleeding event that occurred during the observation period was included in the analysis. Vascular events included symptomatic ischemic stroke, transient ischemic attack, myocardial infarction, hospitalization for unstable angina, aortic aneurysm rupture, symptomatic peripheral artery disease, and revascularization procedures (carotid, cerebral, coronary, or peripheral). Observation was discontinued when the patients died, developed a primary end point, ceased taking antithrombotic medication, or dropped from clinic follow-up or when their antithrombotic treatment was changed so that the patient was no longer eligible to remain in the initial group to which they had been assigned on enrollment.

The χ\(^2\) test or unpaired Student’s t test was used, as appropriate, to compare the baseline clinical characteristics between the single and dual AP groups, as well as between the W and W+AP groups. Annual incidences of end points (unadjusted) were calculated for each group, and the event-free curves of the groups were compared by the log-rank test. Relative risks of events were calculated according to a Cox proportional-hazards regression model after adjustment for age, sex, comorbidities, and risk factors for the dual AP group compared with the single AP group and for the W+AP group compared with the W group. The incidences of the primary end point and ICH were also assessed among the patients having symptomatic ischemic stroke and among the other patients. The change in the international normalized ratio (INR) of the prothrombin time in patients taking warfarin who developed the primary end point was evaluated by Wilcoxon’s matched-pair signed-rank test. A probability value <0.05 was considered statistically significant.

Results
A total of 4009 patients (2728 men; mean±SD age, 69±10 years) were enrolled. Of these patients, 1891 (47.2%) were in the single AP group, 349 (8.7%) were in the dual AP group, 1298 (32.4%) were in the W group, and 471 (11.7%) were in the W+AP group. The main antiplatelet agents used in the single AP group were aspirin (1340 patients; median dose, 100 mg/d), ticlopidine (394; median dose, 200 mg/d), and cilostazol (99; median dose, 200 mg/d); those used in the dual AP group were aspirin plus ticlopidine (220 patients) and aspirin plus cilostazol (49); those used in the W+AP group were aspirin (336 patients; median dose, 81 mg/d) and ticlopidine (69; median dose, 200 mg/d). On enrollment, the INR ranged from 0.98 to 4.93 (median, 1.99) in the W group and from 0.95 to 7.45 (median, 1.95) in the W+AP group. Overall, patients had received antithrombotic therapy for 5.0±4.7 years at the time of enrollment. Baseline clinical characteristics, including comorbidities and risk factors, differed among the 4 groups (Table 1). The comorbidities that precipitated the initiation of antithrombotic therapy included ischemic stroke in 2195 patients (54.8%) and heart disease in 2701 patients (67.3%), including 887 patients (22.1%) who had both.

Unless they developed life-threatening or major bleeding, the patients were seen every 28 days (median) for 2 to 30 months (median, 19 months); follow-up intervals were similar among the 4 groups. During this time period, 7 fatal, 50 nonfatal/life-threatening, and 51 major bleeding events, including 31 symptomatic ICHs, occurred. The annual incidence of life-threatening or major bleeding (the primary end point) was 1.21% in the single AP group, 2.00% in the dual
AP group, 2.06% in the W group, and 3.56% in the W+AP group (Table 2). The cumulative rate of the primary end point differed among the 4 groups (P < 0.001, the Figure). After adjustment for baseline characteristics, the incidence of the primary end point was 1.76-fold higher in the W+AP group than in the W group (95% CI, 1.05 to 2.95; P = 0.031). The annual incidence of symptomatic ICH was 0.34% in the single AP group, 0.60% in the dual AP group, 0.62% in the W group, and 0.96% in the W+AP group (P = 0.034). When the analysis was restricted to patients with a history of ischemic stroke, the incidences of ICH were relatively high compared with those of patients without ischemic stroke in every group. In the W group patients who developed the primary end point, the INR range shifted from 1.02 to 4.21 (median, 2.06) on enrollment to 0.93 to 8.91 (median, 2.20, P = 0.090) on the day of the event (19 patients) or at the time of the last visit before the event (21 patients; 1 to 43 days before the event; median, 16 days); in the W+AP group patients, it shifted from 1.40 to 4.40 (median, 2.07) on enrollment to 1.10 to 4.46 (median, 2.27; P = 0.372) on the day of the event (5 patients) or at the time of the last visit before the event (21 patients; 3 to 49 days; median, 15 days).

The secondary end point, the cumulative rate of any bleeding including minor events, differed among the 4 groups (P = 0.007); after adjustment for baseline characteristics, it was 1.37-fold higher in the dual AP group than in the single AP group (95% CI, 1.07 to 1.76; P = 0.014) and 1.30-fold higher in the W+AP group than in the W group (95% CI, 1.05 to 1.60; P = 0.015; Table 2). During follow-up, 88 patients developed nonfatal ischemic strokes, 34 developed nonfatal cardiovascular events, 31 had revascularization procedures, and 35 died (excluding fatal bleeding). The annual incidence of vascular events or death was 3.02% in the single AP group, 4.59% in the dual AP group, 2.78% in the W group, and 4.25% in the W+AP group (P = 0.031); after adjustment for baseline characteristics, it was 1.65-fold higher in the dual AP group than in the single AP group (95% CI, 1.02 to 2.66; P = 0.014) and tended to be higher in the W+AP group than in the W group (P = 0.085, Table 2).

Finally, to remove the confounding effects of different antiplatelet agents, the incidences of the events were compared between patients taking aspirin alone and those taking aspirin plus ticlopidine and between patients taking warfarin alone and those taking warfarin plus aspirin; these agents were the major choice in each group. The annual incidence of the primary end point (or ICH) was 1.13% (0.27%) in the patients taking aspirin, 2.48% (0.93%) in those taking aspirin plus ticlopidine, 2.06% (0.62%) in those taking warfarin, and 2.63% (0.94%) in those taking warfarin plus aspirin. After adjustment for baseline characteristics, the incidence of the primary end point was 2.60-fold higher in the patients taking aspirin plus ticlopidine than in those taking aspirin (95% CI, 1.07 to 6.36; P = 0.036), and the incidence was not significantly different between the patients taking warfarin and those taking warfarin plus aspirin (P = 0.336). The annual incidence of any bleeding was 11.6% in the patients taking aspirin compared with 17.1% in those taking aspirin plus ticlopidine (adjusted relative risk = 1.45; 95% CI, 1.07 to
1.98; \( P = 0.018 \)) and \( 16.4\% \) in the patients taking warfarin compared with \( 19.0\% \) in those taking warfarin plus aspirin (adjusted relative risk \( = 1.27; 95\% \text{ CI}, 1.00 \text{ to } 1.61; \ P = 0.048 \)).

**Discussion**

This is the first multicenter study involving a large number of patients to determine the incidence of bleeding events during antithrombotic therapy in Japan. The incidences of bleeding events have varied widely among studies, including a meta-analysis by van Walraven et al \(^{11}\) that was based on 6 randomized trials in the last decade,\(^{12-17}\) more recent trials in Western countries,\(^{2,3,18-24}\) and the present study. In patients treated with a single antiplatelet agent, the annual incidence of nonminor bleeding was reported to range between \( 0.2\% \) and \( 3.2\% \), and that of ICH ranged between \( 0.02\% \) and \( 0.47\% \),\(^{2,3,11,18-22}\) These variances often resulted from the differences among studies in the choices and doses of

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### Table 2. Bleeding and Vascular Events

<table>
<thead>
<tr>
<th></th>
<th>Single AP</th>
<th>Dual AP</th>
<th>W</th>
<th>W+AP</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Observation period, mo (median)</strong></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>1–28 (18)</td>
<td>0.2–27 (20)</td>
<td>1–30 (19)</td>
<td>0.5–28 (22)</td>
<td></td>
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<tr>
<td><strong>No. Incidence (%/y)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary end point</td>
<td>32 1.21</td>
<td>10 2.00</td>
<td>40 2.06</td>
<td>26 3.56</td>
</tr>
<tr>
<td>Patients with stroke</td>
<td>18 1.11</td>
<td>8 2.14</td>
<td>14 1.65</td>
<td>15 4.08</td>
</tr>
<tr>
<td>Patients without stroke</td>
<td>14 1.36</td>
<td>2 1.57</td>
<td>26 2.37</td>
<td>11 3.03</td>
</tr>
<tr>
<td>Life threatening bleeding</td>
<td>17 0.64</td>
<td>5 1.00</td>
<td>22 1.13</td>
<td>13 1.78</td>
</tr>
<tr>
<td>Fatal</td>
<td>3 0.11</td>
<td>0 0</td>
<td>2 0.10</td>
<td>2 0.27</td>
</tr>
<tr>
<td>Intracranial</td>
<td>9 0.34</td>
<td>3 0.60</td>
<td>12 0.62</td>
<td>7 0.96</td>
</tr>
<tr>
<td>Patients with stroke</td>
<td>6 0.37</td>
<td>3 0.80</td>
<td>7 0.83</td>
<td>5 1.36</td>
</tr>
<tr>
<td>Patients without stroke</td>
<td>3 0.29</td>
<td>0 0</td>
<td>5 0.46</td>
<td>2 0.55</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>15 0.57</td>
<td>5 1.00</td>
<td>18 0.93</td>
<td>13 1.78</td>
</tr>
<tr>
<td>Gastrointestinal (life-threatening and major)</td>
<td>15 0.57</td>
<td>5 1.00</td>
<td>15 0.77</td>
<td>12 1.64</td>
</tr>
<tr>
<td>Any bleeding</td>
<td>307 11.58</td>
<td>83 16.57</td>
<td>318 16.35</td>
<td>144 19.72</td>
</tr>
<tr>
<td>Vascular events or death*</td>
<td>80 3.02</td>
<td>23 4.59</td>
<td>54 2.78</td>
<td>31 4.25</td>
</tr>
<tr>
<td>Intracranial (nonfatal)</td>
<td>32 1.21</td>
<td>13 2.60</td>
<td>28 1.44</td>
<td>15 2.05</td>
</tr>
<tr>
<td>Cardiovascular (nonfatal)</td>
<td>23 0.87</td>
<td>3 0.60</td>
<td>3 0.15</td>
<td>5 0.69</td>
</tr>
<tr>
<td>Revascularization</td>
<td>16 0.60</td>
<td>4 0.80</td>
<td>6 0.31</td>
<td>5 0.69</td>
</tr>
<tr>
<td>Any death</td>
<td>9 0.34</td>
<td>3 0.60</td>
<td>17 0.87</td>
<td>6 0.82</td>
</tr>
</tbody>
</table>

**Dual AP vs Single AP**

<table>
<thead>
<tr>
<th></th>
<th>Unadjusted</th>
<th>Multivariate Adjusted†</th>
<th>Unadjusted</th>
<th>Multivariate Adjusted†</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>RR (95% CI)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary end point</td>
<td>1.67 (0.82–3.39)</td>
<td>0.159</td>
<td>1.76 (1.07–2.89)</td>
<td>0.026</td>
</tr>
<tr>
<td>Patients with stroke</td>
<td>1.93 (0.84–4.45)</td>
<td>0.121</td>
<td>2.27 (1.05–4.90)</td>
<td>0.037</td>
</tr>
<tr>
<td>Patients without stroke</td>
<td>1.13 (0.72–4.10)</td>
<td>0.873</td>
<td>1.49 (0.77–2.90)</td>
<td>0.240</td>
</tr>
<tr>
<td>Life threatening</td>
<td>1.58 (0.58–4.28)</td>
<td>0.371</td>
<td>1.62 (0.81–3.24)</td>
<td>0.170</td>
</tr>
<tr>
<td>Fatal</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intracranial</td>
<td>1.80 (0.48–6.63)</td>
<td>0.380</td>
<td>1.53 (0.60–3.61)</td>
<td>0.552</td>
</tr>
<tr>
<td>Patients with stroke</td>
<td>2.19 (0.55–8.75)</td>
<td>0.268</td>
<td>1.28 (0.43–4.82)</td>
<td>0.717</td>
</tr>
<tr>
<td>Patients without stroke</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major</td>
<td>1.77 (0.64–4.86)</td>
<td>0.271</td>
<td>1.92 (0.94–3.92)</td>
<td>0.074</td>
</tr>
<tr>
<td>Gastrointestinal (life threatening and major)</td>
<td>1.76 (0.64–4.86)</td>
<td>0.272</td>
<td>2.10 (0.98–4.49)</td>
<td>0.056</td>
</tr>
<tr>
<td>Any bleeding</td>
<td>1.30 (1.02–1.66)</td>
<td>0.034</td>
<td>1.30 (1.07–1.58)</td>
<td>0.010</td>
</tr>
<tr>
<td>Vascular events or death</td>
<td>1.47 (0.92–2.35)</td>
<td>0.104</td>
<td>1.63 (1.04–2.54)</td>
<td>0.032</td>
</tr>
<tr>
<td>Intracranial (nonfatal)</td>
<td>2.07 (1.08–3.97)</td>
<td>0.029</td>
<td>1.45 (0.77–2.73)</td>
<td>0.243</td>
</tr>
<tr>
<td>Cardiovascular (nonfatal)</td>
<td>0.67 (0.20–2.25)</td>
<td>0.519</td>
<td>7.55 (1.45–39.9)</td>
<td>0.016</td>
</tr>
<tr>
<td>Revascularization</td>
<td>1.05 (0.40–2.76)</td>
<td>0.917</td>
<td>4.00 (1.48–10.8)</td>
<td>0.006</td>
</tr>
<tr>
<td>Any death</td>
<td>1.79 (0.48–6.60)</td>
<td>0.385</td>
<td>0.95 (0.37–2.40)</td>
<td>0.099</td>
</tr>
</tbody>
</table>

* Bleeding events were excluded.
† Adjusted for age, sex, comorbidities (ischemic stroke, hemorrhagic stroke, heart disease, neoplasm, and liver cirrhosis), and risk factors (hypertension, diabetes mellitus, hypercholesterolemia, hypocholesterolemia, smoking habits, and alcohol consumption).
The present results do not appear to apply to all of the dual antiplatelet therapy. The combination of aspirin plus ticlopidine was also frequently chosen in the present study. The dose of ticlopidine (median, 200 mg/d) was less than the usual dose prescribed in Western countries (500 mg). In studies involving coronary patients, including CHAMP,19 WARIS-II,20 and the study by Buresly et al,21 ICH was less frequent than in the studies involving stroke patients, because a history of ischemic stroke is strongly predictive of ICH.4

In the present study, the incidence of any bleeding was higher in patients on dual ant platelet therapy than in those on single ant platelet therapy. To restrict the analysis to patients taking aspirin versus patients taking aspirin plus ticlopidine, the incidence of life-threatening or major bleeding was higher in patients on dual ant platelet therapy. The combination of aspirin plus ticlopidine was also frequently chosen in the study by Buresly et al,21 but this combination is rarely chosen in North America or Europe today. From the results of MATCH,2 CHARISMA,3 Buresly et al,21 and the present study, the combination of aspirin plus a thienopyridine derivative appears to cause an increased risk of hemorrhage. An interesting result of ESPRIT22 was that the incidence of bleeding events in patients taking aspirin and dipyridamole was lower than in patients taking aspirin alone. Thus, the present results do not appear to apply to all of the dual ant platelet therapy required to prevent thromboembolic events. Based on Japanese multicenter trials, low-intensity warfarin therapy (INR=1.5 to 2.6) is effective for preventing thromboembolism.28,29

The addition of ant platelet agents to warfarin is common in patients who have atrial fibrillation and a cardiovascular or a cerebrovascular stenotic lesion, although a recent review suggests that the benefits of dual therapy were limited to patients with a mechanical heart valve.7 A meta-analysis of 5 classic trials comparing warfarin plus aspirin with warfarin alone showed that the relative risk of ICH was 2.6; a post hoc analysis of SPORTIF III and V showed that the relative risk of major bleeding was 1.58.30

The limitations of the present study include that the choice of ant thrombotic therapy was not randomized and that the patients in the 4 groups differed significantly in many baseline characteristics that could have affected the occurrence of bleeding events, such as age and comorbidities. However, after adjustment for such factors, dual ant thrombotic therapy was still found to increase bleeding events. The second limitation of the present study was that our patients had been on antithrombotic therapy for an average of 5 years at the time of enrollment, which implies that they tolerated the therapy well. Thus, this might have biased the sample in that a certain amount of self-selection was taking place, whereby patients unable to tolerate some medications would have been eliminated. The incidence of bleeding events might have been higher had the study enrolled patients who had just begun taking antithrombotic therapy on enrollment. Third, the ant platelet medications in this study included primarily aspirin, ticlopidine, and cilostazol, and there was little or no information about clopidogrel or dipyridamole. Finally, because the number of patients taking dual antithrombotic agents was relatively small, there may be some statistical issues.

Based on the results of the present study, the incidence of bleeding events in Japanese patients on antithrombotic therapy seems similar to that reported in Western patients. The relatively low risk for bleeding may have been due to the use of lower doses of ant platelet agents and warfarin in Japanese patients. Second, as has been found in most previous studies, the risk of bleeding events was increased by the addition of an ant platelet agent to warfarin therapy or the addition of another ant platelet agent (at least a thienopyridine derivative) to single ant platelet therapy. In the present study, the patients on dual antithrombotic therapy generally had a high risk of ischemic vascular events. This suggests that dual antithrombotic therapy was often chosen for high vascular risk patients. Trials such as CURE,31 CREDO,32 COMMIT,33 CLARITY,34 and others have shown that dual ant platelet therapy is beneficial in atherosclerotic patients, although MATCH did not. The efficacy of ant platelet plus warfarin combination therapy should be evaluated by prospective, randomized trials. Caution needs to be used when prescribing either dual ant platelet therapy or adding an ant platelet agent to warfarin because such combinations of antithrombotic agents may subject patients to an increased risk of hemorrhage without necessarily reducing ischemic vascular events.
Sources of Funding
This study was partially supported by research grants for cardiovascular diseases (15C-1 and 18C-5) from the Japanese Ministry of Health, Labor and Welfare.

Disclosures
None.

References
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Stroke. 2008;39:1740-1745; originally published online April 3, 2008;
doi: 10.1161/STROKEAHA.107.504993

Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0039-2499. Online ISSN: 1524-4628

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