Ticlopidine Versus Aspirin for the Prevention of Recurrent Stroke

Analysis of Patients With Minor Stroke From the Ticlopidine Aspirin Stroke Study

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Background and Purpose: Ticlopidine has not been formally compared with aspirin in patients with a completed stroke. We therefore performed an analysis on a subgroup of patients from the Ticlopidine Aspirin Stroke Study (TASS) with a recent minor completed stroke as the qualifying ischemic event.

Methods: This was a multicenter, double-blind, randomized trial of patients with a recent history of cerebral ischemia. Eligible patients had a qualifying minor stroke within 3 months of study entry. All patients received either 650 mg aspirin twice daily or 250 mg ticlopidine twice daily for up to 5.8 years. The primary study end point was the first occurrence of nonfatal stroke or death from any cause. A secondary end point was the first occurrence of a fatal or nonfatal stroke.

Results: Minor stroke was the qualifying ischemic event in 927 patients (463 received ticlopidine and 464 received aspirin). The cumulative event rate at 1 year for nonfatal stroke or death was 63% for patients receiving ticlopidine and 10.8% for patients receiving aspirin, a 42% risk reduction in favor of ticlopidine. For fatal or nonfatal stroke, the cumulative event rate at 1 year was 4.8% for patients receiving ticlopidine and 7.5% for those receiving aspirin, a risk reduction of 36% for ticlopidine relative to aspirin. The overall risk reductions were 22.1% for nonfatal stroke or death and 19.9% for fatal or nonfatal stroke. Adverse reactions were reported in 58% of the ticlopidine patients and 51% of the aspirin patients.

Conclusions: The results in this subgroup are consistent with the overall TASS results and show that ticlopidine is somewhat more effective than aspirin for reducing the risk of stroke in patients with a completed minor stroke. (Stroke 1992;23:1723-1727)

Key Words • aspirin • cerebrovascular disorders • clinical trials • ticlopidine

Stroke is one of the leading causes of death and disability in the United States, and atherothrombotic stroke is by far the most common type. Although effective antihypertensive therapy may have reduced the incidence of stroke in the past decade, stroke morbidity and mortality are still considerable.1 Estimates suggest that on a yearly basis, 500,000 people suffer a stroke, and 30-40% of these individuals die as a result.2,3

In individuals who survive a stroke, the risk of recurrent stroke is high. Data from the Framingham Study4 show a cumulative stroke recurrence rate over 5 years of 42% for men and 24% for women, and 65% of these strokes are atherothrombotic in nature. Others have estimated that 25% of survivors can be expected to suffer an additional stroke or other vascular event (e.g., myocardial infarction, vascular death) within 2 years.5 Of further importance, the second stroke is likely to result in more severe disability. In a French study6 in which 84% of patients had a completed stroke as the qualifying event, 77% of the patients who suffered a second ischemic stroke during the trial experienced major sequelae, and only 10% had a complete recovery.

Aspirin has been the mainstay of stroke prevention therapy. Results from a meta-analysis of antiplatelet agents7 have shown aspirin to be effective for stroke prevention. However, questions have been raised about aspirin's efficacy in the prevention of recurrent stroke.6,8 Ticlopidine is a new antiplatelet agent that has been evaluated for the prevention of initial or recurrent stroke in patients at risk for a cerebrovascular event.9,10 Although its exact mechanism of action is not fully understood, it is thought that ticlopidine inhibits ADP-induced platelet aggregation by altering the platelet membrane response to fibrinogen-associated thrombogenic stimuli.11,12

In the Canadian American Ticlopidine Study (CATS),9 ticlopidine reduced the overall risk of vascular death, nonfatal stroke, or nonfatal myocardial infarction by 30% compared with placebo in patients with a recent completed stroke. However, the results from CATS provide no information on the relative efficacy of ticlopidine versus aspirin for prevention of recurrent stroke. In the Ticlopidine Aspirin Stroke Study (TASS),10 ticlopidine reduced the overall risk of nonfatal or fatal stroke by 21% compared with aspirin in patients with a recent reversible cerebrovascular ischemic event. Patients with a recent completed major or
moderate stroke were excluded from participation. However, a minor stroke was the qualifying event in approximately 30% of patients enrolled in TASS. A previous report described the outcome in subgroups of TASS, but the present study presents an opportunity to examine in depth the relative efficacy of ticlopidine and aspirin for prevention of recurrent stroke in patients with minor stroke.

**Subjects and Methods**

Detailed methods for TASS have been reported previously. Briefly, the study was a multicenter, double-blind, randomized trial comparing 650 mg aspirin twice daily with 250 mg ticlopidine twice daily for prevention of stroke in patients with a recent cerebral ischemic event.

To be eligible for randomization, patients must have had a qualifying cerebrovascular event (transient ischemic attack [TIA], amaurosis fugax, reversible ischemic neurological deficit, or minor stroke) within 3 months before study entry. Minor stroke, the focus of this analysis, was defined as a focal ischemic cerebrovascular event lasting more than 24 hours and resulting in minimal permanent neurological deficit, with at least 80% recovery of function within 3 weeks. Patients who had undergone carotid artery surgery or who had suffered a moderate or major stroke were eligible only if the surgery or the stroke had occurred more than 3 months before study entry and a qualifying event also had occurred within the 3 months before study entry.

Patients were at least 40 years of age, and women were not of child-bearing potential. Patients with a history of peptic ulcer disease or upper gastrointestinal bleeding and those with life-threatening diseases were excluded, as were those with aspirin hypersensitivity or a need for chronic aspirin or anticoagulant therapy.

Patients were followed for 2-6 years. Evaluations were conducted before study entry, at 1 month after randomization, and every 4 months thereafter. Evaluation included a physical examination and standard clinical laboratory tests. During the first 3 months of treatment, complete blood counts were obtained every 2 weeks to monitor for ticlopidine-related neutropenia.

The primary study end point was the composite of nonfatal stroke or death from any cause. A secondary end point was the composite of fatal or nonfatal stroke. Data for the subgroup of patients with a minor stroke as the qualifying event were analyzed by means of an intent-to-treat analysis. Only the first end point event for a given patient was counted. Results from a separate on-treatment analysis in which only end points that occurred during treatment or within 10 days of treatment discontinuation are also reported. Cumulative event rates were determined by the Kaplan-Meier method, and overall survival and percent risk reduction were estimated by means of the Cox model, with treatment as a covariate. Differences between treatment groups were compared by the Mantel-Haenszel log-rank test.

**Results**

A total of 3,069 patients were randomly assigned to therapy with aspirin or ticlopidine and were included in the intent-to-treat analysis; 3,034 were included in the on-treatment analysis. Of these, minor stroke was the qualifying event in 927 patients (463 receiving ticlopidine and 464 receiving aspirin); this number included 114 patients on ticlopidine and 112 on aspirin who experienced multiple ischemic events including minor stroke as the qualifying event. These patients are the focus of this report.

The baseline demographic and clinical and medical history of this minor stroke subset of patients are provided in Table 1. There were no significant differences between ticlopidine and aspirin groups with respect to any baseline characteristic. In addition, the minor stroke subgroup was comparable to patients without minor stroke with respect to baseline characteristics. There was a trend toward a higher proportion of black patients in the subgroup with minor stroke (19.8% versus 14.5%), but this was not significant. Aspirin was used within 6 months of study entry in 81% (374) of the patients randomized to ticlopidine and 78% (362) of those randomized to aspirin, although data on the dosage and duration of use was unavailable.

Baseline neurological and cerebrovascular findings are shown in Table 2. As expected, the proportion of patients with an abnormal neurological examination (95%) or abnormal computed tomographic (CT) scan (64%) was considerably higher in patients with minor stroke at baseline compared with the entire TASS population, in which an abnormal neurological examination was reported in 57% and an abnormal CT scan in 50%.

For the primary study end point, nonfatal stroke or death from any cause, the cumulative event rate at 1 year was 6.3% for patients given ticlopidine and 10.8% for those given aspirin. This represents a 42% risk reduction for ticlopidine versus aspirin (Table 3). A
TABLE 2. Baseline Neurological Examination and Cerebrovascular Findings From Patients in TASS With Minor Stroke Only

<table>
<thead>
<tr>
<th>Examination</th>
<th>Ticlopidine group</th>
<th>Aspirin group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Evaluated (n)</td>
<td>Abnormal (%)</td>
</tr>
<tr>
<td>Neurological examination</td>
<td>463</td>
<td>94</td>
</tr>
<tr>
<td>Carotid bruits</td>
<td>463</td>
<td>11</td>
</tr>
<tr>
<td>CT scan</td>
<td>398</td>
<td>66</td>
</tr>
<tr>
<td>Arteriography</td>
<td>221</td>
<td>68</td>
</tr>
<tr>
<td>Carotid</td>
<td>64</td>
<td></td>
</tr>
<tr>
<td>Vertebral</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>Basilar</td>
<td>3</td>
<td></td>
</tr>
</tbody>
</table>

n, Number of patients. TASS, Ticlopidine Aspirin Stroke Study; CT, computed tomographic.

difference in the cumulative event rate between the ticlopidine and aspirin groups was apparent early in the course of therapy and persisted for the duration of the trial. The overall risk reduction was 22.1% \((p=0.06)\) for ticlopidine relative to aspirin (Figure 1).

For the secondary end point, fatal or nonfatal stroke, the cumulative event rate at 1 year was 4.8% for patients given ticlopidine and 7.5% for those given aspirin. This was a 36% reduction in risk with ticlopidine compared with aspirin (Table 3). Again, a difference in the cumulative event rates between treatment groups was present throughout the study. The overall risk reduction for ticlopidine relative to aspirin was 19.9% \((p=0.187)\) (Figure 2).

In the on-treatment analysis, the 1-year risk reductions for ticlopidine relative to aspirin were 47% for nonfatal stroke or death and 46% for fatal or nonfatal stroke (Table 4). The overall risk reductions were 33.5% \((p=0.019)\) for nonfatal stroke or death and 29.8% \((p=0.077)\) for fatal or nonfatal stroke.

The safety of ticlopidine in the subgroup of patients with minor stroke was similar to that seen in the analyses of all TASS patients.10 The overall incidence of adverse experiences was higher in the minor stroke subgroup treated with ticlopidine (58%) than in patients treated with aspirin (51%). However, aspirin-intolerant patients were excluded from the trial. The most frequent adverse experiences were those relating to the digestive system. Diarrhea was reported in 18% of the ticlopidine-treated patients and 9% of the aspirin-treated patients. Diarrhea almost always occurred early in therapy and was usually resolved with temporary reduction in the ticlopidine dose; only 6% of the patients were permanently withdrawn for diarrhea. The second most common adverse experience was rash, which occurred in 11% of the patients receiving ticlopidine and 9% receiving aspirin. Therapy was discontinued for rash in only 3% of the patients receiving ticlopidine and 1% of those receiving aspirin. The majority of reports of rash occurred within the first 3 months of therapy.

Clinically, the most important adverse effect seen with ticlopidine was neutropenia (absolute neutrophil count [ANC] <1,200 cells/mm\(^3\)), which was reported in

TABLE 3. Cumulative Event Rates and Risk Reduction for Primary and Secondary End Points in Patients from TASS With Minor Stroke Only: Intent-to-Treat Analysis

<table>
<thead>
<tr>
<th>End point</th>
<th>Group</th>
<th>Risk reduction (%)</th>
<th>(p^*)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonfatal stroke or death</td>
<td>Ticlopidine</td>
<td>6.3</td>
<td>0.06</td>
</tr>
<tr>
<td></td>
<td>Aspirin</td>
<td>10.8</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(n=463)</td>
<td>14.8</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(n=464)</td>
<td>20.8</td>
<td></td>
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<td></td>
<td></td>
<td>24</td>
<td></td>
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<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>Fatal or nonfatal stroke</td>
<td>Ticlopidine</td>
<td>4.8</td>
<td>0.187</td>
</tr>
<tr>
<td></td>
<td>Aspirin</td>
<td>7.5</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(n=463)</td>
<td>10.8</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(n=464)</td>
<td>14.2</td>
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<td></td>
<td></td>
<td>13.8</td>
<td></td>
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<td></td>
<td></td>
<td>16.0</td>
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<td>11</td>
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</table>


FIGURE 1. Graph showing cumulative event rate per 100 patients for ticlopidine and aspirin for the primary end point of nonfatal stroke or death in patients with minor stroke as the qualifying event (intent-to-treat analysis).

FIGURE 2. Graph showing cumulative event rate per 100 patients for ticlopidine and aspirin for nonfatal or fatal stroke in patients with minor stroke as the qualifying event (intent-to-treat analysis).
12 ticlopidine-treated patients (2.6%) and three of aspirin-treated patients (0.7%) in the minor stroke subgroup. Two cases of severe ticlopidine-induced neutropenia (ANC <450 cells/mm³) occurred within the first 3 months of therapy and resolved rapidly with discontinuation of ticlopidine. The incidence of neutropenia in this subgroup with minor stroke was similar to that of the overall TASS population (2.4%).

Serious gastrointestinal disorders were more common in patients who received aspirin than in the ticlopidine group. For instance, gastrointestinal pain was reported in 9% of the aspirin patients and 4% of the ticlopidine patients. This is consistent with the entire TASS population, in which an increased incidence of serious gastrointestinal complaints including pain, gastritis, hemorrhage, and peptic ulcer was reported with aspirin.

**Discussion**

In the initial report from TASS, ticlopidine was shown to be significantly superior to aspirin for the prevention of atherothrombotic stroke in patients who had experienced a recent transient or mildly persistent episode of cerebral ischemia. In CATS, ticlopidine was also shown to be superior to placebo for prevention of recurrent stroke in patients with a recent completed stroke. However, there are no data comparing the effectiveness of ticlopidine and aspirin in patients with completed stroke. Thus, it is of interest to compare ticlopidine and aspirin for the prevention of recurrent stroke because questions remain about the efficacy of aspirin for this indication. For this reason, we analyzed the data from this minor stroke subgroup of patients from the original TASS population.

The interpretation of data from subgroup analysis is hazardous. Clearly, the number of patients available for comparison is likely to be insufficient to achieve statistical significance. However, in the present setting, the analysis seems justified based on two premises. First, it is desirable to compare ticlopidine and aspirin for secondary stroke prevention, and this analysis of the minor stroke subgroup from TASS does offer that opportunity despite the failure of the study group to publish that intent. The opportunity for a similar comparison may not be possible in the foreseeable future. Second, documentation of a statistically significant reduction of both primary and secondary stroke by ticlopidine in TASS and CATS seems to justify presentation of results that show similar trends despite a smaller sample size. In fact, some of the data do achieve statistical significance.

In this minor stroke subgroup, treatment with 250 mg ticlopidine twice daily significantly reduced the incidence of recurrent nonfatal stroke or death when compared with aspirin. Perhaps because the risk of stroke is highest during the first year after the disease is manifest, the risk reduction also was greatest in the first year of therapy, but the benefits of ticlopidine were maintained throughout the study. In these same patients, the cumulative event rate for fatal or nonfatal stroke also was reduced with ticlopidine compared with aspirin. Although the reduction did not reach statistical significance, the 1-year risk reduction was 36%, comparable to the 42% risk reduction for the primary end point of stroke or death at 1 year. It is not unexpected that ticlopidine was not significantly better than aspirin; a larger number of patients are needed to demonstrate the efficacy of a treatment versus an active therapy than versus placebo.

An interesting finding was the large proportion of patients in both groups who were taking aspirin within 6 months of randomization. Aspirin use, whether for primary or secondary prevention of vascular disease, acute pain, or chronic arthritides, is very common in the United States. While it would be interesting to determine the stroke event rate in the minor stroke subgroup according to prior aspirin use, this analysis would be subject to the limitations previously discussed. Additionally, the number of events would be of a magnitude that is unlikely to be meaningful.

The results from this TASS subgroup of patients with minor stroke allow a comparison with the results reported in CATS. Patients from this TASS subgroup and from CATS were comparable at baseline with respect to age, sex, race, and baseline medical history. In CATS, the risk of fatal or nonfatal stroke in these patients was reduced by 33.5% with ticlopidine compared with placebo ($p=0.008$, one-sided). This result is comparable to the 36% reduction in risk with ticlopidine relative to aspirin in the minor stroke subgroup.

In two previous studies, aspirin was shown to reduce the risk of stroke in patients with a recent completed stroke. In the French study, patients with TIA (16%) or completed minor stroke (64%) were treated with 1,000 mg/day aspirin with or without 225 mg/day dipyridamole, and the rate of stroke occurrence was significantly ($p<0.05$) reduced in both aspirin groups compared with placebo. In the European Stroke Prevention Study, which included patients with TIA (34%), reversible ischemic neurological deficits (6%), or completed strokes (60%), treatment with 990 mg/day aspirin plus 225 mg/day dipyridamole was associated with a 38.1% reduction in fatal and nonfatal stroke ($p<0.001$) over a 2-year period. In contrast, in the Swedish Cooperative Stroke Study, all patients had previously experienced a completed major stroke, and 1.5 g/day aspirin was associated with a stroke rate similar to that seen with placebo. Two recent studies demonstrated the efficacy of low-dose aspirin for stroke prevention. About two-thirds of the patients enrolled in both of these studies...
had a minor stroke as the qualifying cerebral ischemic event.

These studies are difficult to compare directly because of several factors. Results from the French and European trials were confounded by the use of dipyrindamide with aspirin. In addition, the Swedish trial is subject to type II error based on the small numbers of patients in each treatment group. Lastly, each of these three studies enrolled different groups of patients. Females represented 41% of enrolled patients in the European trial, which is about 15% higher than other studies. In contrast, the Swedish study enrolled patients with predominantly (90%) carotid disease. Thus, it is difficult to conclusively state, based on these studies, whether aspirin is effective for prevention of recurrent stroke. We must, in fact, turn to the meta-analysis of the Antiplatelet Trialists' Collaboration to best support this contention.

This subgroup analysis of TASS patients with minor stroke reveals no additional information about the safety of ticlopidine. The lower incidence of adverse events with aspirin may reflect the exclusion of approximately 9% of eligible patients for aspirin intolerance or hypersensitivity. There was a trend for a slightly lower incidence of adverse events in this subgroup of patients with a recent minor stroke compared with patients without minor stroke and with the entire TASS population, but these differences were not statistically significant. The safety experience in this TASS subgroup was similar to that in CATS.

In summary, 250 mg ticlopidine twice daily is a safe and effective pharmacological agent for reducing the risk of recurrent stroke in patients who recently have suffered a minor stroke as well as in patients with previous TIA or completed major stroke. The results from this subgroup analysis indicate that ticlopidine is somewhat more effective than aspirin for preventing recurrent stroke in patients who have experienced a completed stroke.

Appendix

Collaborating Clinical Centers

Centers are listed by location; each entry includes name of investigator and number of patients.:


References

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