Efficacy of ticlopidine and aspirin for prevention of reversible cerebrovascular ischemic events. The Ticlopidine Aspirin Stroke Study

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Stroke 1993;24;1452-1457
Stroke is published by the American Heart Association. 7272 Greenville Avenue, Dallas, TX 72514
 Print ISSN: 0039-2499. Online ISSN: 1524-4628

Efficacy of Ticlopidine and Aspirin for Prevention of Reversible Cerebrovascular Ischemic Events

The Ticlopidine Aspirin Stroke Study

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Background and Purpose: **This subgroup analysis from the Ticlopidine Aspirin Stroke Study (TASS) compared ticlopidine, a new antiplatelet agent, with aspirin for the prevention of recurrent transient ischemic attacks in patients who had a recent reversible cerebrovascular event.**

Methods: **This was a multicenter, double-blind, randomized trial in patients with a recent cerebral ischemic history. Patients with a reversible cerebral ischemic event within 3 months of enrollment were eligible for the study. All patients received either aspirin 650 mg twice daily or ticlopidine 250 mg twice daily for up to 5.8 years. The primary end point in this analysis was the first occurrence of a reversible ischemic event either alone or combined with nonfatal stroke or death and fatal or nonfatal stroke.**

Results: **Overall, ticlopidine was better than aspirin for reducing the risk of reversible ischemic events either alone or as a composite with death and/or stroke or with fatal and/or nonfatal stroke ($P=.007$ to $P<.001$). The risk reductions with ticlopidine were maintained for the duration of the 5-year follow-up. The most frequent or clinically important adverse effects associated with ticlopidine were diarrhea, rash, and neutropenia. Neutropenia was severe in 13 patients but resolved promptly with discontinuation of therapy.**

Conclusions: **The results in this subgroup of patients with reversible ischemic disease, as well as the overall analysis of TASS, suggest that ticlopidine is a more effective agent than aspirin for the prevention of recurrent transient ischemic attacks. (*Stroke*. 1993;24:1452-1457.)**

KEY WORDS • **aspirin** • **cerebral ischemia, transient** • **clinical trials** • **ticlopidine**

Antiplatelet drugs have been investigated for the prevention of cerebrovascular ischemic events including transient ischemic attacks (TIAs) and stroke for more than 20 years. Results from a meta-analysis of antiplatelet agents have shown that aspirin is effective for stroke prevention in patients with cerebral ischemia.[1] In the Canadian Cooperative Study Group, aspirin was superior to placebo for reducing the incidence of stroke in high-risk patients.[2] Although the primary end point was stroke or death, a secondary end point analyzed and reported was TIA or other reversible ischemic events plus stroke or death. On the basis of the findings from this trial, aspirin was approved at a dose of 1300 mg/d for stroke prevention and the reduction of TIAs in men at risk for stroke. The benefits of aspirin for stroke prevention in women are still controversial.

Ticlopidine is a new antiplatelet agent that has been evaluated for the prevention of initial or recurrent stroke in patients at high risk for a cerebrovascular event.[3,4] Although its exact mechanism of action is not fully elucidated, it is thought that ticlopidine inhibits adenosine diphosphate–induced platelet aggregation by altering the platelet membrane response to fibrinogen-associated thrombogenic stimuli.[5,6] The Ticlopidine Aspirin Stroke Study (TASS) was a multicenter, randomized trial comparing ticlopidine and aspirin for the prevention of stroke in patients with a recent reversible cerebrovascular ischemic event on entry.[3] Ticlopidine reduced the overall risk of nonfatal or fatal stroke by 21% and death or stroke by 12% compared with aspirin using an intent-to-treat analysis.

Before the initiation of TASS, tertiary end points were preselected for data collection and analysis in addition to the principal end points of death or stroke and fatal or nonfatal stroke and the secondary end points of nonfatal myocardial infarction and peripheral vascular disease. These "soft" end points included all reversible cerebrovascular ischemic events that occurred after randomization. Thus, both the eligibility criteria—reversible cerebral ischemic events—and the study end points in TASS and the Canadian aspirin trial were similar.

Examination of the effects of antiplatelet therapy on these reversible or soft end points is important because patients with reversible events are at high risk for stroke; the presence of these reversible events indicates the activity of an underlying disease process; and the occurrence of these events during daily life could, on

Received April 14, 1993; final revision received May 19, 1993; accepted May 20, 1993.

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their own, have adverse consequences. This article reports on the efficacy of ticlopidine and aspirin in reducing reversible ischemic events defined as TIA, amaurosis fugax (AF), and reversible ischemic neurological deficit (RIND) in patients enrolled in TASS.

Subjects and Methods

A detailed description of the methods for TASS has been reported previously.[3] Briefly, the study was a multicenter, double-blind, randomized trial comparing aspirin 650 mg twice daily with ticlopidine 250 mg twice daily for the prevention of stroke in patients with a recent cerebral ischemic event. To be eligible for randomization, patients must have had a qualifying cerebrovascular event (TIA, AF, RIND, or minor stroke) within 3 months before study entry. Patients who had undergone carotid artery surgery or who had suffered a moderate or major stroke were eligible only if they had experienced a qualifying ischemic event within the previous 3 months and the surgery or the stroke had occurred more than 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, upper gastrointestinal bleeding, or life-threatening diseases were excluded, as were those with aspirin intolerance or hypersensitivity or patients who had a need for chronic aspirin or anticoagulant therapy.

Evaluations were conducted before study entry, at 1 month after randomization, and every 4 months thereafter. Follow-up evaluations included 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. Follow-up ranged from 2 to 6 years.

For this analysis, the primary end point was the first occurrence of a reversible cerebrovascular ischemic event, either TIA, AF, or RIND. In a post hoc analysis, TIA, when it occurred alone, was established as a secondary end point. These end points were evaluated independently and when they occurred as a composite with the primary end point from TASS (nonfatal stroke or death from any cause) and with the secondary end point from TASS (fatal or nonfatal stroke). Data were interpreted using an intent-to-treat analysis. Only the first end point event for a given patient was counted in an end point composite. Cumulative event rates were determined by the Kaplan-Meier method, and overall survival and percent risk reduction were estimated using the Cox model with treatment as a covariate. Differences between treatment groups were compared by means of the Mantel-Haenszel log-rank test.

Results

During enrollment, 3069 patients were randomly assigned to therapy with aspirin or ticlopidine and were included in the intent-to-treat analysis. The baseline demographics and clinical and medical history have been previously reported and are summarized in Table 1.[3] There were no significant differences between ticlopidine and aspirin groups with respect to any baseline characteristic.

The number of first clinical events for the end point of reversible ischemic events occurring alone and in combination with stroke or death or stroke is shown in Table 2. For the majority of patients, a reversible ischemic event was the first clinical event occurring on therapy. For example, a reversible ischemic event was the first clinical event in 1092 (72%) of 1519 patients who had the composite end point of a reversible ischemic event plus death or nonfatal stroke. Similarly, a reversible ischemic event was the first clinical event in 1092 (82%) of 1332 patients with the composite of a reversible ischemic event plus fatal or nonfatal stroke.

TABLE 1. Baseline Demographics and Clinical Characteristics of Patients in the Ticlopidine Aspirin Stroke Study

	Ticlopidine (n=1529)	Aspirin (n=1540)
Age, y		
Mean±SD	62.7±9.4	63.2±9.3
Range	40–92	39–94
Male	64.4	65.1
Race		
White	80	81
Nonwhite	20	19
Current smoker	41	42
Past or current heart disease	23	25
Moderate or major stroke >3 mo before entry	7	10
Hypertension	59	57
Diabetes	19	20
Myocardial infarction	16	17
CHF/cardiomegaly	12	13
Angina	19	19
Peripheral vascular disease	14	15
Arrhythmia	9	11

Numbers represent percentage of patients except where indicated. CHF indicates congestive heart failure.

The cumulative event rates and risk reductions for the primary end point of reversible ischemic event and the composite end points are shown in Table 3. At 1 year, the risk reduction for ticlopidine versus aspirin for reversible ischemic events was 19.8%, for reversible ischemic events plus nonfatal stroke or death was 23.3%, and for reversible ischemic events plus stroke 22.3%. Overall, ticlopidine was superior to aspirin for reducing the risk of reversible ischemic events alone ($P=.001$) and when combined with death or nonfatal stroke ($P<.001$) and fatal or nonfatal stroke ($P<.001$). For each year of the 5-year follow-up, risk reductions were greater with ticlopidine relative to aspirin.

However, based on data from studies of the natural history of stroke and results from this trial, the risk reduction was greatest during the first year of therapy, when patients are at greatest risk for recurrent cerebral ischemic events. Post hoc analysis revealed that TIA was the most frequent recurrent event of ischemic events reported. Therefore, TIA was considered both when it occurred alone and when it occurred as a composite with death or stroke and with fatal or nonfatal stroke.

TABLE 2. Number of First Clinical Events for Reversible Ischemic Events (Transient Ischemic Attack, Amaurosis Fugax, Reversible Ischemic Neurological Deficit) Alone or With Death or Stroke or With Fatal or Nonfatal Stroke

End Point Event	First Clinical Event	Ticlopidine (n=1529)	Aspirin (n=1540)	Total (n=3069)
TIA, AF, or RIND	TIA, AF, or RIND	530	620	1150
TIA, AF, RIND, stroke, or death				
	TIA, AF, or RIND	503	589	1092
	Nonfatal stroke	106	116	222
	Fatal stroke	5	13	18
	MI death	15	8	23
	Cardiovascular death	37	39	76
	Other death	36	52	88
TIA, AF, RIND, or stroke				
	TIA, AF, or RIND	503	589	1092
	Nonfatal stroke	106	116	222
	Fatal stroke	5	13	18

Data were interpreted using an intent-to-treat analysis. TIA indicates transient ischemic attack; AF, amaurosis fugax; RIND, reversible ischemic neurological deficit; and MI, myocardial infarction.

TABLE 3. Cumulative Event Rates and Risk Reduction for Reversible Ischemic Events Alone and With Death or Stroke or With Fatal or Nonfatal Stroke

	Ticlopidine		Aspirin		
	No. at Risk	Event Rate	No. at Risk	Event Rate	RR, % (95% CI)
Reversible ischemic event (TIA, AF, RIND)					
1 y	1135	23.87	1035	29.76	19.8 (9.7, 28.7)
2 y	846	30.39	775	36.59	16.9 (8.0, 25.0)
3 y	566	34.04	503	40.44	15.8 (7.2, 23.6)
4 y	298	37.38	242	43.96	15.0 (6.3, 22.8)
5 y	76	42.26	65	46.43	9.0 (−2.3, 19.0)
P=.001, Mantel-Haenszel test					
Reversible ischemic event plus nonfatal stroke or death					
1 y	1107	27.25	989	35.51	23.3 (14.7, 31.0)
2 y	801	37.65	723	45.10	16.5 (9.1, 23.4)
3 y	530	44.21	461	50.54	12.5 (5.4, 19.1)
4 y	276	49.87	217	56.96	12.4 (5.5, 18.9)
5 y	71	55.28	62	62.59	11.7 (3.4, 19.2)
P<.001, Mantel-Haenszel test					
Reversible ischemic event plus fatal or nonfatal stroke					
1 y	1107	25.95	989	33.40	22.3 (13.2, 30.4)
2 y	801	34.58	723	41.85	17.4 (9.4, 24.7)
3 y	530	39.41	461	46.13	14.6 (6.8, 21.7)
4 y	276	44.16	217	50.82	13.1 (5.2, 20.3)
5 y	71	48.44	62	54.43	11.0 (1.5, 19.6)
P<.001, Mantel-Haenszel test					

Data were interpreted using an intent-to-treat analysis. RR indicates risk reduction; CI, confidence interval; TIA, transient ischemic attack; AF, amaurosis fugax; and RIND, reversible ischemic neurological deficit.

TABLE 4. Number of First Clinical Events for Transient Ischemic Attack Alone or With Death or Stroke or With Fatal or Nonfatal Stroke

End Point Event	First Clinical Event	Ticlopidine (n=1529)	Aspirin (n=1540)	Total (n=3069)
TIA	TIA	454	521	975
TIA, stroke, or death				
	TIA	430	497	927
	Nonfatal stroke	108	127	235
	Fatal stroke	8	14	22
	MI death	16	8	24
	Cardiovascular death	41	40	81
	Other death	39	55	94
TIA, fatal or nonfatal stroke				
	TIA	430	497	927
	Nonfatal stroke	108	127	235
	Fatal stroke	8	14	22

Data were interpreted using an intent-to-treat analysis. TIA indicates transient ischemic attack; MI, myocardial infarction.

The number of first clinical events for TIA alone and as a composite end point is shown in Table 4. Again, for the majority of patients, the first clinical event was TIA when the composite end points were considered. For the composite of TIA plus death or stroke, 927 (67%) of 1383 patients experienced a TIA as their first clinical event.

The cumulative event rates and risk reductions for TIA occurring alone and occurring as a composite with death or stroke and with stroke events are shown in Table 5. The 1-year risk reductions were 20.4% for TIA alone, 25.2% for TIA plus nonfatal stroke or death, and 24.3% for TIA plus stroke. Overall, ticlopidine was superior to aspirin for reducing the risk of TIA alone ($P=.007$) or the risk of TIA plus death or stroke ($P<.001$). Each year, the risk reductions with ticlopidine were greater than those associated with aspirin, and the greatest reductions occurred during the first year of therapy.

The most frequent adverse experiences were those relating to the digestive system. Diarrhea was reported in 20.4% of ticlopidine-treated patients and in 9.8% of aspirin-treated patients. Diarrhea almost always occurred early in therapy and usually resolved with a temporary reduction in the ticlopidine dose. Only 6% of patients were permanently withdrawn for diarrhea. The second most common adverse experience was rash, which occurred in 11.9% of patients on ticlopidine and in 5.2% of patients on aspirin. The majority of reports of rash occurred within the first 3 months of therapy. Serious gastrointestinal disorders were more common in patients receiving aspirin than in patients receiving ticlopidine. An increased incidence of serious gastrointestinal complaints including pain, gastritis, hemorrhage, and peptic ulcer was reported by the aspirin group.

Clinically, the most important adverse effect reported with ticlopidine was neutropenia. Neutropenia (absolute neutrophil count, <1200 cells per cubic millimeter) was reported in 35 ticlopidine-treated patients and in 12 aspirin-treated patients. Thirteen cases of severe ticlopidine-induced neutropenia (absolute neutrophil count, <450 cells per cubic millimeter) occurred within the first 3 months of therapy but resolved rapidly with discontinuation of ticlopidine.

All serious cases occurred within 90 days of beginning therapy with ticlopidine. Neutropenia from ticlopidine is easily detected and readily managed by monitoring the complete blood cell count every 2 weeks during the first 3 months of therapy. If ticlopidine-induced neutropenia occurs, the neutrophil count recovers rapidly with discontinuation of ticlopidine. Early detection with routine complete blood cell count monitoring during the first 3 months of therapy should prevent any adverse outcomes.

Discussion

In the initial report from TASS, ticlopidine was shown to be superior to aspirin for the prevention of atherothrombotic stroke in patients who had recently experienced a transient or mildly persistent episode of cerebral ischemia.[3] In this analysis of tertiary end points, namely TIA, AF, or RIND, the overall risk reduction with ticlopidine was also greater than the risk reduction with aspirin. In fact, the risk reductions with ticlopidine relative to aspirin were greater at each year of the 5-year follow-up. The risk reductions with ticlopidine were maintained even when reversible ischemic events were combined with the "hard" end points of death or stroke, and fatal or nonfatal stroke.

Transient ischemic attacks are a well-recognized risk factor for cerebral infarction; the risk of stroke after a TIA ranges from 4% to 8% per year.[7] The incidence of TIA in the United States ranges from 116 to 244 per 100 000 population, and much of the variation is due to the dramatic increase in incidence with age.[8] Recurrent TIAs were reported in 30% or more of patients followed in the Hospital Frequency Study.[9] Conneally et al[9] identified multiple TIAs before entry as the greatest risk factor for recurrent TIAs. Fields et al[10] also reported an increased risk of subsequent cerebral ischemic events in the presence of multiple TIAs.

TABLE 5. Cumulative Event Rates and Risk Reduction for Transient Ischemic Attack Alone and With Death or Stroke or With Fatal or Nonfatal Stroke

	Ticlopidine		Aspirin		
	No. at Risk	Event Rate	No. at Risk	Event Rate	RR, % (95% CI)
TIA					
1 y	1192	19.93	1106	25.03	20.4 (9.1, 30.3)
2 y	911	25.59	842	31.08	17.7 (7.6, 26.6)
3 y	611	29.01	557	34.24	15.3 (5.4, 24.1)
4 y	326	31.96	276	36.67	12.8 (2.7, 21.9)
5 y	85	37.01	75	38.76	4.5 (−9.0, 16.3)
P=.007, Mantel-Haenszel test					
TIA plus nonfatal stroke or death					
1 y	1162	23.59	1050	31.55	25.2 (16.0, 33.5)
2 y	862	33.41	780	40.78	18.1 (10.0, 25.4)
3 y	574	40.08	506	45.66	12.2 (4.3, 19.4)
4 y	302	45.87	246	51.51	10.9 (3.2, 18.1)
5 y	79	51.47	69	57.40	10.3 (11, 18.7)
P<.001, Mantel-Haenszel test					
TIA plus fatal or nonfatal stroke					
1 y	1162	22.21	1050	29.34	24.3 (14.4, 33.0)
2 y	862	30.11	780	37.3	19.3 (10.6, 27.1)
3 y	574	34.82	506	40.96	15.0 (6.4, 22.8)
4 y	302	39.62	246	44.87	11.7 (2.8, 19.8)
5 y	79	43.84	69	48.74	10.1 (−0.6, 19.6)
P<.001, Mantel-Haenszel test					

Data were interpreted using an intent-to-treat analysis. RR indicates risk reduction; CI, confidence interval; and TIA, transient ischemic attack.

Most recent clinical trials of antiplatelet therapy for prevention of stroke have used death and stroke or stroke occurring alone as the hard end points. Thus, little clinical data are available regarding the effects of antiplatelet therapy on TIA or reversible cerebral ischemic events, ie, soft end points. Two earlier trials, the Canadian Cooperative Study Group trial[2] and the US trial,[10] observed a greater risk reduction with aspirin versus placebo for the same end points evaluated in this analysis from TASS: TIA or reversible ischemic events plus death from all causes or nonfatal stroke. In the US study, a significant effect of aspirin was observed only when the composite end point of TIA and death or stroke was considered.[10] The greatest reduction was found in patients with multiple TIAs at entry. Similarly, in the Canadian trial a 19% reduction in the risk of reversible ischemic events plus stroke or death was recorded with aspirin versus placebo.[2] More recently, the SALT (Swedish Aspirin Low-dose Trial) Collaborative Group study found a significant (P=.03) reduction in the secondary end point of stroke or two or more TIAs within a week with low-dose aspirin versus placebo.[11] However, no difference was found in the number of TIAs between low-dose aspirin and placebo in the Danish Low-Dose Aspirin trial.[12]

The results in this subgroup of patients with reversible ischemic disease, as well as the overall analysis of TASS, suggest that ticlopidine is more effective than aspirin for prevention of recurrent TIAs. Based on the superiority of ticlopidine for reducing the occurrence of reversible ischemic events, ticlopidine would appear to be an effective option for this indication.

Appendix

Collaborating Clinical Centers: Location, Investigator, and Number of Patients

Richmond, Va, J.W. Harbison, 177; Iowa City, Iowa, H.P. Adams, 138; Houston, Tex, J.C. Grotta, 124; Houston, Tex, J.S. Meyer, 199; Columbus, Mo, J.D. Easton and J.A. Byer, 91; Memphis, Tenn, J.T. Robinson, 91; Cleveland, Ohio, L.A. Hershey, J.W. Schmidley, and G.C. McIntosh, 90; Buffalo, NY, D.L. Ehrenreich, 87; Winnipeg, Manitoba, Canada, B.A. Anderson, 86; Toronto, Ontario, Canada, J.W. Norris, 83; New Orleans, La, L.A. Weisberg, 80; London, Ontario, Canada, H.J.M. Barnett, 79; San Antonio, Tex, J.D. Easton and D.G. Sherman, 75; Cincinnati, Ohio, C.P. Olinger, 70; Boise, Idaho, B.T. Adornato and S.W. Asher, 68; New York, NY, W.K. Hass, 64; Montreal, Quebec, Canada, J.P. Meloche, 64; San Diego, Calif, J.F. Rothrock, 63; St Lambert, Quebec, Canada, A. Bellavance, 62; St Johns, Newfoundland, Canada, W. Pryse-Phillips, 62; Palos Heights, Ill, M.D. Wichter, 62; Minneapolis, Minn, A.C. Klassen, 60; Kansas City, Kan, D.K.

Ziegler, 60; Seattle, Wash, P.D. Swanson, 59; Philadelphia, Pa, R.A. Burns, 58; Charlottesville, Va, G.R. Hanna, 58; Chicago, Ill, M.M. Cohen, 57; Albuquerque, NM, F. Miranda and E.R. Nelson, 53; Springfield, Ill, J.R. Couch, 51; Quebec City, Quebec, Canada, D. Simard, 49; Minneapolis, Minn, M.G. Ettinger, 48; West Haven, Ct, J.D. Wallace and L.L. Levy, 47; Boston, Mass, R.G. Feldman and C.S. Kase, 46; Detroit, Mich, J. Gilroy, 46; Boston, Mass, P.A. Wolf, 44; Hackensack, NJ, H.H. Goldberg, 41; Tucson, Ariz, W.A. Sibley, 41; Los Angeles, Calif, B.H. Dobkin, 38; West Palm Beach, Fla, C.H. Sadowsky, 36; Winston-Salem, NC, L.A. Pearse, 35; Los Angeles, Calif, M.J. Fisher, 34; Palo Alto, Calif, B.T. Adornato and J.R. Lacy, 33; Omaha, Neb, A.H. Greenhouse and K.E. Wilken, 32; Baltimore, Md, T.R. Price, 32; Pittsburgh, Pa, O.M. Reinmuth, 29; Cleveland, Ohio, J.P. Conomy and A.J. Furlan, 27; Jackson, Miss, L.W. Mahalak, 21; Hershey, Pa, R.A. Brennan, 19; Montreal, Quebec, Canada, R. Cote, 16; Chicago, Ill, L.R. Caplan and D.B. Hier, 14; Boston, Mass, C. Mayman, 12; Los Angeles, Calif, W.R. Moore, 11; San Francisco, Calif, A.G. Waltz, 11; Reno, Nev, K. Bigley and J.H. Peacock, 8; North Miami Beach, Fla, M.I. Able, 6; and Vero Beach, Fla, F. Miranda, 2.

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