ORIGINAL ARTICLE

Ticagrelor versus Aspirin in Acute Stroke or Transient Ischemic Attack

S. Claiborne Johnston, M.D., Ph.D., Pierre Amarenco, M.D., Gregory W. Albers, M.D., Hans Denison, M.D., Ph.D., J. Donald Easton, M.D., Scott R. Evans, Ph.D., Peter Held, M.D., Ph.D., Jenny Jonasson, Ph.D., Kazuo Minematsu, M.D., Ph.D., Carlos A. Molina, M.D., Yongjun Wang, M.D., and K.S. Lawrence Wong, M.D., for the SOCRATES Steering Committee and Investigators*

ABSTRACT

BACKGROUND

Ticagrelor may be a more effective antiplatelet therapy than aspirin for the prevention of recurrent stroke and cardiovascular events in patients with acute cerebral ischemia.

METHODS

We conducted an international double-blind, controlled trial in 674 centers in 33 countries, in which 13,199 patients with a nonsevere ischemic stroke or high-risk transient ischemic attack who had not received intravenous or intraarterial thrombolysis and were not considered to have had a cardioembolic stroke were randomly assigned within 24 hours after symptom onset, in a 1:1 ratio, to receive either ticagrelor (180 mg loading dose on day 1 followed by 90 mg twice daily for days 2 through 90) or aspirin (300 mg on day 1 followed by 100 mg daily for days 2 through 90). The primary end point was the time to the occurrence of stroke, myocardial infarction, or death within 90 days.

RESULTS

During the 90 days of treatment, a primary end-point event occurred in 442 of the 6589 patients (6.7%) treated with ticagrelor, versus 497 of the 6610 patients (7.5%) treated with aspirin (hazard ratio, 0.89; 95% confidence interval [CI], 0.78 to 1.01; P=0.07). Ischemic stroke occurred in 385 patients (5.8%) treated with ticagrelor and in 441 patients (6.7%) treated with aspirin (hazard ratio, 0.87; 95% CI, 0.76 to 1.00). Major bleeding occurred in 0.5% of patients treated with ticagrelor and in 0.6% of patients treated with aspirin, intracranial hemorrhage in 0.2% and 0.3%, respectively, and fatal bleeding in 0.1% and 0.1%.

CONCLUSIONS

In our trial involving patients with acute ischemic stroke or transient ischemic attack, ticagrelor was not found to be superior to aspirin in reducing the rate of stroke, myocardial infarction, or death at 90 days. (Funded by AstraZeneca; ClinicalTrials.gov number, NCT01994720.)

From the Dean's Office, Dell Medical School, University of Texas, Austin (S.C.J.); the Department of Neurology and Stroke Center, Bichat University Hospital and Medical School, Paris (P.A.); Stanford University Medical Center, Stanford Stroke Center, Palo Alto (G.W.A.), and the Department of Neurology, University of California, San Francisco, San Francisco (J.D.E.) — both in California; AstraZeneca, Gothenburg, Sweden (H.D., P.H., J.J.); the Department of Biostatistics, Harvard T.H. Chan School of Public Health, Boston (S.R.E.); the National Cerebral and Cardiovascular Center, Suita, Osaka, Japan (K.M.); the Stroke Unit, Hospital Vall d'Hebron, Barcelona (C.A.M.); the Department of Neurology, Tiantan Hospital, Beijing (Y.W.); and the Department of Medicine and Therapeutics, Chinese University of Hong Kong, Hong Kong (K.S.L.W.). Address reprint requests to Dr. Johnston at the Dean's Office, Dell Medical School, University of Texas at Austin, 1912 Speedway, Suite 564, Austin, TX, 78712, or at clay.johnston@utexas.edu.

*A complete list of the Acute Stroke or Transient Ischaemic Attack Treated with Aspirin or Ticagrelor and Patient Outcomes (SOCRATES) steering committee members and site principal investigators is provided in the Supplementary Appendix, available at NEJM.org.

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Ischemic stroke and transient ischemic attack are common, and the risk of subsequent ischemic events is particularly high during the first 90 days after the index cerebrovascular event.[1-4] Aspirin at a dose of 50 to 325 mg daily is commonly used in this context.[5-7] However, the benefit of aspirin in the secondary prevention of ischemic stroke is limited; even with concurrent aspirin treatment, the rate of recurrent stroke is 10 to 15% in the first 90 days, and the rate of new ischemic events when aspirin is used in the long term is only 22% lower than the rate associated with no preventive treatment.[8] Furthermore, even moderate doses of aspirin are associated with relative risks of hemorrhagic events, including gastrointestinal bleeding, that range from 1.5 to 3.1.[9] More intensive antiplatelet therapy through a different mechanism of action may be more effective than aspirin at reducing the risk of recurrent ischemia after transient ischemic attack or acute ischemic stroke, but evidence to support this is limited.[10,11] Ticagrelor is a potent antiplatelet agent that reversibly binds and inhibits the P2Y12 receptor on platelets and is direct-acting, in contrast to clopidogrel, the action of which is dependent on variable and genetically determined metabolic activation.[12,13] The Acute Stroke or Transient Ischaemic Attack Treated with Aspirin or Ticagrelor and Patient Outcomes (SOCRATES) trial was designed to compare ticagrelor with aspirin with regard to their effectiveness for the prevention of major vascular events (a composite of stroke [ischemic or hemorrhagic], myocardial infarction, or death) over a period of 90 days in the treatment of patients with acute cerebral ischemia.

Methods

Study Design and Oversight

SOCRATES was a multicenter, randomized, double-blind, double-dummy, parallel-group trial; patients were enrolled from January 7, 2014, through October 29, 2015, at 674 sites in 33 countries. The trial was approved by the relevant ethics committee at each participating site. The protocol, analysis plan, and descriptions of the trial leadership, committees, investigators, and sites are provided in the Supplementary Appendix, available with the full text of this article at NEJM.org. Details of the study rationale, design, and methods have been described previously.[14]

The executive committee was responsible for the overall design, interpretation, and supervision of the trial, including the development of the protocol and any protocol amendments. The executive committee was also responsible for ensuring the integrity of the data, analysis, and presentation of results.

An independent data and safety monitoring committee reported to the executive committee. It regularly assessed safety outcomes, overall study integrity, and study conduct, at intervals based on the number of patients who had completed the 90-day treatment period throughout the trial, and oversaw a single interim analysis. An independent clinical-event adjudication committee, the members of which were unaware of the treatment assignments, adjudicated the primary and secondary efficacy end points and all bleeding events that were not reported as minimal.

The study was sponsored by AstraZeneca, which collaborated in the execution of the trial and collected the data. All authors had full access to the data and the data analysis. The analyses were performed by AstraZeneca under the direction of the executive committee. The executive committee made the decision to submit the manuscript for publication. The authors vouch for the accuracy and completeness of the data and data analyses and the fidelity of this report to the study protocol. The first author wrote the first draft of the manuscript, which was edited by all the other authors.

Study Population

Eligible patients had an acute ischemic stroke with a National Institutes of Health Stroke Scale (NIHSS) score of 5 or lower (scores range from 0 to 42, with higher scores indicating more severe stroke) or high-risk transient ischemic attack (ABCD^2 stroke risk score of ≥4 [scores range from 0 to 7 with higher scores indicating higher risk of stroke] or symptomatic intracranial or extracranial arterial stenosis) and could undergo randomization within 24 hours after symptom onset, were at least 40 years of age, and had undergone a computed tomographic (CT) or magnetic resonance imaging (MRI) scan before randomization to rule out intracranial bleeding or other conditions that could account for the neurologic symptoms or contraindicate study treatment. The components of the ABCD^2 stroke risk score are age, blood pressure, clinical fea-

tures, duration of transient ischemic attack, and presence or absence of diabetes.

Patients were not eligible for participation if other specific antiplatelet therapy or anticoagulation therapy was planned or if carotid, cerebrovascular, or coronary revascularization was planned that would require halting study treatment within 7 days after randomization. Patients were also not eligible if they had hypersensitivity to ticagrelor or aspirin; had a history of atrial fibrillation, ventricular aneurysm, or suspicion of cardioembolic cause for transient ischemic attack or stroke; underwent intravenous or intraarterial thrombolysis or mechanical thrombectomy within 24 hours before randomization; were in need of therapy with strong cytochrome P-450 3A (CYP3A) inhibitors or CYP3A substrates with narrow therapeutic indexes; required treatment with nonsteroidal antiinflammatory drugs for more than 7 consecutive days; had a known bleeding diathesis or coagulation disorder; had a history of symptomatic nontraumatic intracerebral hemorrhage at any time, gastrointestinal bleed within the past 6 months, or major surgery within 30 days; had severe liver disease; had renal failure requiring dialysis; were pregnant or lactating; or could not understand or comply with study procedures or follow-up. Written informed consent was obtained before any study-specific procedures were performed. Additional information on the inclusion and exclusion criteria are provided in the Supplementary Appendix.

TREATMENT

Within 24 hours after the onset of symptoms of acute ischemic stroke or transient ischemic attack, eligible patients were randomly assigned to a treatment group with the use of an interactive telephone and Web-based system. The loading dose was to be given as soon as possible after randomization. Eligible patients were randomly assigned in a 1:1 ratio to one of two treatment groups. Patients received either ticagrelor (a loading dose of 180 mg given as two 90-mg tablets on day 1, followed by 90 mg twice daily given orally together with loading and daily doses of aspirin placebo) or aspirin (a loading dose of 300 mg given as three 100-mg tablets on day 1, followed by 100 mg daily given orally together with a loading dose and twice-daily doses of ticagrelor placebo). Subsequent maintenance doses were taken in the morning and evening, at approximately 12-hour intervals, for the remainder of the 90-day treatment period. The loading and maintenance doses of ticagrelor were selected on the basis of data from previous phase 2–3 clinical studies. At the end of 90 days of study treatment, patients were treated at the discretion of the investigator and followed for an additional 30 days.

END POINTS

The primary end point for the trial was the time from randomization to the first occurrence of any event from the composite of stroke (ischemic or hemorrhagic), myocardial infarction, or death; each component of the composite end point was based on standard definitions.[14] The predefined secondary end point, to be tested in a hierarchical testing sequence if the difference between the treatment groups with regard to the primary end point was significant, was the time to ischemic stroke. Other, exploratory secondary end points included the time to net clinical outcome, defined as the composite of stroke, myocardial infarction, death, or life-threatening bleeding; the composite of cardiovascular death, myocardial infarction, or ischemic stroke; all strokes, disabling strokes, and fatal strokes individually; and death from any cause, death from cardiovascular causes, and myocardial infarction individually. The full list of prespecified end points is provided in the study protocol.

The safety end points included time to first major bleeding event, assessed with the use of the PLATO bleeding definition (see the Supplementary Appendix)[15]; time to discontinuation of study treatment as a result of any bleeding event; incidence of intracranial hemorrhage; incidence of fatal bleeding; and incidence of serious and selected nonserious adverse events.

STATISTICAL ANALYSIS

The trial was event-driven. To detect a hazard ratio of 0.80 with a final two-sided significance level of 4.98% and 88.7% power, a total of 844 primary end-point events were required. The significance level was adjusted from 5.00% to account for a single interim analysis for efficacy and futility that was performed when half the primary end-point events had been observed. On the basis of the pooled observed event rate, the sample size was recalculated during the trial

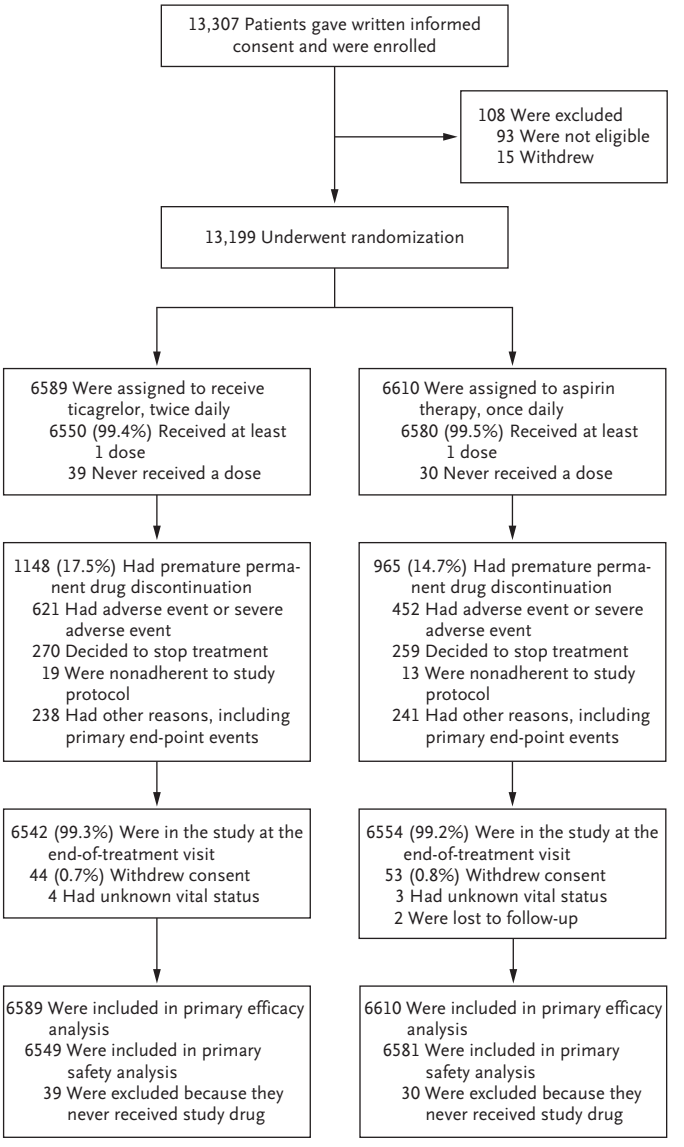

Figure 1. Enrollment and Randomization of Patients.

One patient who was randomly assigned to the ticagrelor group accidentally received aspirin during the entire treatment period; in accordance with the protocol, this patient was included in the ticagrelor group for the primary efficacy analysis and was included in the aspirin group in the safety analysis.

from 9600 to 13,200 patients to accrue the target number of primary events.[14]

All efficacy analyses were based on the intention-to-treat principle and included the full analysis set of patients with adjudicated events. Safety analyses were performed with the cohort that received treatment. The secondary end point, time to first ischemic stroke, was to be tested for confirmation only if the results of the primary analysis were significant. The analyses of other prespecified end points were exploratory. The time from randomization to the first occurrence of any event for a given end point was compared with the use of the Cox proportional hazards model. Interactions between treatment assignment and prespecified subgroups were evaluated by including terms for treatment, subgroup, and treatment-by-subgroup interaction in the Cox model. Interaction terms with a P value of less than 0.05 were considered to be statistically significant.

RESULTS

PATIENT POPULATION

Overall, 13,307 patients were enrolled, and 13,199 patients underwent randomization (Fig. 1). A total of 494 patients (3.7%) presented with ischemic stroke within 4.5 hours after symptom onset, of whom 128 (1.0% of the total patient population) had an NIHSS score higher than 3. Two patients were lost to follow-up, and we were unable to determine the vital status of 7 others after they withdrew their consent. Event statuses for components of the primary end point were ascertained for 98.5% of the potential patient follow-up time (see Table S1 in the Supplementary Appendix for a description of patient visits). The characteristics of the patients at baseline are presented in Table 1 and in Table S2 in the Supplementary Appendix.

PRIMARY AND SECONDARY END POINTS

A primary composite end-point event occurred in 442 of the 6589 patients (6.7%) in the ticagrelor group and in 497 of the 6610 patients (7.5%) in the aspirin group (hazard ratio, 0.89; 95% confidence interval [CI], 0.78 to 1.01; P=0.07) (Fig. 2A and Table 2). On the basis of our hierarchical testing plan, all analyses of secondary end points were therefore considered to be exploratory and were not used to make conclusions regarding significance. The main secondary end point, ischemic stroke, occurred in 385 patients (5.8%) in the ticagrelor group and 441 patients (6.7%) in the aspirin group (hazard ratio, 0.87; 95% CI, 0.76 to 1.00; nominal P=0.046) (Fig. 2B and Table 2). Other secondary end points are reported in Table 2. There were no treatment-by-subgroup interactions in the prespecified subgroups (P>0.05 for all comparisons) (Fig. 3).

Table 1. Baseline Characteristics of the Participants.*

Characteristic	Ticagrelor (N = 6589)	Aspirin (N = 6610)
Age — yr	65.8±11.23	65.9±11.37
Female sex — no. (%)	2759 (41.9)	2724 (41.2)
Race — no. (%)†		
White	4374 (66.4)	4410 (66.7)
Black	119 (1.8)	120 (1.8)
Asian	1957 (29.7)	1949 (29.5)
Other	139 (2.1)	131 (2.0)
Ethnic background — no. (%)†		
Not Hispanic	6023 (91.4)	6050 (91.5)
Hispanic	566 (8.6)	558 (8.4)
Region — no. (%)		
Asia or Australia	1990 (30.2)	1981 (30.0)
Europe	3769 (57.2)	3772 (57.1)
North America	514 (7.8)	540 (8.2)
Central or South America	316 (4.8)	317 (4.8)
Median blood pressure (interquartile range) — mm Hg		
Systolic	150 (137.0–165.0)	150 (135.5–165.0)
Diastolic	84 (78.0–92.0)	84 (77.0–91.0)
Median body-mass index (interquartile range)‡	26.1 (23.5–29.4)	26.0 (23.5–29.3)
Medical history — no. (%)		
Hypertension	4797 (72.8)	4933 (74.6)
Dyslipidemia	2531 (38.4)	2497 (37.8)
Diabetes mellitus	1664 (25.3)	1548 (23.4)
Previous ischemic stroke	765 (11.6)	828 (12.5)
Previous TIA	410 (6.2)	446 (6.7)
Previous myocardial infarction	280 (4.2)	268 (4.1)
Coronary artery disease	573 (8.7)	571 (8.6)
Congestive heart failure	234 (3.6)	248 (3.8)
Taking aspirin before randomization — no. (%)	2130 (32.3)	2102 (31.8)
Taking clopidogrel before randomization — no. (%)	219 (3.3)	237 (3.6)
Time to randomization after onset of symptoms — no. (%)		
<12 hr	2400 (36.4)	2424 (36.7)
≥12 hr	4188 (63.6)	4186 (63.3)
Qualifying event — no. (%)		
TIA	1790 (27.2)	1741 (26.3)
Ischemic stroke	4798 (72.8)	4869 (73.7)
Baseline $ABCD^2$ score among patients with TIA as qualifying event — no./total no. (%)§		
≤5	1313/1790 (73.4)	1257/1741 (72.2)
>5	471/1790 (26.3)	479/1741 (27.5)
Baseline NIHSS score among patients with ischemic stroke as qualifying event — no./total no. (%)¶		
≤3	3235/4798 (67.4)	3282/4869 (67.4)
>3	1541/4798 (32.1)	1566/4869 (32.2)

* The differences in baseline characteristics between the treatment groups were not significant, with the exception of the proportions of patients with a history of diabetes or hypertension (nominal $P<0.05$). TIA denotes transient ischemic attack.
† Race and ethnic background were self-reported.
‡ The body-mass index is the weight in kilograms divided by the square of the height in meters.
§ $ABCD^2$ stroke risk scores range from 0 to 7, with higher scores indicating higher risk; data are provided only for the group of 3531 patients for whom TIA was the qualifying event for inclusion in the trial.
¶ National Institutes of Health Stroke Scale (NIHSS) scores range from 0 to 42, with higher scores indicating more severe stroke; data are provided only for the group of 9667 patients for whom ischemic stroke was the qualifying event for inclusion in the trial.

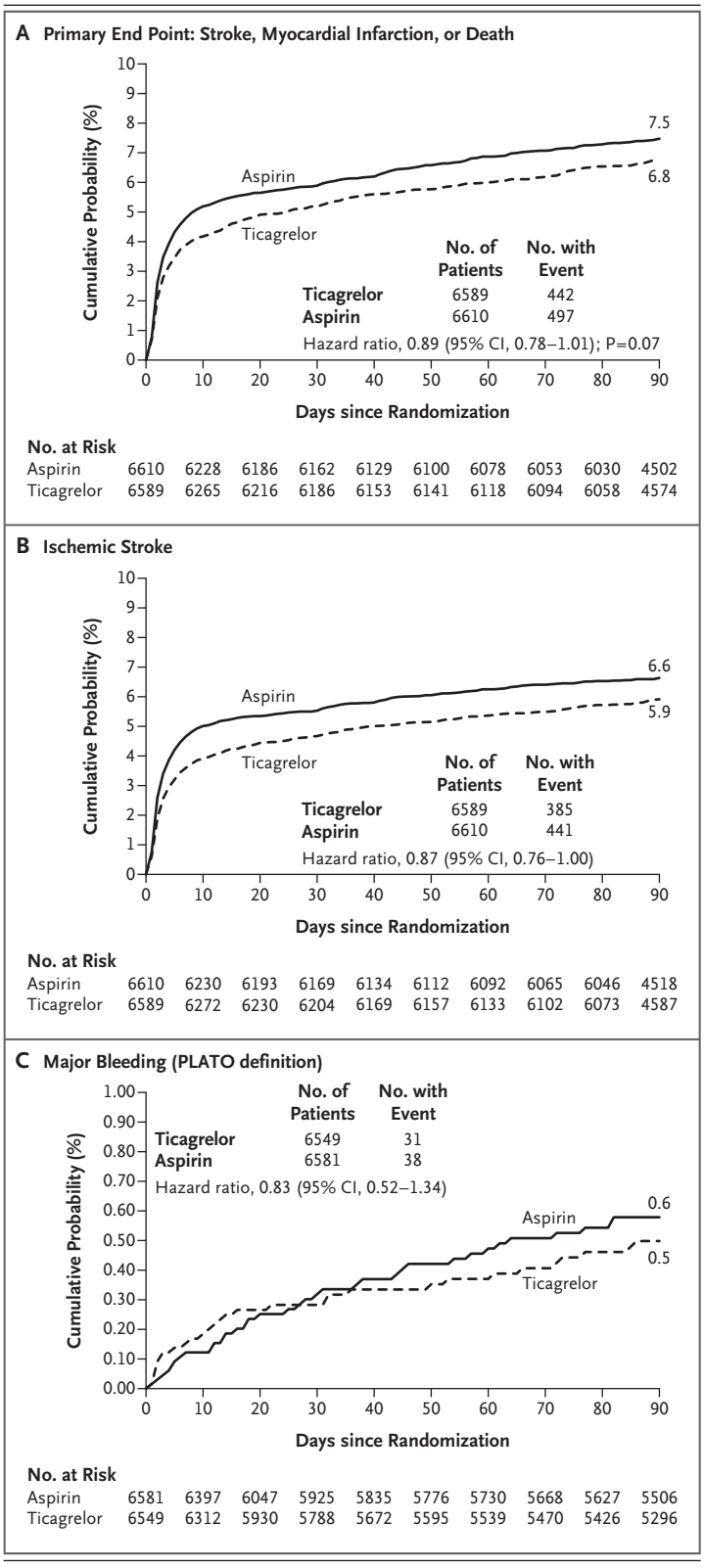

Figure 2. Kaplan–Meier Analysis of Primary and Secondary End Points.

Data in Panels A and B are from the intention-to-treat analysis. Panel C includes events with an onset date on or after the date of the first dose and up to and including 7 days after the date of the last dose of study medication. A description of PLATO-defined bleeding is provided in the Supplementary Appendix.

SAFETY

A primary safety end-point event (PLATO-defined major bleeding) occurred in 31 patients (0.5%) in the ticagrelor group and 38 patients (0.6%) in the aspirin group (hazard ratio, 0.83; 95% CI, 0.52 to 1.34) (Fig. 2C and Table 2). Intracranial hemorrhage occurred in 12 patients (0.2%) in the ticagrelor group and in 18 patients (0.3%) in the aspirin group. Fatal bleeding occurred in 9 patients (0.1%) in the ticagrelor group and in 4 patients (0.1%) in the aspirin group. Similarly, there were no significant differences in the other major safety outcomes (Table 2, and Table S3 in the Supplementary Appendix). Dyspnea was more common in the ticagrelor group than in the aspirin group (6.2% vs. 1.4%). Permanent discontinuation of study treatment occurred in 17.5% of patients in the ticagrelor group, versus 14.7% of patients in the aspirin group (Fig. 1). Dyspnea and bleeding events were the most frequent factors accounting for the difference, with rates of discontinuation due to dyspnea in the ticagrelor and aspirin groups of 1.4% and 0.3%, respectively, and rates of discontinuation due to any bleeding of 1.3% and 0.6%. Serious adverse events and adverse events leading to discontinuation of study treatment are listed in Tables S3 and S4 in the Supplementary Appendix. A net clinical outcome, defined as a composite of stroke, myocardial infarction, death, or life-threatening bleeding, occurred in 6.9% of patients in the ticagrelor group and 7.7% of patients in the aspirin group (hazard ratio, 0.90; 95% CI, 0.79 to 1.02).

DISCUSSION

In this large, international trial of secondary prevention in patients with noncardioembolic ischemic stroke and transient ischemic attack who underwent randomization within 24 hours

Table 2. Efficacy and Safety Outcomes.

Outcome	Ticagrelor (N = 6589)		Aspirin (N = 6610)		Hazard Ratio (95% CI)	P Value
	no. of patients (%)	*event rate**	*no. of patients (%)*	*event rate**		
Primary end point						
Stroke, myocardial infarction, or death	442 (6.7)	6.8	497 (7.5)	7.5	0.89 (0.78–1.01)	0.07
Secondary end points†						
Ischemic stroke	385 (5.8)	5.9	441 (6.7)	6.6	0.87 (0.76–1.00)	0.046‡
Ischemic stroke, myocardial infarction, or cardiovascular death	423 (6.4)	6.5	475 (7.2)	7.2	0.89 (0.78–1.01)	0.07
All stroke	390 (5.9)	6.0	450 (6.8)	6.8	0.86 (0.75–0.99)	0.03‡
Disabling stroke§	277 (4.2)	4.2	307 (4.6)	4.7	0.90 (0.77–1.06)	0.21
Fatal stroke	18 (0.3)	0.3	17 (0.3)	0.3	1.06 (0.55–2.06)	0.86
Myocardial infarction	25 (0.4)	0.4	21 (0.3)	0.3	1.20 (0.67–2.14)	0.55
Death	68 (1.0)	1.0	58 (0.9)	0.9	1.18 (0.83–1.67)	0.36
Cardiovascular death	41 (0.6)	0.6	35 (0.5)	0.5	1.18 (0.75–1.85)	0.48
Net clinical outcome: stroke, myocardial infarction, death, or life-threatening bleeding	457 (6.9)	7.0	508 (7.7)	7.6	0.90 (0.79–1.02)	0.09
Safety end points¶						
Major bleeding	31 (0.5)	0.5	38 (0.6)	0.6	0.83 (0.52–1.34)	0.45
Major bleeding, fatal or life-threatening	22 (0.3)	0.4	27 (0.4)	0.4	0.83 (0.47–1.46)	0.52
Fatal bleeding	9 (0.1)		4 (0.1)			
Intracranial hemorrhage	12 (0.2)	0.2	18 (0.3)	0.3	0.68 (0.33–1.41)	0.30
Major bleeding, other	9 (0.1)	0.1	11 (0.2)	0.2	0.84 (0.35–2.03)	0.70
Major or minor bleeding	106 (1.6)	1.7	82 (1.2)	1.3	1.32 (0.99–1.76)	0.06

* Event rates are Kaplan–Meier percentages at 90 days.
† Ischemic stroke was the only secondary end-point event to be tested in a hierarchical testing sequence if there was a significant difference between the treatment groups with regard to the primary end point; analyses of all other secondary end points were prespecified but considered to be exploratory.
‡ The P value was considered nonsignificant in accordance with the hierarchical testing plan.
§ A stroke was defined as disabling if the patient had a subsequent score on the modified Rankin scale of greater than 1 (indicating death or any degree of disability).
¶ The safety end points involved bleeding according to the PLATO definition (see the Supplementary Appendix). A total of 6549 patients in the ticagrelor group and 6581 patients in the aspirin group were included in the analysis of safety outcomes.

after symptom onset and who did not receive thrombolytic therapy, events included in the primary end point — a composite of stroke, myocardial infarction, or death — were not less common among patients who received ticagrelor than among patients who received aspirin during the 90-day follow-up period. There was no evidence of a higher risk of major or intracranial hemorrhage with ticagrelor than with aspirin, but there were more instances of dyspnea and minor bleeding in the ticagrelor group.

In this trial, we tested the efficacy and safety of monotherapy with ticagrelor versus aspirin in patients who were treated within 24 hours after the onset of a cerebral ischemic event. Approximately one third of the patients were taking aspirin at the time of the qualifying cerebral ischemic event. Because the antiplatelet effects of aspirin typically last several days, the introduction of ticagrelor represented short-term dual antiplatelet therapy. Subgroup analysis did not reveal a significant interaction indicating a benefit of ticagrelor in patients who were taking aspirin at baseline, but further study of the combination of ticagrelor and aspirin may be warranted, given the possibility that the rates of

Subgroup	No. of Patients	Ticagrelor	Aspirin	Hazard Ratio (95% CI)	P Value for Interaction
		total patients (% with event)			
Overall	13,199	6589 (6.7)	6610 (7.5)	0.89 (0.78–1.01)	
Age (yr)					0.06
<65	6,028	3021 (5.7)	3007 (7.0)	0.81 (0.66–0.99)	
65–75	4,176	2064 (7.0)	2112 (8.5)	0.81 (0.65–1.01)	
>75	2,995	1504 (8.4)	1491 (7.2)	1.16 (0.90–1.50)	
Sex					0.89
Male	7,716	3830 (7.0)	3886 (7.8)	0.89 (0.76–1.05)	
Female	5,483	2759 (6.3)	2724 (7.2)	0.88 (0.72–1.08)	
Race					0.21
White	8,784	4374 (5.6)	4410 (5.8)	0.96 (0.81–1.15)	
Black	239	119 (3.4)	120 (7.5)	NA	
Asian	3,906	1957 (9.6)	1949 (11.5)	0.82 (0.67–0.99)	
Other	270	139 (4.3)	131 (5.3)	NA	
Weight					0.76
<70 kg	5,119	2574 (7.8)	2545 (8.8)	0.87 (0.72–1.06)	
≥70 kg	7,997	3978 (6.1)	4019 (6.6)	0.91 (0.76–1.08)	
BMI					0.61
<30	10,304	5110 (7.2)	5194 (7.8)	0.91 (0.79–1.05)	
≥30	2,802	1437 (5.3)	1365 (6.3)	0.83 (0.61–1.14)	
Region					0.30
Asia and Australia	3,971	1990 (9.6)	1981 (11.5)	0.83 (0.68–1.00)	
Europe	7,541	3769 (5.3)	3772 (6.0)	0.87 (0.72–1.05)	
North America	1,054	514 (6.8)	540 (5.2)	1.34 (0.81–2.19)	
Central and South America	633	316 (5.4)	317 (4.7)	1.14 (0.57–2.29)	
Diagnosis of index event					0.38
TIA	3,531	1790 (4.9)	1741 (5.0)	0.98 (0.72–1.31)	
Ischemic stroke, NIHSS ≤3	6,517	3235 (6.2)	3282 (7.6)	0.81 (0.67–0.98)	
Ischemic stroke, NIHSS >3	3,107	1541 (9.8)	1566 (10.0)	0.97 (0.78–1.22)	
Time from index event to randomization					0.22
<12 hr	4,824	2400 (6.9)	2424 (8.5)	0.80 (0.65–0.98)	
≥12 hr	8,374	4188 (6.6)	4186 (7.0)	0.95 (0.80–1.12)	
Diabetes mellitus					0.99
Yes	3,212	1664 (8.4)	1548 (9.5)	0.88 (0.70–1.11)	
No	9,981	4919 (6.1)	5062 (6.9)	0.88 (0.76–1.03)	
Previous antiplatelet therapy					0.51
Yes	4,716	2358 (7.1)	2358 (8.4)	0.84 (0.68–1.03)	
No	8,483	4231 (6.5)	4252 (7.1)	0.92 (0.78–1.08)	
Previous ischemic stroke or TIA					0.33
Yes	2,321	1121 (6.7)	1200 (8.5)	0.78 (0.57–1.04)	
No	10,872	5462 (6.7)	5410 (7.3)	0.92 (0.80–1.06)	
Previous myocardial infarction					0.97
Yes	548	280 (6.4)	268 (7.1)	0.89 (0.46–1.69)	
No	12,645	6303 (6.7)	6342 (7.5)	0.89 (0.78–1.01)	
Previous aspirin therapy					0.10
Yes	4,232	2130 (6.5)	2102 (8.4)	0.76 (0.61–0.95)	
No	8,967	4459 (6.8)	4508 (7.1)	0.96 (0.82–1.12)	
Previous coronary artery disease					0.85
Yes	1,712	852 (6.2)	860 (7.2)	0.86 (0.59–1.24)	
No	11,481	5731 (6.8)	5750 (7.6)	0.89 (0.78–1.02)	
Hypertension					0.82
Yes	9,730	4797 (6.8)	4933 (7.7)	0.88 (0.76–1.02)	
No	3,463	1786 (6.4)	1677 (7.0)	0.91 (0.70–1.18)	

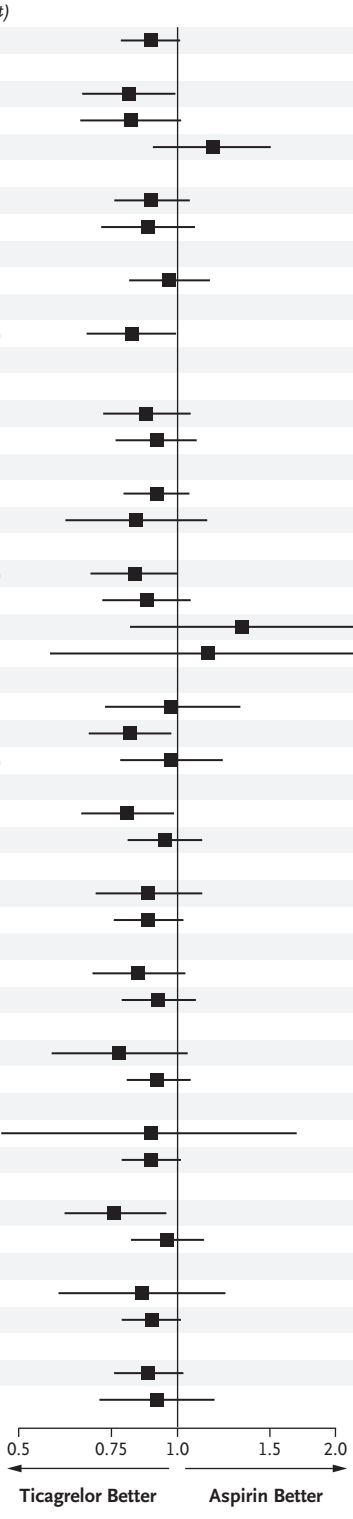

Figure 3 (facing page). Hazard Ratios for the Primary End Point According to Predefined Subgroups.

The body-mass index (BMI) is the weight in kilograms divided by the square of the height in meters. National Institutes of Health Stroke Scale (NIHSS) scores range from 0 to 42, with higher scores indicating more severe stroke. NA denotes not applicable (sample too small), and TIA transient ischemic attack.

ischemic stroke were lower in association with ticagrelor in this group of patients.

Although some studies have suggested that the risk of stroke after transient ischemic attack has decreased in recent years, our trial confirms previous studies that have shown a high risk in the first 2 weeks, with particularly high event rates in the first 2 days.[1,10,16]

The limitations of this trial include the limited enrollment of patients who were at especially high risk for stroke, such as those with high-grade carotid or severe intracranial stenosis. These patients may have undergone vascular interventions or may have been treated with the combination of clopidogrel plus aspirin on the basis of the results of the Clopidogrel in High-Risk Patients with Acute Nondisabling Cerebrovascular Events (CHANCE) trial.[10] The primary end-point event rates in the group with transient ischemic attack were lower than expected, which raises the possibility that we enrolled some patients with nonischemic conditions mimicking a transient ischemic attack, in whom antiplatelet therapy is unlikely to be efficacious. Patients who underwent thrombolysis or thrombectomy were not eligible for participation in this trial, so the results should not be generalized to them.

Although the rate of serious adverse events did not differ significantly between the ticagrelor and aspirin groups, discontinuation of study treatment was more common among patients who received ticagrelor. This difference was primarily due to dyspnea, which is a known adverse effect of ticagrelor treatment.[15,17] Other causes of the higher rate of discontinuation in the ticagrelor group were minor and minimal bleeding events.

In conclusion, in our trial involving patients with acute ischemic stroke or transient ischemic attack, ticagrelor was not found to be superior to aspirin in reducing the risk of the composite end point of stroke, myocardial infarction, or death.

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