

Ticagrelor and Aspirin or Aspirin Alone in Acute Ischemic Stroke or TIA

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ABSTRACT

BACKGROUND

Trials have evaluated the use of clopidogrel and aspirin to prevent stroke after an ischemic stroke or transient ischemic attack (TIA). In a previous trial, ticagrelor was not better than aspirin in preventing vascular events or death after stroke or TIA. The effect of the combination of ticagrelor and aspirin on prevention of stroke has not been well studied.

METHODS

We conducted a randomized, placebo-controlled, double-blind trial involving patients who had had a mild-to-moderate acute noncardioembolic ischemic stroke, with a National Institutes of Health Stroke Scale (NIHSS) score of 5 or less (range, 0 to 42, with higher scores indicating more severe stroke), or TIA and who were not undergoing thrombolysis or thrombectomy. The patients were assigned within 24 hours after symptom onset, in a 1:1 ratio, to receive a 30-day regimen of either ticagrelor (180-mg loading dose followed by 90 mg twice daily) plus aspirin (300 to 325 mg on the first day followed by 75 to 100 mg daily) or matching placebo plus aspirin. The primary outcome was a composite of stroke or death within 30 days. Secondary outcomes were first subsequent ischemic stroke and the incidence of disability within 30 days. The primary safety outcome was severe bleeding.

RESULTS

A total of 11,016 patients underwent randomization (5523 in the ticagrelor–aspirin group and 5493 in the aspirin group). A primary-outcome event occurred in 303 patients (5.5%) in the ticagrelor–aspirin group and in 362 patients (6.6%) in the aspirin group (hazard ratio, 0.83; 95% confidence interval [CI], 0.71 to 0.96; $P=0.02$). Ischemic stroke occurred in 276 patients (5.0%) in the ticagrelor–aspirin group and in 345 patients (6.3%) in the aspirin group (hazard ratio, 0.79; 95% CI, 0.68 to 0.93; $P=0.004$). The incidence of disability did not differ significantly between the two groups. Severe bleeding occurred in 28 patients (0.5%) in the ticagrelor–aspirin group and in 7 patients (0.1%) in the aspirin group ($P=0.001$).

CONCLUSIONS

Among patients with a mild-to-moderate acute noncardioembolic ischemic stroke (NIHSS score ≤ 5) or TIA who were not undergoing intravenous or endovascular thrombolysis, the risk of the composite of stroke or death within 30 days was lower with ticagrelor–aspirin than with aspirin alone, but the incidence of disability did not differ significantly between the two groups. Severe bleeding was more frequent with ticagrelor. (Funded by AstraZeneca; THALES ClinicalTrials.gov number, NCT03354429.)

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AMONG PATIENTS WITH AN ACUTE ISCHEMIC stroke or transient ischemic attack (TIA), the risk of a subsequent ischemic stroke is approximately 5 to 10% in the first few months.¹⁻⁴ Aspirin has been used to prevent a stroke in these patients, and two trials have shown that the combination of aspirin and clopidogrel, an antiplatelet agent that blocks the P2Y₁₂ receptor on platelets, reduced the risk of stroke and other major ischemic events in this population.^{5,6} Clopidogrel requires hepatic conversion to its active form through a pathway that is inefficient in 25% of white and 60% of Asian patients, and efficacy is uncertain in these patients.⁷

Ticagrelor, a direct-acting antiplatelet agent that is not dependent on metabolic activation, reversibly binds and inhibits the P2Y₁₂ receptor on platelets.^{8,9} A trial of ticagrelor alone in patients with acute ischemic stroke or TIA did not show a benefit over aspirin in preventing subsequent cardiovascular events (stroke, myocardial infarction, or death).¹⁰ In an exploratory analysis of that trial involving the subgroup of patients who had received aspirin within 7 days before randomization, treatment with ticagrelor may have reduced the risk of major vascular events.¹¹ This finding suggested that the effect of aspirin received before entry into the trial might have persisted for several days after treatment and that the combination of ticagrelor and aspirin may prevent subsequent strokes. Since the risk of subsequent stroke occurs mainly in the first month after an acute ischemic stroke or TIA,^{5,10} a 30-day treatment period was considered to be appropriate for a trial of ticagrelor and aspirin in preventing subsequent stroke.

The Acute Stroke or Transient Ischaemic Attack Treated with Ticagrelor and ASA [acetylsalicylic acid] for Prevention of Stroke and Death (THALES) trial was designed to test the hypothesis that 30-day treatment with ticagrelor and aspirin would be superior to aspirin alone in reducing the risk of subsequent stroke or death among patients with acute noncardioembolic cerebral ischemia.

METHODS

TRIAL DESIGN AND OVERSIGHT

This multicenter, randomized, double-blind, placebo-controlled, parallel-group trial was conducted at 414 sites in 28 countries. The executive committee designed and oversaw the conduct and

analysis of the trial in collaboration with the sponsor, AstraZeneca. Details of the trial rationale, design, and methods have been described previously¹² and are provided in the protocol, available with the full text of this article at [NEJM.org](https://www.nejm.org). The trial was approved by the relevant ethics committee for each participating site. Written informed consent was provided by all the patients or their representatives before enrollment. Information on the trial leadership, committees, and investigators is provided in the Supplementary Appendix, available at [NEJM.org](https://www.nejm.org). An independent data and safety monitoring committee assessed the conduct of the trial according to patient accrual throughout the trial and conducted a prespecified interim analysis after 70% of the targeted number of primary-outcome events had occurred.

The sponsor, AstraZeneca, provided the trial drug (ticagrelor) and placebo, monitored the trial, and analyzed the data with the oversight of the executive committee. The first author, who had full access to the data, wrote the first draft of the manuscript with no writing assistance from the sponsor. All the authors vouch for the accuracy and completeness of the data, for the adherence of the trial to the trial protocol and statistical analysis plan, and for full reporting of adverse events. Confidentiality agreements were in place between the authors and the sponsor.

PATIENTS

Eligible patients were at least 40 years of age and had had either a mild-to-moderate acute noncardioembolic ischemic stroke as determined according to the clinical judgment of the investigators, with a National Institutes of Health Stroke Scale (NIHSS) score of 5 or less (range, 0 to 42, with higher scores indicating more severe stroke), or a high-risk TIA as determined according to a score of 6 or higher on the ABCD² scale (range, 0 to 7, with higher scores indicating higher risk of stroke) or symptomatic intracranial or extracranial arterial stenosis (≥50% narrowing in the diameter of the lumen of an artery that could account for the TIA). The components of the ABCD² stroke risk score are age, blood pressure, clinical features, duration of TIA, and presence of diabetes mellitus. Randomization occurred within 24 hours after the onset of symptoms or, in patients in whom a stroke was evident on awakening from sleep, within 24 hours from the

time at which the patient's condition was last reported to be normal. Patients underwent computed tomography or magnetic resonance imaging (MRI) of the brain before randomization to rule out intracranial bleeding or conditions other than cerebral ischemia that could account for the neurologic symptoms or contraindicate trial treatment.

Patients were not eligible for participation if intravenous or intraarterial thrombolysis or mechanical thrombectomy was planned within 24 hours before randomization or if there was planned use of anticoagulation or specific antiplatelet therapy other than aspirin. Additional exclusion criteria were a hypersensitivity to ticagrelor or aspirin, a history of atrial fibrillation or ventricular aneurysm or a suspicion of a cardioembolic cause of the TIA or stroke, planned carotid endarterectomy that required discontinuation of the trial medication within 3 days after randomization, a known bleeding diathesis or coagulation disorder, a history of intracerebral hemorrhage, gastrointestinal bleeding within the past 6 months, or major surgery within 30 days before randomization. Additional information on inclusion and exclusion criteria is provided in the protocol.

TRIAL PROCEDURES

We randomly assigned patients to receive either ticagrelor plus aspirin or matching placebo plus aspirin, in accordance with a fixed-randomization schedule, using balanced blocks to ensure an approximate 1:1 ratio of the two regimens. An interactive Web-based response system was used to determine the treatment assignments. After randomization, visits were scheduled at 5 to 9 days, 30 to 34 days, and 60 to 64 days. Visits at 5 to 9 days and at 60 to 64 days could be telephone visits.

Patients received either a loading dose of oral ticagrelor (180 mg given as two 90-mg tablets) or matching placebo as soon as possible after randomization. Subsequent maintenance doses of ticagrelor (90 mg) or placebo twice daily were administered at approximately 12-hour intervals for the remainder of the 30-day treatment period. In addition, patients received a loading dose of aspirin; a dose of 300 to 325 mg was recommended, with lesser doses recommended if patients had already received aspirin after symptom onset but before randomization. Thereafter, as-

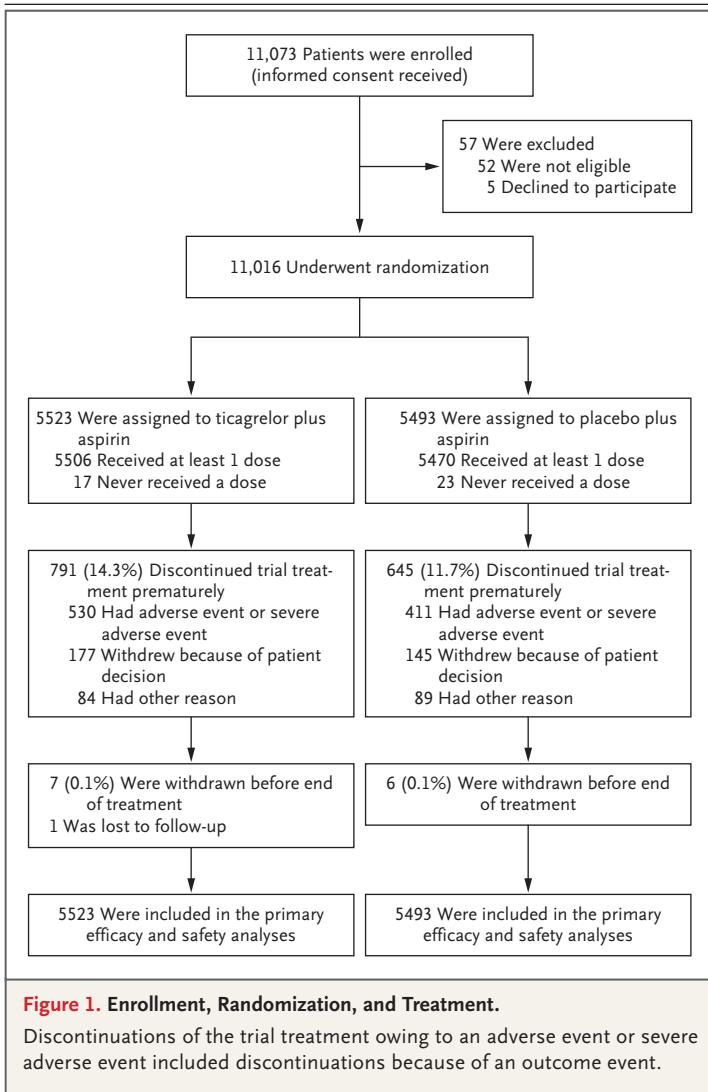
pirin at a dose of 75 to 100 mg daily was recommended. After the 30-day duration of trial treatment, patients were treated according to standards of care at the discretion of the investigator and were followed for an additional 30 days, with continued collection of data on outcomes and safety events.

Adverse events that met the criteria for serious adverse events or that led to discontinuation of the trial treatment were recorded in case report forms by the investigators, who were unaware of the treatment assignments. Stroke events, which included both progression of the index stroke and new stroke events, were classified by the investigators as ischemic, hemorrhagic, or of undetermined cause.

Bleeding events were classified by the investigators as severe, moderate, or mild, according to the definitions used in the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO) trial (see the Supplementary Appendix).¹³ Severe bleeding, as defined according to the GUSTO criteria, was fatal bleeding or intracranial or other bleeding that caused hemodynamic compromise for which intervention was warranted (e.g., systolic blood pressure <90 mm Hg that warranted blood or fluid replacement, vasopressor or inotropic support, or surgical intervention). Intracranial bleeding, including hemorrhagic stroke and symptomatic hemorrhagic transformation, was reported as a severe bleeding event. Asymptomatic hemorrhagic transformation of ischemic brain infarctions and microhemorrhages smaller than 10 mm that were evident only on gradient-echo MRI were not included as severe intracranial bleeding events as defined according to the GUSTO criteria. The standard GUSTO definition was adapted to exclude these events in order to better distinguish clinically relevant events in the population with acute stroke.^{12,14} Investigator-reported outcomes were used, since previous studies had shown that the estimates of treatment effect with investigator reports and with central adjudication were similar.¹⁵⁻¹⁷

OUTCOMES

The primary outcome was a composite of stroke or death in a time-to-first-event analysis from randomization through 30 days of follow-up. Stroke included ischemic stroke, hemorrhagic stroke (symptomatic intraparenchymal, intraventricular,



or subarachnoid hemorrhage), and stroke of undetermined type (ischemic or hemorrhagic); death included all causes of death. Definitions of the outcomes are included in the protocol and in the Study Assessments section in the Supplementary Appendix. The secondary outcomes were the first subsequent ischemic stroke (expressed as a hazard ratio), and disability measured as a score of greater than 1 on the modified Rankin scale¹⁸ (scores range from 0 to 6, with 0 to 1 indicating no disability, 2 to 5 indicating increasing disability, and 6 indicating death) at the end of the treatment visit 30 to 34 days after randomization (expressed as an odds ratio). The exploratory outcomes, including disabling stroke (score >2 on the modified Rankin scale) at the end-of-treatment visit in patients with subsequent stroke,

are described in the protocol and in the statistical analysis plan.

Safety outcomes included the first severe bleeding event (the primary safety outcome), a composite of the first intracranial hemorrhage or fatal bleeding event, the first moderate or severe bleeding event, premature permanent discontinuation of the trial treatment owing to any bleeding, and the incidence of serious adverse events and adverse events leading to premature and permanent discontinuation of the trial treatment.

STATISTICAL ANALYSIS

This event-driven trial was initially powered to detect a hazard ratio of 0.80, favoring treatment with dual antiplatelet agents. On the basis of new data from completed clinical trials,^{6,19} the assumptions were adjusted on May 8, 2019, when 7964 patients had undergone randomization, to a lower hazard ratio requiring fewer primary outcomes and a smaller sample size. We determined that a total of 647 primary events would provide the trial with a power of 90% to detect a hazard ratio of 0.77 with a final two-sided significance level of 0.04996. A P value of 0.05, which was considered to indicate statistical significance, was adjusted to 0.04996 to account for a single interim analysis for efficacy and futility after 70% of the targeted primary-outcome events were observed. The data cutoff for the interim analysis was on June 28, 2019, when 9086 patients had undergone randomization.

All efficacy and safety analyses were based on the intention-to-treat principle and included all the patients who underwent randomization. The results of the analysis of secondary outcomes — the first subsequent ischemic stroke (the first secondary outcome) and overall disability (modified Rankin scale score >1) at day 30 (the second secondary outcome) — were to be tested in a hierarchical testing sequence only if the results of the primary outcome analysis were significant. The analyses of other outcomes, including safety outcomes that were not included in the hierarchical testing sequence, are exploratory. An on-treatment analysis was also performed.

We analyzed the time from randomization to the first occurrence of any event for a given outcome with the use of a Cox proportional-hazards model with a factor for treatment group and Efron's method of handling ties. P values and 95% confidence intervals for the hazard ratios were

Table 1. Baseline Characteristics of the Patients.*

Characteristic	Ticagrelor-Aspirin Group (N=5523)	Aspirin Group (N=5493)
Age — yr	65.2±11.0	65.1±11.1
Female sex — no. (%)	2108 (38.2)	2171 (39.5)
Race — no. (%)†		
White	2973 (53.8)	2948 (53.7)
Black	21 (0.4)	32 (0.6)
Asian	2353 (42.6)	2339 (42.6)
Other	176 (3.2)	174 (3.2)
Geographic region — no. (%)		
Asia or Australia	2373 (43.0)	2356 (42.9)
Europe	2814 (51.0)	2803 (51.0)
North America	12 (0.2)	11 (0.2)
Central or South America	324 (5.9)	323 (5.9)
Median blood pressure (IQR) — mm Hg		
Systolic	150.0 (135.0–163.0)	149.0 (134.0–163.0)
Diastolic	84.0 (79.0–91.0)	84.0 (78.0–91.0)
Median BMI (IQR)‡	25.9 (23.3–29.0)	25.7 (23.2–28.9)
Current smoker — no. (%)	1504 (27.2)	1428 (26.0)
Hypertension — no. (%)	4298 (77.8)	4222 (76.9)
Type 1 or type 2 diabetes mellitus — no. (%)	1589 (28.8)	1557 (28.3)
Previous ischemic stroke — no. (%)	901 (16.3)	914 (16.6)
Previous TIA — no. (%)	275 (5.0)	240 (4.4)
Use of agent before event — no. (%)		
Aspirin	754 (13.7)	679 (12.4)
Clopidogrel	75 (1.4)	75 (1.4)
Time from symptom onset to randomization <12 hr — no. (%)	1812 (32.8)	1776 (32.3)
Qualifying event — no. (%)		
Ischemic stroke	5032 (91.1)	4953 (90.2)
TIA	491 (8.9)	540 (9.8)
ABCD ² score in patients with qualifying TIA — no. (%)§		
≤5	60 (1.1)	71 (1.3)
6–7	431 (7.8)	469 (8.5)
NIHSS score in patients with qualifying ischemic stroke — no. (%)¶		
≤3	3359 (60.8)	3312 (60.3)
>3	1673 (30.3)	1641 (29.9)

* Plus–minus values are means ±SD. There were no significant differences in baseline characteristics between the two groups. IQR denotes interquartile range, and TIA transient ischemic attack.

† Race was determined by patient report.

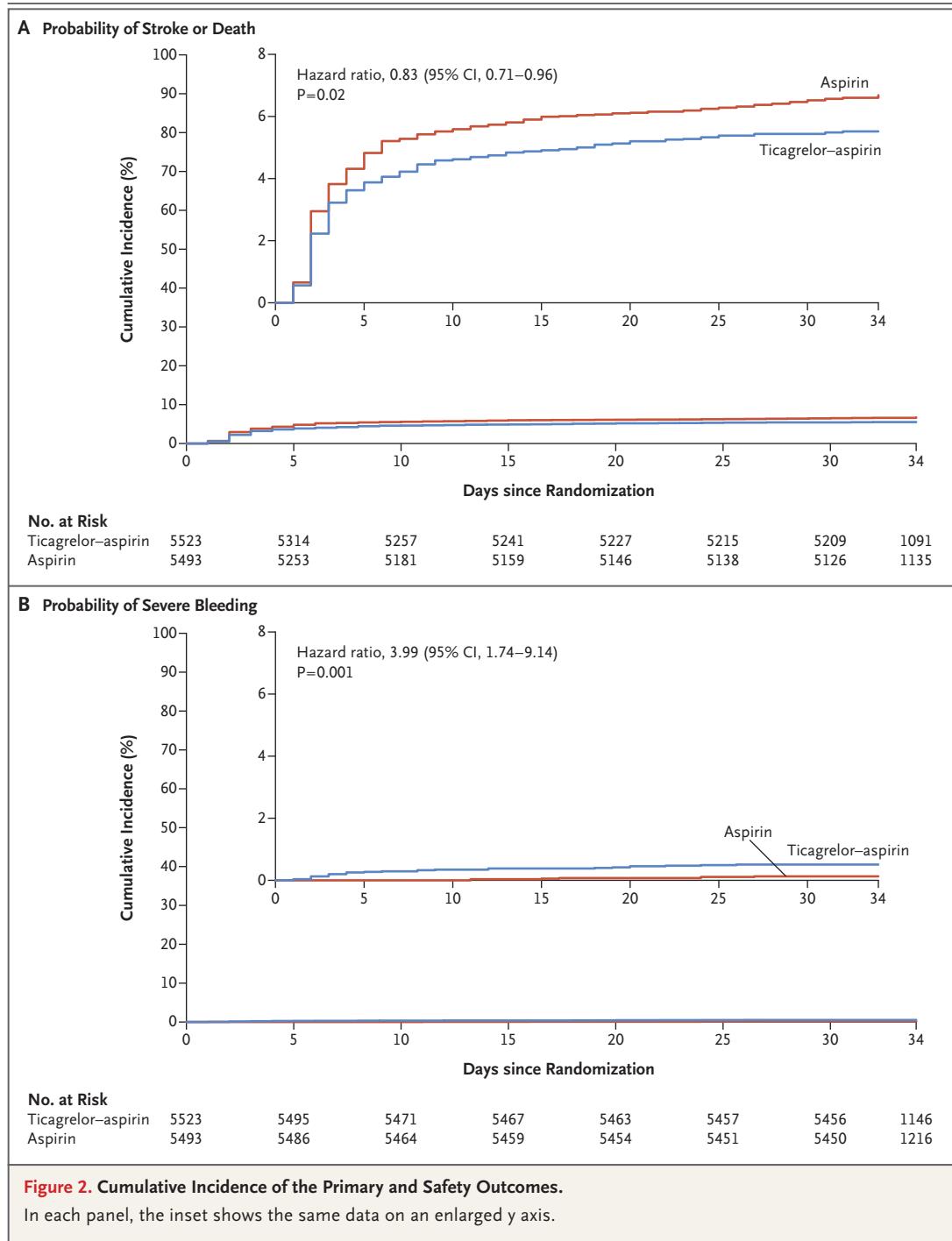
‡ The body-mass index (BMI) is the weight in kilograms divided by the square of the height in meters.

§ Scores on the ABCD² scale range from 0 to 7, with higher scores indicating a greater risk of stroke. The scale is used to estimate the risk of stroke after a TIA on the basis of age, blood pressure, clinical features, duration of TIA, and presence of diabetes mellitus.

¶ Scores on the National Institutes of Health Stroke Scale (NIHSS) range from 0 to 42, with higher scores indicating more severe stroke.

based on the Wald statistic, and a log-cumulative hazard plot was used to assess the proportional-hazards assumption. If the total number of events was less than 15, only the number of patients with events and the percentage of patients were presented without Kaplan–Meier estimates, hazard

ratios, confidence intervals, or P values. Confidence intervals for the exploratory outcomes have not been adjusted for multiple comparisons and, therefore, no conclusions can be drawn from these analyses. Overall disability and disabling stroke were analyzed with the use of a logistic regression



model, with treatment group, history of stroke, and baseline NIHSS score as explanatory variables.

For the secondary outcome of disability, patients with a missing modified Rankin scale score or with missing covariates (baseline NIHSS score and history of stroke) were excluded from the analysis. Patients who died before visit 3 were assigned a modified Rankin scale score of 6 (death), and data were not considered to be missing. A prespecified sensitivity analysis was performed with missing modified Rankin scale scores imputed as scores of greater than 1.

RESULTS

PATIENTS

Between January 22, 2018, and October 7, 2019, a total of 11,073 patients were enrolled, of whom 11,016 underwent randomization (5523 to ticagrelor plus aspirin and 5493 to placebo plus as-

pirin) (Fig. 1). A total of 15 patients withdrew consent during the trial, and 13 of them withdrew during the treatment period; vital status at end of the trial was ascertained for all these patients. One patient was lost to follow-up. Overall, 0.2% of the patients had incomplete follow-up for the primary outcome, and data on disability were missing in 2.7%. Baseline characteristics were similar in the two groups (Table 1). Most patients (91%) presented with ischemic stroke, and 9% presented with TIA. The mean age of the patients was 65 years, and 39% were women. Thirteen percent of the patients were taking aspirin before the initial index stroke or TIA.

During the treatment period, 74% of the patients received an antihypertensive agent, 83% received a statin, and 28% received a glucose-lowering agent. Overall, 99.5% of the patients took aspirin during the treatment period, and 97% received doses of 100 mg per day or less.

Table 2. Efficacy and Safety Outcomes.*

Outcome	Ticagrelor-Aspirin Group (N=5523)		Aspirin Group (N=5493)		Hazard Ratio (95% CI)	P Value
	Patients with Event	Event Rate†	Patients with Event	Event Rate†		
	no. (%)	%	no. (%)	%		
Primary outcome						
Stroke or death	303 (5.5)	5.4	362 (6.6)	6.5	0.83 (0.71–0.96)	0.02
Stroke	284 (5.1)	5.1	347 (6.3)	6.3	0.81 (0.69–0.95)	
Death	36 (0.7)	0.6	27 (0.5)	0.5	1.33 (0.81–2.19)	
Secondary outcomes						
Ischemic stroke	276 (5.0)	5.0	345 (6.3)	6.2	0.79 (0.68–0.93)	0.004
Overall disability‡	1282 (23.8)	NA	1284 (24.1)	NA	0.98 (0.89–1.07)	0.61
Safety outcomes						
Severe bleeding	28 (0.5)	0.5	7 (0.1)	0.1	3.99 (1.74–9.14)	0.001
Intracranial hemorrhage or fatal bleeding	22 (0.4)	0.4	6 (0.1)	0.1	3.66 (1.48–9.02)	0.005
Fatal bleeding	11 (0.2)		2 (<0.1)			
Intracranial hemorrhage	20 (0.4)	0.4	6 (0.1)	0.1	3.33 (1.34–8.28)	0.01
Hemorrhagic stroke	10 (0.2)		2 (<0.1)			
Moderate or severe bleeding	36 (0.7)	0.6	11 (0.2)	0.2	3.27 (1.67–6.43)	<0.001
Premature permanent discontinuation of trial treatment owing to bleeding	152 (2.8)	2.9	32 (0.6)	0.6	4.80 (3.28–7.02)	<0.001

* NA denotes not applicable.

† Event rates are Kaplan-Meier estimates of the percentage of patients with events.

‡ Overall disability was determined by a score greater than 1 on the modified Rankin scale. The odds ratio is shown rather than the hazard ratio (5386 patients in the ticagrelor-aspirin group and 5333 patients in the aspirin group).

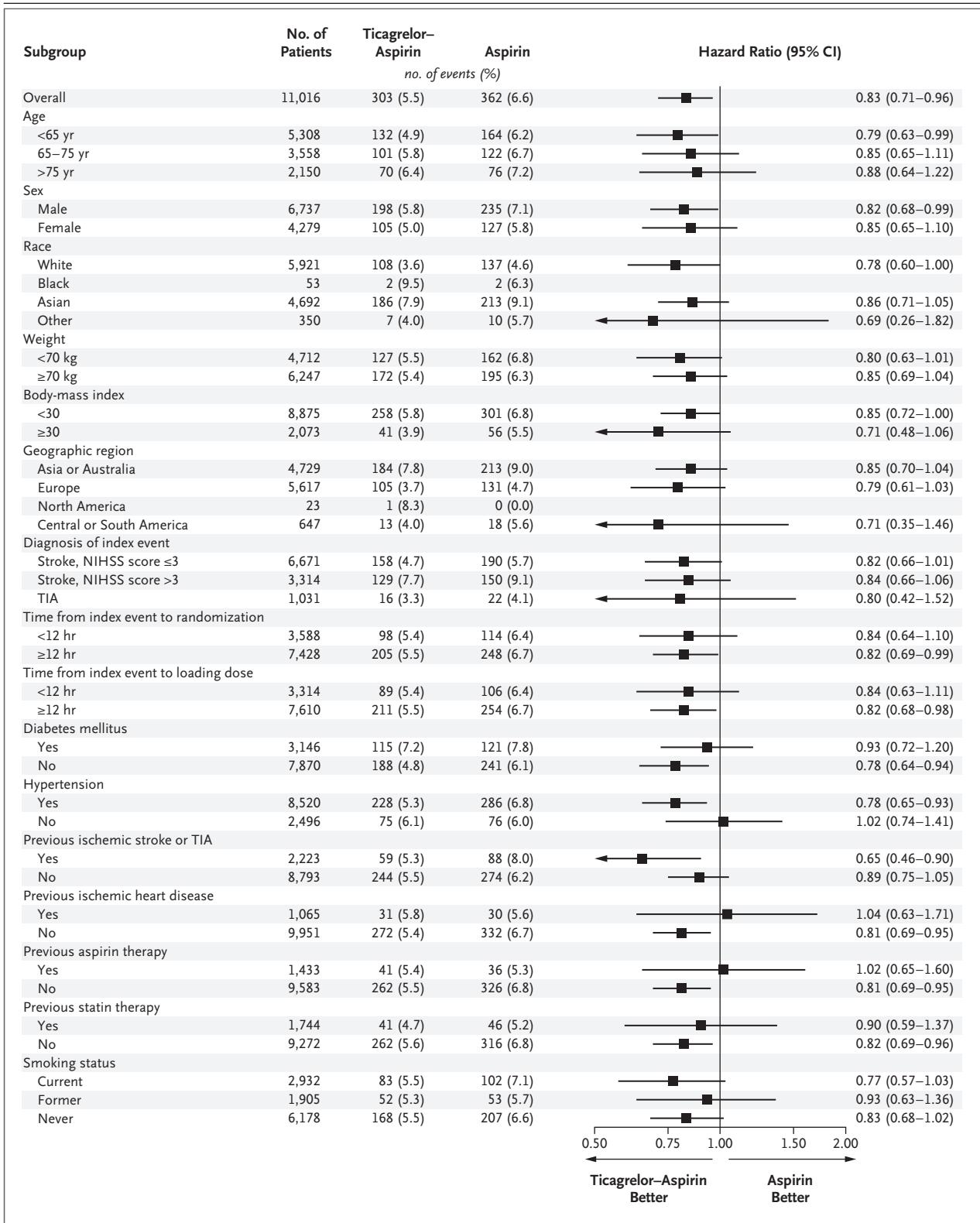


Figure 3 (facing page). Hazard Ratio for the Primary Outcome, According to Prespecified Subgroups.

Race was determined by patient report. The body-mass index 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. TIA denotes transient ischemic attack.

OUTCOMES

A primary-outcome event occurred in 303 patients in the ticagrelor–aspirin group (5.5%) and in 362 patients in the aspirin group (6.6%) (hazard ratio, 0.83; 95% confidence interval [CI], 0.71 to 0.96; $P=0.02$) (Fig. 2A and Table 2); the proportional-hazards assumption was met. The first secondary outcome, subsequent ischemic stroke, occurred in 276 patients in the ticagrelor–aspirin group (5.0%) and in 345 patients in the aspirin group (6.3%) (hazard ratio, 0.79; 95% CI, 0.68 to 0.93; $P=0.004$) (Table 2). The other secondary outcome of overall disability (score >1 on the modified Rankin scale) occurred in 23.8% of the patients in the ticagrelor–aspirin group and in 24.1% of the patients in the aspirin group (odds ratio, 0.98; 95% CI, 0.89 to 1.07; $P=0.61$). A sensitivity analysis for missing data showed similar results for the primary outcome (hazard ratio, 0.83; 95% CI, 0.71 to 0.97). The incidence of overall disability (modified Rankin scale score >1) did not differ significantly between the two treatment groups; the exploratory outcome of disabling stroke (modified Rankin scale score >2) occurred in 2.7% of the patients in the ticagrelor–aspirin group and in 3.5% of the patients in the aspirin group. The results of subgroup analyses are shown in Figure 3. The results of the on-treatment analysis of efficacy were consistent with those of the primary analysis (Table S3 in the Supplementary Appendix).

SAFETY

Severe bleeding, as defined according to the GUSTO criteria (the primary safety outcome event), occurred in 28 patients (0.5%) in the ticagrelor–aspirin group and in 7 patients (0.1%) in the aspirin group (hazard ratio 3.99; 95% CI, 1.74 to 9.14; $P=0.001$) (Fig. 2B and Table 2). A composite outcome event of intracranial hemorrhage or fatal bleeding occurred in 22 patients (0.4%) in the ticagrelor–aspirin group and in 6 patients

(0.1%) in the aspirin group (Table 2). Intracranial hemorrhage occurred in 20 patients (0.4%) in the ticagrelor–aspirin group and in 6 (0.1%) in the aspirin group; 1 additional patient in the ticagrelor–aspirin group had a fatal hemorrhagic stroke that was recorded in the bleeding-event form as a severe bleeding event and a fatal bleeding event but not as an intracranial hemorrhage. Fatal bleeding occurred in 11 patients (0.2%) in the ticagrelor–aspirin group and in 2 patients ($<0.1\%$) in the aspirin group.

Permanent discontinuation of the trial treatment owing to bleeding occurred in 152 patients in the ticagrelor–aspirin group (2.8%) and in 32 patients in the aspirin group (0.6%). Discontinuation of the trial treatment because of dyspnea occurred in 1.0% and 0.2% of the patients in the ticagrelor–aspirin group and the aspirin group, respectively. Bleeding events and dyspnea accounted for the entire between-group difference in discontinuations from the trial treatment. Serious adverse events and adverse events leading to discontinuation of a trial treatment are presented in Tables S1 and S2. The results of an on-treatment analysis of safety were consistent with those of the primary intention-to-treat analysis.

DISCUSSION

In this international randomized trial, patients with mild-to-moderate acute ischemic stroke (NIHSS score ≤ 5) or high-risk TIA who were assigned within 24 hours after symptom onset to receive 30-day treatment with ticagrelor–aspirin had a lower risk of stroke or death at 30 days than those who were assigned to receive aspirin alone. A benefit was observed with ticagrelor–aspirin with respect to the incidence of the secondary outcome of subsequent ischemic stroke, which was lower than with aspirin alone; however, a benefit was not observed with respect to the incidence of overall disability, which was defined by a modified Rankin scale score of greater than 1 (signifying more than minimal disability). Ticagrelor–aspirin was associated with higher risks of severe hemorrhage and cerebral hemorrhage than aspirin alone. The benefit from treatment with ticagrelor–aspirin as compared with aspirin alone would be expected to result in a number needed to treat of 92 to prevent one

primary-outcome event and a number needed to harm of 263 for severe bleeding.

The results of this trial are similar to those in the Platelet-Oriented Inhibition in New TIA and Minor Ischemic Stroke (POINT) trial and the Clopidogrel in High-Risk Patients with Acute Nondisabling Cerebrovascular Events (CHANCE) trial, which compared clopidogrel–aspirin with aspirin alone in patients with acute minor stroke and TIA.^{5,6} In the POINT trial, which involved an international population of patients who received 90-day treatment within 12 hours after an acute ischemic stroke or TIA, the incidence of major ischemic events (ischemic stroke, myocardial infarction, or death from an ischemic vascular event) was 5.0% among patients who received clopidogrel–aspirin and 6.5% among those who received aspirin alone.⁶ In the CHANCE trial, the risk of stroke recurrence among Chinese patients who were treated within 24 hours after a minor ischemic stroke or TIA was 8.2% among those who received a clopidogrel-based regimen (clopidogrel–aspirin for 21 days, followed by clopidogrel alone through day 90) and 11.7% among those who received aspirin alone.⁵ Differences in patient populations and outcome definitions prevent comparisons of the results of these trials with those of the current THALES trial. Generalizability of the results of the current trial is limited by the exclusion of patients who had more severe strokes (NIHSS score >5), had a cardioembolic stroke, or had initiation of treatment more than 24 hours after symptom onset or who underwent or planned to undergo thrombolysis or thrombectomy.

In the THALES trial, similar to the POINT

trial,⁶ an absolute increase in the risk of severe hemorrhage was observed, although there were a small number of events. At variance with the observations in the THALES and POINT trials, no increase in the incidence of moderate-to-severe hemorrhage was reported in the CHANCE trial.⁵

In conclusion, among patients with mild-to-moderate ischemic stroke or high-risk TIA who received a combination of ticagrelor and aspirin, the risk of stroke or death (the composite primary outcome) was lower than that among patients who received aspirin alone. The incidence of overall disability was similar in the two groups, and the risk of severe hemorrhage was higher among patients who received ticagrelor–aspirin than among those who received aspirin alone during a 30-day treatment period.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

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