

ORIGINAL ARTICLE

Clopidogrel with Aspirin in Acute Minor Stroke or Transient Ischemic Attack

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ABSTRACT

BACKGROUND

Stroke is common during the first few weeks after a transient ischemic attack (TIA) or minor ischemic stroke. Combination therapy with clopidogrel and aspirin may provide greater protection against subsequent stroke than aspirin alone.

METHODS

In a randomized, double-blind, placebo-controlled trial conducted at 114 centers in China, we randomly assigned 5170 patients within 24 hours after the onset of minor ischemic stroke or high-risk TIA to combination therapy with clopidogrel and aspirin (clopidogrel at an initial dose of 300 mg, followed by 75 mg per day for 90 days, plus aspirin at a dose of 75 mg per day for the first 21 days) or to placebo plus aspirin (75 mg per day for 90 days). All participants received open-label aspirin at a clinician-determined dose of 75 to 300 mg on day 1. The primary outcome was stroke (ischemic or hemorrhagic) during 90 days of follow-up in an intention-to-treat analysis. Treatment differences were assessed with the use of a Cox proportional-hazards model, with study center as a random effect.

RESULTS

Stroke occurred in 8.2% of patients in the clopidogrel–aspirin group, as compared with 11.7% of those in the aspirin group (hazard ratio, 0.68; 95% confidence interval, 0.57 to 0.81; $P < 0.001$). Moderate or severe hemorrhage occurred in seven patients (0.3%) in the clopidogrel–aspirin group and in eight (0.3%) in the aspirin group ($P = 0.73$); the rate of hemorrhagic stroke was 0.3% in each group.

CONCLUSIONS

Among patients with TIA or minor stroke who can be treated within 24 hours after the onset of symptoms, the combination of clopidogrel and aspirin is superior to aspirin alone for reducing the risk of stroke in the first 90 days and does not increase the risk of hemorrhage. (Funded by the Ministry of Science and Technology of the People's Republic of China; CHANCE ClinicalTrials.gov number, NCT00979589.)

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TRANSIENT ISCHEMIC ATTACK (TIA) AND acute minor ischemic stroke are common and often lead to disabling events. In China, there are approximately 3 million new strokes every year, and approximately 30% of them are minor ischemic strokes.^{1,2} The incidence of TIA in China has not been determined, but on the basis of the incidence in other countries, there are probably more than 2 million TIAs annually in China.³⁻⁵ The risk of another stroke occurring after a TIA or minor stroke is high, with approximately 10 to 20% of patients having a stroke within 3 months after the index event; most of these strokes occur within the first 2 days.⁵⁻⁸

The role of antiplatelet therapy for secondary stroke prevention has been well established. However, aspirin is the only antiplatelet agent that has been studied in the acute phase of stroke, during which its benefit is modest.^{9,10} Aspirin and clopidogrel synergistically inhibit platelet aggregation,^{11,12} and such dual therapy reduces the risk of recurrent ischemic events in patients with the acute coronary syndrome.^{13,14} Large-scale trials of secondary prevention of ischemic events after stroke have not shown a benefit of the combination of clopidogrel and aspirin.¹⁵⁻¹⁷ However, these trials did not study the early, high-risk period after stroke, they included some patients with strokes of moderate severity, and they included few if any patients with TIA. Three small pilot trials have shown trends toward a benefit of the combination therapy and minimal safety concerns in patients with minor stroke or TIA.¹⁸⁻²⁰

We conducted the Clopidogrel in High-Risk Patients with Acute Nondisabling Cerebrovascular Events (CHANCE) trial to test the hypothesis that 3 months of treatment with a combination of clopidogrel and aspirin would reduce the risk of recurrent stroke, as compared with aspirin alone, among patients with acute high-risk TIA or minor ischemic stroke.

METHODS

STUDY OVERSIGHT

We conducted this study according to the protocol and statistical analysis plan, which are available with the full text of this article at NEJM.org. The trial was designed by three of the authors and was overseen by the executive committee, which had full access to the data. Data collection and en-

try were performed by staff at the Tiantan Clinical Trial and Research Center for Stroke, where the data analysis was performed. One of the authors had full access to an independent database for any questions regarding the analyses. All members of the writing committee contributed to and approved an earlier draft of this manuscript, which was prepared without professional editorial assistance. The first and last authors made the decision to submit the manuscript for publication. All the authors assume responsibility for the accuracy and completeness of the data and the fidelity of this report to the study protocol. There was no confidentiality agreement between the study sponsor (the Ministry of Science and Technology of the People's Republic of China) and the investigators. There was no commercial support for this study.

All the participants or their legal proxies provided written informed consent. The CHANCE protocol was approved by the ethics committee at each study center. Clopidogrel and the matching placebo were purchased from Sanofi-Aventis, which had no other role in the study.

STUDY POPULATION

Patients who met the following inclusion criteria were eligible: age of 40 years or older; diagnosis of an acute minor ischemic stroke or TIA; and ability to start the study drug within 24 hours after symptom onset, which was defined as the point at which the patient reported no longer being in a normal condition. Acute minor stroke was defined by a score of 3 or less at the time of randomization on the National Institutes of Health Stroke Scale (NIHSS; scores range from 0 to 42, with higher scores indicating greater deficits). TIA was defined as focal brain ischemia with resolution of symptoms within 24 hours after onset plus a moderate-to-high risk of stroke recurrence (defined as a score of ≥ 4 at the time of randomization on the ABCD,² which assesses the risk of stroke on the basis of age, blood pressure, clinical features, duration of TIA, and presence or absence of diabetes; scores range from 0 to 7, with higher scores indicating greater short-term risk).

All patients with possible clinical neurologic events during the follow-up period underwent computed tomography (CT) or magnetic resonance imaging (MRI) of the head. Patients were excluded if they had any of the following: hemorrhage;

other conditions, such as vascular malformation, tumor, abscess, or other major nonischemic brain disease; isolated sensory symptoms (e.g., numbness), isolated visual changes, or isolated dizziness or vertigo without evidence of acute infarction on baseline CT or MRI of the head; a score of more than 2 on the modified Rankin scale (scores range from 0 [no symptoms] to 6 [death]) immediately before the occurrence of the index ischemic stroke or TIA, indicating moderate disability or worse at baseline; an NIHSS score of 4 or more at randomization; a clear indication for anticoagulation therapy (presumed cardiac source of embolus, such as atrial fibrillation or prosthetic cardiac valve) or a contraindication to clopidogrel or aspirin; history of intracranial hemorrhage; anticipated requirement for long-term nonstudy antiplatelet drugs or for nonsteroidal antiinflammatory drugs affecting platelet function; heparin therapy or oral anticoagulation therapy within 10 days before randomization; gastrointestinal bleeding or major surgery within the previous 3 months; planned or probable revascularization (any angioplasty or vascular surgery) within 3 months after screening (if clinically indicated, vascular imaging was to be performed before randomization, whenever possible); planned surgery or interventional treatment requiring cessation of the study drug; TIA or minor stroke caused by angiography or surgery; or severe noncardiovascular coexisting condition, with a life expectancy of less than 3 months. Women of childbearing age who were not practicing reliable contraception and did not have a documented negative pregnancy test and patients receiving other investigational drugs or devices were also excluded (see Table S1 in the Supplementary Appendix, available at NEJM.org). No patients included in the study were treated with thrombolysis around the time of randomization.

STUDY DESIGN

CHANCE was a randomized, double-blind, placebo-controlled clinical trial conducted at 114 clinical centers in China; details of the rationale for the study and its design have been published previously.²¹ Patients meeting the enrollment criteria were randomly assigned to one of the two treatment groups with the use of a double-blind, double-dummy design. The site investigator called into an automated system that randomly assigned

a number corresponding to a medication kit stored at the study site, and the medication in the kit was administered to the patient.

Both groups received open-label aspirin on day 1 (with the dose ranging from 75 to 300 mg, at the discretion of the treating physician). Patients randomly assigned to the clopidogrel–aspirin group received a loading dose of 300 mg of clopidogrel on day 1, followed by a dose of 75 mg per day on days 2 through 90, aspirin at a dose of 75 mg per day on days 2 through 21, and placebo aspirin on days 22 through 90. Patients randomly assigned to the aspirin group received a placebo version of clopidogrel on days 1 through 90 and aspirin at a dose of 75 mg per day on days 2 through 90. Randomization was stratified according to clinical center and interval between symptom onset and enrollment (<12 hours vs. 12 to 24 hours). The primary objective was to assess the effects of the two treatment regimens on the incidence of stroke in the first 90 days after acute minor stroke or high-risk TIA.

STUDY OUTCOMES

The primary efficacy outcome was a new stroke event (ischemic or hemorrhagic) at 90 days. Ischemic stroke was defined as an acute focal infarction of the brain or retina with one of the following: sudden onset of a new focal neurologic deficit, with clinical or imaging evidence of infarction lasting 24 hours or more and not attributable to a nonischemic cause (i.e., not associated with brain infection, trauma, tumor, seizure, severe metabolic disease, or degenerative neurologic disease); a new focal neurologic deficit lasting for less than 24 hours and not attributable to a nonischemic cause but accompanied by neuroimaging evidence of new brain infarction; or rapid worsening of an existing focal neurologic deficit lasting more than 24 hours and not attributable to a nonischemic cause, accompanied by new ischemic changes on MRI or CT of the brain and clearly distinct from the index ischemic event. Hemorrhagic stroke was defined as acute extravasation of blood into the brain parenchyma or subarachnoid space with associated neurologic symptoms. Recurrent stroke was considered to be disabling if the score on the modified Rankin scale was 2 or more.

The primary safety outcome was a moderate-to-severe bleeding event, according to the Global Utilization of Streptokinase and Tissue Plasmino-

gen Activator for Occluded Coronary Arteries (GUSTO) definition.²² Severe hemorrhage was defined as fatal or intracranial hemorrhage or other hemorrhage causing hemodynamic compromise that required blood or fluid replacement, inotropic support, or surgical intervention. Moderate hemorrhage was defined as bleeding that required transfusion of blood but did not lead to hemodynamic compromise requiring intervention.²²

Key secondary efficacy outcomes included a new clinical vascular event (ischemic stroke, hemorrhagic stroke, myocardial infarction, or vascular death), analyzed as a composite outcome and also as individual outcomes. Vascular death was defined as death due to stroke (ischemic or hemorrhagic), systemic hemorrhage, myocardial infarction, congestive heart failure, pulmonary embolism, sudden death, or arrhythmia. Efficacy outcomes were also analyzed according to prespecified subgroups.

All reported efficacy and safety outcomes were confirmed by a central adjudication committee that was unaware of the study-group assignments. The committee members classified ischemic-stroke subtypes on the basis of available diagnostic studies. A data and safety monitoring board whose members were selected by the sponsor was in place to ensure the safety of patients during the study, with predetermined periodic assessments of safety and stopping rules.

STATISTICAL ANALYSIS

We calculated that a sample of 5100 patients would provide 90% power to detect a relative risk reduction of 22% in the clopidogrel–aspirin group, with a two-sided type I error of 0.05, assuming an event rate of 14% in the aspirin group and a 5% overall rate of withdrawal (defined as medication nonadherence).²¹

No patient withdrew between the time of randomization and the administration of the first dose of study medication; all analyses were based on the population of patients who underwent randomization. We compared the baseline characteristics of the patients in the two study groups. Proportions were used for categorical variables, and medians with interquartile ranges were used for continuous variables. Time to randomization was calculated as a group mean. Differences between study groups in the rate of stroke (ischemic or hemorrhagic) during the 90-

day follow-up period were assessed with the use of a Cox proportional-hazards model, with pooled study centers (≥ 20 patients) as a random effect.

Hazard ratios with 95% confidence intervals are reported. When there were multiple events of the same type, the time to the first event was used in the model. Data from patients who had no events during the study were censored at the time of study termination or death. We used this approach to maximize the time-dependent information in the trial while maintaining the ease of interpretation of risks. For each model, the proportional-hazards assumption was assessed by testing the interaction between treatment and time. In addition, we assessed whether the treatment effect differed in certain prespecified subgroups by testing the treatment-by-subgroup interaction effect with the use of Cox models. All tests were two-sided, and a P value of 0.05 was considered to indicate statistical significance. All statistical analyses were performed with the use of SAS software, version 9.0 (SAS Institute).

RESULTS

STUDY PATIENTS AND FOLLOW-UP

Between October 2009 and July 2012, a total of 41,561 patients with stroke or TIA were screened at 114 clinical sites; 5170 patients were enrolled, with 2584 randomly assigned to the clopidogrel–aspirin group and 2586 to the aspirin group. The most common reasons for exclusion were delayed presentation (26.4% of screened patients); moderate or severe stroke (10.4%); intracranial hemorrhage (7.0%); low-risk TIA, defined as a score of <4 on the ABCD² (6.5%); or contraindication to clopidogrel or aspirin (6.0%) (Fig. S3 in the Supplementary Appendix). The two groups were well balanced regarding baseline characteristics (Table 1).

The median age was 62 years, and 33.8% of the patients were women. A total of 65.7% of the patients had a history of hypertension, 21.1% had diabetes, and 43.0% were current or former smokers. The median time from the onset of the qualifying minor stroke or TIA to randomization was 13 hours. The index event was a TIA in 1445 patients (27.9%). A total of 36 patients (0.7%) — 20 in the clopidogrel–aspirin group and 16 in the aspirin group — were lost to follow-up; 165 patients (6.4%) in the clopidogrel–aspirin group and 146 (5.6%) in the aspirin group discontinued the study medication before

the end of the study (Fig. S3 in the Supplementary Appendix).

PRIMARY OUTCOME

Stroke occurred in 212 patients (8.2%) in the clopidogrel–aspirin group, as compared with 303 patients (11.7%) in the aspirin group (hazard ratio, 0.68; 95% confidence interval [CI], 0.57 to 0.81; $P<0.001$) (Table 2 and Fig. 1). Fatal or disabling stroke occurred in 135 patients (5.2%) in the clopidogrel–aspirin group and in 177 (6.8%) in the aspirin group (hazard ratio, 0.75; 95% CI, 0.60 to 0.94; $P=0.01$). Ischemic stroke occurred in 204 patients (7.9%) in the clopidogrel–aspirin group and in 295 (11.4%) in the aspirin group (hazard ratio, 0.67; 95% CI, 0.56 to 0.81; $P<0.001$). Hemorrhagic stroke occurred in 8 patients in each of the two study groups (0.3% of each group).

KEY SECONDARY AND OTHER EFFICACY OUTCOMES

The composite outcome of vascular events occurred in 216 patients (8.4%) in the clopidogrel–aspirin group, as compared with 307 patients (11.9%) in the aspirin group (hazard ratio, 0.69; 95% CI, 0.58 to 0.82; $P<0.001$) (Table 2, and Fig. S4 in the Supplementary Appendix). Death from any cause occurred in 0.4% of the patients in each group. Vascular death (including death from hemorrhagic stroke) occurred in 6 patients (0.2%) in the clopidogrel–aspirin group and in 5 (0.2%) in the aspirin group. TIA occurred in 39 patients (1.5%) in the clopidogrel–aspirin group and in 47 (1.8%) in the aspirin group ($P=0.36$).

BLEEDING EVENTS

Moderate or severe hemorrhage, as defined by means of the GUSTO criteria, occurred in seven patients (0.3%) in the clopidogrel–aspirin group and in eight (0.3%) in the aspirin group ($P=0.73$) (Table 2). The rate of any bleeding event was 2.3% in the clopidogrel–aspirin group as compared with 1.6% in the aspirin group (hazard ratio, 1.41; 95% CI, 0.95 to 2.10; $P=0.09$) (Table 2).

SUBGROUPS

The reduction in the rate of stroke and combined secondary vascular events with clopidogrel and aspirin was consistent across all major subgroups (Fig. 2, and Fig. S5 in the Supplementary Appendix). There were no significant interactions in any of the 11 predefined subgroups ($P>0.10$ for all comparisons).

Table 1. Baseline Characteristics of the Patients.*

Characteristic	Aspirin (N = 2586)	Clopidogrel and Aspirin (N = 2584)
Age — yr		
Median	62	63
Interquartile range	54–71	55–72
Female sex — no. (%)	898 (34.7)	852 (33.0)
Systolic pressure — mm Hg		
Median	150	150
Interquartile range	136–161	136–161
Diastolic pressure — mm Hg		
Median	90	90
Interquartile range	80–100	80–98
Body-mass index†		
Median	25	25
Interquartile range	23–27	23–26
Medical history — no. (%)		
Ischemic stroke	517 (20.0)	516 (20.0)
TIA	80 (3.1)	94 (3.6)
Myocardial infarction	53 (2.0)	43 (1.7)
Angina	87 (3.4)	97 (3.8)
Congestive heart failure	38 (1.5)	42 (1.6)
Known atrial fibrillation or flutter	48 (1.9)	48 (1.9)
Valvular heart disease	10 (0.4)	4 (0.2)
Hypertension	1683 (65.1)	1716 (66.4)
Diabetes mellitus	543 (21.0)	550 (21.3)
Hypercholesterolemia	283 (10.9)	290 (11.2)
Pulmonary embolism	1 (<0.1)	0
Current or previous smoking — no. (%)	1105 (42.7)	1116 (43.2)
Mean time to randomization — hr	13	13
Time to randomization — no. (%)		
<12 hr	1280 (49.5)	1293 (50.0)
≥12 hr	1306 (50.5)	1291 (50.0)
Qualifying event — no. (%)		
TIA	728 (28.2)	717 (27.7)
Minor stroke	1858 (71.8)	1867 (72.3)
ABCD ² score‡		
Median	4	4
Interquartile range	4–5	4–5

* There were no significant differences between the treatment groups for any characteristic. Additional baseline characteristics are reported in Table S2 in the Supplementary Appendix. TIA denotes transient ischemic attack.

† The body-mass index is the weight in kilograms divided by the square of the height in meters.

‡ Data are only for the 1445 patients who had a TIA. The ABCD² assesses the risk of stroke on the basis of age, blood pressure, clinical features, duration of TIA, and presence or absence of diabetes, with scores ranging from 0 to 7 and higher scores indicating greater short-term risk.

Table 2. Efficacy and Safety Outcomes.

Outcome	Aspirin (N=2586)		Clopidogrel and Aspirin (N=2584)		Hazard Ratio (95% CI)	P Value
	Patients with Event <i>no.</i>	Event Rate %	Patients with Event <i>no.</i>	Event Rate %		
Primary outcome						
Stroke	303	11.7	212	8.2	0.68 (0.57–0.81)	<0.001
Secondary outcomes						
Stroke, myocardial infarction, or death from cardiovascular causes	307	11.9	216	8.4	0.69 (0.58–0.82)	<0.001
Ischemic stroke	295	11.4	204	7.9	0.67 (0.56–0.81)	<0.001
Hemorrhagic stroke	8	0.3	8	0.3	1.01 (0.38–2.70)	0.98
Myocardial infarction	2	0.1	3	0.1	1.44 (0.24–8.63)	0.69
Death from cardiovascular causes	5	0.2	6	0.2	1.16 (0.35–3.79)	0.81
Death from any cause	10	0.4	10	0.4	0.97 (0.40–2.33)	0.94
Transient ischemic attack	47	1.8	39	1.5	0.82 (0.53–1.26)	0.36
Safety outcomes						
Bleeding*						
Severe	4	0.2	4	0.2	0.94 (0.24–3.79)	0.94
Moderate	4	0.2	3	0.1	0.73 (0.16–3.26)	0.68
Mild	19	0.7	30	1.2	1.57 (0.88–2.79)	0.12
Any bleeding	41	1.6	60	2.3	1.41 (0.95–2.10)	0.09

* Bleeding events were defined according to the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries criteria as follows: severe bleeding was defined as fatal or intracranial hemorrhage or other hemorrhage causing hemodynamic compromise that required blood or fluid replacement, inotropic support, or surgical intervention; moderate bleeding as bleeding that required transfusion of blood but did not lead to hemodynamic compromise requiring intervention; and mild bleeding as bleeding not requiring transfusion and not causing hemodynamic compromise (e.g., subcutaneous bleeding, mild hematomas, and oozing from puncture sites).²²

SAFETY

Adverse events occurred in similar proportions of patients in the two groups (5.8% in the clopidogrel–aspirin group and 5.0% in the aspirin group). The proportions of patients with serious adverse events were also similar (1.0% and 0.8% in the clopidogrel–aspirin and aspirin groups, respectively) (Table S4 in the Supplementary Appendix).

DISCUSSION

In this large-scale trial involving patients with high-risk TIA or minor ischemic stroke, we found that the addition of clopidogrel to aspirin within 24 hours after symptom onset reduced the risk of subsequent stroke by 32.0%, as compared with

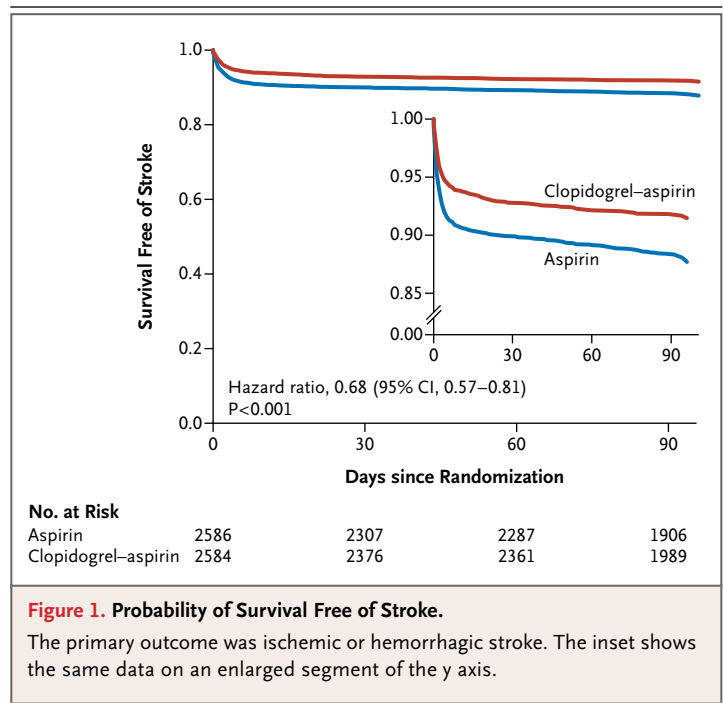
aspirin alone. Event rates during this early period were very high, and clopidogrel was associated with an absolute risk reduction of 3.5 percentage points, equivalent to a number needed to treat of 29 patients to prevent one stroke over a period of 90 days. Combination therapy with clopidogrel and aspirin, as compared with aspirin alone, was not associated with an increased incidence of hemorrhage, although there was a worrisome trend in overall bleeding toward more events with the combination therapy.

The results of our trial differ from those of other trials of combination therapy with clopidogrel and aspirin after cerebral ischemic events.^{7,8,17} One possible explanation is that, unlike previous trials, our trial targeted a population at particularly high risk for recur-

rent ischemia and at low risk for hemorrhage. Previous trials included patients with more severe strokes than our trial did, and they did not enroll patients in the first hours after an index minor stroke or TIA, during which the risk of recurrent ischemia is particularly high. This may explain why other trials did not show a reduction in the risk of ischemic events but did show an increased risk of hemorrhage.

In our study, the curves for survival free of stroke were particularly steep in the first few days, during which the curves representing the treatment groups diverged dramatically. Subsequently, the rates of stroke were similar. This suggests that the requirement for randomization within 24 hours after the onset of symptoms, with nearly half the patients enrolled within 12 hours (and treated shortly thereafter), was important. Although we did not see a relative difference in the efficacy outcome between patients randomly assigned to a study group within 12 hours and those assigned after a longer interval, absolute event rates were higher among those who were enrolled within 12 hours. In clinical practice, treatment with clopidogrel and aspirin as soon as possible after symptom onset is likely to produce the greatest absolute benefit, since ischemic event rates are highest in the initial hours after symptoms appear.

Our trial was conducted entirely in China, a country with approximately 150 to 250 deaths from stroke per 100,000 persons per year, which is five times as high as the rate in the United States.²³ Although diagnostic tools and therapies commonly used in the United States and Europe are available in most hospitals in China, some patients cannot afford this level of care.^{24,25} Secondary prevention practices are also less rigorous in China, where rates of treatment of hypertension, diabetes, and hyperlipidemia are low, as shown in our study population (Table S3 in the Supplementary Appendix). Furthermore, the distribution of stroke subtypes in China differs from that in more developed countries; China has a higher incidence of large-artery intracranial atherosclerosis²⁵ and a higher prevalence of genetic polymorphisms that affect the metabolism of clopidogrel.²⁶ The Platelet-Oriented Inhibition in New TIA and Minor Ischemic Stroke (POINT)



trial (ClinicalTrials.gov number, NCT00991029), sponsored by the National Institutes of Health, which is similar to our trial, is now enrolling patients at sites primarily in the United States.²⁷ The POINT trial is assessing a higher loading dose of clopidogrel (600 mg) and a narrower time window (treatment within 12 hours after symptom onset) than were used in our study.

Several common clinical conditions mimic TIA, including seizures, migraine, peripheral vertigo, syncope, and anxiety.²⁸ To minimize the risk of enrolling patients with TIA mimics, we excluded all patients with isolated sensory symptoms, isolated visual changes, or isolated dizziness or vertigo without evidence of acute infarction on baseline CT or MRI of the head. In addition, enrollment of patients with TIA was limited to those with a high ABCD² score (≥ 4) to increase the likelihood that spells were due to true TIAs and to ensure that we were enrolling patients who were at high risk for subsequent ischemic events.²⁹ The risk of subsequent stroke in the trial was high for this patient population, suggesting that our strategy was successful. Our findings may not apply to other populations of patients with ischemic events.

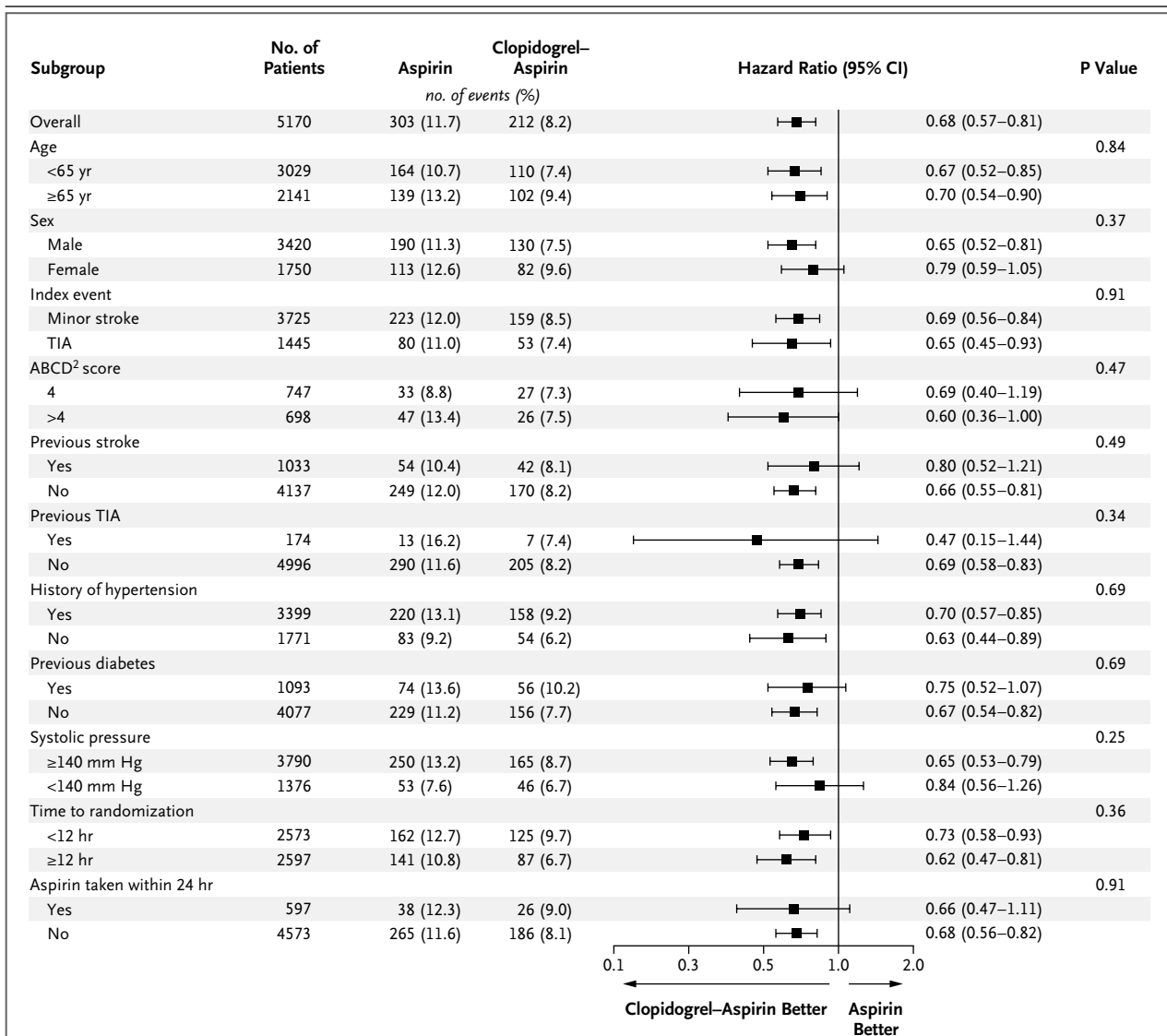


Figure 2. Hazard Ratio for the Primary Outcome in Prespecified Subgroups.

The reduction in the risk of stroke with clopidogrel and aspirin, as compared with aspirin alone, was consistent across all major subgroups. There were no significant interactions in any of the 11 predefined subgroups ($P>0.10$ for all comparisons). Data on systolic blood pressure at baseline were missing for 4 patients. The ABCD² assesses the risk of stroke on the basis of age, blood pressure, clinical features, duration of transient ischemic attack (TIA), and presence or absence of diabetes, with scores ranging from 0 to 7 and higher scores indicating greater short-term risk.

In conclusion, our study shows that among patients with high-risk TIA or minor ischemic stroke who are initially seen within 24 hours after symptom onset, treatment with clopidogrel plus aspirin for 21 days, followed by clopidogrel alone for a total of 90 days, is superior to aspirin alone in reducing the risk of subsequent stroke events. The combination of clopidogrel with as-

pirin did not cause more hemorrhagic events in this patient population than aspirin alone.

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No potential conflict of interest relevant to this article was reported.

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

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