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Dual Antiplatelet Treatment Up to 72 Hours After Ischemic Stroke

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This paper includes 54 characters in the title, 314 words in the abstract, 3097 words in the text, 25 references, 2 tables, 3 figures, 8 supplemental tables, and 2 supplemental figures.

Keywords

Stroke; Transient ischemic attack; Atherosclerosis; Clopidogrel

ABSTRACT

Background

Dual antiplatelet treatment has been shown to reduce recurrence of stroke compared to aspirin alone when initiated early after an acute stroke. The effect of clopidogrel and aspirin versus aspirin alone within 72 hours of acute cerebral ischemia from atherosclerosis has not been well studied.

Methods

We conducted a randomized, double-blind, placebo-controlled, 2-by-2 factorial trial in patients with mild ischemic stroke or high-risk transient ischemic attack (TIA) of presumed atherosclerotic cause, not receiving thrombolysis or thrombectomy in 222 hospitals in China. Patients were randomly assigned within 72 hours after symptom onset in a 1:1 ratio, to receive clopidogrel (300mg on day 1, 75mg daily on days 2-90) and aspirin (100-300mg on day1, 100mg daily on days 2-21), or clopidogrel placebo and aspirin (100-300mg on day1, 100mg daily on days 2-90). There was no interaction between this component of the factorial trial design trial and a second part that tested immediate vs delayed stain treatment and is reported separately. The primary efficacy outcome was a new stroke, and the primary safety outcome was moderate-to-severe bleeding, both within 90 days.

Results

A total of 6100 patients were enrolled, 3050 assigned to each trial group. The qualifying event for enrollment was TIA in 13%. Approximately 13% of patients were assigned to a treatment group within 24 hours and 87% were assigned between 24 and 72 hours of onset of stroke. A new stroke occurred in 222 (7.3%) in the clopidogrel-aspirin group, and 279

(9.2%) in the aspirin group (hazard ratio, 0.79; 95% confidence interval [CI], 0.66-0.94; P=0.008). Moderate-to-severe bleeding occurred in 27 (0.9%) and 13 patients (0.4%), respectively (hazard ratio, 2.08; 95% CI, 1.07-4.04, P=0.03).

Conclusions

Among patients with mild ischemic stroke or high-risk TIA of presumed atherosclerotic cause, combined clopidogrel-aspirin initiated within 72 hours of onset was superior to aspirin alone in reducing the risk of new stroke at 90 days but was associated with a low but increased risk of moderate-to-severe bleeding.

(Funded by 'National Ten-Thousand Talent Plan'- Leadership of Scientific and Technological Innovation, and others; INSPIRES ClinicalTrials.gov number, NCT03635749.)

INTRODUCTION

Patients with acute mild ischemic stroke or transient ischemic attack (TIA) have a risk of recurrent stroke of approximately 5%-10% within 90 days.[1] Guidelines recommend dual antiplatelet therapy (DAPT) with clopidogrel combined with aspirin for patients who can be treated within 24 hours and who have a minor ischemic stroke with a National Institutes of Health Stroke Scale (NIHSS) score of 3 or less and can be treated within 24 hours.[2] The 24 hour time window and low NIHSS scores limit the application of DAPT in stroke.

A time course analyses of the Platelet-Oriented Inhibition in New TIA and Minor Ischemic Stroke (POINT) trial has indicated that combined clopidogrel-aspirin might be beneficial in preventing recurrent stroke initiated as long as 3 days after stroke onset.[3] Meta-analyses have suggested the same for non-cardioembolic ischemic stroke or TIA.[4,5] In an exploratory analysis of the Acute Stroke or Transient Ischemic Attack Treated With Ticagrelor and Acetylsalicylic Acid for Prevention of Stroke and Death (THALES) trial, patients with mild ischemic stroke with an NIHSS score of 4 or 5 treated with ticagrelor and aspirin within 24 hours had a lower risk of subsequent stroke, compared to those treated with aspirin alone, with no increase in the risk of severe bleeding.[6] In addition, the effectiveness of DAPT potentially varies depending on the pathogenesis of ischemic stroke particularly large artery atherosclerotic stenosis or multiple acute infarctions that might benefit from dual treatment.[1,7-11]

In this Intensive Statin and Antiplatelet Therapy for Acute High-risk Intracranial or Extracranial Atherosclerosis (INSPIRES) trial, we tested the hypotheses that DAPT with clopidogrel and aspirin initiated within 72 hours after onset would be superior to aspirin

alone in reducing the risk of new ischemic or hemorrhagic stroke in patients with mild ischemic stroke or high-risk TIA presumably caused by atherosclerosis (stenosis of extracranial or intracranial artery ipsilateral to the ischemic field) or multiple infarctions with non-stenotic atherosclerotic plaque ipsilateral to the ischemic field.

METHODS

Trial design and oversight

This randomized, double-blind, placebo-controlled, multicenter, 2-by-2 factorial trial was conducted at 222 sites in China. Results of the antiplatelet therapy arm are presented here and results of an arm comparing immediate atorvastatin to 3-day delayed statin treatment will be published separately. There was no interaction between the results of the two components of the factorial trial (p= 0.16). Details of the rationale, design, and methods of the trial have been described previously[12] and are provided in the protocol, available at NEJM.org along with the statistical analysis plan. The trial was approved by the ethics committees of Beijing Tiantan Hospital and all other participating sites. Before enrolment, patients or their representatives provided written informed consent. The trial was conducted in accordance with the principles laid down by the 18th World Medical Assembly International Council for Harmonisation Guidelines for Good Clinical Practice that have been established for Chinese trials.[13,14]

The steering committee was responsible for the design and conduct of the trial, interpretation of the data, and ensuring the integrity of the data, analysis, and presentation of results and the fidelity of the trial to the protocol. The Executive Committee collected

blinded data and provided guidance for the trial. An independent Data Safety and Monitoring Board monitored the progress of the trial on a regular basis to guarantee that the trial met ethical requirements and patient safety standards. An independent Clinical Event Adjudication Committee reviewed all clinical outcome events (including stroke, myocardial infarction, death and moderate to severe bleeding) and made final adjudications. The statistical and data management center of the China National Clinical Research Center for Neurological Diseases was responsible for statistical analysis. The Supplementary Appendix, available at NEJM, lists the committee members and investigators.

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Sanofi and Beijing Jialin Pharmaceuticals provided the trial drugs (clopidogrel and atorvastatin) and matched placebos; neither company was involved in the design, implementation, data analysis and interpretation of the study. No confidentiality agreements were in place between the authors and any commercial entity. The first authors, Y.G. and W.C., prepared the initial draft of the manuscript with input from all co-authors. The authors take responsibility for the completeness and accuracy of the data, adherence of the trial to the protocol, and the reporting of adverse events.

Patients

Patients were eligible if they were 35 to 80 years old; had a mild ischemic stroke with a score of 5 or less on the National Institutes of Health Stroke Scale, indicating mild stroke (NIHSS, range 0 to 42, with higher scores indicating more severe stroke) or high-risk TIA with a score of 4 or higher on the $ABCD^2$ score (risk score based on age, blood pressure, clinical features, duration of TIA, and the presence or absence of diabetes mellitus; range from 0 to 7, with higher scores indicating higher stroke risk) within 24-72 hours of onset,

or had an ischemic stroke (NIHSS score 4-5) within 24 hours of symptom onset; met at least one of the following imaging criteria: a. ≥50% stenosis of a major intracranial or extracranial artery confirmed by carotid duplex ultrasound or vascular imaging that likely accounted for the clinical presentation and cerebral infarction; b. acute new multiple infarctions documented by head CT or MRI (excluding previous infarcts) of presumed large-artery atherosclerosis origin, including with non-stenotic unstable plaque ipsilateral to the infarction. Patients with minor ischemic stroke (NIHSS score ≤3) or high-risk TIA ($ABCD^2$ score≥4) within 24 hours of ictus were included in the trial before the time that the American Heart Association (AHA) and the American Stroke Association (ASA) updated their recommendation in 2019 that DAPT be initiated within 24 hours of onset of ischemic stroke with (NIHSS score ≤3 due to non-cardioembolic causes. The protocol was amended at the time of that change to exclude patients who had strokes with NIHSS score ≤3 within the previous 24 hours. [2]

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Patients were ineligible to participate if they had received thrombolysis or endovascular therapy, an additional anticoagulant, defibrinogenation, or antiplatelet therapy except for clopidogrel and aspirin after the index event, as well as DAPT with aspirin and clopidogrel or intensive statin therapy within 2 weeks prior to randomization. Other key exclusion criteria were presumed cardioembolic TIA or ischemic stroke diagnosed by the investigators through medical history, ECG, echocardiography and other appropriate examinations, other determined etiology of ischemic stroke or TIA (e.g., aortic dissection and vasculitis), pre-existing disability with a score of 2 or higher on the modified Rankin Scale (range, from 0 to 6, with 0 to 1 indicating no disability, 2 to 5 increasing disability,

and 6 death). Individuals with a history of intracranial hemorrhage, or planned surgery or revascularization that would have necessitated discontinuation of the trial medications within the subsequent 90 days after randomization were not eligible. Further details are provided in the Protocol, available at NEJM.org.

Trial procedures

Eligible patients were randomly assigned in a 1:1 ratio within 72 hours of symptom onset to receive combined clopidogrel with aspirin or clopidogrel placebo plus aspirin. Random numbers generated centrally, corresponding to trial drug kits, were used for trial group assignment and block sizes of 8, stratified by center were used to balance trial groups numbers. Patients assigned to the clopidogrel-aspirin group received clopidogrel at a loading dose of 300mg on the first day, followed by 75mg daily for the next 89 days, plus aspirin at a dose of 100-300mg on the first day, then 100mg daily for days 2-21 and aspirin placebo for days 22-90. Patients in the aspirin group received clopidogrel placebo for 90 days combined with aspirin at a dose of 100-300mg on day 1, then 100mg daily for days 2-90.

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Patients received the initial dose of trial drugs as soon as feasible within 1 hour after being assigned to a trial group. Patients received standard care based on the latest American Heart Association/American Stroke Association guidelines and Chinese guidelines and were followed up for an additional 9 months after the 90-day randomized portion of the trial to collect data on outcomes and adverse events. [2,15,16]

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Outcomes

The primary outcome was any new stroke (ischemic or hemorrhagic) within 90 days. The

secondary efficacy outcomes were a composite of vascular events (stroke, myocardial infarction, or vascular death) within 90 days, ischemic stroke, TIA, myocardial infarction (MI), vascular death, and poor functional outcome (mRS score of 2-6). The type of vascular events and mRS score at 90 days were used to classify the new stroke or TIA on a six-level scale: 5, fatal stroke (stroke with subsequent death), 4, severe stroke (stroke followed by mRS of 4–5), 3, moderate stroke (stroke followed by mRS of 2–3), 2, mild stroke (stroke followed by mRS of 0–1), 1, TIA and 0, no stroke/TIA. [17] This scale has been used in several trials [18,19] but has not been independently validated in broad populations of stroke patients. Definitions of the vascular events are provided in the Protocol and in the Supplementary Appendix.

Safety outcomes included moderate-to-severe bleeding defined by criteria from the Global Utilization of Streptokinase and tissue-type plasminogen activator for Occluded Coronary Arteries (GUSTO) trial [20] (the primary safety outcome), hepatotoxicity (alanine transaminase or aspartate transaminase > 3 times the upper limit of normal value), muscle toxicity (creatine kinase > 10 times the upper limit of normal value, or presence of muscle pain, myopathy or rhabdomyolysis pertaining to statin treatment in the other component of the trial), all-cause mortality, intracranial hemorrhage, any bleeding and other adverse or severe adverse events within 90 days.

Statistical analysis

Based on previous trials, the risk of new stroke over 90 days was presumed to be 11.5% in the group with aspirin alone, and that dual antiplatelet therapy would reduce this risk by 22%. [7,8,21-23] A sample size of 6100 patients was planned, which would provide the trial a

power of 80% to detect a hazard ratio of 0.80 in favor of DAPT with a two-sided α level of 0.05 based on 5% loss to follow up. Efficacy and safety analyses were performed in accordance with the intention-to-treat principle of all randomized patients.

We estimated the cumulative risks of new stroke events and moderate-to-severe bleeding events within 90 days with the use of Kaplan-Meier method. Differences between the clopidogrel-aspirin group and aspirin group in rates of stroke at 90 days were estimated by the marginal Cox proportional-hazards model adjusted for trial centers (n≥20), and hazard ratio (HR) and 95% confidence interval (CI) are presented. Cox models with trial centers set as a random effect (trial centers with fewer and those with greater than 20 enrolled patients were pooled for this purpose) was also performed for the primary outcome as a sensitivity analysis. The proportional hazards assumption was affirmed by assessment of the interaction between the trial-group and a logarithmic function of survival time and proportionality. Data for patients who did not have a 90-day assessment were censored on the date of a primary outcome event or the last visit if the patient withdrew from the trial or was lost to follow-up, whichever came first. The model utilized time to the first event when there were > 1 occurrences of the same type. Similar approaches were applied to compare the secondary efficacy outcomes of composite vascular events, ischemic stroke, hemorrhagic stroke, myocardial infarction, TIA, vascular death, as well as safety outcomes of bleeding and all-cause mortality. We conducted a shift analysis for the secondary outcome of our ordinal 6 tier scale of stroke and TIA combined with mRS outcome between the two groups via ordinal logistic regression with the proportionality assumption met, to determine a common odds ratio (cOR) and 95% CI. Poor functional outcome,

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hepatotoxicity and muscle toxicity were evaluated using generalized linear model, with relative risk (RR) and 95% CI. All participants who completed the trial and had no major protocol deviations were included in the per protocol set, and the same statistical methods as for the primary outcome were used for efficacy and safety outcomes. In addition, for the primary outcome, we performed a sensitivity analysis in the population with exclusion of those with minor stroke (NIHSS score≤3) or TIA ($ABCD^2$ score ≥4) within 24 hours of stroke that were recruited before the above-described protocol revision. Because of the low rates of mortality in each trial group, we did not conduct a competing risk analysis. Comparisons of other adverse events and serious adverse events were conducted by the Chi-squared test or Fisher's exact test. The primary outcome was analyzed for prespecified subgroups.

The statistical analysis plan did not contain a plan for adjusting the widths of confidence intervals for multiplicity when testing secondary or other outcomes and no definite conclusions can be drawn from these results. The intervals cannot be used to infer treatment effects for secondary outcomes. All statistical analyses were conducted using SAS software V.9.4 (SAS Institute Inc).

RESULTS

Patients

From September 17, 2018 through October 15, 2022 a total of 11,431 patients with ischemic stroke or TIA were screened from 222 hospitals, and 6100 patients underwent randomization with 3050 assigned to the clopidogrel-aspirin group and 3050 to the aspirin

group. Among the enrolled patients, 364 were discontinued from trial drugs and 21 in the clopidogrel-aspirin group and 18 in the aspirin group died from causes other than stroke, respectively but were included in the ITT analysis. At the 90-day follow-up, 4 patients in the clopidogrel-aspirin group and 2 in the aspirin group were lost to follow-up, which was treated as censored data, and 7 patients had missing data regarding disability (Fig.1).

Baseline characteristics were similar between the two groups (Table 1 and Table S1). The median age of participants was 65 years and 35.8% were women. Overall, 87.2% of patients were randomly assigned to a treatment group after 24 hours of symptoms onset. Most (67.6%) had multiple acute infarctions on imaging (on the same or on different sides of the cerebrum), and 19.2% and 13.1% had acute single infarction and TIA as index events, respectively. Among patients with acute ischemic stroke, 76.1% had NIHSS scores no higher than 3. Within 1 month prior to the index event, 13.0% of patients had taken aspirin and 0.7% had taken clopidogrel. Vascular imaging data collected for centralized interpretation was missing or incomplete in 65 patients in the clopidogrel-aspirin group and 67 patients in the aspirin group was incomplete.

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Efficacy outcomes

The primary outcome, incidence of new stroke within 90-days, occurred in 222 patients (7.3%) in the clopidogrel-aspirin group and in 279 patients (9.2%) in the aspirin group (marginal estimate hazard ratio, 0.79; 95% Cl, 0.66 to 0.94; P=0.008) (Fig. 2A and Table 2), with a random-effect estimate hazard ratio of 0.79 (95%CI 0.66 to 0.94). Center effect was nonnegligible (Fig. S1, Table S2). For secondary outcomes, the composite vascular

events occurred in 229 patients (7.5%) in the clopidogrel-aspirin group and in 282 patients (9.3%) in the aspirin group (hazard ratio, 0.80; 95% Cl, 0.67 to 0.96). The overall risks of ischemic stroke were 6.8% vs 9.0% (hazard ratio [HR], 0.75; 95% Cl, 0.63 to 0.90) and for TIA 0.7% vs 1.3% (hazard ratio, 0.54; 95% Cl, 0.32 to 0.91) favoring DAPT. A shift in the severity of stroke/TIA at 90days combined with mRS on the 6-tier scale towards better outcome with DAPT resulted in a cOR of 0.76 (95%CI, 0.64 to 0.91). The widths of confidence intervals for differences between groups in secondary outcomes are not multiplicity adjusted and no definite conclusions can be drawn from these data. Other secondary outcomes are shown in Table 2.

In the subgroup of patients randomized within 24 hours of onset, the risks of primary outcome were 11.5% in the clopidogrel-aspirin group vs 13.4% in the aspirin group (HR, 0.84; 95% Cl, 0.57 to 1.25); between 24 to 48 hours, 7.6% vs 8.9%, (HR, 0.84; 95% Cl, 0.64 to 1.11); and between 48 to 72 hours, and 5.8% vs 8.2% (HR, 0.70; 95% Cl, 0.53 to 0.93), respectively. Other subgroup analyses are shown in Fig.3 and Fig.S2.

The results of efficacy outcomes in the per protocol population were consistent with those in intention-to-treat population (Table S4). The sensitivity analysis after excluding patients with minor ischemic stroke (NIHSS score ≤3) or TIA ($ABCD^2$ score ≥4) within 24 hours showed similar results to the primary outcome (Table S5). As noted earlier, there was no significant interaction between antiplatelet treatment assignment and statin treatment in the two components of the factorial trial (P for interaction=0.16 for the primary outcome).

Safety outcomes

The primary safety outcome of moderate-to-severe bleeding occurred in 27 patients (0.9%)

in the clopidogrel-aspirin group, and 13 patients (0.4%) in the aspirin group (HR, 2.08; 95% Cl, 1.07 to 4.04, P=0.03) (Fig. 2B and Table 2). The risk of any bleeding was significantly higher in the clopidogrel-aspirin group (3.1%) than that in the aspirin group (2.1%) (HR, 1.50; 95% Cl, 1.09 to 2.06). Adverse events occurred in 650 patients (21.3%) in the clopidogrel-aspirin group, and 648 patients (21.3%) in the aspirin group (Table S6); serious adverse events occurred in 107 patients (3.5%) and 89 patients (2.9%), respectively (Table S7). Adverse events or serious adverse events leading to discontinuation of a trial treatment are shown in Table S8. In the analysis in per-protocol population, the results of safety outcomes were similar to those in the primary analysis (Table S4).

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DISCUSSION

In this randomized, double-blind, placebo-controlled, multicenter, 2×2 factorial trial conducted in China, patients with acute mild ischemic stroke or high-risk TIA of presumed atherosclerotic origin who received combined clopidogrel and aspirin within 72 hours of symptom onset had about a 2 percentage points lower absolute risk of stroke at 90 days compared to aspirin alone, with an approximately 2-fold higher risk of moderate-to-severe bleeding, although this risk was low in both groups.

The Clopidogrel in High-Risk Patients with Acute Nondisabling Cerebrovascular Events (CHANCE) and the POINT trials previously published in the *Journal* enrolled patients with minor ischemic stroke (NIHSS score≤3) or high-risk TIA, the results of which indicated that combination of clopidogrel and aspirin begun within 24 hours after onset reduced the risk of subsequent stroke, without increase in risk of bleeding during 90 days, compared to

aspirin alone.[21,24,25] The results of our trial potentially broaden the time window of starting treatment although there was more bleeding with the dual regimen.

In the CHANCE trial, DAPT reduced the absolute risk of recurrent stroke recurrence by 3.5 percentage points, with treatment within 24 hours, which was higher than the approximately 2 percentage point reduction observed in the current trial. This disparity may be attributed to the longer time interval between symptom onset and randomization in our trial, as the risk of stroke recurrence is higher during the acute post-stroke phase and in our trial, only approximately 13% of patients were treated within 24 hours. The incidence of moderate-to-severe bleeding in the DAPT group in our trial was 0.9%. This represents a more than two-fold increased risk compared to the 0.4% incidence with aspirin alone, and it is higher than the 0-0.5% rates reported in most previous studies.[7,9,19,21,26,27]

There are several limitations to this trial. Some important populations of stroke or TIA patients were excluded, such as those of presumed cardioembolic origin, those with moderate or severe stroke (NIHSS score >5), and those had received thrombolysis or thrombectomy. Furthermore, Han Chinese counted for 98.5% of enrolled patients, in whom the higher proportion of intracranial artery stenosis compared to other populations may have contributed to the benefit from DAPT. The results cannot necessarily be generalized to White and Black patients with stroke. Finally, clopidogrel is known to require hepatic cytochrome P450 (CYP) enzymes to generate active metabolites for its antiplatelet effects; however, the genotype of drug metabolism was not included in the criteria for enrollment this trial.[28]

In a trial conducted in China among patients with mild ischemic stroke or high-risk TIA

from presumed intracranial or extracranial atherosclerosis clopidogrel and aspirin initiated within 72 hours of symptom onset had a lower risk of new stroke but a higher risk of moderate-to-severe bleeding compared to aspirin alone over 90-days.

Funding

The study was supported by grants from the National Natural Science Foundation of China (No. 81825007), the National Key R&D Program of China (No. 2017YFC1307900, 2017YFC1307905), Beijing Outstanding Young Scientist Program (No. BJJWZYJH01201910025030), Youth Beijing Scholar Program (No.010), Beijing Talent Project - Class A: Innovation and Development (No. 2018A12), 'National Ten-Thousand Talent Plan'- Leadership of Scientific and Technological Innovation, Sanofi, and Jialin Pharmaceutical.

Ethics approval

The INSPIRES trial was approved by ethics committee at Beijing Tiantan Hospital (IRB approval number: KY2017-065-02) and all participating centers.

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

We will direct readers to the disclosure forms submitted by the authors, which will be posted as supplemental material alongside the article.

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Figure Legends

Figure 1. Flowchart of enrollment and randomization.

Patients who were enrolled inappropriately or discontinued a trial drug were included in the intention-to-treat analysis, as were patients lost to follow-up. The $ABCD^2$ score assesses the risk of stroke on the basis of age, blood pressure, clinical features, duration of transient ischemic attack (TIA), and the presence or absence of diabetes mellitus, with scores ranging from 0 to 7 and higher scores indicating greater risk. The mRS indicates modified Rankin Scale (range 0 to 6 with higher scores indicating worse functional outcome, and NIHSS, National Institutes of Health Stroke Scale (range 0 to 44, higher scores indicating greater neurological deficits).

Figure 2. Cumulative probability of stroke (primary efficacy outcome) and moderate-to-severe bleeding (primary safety outcome).

In each panel, the inset shows the same data on an enlarged y axis.

Figure 3. Hazard ratio for stroke in prespecified subgroups.

The trial was not powered to allow definite conclusions based on the results of the subgroup analyses. Systolic blood pressure data was missing in 6 patients in the clopidogrel-aspirin group and 7 patients in the aspirin group. With ≥50% symptomatic stenosis data was missing in 65 patients in the clopidogrel-aspirin group and 67 patients in the aspirin group.

Table 1. Baseline Characteristics of the Patients. *

Characteristic	Clopidogrel-Aspirin (N = 3050)	Aspirin (N = 3050)
Age, yr-Median (IQR)	65(57-71)	65(57-71)
Female-No. (%)	1063(34.9)	1122(36.8)
Medical History-no. (%)		
Hypertension	2047(67.1)	2036(66.8)
Diabetes mellitus	830(27.2)	828(27.2)
Dyslipidemia	103(3.4)	123(4.0)
Previous ischemic stroke	901(29.5)	908(29.8)
Current smoker-no. (%)	892(29.3)	891(29.2)
Application of agents before events-no. (%)		
Aspirin	390(12.8)	403(13.2)
Clopidogrel	21(0.7)	22(0.7)
Lipid Lowering Agents	296(9.7)	291(9.5)
Qualifying event-no. (%)		
TIA	399(13.1)	402(13.2)
Acute single infarction	588(19.3)	586(19.2)
Acute multiple infarctions	2063(67.6)	2062(67.6)
With ≥50% symptomatic stenosis-no. (%)§		
Yes	2448/2985(82.0)	2467/2983(82.7)
No	537/2985(18.0)	516/2983(17.3)
Time to randomization after onset of symptoms-no. (%)		
≤ 24h	401(13.2)	382(12.5)
24h-48h	1255(41.2)	1297(42.5)
>48h	1394(45.7)	1371(45.0)
NIHSS score in qualifying ischemic stroke-no. (%) †		
≤3	2007/2651(75.7)	2026/2648(76.5)
>3	644/2651(24.3)	622/2648(23.5)

ABCD^2 score in qualifying TIA-no. (%) ‡		
≤5	326/399(81.7)	315/402(78.4)
>5	73/399(18.3)	87/402(21.6)

* IQR indicates interquartile range; TIA, transient ischemic attack.

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

‡ The ABCD^2 score assesses the risk of stroke on the basis of age, blood pressure, clinical features, duration of TIA, and the presence or absence of diabetes mellitus for patients with transient ischemic attack, with scores ranging from 0 to 7 and higher scores indicating greater risk.

§ Data was missing in 132 cases due to the absence of both intracranial and extracranial arterial vascular assessments; or patients did not have more than 50% stenosis in intracranial (or extracranial) arteries, but with the absence of extracranial (or intracranial) vascular assessments.

Table 2. Efficacy and Safety Outcomes. *

Outcome	Clopidogrel-Aspirin (N = 3050)		Aspirin (N = 3050)		Hazard Ratio/ Relative Risks* (95% CI)	P Value
	Patients with Event-no.	Event Rate†, %	Patients with Event-no.	Event Rate†, %		
Primary outcome						
Stroke (including ischemic and hemorrhagic stroke)	222	7.3	279	9.2	0.79 (0.66 to 0.94)	0.008
Secondary outcomes						
Composite vascular event (stroke, myocardial infarction, or vascular death)	229	7.5	282	9.3	0.80 (0.67 to 0.96)	
Ischemic stroke	208	6.8	274	9.0	0.75 (0.63 to 0.90)	
Recurrent stroke	159	5.3	205	6.8	0.77 (0.62 to 0.94)	
TIA with infarction	5	0.2	11	0.4	0.45 (0.16 to 1.29)	
Progressive stroke ó	44	1.5	58	1.9	0.75 (0.51 to 1.11)	
Hemorrhagic stroke	15	0.5	5	0.2	3.01 (1.09 to 8.28)	
TIA	21	0.7	39	1.3	0.54 (0.32 to 0.91)	
Myocardial infarction	5	0.2	2	0.1	2.50 (0.49 to 12.90)	
Vascular death	21	0.7	15	0.5	1.40 (0.72 to 2.72)	
Poor functional outcome (mRS 2-6) ‡	301/3047	9.9	346/3046	11.4	0.87 (0.76 to 0.99)	
Ordinal stroke or TIA§					0.76 (0.64 to 0.91)	
Fatal stroke: score of 6 on mRS	20/3049	0.7	13/3049	0.4		
Severe stroke: score of 4 or	28/3049	0.9	27/3049	0.9		

5 on mRS						
Moderate stroke: score of 2 or 3 on mRS	69/3049	2.3	102/3049	3.3		
Mild stroke: score of 0 or 1 on mRS	104/3049	3.4	136/3049	4.5		
TIA	21/3049	0.7	35/3049	1.1		
No stroke or TIA	2807/3049	92.1	2736/3049	89.7		
Primary safety outcome						
Moderate-to-severe bleeding¶	27	0.9	13	0.4	2.08 (1.07 to 4.04)	0.03
Secondary safety outcomes						
Hepatotoxicity‖	39	1.3	32	1.0	1.22 (0.86 to 1.74)	
Muscle toxicity&	2	0.07	1	0.03	2.00 (0.18 to 22.04)	
All-cause mortality	37	1.2	30	1.0	1.24 (0.76 to 2.00)	
Any bleeding¶	94	3.1	63	2.1	1.50 (1.09 to 2.06)	
Intracranial hemorrhage	17	0.6	8	0.3	2.13 (0.92 to 4.93)	
Mild bleeding	70	2.3	51	1.7	1.38 (0.96 to 1.97)	

* The relative risks are shown for poor functional outcome, hepatotoxicity and muscle toxicity. The common odds ratio is shown for ordinal stroke or TIA. Hazard ratios are shown for other outcomes. The widths of the confidence intervals for secondary outcomes were not adjusted for multiplicity and may not be used for hypothesis testing.

† The event rates of poor functional outcome, ordinal stroke or TIA, hepatotoxicity and muscle toxicity are raw estimates, whereas the rates of other outcomes are Kaplan–Meier estimates of the percentage of patients with events at 90 days.

‡ The mRS score data at 90days was missing in 3 patients in the clopidogrel-aspirin group and 4 patients in the aspirin group.

§ The severity of stroke and TIA is classified on a six-level ordered categorical scale combined vascular events with modified Rankin scale (mRS). The mRS score at 90days was missing in 1 patient with new stroke each in the clopidogrel-aspirin group and aspirin group.

¶ Bleeding events were defined according to the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries criteria.

‖ Hepatotoxicity was defined as alanine transaminase or aspartate transaminase >3 times the upper limit of normal value.

&Muscle toxicity was defined as creatine kinase >10 times the upper limit of normal value, or presence of muscle pain, myopathy or rhabdomyolysis.

Ó The definition of progressive stroke is provided in the Supplementary Appendix (page 16)