ORIGINAL ARTICLE

Ticagrelor versus Clopidogrel in *CYP2C19* Loss-of-Function Carriers with Stroke or TIA

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ABSTRACT

BACKGROUND

Comparisons between ticagrelor and clopidogrel for the secondary prevention of stroke in *CYP2C19* loss-of-function carriers have not been extensively performed.

METHODS

We conducted a randomized, double-blind, placebo-controlled trial at 202 centers in China involving patients with a minor ischemic stroke or transient ischemic attack (TIA) who carried *CYP2C19* loss-of-function alleles. Patients were assigned within 24 hours after symptom onset, in a 1:1 ratio, to receive ticagrelor (180 mg on day 1 followed by 90 mg twice daily on days 2 through 90) and placebo clopidogrel or to receive clopidogrel (300 mg on day 1 followed by 75 mg once daily on days 2 through 90) and placebo ticagrelor; both groups received aspirin for 21 days. The primary efficacy outcome was new stroke, and the primary safety outcome was severe or moderate bleeding, both within 90 days.

RESULTS

A total of 11,255 patients were screened and 6412 patients were enrolled, with 3205 assigned to the ticagrelor group and 3207 to the clopidogrel group. The median age of the patients was 64.8 years, and 33.8% were women; 98.0% belonged to the Han Chinese ethnic group. Stroke occurred within 90 days in 191 patients (6.0%) in the ticagrelor group and 243 patients (7.6%) in the clopidogrel group (hazard ratio, 0.77; 95% confidence interval, 0.64 to 0.94; P=0.008). Secondary outcomes were generally in the same direction as the primary outcome. Severe or moderate bleeding occurred in 9 patients (0.3%) in the ticagrelor group and in 11 patients (0.3%) in the clopidogrel group; any bleeding occurred in 170 patients (5.3%) and 80 patients (2.5%), respectively.

CONCLUSIONS

Among Chinese patients with minor ischemic stroke or TIA who were carriers of *CYP2C19* loss-of-function alleles, the risk of stroke at 90 days was modestly lower with ticagrelor than with clopidogrel. The risk of severe or moderate bleeding did not differ between the two treatment groups, but ticagrelor was associated with more total bleeding events than clopidogrel. (Funded by the Ministry of Science and Technology of the People's Republic of China and others; CHANCE-2 ClinicalTrials.gov number, NCT04078737.)

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Among patients with an acute minor ischemic stroke or transient ischemic attack (TIA), the risk of another stroke within 3 months after the initial event is approximately 5 to 10%.[1-3] Dual antiplatelet therapy with clopidogrel and aspirin has been shown to be more effective than aspirin alone for reducing subsequent events in patients with minor stroke or TIA in the CHANCE (Clopidogrel in High-Risk Patients with Acute Nondisabling Cerebrovascular Events)[4] and POINT (Platelet-Oriented Inhibition in New TIA and Minor Ischemic Stroke)[5] trials. However, clopidogrel is a prodrug requiring conversion into its active metabolite by hepatic cytochrome p450 (CYP). Clopidogrel is less effective for the secondary prevention of stroke in carriers of *CYP2C19* loss-of-function alleles, which are present in 25% of White patients and in 60% of Asian patients.[6,7]

Ticagrelor, a reversible oral antagonist that directly blocks platelet P2Y12 receptor and does not require metabolic activation for its antiplatelet effect, may yield similar or greater levels of inhibition of platelet aggregation than clopidogrel.[8,9] Ticagrelor plus aspirin was superior to aspirin alone in reducing stroke or death among patients with acute mild-to-moderate ischemic stroke or high-risk TIA.[10] In the PRINCE (Platelet Reactivity in Acute Stroke or Transient Ischaemic Attack) trial, patients with minor stroke or TIA who were treated with ticagrelor plus aspirin had a lower platelet reactivity than those who were treated with clopidogrel plus aspirin, particularly in *CYP2C19* loss-of-function allele carriers.[11] This finding suggests that the combination of ticagrelor and aspirin may result in a lower risk of subsequent stroke than the combination of clopidogrel and aspirin among patients with minor stroke or TIA who are carriers of *CYP2C19* loss-of-function alleles. The current Ticagrelor or Clopidogrel with Aspirin in High-Risk Patients with Acute Nondisabling Cerebrovascular Events II (CHANCE-2) trial was designed to test the hypothesis that dual treatment with ticagrelor and aspirin would be superior to clopidogrel and aspirin in reducing the risk of subsequent stroke among patients with minor ischemic stroke or high-risk TIA who were *CYP2C19* loss-of-function allele carriers.

Methods

Trial Design and Oversight

This was an investigator-initiated, multicenter, randomized, double-blind, placebo-controlled trial conducted at 202 centers in China. The steering committee designed and oversaw the conduct and analysis of the trial. Details of the trial rationale, design, and methods have been described previously[12] and are provided in the protocol, available with the full text of this article at NEJM.org. Information on the statistical analysis plan, trial leadership, committees, sites, and investigators is provided in the Supplementary Appendix, also available at NEJM.org. The trial was approved by the ethics committee at Beijing Tiantan Hospital and at each participating site. Written informed consent for participation in the trial was provided by the patients or their representatives.

A Quick Take is available at NEJM.org

The steering committee was responsible for the design and supervision of the trial, the development of and amendments to the protocol, and the interpretation of the data as well as for ensuring the integrity of the data, analysis, and presentation of results and the fidelity of the trial to the protocol. An independent clinical-event adjudication committee whose members were unaware of the trial-group assignments adjudicated the primary and secondary efficacy outcomes and bleeding events. An independent data and safety monitoring committee monitored the progress of the trial, with regular assessment of safety outcomes, overall trial integrity, and trial conduct.

The trial drugs (ticagrelor and clopidogrel) and placebos were produced and provided by Shenzhen Salubris Pharmaceuticals, which had no role in the trial design or conduct, data analysis, or manuscript preparation. There were no confidentiality agreements in place between the authors and any commercial entity. The investigators were responsible for data collection, and the clinical coordinating center undertook site monitoring and data collation. The statistical and data management center was responsible for statistical analysis. The first author had full access to the data and wrote the first draft of the manuscript without assistance from any commercial entity.

TRIAL PATIENTS

Patients were eligible if they carried a *CYP2C19* loss-of-function allele as determined by point-of-care testing as described below, were 40 years of age or older, had either an acute nondisabling ischemic stroke with a National Institutes of Health Stroke Scale (NIHSS) score of 3 or less (range, 0 to 42, with higher scores indicating more severe stroke) or a high-risk TIA as determined according to an ABCD^2 score of 4 or higher (stroke risk score based on age, blood pressure, clinical features, duration of TIA, and the presence or absence of diabetes mellitus; range, 0 to 7, with higher scores indicating a higher risk of stroke), and could start the trial drug within 24 hours from the time at which the patient's condition was last reported to be normal.

Patients were not eligible for participation if they had received intravenous thrombolytic therapy or mechanical thrombectomy or if surgery or interventional treatment requiring trial-drug cessation had been scheduled. Additional exclusion criteria were moderate-to-severe disability (score on the modified Rankin scale of 3 to 5 [range, 0 to 6, with 0 to 1 indicating no disability, 2 to 5 increasing disability, and 6 death]), a history of intracranial hemorrhage or amyloid angiopathy, dual antiplatelet treatment in the 72 hours before randomization, current treatment with heparin therapy or oral anticoagulation (presumed cardiac source of embolus, such as atrial fibrillation, prosthetic cardiac valve, and known or suspected endocarditis), or a contraindication to ticagrelor, clopidogrel, or aspirin. Additional information on inclusion and exclusion criteria is provided in the protocol.

POINT-OF-CARE GENOTYPING

Rapid genotyping for three single-nucleotide polymorphisms — *CYP2C19**2 (681G→A, rs4244285), *CYP2C19**3 (636G→A, rs4986893), and *CYP2C19**17 (–806C→T, rs12248560) — was implemented with the use of the GMEX point-of-care genotyping system (Chongqing Jingyin Bioscience, which also had no role in the trial) immediately after informed consent was obtained for screening. The GMEX system can provide rapid (average turnaround time, 85 minutes) genotyping results with 100% agreement with those determined by use of the YZY Kit and Sanger sequencing for all three *CYP2C19* alleles (*2, *3, and *17).[13] Patients with at least two *2 or *3 alleles (*2/*2, *2/*3, or *3/*3) were classified as "poor metabolizers," and those with one *2 or *3 allele (*1/*2 or *1/*3) were classified as "intermediate metabolizers." Only patients with at least one loss-of-function allele (*2 or *3) were classified as loss-of-function carriers[6] and were enrolled in the trial.

TREATMENT

Within 24 hours after symptom onset, eligible patients carrying *CYP2C19* loss-of-function alleles were randomly assigned in a 1:1 ratio to receive ticagrelor–aspirin or clopidogrel–aspirin. Patients were randomly assigned a number corresponding to a medication kit that was given to each patient.

Patients in the ticagrelor group received placebo clopidogrel plus a 180-mg loading dose of ticagrelor on day 1, followed by 90 mg twice daily on days 2 through 90. Patients in the clopidogrel group received placebo ticagrelor plus a 300-mg loading dose of clopidogrel on day 1, followed by 75 mg daily on days 2 through 90. All the patients in the two groups received open-label aspirin at a loading dose of 75 to 300 mg, followed by 75 mg daily for 21 days. After the 3-month trial treatment, patients were treated according to the standard of care at the discretion of the local investigator and were followed for an additional 9 months, with continued collection of data on outcomes and safety events, which have not yet been analyzed.

OUTCOMES

The primary outcome was new ischemic or hemorrhagic stroke at 90 days. Secondary outcomes included new stroke within 30 days, a vascular event (a composite of stroke, TIA, myocardial infarction, or death from vascular causes), ischemic stroke, disabling stroke (score on the modified Rankin scale, ≥2) at 90 days, and severity of stroke or TIA on an ordinal scale (a six-level scale that incorporates stroke or TIA events with a score on the modified Rankin scale at 3 months as follows[14]: fatal stroke [stroke with subsequent score on the modified Rankin scale of 6], severe stroke [stroke with subsequent score on the modified Rankin scale of 4 or 5], moderate stroke [stroke with subsequent score on the modified Rankin scale of 2 or 3], mild stroke

[stroke with subsequent score on the modified Rankin scale of 0 or 1], TIA, and no stroke or TIA). Further definitions of outcomes are provided in the protocol.

The primary safety outcome was severe or moderate bleeding as defined by the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO) criteria at 90 days.[15] Secondary safety outcomes included any bleeding, death, adverse events, and severe adverse events through 90 days of follow-up.

All efficacy and safety outcomes were confirmed by an independent clinical-event adjudication committee, whose members were unaware of the trial-group assignments. The committee members classified ischemic stroke subtypes on the basis of available medical records, including imaging.

STATISTICAL ANALYSIS

We determined that a total of 6396 carriers of *CYP2C19* loss-of-function alleles would provide 90% power to detect a relative risk reduction of 25% in new stroke (primary outcome) in the ticagrelor–aspirin group as compared with the clopidogrel–aspirin group, with a final two-sided significance level of 0.048, assuming an incidence of new stroke of 9.4% in the clopidogrel–aspirin group[6] and an overall dropout rate of 5%. Assuming a 58.8% prevalence of *CYP2C19* loss-of-function allele carriers in a Chinese population,[6] we projected that screening 10,878 patients would be necessary. A P value of 0.05 was adjusted to 0.048 to account for a single interim analysis of the primary efficacy outcome with the use of an O'Brien–Fleming spending function. The independent data and safety monitoring committee reviewed overall incidences of trial outcomes and suggested continuing the trial without unblinding. Because the committee determined from examination of overall event rates that there was no necessity for unblinding of treatment assignments, comparisons of efficacy and safety outcome between two treatment groups were not performed in the interim analysis. No alpha was considered to have been expended, and the type I error level of the statistical significance was set at a two-sided alpha of 0.05 in the final analysis.

Efficacy and safety analyses were performed in the intention-to-treat population. The cumulative risks of the primary outcome of any ischemic or hemorrhagic event during the 90-day follow-up were estimated from Kaplan–Meier plots. Differences between trial group in the incidence of stroke (ischemic or hemorrhagic) during the 90-day follow-up period were assessed with the use of a Cox proportional-hazards model, with trial centers set as a random effect; hazard ratios and 95% confidence intervals were reported. Proportionality was tested by including a time-dependent covariate with interaction of the trial group and a logarithmic function of survival time in the model, and proportionality was affirmed. Data on patients were censored at their last follow-up assessment if a clinical event had occurred, at the end of trial, at the time of withdrawal from the trial, or at the last visit if primary outcome data were missing. When there were multiple events of the same type, the time to the first event was used in the model. Similar approaches were used for comparison of the secondary outcomes of new stroke events, clinical vascular events, ischemic stroke, and disabling stroke and for comparison of the safety outcomes of severe or moderate bleeding, any bleeding, and death. Shift analysis was performed for comparison of the secondary outcome of ordinal stroke or TIA between the two treatment groups with the use of logistic regression, and the common odds ratio and 95% confidence interval were calculated. A post hoc analysis with death from nonvascular causes as a competing risk was performed.

Because the statistical analysis plan did not include a provision for correcting the widths of confidence intervals for multiple comparisons, secondary and other outcomes are reported as point estimates with unadjusted 95% confidence intervals, and no definite conclusions can be drawn regarding these outcomes. Statistical analyses were performed with use of SAS software, version 9.4 (SAS Institute).

RESULTS

PATIENT POPULATION

Between September 23, 2019, and March 22, 2021, a total of 11,255 patients with ischemic stroke or TIA were screened and genotyped at 202 clinical sites; 6412 patients (57.0%) were

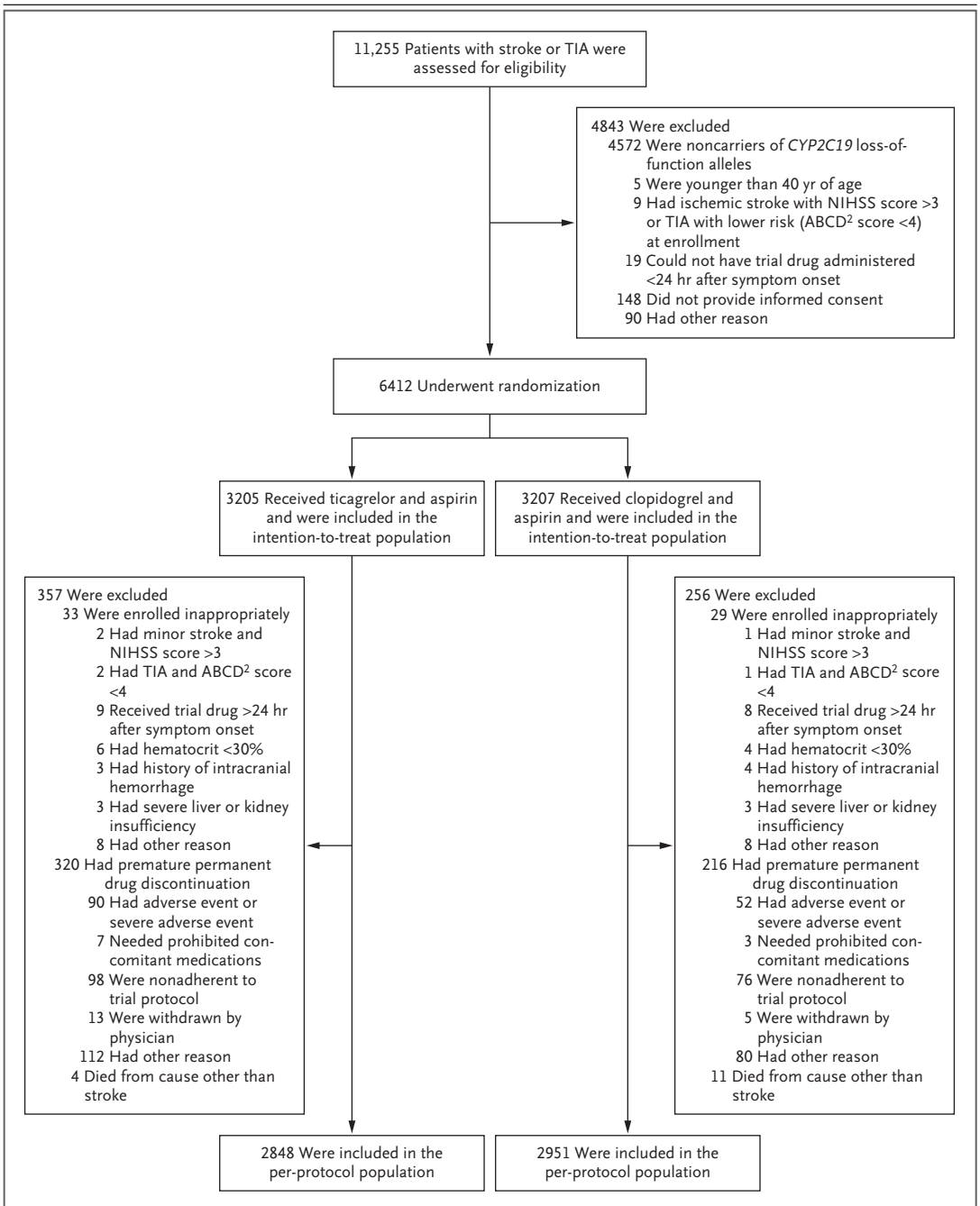


Figure 1. Enrollment and Randomization of the Patients.

Scores on the National Institutes of Health Stroke Scale (NIHSS) range from 0 to 42, 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 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.

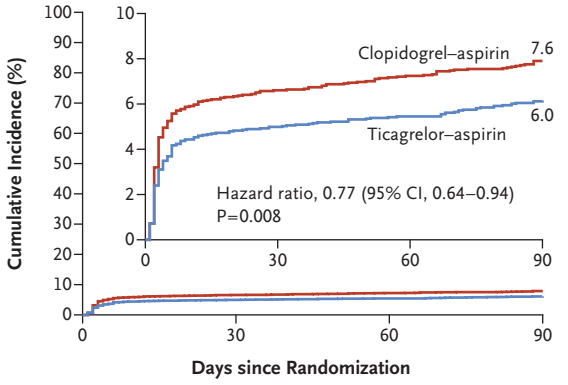
enrolled, with 3205 randomly assigned to the ticagrelor–aspirin group and 3207 to the clopidogrel–aspirin group. A total of 4572 patients were excluded because they were noncarriers of *CYP2C19* loss-of-function alleles. Overall, treatment was discontinued prematurely in 536 pa-

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Ticagrelor–Aspirin (N=3205)	Clopidogrel–Aspirin (N=3207)
Median age (IQR) — yr	65.0 (57.0–71.7)	64.6 (56.9–71.1)
Female sex — no. (%)	1090 (34.0)	1080 (33.7)
Han Chinese ethnic group — no. (%)†	3144 (98.1)	3138 (97.8)
Medical history — no. (%)		
Hypertension	2356 (73.5)	2374 (74.0)
Diabetes mellitus	1033 (32.2)	1009 (31.5)
Dyslipidemia	888 (27.7)	895 (27.9)
Previous ischemic stroke	669 (20.9)	681 (21.2)
Previous TIA	46 (1.4)	42 (1.3)
Myocardial infarction	54 (1.7)	42 (1.3)
Current smoker — no. (%)	995 (31.0)	986 (30.7)
Type of *CYP2C19* loss-of-function allele carrier — no. (%)‡		
Intermediate metabolizer	2486 (77.6)	2515 (78.4)
Poor metabolizer	719 (22.4)	692 (21.6)
Median time from symptom onset to randomization (IQR) — hr	13.5 (9.0–20.3)	14.3 (8.9–20.7)
Qualifying event — no. (%)		
Ischemic stroke	2577 (80.4)	2581 (80.5)
TIA	628 (19.6)	626 (19.5)
Median NIHSS score in patients with qualifying ischemic stroke (IQR)§	2 (1–3)	2 (1–3)
Median ABCD^2 score in patients with qualifying TIA (IQR)¶	4.5 (4–5)	4 (4–5)
Previous antiplatelet therapy — no. (%)‖	385 (12.0)	363 (11.3)
Previous lipid-lowering therapy — no. (%)‖	258 (8.0)	241 (7.5)
Symptomatic intracranial-artery stenosis — no./total no. (%)	841/2969 (28.3)	798/2951 (27.0)
Symptomatic extracranial-artery stenosis — no./total no. (%)	143/2969 (4.8)	128/2951 (4.3)

* IQR denotes interquartile range, and TIA transient ischemic attack.
† Ethnic group was reported by the patient and verified by identification card.
‡ Patients with one *CYP2C19**2 or *CYP2C19**3 allele were classified as "intermediate metabolizers," and those with at least two *CYP2C19**2 or *CYP2C19**3 alleles were classified as "poor metabolizers."
§ Scores on the National Institutes of Health Stroke Scale (NIHSS) range from 0 to 42, 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, with scores ranging from 0 to 7 and higher scores indicating greater risk.
‖ Patients received medication within 1 month before symptom onset.

tients, and 15 patients died of causes other than stroke. All the patients completed 90 days of follow-up (Fig. 1). The characteristics of the patients at baseline were similar in the two treatment groups (Table 1 and Table S1 in the Supplementary Appendix). The median age of the patients was 64.8 years, and 33.8% were women. Most patients (80.4%) presented with ischemic stroke, and 19.6% presented with TIA. The median time from symptom onset to randomization was 14 hours. The average turnaround time of point-of-care testing was 80.3 minutes (95% confidence interval [CI], 80.1 to 80.5). Among enrolled patients, 5001 (78.0%) were intermediate metabolizers and 1411 (22.0%) were poor metabolizers, as defined above. Concomitant treatment and prohibited medications taken during the treatment period are reported in Tables S2 and S3. There were no missing primary outcome data.



No. at Risk

Clopidogrel–aspirin	3207	2994	2973	2486
Ticagrelor–aspirin	3205	3046	3031	2554

Figure 2. Cumulative Incidence of Stroke (Primary Outcome).
The inset shows the same data on an enlarged y axis.

PRIMARY AND SECONDARY OUTCOMES

A primary-outcome event, new ischemic or hemorrhagic stroke within 90 days, occurred in 191 of the 3205 patients (6.0%) in the ticagrelor–aspirin group and in 243 of the 3207 patients (7.6%) in the clopidogrel–aspirin group (hazard ratio, 0.77; 95% CI, 0.64 to 0.94; P=0.008) (Fig. 2 and Table 2). Post hoc analysis of the primary outcome with death from nonvascular causes as a competing risk yielded results similar to those of the primary analysis (hazard ratio, 0.80; 95% CI, 0.66 to 0.96).

With respect to secondary outcomes, confidence intervals of which were not adjusted for multiple comparisons, new stroke within 30 days occurred in 156 patients (4.9%) in the ticagrelor–aspirin group and in 205 patients (6.4%) in the clopidogrel–aspirin group (hazard ratio, 0.75; 95% CI, 0.61 to 0.93) (Table 2). A vascular event occurred in 229 patients (7.2%) in the ticagrelor–aspirin group and in 293 patients (9.2%) in the clopidogrel–aspirin group (hazard ratio, 0.77; 95% CI, 0.65 to 0.92). Ischemic stroke occurred in 189 patients (5.9%) in the ticagrelor–aspirin group and in 238 patients (7.4%) in the clopidogrel–aspirin group. Other secondary outcomes are presented in Table 2. The results of subgroup analyses for the primary outcome are shown in Figure 3. Similar efficacy was observed in intermediate metabolizers and poor metabolizers (Fig. S1). The results of the per-protocol analysis were consistent with those of the primary intention-to-treat analysis (Table S4).

SAFETY OUTCOMES

A primary safety outcome of moderate or severe bleeding, as defined by the GUSTO criteria, occurred in 9 patients (0.3%) in the ticagrelor–aspirin group and in 11 patients (0.3%) in the clopidogrel–aspirin group (hazard ratio, 0.82; 95% CI, 0.34 to 1.98) (Table 2). Intracranial hemorrhage occurred in 3 patients (0.1%) in the ticagrelor–aspirin group and in 6 patients (0.2%) in the clopidogrel–aspirin group. Fatal bleeding occurred in 3 patients (0.1%) in each group. The incidence of any bleeding was 5.3% in the ticagrelor–aspirin group, as compared with 2.5% in the clopidogrel–aspirin group (Table 2). Adverse events occurred in 540 patients (16.8%) in the ticagrelor–aspirin group, as compared with 427 patients (13.3%) in the clopidogrel–aspirin group (Table S5). Dyspnea and arrhythmias were more frequent with ticagrelor than with clopidogrel and were the primary causes of between-group differences in discontinuation. Serious adverse events occurred in 78 patients (2.4%) in the ticagrelor–aspirin group and in 84 patients (2.6%) in the clopidogrel–aspirin group (Table S6). Adverse events or serious adverse events leading to discontinuation of a trial treatment are shown in Table S7. The results of the per-protocol analysis of safety were consistent with those of the primary intention-to-treat analysis (Table S4).

DISCUSSION

In this randomized, double-blind, placebo-controlled trial conducted almost exclusively in Han Chinese participants, those with minor ischemic stroke or high-risk TIA who were *CYP2C19* loss-of-function allele carriers had a lower risk of stroke at 90 days with ticagrelor and aspirin than with clopidogrel and aspirin. Overall, the incidence of adverse events and total bleeding events was greater with ticagrelor–aspirin treatment, mainly owing to mild bleeding, but there was not an increased incidence of moderate or severe bleeding. Dyspnea and arrhythmia were more frequent in the ticagrelor group.

Clopidogrel is a prodrug requiring hepatic conversion into its active metabolite, a process that may be influenced by *CYP2C19* genetic poly-

Table 2. Efficacy and Safety Outcomes.

Outcome	Ticagrelor–Aspirin (N=3205)		Clopidogrel–Aspirin (N=3207)		Hazard Ratio or Odds Ratio (95% CI)*	P Value
	Patients with Event	Incidence†	Patients with Event	Incidence†		
	no.	%	*no.*	%		
Primary outcome						
Stroke	191	6.0	243	7.6	0.77 (0.64–0.94)	0.008
Secondary outcome‡						
Stroke within 30 days	156	4.9	205	6.4	0.75 (0.61–0.93)	
Vascular event§	229	7.2	293	9.2	0.77 (0.65–0.92)	
Ischemic stroke	189	5.9	238	7.4	0.78 (0.65–0.95)	
Stroke with any disability¶	97	3.1	92	2.9	1.02 (0.77–1.36)	
Ordinal stroke or TIA‖					0.79 (0.66–0.94)	
Fatal stroke: score of 6 on modified Rankin scale	4	0.1	8	0.2		
Severe stroke: score of 4 or 5 on modified Rankin scale	30	0.9	21	0.7		
Moderate stroke: score of 2 or 3 on modified Rankin scale	63	2.0	63	2.0		
Mild stroke: score of 0 or 1 on modified Rankin scale	94	2.9	151	4.7		
TIA	34	1.1	40	1.2		
No stroke or TIA	2980	93.0	2924	91.2		
Primary safety outcome						
Severe or moderate bleeding**	9	0.3	11	0.3	0.82 (0.34–1.98)	0.66
Fatal bleeding	3	0.1	3	0.1	0.97 (0.20–4.81)	
Intracranial hemorrhage	3	0.1	6	0.2	0.49 (0.12–1.96)	
Secondary safety outcome						
Any bleeding	170	5.3	80	2.5	2.18 (1.66–2.85)	
Mild bleeding**	161	5.0	69	2.2	2.41 (1.81–3.20)	
Death	9	0.3	18	0.6	0.50 (0.22–1.11)	

* The common odds ratio is shown for ordinal stroke or TIA. Hazard ratios are shown for other outcomes.
† The incidences of ordinal stroke or TIA are raw estimates, whereas the incidences of other outcomes are Kaplan–Meier estimates of the percentage of patients with events at 90 days.
‡ Because of the lack of a prespecified plan for correction of the widths of confidence intervals for multiple comparisons, no definite conclusions can be drawn from secondary outcome results.
§ Vascular events were a composite of ischemic stroke, hemorrhagic stroke, TIA, myocardial infarction, or death from vascular causes.
¶ A stroke was defined as disabling if the patient had a score on the modified Rankin scale greater than 1. Scores range from 0 to 6, with 0 to 1 indicating no disability, 2 to 5 increasing disability, and 6 death.
‖ Severity was measured with the use of a six-level ordinal scale that incorporates subsequent stroke or TIA events and the score on the modified Rankin scale at 3 months.
** Severe or moderate bleeding and mild bleeding were defined according to Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO) criteria.

morphisms.[6,7] Therefore, use of clopidogrel in carriers of *CYP2C19* loss-of-function alleles is of interest.[16] In patients who have acute coronary syndrome or are undergoing percutaneous coronary intervention, a genotype-guided strategy for the use of P2Y12 inhibitors reduced major adverse cardiovascular events in the PHARMCLO (Pharmacogenetics of Clopidogrel in Patients with Acute Coronary Syndromes) trial[17] but not in the POPular Genetics (CYP2C19 Genotype-

Subgroup	No. of Patients	Ticagrelor–Aspirin	Clopidogrel–Aspirin	Hazard Ratio (95% CI)
		no. of events (%)		
Overall	6412	191 (6.0)	243 (7.6)	0.77 (0.64–0.94)
Age				
<65 yr	3251	82 (5.1)	125 (7.6)	0.68 (0.51–0.90)
≥65 yr	3161	109 (6.8)	118 (7.6)	0.88 (0.67–1.14)
Sex				
Male	4242	120 (5.7)	163 (7.7)	0.73 (0.57–0.92)
Female	2170	71 (6.5)	80 (7.4)	0.87 (0.62–1.21)
Body-mass index				
<25	3682	109 (6.1)	137 (7.3)	0.82 (0.64–1.06)
≥25	2730	82 (5.8)	106 (8.0)	0.72 (0.54–0.97)
Index event				
Ischemic stroke	5158	153 (5.9)	203 (7.9)	0.75 (0.61–0.93)
TIA	1254	38 (6.1)	40 (6.4)	0.85 (0.52–1.37)
Time to randomization				
<12 hr	2626	85 (6.4)	104 (8.0)	0.76 (0.57–1.02)
≥12 hr	3786	106 (5.6)	139 (7.3)	0.76 (0.58–0.98)
Diabetes				
Yes	2042	81 (7.8)	94 (9.3)	0.79 (0.58–1.08)
No	4370	110 (5.1)	149 (6.8)	0.73 (0.57–0.93)
Hypertension				
Yes	4730	159 (6.7)	183 (7.7)	0.85 (0.69–1.06)
No	1682	32 (3.8)	60 (7.2)	0.55 (0.35–0.86)
Type of *CYP2C19* LOF allele carrier				
Intermediate metabolizer	5001	150 (6.0)	191 (7.6)	0.78 (0.63–0.97)
Poor metabolizer	1411	41 (5.7)	52 (7.5)	0.77 (0.50–1.18)
Previous ischemic stroke or TIA				
Yes	1418	53 (7.6)	52 (7.2)	1.07 (0.72–1.60)
No	4994	138 (5.5)	191 (7.7)	0.70 (0.57–0.88)
Current smoker				
Yes	1981	46 (4.6)	68 (6.9)	0.66 (0.45–0.98)
No	4431	145 (6.6)	175 (7.9)	0.83 (0.67–1.04)
Previous antiplatelet therapy				
Yes	748	30 (7.8)	23 (6.3)	1.30 (0.69–2.44)
No	5664	161 (5.7)	220 (7.7)	0.72 (0.59–0.88)
Previous lipid-lowering therapy				
Yes	499	23 (8.9)	17 (7.1)	1.08 (0.52–2.23)
No	5913	168 (5.7)	226 (7.6)	0.74 (0.60–0.90)
Symptomatic intracranial-artery stenosis				
Yes	1639	81 (9.6)	91 (11.4)	0.76 (0.55–1.04)
No	4281	90 (4.2)	142 (6.6)	0.62 (0.47–0.81)
Symptomatic extracranial-artery stenosis				
Yes	271	19 (13.3)	15 (11.7)	1.14 (0.58–2.25)
No	5649	152 (5.4)	218 (7.7)	0.68 (0.56–0.84)

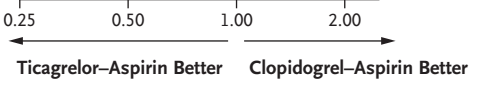


Figure 3. Hazard Ratio for Stroke in Prespecified Subgroups.
The body-mass index is the weight in kilograms divided by the square of the height in meters. LOF denotes loss of function.

Guided Antiplatelet Therapy in ST-Segment Elevation Myocardial Infarction Patients — Patient Outcome after Primary PCI)[18] and TAILOR-PCI (Tailored Antiplatelet Initiation to Lessen Outcomes Due to Decreased Clopidogrel Response after Percutaneous Coronary Intervention)[19] trials. The present trial may provide support for the use of ticagrelor–aspirin, as compared with clopidogrel–aspirin, in reducing the risk of new stroke among patients presenting with minor ischemic

stroke or high-risk TIA who are also *CYP2C19* loss-of-function allele carriers, but there were also more bleeding events with ticagrelor. In addition to the inability to directly compare stroke trials with cardiovascular trials involving antiplatelet agents, the current CHANCE-2 trial and previously reported cardiovascular trials differ with respect to the mechanism of coronary artery disease and ischemic stroke, medications (ticagrelor or prasugrel in some trials), and the inclusion in other trials of patients who were classified as "extensive metabolizers" (those without a *2, *3, or *17 allele [*1/*1]).

In our trial, the curves representing the cumulative hazard of stroke diverged approximately during the first week or slightly later and were subsequently similar, which suggests that any benefit of ticagrelor over clopidogrel in *CYP2C19* loss-of-function allele carriers occurred predominantly soon after stroke. The ticagrelor–aspirin group had higher incidences of total adverse events and events leading to the discontinuation of trial treatment, particularly owing to mild bleeding, dyspnea, or arrhythmia, similar to previous trials of ticagrelor.[10,11,20]

Ticagrelor may be clinically useful as an alternative antiplatelet agent in patients with stroke carrying *CYP2C19* loss-of-function alleles for whom the efficacy of clopidogrel might be reduced,[6] especially in East Asian populations for whom the burden of stroke recurrence and the prevalence of *CYP2C19* loss-of-function alleles are high.[7] However, the clinical usefulness of pharmacogenomics-guided selection of antiplatelet therapy is limited by the availability of rapid *CYP2C19* genotyping techniques and tool kits, and the cost-effectiveness of a genotype-guided strategy needs further investigation.

Our results are not generalizable to non-Han patients, because Han patients made up 98.0% of those enrolled. This population also has a higher incidence of intracranial-artery stenosis than non-Asian populations, and ticagrelor and clopidogrel may have different effects in non-Han patients with loss-of-function alleles. Despite the effort of recruiting hospitals for this trial in provinces where most minority populations reside, there were very few hospitals that were equipped to conduct clinical trials and that voluntarily participated. A limitation of this trial is the exclusion of patients who constitute important subpopulations of those presenting with stroke and TIA, such as those with cardioembolic stroke, moderate or severe stroke (NIHSS score, >3), delayed presentation after stroke that would preclude treatment within 24 hours, and receipt of thrombolysis or thrombectomy.

In our trial involving mainly Han Chinese patients with acute minor ischemic stroke or high-risk TIA treated within 24 hours after symptom onset who were carriers of the *CYP2C19* loss-of-function alleles, the use of ticagrelor and aspirin was superior to the use of clopidogrel and aspirin in reducing the risk of subsequent stroke. The risk of severe or moderate bleeding did not differ between the two treatment groups, but the risk of any bleeding was higher with ticagrelor than with clopidogrel.

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

APPENDIX

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