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Tirofiban for Stroke without Large or Medium-Sized Vessel Occlusion

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ABSTRACT

BACKGROUND

The effects of the glycoprotein IIb/IIIa receptor inhibitor tirofiban in patients with acute ischemic stroke but who have no evidence of complete occlusion of large or medium-sized vessels have not been extensively studied.

METHODS

In a multicenter trial in China, we enrolled patients with ischemic stroke without occlusion of large or medium-sized vessels and with a National Institutes of Health Stroke Scale score of 5 or more and at least one moderately to severely weak limb. Eligible patients had any of four clinical presentations: ineligible for thrombolysis or thrombectomy and within 24 hours after the patient was last known to be well; progression of stroke symptoms 24 to 96 hours after onset; early neurologic deterioration after thrombolysis; or thrombolysis with no improvement at 4 to 24 hours. Patients were assigned to receive intravenous tirofiban (plus oral placebo) or oral aspirin (100 mg per day, plus intravenous placebo) for 2 days; all patients then received oral aspirin until day 90. The primary efficacy end point was an excellent outcome, defined as a score of 0 or 1 on the modified Rankin scale (range, 0 [no symptoms] to 6 [death]) at 90 days. Secondary end points included functional independence at 90 days and a quality-of-life score. The primary safety end points were death and symptomatic intracranial hemorrhage.

RESULTS

A total of 606 patients were assigned to the tirofiban group and 571 to the aspirin group. Most patients had small infarctions that were presumed to be atherosclerotic. The percentage of patients with a score of 0 or 1 on the modified Rankin scale at 90 days was 29.1% with tirofiban and 22.2% with aspirin (adjusted risk ratio, 1.26; 95% confidence interval, 1.04 to 1.53, P=0.02). Results for secondary end points were generally not consistent with the results of the primary analysis. Mortality was similar in the two groups. The incidence of symptomatic intracranial hemorrhage was 1.0% in the tirofiban group and 0% in the aspirin group.

CONCLUSIONS

In this trial involving heterogeneous groups of patients with stroke of recent onset or progression of stroke symptoms and nonoccluded large and medium-sized cerebral vessels, intravenous tirofiban was associated with a greater likelihood of an excellent outcome than low-dose aspirin. Incidences of intracranial hemorrhages were low but slightly higher with tirofiban. (Funded by the National Natural Science Foundation of China; RESCUE BT2 Chinese Clinical Trial Registry number, ChiCTR2000029502.)

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*The RESCUE BT2 Investigators are listed in the Supplementary Appendix, available at NEJM.org.

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A Quick Take is available at NEJM.org

The brief window of time for successful intervention after stroke onset and the contraindications to treatment limit the use of intravenous thrombolysis (IVT) to less than 10% of patients with stroke, as estimated in China,[1] and endovascular thrombectomy (EVT) is effective mainly for strokes due to the occlusion of large or medium-sized vessels. As a result, there are many patients with recent onset or recent progression of acute stroke with stenosis of large or medium-sized vessels or occlusion of penetrating arteries or distal branch vessels, presumed to be due mainly to atherosclerosis, but without large or medium-sized artery occlusion, for whom currently available therapies may not be appropriate. This group includes patients who may have one of several different clinical courses. First are patients who present within 24 hours after stroke onset but are ineligible for intravenous or endovascular reperfusion therapy. For these patients, one treatment option is aspirin or other antiplatelet agents, but these have limited benefits.[2] Second are patients who have not been treated with reperfusion therapies because they have patent proximal cerebral vessels but have progression of stroke symptoms 24 to 96 hours after onset. Third and fourth are patients who receive IVT but have early neurologic deterioration or no neurologic improvement after treatment, respectively, circumstances that have been estimated to occur in more than half the patients who have received IVT and that are associated with poor outcomes.[3,4]

As a result of the success of glycoprotein IIb/IIIa receptor inhibitors in treating patients with acute coronary syndromes, there is potential of this and similar agents to inhibit activated platelet–mediated thrombosis in acute stroke.[5] Tirofiban is a fast-acting, highly selective, low-molecular-weight nonpeptide glycoprotein IIb/IIIa receptor inhibitor with a short half-life that allows bleeding time to revert to normal within approximately 3 hours after its administration is stopped. The safety and efficacy of tirofiban in the early management of stroke were assessed in the Study of Efficacy of Tirofiban in Acute Ischaemic Stroke,[6] which was stopped early for lack of efficacy, and the Safety of Tirofiban in Acute Ischemic Stroke trial,[7] which showed no beneficial effect on stroke outcomes at 1 week or 5 months. Similarly, in a randomized trial involving patients with large cerebral vessel occlusion, in which tirofiban was administered before thrombectomy (conducted by some of the same investigators as in the current trial), there was no significant difference in outcome at 90 days as compared to placebo.[8] However, several uncontrolled observational studies have suggested that tirofiban alone or as adjunctive therapy to IVT may be effective in selected patients with acute stroke.[3,9,10]

We conducted the Efficacy and Safety of Tirofiban Compared with Aspirin in the Treatment of Acute Ischemic Stroke (RESCUE BT2) trial involving patients without large or medium-sized vessel occlusion. The trial population included patients within 24 hours after stroke onset who were ineligible for thrombolysis or thrombectomy, those who had progression of stroke symptoms, and those whose condition deteriorated or failed to improve after thrombolysis.

METHODS

TRIAL DESIGN

This was a multicenter, double-blind, double-dummy, randomized clinical trial conducted in China. The trial protocol was approved by a central medical ethics committee and the research board at each participating center. All enrolled patients or their legal representatives provided written informed consent before enrollment. The protocol is available with the full text of this article at NEJM.org and has been published previously.[11]

The trial was designed and conducted by a steering committee composed of independent academic investigators and was monitored by an independent data and safety monitoring board. An independent clinical events committee adjudicated efficacy outcomes, safety outcomes, complications, and adverse events. A core laboratory with staff who were unaware of the trial-group assignments assessed neuroimaging studies. The trial was conducted in accordance with the ethical principles of the Declaration of Helsinki and the Good Clinical Practice guidelines of the International Council for Harmonisation. The authors vouch for the completeness and accuracy of the reported data, the fidelity of the trial to the protocol, and the complete reporting of adverse events.

PATIENTS

Patients were adults 18 years of age or older with an acute stroke who had been able to complete

usual activities in daily life without support before the stroke. Patients were eligible if they had any of the following presentations of acute ischemic stroke: within 24 hours after the time that the patient was last known to be well and ineligible for IVT, mainly owing to arrival more than 4.5 hours after stroke onset or other contraindication, or ineligible for EVT owing to no large or medium-sized vessel occlusion; more than 24 hours and less than 96 hours after the time that the patient was last known to be well but within 24 hours after progression of ischemic stroke symptoms, as determined by an increase of at least 2 points in the score on the National Institutes of Health Stroke Scale (NIHSS; range, 0 to 42, with higher scores indicating more severe neurologic deficits) and ineligible for IVT or EVT; treated with IVT, followed by early neurologic deterioration (defined as an increase of ≥4 points in the NIHSS score) within the first 24 hours; or treated with IVT, followed by no neurologic improvement (with no improvement defined as a decrease of <2 points in the NIHSS score) within 4 to 24 hours after thrombolytic therapy. Patients were required to have an NIHSS score of at least 5 before trial entry, with at least one limb with an NIHSS motor item score of 2, 3, or 4 (range, 0 to 4, with higher scores indicating greater weakness). Computed tomographic (CT) angiography, magnetic resonance angiography, or digital subtraction angiography were performed to identify patients without visible large or medium-sized intracranial vessel occlusion as a requirement for enrollment. Patients with nonocclusive stenoses of these vessels were enrolled, as were patients with ischemia on imaging in the territory of small, penetrating arteries. Patients with imaging-confirmed intracranial hemorrhage and any definite source of cardiac embolism were excluded from the trial.

On the basis of clinical features, imaging of the brain, and vessel imaging, the presumed mechanism of ischemic stroke was categorized with the use of a combination of the Chinese Ischemic Stroke Subclassification system[12] and the system of Kim and colleagues,[13] as follows: penetrating artery disease, artery-to-artery embolism, hypoperfusion or impaired emboli clearance beyond a stenosis, in situ thrombo-occlusion distal to a stenosed artery, two or more of the above mechanisms, mechanism could not be determined, and cardioembolism. Further details are provided in the Supplementary Appendix, available at NEJM.org.

RANDOMIZATION AND TREATMENT

Patients were randomly assigned in a 1:1 ratio to the tirofiban group or the aspirin group. Intravenous tirofiban was administered at a dose of 0.4 μg per kilogram of body weight per minute for 30 minutes, followed by a continuous infusion of 0.1 μg per kilogram per minute for up to 48 hours. Patients in the tirofiban group also received oral placebo daily for 2 days. Patients in the aspirin group were assigned to receive intravenous placebo and oral aspirin (100 mg per day) for 2 days. Beginning approximately at the 44th hour after administration of intravenous tirofiban or placebo, all the patients received oral aspirin at a dose of 100 mg per day until day 90. Randomization used a centralized Web site and was stratified according to participating center with a permutation block size of 4. The placebos were identical in appearance to the active trial drugs and were administered in the same fashion. Oral aspirin or placebo was to be administered consistent with current Chinese Stroke Association guidelines that suggest starting aspirin 24 to 48 hours after stroke.[14] Tirofiban, saline placebo, and placebo of enteric-coated aspirin tablets from Bayer Schering Pharma were provided by Lunan Pharmaceutical Group; these commercial entities had no role in the trial or preparation of the manuscript.

OUTCOME MEASURES

The primary efficacy end point was an excellent outcome, defined as a score of 0 or 1 on the modified Rankin scale (an ordinal global disability scale with scores ranging from 0 [no symptoms] to 6 [death]) at 90 days after randomization. The score assessment was based on central evaluation by means of video or audio by evaluators who were unaware of the trial-group assignments. The primary end point was also centrally adjudicated on the basis of telephone, audio, or video assessments.

A secondary efficacy end point was a favorable outcome at 90 days, as assessed with the use of a global outcome analysis that included four outcomes at 90 days: a score of 0 or 1 on the modified Rankin scale, an NIHSS score of 0 or 1, a Barthel Index score of 95 to 100 (range, 0 to 100, with higher scores indicating better independent function), and a score of 5 on the

Glasgow Outcome Scale (range, 1 to 5, with higher scores indicating better neurologic recovery). Other secondary efficacy end points were the level of disability at 90 days, as assessed by the shift across all seven levels of the modified Rankin scale; functional independence (score of 0, 1, or 2 on the modified Rankin scale) at 90 days; the score of the EuroQol 5-Dimension 5-Level questionnaire (EQ-5D-5L; range, −0.39 to 1, with lower scores indicating a worse quality of life) at 90 days; an excellent outcome (score of 0 or 1 on the modified Rankin scale) at 30 days; and functional independence (score of 0, 1, or 2 on the modified Rankin scale) at 30 days.

The primary safety end points were death from any cause within 90 days and symptomatic intracranial hemorrhage, as assessed according to modified Heidelberg bleeding classification within 48 hours after treatment.[15] Other safety measures included the incidence of any intracranial hemorrhage within 48 hours after treatment, the incidence of serious adverse events, and the incidence of any adverse events. If there were signs of neurologic deterioration indicating cerebral hemorrhage, further imaging was to be conducted for follow-up. In addition, local doctors could perform follow-up imaging on the basis of their clinical practice.

STATISTICAL ANALYSIS

The sample-size calculation was based on previous trials,[6,7] with an expected between-group difference of 8 percentage points in the percentage of patients with an excellent outcome (38.% in the tirofiban group and 30.0% in the aspirin group). We calculated that 550 patients per group would be required for the trial to have a power of 80% to detect the expected treatment effect with a two-sided alpha level of 0.05. Taking into account an approximate 5% nonadherence or dropout rate, we intended to enroll 1158 patients.

The primary end-point analysis was based on the modified intention-to-treat population, which was composed of all the patients who underwent randomization independent of treatment received and who completed the trial. We also performed sensitivity analyses of the primary end point, including per-protocol analysis; imputation of missing primary end-point data under the scenarios of worst possible outcome, best possible outcome, and multiple imputation; and a random-effects model to control for center effect.

Figure 1 (facing page). Screening, Randomization, and Follow-up.

The intention-to-treat population included all the patients who were randomly assigned to a trial group. The per-protocol population included all the patients who had undergone randomization, who had received intravenous tirofiban or oral aspirin, and who had not been excluded because of a major protocol violation. Scores on the National Institutes of Health Stroke Scale (NIHSS) range from 0 to 42, with higher scores indicating more severe neurologic deficits.

We used a modified Poisson regression model with robust error estimation to estimate the risk ratio and 95% confidence intervals associated with treatment effect in the analysis of prespecified primary end point and other dichotomous end points, with adjustment for prespecified covariates. The secondary efficacy end point of the global outcome was analyzed with the use of a generalized estimating equation to fit a logistic-regression model.[16] The full range score on the modified Rankin scale was analyzed by fitting an ordinal logistic-regression model. A win ratio approach was also used to compare the modified Rankin scale score and the EQ-5D-5L score.[17] Safety outcomes were assessed in the safety population, which was defined as patients who received any amount of tirofiban or aspirin. To control for multiple comparisons, the secondary efficacy end points were prespecified to be analyzed with the use of a sequential gatekeeping method in the order presented above. For the primary end point and all subsequent end points, a P value of more than 0.05 was considered to indicate no significant difference between the two groups.

RESULTS

PATIENTS

From October 20, 2020, through June 30, 2022, a total of 1616 patients underwent screening at 117 centers in China, of whom 439 did not meet the eligibility criteria (Fig. 1 and Fig. S1 in the Supplementary Appendix). Among the excluded patients, 119 had an NIHSS score of less than 5, and 113 had an NIHSS score of 5 or more but no

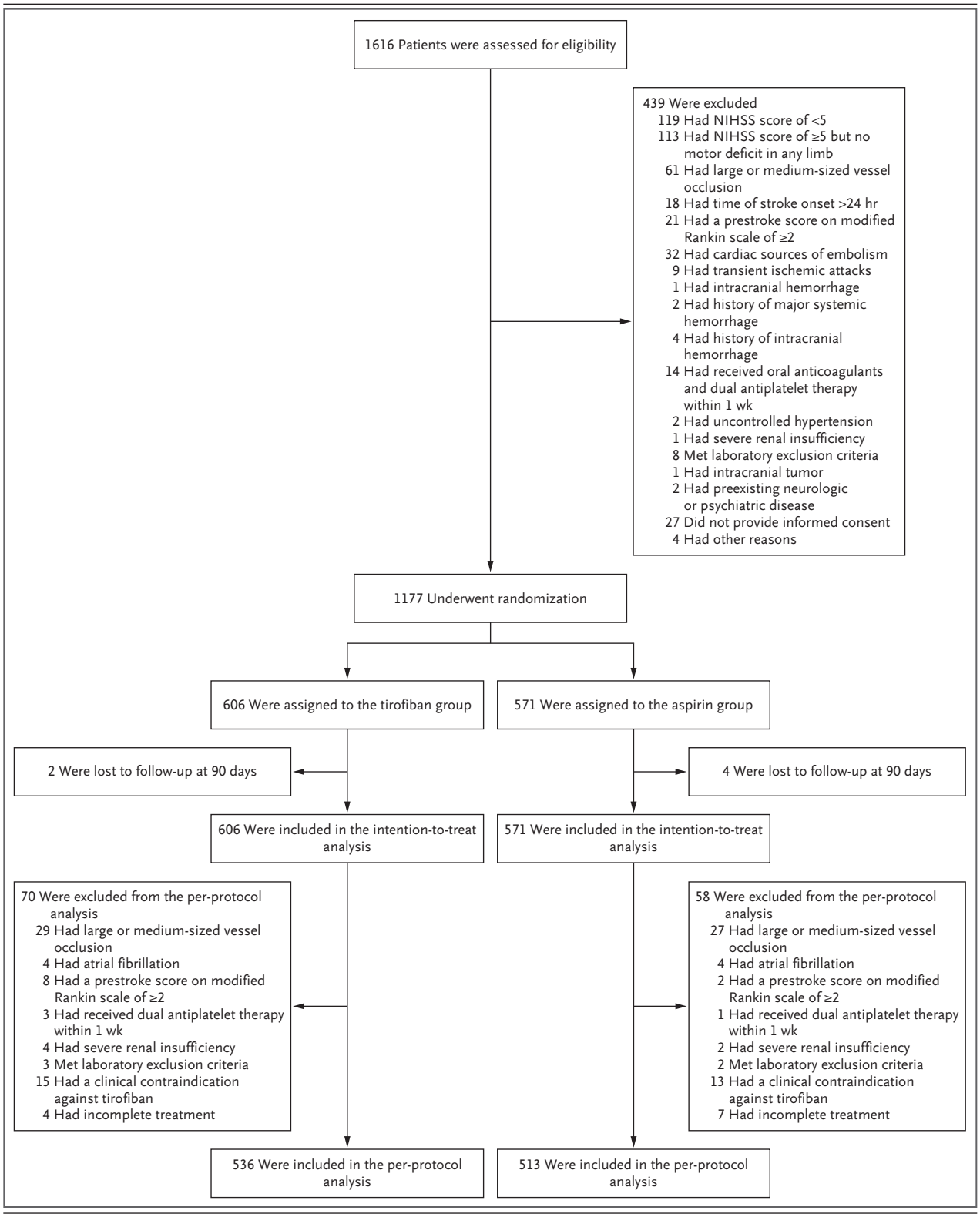

Table 1. Demographic and Clinical Characteristics of the Patients at Baseline.*

Characteristic	Tirofiban Group (N=606)	Aspirin Group (N=571)
Median age (IQR) — yr	68.0 (58.0–75.0)	68.0 (59.0–76.0)
Male sex — no. (%)	379 (62.5)	373 (65.3)
Han Chinese ethnic group — no. (%)†	576 (95.0)	546 (95.6)
Clinical history — no. (%)		
Hypertension	375 (61.9)	381 (66.7)
Hyperlipidemia	189 (31.2)	193 (33.8)
Coronary heart disease	50 (8.3)	54 (9.5)
Diabetes mellitus	162 (26.7)	167 (29.2)
Cerebral infarction	96 (15.8)	83 (14.5)
Smoking	213 (35.1)	188 (32.9)
History of antiplatelet use	20 (3.3)	21 (3.7)
History of anticoagulation	1 (0.2)	0
NIHSS score‡		
Median (IQR)	9.0 (7.0–10.0)	9.0 (7.0–10.0)
Distribution — no. (%)		
5–9	394 (65.0)	359 (62.9)
≥10	212 (35.0)	212 (37.1)
Median ASPECTS (IQR)§	9.0 (9.0–10.0)	9.0 (9.0–10.0)
Median systolic blood pressure at hospital arrival (IQR) — mm Hg	155 (142–166)	156 (144–167)
Median glucose level at hospital arrival (IQR) — mmol/liter¶	6.6 (5.6–8.5)	6.4 (5.4–8.7)
Presentation type — no. (%)		
Ineligible for reperfusion treatment and within 24 hr after stroke onset	332 (54.8)	318 (55.7)
Ineligible for reperfusion treatment and progression 24–96 hr after stroke onset	199 (32.8)	180 (31.5)
IVT followed by early neurologic deterioration	45 (7.4)	45 (7.9)
IVT followed by no neurologic improvement	30 (5.0)	28 (4.9)
Localization of presenting deficit — no. (%)		
Anterior circulation	489 (80.7)	456 (79.9)
Posterior circulation	92 (15.2)	94 (16.5)
Anterior circulation plus posterior circulation	5 (0.8)	7 (1.2)
Unknown‖	20 (3.3)	14 (2.5)
Presumed mechanism of ischemic cerebral event — no./total no. (%)**		
Artery-to-artery embolism	56/601 (9.3)	50/566 (8.8)
Hypoperfusion or impaired emboli clearance beyond a stenosis	25/601 (4.2)	30/566 (5.3)
Penetrating artery disease	438/601 (72.9)	417/566 (73.7)
In situ thrombo-occlusion distal to a stenosed artery	8/601 (1.3)	8/566 (1.4)
Mixture of the above	48/601 (8.0)	42/566 (7.4)
Unknown	26/601 (4.3)	19/566 (3.4)
Median time from stroke onset or progression of stroke symptoms to randomization (IQR) — hr	10.9 (7.2–16.1)	11.2 (7.4–16.8)

Table 1. (Continued.)

Characteristic	Tirofiban Group (N=606)	Aspirin Group (N=571)
Median time from stroke onset or progression of stroke symptoms to initial treatment (IQR) — hr	11.3 (7.5–16.5)	11.5 (7.8–17.1)

* Percentages may not total 100 because of rounding. IQR denotes interquartile range, and IVT intravenous thrombolysis.
† Ethnic group was reported by the patient and verified by means of identification card.
‡ Scores on the National Institutes of Health Stroke Scale (NIHSS) range from 0 to 42, with higher scores indicating more severe neurologic deficits.
§ The Alberta Stroke Program Early Computed Tomography Score (ASPECTS) is an imaging measure of the extent of ischemic stroke. Scores range from 0 to 10, with higher scores indicating a smaller infarct core. Listed are values for the core laboratory assessment.
¶ Data on the glucose level at baseline were missing for 10 patients in the tirofiban group and 5 patients in the aspirin group.
‖ A lack of magnetic resonance imaging prevented localization of the presenting deficit in 34 patients.
** The presumed mechanisms of ischemic cerebral events were assigned on the basis of clinical features, parenchymal imaging, and vessel imaging, with the use of a combination of the Chinese Ischemic Stroke Subclassification system[12] and the system of Kim and colleagues.[13] Further details are provided in the Supplementary Appendix. In addition to the 1167 patients in this table, another 10 patients had a final mechanistic diagnosis of cardioembolism related to the emergence of a cardiac source after enrollment, including 5 of 606 (0.8%) in the tirofiban group and 5 of 571 (0.9%) in the aspirin group.

motor deficit in any limb. A total of 1177 patients were enrolled, with 606 assigned to the tirofiban group and 571 to the aspirin group. No patient crossover to the other treatment strategy or nonreceipt of assigned trial drug occurred. Six patients were lost to follow-up at 90 days. Outcomes at 90 days were obtained in 1171 patients (99.5% of those who underwent randomization, 794 with telephone or audio assessments and 377 with video assessments).

BASELINE CHARACTERISTICS

The characteristics of the patients at baseline were similar in the two groups (Table 1 and Tables S1 and S2). The representativeness of the enrolled patients is summarized in Table S3. The median NIHSS score before trial entry was 9 (interquartile range, 7 to 10) in the two groups; the median time from stroke onset or progression of stroke symptoms to randomization was 10.9 hours (interquartile range, 7.2 to 16.1) in the tirofiban group and 11.2 hours (interquartile range, 7.4 to 16.8) in the aspirin group. The most common reason for enrollment was ineligibility for reperfusion within 24 hours after onset of stroke owing to the time window, contraindication for IVT, or no large or medium-sized vessel occlusion for EVT. Approximately 15% of the patients had a posterior circulation stroke. Information on occlusion distal to large and medium-sized vessels was not consistently available. The median Alberta Stroke Program Early Computed Tomography Score (ASPECTS; range, 0 to 10, with higher scores indicating less volume of infarction or ischemia) was 9 in both groups; therefore, patients had small infarctions.

EFFICACY END POINTS

An excellent outcome (score of 0 or 1 on the modified Rankin scale) occurred in 176 of 604 patients (29.1%) in the tirofiban group and in 126 of 567 patients (22.2%) in the aspirin group (adjusted risk ratio, 1.26; 95% confidence interval [CI], 1.04 to 1.53; P=0.02) (Fig. 2, Table 2, and Table S4). For the first secondary end point of a favorable outcome as assessed across four scales with the global outcome statistic, the adjusted common odds ratio (tirofiban group vs. aspirin group) was 1.38 (95% CI, 1.07 to 1.78; P=0.01). The median score on the modified Rankin scale at 90 days was 2 (interquartile range, 1 to 3) in the tirofiban group and 2 (interquartile range, 2 to 3) in the aspirin group (adjusted common odds ratio for a shift in the direction of a better outcome on the modifed Rankin scale, 1.23; 95% CI, 1.00 to 1.51; P=0.06) (Fig. 2). Because this test in the secondary-end-point gatekeeping sequence did not meet

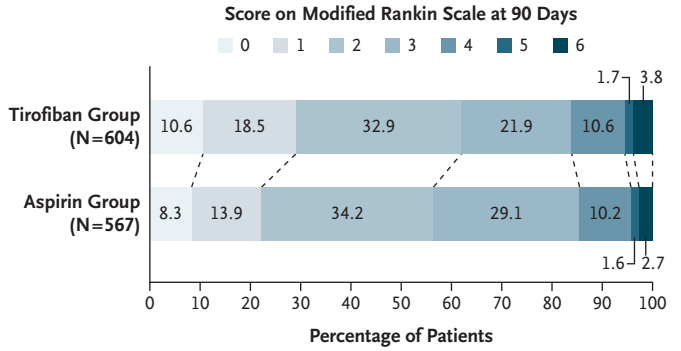

Figure 2. Distribution of Scores on the Modified Rankin Scale at 90 Days (Intention-to-Treat Population).

Shown are the distribution of scores on the modified Rankin scale among patients in the tirofiban group and the aspirin group. Scores range from 0 to 6, with 0 indicating no symptoms, 1 no clinically significant disability, 2 slight disability, 3 moderate disability, 4 moderately severe disability, 5 severe disability, and 6 death. Data for two patients in the tirofiban group and four patients in the aspirin group were missing and were not included in the chart.

the prespecified threshold for statistical significance, results for this end point and all subsequent secondary end points are considered to be not significantly different between groups. The per-protocol analysis yielded results that were similar to those of the primary analysis (Fig. S2 and Table S5). The results of subgroup analyses are shown in Figure S5 and Table S6. The effect of tirofiban in sensitivity analyses was in the same direction as in the primary analysis, but no definite conclusions can be drawn from these results (Table S7).

SAFETY END POINTS

Death occurred in 23 of 604 patients (3.8%) in the tirofiban group and in 15 of 567 patients (2.6%) in the aspirin group (adjusted risk ratio, 1.62; 95% CI, 0.88 to 2.95; P=0.12) (Table 3 and Fig. S3). Symptomatic intracranial hemorrhage occurred in 6 of 606 patients (1.0%) in the tirofiban group and in 0 of 571 patients in the aspirin group (Table 3 and Fig. S4); this represented a significantly higher percentage in the tirofiban group. The percentage of patients with serious adverse events was similar in the two groups, as was the percentage of patients with any adverse event (Table 3 and Tables S8, S9, and S10).

In the tirofiban group, 235 of 606 patients (38.8%) underwent follow-up imaging with the use of computed tomography (CT), 280 (46.2%) underwent follow-up imaging with the use of diffusion-weighted imaging (DWI), and 91 (15.0%) underwent no follow-up imaging. In the aspirin group, 187 of 571 patients (32.7%) underwent follow-up imaging with the use of CT, 271 (47.5%) underwent follow-up imaging with the use of DWI, and 113 (19.8%) underwent no follow-up imaging.

DISCUSSION

In this trial involving patients with acute ischemic stroke of recent onset or progression of ischemic symptoms, who were generally ineligible for conventional reperfusion treatments or whose condition had either worsened or had no improvement after thrombolytic therapy, and who had no large or medium-sized intracranial vessel occlusion, intravenous tirofiban was associated with a higher likelihood of an excellent outcome at 90 days than oral aspirin. Results for secondary end points, with the exception of improvement on a global outcome combining measures of disability, did not differ significantly between the two groups because they failed in a hierarchical statistical analysis. The incidence of symptomatic intracranial hemorrhage was low in both groups but was slightly higher with tirofiban. Most of the strokes were presumed to have an atherosclerotic origin.

Two main differences in trial design may have contributed to the contrast between the current findings and those of two previous small, randomized clinical trials that suggested safety but did not show benefit of tirofiban.[6,7] First, the sample size of this trial was 5 to 10 times as large as the sample size in those trials, which were powered to detect only very large beneficial treatment effects. Second, one of the previous trials enrolled a population with, on average, milder presenting stroke severity, which limited the opportunity for treatment to show a differential benefit.[7] In addition, our trial, unlike previous ones, required patients to have moderate or major motor deficits in at least one limb at entry, a factor that is associated with poor final outcomes. Our trial results are consistent with those of the Efficacy and Safety of Tirofiban in Clinical Patients with Acute Ischemic Stroke (ESCAPIST) trial,[23] which showed efficacy and safety of intravenous tirofiban in

Table 2. Primary and Secondary Efficacy End Points (Intention-to-Treat Population).*

End Point	Tirofiban Group (N=606)	Aspirin Group (N=571)	Effect Measure†	Effect Value (95% CI)†	P Value
Primary efficacy end point					
Score of 0 or 1 on the modified Rankin scale at 90 days — no./total no. (%)‡	176/604 (29.1)	126/567 (22.2)	Risk ratio	1.26 (1.04–1.53)	0.02
Secondary efficacy end points					
Global outcome at 90 days§	—	—	Common odds ratio	1.38 (1.07–1.78)	0.01
Median score on the modified Rankin scale at 90 days (IQR)¶	2 (1–3)	2 (2–3)	Common odds ratio	1.23 (1.00–1.51)	0.06‖
Score of 0, 1, or 2 on the modified Rankin scale at 90 days — no./total no. (%)	375/604 (62.1)	320/567 (56.4)	Risk ratio	1.07 (0.98–1.16)	—
Median EQ-5D-5L score at 90 days (IQR)**	0.83 (0.64–0.93)	0.78 (0.56–0.84)	Win ratio	1.40 (1.23–1.62)	—
Score of 0 or 1 on the modified Rankin scale at 30 days — no./total no. (%)	139/605 (23.0)	96/568 (16.9)	Risk ratio	1.29 (1.03–1.62)	—
Score of 0, 1, or 2 on the modified Rankin scale at 30 days — no./total no. (%)	307/605 (50.7)	263/568 (46.3)	Risk ratio	1.06 (0.95–1.18)	—

* Statistics on the assessment of the goodness of fit of the models are provided in Tables S11 and S12 in the Supplementary Appendix.
† Common odds ratios and risk ratios for the tirofiban group as compared with the aspirin group were adjusted for age, severity of stroke symptoms, IVT (yes or no), and time from stroke onset or progression of stroke symptoms to randomization but were not adjusted for multiple comparisons.
‡ Scores on the modified Rankin scale of functional disability range from 0 (no symptoms) to 6 (death).
§ The global outcome analysis is a multidimensional calculation of a favorable outcome that combines the estimation of treatment effect on four different scales into a single odds ratio, so there is no corresponding global numerator. The four measures are a score of 0 or 1 on the modified Rankin scale, an NIHSS score of 0 or 1, a score of 95 to 100 on the Barthel Index (which assesses 10 categories of daily function, with scores ranging from 0 to 100 and with higher scores indicating better independent function), and a score of 5 on the Glasgow Outcome Scale (which ranges from 1 to 5, with higher scores indicating better neurologic recovery). Data were missing for two patients in the tirofiban group and four patients in the aspirin group.
¶ A partial proportional-odds model with age, baseline NIHSS score, and time from stroke onset to randomization as covariates but allowing nonproportionality only in age was used to estimate the common odds ratio for a shift in the direction of a better outcome on the modifed Rankin scale on the modified Rankin scale. Data were missing for two patients in the tirofiban group and four patients in the aspirin group.
‖ Because this test in the secondary-end-point gatekeeping sequence did not meet the prespecified threshold for statistical significance, results for this end point and all subsequent secondary end points are considered to be not significantly different between the two groups.
** Total scores on the EuroQol 5-Dimension 5-Level questionnaire (EQ-5D-5L) range from –0.391 to 1, with higher scores indicating a better quality of life across the five dimensions of mobility, self-care, usual activities, pain or discomfort, and anxiety or depression. Data were missing for two patients in the tirofiban group and four patients in the aspirin group.

patients with ischemic stroke without presumed cardioembolism within 12 hours after stroke onset. Distinct from ESCAPIST, the current trial enrolled patients with more severe symptoms (median NIHSS score at baseline of 9, as compared with 5 or 6 in the ESCAPIST trial) and allowed for an extended time window (24 hours vs. 12 hours), which may have resulted in a lower incidence of an excellent outcome in our trial. In addition, our trial included a broader population of patients with a recent onset of ischemia or progression of ischemia, which contributed to the larger sample. In contrast to the current trial, the Endovascular Treatment With versus Without Tirofiban for Patients with Large Vessel Occlusion Stroke (RESCUE BT) trial failed to show a difference from placebo in primary or secondary outcomes[8]; however, that trial enrolled patients with proximal large-vessel occlusion, who were excluded from the current trial.

Our trial has limitations. First, the type of patient presentation varied, with enrollment of patients ineligible for reperfusion therapy and of patients receiving thrombolysis or thrombectomy with subsequent progression of stroke symptoms. However, the patients shared several commonalities. Most had presumed atherothrombotic events as the cause of stroke, and many

Table 3. Safety End Points.

End Point	Tirofiban Group (N=606)	Aspirin Group (N=571)	P Value
Primary end points			
Death — no. of patients/total no. (%)	23/604 (3.8)*	15/567 (2.6)*	0.12
Symptomatic intracranial hemorrhage — no. of patients (%)†			
As defined in HBC criteria‡	6 (1.0)	0	0.03
Hemorrhage infarction type 1	1 (0.2)	—	—
Hemorrhage infarction type 2	1 (0.2)	—	—
Parenchymal hematoma type 1	1 (0.2)	—	—
Parenchymal hematoma type 2§	3 (0.5)	—	—
As defined by NINDS criteria¶	6 (1.0)	0	0.03
As defined by ECASS II criteria‖	5 (0.8)	0	0.06
As defined by ECASS III criteria**	5 (0.8)	0	0.06
As defined by SITS-MOST criteria††	4 (0.7)	0	0.13
Secondary end points — no. of patients (%)			
Intracranial hemorrhage on any imaging	6 (1.0)	0	0.03
Serious adverse event‡‡	97 (16.0)	74 (13.0)	0.14
Any adverse event§§	380 (62.7)	349 (61.1)	0.58
Bleeding event¶¶			
Severe	9 (1.5)	1 (0.2)	—
Moderate	2 (0.3)	0	—
Mild	59 (9.7)	32 (5.6)	—

* The adjusted risk ratio for the tirofiban group as compared with the aspirin group was 1.62 (95% CI, 0.88 to 2.95). The risk ratio was adjusted for age, severity of stroke symptoms, IVT (yes or no), and time from stroke onset or progression of stroke symptoms to randomization.

† This end point was defined as symptomatic intracranial hemorrhage detected by brain imaging as a relevant change in neurologic status and the absence of another explanation for deterioration.

‡ The definition according to the Heidelberg bleeding classification (HBC) was symptomatic intracranial hemorrhage detected by brain imaging as a relevant change in neurologic status; the absence of another explanation for deterioration; an event leading to intubation, hemicraniectomy, or external ventricular draining placement; or other major medical or surgical intervention.

§ One patient had parenchymal hematoma type 2 combined with remote parenchymal hematoma and intraventricular hemorrhage.

¶ The definition according to the National Institute of Neurological Disorders and Stroke (NINDS) was any new hemorrhage associated with any neurologic deterioration.[18]

‖ The definition according to the European Cooperative Acute Stroke Study (ECASS) II was any hemorrhage with neurologic deterioration, as indicated by an NIHSS score that was higher by 4 points or more than the value at baseline or the lowest value in the first 7 days, or any hemorrhage leading to death.[19]

** The definition according to the ECASS III was the same as that in the ECASS II, plus the hemorrhage must have been identified as the predominant cause of the neurologic deterioration.[20]

†† The definition of symptomatic intracranial hemorrhage according to the Safe Implementation of Thrombolysis in Stroke–Monitoring Study (SITS-MOST) was local or remote parenchymal hematoma type 2 on the imaging scan obtained 22 to 36 hours after treatment, plus neurologic deterioration, as indicated by an NIHSS score that was higher by 4 points or more than the baseline value or the lowest value between baseline and 24 hours, or hemorrhage leading to death.[21]

‡‡ A summary and details of serious adverse events are provided in Tables S8 and S9.

§§ A summary of adverse events is provided in Table S10.

¶¶ 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]

such events were due to small deep infarcts presumably arising from micro-atherosclerosis within or at the ostium of a deep penetrating artery,[24] which limits the generalizability of the trial results to populations that have mainly cardioembolic strokes. All enrolled patients had at least moderately severe deficits. Most had neurologic signs that were fluctuating or progressing but had only small or modest established infarct volumes on imaging as determined by the ASPECTS. Although a small infarct volume was not an enrollment criterion, the observed volumes were concordant with the absence of large-vessel occlusion. All the patients therefore had a potential basis for a response to pharmacologic therapy to block platelet aggregation and promote disaggregation of newly formed platelet aggregates.[25-27] Second, only a small proportion of enrolled patients had been treated with IVT. Third, the observed incidences of an excellent outcome in both trial groups were lower than expected. This might be because a large proportion of patients were recruited from nonacademic hospitals and may not have received out-of-hospital rehabilitation after their strokes, limiting functional recovery in both groups. Fourth, follow-up imaging at 24 to 36 hours in the absence of neurologic worsening was not required, which limits ascertainment of the incidence of asymptomatic hemorrhagic transformation.

Among patients with acute ischemic stroke of recent onset and no large or medium-sized intracranial vessel occlusion and who were not eligible for reperfusion therapy or whose symptoms progressed after thrombolysis, intravenous tirofiban resulted in a greater likelihood of an excellent outcome at 90 days than oral aspirin. Results for secondary end points did not consistently support the primary end-point analysis. The incidence of symptomatic intracranial hemorrhage was low in both groups but slightly higher with tirofiban.

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APPENDIX

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