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Tirofiban for Disabling Stroke Without Large or Medium Size Vessel Occlusion

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Abstract:	BACKGROUND We aimed to assess the efficacy and safety of the tirofiban compared with aspirin for patients with acute ischemic stroke without large or medium size vessel occlusion within 24h of stroke onset or stroke symptom progression. METHODS In a multicenter trial in China, we randomly assigned patients with strokes without large or medium vessels occlusion and National Institute of Health Stroke Scale ≥5 with at least one limb with NIHSS motor item score of 2-4 in a 1:1 ratio to intravenous tirofiban therapy or oral aspirin 100 mg/d followed by aspirin 90 days in both groups. The primary efficacy endpoint was excellent outcome, defined as 0 or 1 on the modified Rankin Scale at 90 days. The primary safety endpoints included death and symptomatic intracranial hemorrhage. RESULTS We enrolled a total of 1177 patients and randomly assigned 606 to the tirofiban group and 571 to the aspirin group. The percentage with mRS of 0-1 with tirofiban was 29.1% vs. 22.2% for aspirin (adjusted risk ratio, 1.26; 95% CI; 1.04 to 1.53, P=0.02). Three of 6 secondary outcomes supported the primary analysis, including the prespecified lead secondary outcome. The incidence of symptomatic intracranial hemorrhage was 1.0% vs. 0%, respectively (P=0.03). CONCLUSIONS In a trial conducted in China of stroke patients with recent onset or progression of ischemia and without large or medium size intracranial vessel occlusion, intravenous tirofiban resulted in a higher overall proportion of excellent outcomes compared to low-dose aspirin but was associated with more intracranial hemorrhages.

Title page

Tirofiban for Disabling Stroke Without Large or Medium Size Vessel Occlusion

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ABSTRACT

BACKGROUND

We aimed to assess the efficacy and safety of the glycoprotein IIb/IIIa receptor inhibitor tirofiban compared with aspirin for patients with acute ischemic stroke without large or medium size vessel occlusion within 24h of stroke onset or stroke symptom progression.

METHODS

In a multicenter trial in China, we randomly assigned patients with strokes without large or medium size vessels occlusion and National Institute of Health Stroke Scale ≥5 with at least one limb with NIHSS motor item score of 2-4 (NIHSS, range 0 to 42, higher indicating greater deficit) in a 1:1 ratio to intravenous tirofiban therapy or oral aspirin 100 mg/d followed by aspirin 90 days in both groups. Enrolled patients all had recent onset or progression of ischemia, as evident by any of 4 presenting courses: ineligible for thrombolysis or thrombectomy; progression of stroke symptoms between 24 and 96 hours from stroke onset; worsening after thrombolysis; and thrombolysis with no improvement at 4 to 24 hours. The primary efficacy endpoint was excellent outcome, defined as 0 or 1 on the modified Rankin Scale (mRS, ranging from 0 [no symptoms] to 6 [death]) at 90 days. The primary safety endpoints included death and symptomatic intracranial hemorrhage.

RESULTS

We enrolled a total of 1177 patients and randomly assigned 606 to the tirofiban group and 571 to the aspirin group. The percentage with mRS of 0-1 with tirofiban was 29.1% *vs.* 22.2% for aspirin (adjusted risk ratio, 1.26; 95% confidence interval [CI]; 1.04 to 1.53, P=0.02). Three of 6 secondary outcomes supported the primary analysis, including the prespecified lead secondary outcome (improvement on a global score combining measures of disability, neurologic deficit, and instrumental activities of daily living). The incidence of symptomatic intracranial hemorrhage was 1.0% *vs.* 0%, respectively (P=0.03).

CONCLUSIONS

In a trial conducted in China of stroke patients with recent onset or progression of ischemia and without large or medium size intracranial vessel occlusion, intravenous tirofiban resulted in a higher overall proportion of excellent outcomes compared to low-dose aspirin but was associated with more intracranial hemorrhages.

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INTRODUCTION

The therapeutic time-window after stroke onset and contraindications to treatment limit the use of intravenous thrombolysis (IVT) to less than 10% of stroke patients[1] and endovascular thrombectomy (EVT) is effective mainly in the treatment of acute large or medium size vessel occlusion stroke. As a result, there are patients with recent onset or recent progression of acute stroke without large or medium artery occlusion for whom currently available therapies are suboptimal. This patient group includes individuals with 4 presenting courses. First are patients who present within 24h of onset but are ineligible for intravenous or endovascular reperfusion therapy. For these patients one treatment option is aspirin or other antiplatelet agents in the acute phase that have limited benefit.[2] Second are patients not treated with reperfusion therapies who have progression of stroke symptoms 24-96h after onset. Third and fourth are patients who receive IVT but have neurological deterioration or no improvement within the first 24h after treatment, a circumstance that has been estimated to occur in more than half of patients who have received IVT and is associated with poor outcome.[3]

As a result of success of glycoprotein IIb/IIIa inhibitors in treating patients with acute coronary syndromes, there is potential of this and similar agents to inhibit the activated platelet-mediated thrombosis in acute stroke.[4]–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 3h of its stopping administration. The safety and efficacy of tirofiban in the early management of stroke were assessed in the SETIS[5] trial that was stopped early for lack of efficacy

and the SaTIS[6] trial that found no beneficial effect on stroke outcome at 1 week or 5 months. Several uncontrolled observational studies have suggested that tirofiban alone or as adjunctive therapy to IVT may be effective in selected AIS patients.[3,7,8]

We conducted a trial of the efficacy and safety of tirofiban compared to aspirin in the treatment of acute ischemic stroke (RESCUE BT2) in patients without large or medium size vessel occlusion within 24h of stroke onset or stroke symptom progression who were ineligible for conventional treatment, deteriorated, or failed to improve after thrombolysis.

METHODS

TRIAL DESIGN

This was a multicenter, randomized, double-blind, double-dummy clinical trial in China. The trial protocol was approved by a central medical ethics committee and the research board of each participating center. All enrolled patients or their legal representatives provided written informed consent before randomization. The protocol is provided in the Supplement Appendix and has been published previously.[9]

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 event events. A core laboratory assessed all neuroimaging studies in a blinded manner.

This trial was funded by the National Natural Science Foundation of China (Project

Number: 82071323). Tirofiban and its placebo (saline), and placebo of aspirin enteric-coated tablets were manufactured and provided by Lunan Pharmaceutical Group Co., Ltd., Linyi, China. Aspirin enteric-coated tablets were produced by Bayer Schering Pharma, and purchased and provided by Lunan Pharmaceutical Group Co., Ltd., Linyi, China. These entities were not involved in the design of the trial; in the collection, analysis, or interpretation of the data; or in the preparation of the manuscript or the decision to submit for publication. An independent data-monitoring committee oversaw the trial and reviewed the trial data regularly. The first and last authors design the study. The first author wrote the first and subsequent drafts of the manuscript with inputs from all the authors. Members of the executive committee collected the data and made the decision to submit the manuscript for publication. The authors vouch for the completeness and accuracy of the reported data and the fidelity of the trial to the protocol and for complete reporting of adverse events. An independent statistician was responsible for the statistical analysis.

PATIENTS

Patients were adults aged 18 years 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 exhibited any of the following presentations: 1) they were within 24h of time last known well and ineligible for IVT (due to arrival after 4.5 hours or other contraindication) or EVT (due to no large or medium size vessel occlusion target); 2) were more than 24h and less than 96h after time last known well but within 24h of

ischemic stroke progression [worsening of ≥2 points on the National Institutes of Health Stroke Scale (NIHSS)] and ineligible for IVT or EVT; 3) treated with IVT followed by early neurological deterioration (worse NIHSS by ≥4 points) within the first 24h; 4) treated with IVT followed by no neurological improvement (neurological improvement was defined as a decrease in the NIHSS score by ≥2 points) within 4-24h post-lytic therapy. Patients had a ischemic stroke with NIHSS score of ≥5 prior to trial entry with at least one limb with NIHSS motor item score of 2-4. CT angiography, MR angiography, or digital subtraction angiography were performed to identify patients without visible large or medium intracranial vessel occlusion. Patients with imaging-confirmed intracranial hemorrhage and any definite source of cardiac embolism were excluded from the trial (Details in Supplementary Appendix).

RANDOMIZATION AND TREATMENT

Patients were randomly assigned in a 1:1 ratio to receive either intravenous tirofiban 0.4μg/kg/min for 30 minutes followed by a continuous infusion of 0.1μg/kg/min for up to 48h with oral aspirin placebo therapy (tirofiban group) or oral aspirin 100mg per day for 2 days in tirofiban group and aspirin group with intravenous tirofiban placebo therapy (aspirin group). Beginning approximately at the 44th hour after administration of intravenous trial drug, all patients were to receive oral aspirin tablets at 100mg per day until day 90. Randomization used a centralized website and stratified according to the participating center with a permutation block size of 4. The placebos were identical in appearance to active study drugs. aspirin placebo or oral aspirin was to be

administered Concomitant treatment was performed according to the current Chinese Stroke Association guidelines.[10]

OUTCOME MEASURES

The primary efficacy endpoint was an excellent outcome, defined as a score of 0 or 1 on the modified Rankin Scale at 90 days after randomization (mRS, an ordinal global disability scale from 0 [no symptoms]to 6 [death]). The primary score assessment was based on central evaluation by means of video or audio by evaluators who were blinded to treatment assignment. The primary mRS endpoint was centrally adjudicated based on video in 794 evaluations and audio in 377 evaluations. The secondary efficacy endpoints were: 1) favorable outcome, according to 90 days scores as assessed by a global test statistic that simultaneously tests for day 90 effect on 0 or 1 on the mRS, 0 or 1 on the NIHSS, 95 to 100 on the Barthel Index [ranging from 0 to 100, with higher values indicating better independent function], and a score of 5 on the Glasgow Outcome Scale [ranging from 1 to 5, with higher values indicating better neurologic recovery]); 2) level of disability at 90 days as assessed by shift across all 7 levels of the mRS; 3) the proportion of patients functionally independent (mRS score of 0 to 2) at 90 days; 4) score of the European Quality of Life 5-Dimension 5-level scale (EQ-5D-5L; range, −0.39 to 1; lower scores denote a worse quality of life) at 90 days; 5) the proportion of patients with excellent outcome at 30 days; and 6) the proportion of patients functionally independent at 30 days.

The primary safety endpoints were all-cause mortality within 90 days and the incidence of symptomatic intracranial hemorrhage (sICH) assessed according to modified Heidelberg bleeding classification within 48h after treatment.[11] Other safety measures included the incidence of any intracranial hemorrhage within 48h after treatment, the incidence of serious adverse events, and the incidence of any adverse events.

STATISTICAL ANALYSIS

The sample-size calculation was based on the previous studies[5,6] with an expected absolute between-group difference of 8 percentage points in proportion of patients with the primary efficacy outcome (30.0% in the aspirin group and 38.0% in the tirofiban group). We calculated that 550 patients per group would be required to have a power of 80% to show the expected treatment effect with a two-sided alpha of 0.05. Taking into account an approximate 5% non-adherence or dropout rate, we intended to enroll 1158 patients.

The primary outcome analysis was based on a complete case of the intention-to-treat population, which included patients with a valid assessment of mRS at 90 days. We also performed some sensitivity analyses of primary outcome including per-protocol analysis, imputation of missing primary outcome under the scenarios of worst possible outcome, best possible outcome, and multiple imputation, and random effect model to control for center effect.

We used modified Poisson regression model with robust error estimation to estimate the risk ratio and 95% confidence intervals (CI) associated with treatment effect in the

analysis of prespecified primary outcome and other dichotomous outcome adjusted for prespecified covariates. Secondary efficacy outcome of the global outcome score was analyzed using generalized estimating equation logistic regression model.[12] The full range score on the mRS score was analyzed by fitting an ordinal logistic regression model. A win ratio approach was also used to compare the mRS score and the EQ-5D-5L score.[13] The confidence intervals for efficacy comparisons reported in the manuscript have not been adjusted for multiplicity and cannot be used as hypothesis tests. Efficacy outcomes were assessed in the intention-to-treat population and repeated in per-protocol population. Safety outcomes were assessed in the safety population. To control multiplicity, the secondary efficacy endpoints were prespecified to be analyzed using sequential gatekeeping method.

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. Among the excluded patients, 119 had a NIHSS score <5 and 113 had a NIHSS score ≥ 5 but without motor deficit of any limbs. (Fig. 1 and Fig. S1 in the Supplementary Appendix). A total of 1177 patients were enrolled, 606 (51.5%) in the tirofiban group and 571 (48.5%) in the aspirin group. No patient crossover to the other treatment strategy or non-receipt of assigned study drug occurred. Six patients lost follow-up at 90 days.

BASELINE CHARACTERISTICS

Baseline characteristics of the two groups were similar (Table 1and Table S1 and S2 in the Supplementary Appendix). The background information of the enrolled patients is summarized in Table S3. The median NIHSS score prior to trial entry was 9 (interquartile range [IQR], 7-10) in the two groups; the median time from stroke onset or stroke symptom progression to randomization was 10.9h (IQR, 7.2-16.1) in the tirofiban group and 11.2h (IQR, 7.4-16.8) in the aspirin group. The most common reason for enrollment was ineligibility for reperfusion within 24 hours of onset of stroke due to the time-window and contraindication for IVT and no large or medium size vessel occlusion for EVT. Approximately 15% of participants had a posterior circulation stroke.

EFFICACY OUTCOME

Tirofiban therapy was associated with excellent outcome of mRS 0-1 in 176 of 604 patients (29.1%) in the tirofiban group and in 126 of the 567 patients (22.2%) in the aspirin group (adjusted risk ratio, 1.26; 95% CI, 1.04 to 1.53; P=0.02) (Fig. 2, Table 2 and Table S4). For the first secondary outcome of favorable outcome as assessed across 4 scales with the global statistic the adjusted odds ratio was 1.38 (adjusted common odds ratio, 95% CI, 1.07 to 1.78, P = 0.01). The median score on the mRS at 90 days was 2 (IQR, 1 to 3) in tirofiban group and 2 (IQR, 2 to 3) in the aspirin group (adjusted common odds ratio, 1.23; 95% CI, 1.00 to 1.51, p = 0.06). As this second test in the

secondary endpoint gatekeeping sequence did not meet the prespecified threshold for statistical significance, all subsequent secondary outcomes were considered exploratory. (Supplemental Appendix) The per-protocol analysis yielded similar results to the primary analysis (Fig. S2 and Table S5 in the Supplementary Appendix). The results of subgroup analysis are given in Fig. S3 and Table S6 in the Supplementary Appendix. The beneficial effect of tirofiban remained robust in all sensitivity analyses (Table S7 in the Supplementary Appendix).

SAFETY OUTCOMES

Death occurred in 23 patients (3.8%) in the tirofiban group and in 15 patients (2.7%) in the aspirin group (adjusted risk ratio, 1.62; 95% CI, 0.88 to 2.95; P=0.12) (Table 3 and Fig. S4 in the Supplementary Appendix). Symptomatic intracranial hemorrhage and any intracranial hemorrhage events occurred in 6 (1%) patients in the tirofiban group, and none of the patients in the aspirin group had sICH and ICH (Table 3 and Fig. S5 in the Supplementary Appendix). Number of patients with serious adverse events and all adverse events were similar between the two groups (Table 3 and Table S8, Table S9 and Table S10 in the Supplementary Appendix).

DISCUSSION

In this trial involving patients with acute ischemic stroke with recent onset or progression of ischemia who were generally ineligible for conventional reperfusion or worsened or with no improvement after thrombolytic therapy, and who had no large or

medium size intracranial vessel occlusion, treatment with intravenous tirofiban compared with oral aspirin increased the likelihood of excellent outcome at 90 days. Three of 6 secondary outcomes supported the primary analysis, included the prespecified lead secondary outcome (improvement on a global score combining measures of disability, neurologic deficit, and instrumental activities of daily living). The overall rate of sICH was low in both groups but was higher with tirofiban as compared with aspirin.

There are several trial design differences contributing to the contrast between the current study's finding of benefit of tirofiban and the two prior small randomized clinical trials that showed safety but not functional outcome benefit.[5,6] First, the sample size of this study was 5- to 10- fold larger than the prior trials, which were powered to detect only very large-beneficial treatment effects. Second one of the previous trials enrolled population with on average milder presenting stroke severity, limiting the opportunity for treatment to show differential benefit.[6] In addition, this trial, unlike prior ones, required patients to have major motor deficits at entry, a factor for poor final outcome. This trial, consistent with the ESCAPIST[14] trial, demonstrated the efficacy and safety in patients with AIS without cardioembolism within 12 hours of stroke onset. Distinct from the ESCAPIT trial, the current trial enrolled patients with more severe symptoms (median baseline NIHSS score 5-6 vs. 9) and extended time-window (12h vs. 24h), which result in a lower rate of excellent outcome in our trial. In addition, this trial included broader population of patients with recent onset of ischemia or progression of ischemia, contributing to the larger sample size.

Our study has limitations. First the mode of patient presentation varied, with enrollment of both patients ineligible for reperfusion therapy and patients receiving intravenous thrombolysis and if patients early after stroke onset and early after stroke progression. However, the patients shared several commonalities. All were in an unstable ischemic period, due to recent onset or recent progression. More than 90% had thrombotic events as their cause. All had at least moderately severe deficits. But also, the great preponderance had only small established infarct volumes on imaging. All therefore had a physiologic basis for response to pharmacologic therapy to block platelet aggregation and also promote disaggregation of newly formed platelet aggregates.[15-17] Moreover, this trial's population was less heterogenous than that for the 2 already-existed AIS pharmacologic therapies. Both early aspirin and intravenous thrombolysis are indicated for a more heterogenous population that includes patients with visualized large and medium vessel occlusions in addition to their absence and that includes cardioembolic stroke in addition to atherothrombotic stroke. Second, only a small proportion of enrolled patients had been treated with intravenous thrombolysis. We are planning a new study to explore the efficacy and safety of tirofiban in those patients who worsening or with no improvement after IVT. Third, the observed rates of excellent outcome in both treatment groups are lower than expected. This might be because a large proportion of patients were recruited from non-academic hospitals and were not active in out-of-hospital rehabilitation, limiting functional recovery in both groups. Fourth, follow-up imaging at 24-36h in the absence of neurologic worsening was not required, limiting ascertainment of the rate of asymptomatic hemorrhagic

transformation. Fifth, the study population was Asian and most of the population socioeconomically did not have extensive access to posthospitalization care and rehabilitation. Caution should be warranted in generalizing the results.

In conclusion, among patients with acute ischemic stroke with recent onset or progression of ischemia and no large or medium size intracranial vessel occlusion, and who were not eligible for reperfusion therapy or progressed after thrombolysis, intravenous tirofiban resulted in higher rates of excellent outcome at 90 days than oral aspirin but was associated with a small increase in symptomatic intracranial hemorrhage.

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Figure Legends

Figure 1. Enrollment and Outcomes.

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. NIHSS denotes the National Institutes of Health Stroke Scale, mRS modified Rankin Scale.

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

Shown are the distribution of the score on the modified Rankin scale among patients in the tirofiban group and the aspirin group. Score 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. Numbers indicate rounded proportions. 2 patients in the tirofiban group and 4 patients aspirin group without valid assessment due to loss of follow-up were not included in the chart.

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

Characteristics	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. (%) †	576/606 (95.0)	546/571 (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 antiplatelet	20 (3.3)	21 (3.7)
History anticoagulation	1 (0.2)	0 (0.0)
NIHSS score ‡		
Median (IQR)	9.0 (7.0–10.0)	9.0 (7.0–10.0)
5–9 — no. (%)	394 (65.0)	359 (62.9)
10 or more — no. (%)	212 (35.0)	212 (37.1)
Median ASPECTS value (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 24h of onset	332 (54.8)	318 (55.7)
Ineligible for reperfusion treatment and progression 24-96h post-onset	199 (32.8)	180 (31.5)
IVT followed by early neurological deterioration	45 (7.4)	45 (7.9)
IVT followed by no neurological 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)
Ischemic cerebral event mechanism — no. (%) **		
Arterial-to-arterial embolism	56 (9.3)	50 (8.8)
Hemodynamic impairment	25 (4.2)	30 (5.3)
Local branch occlusion	438 (72.9)	417 (73.7)
In situ thrombo-occlusion	8 (1.3)	8 (1.4)
Mixture	48 (8.0)	42 (7.4)
Unknown	26 (4.3)	19 (3.4)
Median time from stroke onset or stroke symptom progression to randomization (IQR) — hr	10.9 (7.2–16.1)	11.2 (7.4–16.8)
Median time from stroke onset or stroke symptom progression to treatment initial (IQR) — hr	11.3 (7.5–16.5)	11.5 (7.8–17.1)

* IQR denotes interquartile range, IVT intravenous thrombolysis.

† Ethnicity group reported by the patient and verified by identification card.

‡ Scores on the National Institutes of Health Stroke Scale (NIHSS) range from 0 to 42, with higher scores indicating more severe neurological 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 glucose at baseline were missing for 10 patients in tirofiban group and 5 patients in aspirin group.

‖ 34 Patients were unable to localize the presenting deficit due to lack of Magnetic Resonance Imaging.

** The ischemic cerebral event mechanisms were assigned by the imaging, and detailed description was listed in the Supplementary Appendix. The data on ischemic cerebral event etiology had been excluded cardiac sources of embolism 5 patients in tirofiban group and 5 patients in aspirin group.

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

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

* mRS denotes modified Rankin scale, IQR interquartile range, NIHSS National Institutes of Health Stroke Scale, GOS Glasgow Outcome Scale, and EQ-5D-5L EuroQol-5 Dimensions 5 Level. Statistics on the assessment of model goodness-of-fit are provided in Table S11 and Table S12 in the Supplementary Appendix.

† Common odds ratio, risk ratio for the tirofiban group, as compared with the aspirin group. Common odds ratio and risk ratio were adjusted for age, stroke symptom severity, intravenous thrombolysis, and time from stroke onset or stroke symptom progression to randomization, but were not adjusted for multiple comparisons.

‡ The modified Rankin Scale of functional disability ranges from 0 (no symptoms) to 6 (death).

§ The Global Outcome Score 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 mRS and on the NIHSS, a score of 95 to 100 on the Barthel Index (which assesses 10 categories of daily function and ranges from 0 to 100, with higher values indicating better independent function), and a score of 5 on the Glasgow Outcome Scale (which ranges from 1 to 5, with higher values indicating better neurologic recovery).

¶ A partial proportional odds model with age, baseline NIHSS score, time from stroke onset to randomization as covariates but allowing nonproportionality only in age was

used to estimate the common odds ratio.

‖ Total scores on the EQ-5D-5L scale 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.

Table 3. Safety Outcomes. *

Outcomes	Tirofiban Group (N=606)	Aspirin Group (N=571)	Treatment Effect (95% CI)	P Value
	no. (%)			
Primary				
Mortality †	23/604 (3.81)	15/567 (2.65)		
Adjusted Risk Ratio ‡			1.62 (0.88 to 2.95)	0.12
Symptomatic intracranial hemorrhage §				
As defined in HBC ¶	6/606 (0.99)	0/571		0.03
By imaging subtype				
Hemorrhage infarction type 1	1/606 (0.16)			
Hemorrhage infarction type 2	1/606 (0.16)			
Parenchymal hematoma type 1	1/606 (0.16)			
Parenchymal hematoma type 2 ‖	3/606 (0.5)			
As defined in NINDS **	6/606 (0.99)	0/571		0.03
As defined in ECASS II ††	5/606 (0.83)	0/571		0.06
As defined in ECASS III ‡‡	5/606 (0.83)	0/571		0.06
As defined in SIST-MOST §§	4/606 (0.66)	0/571		0.13
Secondary				
Any imaging intracranial hemorrhage	6/606 (0.99)	0/571		0.03
Patients with SAE ¶¶	97/606 (16.0)	74/571 (13.0)		0.14
Patients with AE ‖‖	380/606 (62.7)	349/571 (61.1)		0.58
Patients with bleeding event ***				
Severe	9/606 (1.5)	1/571 (0.2)		
Moderate	2/606 (0.3)	0/571		
Mild	59/606 (9.7)	32/571 (5.6)		

* HBC denotes Heidelberg bleeding classification, NINDS National Institute of Neurological Disorders and Stroke, ECASS European Cooperative Acute Stroke Study, SIST-MOST Safe Implementation of Thrombolysis in Stroke Monitoring Study, SAE serious adverse events, AE adverse events.

† The mortality was analyzed in 604 patients in the Tirofiban group and in 567 in the Aspirin group because of loss to follow-up.

‡ Risk Ratio was adjusted for age, stroke symptom severity, intravenous thrombolysis, time from stroke onset or stroke symptom progression to randomization.

§ Symptomatic intracranial hemorrhage detected by brain imaging as a relevant change in neurological status; absence of another explanation for deterioration.

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

‖ There's one patient who 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 ECASS III was the same as that in 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 a score on the NIHSS 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]

¶¶ Summary and details of SAE were in Table S8 and S9 in Supplementary Appendix

‖‖ Summary of AE was in Table S10 in Supplementary Appendix

*** 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]