


Safety of Glycoprotein IIb-IIIa Inhibitors Used in Stroke-Related Treatment: A Systematic Review and Meta-Analysis

Clinical and Applied
Thrombosis/Hemostasis
Volume 26: 1-11
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DOI: 10.1177/1076029620942594
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Abstract

Background: Endovascular therapy and intravenous thrombolysis with recombinant tissue plasminogen activator are the 2 most recommended treatments for acute ischemic stroke (AIS). Glycoprotein (GP) IIb-IIIa inhibitors are short-acting selective reversible antiplatelet agents that emerged as promising therapeutic agents for AIS about 10 years ago. Given the unclear safety profile and application coverage of GP inhibitors, we conducted this meta-analysis to explore the same. **Methods:** We used GP IIb-IIIa inhibitors, intracranial hemorrhage, and mortality as the key words on Medline, Web of Science, and the Embase databases. Randomized controlled trials, prospective literatures, and retrospective studies in English published between 1990 and 2020 were screened. The outcomes were relative risk (RR) of death and 90-day intracerebral hemorrhage (ICH). We pooled the results in 2 categories and conducted a subgroup analysis stratified by different drugs. The choice of the effects model depended on the value of I^2 . **Results:** In all, 3700 patients from 20 studies were included. No GP IIb-IIIa inhibitors were found to have a remarkable influence on the ICH rate. The RR values of symptomatic ICH for abciximab and eptifibatide were 4.26 (1.89, 9.59) and 0.17 (0.04, 0.69), respectively. Both tirofiban and abciximab could decrease the mortality rate within 90 days. Age > 70 years, National Institutes of Health Stroke Scale > 15, and overall dose > 10 mg are risk factors for ICH events with tirofiban usage. Thrombectomy combined with tirofiban was safe for arterial reocclusion prevention. **Conclusions:** In stroke-related treatment, administration of GP IIb-IIIa inhibitors could be safe, but care should be taken regarding drug species and doses. Abciximab can increase the risk of symptomatic intracranial hemorrhage. Tirofiban and eptifibatide can be considered safe in low doses. Suitable patients should be selected using strict criteria.

Keywords

glycoprotein IIb-IIIa inhibitors, ischemic stroke, intracranial hemorrhage, dose

Date received: 14 April 2020; revised: 28 May 2020; accepted: 24 June 2020.

Introduction

Stroke may occur in one of 6 people in their lifetime around the world, and around 5.8 million people die annually from stroke (<http://world-stroke.org>). About 70% of all strokes are ischemic in nature. Acute ischemic stroke (AIS) is defined as the sudden loss of blood flow to a brain area with resulting loss of neurologic function.¹ Thus, early vessel recanalization has been the major target in AIS treatment.² Over the past 2 decades, intravenous thrombolysis has been the main method to achieve vessel recanalization for ischemia-reperfusion.¹ Therapy with intravenous recombinant tissue plasminogen activator (rt-PA) is the first-line option when contraindications are absent.^{3,4} Endovascular treatment proved to be effective in improving functional outcomes for selected patients with AIS⁵

and is recommended by current clinical practice guideline.⁶ However, the application of intravenous rt-PA is limited by a narrow therapeutic time window and relatively poor

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revascularization rates,⁷ and endovascular therapy can cause injury to endothelial cells leading to activation of local platelet aggregation and subsequent early reocclusion.⁸ Demands for more effective and safe thrombolytic agents are required.

Glycoprotein (GP) IIb-IIIa inhibitors are short-acting, reversible, selective platelet antagonists that act by antagonizing the GP IIb-IIIa receptors on the platelet surface and block the final common pathway to platelet aggregation by preventing fibrinogen molecules between adjacent platelets from binding. Thus, GP IIb-IIIa inhibitors could favor endogenous thrombolysis by suppressing thrombus growth and preventing thrombus reformation through competitive inhibition with fibrinogen. Since being approved by the Food and Drug Administration (FDA) for treatment of acute coronary syndrome, GP IIb-IIIa inhibitors have been widely used in percutaneous coronary intervention including angioplasty, thrombectomy, and stent implantation.⁹ Additional data showed that GP antagonists have neuroprotective properties and could improve cerebral microcirculatory blood flow.¹⁰ Hence, researchers have attempted to explore the applicability of GP IIb-IIIa inhibitors in AIS treatment on the basis of existing research in ischemic heart disease.

Tirofiban, eptifibatide, and abciximab are 3 GP IIa-IIIb receptor antagonists approved by the US FDA.¹¹ Yet, their safety in treating stroke and preventing reocclusion after intervention remains debatable. A trial on abciximab therapy for stroke—Abciximab Emergent Stroke Treatment Trial (AbESTT-II)—which enrolled patients with stroke within 6 hours from onset, was stopped ahead of schedule owing to a 6-fold increase in the symptomatic intracranial hemorrhage (SICH) rate.¹² Kellert et al reported that tirofiban raised the risk for fatal intracranial hemorrhage (ICH) in patients with stroke after mechanical thrombectomy in a prospective non-randomized study,⁸ while another recent study found that half-dose abciximab is safe and effective as intravascular therapy for acute stroke.¹³ Ciccone et al¹⁴ last updated the Cochrane systematic review on GP antagonists in 2014 and concluded that GP antagonists not only did not reduce mortality but also significantly increased the risk of SICH. However, their study was based on only 4 randomized controlled trials (RCTs; 3 on abciximab and 1 on tirofiban). By contrast, our analysis addresses what was lacking in the Cochrane review, by discussing the efficacy of GP antagonists combined with mechanical thrombectomy in AIS treatment. Considering the fact that safety profile of GP antagonists is unclear in both clinical trials and retrospective studies, a more comprehensive systematic review is essential.

The present meta-analysis aimed to present the respective ICH risk for 3 GP IIa-IIIb receptor antagonists. The initial analysis was conducted only on RCTs, followed by another one on all study types. For tirofiban, we reported its relationship with age, National Institute of Health stroke scale (NIHSS) at admission, and total dose through regression analysis. Overall, we intended to provide an overview on tirofiban, eptifibatide, and abciximab in AIS and discuss factors that might amplify the incidence of adverse events.

Methods

Search Strategy and Selection Criteria

Published literature from January 1, 1990, through January 30, 2020, were independently retrieved by 2 authors on Medline, Web of Science, and the Embase databases. We screened literature relevant to GP IIb-IIIa inhibitors (Tirofiban, Eptifibatide, Abciximab, etc), stroke, and ICH. Two reviewers independently screened relevant articles through titles and abstracts after duplicate records were eliminated on endnote. A review of the full text of eligible articles was conducted. A third reviewer was consulted if disagreement occurred. A trial or study was included if: (1) it focused on patients with AIS; (2) patients in the experiment group were given abciximab, eptifibatide, or tirofiban; (3) patients in the control group were given placebo (saline) or aspirin, or it was an open-control trial; (4) it was an RCT or a prospective nonrandomized study or a retrospective control study; (5) additional therapies such as thrombolytic therapy (eg, rt-PA), antiplatelet agents, nonsteroidal anti-inflammation drugs, and mechanical thrombectomy were applied in all study arms; (6) ICH, SICH, or death were reported within 90 days; and (7) drug administration was described with adequate details such as dose and infusion speed.

We use the Cochrane risk of bias assessment tool to assess the methodological quality of the selected RCTs and used the Newcastle-Ottawa score to assess the methodological quality of cohort studies. This systematic review reports Preferred Reporting Items for Systematic reviews and Meta-Analyses statement (Figure 1).¹⁵

Data Extraction and Risk Outcomes

The following aspects were extracted from the included studies: (1) Basic demographic characteristics including sex, mean and median age, NIHSS at admission, number of cases in each group, and onset to treatment time; (2) Disease history: hypertension, hyperlipidemia, diabetes, atrial fibrillation; (3) Medication regimen: type of GP receptor inhibitor, total dose, infusion speed, combined thrombolysis, or interventional therapy schedule; and (4) Risk outcomes: caseload of any ICH, SICH, and death within 90 days in each group. Risk ratio (RR) of any ICH and SICH was calculated and analyzed separately. If cases of ICH or SICH in the experimental group was zero, the study was not considered for analysis of ICH or SICH.

Subgroup Analysis and Metaregression Analysis Strategy

We evaluated the GP receptor inhibitor risk in 2 sets. One merely incorporated RCTs, and another included all type of studies including RCTs, cohort, and case-control studies. Regardless of heterogeneity, we first conducted a subgroup analysis with different GP receptor inhibitor types. More comprehensive analysis was performed if heterogeneity in the subgroup was large ($I^2 \geq 75\%$). The total dose of tirofiban was divided into “>10 mg” and “≤10 mg”; patient age was divided

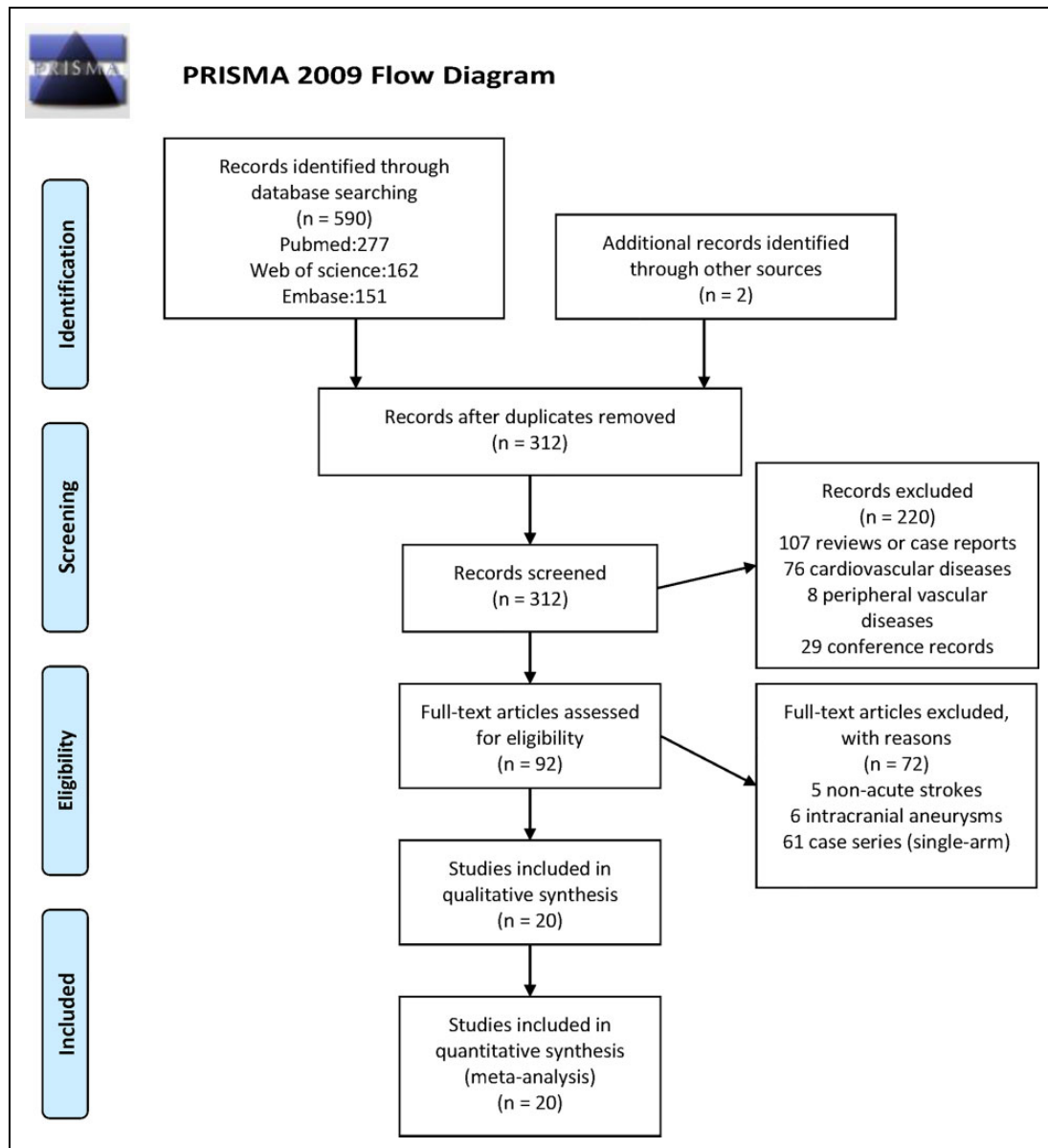


Figure 1. PRISMA 2009 flow diagram. PRISMA indicates Preferred Reporting Items for Systematic reviews and Meta-Analyses.

as “<65 years,” “65 to 70 years,” and “>70 years”; NIHSS at admission was divided as “ ≤ 15 ” and “ > 15 .” Further, based on whether thrombectomy was performed, there are groups of “thrombectomy” and “no thrombectomy”. Next, we conducted a metaregression analysis to further explore the effect of continuous variables such as age and NIHSS on outcomes.

Statistical Analysis

If the lower bound of the 95% CI was > 1 , we considered the GP receptor inhibitors to increase the risk for ICH and mortality. If the lower bound of the 95% CI was < 1 , we considered the GP receptor inhibitors as a protective factor for ICH. Cochran Q test and I^2 test were used in our analysis to quantify the heterogeneity among trials. Cochran Q test was used to verify subgroup differences. If $P \leq .05$, the between-subgroup

differences were considered to be statistically significant. The random effect model was used for data analysis when $I^2 > 75\%$; otherwise, the fixed effect model was used. We carried out the Z test to evaluate statistical significance in metaregression analysis and checked publication bias through funnel plots and Egger regression asymmetry test. All statistical analysis was performed using the R package (version 3.6.1).

Results

Characteristics of Analyzed Studies

Ultimately, 7 RCTs,^{16,17,12,18-21} 11 prospective studies,^{22-24,8,25-28,2,29,30} and 2 retrospective studies^{31,32} with 3700 patients in total were included (Table 1). In all, 5 studies used abciximab, 2 used eptifibatide, and 13 used tirofiban.

Table 1. The Basic Characteristics of Included Studies.^a

Study (reference)	Agent	Study type	Intervention	Age (GPI vs control)	Women: Men (GPI vs control)	Dose
Adams and Bogousslavsky ¹⁶ arm 1	Abciximab	RCT	No	66 ± 13 vs 64 ± 17	(10:5) vs (8:12)	0.15 mg/kg bolus
Adams et al arm 2	Abciximab	RCT	No	63 ± 13	(6:6)	0.2 mg/kg bolus
Adams et al arm 3	Abciximab	RCT	No	64 ± 15	(5:9)	0.2 mg/kg bolus + 0.125 µg/kg/min (12 hours)
Adams et al arm 4	Abciximab	RCT	No	72 ± 14	(5:8)	0.25 mg/kg bolus + 0.125 µg/kg/min (12 hours)
Eckert et al ²³	Abciximab	Prospective	Angioplasty/ stenting	69 (31-84) vs 61 (28-79)	(17:30) vs (7:34)	0.25 mg/kg bolus + 0.125 µg/kg/min (12 hours)
AbESTT ¹⁷	Abciximab	RCT	No	67 ± 13 vs 68 ± 12	(80:120) vs (95:105)	0.25 mg/kg bolus + 0.125 µg/kg/min (12 hours)
AbESTT-II ¹²	Abciximab	RCT	No	68 ± 14 vs 70 ± 13	(103:118) vs (97:121)	0.25 mg/kg bolus + 0.125 µg/kg/min (12 hours)
Nagel et al ²⁴	Abciximab	Prospective	No	65 (28-83) vs 65 (19-86)	(17:26) vs (12:20)	0.25 mg/kg bolus + 0.125 µg/kg/min (12 hours)
Pancioli et al (CLEAR) ¹⁸	Eptifibatid	RCT	No	71 (62-77) vs 61 (55-74)	NA	75 µg/kg bolus + 0.75 µg/kg/min (2 hours)
Pancioli et al (CLEAR-ER) ²¹	Eptifibatid	RCT	No	71 (58-81) vs 75 (60-81)	(48:53) vs (12:13)	135 µg/kg bolus + 0.75 µg/kg/min (2 hours)
Torgano et al (SETIS) ¹⁹	Tirofiban	RCT	No	71 ± 13 vs 73 ± 8	(39:36) vs (38:37)	0.6 µg/kg/min (30 minutes) + 0.15 µg/kg/min (72 hours)
Siebler et al (SaTIS) ²⁰	Tirofiban	RCT	No	67 (34-81) vs 65 (30-82)	(57:74) vs (48:81)	0.4 µg/kg/min (30 minutes) + 0.1 µg/kg/min (48 hours)
Junghans et al ²²	Tirofiban	Prospective	No	62 (36-80) vs 62 (27-77)	(4:14) vs (6:11)	0.4 µg/kg/min (30 minutes) + 0.1 µg/kg/min (24 hours)
Li et al ²⁵	Tirofiban	Prospective	No	66 (29-86) vs 68 (37-86)	(16:25) vs (17:24)	0.4 µg/kg/min (30 minutes) + 0.1 µg/kg/min (24 hours)
Lin et al ²⁶	Tirofiban	Prospective	No	63 (47-82) vs 70 (44-89)	(5:17) vs (5:17)	0.4 µg/kg/min (30 minutes) + 0.1 µg/kg/min (24 hours)
Zhao et al ²⁷	Tirofiban	Prospective	Thrombectomy	61 ± 13 vs 60 ± 12	(21:69) vs (30:60)	5 mg bolus + 0.2-0.25 mg/h (12-24 hours)
Wu et al ²⁸	Tirofiban	Prospective	Thrombectomy	70 (63-76) vs 71 (63-80)	(36:58) vs (56:68)	3.3-10 µg/kg, 50 µg/min
Neuberger et al ²	Tirofiban	Prospective	Thrombectomy	NA	NA	0.4 µg/kg/min (30 minutes) + 0.1 µg/kg/min (48 hours)
Zhang et al ³²	Tirofiban	Retrospective	Thrombectomy	64 ± 13 vs 64 ± 12	(62:92) vs (202:276)	0.25-1.0 mg, 50 µg/min
Kellert et al ⁶	Tirofiban	Prospective	Thrombectomy	64 ± 13 vs 67 ± 14	NA	0.4 µg/kg/min (30 minutes) + 0.1 µg/kg/min (48 hours)
Quan et al ²⁹	Tirofiban	Prospective	Thrombectomy	NA	NA	5 mg bolus + 0.2-0.25 mg/h (12-24 hours)
Sun et al ³⁰	Tirofiban	Prospective	Thrombectomy	66 ± 15 vs 66 ± 13	(20:51) vs (38:86)	0.25-0.5 mg, 1 mL/min
Yu et al ³¹	Tirofiban	Retrospective	Thrombectomy	70 ± 10 vs 67 ± 10	(14:12) vs (13:15)	0.25-0.5 mg, 1 mL/min

Abbreviations: AbESTT, Abciximab Emergent Stroke Treatment Trial; CLEAR, Combined Approach to Lysis Utilizing Eptifibatid and recombinant tissue plasminogen activator; CLEAR-ER, Combined Approach to Lysis Utilizing Eptifibatid and recombinant tissue plasminogen activator in acute ischemic stroke-enhanced regimen; GPI, glycoprotein inhibitors; NA, not applicable; RCT, randomized control trials; SaTIS, Safety of Tirofiban in a cure Ischemic Stroke; SETIS, Study of Efficacy of Tirofiban in acute Ischemic Stroke.

^aIn total, 5 studies discussed abciximab, 3 discussed eptifibatid, 13 discussed tirofiban, and 1 discussed eptifibatid and abciximab.

Table 2. Results of the Methodological Quality Assessment of Randomized Control Trials Included in Our Analyses.^a

Study (Reference)	Random sequence generation	Allocation concealment	Blinding of participant/ personnel	Blinding of outcome assessment	Incomplete outcome data	Selective outcome reporting
Adams et al ¹⁶	Low	Low	Low	Low	Low	Low
AbESTT ¹⁷	Low	Low	Low	Low	Unclear	Low
AbESTT-II ¹²	Low	Low	Low	Unclear	Unclear	Low
CLEAR ¹⁸	Low	Low	Low	Low	Low	Low
CLEAR-ER ²¹	Low	Low	Low	Low	Low	Low
SETIS ¹⁹	Low	Unclear	Low	Low	Low	Low
SaTIS ²⁰	Low	Low	Low	Low	Low	Low

Abbreviations: AbESTT, Abciximab Emergent Stroke Treatment Trial; CLEAR, Combined Approach to Lysis Utilizing Eptifibatide and recombinant tissue plasminogen activator; CLEAR-ER, Combined Approach to Lysis Utilizing Eptifibatide and recombinant tissue plasminogen activator in acute ischemic stroke-enhanced regimen; SaTIS, Safety of Tirofiban in acute Ischemic Stroke; SETIS, Study of Efficacy of Tirofiban in acute Ischemic Stroke.

^aCochrane risk of bias assessment tool was used.

Table 3. Results of the Methodological Quality Assessment of Prospective and Retrospective Cohort Studies Included in Our Analyses.^a

Study (year)	Selection (maximum 4 stars)	Comparability (maximum 2 stars)	Outcome (maximum 3 stars)	Total Newcastle-Ottawa score
Eckert et al ²³	4	1	2	7
Nagel et al ²⁴	4	1	2	7
Junghans et al ²²	3	2	2	7
Li et al ²⁵	3	2	2	7
Lin et al ²⁶	3	1	2	6
Wu et al ²⁸	3	1	2	6
Zhao et al ²⁷	3	2	3	7
Neuberger et al ²	4	1	2	7
Zhang et al ³²	3	1	2	6
Kellert et al ⁸	3	1	2	6
Quan et al ²⁹	3	1	2	6
Sun et al ³⁰	3	2	2	7
Yu et al ³¹	3	2	2	7

^aThe Newcastle-Ottawa score was used. Most included studies carried out a 3-month follow-up. Zhao et al carried out a 1-year follow-up.

Patients in 9 studies received interventional therapy incorporating carotid stenting, angioplasty, or thrombectomy. The whole process of literature selection is presented in a flowchart in Figure 1. Results of assessing the methodological quality RCTs (by Cochrane risk of bias assessment tool) and cohort studies (by Newcastle-Ottawa score) are presented in Tables 2 and 3, respectively.

Risk Ratio for Any ICH

The pooled relative risk value for ICH was 1.05 (95% CI: 0.82-1.34) in RCTs and 1.21 [95% CI: 0.90-1.62] in all studies (Table 4). It indicates that GP receptor antagonists will not increase the risk of ICH. Furthermore, our results of the subgroup analysis on drug species showed that abciximab, eptifibatide, or tirofiban had any significantly influence on ICH.

Risk Ratio for Symptomatic ICH

The pooled relative risk value for SICH was 1.78 (95% CI: 1.04-3.04) in RCTs (Figure 2) and 1.16 (95% CI: 0.92-1.46)

in all studies (Table 4). This suggests that GP receptor antagonists can possibly induce SICH. In subsequent subgroup analysis, the consolidated results of both RCTs only and all studies showed that abciximab could significantly increase SICH risk (RR: 4.26 [1.89-9.59] in RCT and 1.88 [1.17-3.00] in all studies). Surprisingly, however, eptifibatide showed an effect of reducing SICH risk (RR: 0.17 [0.04-0.69] in RCT). Owing to the high heterogeneity of tirofiban, we subsequently performed a subgroup analysis in greater detail (I^2 : 84.9% for ICH and 54.3% for SICH).

Risk Ratio for Mortality Within 90 days

The results incorporating only RCTs suggested that GP receptor antagonists have no effect on mortality in general, whereas the results incorporating all included studies showed that abciximab and tirofiban showed lowered mortality (RR: 0.70 [0.54-0.90] for abciximab; 0.75 [0.61-0.93] for tirofiban). Moreover, eptifibatide did not seem to have any influence on mortality of patients with ischemic stroke (RR: 1.47 [0.69-3.09]).

Table 4. The Risk Ratio of 3 Glycoprotein IIb/IIIa Inhibitors.^a

	No.	ICH (95% CI)	No.	SICH (95% CI)	No.	Mortality (95% CI)
Analysis for only randomized control trials						
Total	6	1.05 (0.82-1.34)	6	1.78 (1.04-3.04)	7	0.92 (0.66-1.28)
Abciximab	2	1.87 (0.64-5.48)	2	4.26 (1.89-9.59)	3	0.93 (0.60-1.45)
Eptifibatide	2	0.59 (0.33-1.08)	2	0.17 (0.04-0.69)	2	1.47 (0.69-3.09)
Tirofiban	2	1.13 (0.77-1.63)	2	0.50 (0.092-71)	2	0.58 (0.28-1.20)
Analysis for all type studies						
Total	15	1.21 (0.90-1.62)	16	1.16 (0.92-1.46)	14	0.76 (0.65-0.89)
Abciximab	3	1.27 (0.89-1.81)	4	1.88 (1.17-3.00)	5	0.70 (0.54-0.90)
Eptifibatide	2	0.59 (0.32-1.08)	2	0.17 (0.04-0.69)	2	1.47 (0.69-3.09)
Tirofiban	10	1.27 (0.84-1.93)	10	1.04 (0.78-1.38)	7	0.75 (0.61-0.93)

Abbreviations: ICH, intracerebral hemorrhage; SICH, symptomatic intracranial hemorrhage.

^aNo. means number of studies analyzed.

The boldface values means the risk ratio is significant.

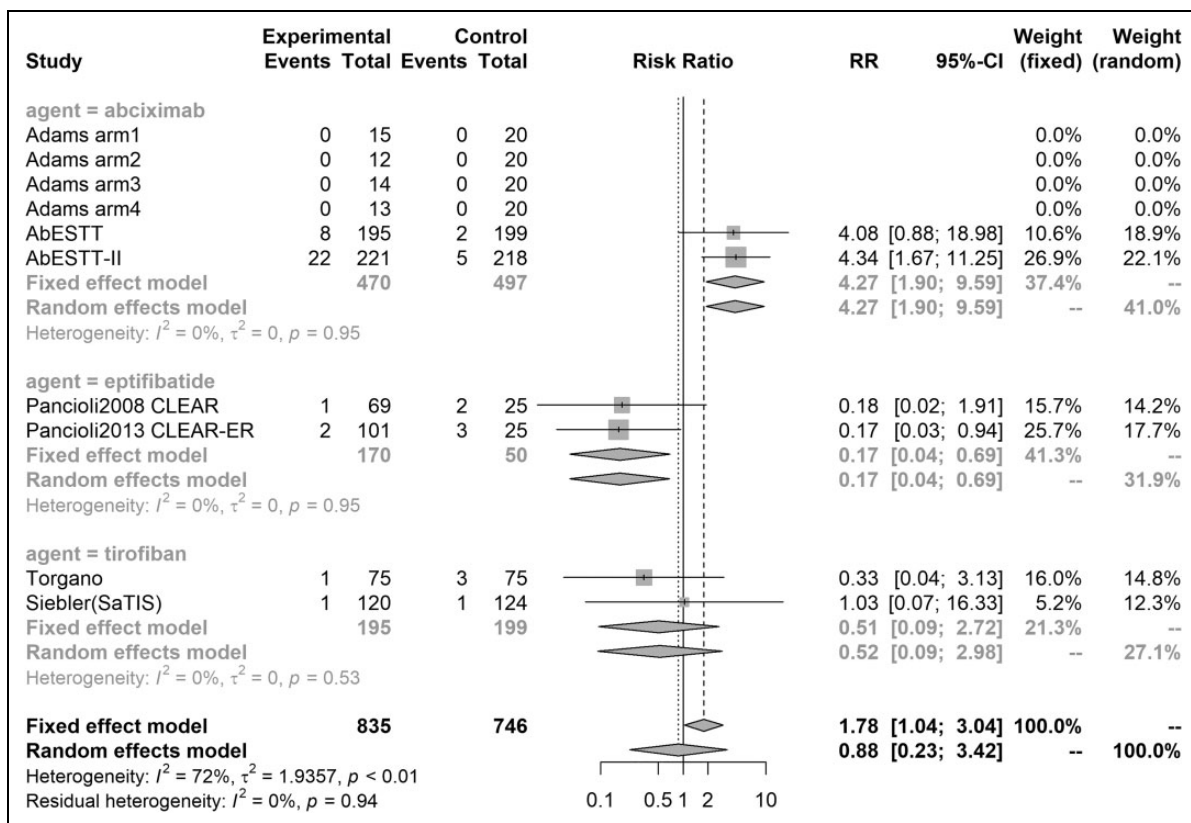


Figure 2. Forest plot of meta-analysis for SICH in RCTs. No heterogeneity was observed for any agent. RCTs indicates randomized controlled trials; SICH, symptomatic intracranial hemorrhage.

Subgroup Analysis and Metaregression Analysis for Tirofiban

As mentioned above, a more comprehensive subgroup analysis was conducted to identify potential risk factors for tirofiban use. Eventually, we found that while thrombectomy is not one of the factors, overall tirofiban dose >10 mg, age > 70 years, and NIHSS score > 15 all play important roles in the incidence of ICH events (Figures 3 and 4). Thrombectomy combined

with tirofiban showed no risk for both ICH and SICH. When the overall tirofiban dose is >10 mg, the RR value of ICH was 1.46 (1.07-1.99), while that of SICH is 1.92 (1.02-3.62). When the initial NIHSS score was >15, the RR for ICH was 1.77 (1.14-2.73), implying an evident hazard, and the RR for SICH was 2.04 (0.88-4.75). In the metaregression model, we found a positive correlation between NIHSS and RR for SICH ($P = .001$, Figure 5), as well as between age and RR for ICH

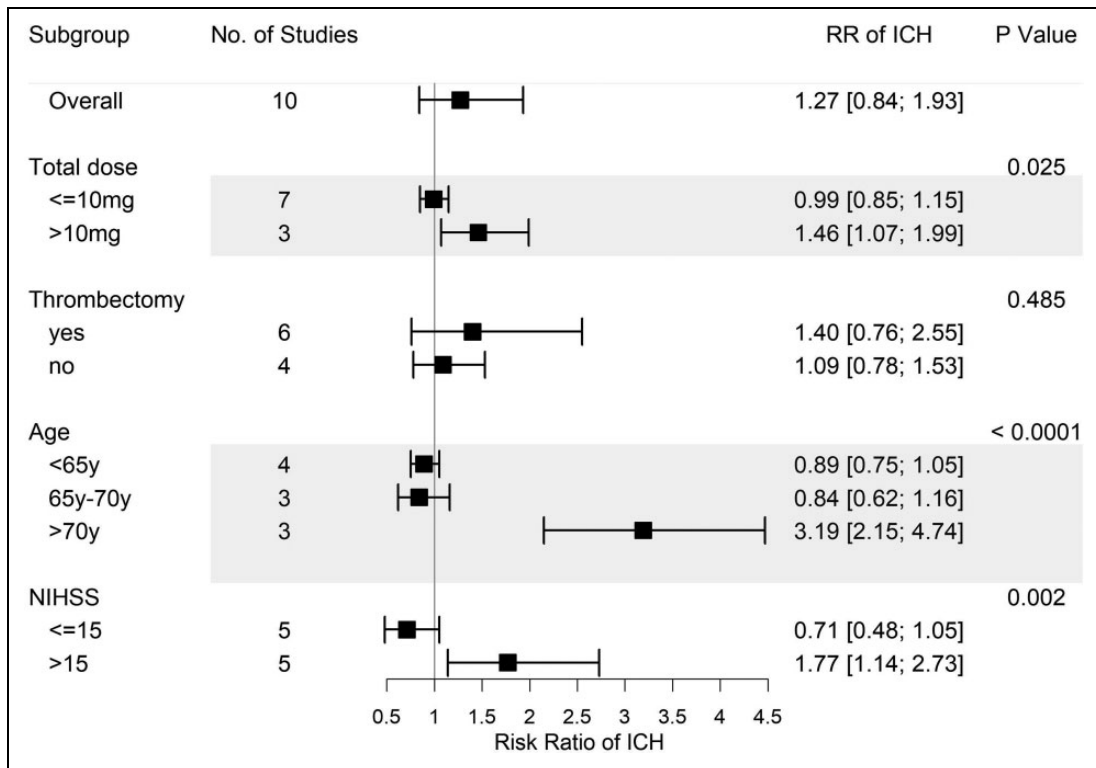


Figure 3. Subgroup analysis of ICH for tirofiban. Total dose > 10 mg, age > 70 years, and baseline NIHSS score > 15 are risk factors for ICH. ICH indicates intracerebral hemorrhage; NIHSS, National Institute of Health stroke scale.

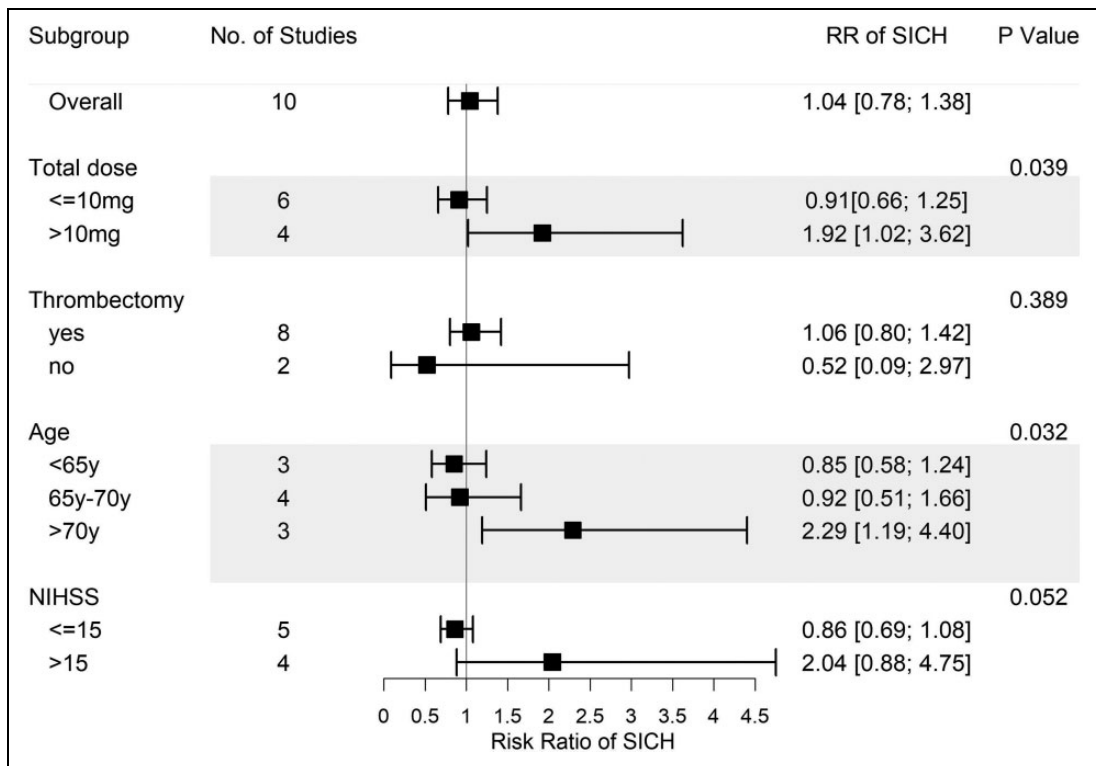


Figure 4. Subgroup analysis of SICH for tirofiban. Total dose > 10 mg and age > 70 years are illustrated as risk factors for SICH. SICH indicates symptomatic intracranial hemorrhage.

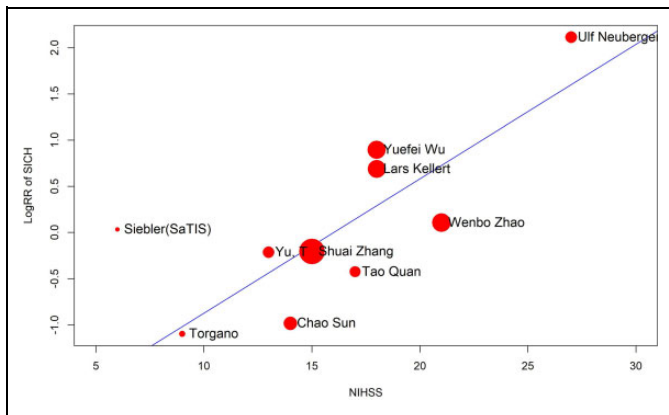


Figure 5. Bubble plot of metaregression analysis for baseline NIHSS score. The risk of SICH is positively related to baseline NIHSS. NIHSS indicates National Institute of Health stroke scale; SICH, symptomatic intracranial hemorrhage.

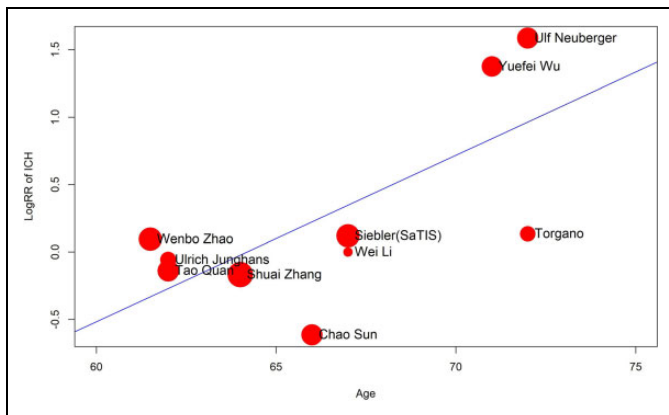


Figure 6. Bubble plot of metaregression analysis for age. The risk of ICH is positively related to age. ICH indicates intracerebral hemorrhage.

($P = .0024$, Figure 6). Thus, we believe that tirofiban is safe in low doses for selected patients. However, older patients or those with high NIHSS score should be treated with caution.

Publication Bias

No significant publication bias was noted in the analysis by funnel plots (Figure 7) and Egger regression asymmetry test ($P = .253$ for ICH, $P = .862$ for SICH).

Discussion

To assess the safety of combined treatment with GP IIb-IIIa inhibitors in stroke-related treatment, the ICH and mortality at 90 days were considered as the evaluation criteria. As SICH is a relatively fatal bleeding condition in ICH, short-term SICH incidence was also accepted as a separate evaluation standard. We chose 3 agents that are commonly used in clinical practice, namely tirofiban, eptifibatide, and abciximab; searched the

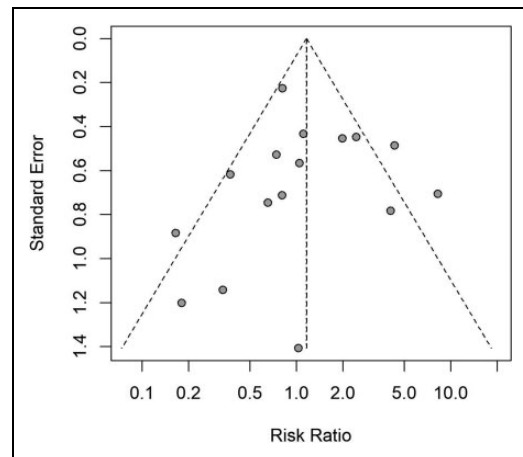


Figure 7. Funnel plot of SICH, including all study types. This figure showed no publication bias existing among included studies. SICH indicates symptomatic intracranial hemorrhage.

relevant literature; pooled and compared results in category; and conducted further subgroup and regression analyses.

Unlike us, Ciccone et al excluded 2 eptifibatide RCTs because they speculated that a lower dose of rt-PA in the experimental group than in the control group might result in bias.¹⁴ No RCT yet has proven that low dose rt-PA is safer than the standard dose. Two systematic reviews (Liu et al³³ and Liu et al³⁴) also reported no significant difference in SICH incidence between low-dose rt-PA and standard-dose rt-PA. A recent prospective study showed that bleeding risk in the 0.6 mg/kg rt-PA group and 0.9 mg/kg rt-PA group was not significantly different.³⁵ Based on their results, we overlooked the dose difference of rt-PA between the CLEAR and CLEAR-ER trials and included both these studies in our analysis. The Safety of Tirofiban in acute Ischemic Stroke (SaTIS) trial was also excluded in the Cochrane systematic review, because the maximum time from onset to inclusion in SaTIS was 22 hours.²⁰ We speculated that with the same distribution in the experimental and control groups, the onset-to-inclusion time would not bias the final outcomes. Thus, we also included the SaTIS trial.

The American Heart Association published a new international guideline in 2019,¹⁵ in which the level of evidence of tirofiban and eptifibatide in AIS treatment is B-R and the class of recommendation is IIb, indicating that benefits for patients are generally greater than the inherent risks. According to our results, for younger patients with lower NIHSS scores, the ICH risk presented a tendency to decrease. Therefore, based on multiple studies, we thought our conclusion can be used as a reference for the development of guidelines and future clinical practice. Furthermore, the administration of abciximab was proposed to be potentially harmful in the guideline according to the results of the AbESTT trial. We will discuss later in the text when we discuss AbESTT trial.

Mechanical thrombectomy has been used for AIS treatment since 2005.³⁶ Accordingly, concerns about postoperative

arterial reocclusion were raised. Glycoprotein antagonists, with strong antiplatelet ability, were found superior to prevent arterial reocclusion. Owing to the lack of strong evidence provided by RCT, the Cochrane SR did not investigate its application in this area. Different from them, we included nonrandomized studies in this regard and carried out a preliminary discussion. The 2019 guideline suggested that the efficacy and safety of GP IIa-IIIb inhibitors combined with endovascular therapy are unclear. However, this conclusion was based on 3 retrospective single-arm studies (no control group) with an evidence level of C-LD (low evidence grade).^{37,38,13} Of 3 studies, 2 were about abciximab and 1 was about tirofiban and abciximab. Therefore, whether the level or the quantity of evidence was inadequate. Instead, we concluded that tirofiban is safe to use when combined with thrombectomy, especially at low doses.

Subgroup results showed that abciximab can remarkably increase a 4-fold risk for SICH but may reduce the 90-day mortality. Adam et al conducted the first clinical trial for abciximab with no occurrence of SICH. This likely ascribes to the low drug dose and small sample size (≤ 15 in each experimental group).¹⁶ In a large international trial (AbESTT II) conducted in 2008, Adams et al reported that the experiment group with abciximab presented a high proportion of hemorrhage, because of which the trial had to be discontinued. Although the superiority of abciximab in ischemic stroke was not demonstrated, the authors, based on their research in phase II, proposed a view that such hemorrhagic ratio is acceptable provided the ultimate outcome can be improved.¹² In AbESTT, the experimental group had 8 cases of SICH out of 195 patients; however, the ratio increased to 22 of 221 in the AbESTT-II trial.^{16,12} In addition, 4 studies focused on carotid stent/angioplasty.³⁹⁻⁴² In these studies, all control groups reported no ICH, while all abciximab groups reported ICH and 3 reported SICH. Our conclusions were consistent with their theory. However, the efficacy of abciximab needs more studies and analyses to be confirmed. In this article, we exclusively focused on the safety of drugs. Interestingly, the results of the AbESTT trial indicated that the therapeutic window of abciximab can extend to 24 hours,¹⁶ while AbESTT II in 2008 showed a reasonable and safe window within 6 hours from onset.¹² Therefore, the time window of administration may also act as a factor for safety. It is also worth noting that AbESTT, AbESTT-II, and the aforementioned 4 case-control studies administered full dose in cardiac trials, so the application of low-dose abciximab still deserves further research.

Although eptifibatide exhibited no statistically significant impact on any ICH and death, the incidence of SICH was reduced after administration of eptifibatide. The CLEAR trial, the first randomized blind trial on safety of low-dose rt-PA combined with GP IIb-IIIa, showed encouraging results of this combination regimen, perhaps owing to the extremely small dose in CLEAR. However, a limitation of the CLEAR-trial is that the eptifibatide group had a much lower baseline of NIHSS (median: 12.0) than the control group.¹⁸ In addition, the CLEAR-ER trial highlighted concerns regarding systemic bleeding, given that cases of fatal, moderate, and mild bleeding

were 1, 4, and 12, respectively, in the eptifibatide group but 0 in the standard therapy group.²¹ Again, the time window of eptifibatide in stroke merits further discussion.

Tirofiban is a highly selective, fast-acting, nonpeptide GP IIa-IIIb inhibitor with short halftime and debatable safety in ischemic stroke. Our subgroup results indicated that tirofiban does not influence ICH or SICH and can lower the 90-day mortality. However, a significant interstudy heterogeneity was detected while merging data. Consequently, further analysis on tirofiban was conducted. Eventually, we found that total dose >10 mg, age >70 years, and NIHSS >15 are risks for ICH events, and thrombectomy was not one of them. Based on these findings, we believe that tirofiban is safe to use but in low doses and is not suggested in either patients with high NIHSS score or older individuals. Kellert et al reported that the occurrence of fatal hemorrhage significantly increased for patients who received tirofiban after mechanical thrombectomy. To this point, we believe it could be attributed to the relatively high drug dose and severe baseline NIHSS score. In their study, the authors noted that the risk was mainly demonstrated in patients with anterior circulation stroke.⁸ Considering those patients who had lower NIHSS score and shorter time window at admission than those with posterior circulation stroke, which could minimize the events of fatal ICH, the results contradicted our assumption. This correlation between tirofiban-induced hemorrhage and lesion location suggested by Kellert et al still needs validation. Jeong and Jin in 2013 reported that they administered tirofiban through the arterial route and in a lower dose than recommended to avoid surgical complications such as ICH. The results eventually proved that small dose administration is safe and rewarding.⁴³ A larger clinical trial in 2011 by Siebler et al also reported the safety of tirofiban in ischemic stroke. They believed tirofiban would not carry an extra risk of ICH compared to standard care. Furthermore, patients treated with tirofiban were associated with lower mortality in the 5-month follow-up and higher survival rate at 3 months post-treatment.²⁰ Pharmacologically speaking, with only a 2-hour halftime period, tirofiban has a lower risk of inducing continuous bleeding. Considering the benefits for cardiovascular disease, it is very much likely that tirofiban may be more advantageous to a certain group of people. Other than these, we also found that the risk of SICH was positively associated with the NIHSS score. A similar relationship exists between age and ICH. Thus, age and NIHSS score at admission influence postoperative ICH. This is consistent with the conclusions of Kellert et al,⁸ in that age and NIHSS score of patients with stroke are both independent predictors of poor prognosis.

A common side effect of all types of GP IIb-IIIa inhibitors is thrombocytopenia. Currently, there has not been clear evidence to show that this could result in poor outcomes. In the AbESTT II trial, the incidence of thrombocytopenia was relatively low and no adverse consequences were reported.¹⁶ Moreover, as reported in Qureshi et al, the platelet function of patients could distinctly recover within 4 hours after eptifibatide was discontinued.⁴⁴

Torgano et al concluded in a study of 150 patients with AIS that tirofiban administered within 6 hours of symptom onset did not further escalate the risk for these patients.¹⁹ Another simultaneous trial, the SaTIS, investigated the safety of low-dose tirofiban within 22 hours of symptom onset. Authors of the SaTIS trial concluded that compared to standard care, tirofiban does not increase ICH risk.²⁰ A recent study suggested that because it is difficult to avoid the use of abciximab during stenting in AIS, more balance is required between the antiplatelet effects and safety of a given drug.¹³ Qureshi et al concluded that eptifibatide could be safely used intravenously after low-dose intra-arterial thrombolysis.⁴⁴ The CLEAR trial, which assessed the safety of combination therapy within 3 hours from symptom onset, proposed that a reduced dose of rt-PA with eptifibatide was reasonably safe to allow further exploration of the dose range.¹⁸

Conclusion

Our results provided convincing evidence that abciximab enhances the risk of SICH when used for AIS treatment and prevention of artery reocclusion. Further, eptifibatide and tirofiban are promising therapeutic agents at a reduced dose. However, patient age and NIHSS score as independent risk factors should be taken into consideration by clinicians. Further investigations on the safety and efficacy of low-dose abciximab should be performed as the evidence available thus far is inadequate.


Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

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