Stroke

CLINICAL AND POPULATION SCIENCES

Combined Approach to Eptifibatide and Thrombectomy in Acute Ischemic Stroke Because of Large Vessel Occlusion: A Matched-Control Analysis

Gaoting Ma, MD, PhD*; Xuan Sun, MD, PhD*; Huiran Cheng, MM; W. Scott Burgin, MD; Weiliang Luo, MD; Weihua Jia, PhD; Yajie Liu, MD; Wenlong He, MM; Xiaokun Geng, MD; Liangfu Zhu, MD; Xingyu Chen, MD; Huaizhang Shi, MD; Haowen Xu, MD; Litong Zhang, MM; Anxin Wang, PhD; Dapeng Mo, MD; Ning Ma, MD; Feng Gao, MD; Ligang Song, PhD; Xiaochuan Huo, PhD; Yiming Deng, PhD; Lian Liu, PhD; Gang Luo, PhD; Baixue Jia, PhD; Xu Tong, PhD; Liping Liu, MD; Zeguang Ren, MD, PhD; Zhongrong Miao, MD, PhD; on behalf of EPOCH Study and ANGEL-ACT Study Groups†

BACKGROUND: In patients undergoing mechanical thrombectomy (MT), adjunctive antithrombotic might improve angiographic reperfusion, reduce the risk of distal emboli and reocclusion but possibly expose patients to a higher intracranial hemorrhage risk. This study evaluated the safety and efficacy of combined MT plus eptifibatide for acute ischemic stroke.

METHODS: This was a propensity-matched analysis of data from 2 prospective trials in Chinese populations: the ANGEL-ACT trial (Endovascular Treatment Key Technique and Emergency Workflow Improvement of Acute Ischemic Stroke) in 111 hospitals between November 2017 and March 2019, and the EPOCH trial (Eptifibatide in Endovascular Treatment of Acute Ischemic Stroke) in 15 hospitals between April 2019 and March 2020. The primary efficacy outcome was good outcome (modified Rankin Scale score 0–2) at 3 months. Secondary efficacy outcomes included the distribution of 3-month modified Rankin Scale scores and poor outcome (modified Rankin Scale score 5–6) and successful recanalization. The safety outcomes included any intracranial hemorrhage, symptomatic intracranial hemorrhage, and 3-month mortality. Mixed-effects logistic regression models were used to account for within-hospital clustering in adjusted analyses.

RESULTS: Eighty-one combination arm EPOCH subjects were matched with 81 ANGEL-ACT noneptifibatide patients. Compared with the no eptifibatide group, the eptifibatide group had significantly higher rates of successful recanalization (91.3% versus 81.5%; P=0.043) and 3-month good outcomes (53.1% versus 33.3%; P=0.016). No significant difference was found in the remaining outcome measures between the 2 groups. All outcome measures of propensity score matching were consistent with mixed-effects logistic regression models in the total population.

CONCLUSIONS: This matched-control study demonstrated that MT combined with eptifibatide did not raise major safety concerns and showed a trend of better efficacy outcomes compared with MT alone. Overall, eptifibatide shows potential as a periprocedural adjunctive antithrombotic therapy when combined with MT. Further randomized controlled trials of MT plus eptifibatide should be prioritized.

REGISTRATION: URL: https://www.clinicaltrials.gov; Unique identifier: NCT03844594 (EPOCH), NCT03370939 (ANGEL-ACT).

GRAPHIC ABSTRACT: A graphic abstract is available for this article.

Key Words: eptifibatide ■ glycoprotein IIb/IIIa inhibitor ■ ischemic stroke ■ mechanical thrombectomy

Correspondence to: Zhongrong Miao, MD, PhD, Department of Interventional Neuroradiology, Beijing Tiantan Hospital, Capital Medical University, No.119 S 4th Ring W Rd, Fengtai District, Beijing, 100070, China. Email zhongrongm@163.com
*G. Ma and X. Sun contributed equally.
†A list of the EPOCH study and ANGEL-ACT study groups are given in the Supplemental Material.
This manuscript was sent to Georgios Tsivgoulis, Guest Editor, for review by expert referees, editorial decision, and final disposition.
Supplemental Material is available at https://www.ahajournals.org/doi/suppl/10.1161/STROKEAHA.121.036754.

Stroke is available at www.ahajournals.org/journal/str

Nonstandard Abbreviations and Acronyms

AIS	acute ischemic stroke
ANGEL-ACT	Endovascular Treatment Key Technique and Emergency Work Flow Improvement of Acute Ischemic Stroke
ASPECTS	Alberta Stroke Program Early CT Score
EPOCH	Eptifibatide in Endovascular Treatment of Acute Ischemic Stroke
GPI	glycoprotein IIb/IIIa inhibitor
ICH	intracranial hemorrhage
IMR	incomplete microvascular reperfusion
LKW	last known well
LVO	large vessel occlusion
mRS	modified Rankin Scale
MT	mechanical thrombectomy
PS	propensity score
sICH	symptomatic intracranial hemorrhage

Mechanical thrombectomy (MT) is becoming routine in many countries for large vessel occlusion (LVO) stroke.[1] Despite high rates of successful recanalization (≈85%), about 50% of patients do not reach functional independence at 3 months.[2] Periprocedural factors may play a role in prognosis, including anesthetic technique,[3] blood pressure management,[4] antithrombotic management,[5] and endovascular tools.[6] Adjunctive antithrombotic therapy might improve angiographic reperfusion by reducing the risk of distal emboli and arterial reocclusion but might also expose patients to a higher intracranial hemorrhage (ICH) risk. In addition, the concept of incomplete microvascular reperfusion (IMR),[7] derived from observations of focal no-reflow following focal ischemia, may partially explain poor outcomes even after fast and complete proximal reperfusion. Antithrombotic agents in experimental systems have shown a reduction in IMR and improved outcomes.

The Glycoprotein IIb/IIIa inhibitors (GPIs), including abciximab, tirofiban, and eptifibatide, are fast-acting, reversible, and highly selective antithrombotic agents. While recent observational studies indicate a promising role for GPI in the perioperative treatment of MT,[8–12] most published studies are related to tirofiban, with few reports about eptifibatide. Here, we conducted a propensity score (PS) matching analysis to assess the safety and efficacy of combined MT plus eptifibatide for acute ischemic stroke (AIS).

METHODS

Data Availability

Data are available to researchers on request for purposes of reproducing the results or replicating the procedure by directly contacting the corresponding author.

Study Population

This study was a propensity-matched analysis of data from 2 prospective trials. The ANGEL-ACT trial (Endovascular Treatment Key Technique and Emergency Workflow Improvement of Acute Ischemic Stroke) was a nationwide prospective registry of consecutive adult patients with an acute, symptomatic, radiologically confirmed LVO treated with MT at 111 stroke centers across 26 provinces in China between November 2017 and March 2019.[13] Eptifibatide in Endovascular Treatment of Acute Ischemic Stroke (EPOCH) was a single-arm, open-label, multicenter trial of MT plus eptifibatide in patients with AIS treated with MT within 24 hours of last known well (LKW) in 15 hospitals in China between April 2019 and March 2020. The main inclusion criteria of EPOCH trial included age ≥18 years; diagnosis of AIS; received any type of endovascular treatment, including intraarterial thrombolysis, MT, angioplasty with or without stenting. The main exclusion criteria were intracranial hemorrhages and no evidence of LVO. The institutional review board of each site approved the study protocols, and written informed consent was obtained from each patient before study entry.

Data Collection

The prospectively collected variables included age, sex, baseline modified Rankin Scale (mRS) score, baseline National Institutes of Health Stroke Scale score, intravenous thrombolysis, GPI treatment information, neuroimaging results (eg, Alberta Stroke Program Early CT Score [ASPECTS], occlusion site, etc), stroke mechanism,[14,15] MT procedure details, and follow-up outcomes. The core image interpretations of ANGEL-ACT and EPOCH were both completed by Angel Interventional Neurology Core laboratory (AINR-CoreLab), thus ensuring the consistency of interpretation standards.

MT Procedure

All procedures were performed via a transfemoral approach. Local or general anesthesia was chosen according to the level of patient cooperation and the patient's medical condition. If no relevant contraindication existed, patients received intravenous thrombolysis before MT. The MT device and intervention strategies were left to the discretion of the interventionists.

In the ANGEL-ACT trial, intravenous heparin during the procedure was selectable according to in-house standards. In the event of underlying residual stenosis, intraprocedural GPIs (tirofiban is the only kind of GPI in ANGEL-ACT trial) or oral antiplatelet agents (generally aspirin and clopidogrel) were considered. In addition, tirofiban use was permitted proactively before MT or as a subsequent rescue technique for recanalization-refractory occlusions. If no antiplatelet agents were used during the procedure, and the patient had not received intravenous thrombolytics, the initiation of dual antiplatelet agents (generally aspirin and clopidogrel) within 24 hours was at the researchers' discretion.

In the EPOCH trial, eptifibatide (Shanxi Deyuantang Pharmaceutical Co, Ltd, China) was recommended to begin immediately after groin puncture. This consisted of a single intravenous or intraarterial bolus of 135 to 180 μg/kg administered over <5 minutes, followed by a continuous intravenous infusion of 0.75 to 2 μg/kg per min for 24 hours (Table S1). In

recanalization-refractory subjects, a second 180 mg/kg bolus was allowed at the discretion of the interventionalists. Systemic heparinization and additional intraprocedural antiplatelet agents were prohibited, but intermittent heparin flushes (10 IU/mL) were allowed for maintaining access catheter patency. Once postprocedural ICH was excluded, daily oral antiplatelet therapy was initiated (aspirin 300 mg and clopidogrel 300 mg as a loading dose), accompanied by a 4-hour bridging eptifibatide infusion.

End Points

The primary efficacy outcome was good outcome at 3 months (mRS score 0–2). Secondary efficacy outcomes included the distribution of 3-month mRS scores and poor outcome (mRS score 5–6), and successful recanalization after MT. The 3-month follow-up was ascertained using a standardized telephone interview performed by trained investigators blinded to the baseline and procedural data. The mRS is an ordinal measure of global disability with 7 levels ranging from 0 (no symptoms, best) to 5 (severe disability-bedridden) and 6 (dead).[16] Successful recanalization was defined as modified Thrombolysis in Cerebral Infarction of 2b-3 at final angiography.[15] The safety outcomes included any ICH, symptomatic intracranial hemorrhage (sICH) according to the Heidelberg criteria,[17] and 3-month mortality.

Statistical Analysis

Descriptive statistics were used to summarize patient characteristics and outcomes. Continuous and ordinal variables were described by median (interquartile range), and categorical variables were described by the number (percentage). A comparison of the baseline and procedural characteristics between the 2 groups was performed using the Kruskal-Wallis test for continuous or ordinal variables and Fisher's exact test for categorical variables. To achieve a well-balanced baseline between the groups, a PS matching was performed. All variables in Table 1 were used to generate the PSs. The subjects were allocated using a 1:1 matching protocol without replacement (greedy-matching algorithm), with a caliper width ≤0.2 of the SD of the logit of the PSs.[18,19] For comparing the outcomes between the groups in the matched population, the odds ratios with their 95% CIs were analyzed using a binary logistic regression model. In addition, we undertook mixed-effects logistic regression modeling for clinical outcomes to account for clustering in individual centers. As a sensitivity analysis, we also compared all outcome measures between the 2 groups in the total population using mixed-effects logistic regression models adjusted for the variables with a significant difference of $P<0.05$ and center as random effect. Finally, we explored whether the effects of the treatment options on the good outcomes and successful recanalization differed in certain subgroups by testing the treatment-by-subgroup interaction effect using a mixed-effects logistic regression model. All outcomes were analyzed with complete case analysis as the data missingness were low (maximum 5.3% for sICH in the no eptifibatide group before PS matching). All analyses were conducted with SAS software version 9.4 (SAS Institute Inc, Cary, NC). A 2-sided P of < 0.05 was considered to be statistically significant.

RESULTS

Patients

A total of 1793 subjects enrolled in the ANGEL-ACT registry, including 1396 (77.9%) with anterior circulation stroke and 397 (22.1%) with posterior circulation stroke. Of those, 1723 patients received MT within 24 hours after LKW. Sixteen patients were excluded for LKW time/date missing or unknown, 36 for LKW to groin puncture time >24 hours, 24 for missing critical data, and 891 for MT combined with tirofiban. A total of 115 subjects enrolled in the EPOCH study, including 79 (68.7%) with anterior circulation stroke and 36 (31.3%) with posterior circulation stroke. The EPOCH study was halted early by the independent Data and Safety Monitoring Board after a planned interim analysis of 115 consecutive subjects demonstrated a low sICH rate (4.4%). Of those, 9 patients were excluded for non-LVOs on angiography, 3 for LKW to groin puncture time > 24 hours, and 1 for missing critical data. Finally, 102 in EPOCH and 826 patients in ANGEL-ACT were included in this analysis, and 81 combination arm EPOCH subjects were matched with 81 ANGEL-ACT no eptifibatide subjects (Figure 1).

In the prematched population, 36 (35.3%) subjects were treated with intravenous eptifibatide and 66 (64.7%) were treated intraarterial. Seven (6.9%) of them received a second intraarterial bolus administration. In the PS matching population, 33 (40.7%) subjects were treated with intravenous eptifibatide and 48 (59.3%) were treated with intraarterial. Two (2.5%) of them received a second intraarterial bolus administration.

Baseline and Procedural Characteristics

Compared with the no eptifibatide group, patients in the eptifibatide group were younger (63 [56–68] versus 67 [57–75]; $P=0.002$), had a higher rate of male sex (80.4% versus 57.3%; $P<0.001$), higher rate of large artery atherosclerosis (77.5% versus 32.2%; $P=0.001$), higher frequency emergency stenting (41.2% versus 9.4%; $P<0.001$), more device pass numbers (2 [1–3] versus 1 [1–2]; $P<0.001$), lower baseline National Institutes of Health Stroke Scale score (15 [10–20] versus 17 [12–22]; $P=0.019$), lower ASPECTS score (7 [6–8] versus 10 [7–10]; $P<0.001$), longer LKW to puncture time (400 [290–545] versus 279 [200–386]; $P<0.001$), and lower rate of anterior circulation stroke (71.6% versus 82.7%; $P=0.010$). No significant differences were observed between the 2 groups regarding the intravenous thrombolysis (Table 1).

PS Matching

Eighty-one eptifibatide arm EPOCH subjects were matched with 81 no eptifibatide ANGEL-ACT subjects. After PS matching, all the covariates showed no statistical difference between the 2 groups (Table 1). Both the no eptifibatide group and the eptifibatide group had a

 Stroke. 2022;53:1580–1588. DOI: 10.1161/STROKEAHA.121.036754

Table 1. Baseline and Procedural Characteristics

Baseline Characteristic	Before PS matching				After PS matching			
	No eptifibatide (N=826)	Eptifibatide (N=102)	Standardized difference (%)	*P* value	No eptifibatide (N=81)	Eptifibatide (N=81)	Standardized difference (%)	*P* value
Age, median (IQR), y	67 (57–75)	63 (56–68)	30.0	0.002	61 (52–71)	64 (57–69)	9.1	0.477
Male sex	473 (57.3)	82 (80.4)	51.6	<0.001	69 (85.2)	69 (85.2)	0.0	1.000
Baseline NIHSS score, median (IQR)	17 (12–22)	15 (10–20)	17.4	0.019	14 (11–22)	15 (11–23)	3.5	0.816
ASPECTS, median (IQR)*	10 (7–10)	7 (6–8)	80.5	<0.001	7 (6–9)	7 (6–9)	0.6	0.962
LKW to puncture time, median (IQR), min	279 (200–386)	400 (290–545)	62.6	<0.001	335 (250–555)	370 (273–510)	5.2	0.592
Intravenous thrombolysis	258 (31.2)	27 (26.5)	10.5	0.364	21 (25.9)	21 (25.9)	0.0	1.000
Anterior circulation stroke	683 (82.7)	73 (71.6)	26.7	0.010	58 (71.6)	58 (71.6)	0.0	1.000
LAA	266 (32.2)	79 (77.5)	102.1	<0.001	58 (71.6)	58 (71.6)	0.0	1.000
Emergency stenting	78 (9.4)	42 (41.2)	78.4	<0.001	22 (27.2)	26 (32.1)	10.8	0.606
Thrombectomy pass numbers, median (IQR)	1 (1–2)	2 (1–3)	31.8	<0.001	2 (1–3)	2 (1–3)	7.2	0.192

Values are numbers with percentages in parentheses, unless indicated otherwise. ASPECTS indicates Alberta Stroke Program Early CT Score; IQR, interquartile range; LAA, large artery atherosclerosis; LKW, last known well; NIHSS, National Institutes of Health Stroke Scale; and PS, propensity score.

*ASPECTS for anterior circulation stroke and posterior circulation ASPECTS for posterior circulation stroke.

high rate of male sex (85.2%) after PS matching. In addition, the 2 groups had high rates of large artery atherosclerosis (71.6%) and emergency stenting (>25%).

Outcomes Measures

A comparison of the outcome measures is shown in Table 2. After PS matching, compared with the no eptifibatide group, the eptifibatide group had a significantly higher rate of successful recanalization (91.3% versus 81.5%; *P*=0.043) and 3-month good outcome (53.1% versus 33.3%; *P*=0.016). The shift on the 90-day mRS score is depicted in Figure 2. No significant difference was found in the other outcome measures between the 2 groups (*P*>0.05).

The clinical outcomes of PS matching were consistent with mixed-effects logistic regression models in the total

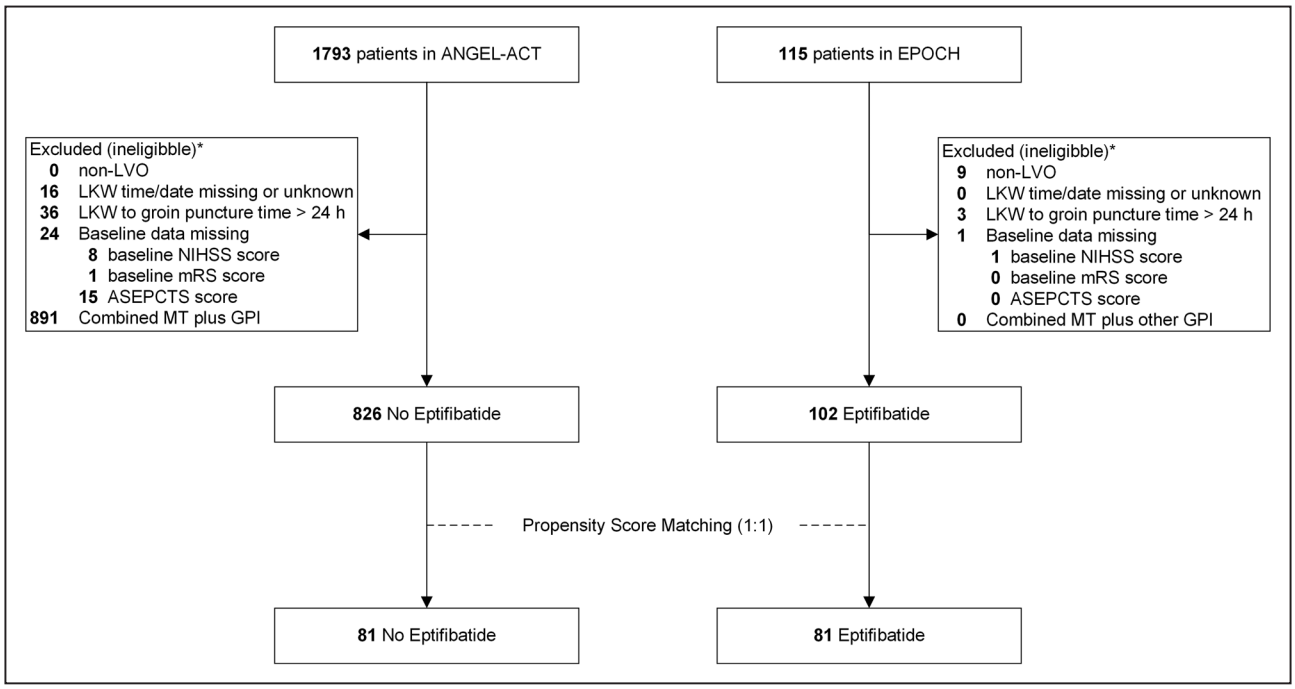

Figure 1. Flowchart of patient selection.

ANGEL-ACT indicates Endovascular Treatment Key Technique and Emergency Work Flow Improvement of Acute Ischemic Stroke; ASPECTS, Alberta Stroke Program Early CT Score; EPOCH, Eptifibatide in Endovascular Treatment of Acute Ischemic Stroke; GPI, glycoprotein IIb/IIIa inhibitor; LKW, last known well; LVO, large vessel occlusion; mRS, modified Rankin Scale; MT, mechanical thrombectomy; and NIHSS, National Institutes of Health Stroke Scale. *Criteria are listed in the order in which applied.

Table 2. Efficacy and Safety Outcomes

	Before PS matching						After PS matching			
	No eptifibatide	Eptifibatide	Unadjusted analysis		Adjusted analysis*		No eptifibatide	Eptifibatide	Adjusted analysis†	
Outcome variable	(N=826)	(N=102)	OR (95% CI)	*P* value	OR (95% CI)	*P* value	(N=81)	(N=81)	OR (95% CI)	*P* value
ICH	195/789 (24.7)	20/102 (19.6)	0.74 (0.44–1.24)	0.258	0.87 (0.42–1.80)	0.715	26/79 (32.9)	18/81 (22.2)	0.58 (0.25–1.35)	0.207
sICH‡	65/782 (8.3)	5/102 (4.9)	0.57 (0.22–1.45)	0.236	0.51 (0.18–1.45)	0.204	9/79 (11.4)	4/81 (4.9)	0.36 (0.07–1.85)	0.221
Successful recanalization§	713/826 (86.3)	94/101 (93.1)	2.13 (0.96–4.70)	0.062	2.66 (1.15–6.14)	0.022	66/81 (81.5)	73/80 (91.3)	2.37 (1.03–5.47)	0.043
3-mo mRS score, median (IQR)	3 (0–5)	2 (1–4)	1.15 (0.80–1.65)	0.467	1.14 (0.77–1.68)	0.509	4 (1–5)	2 (1–4)	1.32 (0.61–2.85)	0.474
3-mo good outcome‖	330/786 (42.0)	56/102 (54.9)	1.68 (1.11–2.55)	0.014	1.87 (1.25–2.82)	0.003	26/78 (33.3)	43/81 (53.1)	2.26 (1.17–4.39)	0.016
3-mo poor outcome¶	244/786 (31.0)	23/102 (22.6)	0.65 (0.40–1.05)	0.080	0.70 (0.37–1.33)	0.280	22/78 (28.2)	20/81 (24.7)	0.83 (0.31–2.24)	0.719
3-mo death	132/786 (16.8)	17/102 (16.7)	0.99 (0.57–1.72)	0.974	1.02 (0.46–2.26)	0.960	11/78 (14.1)	15/81 (18.5)	1.38 (0.42–4.58)	0.594

Data are shown as the event number/total number (%), unless otherwise indicated. ASPECTS indicates Alberta Stroke Program Early CT Score; ICH, intracranial hemorrhage; IQR, interquartile range; LAA, large artery atherosclerosis; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; OR, odds ratio; PS, propensity score; and sICH, symptomatic intracranial hemorrhage.

*Adjusted for age, sex, baseline NIHSS score, ASPECTS, LKW to puncture time, anterior circulation stroke, LAA, emergency stenting, thrombectomy pass numbers, and centers.

†Adjusted for centers.

‡According to the Heidelberg Bleeding Classification.

§Successful recanalization is defined by the modified Thrombolysis in Cerebral Infarction score of 2b-3 after mechanical thrombectomy.

‖Good outcome is defined as modified Rankin Scale score 0–2.

¶Poor outcome is defined as modified Rankin Scale score 5–6.

population (Table 2). After adjusted analysis in the pre-matched population, we also found that patients in the eptifibatide group had higher rates of successful recanalization (93.1% versus 86.3%; *P*=0.022) and 3-month good outcome (54.9% versus 42.0%, *P*=0.003). No significant difference was found in the other outcome measures between the 2 groups (*P*>0.05).

Subgroup Analysis

As shown in Figure 3 and Figure S1, we did an exploratory subgroup analysis stratified by age (<65 versus ≥65 years), sex (male versus female), baseline National Institutes of Health Stroke Scale score (≤15 versus >15 points), baseline ASPECTS (0–8 versus 9–10 points), LKW to puncture time (≤360 versus >360 min), occlusion site (anterior circulation versus posterior circulation), underlying intracranial atherosclerotic disease (yes versus no), and etiological stroke subtypes (large artery atherosclerosis versus cardioembolism versus other or unknown etiology). Using a mixed-effects logistic regression model, there was interaction with eptifibatide and age≥65 on successful recanalization ($P_{interaction}$=0.030). No interaction of the treatment allocations on the 3-month good outcome and successful recanalization was seen in other subgroups ($P_{interaction}$>0.05).

DISCUSSION

In this study, we found a direction of effect in favor of the combination of MT plus eptifibatide over MT alone in LVO-related AIS. In patients with AIS undergoing MT, the combined use of eptifibatide was associated with increased rates of successful recanalization and 3-month good outcome and was not associated with increased risk of hemorrhagic outcomes or 3-month mortality. These findings support the design of randomized controlled trials to establish the efficacy of MT plus eptifibatide for improving LVO-related AIS outcomes.

As an adjunct to intravenous thrombolysis, low-dose or standard-dose alteplase combined with eptifibatide did not raise major safety concerns in previous studies.[20–24] In the matched population, the bridging therapy patients combined with eptifibatide also did not increase the risk of ICH (28.6% [6/21] versus 45% [9/20]) or sICH (14.3% [3/21] versus 15.0% [3/20]). Overall, the eptifibatide group seemed to have lower rates of hemorrhagic outcomes, although there were no statistically significant differences. This may be partially attributed to several mechanisms. First may be the short half-life of eptifibatide, which requires continuous infusion to maintain platelet inhibition. In the event of early detection of asymptomatic ICH on imaging, eptifibatide discontinuation may allow quick platelet aggregation recovery, potentially ameliorating subsequent clinical decline into an sICH. Second, the coadministration of GPI and heparin may slightly increase the risk of hemorrhagic complications in patients with AIS.[25] In the eptifibatide group, heparinization was prohibited, which might contribute to fewer hemorrhagic outcomes. Third, GPI might dose-dependently increase the risk of ICH.[8,10] In the animal study of AIS, a full dose of GPI resulted in 57% (4/7) of ICH, whereas the ICH rate dropped significantly to 6.7% (1/15) with 10% or 20% of the full dose applied.[8] In a clinical study of tirofiban, ICH rates increased significantly with the increase of tirofiban dose in MT patients (*P*=0.010).[10] In this study, a moderate dose of bolus (130±33 μg/kg) plus a low dose of intravenous continuous of eptifibatide (0.71±0.15 μg/kg per min) were used, which may lower the rates of hemorrhagic

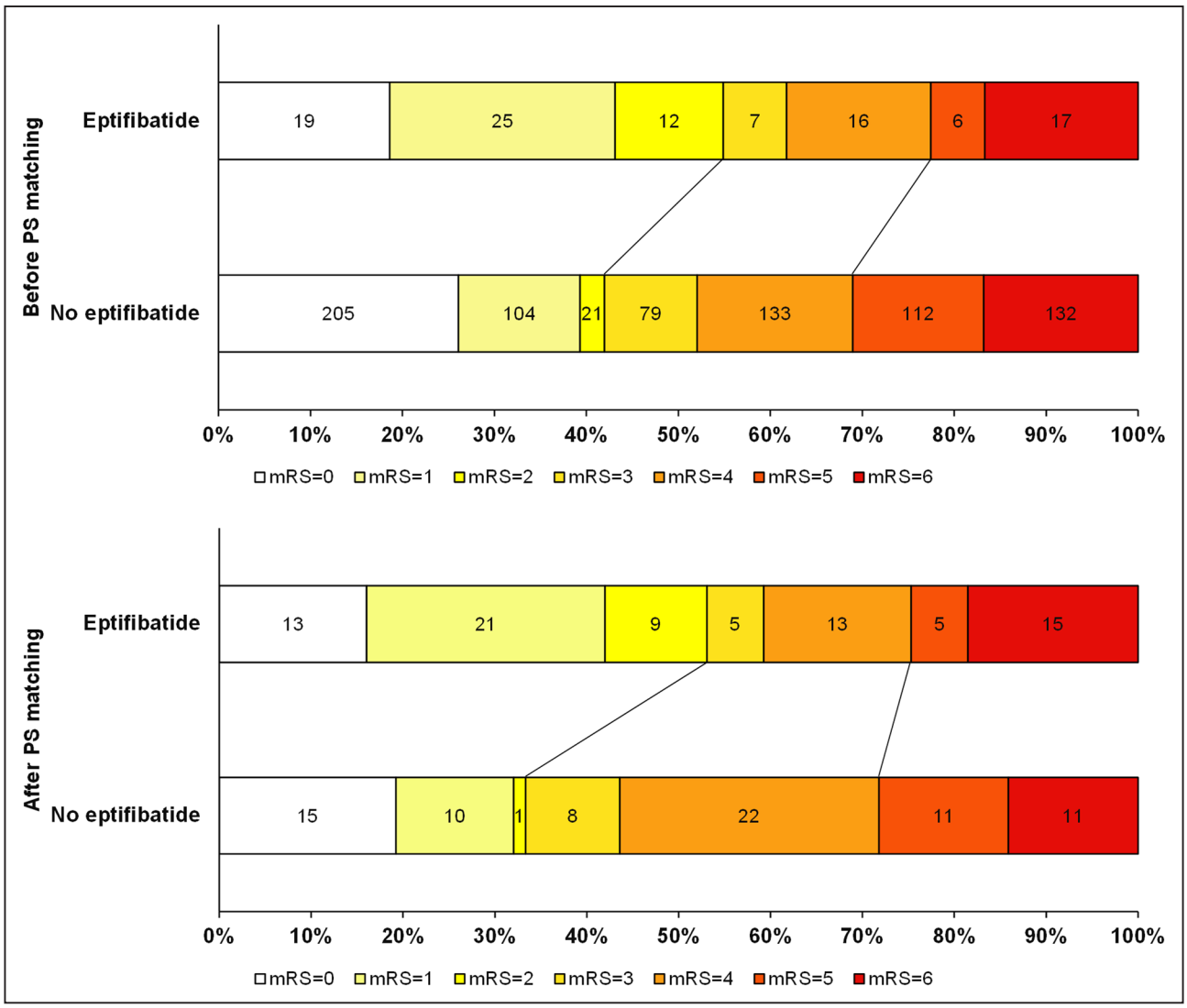

Figure 2. The shift on the 3-mo modified Rankin Scale (mRS) score of no eptifibatide vs eptifibatide.

outcomes. Finally, a higher degree of recanalization following MT is associated with a reduced risk of hemorrhagic outcomes.[26] So, higher successful recanalization rate in the eptifibatide group may reduce the likelihood of ICH and sICH.

The finding that eptifibatide could improve recanalization rate was consistent with 2 recent meta-analyses of GPIs.[27,28] Unlike retrospective studies, eptifibatide treatment was initiated before MT, as early as the groin puncture. The early administration of eptifibatide appeared to have a facilitating effect in dissolving platelet-rich clots and improving recanalization.[11,29,30] In addition, intraarterial administration was the most commonly used in the present study. Intraarterial administration seems to be more effective in improving successful recanalization (Tables S2 and S3).

Ordinal or dichotomous analyses of mRS have been commonly recommended for evaluating outcomes in stroke trials.[31] Of the 3 approaches analyzed in this analysis, dichotomization at good outcomes (mRS score 0–2) demonstrated the only statistically significant finding in favor of MT plus eptifibatide when compared with MT alone. But in general, the eptifibatide group showed a trend of better clinical outcomes. The higher rate of successful recanalization is one of the main reasons. In addition, this is possibly related to the impact of periprocedural antiplatelet therapy on preventing and treating IMR. Previous studies have shown that a poor outcome after complete recanalization may be partly explained by IMR.[32–34] IMR may be associated with pericyte contraction, intraprocedural microembolization, in situ microthrombi formation, and cellular plugging. These processes may be related to platelet activation, increased hemostasis, and the formation of neutrophil extracellular traps.[35,36] Inhibiting continuing thrombosis, using a platelet aggregation inhibitor such as eptifibatide, may help to reduce the risk of IMR. Furthermore, MT devices cause known endothelial injuries, which can trigger platelet aggregation resulting in distal microvascular occlusion or reocclusion.[37,38] It is therefore likely that periprocedural administration of

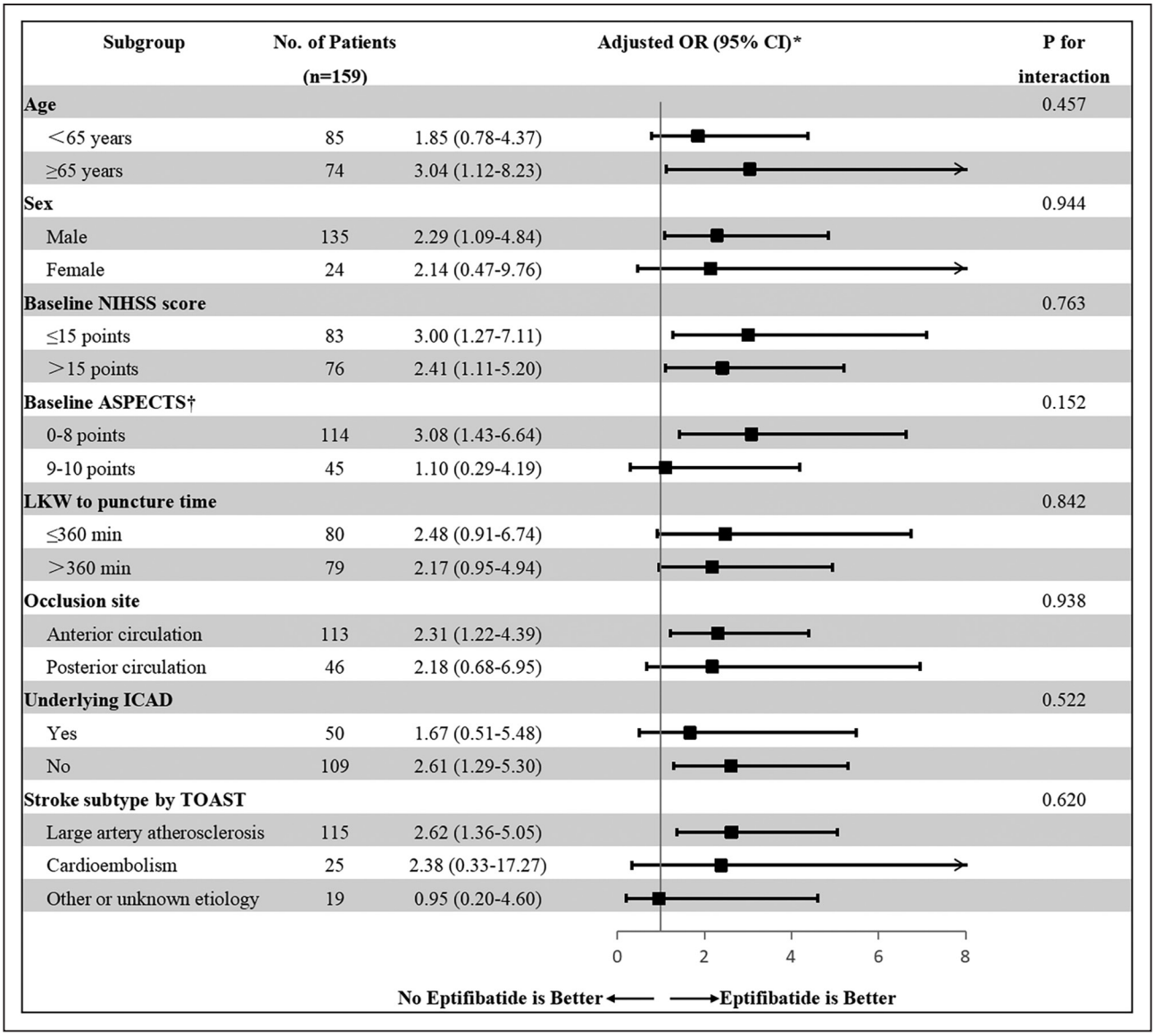

Figure 3. Subgroup analyses regarding the 3-mo good outcome of no eptifibatide vs eptifibatide in the postmatched population.

ASPECTS indicates Alberta Stroke Program Early CT Score; ICAD, intracranial atherosclerotic disease; LKW, last known well; NIHSS, National Institutes of Health Stroke Scale; OR, odds ratio; and TOAST, Trial of ORG 10172 in Acute Stroke Treatment. *Adjusted for centers. †ASPECTS for anterior circulation stroke and posterior circulation ASPECTS for posterior circulation stroke.

eptifibatide could improve microvascular reperfusion and reduce intracranial large vessel reocclusion.

These results must be considered in the context of the subsets of patients evaluated in this study. Regarding initial imaging severity, most patients had relatively preserved noncontrasted head computed tomography scans, with an ASPECTS score ≥6 in >80% of the PS-matched population. This is consistent with most current recommendations for endovascular reperfusion or GPI utilization. It is well known that lower ASPECTS are a significant predictor of sICH and poor outcomes.[39,40] Moreover, as in previous studies on GPIs, it is unclear if these results can be generalized to populations with relatively low large artery atherosclerosis rates.[9,11]

To the best of our knowledge, the EPOCH trial was the first prospective, multicenter, safety trial of the combination of MT and eptifibatide for LVO-related AIS. For the first time, this PS matching analysis compared MT plus eptifibatide and MT alone in patients with LVO-related AIS. These results support the prospects of combining MT and perioperative eptifibatide. Indeed, only well-conducted randomized controlled trials will be able to accurately evaluate the safety and efficacy of adjunctive antithrombotic for LVO patients undergoing MT. Ongoing randomized controlled trials of combined therapies (MR CLEAN-MED [ISRCTN76741621]; and RESCUE BT [ChiCTR-INR-17014167]) may be able to evaluate these interventions better.

Limitations

This analysis comes from 2 cohorts rather than a randomized study. The baseline characteristics are not evenly distributed among the groups, limiting the ability to adjust for potential confounders despite adjustment and matching. Second, recent studies recommended the linear or weighted ordinal approaches for evaluating mRS outcomes in future stroke trials.[41,42] Given that the effect size in our analysis showed no significant difference at ordinal analyses but was positive with mRS score 0 to 2, caution must be taken in interpreting our results and full consideration given to all approaches in selecting an analysis plan for the primary outcome in a planned phase III trial. Third, potential therapeutic mechanisms were not investigated because of the nature of this study. Fourth, although the same core laboratory evaluated the imaging end points for each trial, outcomes were not centrally determined across the 2 trials. This could lead to discrepancies between these assessments. Finally, both studies were conducted in Chinese populations, potentially limiting the generalizability to non-Chinese populations.

Conclusions

This matched-control study demonstrated that MT combined with eptifibatide did not raise major safety concerns and showed a trend of better efficacy outcomes compared with MT alone. Overall, eptifibatide shows potential as a periprocedural adjunctive antithrombotic therapy when combined with MT. Further randomized controlled trials of MT plus eptifibatide should be prioritized.

ARTICLE INFORMATION

Received July 26, 2021; final revision received October 6, 2021; accepted November 19, 2021.

Affiliations

Department of Interventional Neuroradiology, Beijing Tiantan Hospital, Capital Medical University, China (G.M., X.S., D.M., N.M., F.G., L.S., X.H., Y.D., L.L., G.L., B.J., X.Y., Z.M.). Department of Neurosurgery, Anyang People's Hospital, China (H.C., L.Z.). Department of Neurology, Morsani College of Medicine University of South Florida, Tampa (W.S.B.). Department of Neurology, Huizhou Municipal Central Hospital, China (W.L.). Department of Neurology, Beijing Shijingshan Teaching Hospital, Capital Medical University, China (W.J.). Department of Neurology, Shenzhen Hospital, Southern Medical University, China (Y.L.). Department of Neurology, Xinxiang Central Hospital, China (W.H.). Department of Neurology, Beijing Luhe Hospital, Capital Medical University, China (X.G.). Department of Cerebral Vascular Diseases, Interventional Center, Henan Provincial People's Hospital, Zhengzhou, China (L.Z.). Department of Neurology, Zhongshan Hospital Xiamen University, China (X.C.). Department of Neurosurgery, the First Affiliated Hospital of Harbin Medical University, China (H.S.). Department of Interventional Radiology, the First Affiliated Hospital of Zhengzhou University, China (H.X,). China National Clinical Research Center for Neurological Diseases, Beijing Tiantan Hospital, Capital Medical University (A.W.). Department of Neurology, Beijing Tiantan Hospital, Capital Medical University, China (L.L.). Department of Neurosurgery, University of South Florida, Tampa (Z.R.).

Acknowledgments

Drs Miao and Sun designed, led the study, and had full access to all of the data in the study and took responsibility for the integrity of the data and the accuracy of the data analysis. Drs Ma and Sun prepared the first draft of the report. Dr Wang did statistical analyses. All authors except Drs Burgin, Wang, and Ren participated in patient enrollment, collection of data. All authors critically reviewed the report and approved the final version. All authors critically reviewed the report and approved the final version. We thank all the participating centers for enrolling patients and the AINR-CoreLab for imaging analysis.

Sources of Funding

This study is supported by the National Key Research and Development Program of China (2016 YFC1301500).

Disclosures

Dr Wang reports Grants from Young Elite Scientists Sponsorship Program by CAST (2018QNRC001) and Beijing Municipal Administration of Hospitals Incubating Program (PX2020021). Dr Mo reports grants from the National Key Research and Development Program of China (2018YFC1312801). Dr Miao reports grants from Shanxi Deyuantang Pharmaceutical Co, Ltd, China. Dr Ren reports consultant of Penumbra company, United States. All other authors report no conflicts.

Supplemental Material

Tables S1–S3
Figure S1
EPOCH Study Group
ANGEL-ACT Study Group

REFERENCES

1. Warner JJ, Harrington RA, Sacco RL, Elkind MSV. Guidelines for the early management of patients with acute ischemic stroke: 2019 update to the 2018 guidelines for the early management of acute ischemic stroke. *Stroke*. 2019;50:3331–3332. doi: 10.1161/STROKEAHA.119.027708
2. Goyal M, Menon BK, van Zwam WH, Dippel DW, Mitchell PJ, Demchuk AM, Dávalos A, Majoie CB, van der Lugt A, de Miquel MA, et al; HERMES collaborators. Endovascular thrombectomy after large-vessel ischaemic stroke: a meta-analysis of individual patient data from five randomised trials. *Lancet*. 2016;387:1723–1731. doi: 10.1016/S0140-6736(16)00163-X
3. Schönenberger S, Möhlenbruch M, Pfaff J, Mundiyanapurath S, Kieser M, Bendszus M, Hacke W, Bösel J. Sedation vs. Intubation for Endovascular Stroke TreAtment (SIESTA) - a randomized monocentric trial. *Int J Stroke*. 2015;10:969–978. doi: 10.1111/ijs.12488
4. Maïer B, Gory B, Taylor G, Labreuche J, Blanc R, Obadia M, Abrivard M, Smajda S, Desilles JP, Redjem H, et al; Endovascular Treatment in Ischemic Stroke (ETIS) Research Investigators. Mortality and disability according to baseline blood pressure in acute ischemic stroke patients treated by thrombectomy: a collaborative pooled analysis. *J Am Heart Assoc*. 2017;6:e006484. doi: 10.1161/JAHA.117.006484
5. van de Graaf RA, Chalos V, Del Zoppo GJ, van der Lugt A, Dippel DWJ, Roozenbeek B. Periprocedural antithrombotic treatment during acute mechanical thrombectomy for ischemic stroke: a systematic review. *Front Neurol*. 2018;9:238. doi: 10.3389/fneur.2018.00238
6. Turk AS 3rd, Siddiqui A, Fifi JT, De Leacy RA, Fiorella DJ, Gu E, Levy EI, Snyder KV, Hanel RA, Aghaebrahim A, et al. Aspiration thrombectomy versus stent retriever thrombectomy as first-line approach for large vessel occlusion (COMPASS): a multicentre, randomised, open label, blinded outcome, non-inferiority trial. *Lancet*. 2019;393:998–1008. doi: 10.1016/S0140-6736(19)30297-1
7. Dalkara T, Arsava EM. Can restoring incomplete microcirculatory reperfusion improve stroke outcome after thrombolysis? *J Cereb Blood Flow Metab*. 2012;32:2091–2099. doi: 10.1038/jcbfm.2012.139
8. Kleinschnitz C, Pozgajova M, Pham M, Bendszus M, Nieswandt B, Stoll G. Targeting platelets in acute experimental stroke: impact of glycoprotein Ib, VI, and IIb/IIIa blockade on infarct size, functional outcome, and intracranial bleeding. *Circulation*. 2007;115:2323–2330. doi: 10.1161/CIRCULATIONAHA.107.691279
9. Zhao W, Che R, Shang S, Wu C, Li C, Wu L, Chen J, Duan J, Song H, Zhang H, et al. Low-dose tirofiban improves functional outcome in acute ischemic stroke patients treated with endovascular thrombectomy. *Stroke*. 2017;48:3289–3294. doi: 10.1161/STROKEAHA.117.019193
10. Wu Y, Yin C, Yang J, Jiang L, Parsons MW, Lin L. Endovascular thrombectomy. *Stroke*. 2018;49:2783–2785. doi: 10.1161/STROKEAHA.118.022919
11. Yang J, Wu Y, Gao X, Bivard A, Levi CR, Parsons MW, Lin L; INSPIRE Study Group†. Intraarterial versus intravenous tirofiban as an adjunct

to endovascular thrombectomy for acute ischemic Stroke. *Stroke*. 2020;51:2925–2933. doi: 10.1161/STROKEAHA.120.029994
12. Baek BH, Yoon W, Lee YY, Kim SK, Kim JT, Park MS. Intravenous tirofiban infusion after angioplasty and stenting in intracranial atherosclerotic stenosis-related stroke. *Stroke*. 2021;52:1601–1608. doi: 10.1161/STROKEAHA.120.033551
13. Jia B, Ren Z, Mokin M, Burgin WS, Bauer CT, Fiehler J, Mo D, Ma N, Gao F, Huo X, et al; ANGEL-ACT Study Group†. Current status of endovascular treatment for acute large vessel occlusion in China: a real-world nationwide registry. *Stroke*. 2021;52:1203–1212. doi: 10.1161/STROKEAHA.120.031869
14. Adams HP Jr, Bendixen BH, Kappelle LJ, Biller J, Love BB, Gordon DL, Marsh EE 3rd. Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. TOAST. Trial of Org 10172 in Acute Stroke Treatment. *Stroke*. 1993;24:35–41. doi: 10.1161/01.str.24.1.35
15. Zaidat OO, Yoo AJ, Khatri P, Tomsick TA, von Kummer R, Saver JL, Marks MP, Prabhakaran S, Kallmes DF, Fitzsimmons BF, et al; Cerebral Angiographic Revascularization Grading (CARG) Collaborators; STIR Revascularization working group; STIR Thrombolysis in Cerebral Infarction (TICI) Task Force. Recommendations on angiographic revascularization grading standards for acute ischemic stroke: a consensus statement. *Stroke*. 2013;44:2650–2663. doi: 10.1161/STROKEAHA.113.001972
16. van Swieten JC, Koudstaal PJ, Visser MC, Schouten HJ, van Gijn J. Interobserver agreement for the assessment of handicap in stroke patients. *Stroke*. 1988;19:604–607. doi: 10.1161/01.str.19.5.604
17. von Kummer R, Broderick JP, Campbell BC, Demchuk A, Goyal M, Hill MD, Treurniet KM, Majoie CB, Marquering HA, Mazya MV, et al. The heidelberg bleeding classification: classification of bleeding events after ischemic stroke and reperfusion therapy. *Stroke*. 2015;46:2981–2986. doi: 10.1161/STROKEAHA.115.010049
18. Rosenbaum PR, Rubin DB. Constructing a control group using multivariate matched sampling methods that incorporate the propensity score. *American Statistician*. 1985;39:33–38. doi: 10.2307/2683903
19. Rosenbaum PR. Optimal matching for observational studies. *J Am Statist Assoc*. 1989;84:1024–1032. doi: 10.2307/2290079
20. Pancioli AM, Broderick J, Brott T, Tomsick T, Khoury J, Bean J, del Zoppo G, Kleindorfer D, Woo D, Khatri P, et al; CLEAR Trial Investigators. The combined approach to lysis utilizing eptifibatide and rt-PA in acute ischemic stroke: the CLEAR stroke trial. *Stroke*. 2008;39:3268–3276. doi: 10.1161/STROKEAHA.108.517656
21. Pancioli AM, Adeoye O, Schmit PA, Khoury J, Levine SR, Tomsick TA, Sucharew H, Brooks CE, Crocco TJ, Gutmann L, et al; CLEAR-ER Investigators. Combined approach to lysis utilizing eptifibatide and recombinant tissue plasminogen activator in acute ischemic stroke-enhanced regimen stroke trial. *Stroke*. 2013;44:2381–2387. doi: 10.1161/STROKEAHA.113.001059
22. Adeoye O, Sucharew H, Khoury J, Tomsick T, Khatri P, Palesch Y, Schmit PA, Pancioli AM, Broderick JP; CLEAR-ER, IMS III, and ALIAS Part 2 Investigators. Recombinant tissue-type plasminogen activator plus eptifibatide versus recombinant tissue-type plasminogen activator alone in acute ischemic stroke: propensity score-matched post hoc analysis. *Stroke*. 2015;46:461–464. doi: 10.1161/STROKEAHA.114.006743
23. Adeoye O, Sucharew H, Khoury J, Vagal A, Schmit PA, Ewing I, Levine SR, Demel S, Eckerle B, Katz B, et al. Combined approach to lysis utilizing eptifibatide and recombinant tissue-type plasminogen activator in acute ischemic stroke-full dose regimen stroke trial. *Stroke*. 2015;46:2529–2533. doi: 10.1161/STROKEAHA.115.010260
24. Berge E, Whiteley W, Audebert H, De Marchis GM, Fonseca AC, Padiglioni C, de la Ossa NP, Strbian D, Tsivgoulis G, Turc G. European Stroke Organisation (ESO) guidelines on intravenous thrombolysis for acute ischaemic stroke. *Eur Stroke J*. 2021;6:I–LXII. doi: 10.1177/2396987321989865
25. Qiu T, Li C, Huang L, Xiao H, Deng X, Dai X, Fu S, Wang J, Gong Q, Luo Q, et al. Tirofiban combined with heparin's effect and safety in the treatment of mild to moderate acute ischemic stroke. *Neurol Res*. 2021;43:220–224. doi: 10.1080/01616412.2020.1839690
26. Desai SM, Tonetti DA, Morrison AA, Gross BA, Jankowitz BT, Jovin TG, Jadhav AP. Relationship between reperfusion and intracranial hemorrhage after thrombectomy. *J Neurointerv Surg*. 2020;12:448–453. doi: 10.1136/neurintsurg-2019-015337
27. Sun Y, Guo ZN, Yan X, Wang M, Zhang P, Qin H, Wang Y, Zhu H, Yang Y. Safety and efficacy of tirofiban combined with endovascular therapy compared with endovascular therapy alone in acute ischemic stroke: a meta-analysis. *Neuroradiology*. 2021;63:17–25. doi: 10.1007/s00234-020-02530-9
28. Tang L, Tang X, Yang Q. The application of tirofiban in the endovascular treatment of acute ischemic stroke: a meta-analysis. *Cerebrovasc Dis*. 2021;50:121–131. doi: 10.1159/000512601
29. Collet JP, Montalescot G, Lesty C, Weisel JW. A structural and dynamic investigation of the facilitating effect of glycoprotein IIb/IIIa inhibitors in dissolving platelet-rich clots. *Circ Res*. 2002;90:428–434. doi: 10.1161/hh0402.105095
30. Montalescot G, Borentain M, Payot L, Collet JP, Thomas D. Early vs late administration of glycoprotein IIb/IIIa inhibitors in primary percutaneous coronary intervention of acute ST-segment elevation myocardial infarction: a meta-analysis. *JAMA*. 2004;292:362–366. doi: 10.1001/jama.292.3.362
31. Bath PM, Lees KR, Schellinger PD, Altman H, Bland M, Hogg C, Howard G, Saver JL; European Stroke Organisation Outcomes Working Group. Statistical analysis of the primary outcome in acute stroke trials. *Stroke*. 2012;43:1171–1178. doi: 10.1161/STROKEAHA.111.641456
32. Ames A 3rd, Wright RL, Kowada M, Thurston JM, Majno G. Cerebral ischemia. II. The no-reflow phenomenon. *Am J Pathol*. 1968;52:437–453.
33. Bekkers SC, Yazdani SK, Virmani R, Waltenberger J. Microvascular obstruction: underlying pathophysiology and clinical diagnosis. *J Am Coll Cardiol*. 2010;55:1649–1660. doi: 10.1016/j.jacc.2009.12.037
34. Chalos V, van de Graaf RA, Roozenbeek B, van Es ACGM, den Hertog HM, Staals J, van Dijk L, Jenniskens SFM, van Oostenbrugge RJ, van Zwam WH, et al; MR CLEAN-MED investigators. Multicenter randomized clinical trial of endovascular treatment for acute ischemic stroke. The effect of periprocedural medication: acetylsalicylic acid, unfractionated heparin, both, or neither (MR CLEAN-MED). Rationale and study design. *Trials*. 2020;21:644. doi: 10.1186/s13063-020-04514-9
35. Yemisci M, Gursoy-Ozdemir Y, Vural A, Can A, Topalkara K, Dalkara T. Pericyte contraction induced by oxidative-nitrative stress impairs capillary reflow despite successful opening of an occluded cerebral artery. *Nat Med*. 2009;15:1031–1037. doi: 10.1038/nm.2022
36. Martinod K, Wagner DD. Thrombosis: tangled up in NETs. *Blood*. 2014;123:2768–2776. doi: 10.1182/blood-2013-10-463646
37. Park S, Hwang SM, Song JS, Suh DC, Lee DH. Evaluation of the Solitaire system in a canine arterial thromboembolic occlusion model: is it safe for the endothelium? *Interv Neuroradiol*. 2013;19:417–424. doi: 10.1177/159101991301900403
38. Teng D, Pannell JS, Rennert RC, Li J, Li YS, Wong VW, Chien S, Khalessi AA. Endothelial trauma from mechanical thrombectomy in acute stroke: in vitro live-cell platform with animal validation. *Stroke*. 2015;46:1099–1106. doi: 10.1161/STROKEAHA.114.007494
39. Goyal M, Menon BK, Coutts SB, Hill MD, Demchuk AM; Penumbra Pivotal Stroke Trial Investigators, Calgary Stroke Program, and the Seaman MR Research Center. Effect of baseline CT scan appearance and time to recanalization on clinical outcomes in endovascular thrombectomy of acute ischemic strokes. *Stroke*. 2011;42:93–97. doi: 10.1161/STROKEAHA.110.594481
40. Venditti L, Chassin O, Ancelet C, Legris N, Sarov M, Lapergue B, Mihalea C, Ozanne A, Gallas S, Cortese J, et al. Pre-procedural predictive factors of symptomatic intracranial hemorrhage after thrombectomy in stroke. *J Neurol*. 2021;268:1867–1875. doi: 10.1007/s00415-020-10364-x
41. Ganesh A, Luengo-Fernandez R, Wharton RM, Rothwell PM; Oxford Vascular Study. Ordinal vs dichotomous analyses of modified Rankin Scale, 5-year outcome, and cost of stroke. *Neurology*. 2018;91:e1951–e1960. doi: 10.1212/WNL.0000000000006554
42. Ganesh A, Luengo-Fernandez R, Pendlebury ST, Rothwell PM; Oxford Vascular Study. Weights for ordinal analyses of the modified Rankin Scale in stroke trials: a population-based cohort study. *EClinicalMedicine*. 2020;23:100415. doi: 10.1016/j.eclinm.2020.100415