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ORIGINAL RESEARCH

Adjunct Intraarterial or Intravenous Tirofiban Versus No Tirofiban After Successful Recanalization of Basilar Artery Occlusion Stroke: The BASILAR Registry

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BACKGROUND: Approximately half of patients who achieve successful reperfusion do not achieve functional independence. The present study sought to investigate the clinical outcomes and safety of intraarterial or intravenous tirofiban as adjunct therapy in patients with acute basilar artery occlusion who had achieved successful recanalization with endovascular treatment.

METHODS AND RESULTS: In the national, prospective BASILAR (Endovascular Treatment for Acute Basilar Artery Occlusion Study) registry, 458 patients who met inclusion criteria were divided into 3 groups based on tirofiban administration (no tirofiban, n=262; intravenous tirofiban, n=101; intraarterial+intravenous tirofiban, n=95). Their clinical outcomes were compared with 90-day modified Rankin Scale scores. Adjusted odds ratios (aORs) and 95% CIs were obtained by logistic regression models and propensity score matching. Safety outcomes included any intracranial hemorrhage (ICH), symptomatic ICH, and mortality. Among 458 included patients, 184 (40.2%) achieved a favorable outcome (modified Rankin Scale score 0–3). There were no differences between the intravenous tirofiban group and the no tirofiban group in terms of safety and clinical outcomes (all $P>0.05$). Compared with the no tirofiban group, the intraarterial+intravenous tirofiban group had higher odds of 90-day modified Rankin Scale score 0 to 3 (aOR, 2.44 [95% CI, 1.30–4.64], $P=0.006$) and lower 3-month mortality (aOR, 0.38 [95% CI, 0.19–0.71], $P=0.002$) without an increase in any ICH (aOR, 0.34 [95% CI, 0.09–1.01], $P=0.07$) or symptomatic ICH (aOR, 0.23 [95% CI, 0.03–0.90], $P=0.05$). Similar results of intraarterial+intravenous tirofiban on improving clinical outcomes were detected in novel cohorts constructed by propensity score matching.

CONCLUSIONS: Intraarterial+intravenous rather than intravenous tirofiban improved clinical outcomes without increasing the frequency of symptomatic ICH among patients with basilar artery occlusion after successful endovascular treatment. Further studies are needed to delineate the roles of intraarterial+intravenous tirofiban in patients with basilar artery occlusion receiving endovascular treatment.

Key Words: basilar artery occlusion ■ endovascular treatment ■ intra-arterial ■ prognosis ■ tirofiban

Accounting for nearly 1% of all forms of ischemic stroke, acute basilar artery occlusion (BAO) is a rare and devastating neurological disorder.[1] Across 4 randomized clinical trials, more than 40% of patients with BAO did not achieve long-term favorable clinical outcomes with endovascular treatment (EVT)

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CLINICAL PERSPECTIVE

What Is New?

- We investigated the role of intraarterial or intravenous tirofiban as adjunct therapy in patients with acute ischemic stroke with basilar artery occlusion who had achieved successful recanalization with endovascular treatment within 24 hours after symptom onset.
- Intraarterial combined with intravenous tirofiban rather than intravenous tirofiban alone improved clinical outcomes without increasing symptomatic intracranial hemorrhage risk in patients with acute ischemic stroke and basilar artery occlusion after successful endovascular treatment.

What Are the Clinical Implications?

- Intraarterial combined with intravenous tirofiban can be a therapeutic option after successful endovascular stroke treatment for improving neurological outcomes without an increased symptomatic intracranial hemorrhage risk in patients with basilar artery occlusion.

Nonstandard Abbreviations and Acronyms

BAO	basilar artery occlusion
BASILAR	Endovascular Treatment for Acute Basilar Artery Occlusion registry
EVT	endovascular treatment
ICH	intracranial hemorrhage
mRS	modified Rankin Scale
NIHSS	National Institute of Health Stroke Scale
pc-ASPECTS	posterior circulation Acute Stroke Prognosis Early Computed Tomography score

despite successful recanalization.[2–5] In light of these data, exploring strategies to improve outcomes of patients with BAO is important.

Endothelial impairment, plaque disruption, and thrombus escape, which frequently occur during the process of mechanical recanalization, could lead to the activation of platelets and subsequent platelet aggregation in the cerebral vessels.[6] Hence, use of glycoprotein IIb/IIIa receptor antagonist (eg, tirofiban) in patients with ischemic stroke has been regarded as a promising strategy to improve patient outcomes. Glycoprotein IIb/IIIa receptor antagonists act by blocking the final pathway of platelet aggregation, decreasing the frequency of thromboembolic complications and preventing early arterial reocclusion.[7] Though numerous studies have evaluated the role of tirofiban in patients with anterior circulation stroke, data regarding its use among BAO individuals undergoing EVT have been limited. Patients with BAO are characterized by a different clinical presentation, pathophysiology, and response to thrombolytics compared with patients with anterior circulation stroke.[8,9] In addition, the heterogeneity of the administration routes of tirofiban may lead to disparate outcomes among patients with ischemic stroke.[10] Intraarterial injection could provide higher local drug concentration and reduced time to reach effective concentration than intravenous route administration; however, it might also increase the frequency of adverse events.[11] The optimal dosing and route of administration of tirofiban for patients with BAO receiving EVT remain unclear.

Therefore, based on our nationwide prospective BASILAR (Endovascular Treatment for Acute Basilar Artery Occlusion Study) registry, the present study sought to investigate the efficacy and safety of tirofiban as an adjunct therapy for patients with BAO who achieved recanalization by EVT.[12] The optimal protocol of applying tirofiban was also explored by comparing outcomes among successfully recanalized patients with BAO receiving different administration routes of tirofiban (intraarterial+intravenous tirofiban versus intravenous tirofiban versus no tirofiban).

METHODS

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Study Design and Participants

BASILAR was a nationwide prospective registry in China of consecutive patients with BAO presenting within 24 hours of estimated occlusion time. The study was registered on the Chinese Clinical Trial Registry (http://www.chictr.org.cn; ChiCTR1800014759). The study rationale, protocol, and primary results of the BASILAR registry have been described previously.[12] The medical ethics committee at each participating center approved the study protocol. Signed informed consent was provided by all patients or their legal representative. This study is reported according to the Strengthening the Reporting of Observational Studies in Epidemiology statement.[13]

Among 829 patients in the BASILAR registry, we included patients who met the following criteria in this analysis: (1) EVT performed within 24 hours after stroke onset, (2) successful recanalization defined as expanded thrombolysis in cerebral infarction (expanded

Thrombolysis in Cerebral Infarction grade 2b–3), and (3) data were available on tirofiban treatment. Patients who received intravenous thrombolysis before EVT were permitted in this analysis. Patients who were excluded were (1) treated by thrombolytic agents after EVT, such as urokinase, alteplase; (2) with incomplete information on tirofiban use; or (3) treated by intraarterial tirofiban before achieving recanalization.

Procedures and Data Collection

We retrospectively abstracted data on the baseline characteristics, including age, sex, vascular risk factors (diabetes, hypertension, atrial fibrillation, and dyslipidemia), National Institute of Health Stroke Scale (NIHSS) score at admission, and posterior circulation Acute Stroke Prognosis Early Computed Tomography score (pc-ASPECTS). The collateral circulation was assessed by the posterior circulation collateral score based on the presence of collateral pathways visualized on computed tomography angiography.[14] Clinical outcomes were evaluated by (1) the proportion of favorable outcome, defined as a score of 0 to 3 on the modified Rankin (mRS) scale at 90 days; (2) the proportion of functional independence (mRS 0–2) at 90 days; and (3) the proportion of excellent outcome (mRS 0–1) at 90 days. Safety outcomes included (1) mortality at 90 days, (2) any intracranial hemorrhage (ICH), and (3) symptomatic ICH within 48 hours, which were assessed according to the Heidelberg Bleeding Classification.[15]

Tirofiban Administration

The decision to administer tirofiban and its route of administration was at the discretion of the neurointerventionalist. In general, tirofiban was administered under the following conditions: (1) balloon angioplasty with or without stenting were performed during EVT, (2) 3 or more attempts of stent-retriever for presumed endothelium injury, (3) prevention of arterial reocclusion in patients at high risk as characterized by progressive arterial restenosis, or (4) treatment of distal embolization during procedure. The recommended regimen of intravenous tirofiban treatment was consistent with its usage in acute coronary syndrome, namely 0.4 μg/kg per min over 30 minutes followed by 0.1 μg/kg per min infusion for up to 24 hours. In addition to patients receiving intravenous tirofiban alone, those who were treated with an intraarterial bolus of tirofiban 0.2 to 0.5 mg after arterial recanalization by EVT, and followed by an intravenous infusion of tirofiban up to 24 hours, were included in the present study.[16]

Statistical Analysis

Proportion tests for categorical variables were performed using the chi-square test. Depending on the normality of the distribution as assessed by the Kolmogorov–Smirnov test, continuous variables were compared using Student's *t* test for independent samples, or the Mann–Whitney *U* test or Kruskal–Wallis test for nonnormal data. Data are presented as mean±SD, median (interquartile range), or as number (percentage), where appropriate.

To determine the independent prognostic factors for favorable outcomes, binary and multivariable logistic regression analyses were performed. The effect size of any and symptomatic ICH was risk ratios (RRs), which was estimated using the modified Poisson regression model. The following variables, diabetes, age, sex, pc-ASPECTS score, NIHSS score at admission, Trial of ORG 10172 in Acute Stroke Treatment, occlusion site, onset to recanalization time, and posterior circulation collateral score score, were included in multivariable regression models. The unadjusted and adjusted odds ratio (OR) and RR with 95% CIs were presented. Propensity score matching (PSM) was applied to match subjects with a similar distribution of confounders to create novel cohorts with different administration routes of tirofiban.[17] Based on the MatchIt package of R statistical software,[18] PSM was performed with a 1:1 matching based on the nearest-neighbor matching algorithm with a caliper width of 0.05 of the propensity score with age, sex, baseline pc-ASPECTS score, NIHSS score at admission, Trial of ORG 10172 in Acute Stroke Treatment classification, and occlusion site as covariates. After PSM, conditional logistic regression and conditional Poisson regression models were used to investigate the roles of different administration routes of tirofiban on outcomes, respectively. A 2-tailed $P<0.05$ was considered statistically significant. No data were imputed because there were no missing data for the 90-day mRS score and baseline variables included in the multivariate regression analysis. All statistical analyses were performed using the R software version 4.1.2 (https://www.r-project.org).

RESULTS

Characteristics of Included Patients

Of the 829 patients in the BASILAR registry, 182 patients were treated with standard medical treatment, 125 had failed reperfusion, and 64 did not meet the inclusion criteria of the present cohort. In the remaining 458 patients, 262, 101, and 95 patients received no tirofiban, intravenous tirofiban, and intraarterial combined with intravenous tirofiban treatment, respectively (Figure 1). The clinical characteristics of included patients are shown in Table 1. The median age (interquartile range) was 64 (57–72) years; 342 patients (74.67%) were men. Among these 458 patients, 274 (59.8%) patients did not achieve favorable outcome (90-day

mRS score >3). Compared with the poor outcome group, the median [interquartile range] NIHSS score at admission was lower (18.5 [12.0–27.0] versus 30.0 [22.0–34.0], *P*<0.001), pc-ASPECTS score was higher (9 [8–10] versus 8 [6–9], *P*<0.001), and time from onset to puncture was shorter (301.5 [204.5–433.3] versus 356.0 [240.0–506.8] minutes, *P*=0.02) in those with favorable outcome. There were 262 patients in the no tirofiban group, 101 in the intravenous tirofiban group and 95 in the intraarterial+intravenous tirofiban group respectively (Table 2). The 3 groups differed by their age, admission NIHSS score, presence of diabetes, stroke cause, baseline pc-ASPECTS score, occlusion site, and posterior circulation collateral score (all *P*<0.05). Overall, large artery atherosclerosis was the underlying cause of the large vessel occlusion in 63.3% of patients.

Clinical Outcomes

Figure 2 shows the distribution of the 90-day mRS scores in patients stratified by the different administration routes of tirofiban. Patients treated with intraarterial+intravenous tirofiban were more likely to achieve 90-day mRS score of 0 or 1 (adjusted OR [aOR], 2.55 [95% CI, 1.29–5.14]; *P*=0.008), 90-day mRS score of 0 to 2 (aOR, 2.66 [95% CI, 1.38–5.23]; *P*=0.004), and 90-day mRS score of 0 to 3 (aOR, 2.44 [95% CI, 1.30–4.64]; *P*=0.006) compared with patients not treated with tirofiban (Table 3). There was no difference in the 90-day mRS outcomes between the intravenous tirofiban versus no tirofiban group: mRS score 0 to 3 (aOR, 1.57 [95% CI, 0.83–3.00]; *P*=0.19), mRS score 0 to 2 (aOR, 1.62 [95% CI, 0.77–3.43]; *P*=0.20) and mRS score 0 or 1 (aOR, 0.65 [95% CI, 0.21–1.78]; *P*=0.42) (Table 3).

Safety Outcomes

Overall, symptomatic ICH occurred in 26 (5.68%) patients, and the rate of symptomatic ICH was similar among the 3 groups treated by different administration routes of tirofiban (intravenous tirofiban versus no tirofiban: aOR, 0.74 [95% CI, 0.28–1.80];

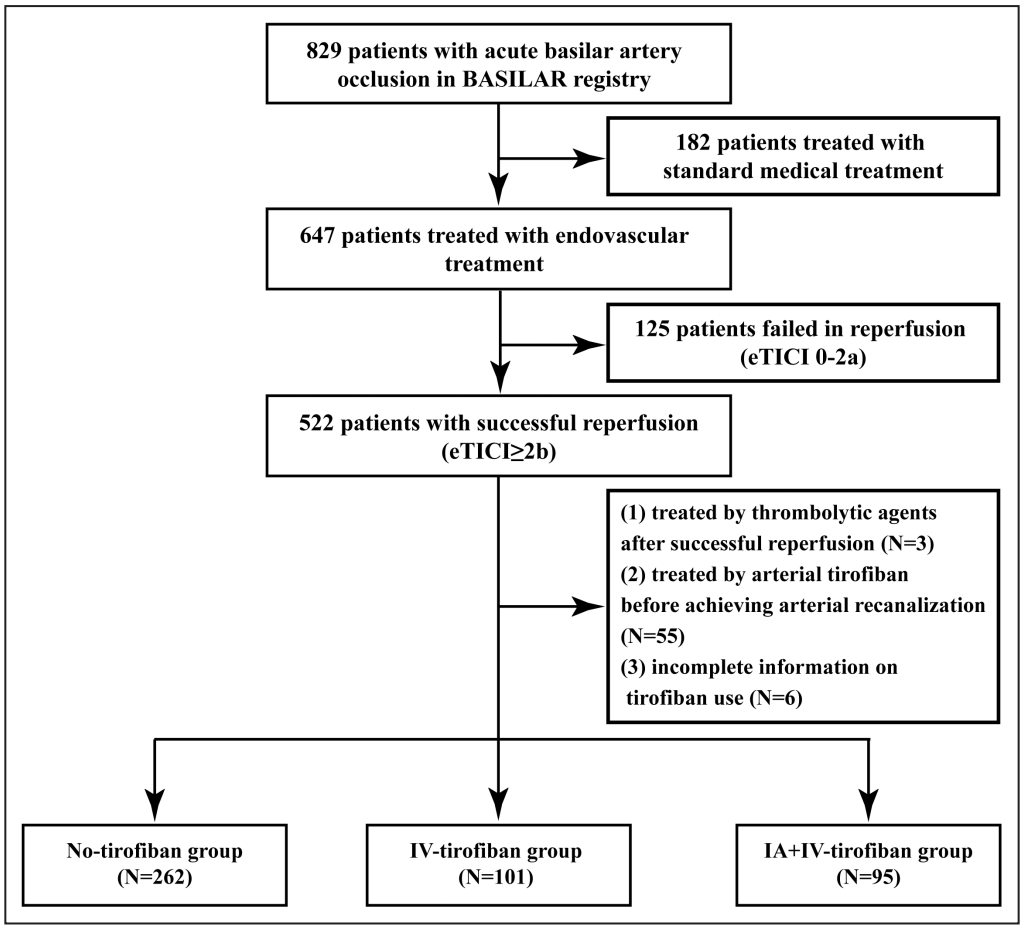

Figure 1. Flow chart of patient selection
BASILAR indicates Endovascular Treatment for Acute Basilar Artery Occlusion Study; eTICI, expanded Thrombolysis in Cerebral Infarction; IA, intraarterial; and IV, intravenous.

Table 1. Clinical Manifestations of Patients Stratified by Clinical Outcomes

	All patients	Poor outcome	Favorable outcome	
	(N=458)	(mRS score >3, n=274)	(mRS score ≤3, n=184)	*P*
Age, y, median (IQR)	64.00 (57.00–72.00)	65.00 (58.00–73.00)	63.00 (54.75–71.25)	0.06
Men, n (%)	342 (74.67)	208 (75.91)	134 (72.83)	0.46
Baseline NIHSS, median (IQR)	26.00 (16.00–32.00)	30.00 (22.00–34.00)	18.50 (12.00–27.00)	<0.001
Baseline posterior circulation Acute Stroke Prognosis Early Computed Tomography Score, median (IQR)	8.00 (7.00–9.00)	8.00 (6.00–9.00)	9.00 (8.00–10.00)	<0.001
Admission systolic BP, mm Hg, median (IQR)*	150.00 (133.00–165.75)	151.00 (135.00–168.00)	147.50 (130.75–162.00)	0.14
Admission diastolic BP, mm Hg, median (IQR)*	84.00 (77.25–96.00)	84.00 (78.00–96.00)	84.00 (77.00–95.25)	0.56
24 h NIHSS score after EVT, median (IQR)	24.00 (10.00–34.00)	32.00 (24.00–35.00)	9.00 (3.00–16.00)	<0.001
7 d NIHSS score after EVT, median (IQR)	17.00 (5.00–35.00)	32.00 (19.00–36.00)	3.50 (1.00–7.00)	<0.001
Intravenous thrombolysis, n (%)	98 (21.40)	59 (21.53)	39 (21.20)	0.93
Prestroke mRS score, n (%)				0.09
0	391 (85.37)	226 (82.48)	165 (89.67)	
1	46 (10.04)	32 (11.68)	14 (7.61)	
2	21 (4.59)	16 (5.84)	5 (2.72)	
History of risk factors, n (%)				
Hypertension	314 (68.56)	188 (68.61)	126 (68.48)	0.98
Diabetes	103 (22.49)	74 (27.01)	29 (15.76)	0.005
Dyslipidemia	144 (31.44)	78 (28.47)	66 (35.87)	0.09
Atrial fibrillation	100 (21.83)	57 (20.80)	43 (23.37)	0.52
Smoking	171 (37.34)	102 (37.23)	69 (37.50)	0.95
Transient ischemic attack	6 (1.31)	4 (1.46)	2 (1.09)	0.73
Trial of ORG 10172 in Acute Stroke Treatment classification, n (%)				0.22
Left atrial appendage	290 (63.32)	183 (66.79)	107 (58.15)	
Cardioembolism	126 (27.51)	70 (25.55)	56 (30.43)	
Stroke of other determined cause	12 (2.62)	7 (2.55)	5 (2.72)	
Stroke of undetermined cause	30 (6.55)	14 (5.11)	16 (8.70)	
Imaging parameters				
Occlusion site, n (%)				0.14
BA distal	172 (37.55)	92 (33.58)	80 (43.48)	
BA middle	124 (27.07)	79 (28.83)	45 (24.45)	
BA proximal	74 (16.16)	44 (16.06)	30 (16.30)	
V4 segment of vertebral artery	88 (19.21)	59 (21.53)	29 (15.76)	
Posterior circulation collateral score score, median (IQR)	5.00 (3.00–6.00)	4.00 (3.00–6.00)	5.00 (4.00–6.00)	<0.001
Reperfusion status, expanded Thrombolysis in Cerebral Infarction, n (%)				<0.001
2b	108 (23.58)	82 (29.93)	26 (14.13)	
2c	95 (20.74)	63 (22.99)	32 (17.39)	
3	255 (55.68)	129 (47.08)	126 (68.48)	
Treatment delay, min, median (IQR)				
Onset to puncture	331.00 (222.25–493.75)	356.00 (240.00–506.75)	301.50 (204.50–433.25)	0.02
Puncture to recanalization	102.00 (69.00–141.00)	108.50 (75.25–154.75)	86.00 (62.00–128.00)	<0.001
Onset to recanalization	442.00 (327.00–610.50)	472.50 (348.00–645.00)	401.50 (310.00–553.50)	0.004

BA indicates basilar artery; BP, blood pressure; EVT, endovascular treatment; IQR, interquartile range; mRS, modified Rankin Scale; and NIHSS, National Institutes of Health Stroke Scale.

*Data were not available for 1 patient in the poor outcome group.

Table 2. Clinical Features of Patients Stratified by Tirofiban Administration

	No tirofiban	Intravenous tirofiban	Intraarterial+intravenous tirofiban	
	(N=262)	(N=101)	(N=95)	*P*
Age, y, median (IQR)	66.00 (58.25–74.00)	62.00 (57.00–70.00)	63.00 (55.00–70.50)	0.006
Men, n (%)	190 (72.52)	77 (76.24)	75 (78.95)	0.43
Baseline NIHSS score, median (IQR)	26.00 (15.25–33.00)	28.00 (20.00–34.00)	23.00 (15.00–30.00)	0.01
Initial posterior circulation Acute Stroke Prognosis Early Computed Tomography Score, median (IQR)	8.00 (7.00–10.00)	8.00 (7.00–8.00)	8.00 (7.00–9.00)	0.001
Admission systolic BP, mm Hg, median (IQR)*	149.00 (132.00–162.75)	151.00 (135.00–174.00)	148.00 (135.00–170.00)	0.50
Admission diastolic BP, mm Hg, median (IQR)*	83.00 (75.00–91.00)	88.00 (79.00100.00)	85.00 (79.00100.00)	0.03
24 h NIHSS score after EVT, median (IQR)	26.00 (11.00–34.00)	26.00 (12.00–35.00)	19.00 (6.50–31.00)	0.04
7 d NIHSS score after EVT, median (IQR)	18.00 (5.00–35.00)	20.00 (8.00–36.00)	9.00 (2.00–26.00)	0.003
Intravenous thrombolysis, n (%)	56 (21.37)	20 (19.80)	10 (10.53)	0.07
Stenting, n (%)	70/260 (26.92)	53 (52.48)	38 (40.00)	<0.001
Intraarterial thrombolysis, n (%)	33 (12.60)	4 (3.96)	11 (11.58)	0.051
Postprocedural anticoagulation therapy, n (%)	17 (6.49)	1 (0.99)	0 (0)	0.005
Prestroke mRS score, n (%)				0.22
0	215 (82.06)	91 (90.10)	85 (89.47)	
1	33 (12.60)	6 (5.94)	7 (7.37)	
2	14 (5.34)	4 (3.96)	3 (3.16)	
History of risk factors, n (%)				
Hypertension	172 (65.65)	74 (73.27)	68 (71.58)	0.29
Diabetes	52 (19.85)	20 (19.80)	31 (32.63)	0.03
Dyslipidemia	82 (31.30)	24 (23.76)	38 (40.00)	0.05
Atrial fibrillation	77 (29.39)	18 (17.82)	5 (5.26)	<0.001
Smoking	93 (35.50)	44 (43.56)	34 (35.79)	0.34
Transient ischemic attack	4 (1.53)	0 (0.00)	2 (2.11)	0.39
Trial of ORG 10172 in Acute Stroke Treatment classification, n (%)				<0.001
Left atrial appendage	142 (54.20)	71 (70.30)	77 (81.05)	
Cardioembolism	96 (36.64)	20 (19.80)	10 (10.53)	
Stroke of other determined cause	4 (1.53)	3 (2.97)	5 (5.26)	
Stroke of undetermined cause	20 (7.63)	7 (6.93)	3 (3.16)	
Imaging parameters				
Occlusion site, n (%)				<0.001
BA distal	112 (42.75)	39 (38.61)	21 (22.11)	
BA middle	75 (28.63)	27 (26.73)	22 (23.16)	
BA proximal	30 (11.45)	17 (16.83)	27 (28.42)	
V4 segment of vertebral artery	45 (17.17)	18 (17.82)	25 (26.32)	
Posterior circulation collateral score score, median (IQR)	5.00 (4.00–6.00)	4.00 (2.00–5.00)	5.00 (3.00–6.00)	<0.001
Reperfusion status, expanded Thrombolysis in Cerebral Infarction, n (%)				0.10
2b	67 (25.57)	19 (18.81)	22 (23.16)	
2c	47 (17.94)	20 (19.80)	28 (29.47)	
3	148 (56.49)	62 (61.39)	45 (47.37)	

Continued

Table 2. Continued

	No tirofiban (N=262)	Intravenous tirofiban (N=101)	Intraarterial+intravenous tirofiban (N=95)	*P*
Treatment delay, min, median (IQR)				
Onset to puncture	349.00 (240.75–503.75)	315.00 (201.00–487.00)	298.00 (186.50–473.50)	0.11
Puncture to recanalization	96.50 (65.00–137.00)	104.00 (75.00–139.00)	113.00 (75.00–154.50)	0.07
Onset to recanalization	453.00 (334.25–633.25)	429.00 (315.00–592.00)	431.00 (314.00–603.00)	0.41

BA indicates basilar artery; BP, blood pressure; EVT, endovascular treatment; IQR, interquartile range; mRS, modified Rankin Scale; and NIHSS, National Institutes of Health Stroke Scale.

*Data were not available for 1 patient in the intravenous tirofiban group.

P=0.52; intraarterial+intravenous tirofiban versus no tirofiban: aOR, 0.23 [95% CI, 0.03–0.90]; *P*=0.05). There was significantly lower mortality in the tirofiban intraarterial+intravenous group compared with the no tirofiban group (22.1% versus 39.3%, aOR, 0.38 [95% CI, 0.19–0.71]; *P*=0.002) whereas no difference in mortality was noted in the intravenous tirofiban versus no tirofiban group (41.6% versus 39.3%, aOR, 1.55 [95% CI, 0.83–2.92]; *P*=0.17) (Table 3).

Propensity Score Matching Analysis

Baseline characteristics were balanced in the no tirofiban and intraarterial+intravenous-tirofiban groups after 1:1 PSM (Table S1). The proportions for the 90-day mRS scores 0 to 1, 0 to 2, and 0 to 3 in the intraarterial+intravenous tirofiban group remained higher than those in the no tirofiban group (respectively, 32.5% versus 18.8%, aOR, 2.92 [95% CI, 1.12–8.16]; *P*=0.03; 40.0% versus 23.8%, aOR, 3.24 [95% CI, 1.33–8.48]; *P*=0.01; 48.8% versus 30.0%, aOR, 2.95 [95% CI, 1.27–7.23]; *P*=0.01, Table S2).

Table S3 exhibits the baseline characteristics in the no tirofiban and intravenous-tirofiban groups after 1:1 PSM. The proportions for 90-day mRS scores 0 to 1, 0 to 2, and 0 to 3 were comparable between the intravenous tirofiban group and no tirofiban group (all *P*>0.05; Table S4). A subgroup analysis according to stroke cause (left atrial appendage versus non-left atrial appendage) is provided; for more details please refer to Table S5.

DISCUSSION

Based on national data from the BASILAR registry, our study revealed that (1) neither intraarterial+intravenous tirofiban nor intravenous tirofiban alone increased the risk of ICH or symptomatic ICH in patients with BAO after achieving recanalization by EVT, and (2) intraarterial+intravenous rather than intravenous tirofiban was associated with improved functional outcomes at 3 months compared with no tirofiban. Intraarterial+intravenous tirofiban may act as an effective adjunct approach to EVT in successfully recanalized patients with BAO.

Though the application of tirofiban was regarded as a promising strategy to improve the prognosis for patients with ischemic stroke who underwent EVT, findings regarding its efficacy have been conflicting. Several studies reported that tirofiban could lead to neurological deterioration by increasing ICH risk,[19] and a meta-analysis of 7 studies revealed that tirofiban was not associated with higher rate of ICH but trended toward lower mortality.[20] However, most of these studies did not report detailed information about the dose or the duration of intraarterial tirofiban in their cohorts.[16,19,20] A recent study from Guo et al illustrated that

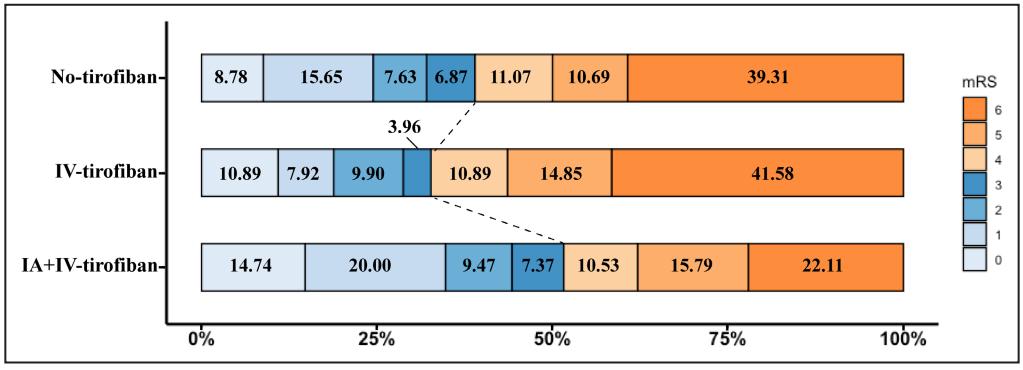

Figure 2. Distribution of the modified Rankin Scale score at 3 months among the 3 groups
IA indicates intraarterial; IV, intravenous; and mRS, modified Rankin Scale.

Table 3. Clinical and Safety Outcomes

	No tirofiban	Intravenous tirofiban	Intraarterial+ intravenous tirofiban	Intravenous tirofiban vs no tirofiban			Intraarterial+intravenous tirofiban vs no tirofiban		
	(N=262)	(N=101)	(N=95)	Unadjusted OR or RR (95% CI)	Adjusted OR or RR (95% CI)	*P**	Unadjusted OR or RR (95% CI)	Adjusted OR or RR (95% CI)	*P**
90-d Outcomes									
Modified Rankin scale score of 0–3, n (%)	102 (38.93)	33 (32.67)	49 (51.58)	0.85 (0.51–1.40)†	1.57 (0.83–3.00)†	0.19	1.67 (1.04–2.69)†	2.44 (1.30–4.64)†	0.006
Modified Rankin scale score of 0–2, n (%)	84 (32.06)	29 (28.71)	42 (44.21)	0.72 (0.40–1.25)†	1.62 (0.77–3.43)†	0.20	1.68 (1.04–2.72)†	2.66 (1.38–5.23)†	0.004
Modified Rankin scale score of 0–1, n (%)	64 (24.43)	19 (18.81)	33 (34.74)	0.86 (0.30–2.11)†	0.65 (0.21–1.78)†	0.42	1.65 (1.00–2.73)†	2.55 (1.29–5.14)†	0.008
Mortality, n (%)	103 (39.31)	42 (41.58)	21 (22.11)	0.76 (0.47–1.23)†	1.55 (0.83–2.92)†	0.17	0.44 (0.25–0.74)†	0.38 (0.19–0.71)†	0.002
Intracranial hemorrhage									
Any intracranial hemorrhage, n (%)	26 (9.92)	8 (7.92)	4 (4.21)	0.80 (0.37–1.70)‡	0.80 (0.34–1.87)‡	0.61	0.42 (0.15–1.18)‡	0.40 (0.15–1.05)‡	0.06
Symptomatic intracranial hemorrhage, n (%)	18 (6.87)	6 (5.94)	2 (2.11)	0.87 (0.35–2.12)‡	0.71 (0.26–1.94)‡	0.50	0.31 (0.07–1.30)‡	0.26 (0.06–1.04)‡	0.06

*The *P* value of the adjusted odds ratio (OR) or risk ratio (RR). The following variables were included in multivariable regression models: diabetes, age, sex, posterior circulation Acute Stroke Prognosis Early Computed Tomography Score, National Institutes of Health Stroke Scale score at admission, Trial of ORG 10172 in Acute Stroke Treatment, occlusion site, onset to recanalization time, and posterior circulation collateral score score.

†This value is odds ratio.

‡This value is risk ratio.

half of the patients receiving intravenous tirofiban were also treated with intraarterial local tirofiban in clinical practice in China, and simultaneous intraarterial+intravenous tirofiban rather than intravenous tirofiban improved outcomes of patients with anterior circulation stroke.[16] In our preceding RESCUE-BT trial, we found that intravenous tirofiban preceding thrombectomy failed to improve the clinical outcomes of patients with anterior circulation stroke.[21,22] To date, limited research has explored the role of tirofiban in BAO. A retrospective study of 120 patients with BAO, showed that intravenous tirofiban or abciximab was safe in treating individuals with BAO but did not improve their clinical outcomes.[23] Consistent with previous findings, our results showed that nearly half of patients with BAO treated with intravenous tirofiban also received intraarterial tirofiban, and intravenous tirofiban alone may not exhibit beneficial effects on outcomes in patients with BAO after EVT.

Several single-center retrospective analyses explored the role of intraarterial tirofiban among patients with anterior circulation stroke receiving EVT. Wu et al found a dose-dependent effect of intraarterial tirofiban on ICH and symptomatic ICH.[24] A full dose of intraarterial tirofiban (10 μg/kg) followed by continuous intravenous tirofiban led to a higher hemorrhagic risk compared with a full dose of intravenous tirofiban or no tirofiban, while a low dose of intraarterial+intravenous tirofiban improved the outcomes of patients with anterior circulation stroke after EVT.[11,16] The dose of tirofiban in this study was also relatively low, which was approximately identical to that in the study by Guo et al and assured the safety of the current dosing regimen of tirofiban.[16]

The pharmacological mechanism of tirofiban is to prevent activation and aggregation of platelets.[21] Research in vivo showed that tirofiban could also strengthen the integrity of the blood–brain barrier by attenuating an upregulated inflammatory response as a result of ischemic stroke.[25] Compared with intravenous tirofiban, an intraarterial bolus injection might increase local drug concentration more rapidly and provide direct contact of tirofiban to the thrombus to inhibit subsequent platelet aggregation, which could further improve the microcirculation perfusion or prevent proximal reocclusion.[25]

In our study, the imbalance of baseline clinical characteristics between the 2 groups may have increased the proportion of favorable outcomes in the intraarterial+intravenoustirofiban group. The age and NIHSS score at admission were significantly lower in the IA+ intravenous tirofiban group, which may be due to the fact that patients selected to receive tirofiban were

those who were thought to be at lower risk of ICH.[21,26] After including these imbalanced factors in multivariable regression models as covariates and correcting them in PSM analysis, our findings also demonstrated that intraarterial+intravenous tirofiban could improve outcomes of BAO and provide a basis for patient selection for tirofiban treatment and inform further clinical trial design.

In the present study, the incidence of any ICH and symptomatic ICH was higher in patients treated without tirofiban compared with those treated with intravenous or intraarterial+IV tirofiban. This finding differs from our previous RESCUE BT (Endovascular Treatment With Vs Without Tirofiban for Patients With Large Vessel Occlusion Stroke) randomized trial.[21] The following points may explain this unusual result. First, tirofiban is used more often for patients with large arterial atherosclerosis rather than cardioembolism (intraarterial+intravenous tirofiban 81.1% versus intravenous tirofiban 70.3% versus no tirofiban 54.2%), which might reduce the frequency of ICH. Besides, patients in the no tirofiban group received intraarterial thrombolysis more often than patients in the intravenous and intraarterial+intravenous tirofiban groups during EVT. Moreover, the proportion of patients receiving anticoagulation treatment after endovascular thrombectomy was higher in the no tirofiban group than in the intravenous and intraarterial+intravenous tirofiban groups. Last, the rate of patients receiving intravenous thrombolysis was numerically higher in the no tirofiban group than in the intravenous and intraarterial+intravenous tirofiban groups. These confounders may have contributed to the increased incidence of ICH in the no tirofiban group.

The strength of our cohort consisted of the large number of patients extracted from the nationwide registry of BASILAR with long-term follow-up outcomes. However, this study had limitations due to its nonrandomized controlled design. Although multivariable regression and PSM analyses were used in mitigating selection bias, unknown confounders could not be controlled. The sample size was relatively small. As all patients in this cohort were recruited in China, with a high incidence of large artery atherosclerosis, this might limit the interpretation and generalizability of these results. These results may need to be generalized to other populations. The benefit or safety of tirofiban in patients with unsuccessful recanalization of BAO also remains unknown. The efficacy and safety of intraarterial+intravenous tirofiban should be assessed in a multicenter randomized clinical trial.

CONCLUSION

Based on our BASILAR registry data, the present research was the first to demonstrate the clinical outcomes and safety of intraarterial+intravenous tirofiban in improving long-term outcomes among patients with BAO after achieving successful recanalization by EVT. Given the limitations of the current study, further study with a randomized trial is warranted to confirm our findings and determine the optimal tirofiban protocol.

ARTICLE INFORMATION

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T. Nguyen discloses they are on the advisory board with Idorsia, Brainomix. The remaining authors have no disclosures to report.

Supplemental Material

Tables S1–S5

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