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Intravenous thrombolysis plus tirofiban versus tirofiban alone in Caucasian patients with acute anterior choroidal or paramedian pontine infarction

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Abstract:

BACKGROUND: Tirofiban has been shown to be superior to aspirin in achieving functional independence at 3 months for acute ischemic stroke of atheromatous or microatheromatous origin. As intravenous thrombolysis (IVT) has previously been shown to be nonsuperior to aspirin in achieving functional independence at 3 months for anterior choroidal or paramedian pontine infarction (ACI/PPI), we aimed to compare the outcomes of Caucasian patients receiving IVT plus tirofiban (IVT + T) with those receiving tirofiban alone for acute ACI/PPI.

METHODS: A retrospective study was conducted in patients aged ≥ 18 years with ACI/PPI treated in our stroke unit between December 1, 2020, and April 30, 2023, who received therapeutic intervention within 9 hours of symptom onset or after awakening with stroke symptoms. Modified Rankin Scale (mRS) ≤ 1 at 3 months was the primary endpoint. Secondary endpoints were National Institutes of Health Stroke Scale (NIHSS) ≤ 2 at day 7 or discharge and post-procedural neurological deterioration (PPND) within 72 hours. Symptomatic intracranial hemorrhage (SICH) and major systemic bleeding (MSB) were the safety measures of the study.

RESULTS: A total of 24 patients were enrolled in the tirofiban group and 43 patients in the IVT + T group. Compared to tirofiban alone, IVT + T was associated with a higher probability of achieving mRS ≤1 at 3 months (adjusted odds ratio [aOR], 8.79; 95% confidence interval [CI], 2.06–37.52; $P = 0.003$) and National Institutes of Health Stroke Scale ≤2 at day 7 or discharge (aOR, 3.70; 95% CI, 1.05–12.99; $P = 0.041$). No significant difference was seen between the two groups in preventing postprocedural neurological deterioration. One case of SICH and two cases of MSB occurred in the IVT + T group and no cases in the tirofiban group. One case of inhospital mortality was recorded in the IVT + T group.

CONCLUSIONS: Our results showed that IVT + T may be safe and effective in Caucasian patients with acute ACI/PPI.

Keywords:

Acute ischemic stroke, anterior choroidal artery, intravenous thrombolysis, paramedian pontine artery, tirofiban

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Introduction

Intravenous thrombolysis (IVT) is an effective therapy for acute ischemic stroke (AIS), allowing resolution or improvement of neurological deficits and reducing the risk of significant disability after stroke.[1] However, the effectiveness of IVT in perforating artery cerebral infarction (PACI) remains controversial. To date, no randomized clinical trial has assessed the effectiveness of IVT in these types of ischemic strokes. Several nonrandomized studies have previously shown the ineffectiveness of IVT in patients with PACI, and 47%–57% of them will present neurological deterioration (ND) despite IVT, increasing the risk of significant disability after a stroke.[2-4] Only one study reported the effectiveness of IVT in patients with PACI in reducing the risk of ND and achieving functional independence at 3 months.[5] ND after IVT in patients with PACI would probably be related to secondary reocclusion of the perforating arteries due not only to their small diameter but also to the activation of platelets secondary to the ulcerated plaque[6] or prothrombotic effect of IVT promoting the formation of thrombin that cause platelet aggregation. Studies have shown that intravenous administration of tirofiban immediately or within 24 h after IVT would significantly reduce the incidence of ND after post-IVT clinical improvement and increase the incidence of functional independence at 3 months in patients with AIS of atheromatous or microatheromatous origin without significantly increased bleeding risk.[6,7] Tirofiban is a highly selective inhibitor of nonpeptide glycoprotein IIb/IIIa (GP IIb/IIIa) receptors to which it blocks binding with fibrinogen, and after the cessation of its administration, the bleeding time returns to normal within around 4 h.[6] This inhibitory effect of tirofiban, which blocks the binding of fibrinogen to GP IIb/IIIa receptors, inhibits platelet aggregation and thrombus reformation and, therefore, probably arterial reocclusion.

Although it is an effective therapy for AIS, IVT is not recommended in several situations, such as anticoagulation with Vitamin K antagonists with INR >1.7 or with direct oral anticoagulants with specific coagulation tests available and platelet count <100,000/mm^3.[1,8] When IVT is not recommended, particularly in patients with PACI in whom endovascular treatment is not feasible, the recommended therapeutic option is aspirin or another antiplatelet agent or their combination[1] or continuation of ongoing anticoagulant. Recently, a multicenter randomized clinical trial showed the superiority of intravenous tirofiban compared to aspirin in the probability of achieving an excellent functional outcome at 3 months in patients with AIS without occlusion of large- or medium-sized intracranial vessels who were not eligible for conventional reperfusion treatments or whose symptoms progressed or not improved after IVT.[9]

This study aimed to compare the outcomes of Caucasian patients receiving IVT plus tirofiban (IVT + T) with those receiving tirofiban alone for PACI (mainly anterior choroidal or paramedian pontine infarction [ACI/PPI]). As it has been previously shown that IVT is not superior to antiplatelet treatment in ACI or PPI to prevent ND and achieve functional independence at 3 months,[2-4] and as tirofiban is superior to aspirin in AISs of atheromatous or microatheromatous origin to obtain functional independence at 3 months,[9] we hypothesize that the combination IVT + T would be more effective to tirofiban alone in reducing the risk of ND and obtaining functional independence at 3 months without significantly increased bleeding risk.

Methods

Study design and patients

A retrospective study was conducted on patients with ACI/PPI who were treated in our stroke unit between December 1, 2020, and April 30, 2023. The study included patients aged ≥18 years with ACI/PPI revealed by cerebral magnetic resonance imaging (MRI) who received therapeutic intervention within 9 h of symptom onset or after awakening with stroke symptoms. The study did not include patients with severe disability (Modified Rankin Scale [mRS] ≥3) before the stroke. This study has been approved by the institutional review board of our institution (ref: 2022/0039). An information note including the purpose of the study and the data to be collected anonymously was sent to each patient to inform them of their participation in the study, and the possibility to withdraw was offered to them. Informed consent to participate in this research was obtained for all patients.

Procedures

On admission, each patient underwent a cerebral MRI for suspicion of stroke. ACI and PPI were defined as follows:[5,10] (1) infarction involving 3 axial slices on diffusion-weighted imaging (DWI) with a diameter ≥15 mm in the perforating vascular territory of the anterior choroidal artery (medial globus pallidus, tail of the caudate nucleus, corona radiate, and posterior arm of the internal capsule) [Figure 1] or ischemic lesions of the pons involving the ventral surface in the territory of the paramedian pontine artery [Figure 2] and (2) absence of large artery stenosis (>50%) or occlusion and absence of cardioembolism. When cerebral MRI showed ACI or PPI, and when IVT was not contraindicated, patients systematically received tenecteplase or alteplase at the recommended doses.[11] Within the next 4 h after IVT and without prior control brain imaging, according to the routine practice of our stroke unit since June 2018, patients with ACI or PPI systematically received intravenous tirofiban 0.4 μg/kg/min for 30 min, followed by a continuous intravenous infusion of 0.1 μg/kg/min

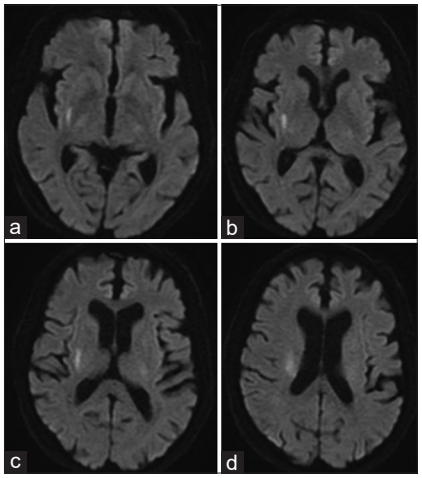

Figure 1: Cerebral magnetic resonance imaging showing on diffusion-weighted imaging (images a, b, c and d) infarction in the perforating vascular territory of the anterior choroidal artery

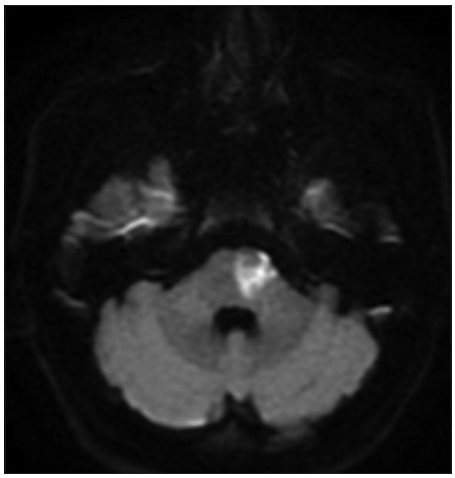

Figure 2: Cerebral magnetic resonance imaging showing on diffusion-weighted imaging ischemic lesions of the pons involving the ventral surface in the territory of the paramedian pontine artery

for 48 h (IVT + T group). When IVT is not feasible due to ongoing direct oral anticoagulant treatment, DWI-fluid-attenuated inversion recovery match, or other reasons, patients only receive tirofiban according to the above protocol (tirofiban group).

Clinical evaluation

Neurological deficits were evaluated for each patient at admission, at day 7, or discharge, and a National Institutes of Health Stroke Scale (NIHSS) was calculated at each neurological evaluation. NIHSS was also calculated at any time a patient had signs of ND. Progression or fluctuation of stroke symptoms was defined as an increase of ≥ 4 points in total NIHSS or ≥ 2 points in motor function but with a return to baseline neurological status in the case of motor fluctuation.[12] To assess the degree of disability or dependence in activities of daily living at 3 months, the mRS was used, ranging from 0 (no deficit) to 6 (death).

Safety evaluation

A cerebral MRI was systematically performed within 24–36 h in the patients receiving IVT + T. A cerebral MRI was also performed at any time if a patient had signs of ND. The presence of intracranial hemorrhage on MRI was recorded. Intracranial hemorrhage causing ND with an increase of ≥4 points in the total NIHSS or ≥2 points in any NIHSS category was defined as symptomatic intracranial hemorrhage (SICH).[13] In all patients, the presence of systemic bleeding was recorded. A decrease in hemoglobin of ≥2 g/dl was defined as a major systemic bleeding (MSB).[14]

Study outcomes

Achievement of mRS ≤1 at 3 months was the primary endpoint. The secondary endpoints were NIHSS ≤2 at day 7 or discharge and postprocedural ND (PPND) within 72 h. SICH and MSB were the safety measures of the study.

Statistical analysis

The primary and secondary efficacy endpoints of the study, as well as safety measures, were assessed using a binary logistic regression model. Unadjusted odds ratio and adjusted odds ratio (aOR) with 95% confidence intervals (CIs) are provided. Adjustments were made for important prognostic factors, including age, sex, infarct size, and baseline NIHSS. SPSS statistical software package (IBM Corporation, Version 25.0. Armonk, NY, USA) was used for statistical analysis. $P \leq 0.05$ was considered statistically significant.

Clinical trial registry

This work is a retrospective analytical study. No clinical trials were involved.

Results

Baseline characteristics

During the study period, 219 patients with ACI/PPI were enrolled, of whom 152 were excluded, as shown in Figure 3 (prestroke mRS ≥3 = 11, the onset of symptoms to therapeutic intervention >9 h = 71, and intracranial occlusions [intracranial carotid, middle cerebral artery, and basilar artery] =70). A total of 67 patients (mean age 67.97 years; 38.8% women; median NIHSS 4; 20.9% current smokers; 10.4% former smokers; 4.5% of patients with a history of coronary artery disease; 48 cases of ACI and 19 cases of PPI) were included in the study. Were included in this study (24 patients in the tirofiban group and 43 patients in the IVT + T group). The baseline characteristics of the patients

were similar in the two groups, except for the variable infarct site [Table 1].

Primary efficacy endpoint

The median mRS at 3 months was 1 (IQR, 0–2) in the IVT + T group and 2 (IQR, 1–3) in the tirofiban group (aOR, 1.73; 95% CI, 1.13–2.64; $P = 0.012$) [Table 2]. An excellent functional outcome (mRS of 0–1) was achieved in 25 patients of 43 (58.1%) in the IVT + T group and 7 patients of 24 (29.2%) in the tirofiban group (aOR, 8.79; 95% CI, 2.06–37.52; $P = 0.003$) [Figure 4].

Secondary efficacy endpoints

Compared to tirofiban alone, IVT + T was associated with a higher probability of achieving NIHSS ≤2 at day 7 or discharge (aOR, 3.70; 95% CI, 1.05–12.99; $P = 0.041$). PPND within 72 h occurred in 5 patients of 24 (20.8%) in the tirofiban group and 3 patients of 43 (7%) in the IVT + T group (aOR, 0.28; 95% CI, 0.05–1.56; $P = 0.148$).

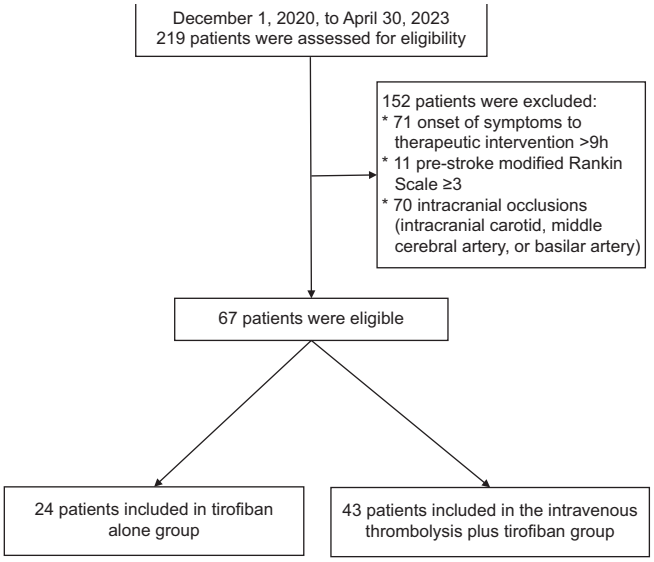

Figure 3: Flowchart of the study

Safety endpoints

Intracranial hemorrhage occurred in 3 patients of 43 (7%) in the IVT + T group and 0 patients of 24 in the tirofiban group. One case of SICH occurred in the IVT + T group. MSB occurred in 2 of 43 patients (4.7%) in the IVT + T group and 0 patients of 24 in the tirofiban group. One case of inhospital mortality related to SICH and MSB occurred in the IVT + T group.

Discussion

This study in Caucasian patients with acute ACI or PPI showed that IVT + T increased the likelihood of achieving NIHSS ≤2 at day 7 or discharge and mRS ≤1 at 3 months compared to tirofiban alone, a drug with antiplatelet activity superior to that of aspirin in the treatment of AIS of atheromatous or microatheromatous origin.[9] The combination of IVT + T seemed more effective than tirofiban alone in preventing PPND within 72 h but without statistical significance. With respect to safety measures, IVT + T was not associated with an increased risk of major bleeding compared to tirofiban alone.

In acute ACI or PPI, several previous studies have shown that IVT alone is not superior to aspirin in preventing ND.[2-4] However, previous studies have shown that IVT + T compared to IVT alone was more effective in preventing ND in Asian patients with AIS of atheromatous or microatheromatous origin,[6,7] as is probably the case for most ACI and PPI. Post-IVT ND

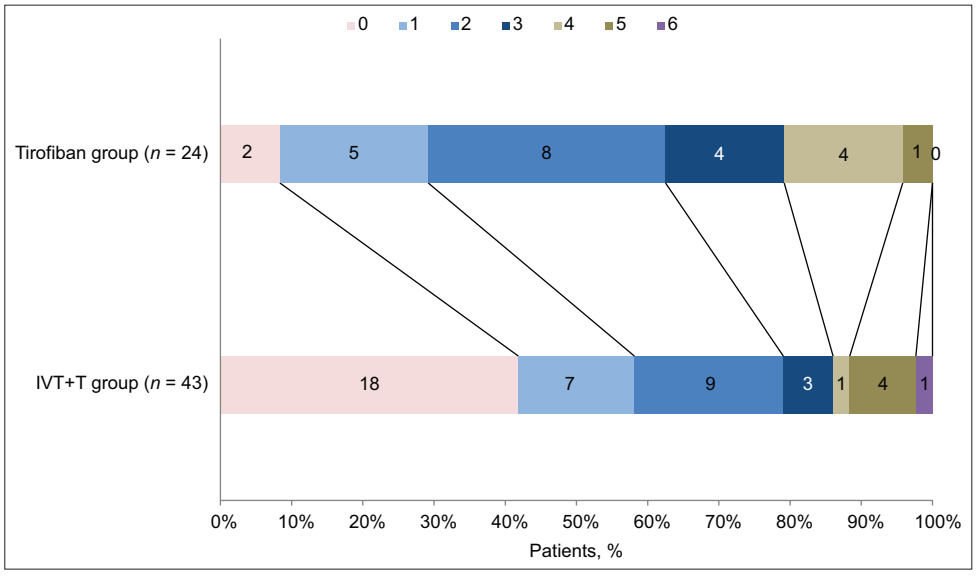

Figure 4: Distribution of the Modified Rankin Scale at 3 months according to study groups. No inhospital mortality occurred in the tirofiban group at 3 months. IVT + T: Intravenous thrombolysis + tirofiban

Table 1: Baseline characteristics

Characteristics	Overall (*n*=67)	Tirofiban (*n*=24)	IVT + tirofiban (*n*=43)	*P*
Age (years), mean (SD)	67.97 (14.74)	68.79 (12.74)	67.51 (15.87)	0.736
Male sex, *n* (%)	41 (61.2)	16 (66.7)	25 (58.1)	0.604
Hypertension, *n* (%)	43 (64.2)	19 (79.2)	24 (55.8)	0.067
Diabetes, *n* (%)	20 (29.9)	8 (33.3)	12 (27.9)	0.782
Current smoking, *n* (%)	14 (20.9)	7 (29.2)	7 (16.3)	0.266
Former smoking, *n* (%)	7 (10.4)	1 (4.2)	6 (14.0)	
No smoking, *n* (%)	46 (68.7)	16 (66.6)	30 (69.7)	
Dyslipidemia, *n* (%)	18 (26.9)	7 (29.2)	11 (25.6)	0.780
History of stroke or TIA, *n* (%)	12 (17.9)	4 (16.7)	8 (18.6)	1.000
Prestroke mRS, *n* (%)				
0	65 (97)	24 (100)	41 (95.3)	1.000
1	1 (1.5)	0	1 (2.3)	
2	1 (1.5)	0	1 (2.3)	
Atrial fibrillation, *n* (%)	5 (7.5)	2 (8.3)	3 (7.0)	1.000
CAD, *n* (%)	3 (4.5)	2 (8.3)	1 (2.3)	0.290
PVD, *n* (%)	2 (3.0)	1 (4.2)	1 (2.3)	1.000
PAM, *n* (%)	12 (17.9)	5 (20.8)	7 (16.3)	0.743
Prior anticoagulation, *n* (%)	5 (7.5)	2 (8.3)	3 (7.0)	1.000
Fluctuation, *n* (%)	12 (17.9)	5 (20.8)	7 (16.3)	0.743
POS, *n* (%)	8 (11.9)	2 (8.3)	6 (14.0)	0.701
Regressive symptoms, *n* (%)	7 (10.4)	3 (12.5)	4 (9.3)	0.695
SBP (mmHg), mean (SD)	170.38 (31.28)	165.22 (29.42)	173.14 (32.23)	0.331
DBP (mmHg), mean (SD)	94.33 (20.20)	91.57 (18.05)	95.81 (21.31)	0.420
Baseline NIHSS				
Median (IQR)	4 (2–8)	3.5 (2.25–6)	5 (2–9)	0.200
≤2	19 (28.4)	6 (25.0)	13 (30.2)	0.325
3–5	20 (29.9)	10 (41.7)	10 (23.3)	
≥6	28 (41.8)	8 (33.3)	20 (46.5)	
Infarct site				
ACA, *n* (%)	48 (71.6)	21 (87.5)	27 (62.8)	0.047
PPA, *n* (%)	19 (28.4)	3 (12.5)	16 (37.2)	
OTT, median (IQR)	208 (144–257)	-	208 (144–257)	-
OTTA, mean (SD)	295.46 (126.86)	320.50 (146.81)	281.49 (113.71)	0.230
TTA, median (IQR)	32 (7–109)	-	32 (7–109)	-
Reasons for non-IVT				
DWI-FLAIR match	14 (58.3)	14 (58.3)	-	-
DOAC plasma levels ≥130 ng/ml	2 (8.3)	2 (8.3)	-	-
NDSs with NIHSS ≤2	3 (4.5)	3 (12.5)	-	-
Unspecified reasons	5 (20.8)	5 (20.8)	-	-

ACA: Anterior choroidal artery, CAD: Coronary artery disease, DBP: Diastolic blood pressure, DOAC: Direct oral anticoagulant, DWI: Diffusion-weighted imaging, FLAIR: Fluid-attenuated inversion recovery, IQR: Interquartile range, IVT: Intravenous thrombolysis, mRS: Modified Rankin Scale, NIHSS: National Institute of Health Stroke Score, NDS: Nondisabling symptom, OTT: Onset-to-thrombolysis, OTTA: Onset-to-tirofiban administration, PAM: Prior antiplatelet medication, POS: Progressive onset of symptoms, PPA: Paramedian pontine artery, PVD: Peripheral vascular disease, SBP: Systolic blood pressure, SD: Standard deviation, TIA: Transient ischemic attack, TTA: Thrombolysis-to-tirofiban administration

is probably due to arterial reocclusion secondary to thrombus reformation on the ulcerated plaque. Tirofiban inhibits, by its antiplatelet activity, the reformation of the thrombus after IVT and helps to prevent ND.[7] The present study showed that IVT + T seemed more effective in preventing ND than tirofiban alone, which is consistent with previous studies.[6,7] Our findings also showed that IVT + T, compared to tirofiban alone, was associated with a higher probability of achieving NIHSS ≤2 at day 7 or discharge and, consequently, early functional independence. It has previously been shown that IVT alone was not superior to aspirin in achieving mRS ≤2 at 3 months.[3,4] In the present study, at 3 months, 58.1% of patients in the IVT + T group had mRS ≤1 compared to 29.2% of patients in the tirofiban group ($P = 0.003$), which suggests that IVT + T was associated with a higher probability of achieving mRS ≤1 at 3 months. This is consistent with the results of previous studies in which IVT + T was more effective than IVT alone in achieving mRS ≤2 at 3 months in Asian patients with AIS of atheromatous or microatheromatous origin.[6,7] As previously shown, IVT + T is not associated

Table 2: Study outcomes

Variable	Tirofiban (*n*=24)	IVT + tirofiban (*n*=43)	Crude OR (95% CI)	*P*	AOR (95% CI)	*P*
Primary efficacy endpoint						
mRS, median (IQR)	2 (1–3)	1 (0–2)	1.34 (0.98–1.83)	0.072	1.73 (1.13–2.64)	0.012
mRS 0–1, *n* (%)	7 (29.2)	25 (58.1)	3.37 (1.16–9.82)	0.026	8.79 (2.06–37.52)	0.003
mRS 0–2, *n* (%)	15 (62.5)	34 (79.1)	2.27 (0.75–6.85)	0.147	2.71 (0.72–10.25)	0.143
Secondary efficacy endpoints						
NIHSS at 5–7 days or discharge, median (IQR)	3 (1.25–5.75)	2 (0–4)	1.10 (0.95–1.28)	0.208	1.23 (1.00–1.52)	0.053
NIHSS at 5–7 days or discharge ≤2, *n* (%)	11 (45.8)	29 (67.4)	2.45 (0.88–6.83)	0.087	3.70 (1.05–12.99)	0.041
ND, *n* (%)	5 (20.8)	3 (7.0)	0.29 (0.06–1.32)	0.108	0.28 (0.05–1.56)	0.148
Safety endpoints, *n* (%)						
Intracranial hemorrhage	0	3 (7.0)	0.62 (0.51–0.75)	0.548	-	-
SICH	0	1 (2.3)	-	-	-	-
MSB	0	2 (4.7)	0.63 (0.52–0.76)	0.533	-	-
Inhospital mortality	0	1 (2.3)	-	-	-	-

IQR: Interquartile range, MSB: Major systemic bleeding, mRS: Modified Rankin Scale, NIHSS: National Institute Of Health Stroke Score, OR: Odds ratio, SICH: Symptomatic intracranial hemorrhage, IVT: Intravenous thrombolysis, CI: Confidence interval, ND: Neurological deterioration, AOR: Adjusted OR

with an increased risk of major bleeding compared to IVT alone.[6,7,15] In the present study, two cases of MSB (4.7%) and one case of SICH (2.3%) occurred in the IVT + T group, whereas there were no hemorrhagic complications in the tirofiban group. In the European Cooperative Acute Stroke Study III trial comparing IVT versus placebo, the rate of intracranial hemorrhages was 27%, including 2.4% for SICH.[16] These results are comparable to ours (2.3%), suggesting that IVT + T would not significantly increase the risk of bleeding.

The present study included only patients with ACI and PPI, which were presumably caused by microatheromatous at the ostium of the corresponding arteries,[17] which limits the generalizability of the study results to patients with atheromatous or cardioembolic ischemic stroke.

The main limitations of this study are as follows: (1) because of the retrospective, monocentric, and nonrandomized nature of the study, the findings need to be interpreted with caution, and the universal applicability of these findings requires further research, (2) the number of patients included was small because ACI and PPI are relatively uncommon in Caucasian populations compared to Asian populations,[5] and (3) some variables in baseline characteristics were not well balanced between the two groups, especially arterial hypertension and infarct site, which can affect the study findings to a certain extent.

Conclusions

Our findings showed that IVT + T may be an effective therapy in Caucasian patients with acute ACI or PPI without any increased bleeding risk compared to tirofiban alone. However, larger multicenter, prospective, randomized studies are necessary for confirmation of our findings.

Author contributions

Concepts, design, literature search, statistical analysis, guarantor: MTD; Clinical studies, data acquisition, data analysis, manuscript preparation, manuscript editing: All authors; Manuscript review: RVYZ, NRAT, MB, DS, TA, MA, OL, NC, DS.

Ethical statement

The study was conducted according to the principles of the Declaration of Helsinki for Medical Research Involving Human Subjects and approved by the ethics committee of Centre Hospitalier Sud-Francilien (ref: 2022/0039, dated on May 16, 2023).

Data availability statement

The datasets generated during and/or analyzed during the current study are not publicly available due to privacy or ethical restrictions but are available from the corresponding author on reasonable request.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

Acknowledgment

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