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Research Article

# Efficacy and safety of tirofiban injection with intracranial stenting in early reocclusion due to intracranial atherosclerosis

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ABSTRACT

*Objective:* We aimed to develop an optimal protocol for failed mechanical thrombectomy (MT) in cases of emergent large vessel occlusion (ELVO) with intracranial atherosclerosis (ICAS).

*Methods:* A total of 117 patients without underlying heart disease who were not taking antiplatelet drugs had early reocclusion during MT for ELVO due to ICAS. They were divided into the following 3 groups according to rescue treatment methods: 1) Combined intravenous (IV) + intra-arterial (IA) tirofiban group (n = 48), emergent percutaneous transluminal angioplasty (PTA) and intracranial stenting (ICS) followed by IA injection of tirofiban and a continuous IV tirofiban infusion for 8 h; 2) IA tirofiban group (n = 33), only IA 0.5–1.0 mg tirofiban infusion for 5 min regardless of PTA or ICS; and 3) no tirofiban group (n = 36), no tirofiban injection regardless of PTA or ICS.

*Results:* ICS was more frequently performed in the combined IV + IA tirofiban group than in the IA tirofiban group (100% vs 46%, $p < 0.05$). The proportion of m-TICI grades 2b and 3 (93.8% vs. 63.6%, $p < 0.05$), especially the proportion of m-TICI grade 3 (81.3% vs. 36.4%, $p < 0.05$), was higher in the combined IV + IA tirofiban group than in the IA tirofiban group. The rate of postoperative intracranial hemorrhage was not significantly different among the three groups. The rate of modified Rankin scale scores of 0–2 at 3 months after MT was highest in the combined IV + IA tirofiban group (63%), followed by the IA tirofiban (46%) and no tirofiban groups (8%, $p < 0.05$).

*Conclusion:* ICS with IA and continuous IV tirofiban injections for 8 h is an effective and safe protocol for failed MT in patients with ELVO with ICAS.

*Abbreviations:* AIS, acute ischemic stroke; ASPECTS, Alberta Stroke Program Early CT Score; CT, computed tomography; DM, diabetes mellitus; ECASS, European Cooperative Acute Stroke Study; ELVO, emergent large vessel occlusion; GPI, glycoprotein IIb/IIIa inhibitor; HI, hemorrhagic infarction; IA, Intra-arterial; ICA, internal carotid artery; ICAS, Intracranial atherosclerosis; ICH, intracranial hemorrhages; ICS, intracranial stenting; IV, intravenous; MCA, middle cerebral artery; MRA, magnetic resonance angiography; MRI, magnetic resonance imaging; mRS, modified Rankin scale; MT, mechanical thrombectomy; m-TICI, modified treatment in cerebral infarction score; NIHSS, National Institutes of Health Stroke Scale; PH, parenchymal hemorrhage; PTA, percutaneous transluminal angioplasty; PTA/S, percutaneous transluminal angioplasty and stenting; SAMMPRIS, Stenting versus Aggressive Medical Therapy for Intracranial Arterial Stenosis; TIA, transient ischemic accident; TOAST, stroke subtypes according to the Trial of ORG 10172 in acute stroke treatment; tPA, tissue plasminogen activator; VBA, vertebrobasilar artery; WASID, Warfarin-Aspirin Symptomatic Intracranial Disease; WEAVE, Wingspan Stent System Post-Market Surveillance.

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## 1. Introduction

Intracranial atherosclerosis (ICAS) is the most common cause of acute ischemic stroke (AIS) in Asia [1]. The incidence of ICAS in east Asian populations (approximately 15–35%) is higher than that in Western populations [2,3], although a recent study revealed a much higher prevalence of ICAS in Europe than previously thought [4]. According to stroke statistics in Korea from 2008 to 2015, 36.7% of those who experienced AIS were diagnosed with large artery atherosclerosis, which is the leading cause of AIS [5]. Moreover, approximately 5.5% of AIS patients undergo stent-retriever thrombectomy for ICAS [6].

Endovascular treatment of AIS with emergent large vessel occlusion (ELVO) can result in successful recanalization of the occluded vessel. However, the therapeutic response is less positive in cases of AIS with ICAS than in those of AIS with cardiac embolism. Unlike an embolism, if ICAS is the cause of ELVO, flow decrement remains after thrombectomy. Notably, AIS can also induce recurrent occlusion after endovascular treatment. Some studies have suggested using the antiplatelet medication to prevent reocclusion in patients with ICAS, but the results have been inconsistent. This study aimed to explore the optimal protocol for preventing reocclusion in patients with ICAS.

## 2. Materials and methods

Between January 2011 and December 2019, 264 patients underwent mechanical thrombectomy (MT) for AIS at three centers. Clinical and radiological data were prospectively collected and analyzed. We collected the following information: 1) demographics, 2) risk factors for a cerebrovascular accident, 3) National Institutes of Health Stroke Scale (NIHSS) [7], 4) baseline Albert Stroke Program Early Computed Tomography Score (ASPECTS) [8,9], 5) stroke subtypes according to the Trial of ORG 10172 in acute stroke treatment (TOAST) classification [10], 6) use of intravenous (IV) tissue plasminogen activator (tPA), 7) time to procedure, 8) procedure duration, 9) angiographic outcome: modified treatment in cerebral infarction score (m-TICI) [11], and 10) 3-month modified Rankin scale (mRS) score [12,13]. Time to the procedure was defined as the interval between the time of onset of symptoms or the last normal time and the time of the MT.

## 3. Inclusion and exclusion criteria

All patients had undergone non-enhanced head computed tomography (CT), multiphase head CT angiography, brain diffusion-weighted magnetic resonance imaging (MRI), and head magnetic resonance angiography (MRA) before MT. Inclusion criteria for the MT procedures were as follows: 1) presentation within 8 h after AIS symptom onset in the anterior circulation [14–17], and within 24 h of posterior circulation [18–19], 2) good collateral status on multiphase head CT angiography based on extended criteria within 24 h of stroke onset for an anterior circulation stroke since 2018 [20,21], 3) initial NIHSS score $\geq$ 4 [22–26]; 4) no intracranial hemorrhage detected on head CT or MRI; 5) ASPECTS $\geq$ 6 for anterior circulation [27–30]; 6) premorbid mRS score $\leq$ 2 [27]; 7) locations of the occluded vessel (internal carotid artery, M1 of the middle cerebral artery [MCA], and vertebrobasilar artery [VBA]) confirmed by cerebral angiography; and 8) reocclusion during MT in patients with larger artery atherosclerosis.

The exclusion criteria were as follows: 1) cardiac embolism with undetermined stroke etiology according to TOAST classification; 2) underlying heart diseases, such as atrial fibrillation, coronary vessel disease, or congestive heart failure; 3) extracranial atherosclerosis; 4) in-stent thrombosis; 5) previous dual antiplatelet therapy; 6) treatment with emergent extracranial-intracranial artery bypass surgery; and 7) angiographic features mimicking ICAS, such as dissection, vasospasm, or remnant thrombus. Vasospasm was defined as vessel dilatation on follow-up angiography after an injection of 5–10 mg of intra-arterial (IA) verapamil for 5 min. Dissection was identified by an intimal flap, double-lumen sign, or pearl-and-string pattern on catheter angiography. Remnant thrombus was defined as vessel dilatation without focal stenosis after repeat stent retrieval.

The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Research Ethics Committee of Soonchunhyang University Hospital (IRB number, SCHCH-2018-07-025). This study was performed under the National Stroke Quality Assessment Research with National Health Insurance Administration. Patients' personal information was protected and kept anonymous. Patient consent was waived due to the retrospective nature of the study.

## 4. Mechanical thrombectomy

MT was performed under local anesthesia in each patient. Stent-retriever thrombectomy was performed in all cases using a Solitaire (Medtronic Inc., Dublin, Ireland) or Trevo (Stryker Inc., Fremont, CA, USA) stent. The thrombectomy technique has been described in a previous report [31]. Failed thrombectomy was defined as emergent reocclusion or flow stagnation on the occluded site, with underlying moderate to severe ICAS revealed on sequential angiography after 3 passes of stent retrievals. Based on Warfarin-Aspirin Symptomatic Intracranial Disease (WASID) criteria, moderate intracranial stenosis was defined as 50 to 69% stenosis on cerebral angiography, and severe stenosis was defined as 70 to 99% stenosis [32,33]. Reocclusion was classified into early reocclusion and late reocclusion. Early reocclusion was defined as immediate occlusion of the treated vessel within 10 min; follow-up angiography was performed 10 min after the end of endovascular treatment to confirm early reocclusion. Late reocclusion was defined as successful recanalization at the end of endovascular treatment, but reocclusion was detected after 24 h; it was confirmed by MRA performed 24 h after the end of treatment.

In failed thrombectomy, rescue treatments such as tirofiban injection, percutaneous transluminal angioplasty (PTA), or intracranial stenting (ICS) were performed. The rescue treatment was chosen based on either the neurointerventionists' preference, period of treatment, perforating arteries, or the tortuosity of the intracranial artery. MT was mainly performed from 2011 to 2015, but some neurointerventionists performed rescue treatments for failed thrombectomy from 2016 to 2020.

Patient data were divided into three groups as follows: 1) Combined IV + IA tirofiban group: 0.5–1.0 mg of IA tirofiban infusion after PTA with ICS and a continuous IV tirofiban infusion for 8 h; 2) IA tirofiban group: only an IA 0.5–1.0 mg tirofiban infusion for 5 min after emergent percutaneous transluminal angioplasty or stenting (PTA/S); and 3) no tirofiban group: PTA/S without tirofiban injection.

In the combined IV + IA tirofiban group, PTA with Gateway (Stryker Inc., Fremont, California), ICS with Wingspan (Stryker Inc., Fremont, California), or Pro-kinetic energy (Biotronik, Berlin) stents in ICAS lesions were performed. If reocclusion and stenosis ($\geq$50% as defined by the WASID criteria) were detected [32,33], a flat-panel detector scan (XpertCT, Allura Xpert FD 20/20; Philips) was performed to exclude intracranial hemorrhage or dye leakage prior to infusion of tirofiban. After ruling these out, ICS was performed if necessary. After PTA/S, 0.5–1.0 mg of tirofiban diluted with 10 mL of normal saline was administered at a rate of 1 mg/min (Table 1). Subsequently, a mixture of 6.25 mg of tirofiban and 100 mL of normal saline was continuously infused for 8 h in proportion to the patient's weight and creatinine clearance. Aspirin (400 mg) and clopidogrel (450 mg) were added 2 h before the end of the IV tirofiban injection if ICS had been performed. In the IA tirofiban group, the protocol was virtually the same, except that the IV continuous infusion of tirofiban was not carried out. In the no-tirofiban group, tirofiban or other antiplatelet, such as intravenous aspirin, were not administered. Instead, aspirin (400 mg) and clopidogrel (450 mg) were administered immediately after the MT.

**Table 1**
Intravenous continuous tirofiban infusion dosage.

| Patient weight (kg) | Normal patient (CrCl > 60 mL/min) (ml/h) | AKI or CKD (CrCl ≤ 60 mL/min) (ml/h) |
|---|---|---|
| 30–37 | 4 | 2 |
| 38–48 | 5 | 3 |
| 46–54 | 6 | 3 |
| 55–62 | 7 | 4 |
| 63–70 | 8 | 4 |
| 71–79 | 9 | 5 |
| 80–87 | 10 | 5 |
| 88–95 | 11 | 6 |
| 96–104 | 12 | 6 |

Abbreviations: AKI: acute kidney injury; CKD: chronic kidney disease; CrCl: creatinine clearance.

## 5. Outcome measures

Diffusion-weighted MRI was performed to evaluate postoperative infarct volume or postoperative hemorrhage, and perfusion-weighted MRI was used to evaluate hyperperfusion syndrome or penumbra approximately 24 h after MT [15,16]. Brain MRA was also performed to evaluate late reocclusion. Brain CT was performed only when postoperative hemorrhage or contrast leakage was suspected.

Post-procedural intracranial hemorrhages (ICH) were assessed using brain CT or MRI. Based on the European Cooperative Acute Stroke Study II criteria, hemorrhage transformation was categorized into 4 grades [34]: hemorrhagic infarction (HI) 1, HI 2, parenchymal hemorrhage (PH) 1, and pH 2. According to ECASS III criteria, symptomatic intracranial hemorrhage was defined based on any hemorrhage with neurologic deterioration as follows: NIHSS scores > 4 points more than baseline or the lowest value in the first 7 days, or hemorrhage causing death [35]. Reperfusion status was assessed by final angiography after MT according to m-TICI. Successful recanalization was defined as an m-TICI grade of 2b or 3 [11]. Clinical outcomes were assessed using the mRS score at 3 months after treatment, and a favorable outcome was defined as a score ≤ 2 [36,37].

### 5.1. Statistical analysis

Continuous variables are presented as means and confidence intervals. Discrete variables are presented as counts (n) and percentages (%). Fisher's exact test was used to compare categorical and binary variables, and an analysis of variance was used to compare continuous variables. All statistical analyses were performed using SPSS software (version 23.0; IBM SPSS). A $p$-value $< 0.05$ was considered statistically significant.

## 6. Results

### 6.1. Patients

A total of 792 patients underwent MT for ELVO during the study period. Patients diagnosed with cardiac embolism (n = 417), extracranial atherosclerosis (n = 66), guiding failure (n = 57), in-stent thrombosis (n = 15), IA dissection (n = 12), vasospasm (n = 6), or remnant thrombosis (n = 3) were excluded. Of the remaining 216 patients with atherosclerotic ELVO, 72 patients had successful recanalization after MT within 3 passes. A total of 12 patients had undergone emergent extracranial-intracranial bypass surgery, 12 patients had previously taken dual antiplatelet medication, and 3 patients had coagulopathy that was inadequate for further treatment. The remaining 117 patients (63 men and 54 women; median age, 72 years; range, 36–102 years) had failed thrombectomy procedures (Fig. 1). Data from these patients were included in our analysis (Table 2). The combined IV + IA tirofiban group included 48 patients, the IA tirofiban group included 33 patients, and the no tirofiban group included 36 patients. AIS with underlying ICAS in failed thrombectomy was most frequently observed in the MCA (n = 54), followed by the distal internal carotid artery (n = 33) and VBA (n = 30). Among them, 78 (67%) patients had hypertension, 42 (36%) had diabetes mellitus (DM) and were current smokers, 24 (21%) had a history of stroke or transient ischemic accident (TIA), and 18 (15%) had dyslipidemia. The mean initial NIHSS score was 12.9. IV tPA was administered before MT in 36 (31%) patients.

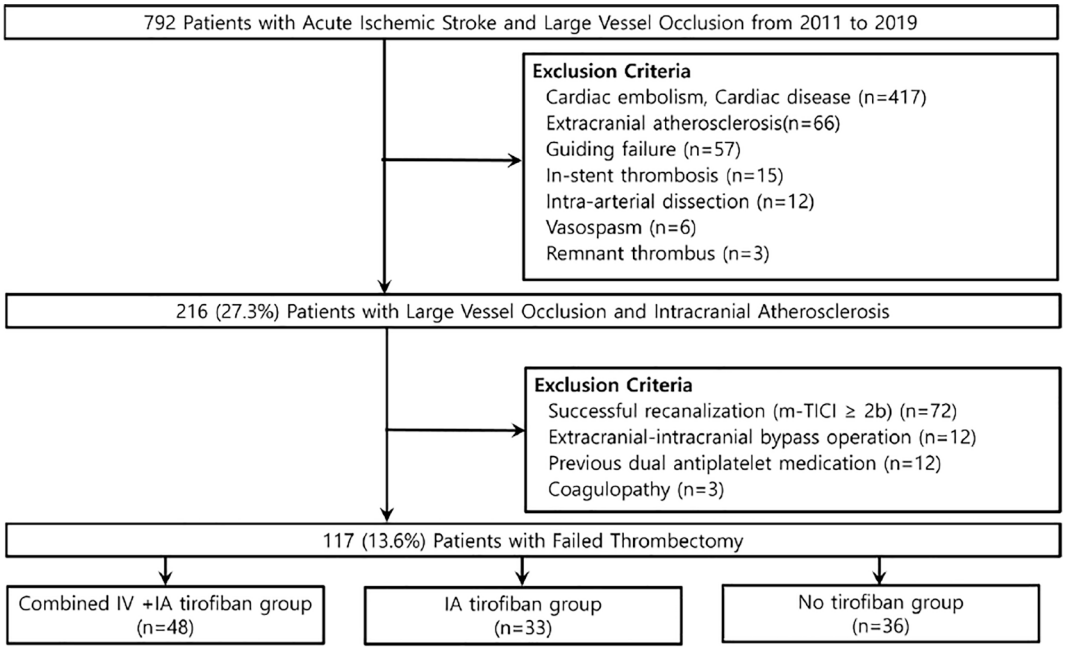


**Fig. 1.** Flow chart showing enrollment of acute ischemic stroke patients with large vessel occlusion with intracranial stenosis from 2011 to 2019. m-TICI, modified treatment in cerebral infarction; IV, intravenous; IA, intra-arterial.

**Table 2**
Comparison of baseline characteristics and outcomes of patients classified by injection of tirofiban.

| | Combined IV + IA Tirofiban | IA Tirofiban | No Tirofiban | P-values |
|---|---|---|---|---|
| n (%) | 48 (41%) | 33 (28%) | 36 (31%) | |
| Age (yrs.) | 68.6 ± 3.3 | 64.4 ± 9.0 | 78.2 ± 5.1 | <0.05 |
| Sex (Male:Female) | 27:21 | 21:12 | 15:21 | 0.5549 |
| Past History, n (%) | | | | |
| Hypertension, n (%) | 33 (68.8) | 18 (54.5) | 27 (75.0) | 0.7876 |
| Diabetes mellitus, n (%) | 18 (37.5) | 9 (27.3) | 15 (41.7) | 0.7607 |
| Dyslipidemia, n (%) | 12 (25.0) | 3 (9.1) | 3 (8.3) | 0.3810 |
| Current smoking, n (%) | 24 (50.0) | 15 (45.5) | 3 (8.3) | 0.0555 |
| History of stroke or TIA, n (%) | 12 (25.0) | 6 (18.2) | 6 (16.7) | 0.8423 |
| Initial NIHSS, mean ± SD | 10.8 ± 4.0 | 10.3 ± 2.3 | 18 ± 4.0 | <0.05 |
| Baseline ASPECTS, mean ± SD | 8.4 ± 1.0 | 8.4 ± 1.6 | 8.3 ± 1.9 | 0.9774 |
| Location, n, (%) | | | | |
| Distal ICA, n (%) | 9 (18.8) | 9 (27.3) | 15 (41.7) | 0.4096 |
| MCA, n (%) | 27 (56.3) | 15 (45.5) | 12 (33.3) | 0.4838 |
| VBA, n (%) | 12 (25.0) | 9 (27.3) | 9 (25.0) | 0.9893 |
| Mean of time to procedure (min) | 563 ± 148 | 427 ± 214 | 412 ± 127 | 0.3457 |
| Mean procedure time (min) | 94 ± 27 | 115 ± 39 | 143 ± 42 | 0.1572 |
| IV tPA, n (%) | 9 (18.8) | 15 (45.5) | 12 (33.3) | 0.3269 |
| Angioplasty, n (%) | 48 (100.) | 27 (81.8) | 21 (58.3) | <0.05 |
| PTA, n (%) | 0 (0) | 12 (36.4) | 6 (16.7) | 0.1331 |
| PTA and ICS, n (%) | 48 (100) | 15 (45.5) | 15 (41.7) | <0.05 |
| m-TICI, n (%) | | | | |
| 1, n (%) | 0 (0.0) | 6 (18.2) | 9 (25.0) | 0.1207 |
| 2a, n (%) | 3 (6.3) | 6 (18.2) | 18 (50.0) | <0.05 |
| 2b, n (%) | 6 (12.5) | 6 (27.3) | 6 (16.7) | 0.6110 |
| 3, n (%) | 39 (81.3) | 12 (36.4) | 3 (8.3) | <0.05 |
| m-TICI ≥ 2b, n (%) | 45 (93.8) | 21 (63.6) | 9 (25.0) | <0.05 |
| Late reocclusion, n (%) | 0 (0.0) | 2 (9.5) | 2 (22.2) | <0.05 |
| Postoperative ICH, n (%) | 3 (6.3) | 3 (9.1) | 6 (16.7) | 0.6600 |
| HI 1, n (%) | 1 (2.1) | 1 (3.0) | 2 (5.6) | 0.8192 |
| HI 2, n (%) | 2 (4.2) | 0 (0.0) | 1 (2.8) | 0.7808 |
| PH 1, n (%) | 0 (0.0) | 2 (6.1) | 2 (5.6) | 0.1880 |
| PH 2, n (%) | 0 (0.0) | 0 (0.0) | 1 (2.8) | 0.1706 |
| 3-month mRS 0-2, n (%) | 30 (62.5) | 15 (45.5) | 3 (8.3) | <0.05 |

Abbreviations: ASPECTS: Albert Stroke Program Early Computed Tomography Score; ECASS: European Cooperative Acute Stroke Study; HI: hemorrhagic infarction; IA: intra-arterial; ICA: internal carotid artery; ICH: intracranial hemorrhage; ICS; intracranial stenting, IV: intravenous; LNT: last normal time; MCA: middle cerebral artery; mRS: modified Rankin scale; m-TICI: modified treatment in cerebral infarction; NIHSS: National Institute of Health Stroke Scale; PH: parenchymal hemorrhage; PTA: percutaneous transluminal angioplasty; SD: standard deviation; TIA: transient ischemic attack; tPA: tissue plasminogen activator; VBA: vertebrobasilar artery.

### 6.2. Comparison of baseline characteristics among the three groups

Comparisons of baseline characteristics among the three groups (combined IV + IA tirofiban, IA tirofiban, and no tirofiban) are shown in Table 2. Mean age (78.2 years vs. 68.6 years or 64.4 years, $p < 0.05$) and mean initial NIHSS scores (18.0 vs. 10.8 or 10.3, $p < 0.05$) were higher in the no tirofiban group than in the combined IV + IA tirofiban or IA tirofiban group. There were no significant differences in sex, premorbid diseases (such as hypertension, DM, dyslipidemia, history of stroke, or TIA), baseline ASPECTS, occlusion site, use of IV tPA, mean time to procedure, or mean procedure time among the three groups. PTA/S was more frequently used in the combined IV + IA tirofiban and IA tirofiban groups than in the no tirofiban group (100% and 81.8% vs. 58.3%, $p < 0.05$). Emergent ICS was performed more frequently in the combined IV + IA tirofiban group than in the IA tirofiban or no tirofiban group (100% vs. 45.5% or 41.7%, $p < 0.05$).

### 6.3. Outcomes

Fig. 2A shows the recanalization rates according to rescue techniques used in patients with AIS and ELVO because of ICAS lesions. Modified TICI scores of 2b or 3 were significantly higher in the combined IV + IA tirofiban group than in the IA tirofiban or no tirofiban group (93.8% vs. 63.6% or 25%, $p < 0.05$). The percentage of m-TICI 3 recanalization was significantly higher in the combined IV + IA tirofiban group than in the IA tirofiban or no tirofiban group (81.3% vs. 36.4% or 8.3%, $p < 0.05$). As shown in Fig. 2B, late reocclusion on follow-up MRA occurred less in the combined IV + IA tirofiban group than in the IA tirofiban or no tirofiban group (0.0% vs. 9.5% or 22.2%, $p < 0.05$). The percentage of postoperative ICH was not significantly different among the three groups ($p = 0.66$; Fig. 2C). There was one case of symptomatic parenchymal hemorrhage in the no tirofiban group (ECASS pH 2 grade). As shown in Fig. 2D, the percentage of mRS 0–2 at 3 months after MT was higher in the combined IV + IA tirofiban group than in the IA tirofiban or no tirofiban group (62.5% vs. 45.5% or 8.3%, $p < 0.05$).

## 7. Discussion

Successful recanalization is an important predictor of good clinical outcomes in endovascular treatment of ELVO [38]. The main finding of this study was that emergent ICS with IA loading and a continuous IV tirofiban infusion achieved the most successful recanalization rate. Moreover, recent studies have observed that patients with m-TICI grade 3 recanalization after thrombectomy have better outcomes than those with m-TICI grade 2b [39]. In this study, the combined IV + IA tirofiban group achieved m-TICI grade 2b or 3 recanalization at a high rate (n = 45, 93.8%), especially m-TICI 3 (n = 39, 81.3%). Additionally, unlike the other two groups, the combined IV + IA tirofiban group had no late reocclusion, which was achieved by alleviating the remaining stenosis with ICS and suppressing platelet aggregation with tirofiban injection to maintain the patency of blood flow in the steno-occlusive lesion.

Occlusion of the intracranial artery begins with in situ thrombi due to plaque rupture [40]. When a vulnerable plaque ruptures, it evokes inflammatory processes in the hyperacute stage and induces platelet aggregation, a major component of white thrombi [40]. To remove thrombi, MT with stent-retriever or contact aspiration can be performed. However, friction between the devices and the endothelium can cause endothelial erosion. In endothelial layer erosion, collagen and tissue factors are exposed to potent thrombogenic proteins [40,41]. This mechanism causes in situ thrombi, leading to a vicious cycle of reocclusion. The remaining stenosis may also lead to reocclusion [42,43]. Thus, it is important to stop this vicious cycle and prevent reocclusion by stabilizing the endothelium to attenuate inflammatory processes and alleviating the remaining stenosis for ELVO with ICAS refractory to MT.

In contrast to embolic ELVO, reocclusion occurs more frequently in patients with ICAS, and it increases the procedure time and decreases the success rate of recanalization in ICAS lesions [3,44]. Therefore, patients with AIS due to ICAS have worse outcomes than those with cardiac embolisms [3,44]. However, treatment guidelines for AIS due to ICAS have not yet been established. Some studies have reported rescue techniques for failed thrombectomy due to ICAS and successful recanalization with ICS or tirofiban injection only. For example, Baek et al. showed that the rate of an m-TICI grade of 2b or 3 was 80.4% (45of56) in the ELVO with ICAS group [45]. However, among the 27 patients who required rescue techniques, only 11 (40.7%) achieved successful recanalization, while 15 (55.6%) required rescue stenting [45]. Moreover, Kang et al. found that 74.3% (26of35) of reocclusion patients achieved successful recanalization with an IA tirofiban injection [42]. Notably, the present study demonstrated the highest successful recanalization rate (approximately 93.8%), and 81.3% of patients had m-TICI

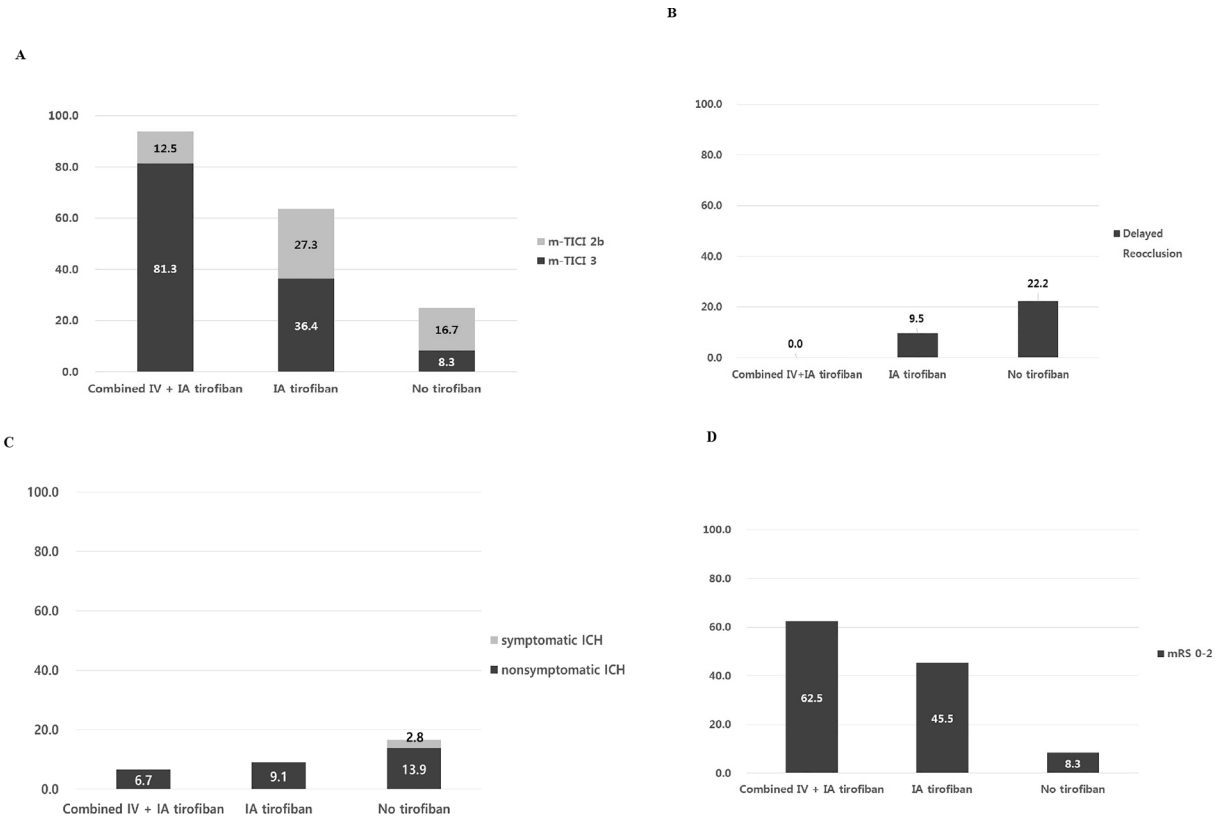


**Fig. 2.** (A) Proportions of m-TICI grades 2b and 3, (B) Rate of late reocclusion, (C) Rate of postoperative hemorrhage, and (D) proportion of 3-month mRS scores 0-2 according to each rescue treatment for those with failed thrombectomy with ICAS. IA, intra-arterial; ICAS, intracranial atherosclerosis; ICH, intracranial hemorrhage; IV, intravenous; mRS, modified Rankin scale; m-TICI, modified treatment in cerebral infarction.

grade 3.

Endovascular treatment with tirofiban injection for ELVO is based on efficacy and safety of tirofiban in stent-assisted coiling for a ruptured aneurysm [46–48]. Tirofiban prevents the formation of white thrombi by competitively interfering with fibrinogen attached to glycoprotein IIb/IIIa receptors on platelets [48]. Tirofiban is a small non-peptide tyrosine derivative that can competitively bind to glycoprotein IIb/IIIa receptors and prevent bridging fibrinogen or von Willebrand factor from adhering to platelets, and its half-life is approximately 2–3 h [46]. Abciximab, a monoclonal antibody that can bind to the glycoprotein IIb/IIIa receptor, has antiplatelet effects for more than 12 h [49]. Studies have demonstrated that tirofiban is relatively effective for thrombolysis and safe in terms of hemorrhagic risk due to its short half-life compared with other glycoprotein IIb/IIIa inhibitors (GPIs) [42,49]. Moreover, all GPIs have a risk of causing thrombocytopenia, which is defined as a platelet count below 90,000/mm [46,49]. Notably, the risk of thrombocytopenia associated with tirofiban is significantly lower than that of other GPIs [46]. In our study, postoperative ICH occurred in 6 patients after tirofiban injection; however, the hemorrhage volume was small, and the patients had no other symptoms related to hemorrhage.

Intracranial stenting can maintain the patency by alleviating the remaining stenosis. According to the Stenting versus Aggressive Medical Therapy for Intracranial Arterial Stenosis (SAMMPRIS) trial [50], ICS has some safety issues regarding perforator infarction and ICH. However, the Wingspan Stent System Post-Market Surveillance (WEAVE) trial showed that a revised plan for ICS could result in a lower complication rate than that observed in the SAMMPRIS trial [51]. However, a recent study by Baraccchini et al. observed that patients with rescue stenting from refractory MT had a better prognosis than those without ICS [52]. With the development of devices such as distal access catheters, emergent ICS is relatively safer than before. However, in the perforating artery-rich zone, intracranial stenting can cause perforator infarction due to a snow-flow effect, so it should not be performed in this zone.

In many studies, mild stroke is defined NIHSS scores ≤5, and moderate to severe stroke is defined as NIHSS scores ≥6 [17,21,29,53]. Based on the 2018 American Heart Association/American Stroke Association guidelines for the early management of patients with acute ischemic stroke, the indication of MT is NIHSS scores of ≥6 [27]. However, in South Korea, there are no criteria for NIHSS scores in the guideline for MT. In our centers, MT is performed for ELVO with NIHSS scores ≥4 [22]. However, recent studies suggest that MT should be performed even in mild strokes with NIHSS scores ≤5 [23–26]. Large artery occlusion is an important risk factor for early neurologic deterioration, suggesting it is more beneficial to prevent clinical deterioration in large artery occlusion, even in mild stroke [54,23–26]. Therefore, an indication of endovascular treatment for AIS with ELVO should be extended regardless of NIHSS.

Fig. 3 shows an optimal protocol for patients with ICAS lesions refractory to MT. The combination of emergent PTA/S and tirofiban injections can achieve successful recanalization in moderate-to-severe cases of ICAS. If neurointerventionists encounter reocclusion despite repeated MT, it is important to break the cycle by preventing platelet aggregation through the administration of tirofiban intra-arterially, and IA tirofiban injection shows immediate effects. Coincidentally, administering continuous IV tirofiban provides long-standing effects and alleviates residual stenosis to prevent reocclusion.

This study has some limitations. Because it was a retrospective study, there were uncontrolled confounding biases. First, treatment modality was mainly determined by timing and neurointerventionists' preference. From 2011 to 2015, maximal medical treatment, such as dual antiplatelet and induced hypertension, was mainly used in failed MT, whereas from 2016 to 2020, rescue treatment was applied in about 70% of failed MT cases. Furthermore, endovascular treatment devices have

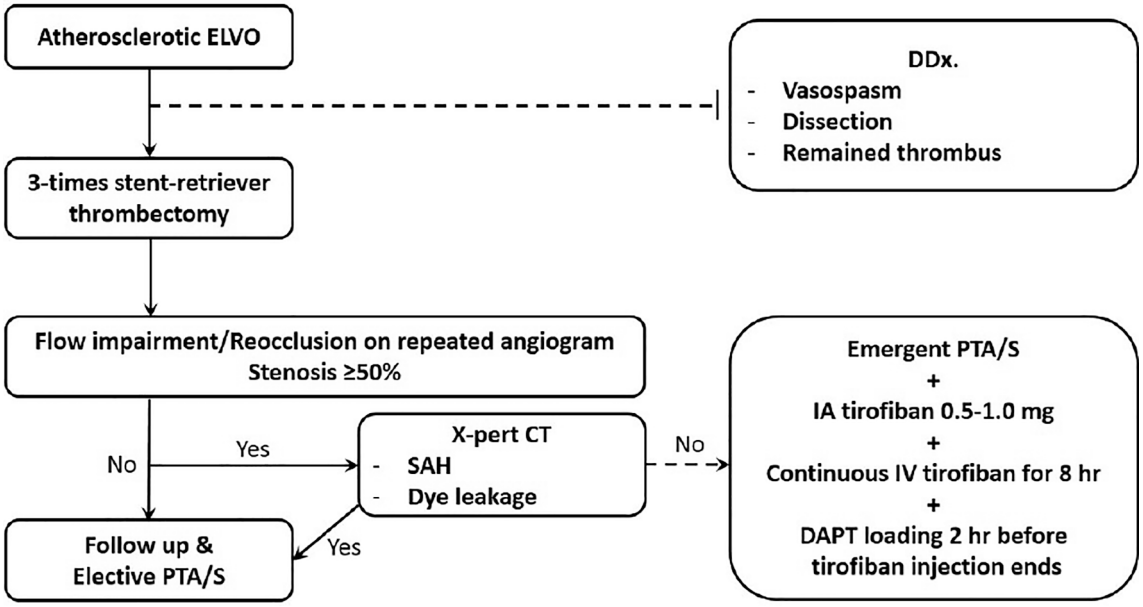


**Fig. 3.** Protocol for emergent large vessel occlusion with failed thrombectomy. ELVO, emergent large vessel occlusion; CT, computed tomography; SAH, subarachnoid hemorrhage; PTA/S, percutaneous transluminal angioplasty or stenting; IA, intra-arterial; IV, intravenous; DAPT: dual antiplatelet therapy.

developed rapidly over the past 10 years, so the devices used in 2011 were outdated compared with the recent devices. Moreover, since the rescue treatment was applied according to the neurointerventionists' preference, it was inevitably affected by their skill. Second, higher NIHSS scores and older age in the no tirofiban group were important factors for poor outcomes in acute ischemic stroke [55], and the effect of the development of thrombectomy devices could not be excluded. Even though the successful recanalization rate reached 93.8% in the combined IV + IA tirofiban group, late reocclusion did not occur, and good clinical outcomes were achieved in 62.5% of the patients. Further randomized prospective studies involving the same participants as this study are needed to identify a new optimal strategy for ELVO with ICAS refractory to MT.

## 8. Conclusion

Our findings suggest that when encountering cases of reocclusion from ELVO with ICAS, despite the removal of the thrombus, changing the treatment strategy with ICS and stabilizing the endothelium with IA and IV tirofiban injections could lead to successful recanalization and good clinical outcomes.

### *CRediT authorship contribution statement*

**Yun Ho Noh:** Data curation, Writing – review & editing. **Ji Young Lee:** Visualization. **Seok Mann Yoon:** Resources, Visualization. **Yu Jin Ha:** Data curation. **Jaewoo Chung:** Visualization. **Jung Ho Ko:** Visualization. **Dong Seong Shin:** Resources. **Jae-Min Ahn:** Resources. **Hyuk Jin Oh:** Resources. **Jai-Joon Shim:** Visualization. **Man Ryul Lee:** Conceptualization, Funding acquisition. **Jae Sang Oh:** Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing.

### Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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### *Informed consent statement*

Patient consent was waived due to the retrospective nature of the study.

### *Institutional review board statement*

The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Research Ethics Committee of Soonchunhyang University Hospital (IRB number SCHCH-2018-07-025). This study was performed under the National Stroke Quality Assessment Research with National Health Insurance Administration. Patients' personal information was protected and kept anonymous.

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