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ORIGINAL RESEARCH

Endovascular Treatment for Minor Acute Ischemic Strokes With Large Vessel Occlusion

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BACKGROUND: It remains uncertain whether patients with minor acute ischemic stroke with large vessel occlusion benefit from endovascular treatment (EVT). We aim to evaluate the outcomes of EVT in minor acute ischemic stroke with anterior circulation large vessel occlusion.

METHODS AND RESULTS: Based on a nationwide prospective stroke registry, patients with minor acute ischemic stroke with anterior circulation large vessel occlusion within 24 hours of onset were divided into groups receiving standard medical treatment plus EVT or standard medical treatment alone. Primary outcome was excellent functional outcome defined as modified Rankin Scale score 0 to 1 at 90 days. In addition, a multivariable logistic regression model was used to analyze the effect of EVT guided by perfusion imaging. A total of 572 patients with median age 68 years (interquartile range=60–77) and median National Institutes of Health Stroke score 3 (interquartile range =2–4) were identified and 123 patients were treated with standard medical treatment plus EVT. EVT was not associated with excellent functional outcome (unadjusted odds ratio [OR], 0.771 [95% CI, 0.516–1.151]; adjusted OR, 0.793 [95% CI, 0.515–1.219]; *P*=0.290). However, therapy selection guided by perfusion imaging was a modifier of EVT effect on outcomes, as EVT was significantly associated with excellent functional outcome (60.0% versus 50.8%, unadjusted OR, 1.451 [95% CI, 0.643–3.272]; adjusted OR, 2.849 [95% CI, 1.006–8.067]; *P*=0.049) but not with symptomatic intracerebral hemorrhage in the imaging-guided group.

CONCLUSIONS: Although functional outcomes in minor acute ischemic stroke caused by anterior circulation large vessel occlusion were not improved from the routine use of EVT, our results suggested that EVT guided by perfusion imaging could be beneficial for those patients.

REGISTRATION: URL: https://www.clinicaltrials.gov; Unique identifier: NCT 04487340.

Key Words: endovascular treatment ■ large vessel occlusion ■ minor acute ischemic stroke ■ perfusion imaging

Minor acute ischemic stroke (AIS) is a common medical condition accounting for more than 50% of AIS.[1] Of the patients with minor AIS, 28.3% are unable to discharge home, and 28.5% cannot walk independently.[2] For approximately 21% of patients, minor AIS is caused by large vessel occlusion (LVO), which is thought to be associated with early neurological deterioration and poor outcome.[3] Intravenous thrombolysis (IVT) is currently recommended for patients with mild but disabling symptoms.[4] However, the benefit of IVT could be hampered in patients with minor AIS with LVO because of the substantial risk of early neurological deterioration and poor 3-month outcome.[5]

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CLINICAL PERSPECTIVE

What Is New?

- Overall outcomes were similar in standard medical treatment plus endovascular treatment as compared with standard medical treatment alone in patients with minor acute ischemic stroke with anterior circulation large vessel occlusion.
- Standard medical treatment plus endovascular treatment achieved a higher rate of excellent functional outcome at 90 days than standard medical treatment alone when guided by perfusion imaging.

What Are the Clinical Implications?

- In minor acute ischemic stroke caused by anterior circulation large vessel occlusion, perfusion imaging could be considered to guide endovascular treatment.

Nonstandard Abbreviations and Acronyms

AIS	acute ischemic stroke
CTP	computed tomographic perfusion
EVT	endovascular treatment
IVT	intravenous thrombolysis
LVO	large vessel occlusion
mRS	modified Rankin Scale
NIHSS	National Institutes of Health Stroke Scale
sICH	symptomatic intracerebral hemorrhage
SMT	standard medical treatment

Endovascular treatment (EVT) is recommended for patients with stroke and anterior circulation LVO with National Institutes of Health Stroke Scale (NIHSS) score ≥6.[4,6] Nevertheless, it remains uncertain whether EVT is superior to standard medical treatment (SMT) alone in minor AIS with LVO. Several observational studies have compared clinical outcomes between EVT plus SMT and SMT alone in these patients,[7–13] with controversial results partially owing to single-arm nature, small sample sizes, and unavailable data regarding stroke type of initial deficit (disabling or nondisabling).[7,9,10,13,14] Meanwhile, perfusion imaging including computed tomographic perfusion (CTP) scan can reflect the pathophysiological state of patients with AIS and is recommended as a selection criterion in patients with LVO beyond a 6-hour window,[4] which may select patients suitable for EVT in minor AIS with LVO.

Based on these considerations, we aim to (1) investigate the efficacy and safety of EVT in a large multicentric cohort of patients with minor AIS with anterior circulation LVO; and (2) hypothesize that therapy selection guided by perfusion imaging would increase the benefits of EVT in minor AIS with LVO.

METHODS

Data Availability

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

Study Design

This study was a retrospective analysis based on a prospective multicenter stroke registry, CASE-II (Computer-based Online Database of Acute Stroke Patients for Stroke Management Quality Evaluation; NCT 04487340). Initiated in 2016, CASE-II was designed to examine the current status of stroke care in China for developing strategies to improve stroke care. The study protocol was approved by the ethics committee of the Second Affiliated Hospital of Zhejiang University, School of Medicine. The study was conducted according to the principles expressed in the Declaration of Helsinki. Written informed consent for EVT was obtained from all patients or their legally authorized representatives. Because patient information in the CASE-II was deidentified and anonymized before being released to the researchers, the informed consent requirement for this study was waived by the institutional review board.

Patient Selection

This study collected data between March 2017 and June 2021. We included patients with the following characteristics: (1) age ≥18 years old; (2) baseline NIHSS ≤5; (3) arrived at stroke centers within 24 hours of onset; and (4) anterior circulation LVO on pretreatment cerebral angiographic-imaging (internal carotid artery, first segment of the middle cerebral artery, second segment of middle cerebral artery, anterior cerebral artery occlusion on computed tomographic angiography, magnetic resonance angiography, or digital subtraction angiography); and (5) treated with SMT (including IVT), with or without additional EVT. Patients without prestroke functional independence (modified Rankin Scale [mRS] score ≥2) and lost to follow-up at 90 days after stroke onset were excluded. Patients with minor AIS were defined as patients with an admission NIHSS score of 0 to 5. Minor nondisabling AIS was identified as baseline NIHSS ≤5 and a score 0 or 1 on each baseline NIHSS score item (items 1a to 1c being 0).[15]

Treatments

Patients were divided into the SMT group or EVT group according to the treatment they received. The SMT group received treatment based on current guidelines, including IVT, antiplatelet drugs, systematic anticoagulation, or combinations of these medical treatments.[4] Patients in the EVT group received SMT plus EVT, including those who eventually received rescue EVT because of neurological deterioration. EVT included mechanical thrombectomy with stent retrievers or aspiration catheter, balloon angioplasty, stenting, intra-arterial thrombolysis, or combinations of these approaches.

Data Collection

We recorded patients' baseline characteristics; stroke risk factors; prior medication history; NIHSS score on admission, before performing EVT, and at 24 hours; type of initial deficit (disabling or nondisabling stroke); onset to door time; onset to needle time; presumed stroke cause assessed based on the Trial of ORG 10172 in Acute Stroke Treatment classification[16]; type of treatment; recanalization evaluated on 24-hour follow-up imaging using arterial occlusive lesion scale[17]; and mRS score before onset and 90 days. For patients receiving EVT, we additionally collected the time interval between symptom onset and groin puncture.

Study Outcomes

The primary outcome was the mRS score 0 to 1 at 90 days. Meanwhile, good functional outcome (mRS score 0–2) was used as the secondary outcome. All patients were followed up at 90 days by certified external clinical evaluators during a standardized telephone interview. All telephone interviews were recorded and traceable. The mRS is a 7-level scale for assessing neurologic functional disability, which ranges from 0 to 6.[18] Grade 0 represents no symptoms at all. Grade 1 represents no significant disability despite symptoms (able to carry out all usual duties and activities). Grade 2 represents slight disability (unable to carry out all previous activities but able to look after own affairs without assistance). Grade 3 represents moderate disability (requiring some help, but able to walk without assistance). Grade 4 represents moderately severe disability (unable to walk without assistance, and unable to attend to own bodily needs without assistance). Grade 5 represents severe disability (bedridden, incontinent, and requiring constant nursing care and attention). Grade 6 represents death.

Safety outcomes were the rate of symptomatic intracerebral hemorrhage (sICH) and 90-day mortality. sICH was defined as intracranial hemorrhage at 24 hours associated with an increase of ≥4 points of NIHSS from baseline, according to the ECASS II (European Cooperative Acute Stroke Study II) trial.[19]

Radiologic Assessment

We evaluated perfusion parameters (ischemic core volume and penumbra volume) on baseline CTP, the location of the vessel occlusion on baseline vessel imaging (computed tomographic angiography, magnetic resonance angiography, or digital subtraction angiography), vessel recanalization on follow-up computed tomographic angiography or MRA within 24 hours, and the presence of intracerebral hemorrhage on follow-up computed tomography or magnetic resonance imaging. Ischemic core was defined as relative cerebral blood flow <30% on CTP, hypoperfusion was defined as time to max (Tmax) >6 s, and penumbra was defined as hypoperfused lesion beyond core infarct. Vessel recanalization was evaluated using arterial occlusive lesion scale, which was classified as recanalization (score of 2 or 3) and no recanalization (score of 0 or 1).

Patients who underwent CTP at baseline and determined whether to perform EVT according to perfusion imaging evaluation were assigned to the imaging-guided group. The perfusion imaging evaluation criteria were referenced to the DEFUSE 3 (Endovascular Therapy Following Imaging Evaluation for Ischemic Stroke 3) trial.[20] The evaluation criteria were ischemic core volume <70 mL, penumbra ≥15 mL, and mismatch ratio ≥1.8. Patients for whom it was determined whether to perform EVT without perfusion imaging evaluation were assigned to the nonimaging-guided group.

Statistical Analysis

We compared baseline characteristics and outcomes between the SMT groups and EVT groups. Continuous variables were described as mean ± SD or median (interquartile range) and categorical variables as numbers and percentages. Univariate analysis was performed using the Mann–Whitney *U*-test, *t*-test, χ^2 test, or Fisher's exact test. Multivariable logistic regression model was used to evaluate study outcomes. All baseline variables with a *P* value <0.1 were then included in the multivariable logistic regression analysis to adjust for the effects of confounding variables.

For propensity score matching analysis, patients with EVT and SMT were matched 1:1 to eliminate the potential bias owing to imbalance in baseline covariate distributions. Propensity score matching was based on the main variables that could potentially influence treatment choice (EVT versus SMT), including age, female sex, baseline NIHSS score, atrial fibrillation, stroke cause, prestroke antithrombotic therapy, and IVT. We used a conservative caliper size of 0.1 SDs

of the logit of the propensity score matching to provide adequate matching. Between-group differences in baseline characteristics were compared using standardized difference (difference >0.1 was considered meaningful).

To analyze the effect of EVT guided by perfusion imaging, we compared the rate of clinical outcomes between treatment groups in the imaging-guided group and nonimaging-guided group. Subgroup analyses were performed by stratifying patients with different baseline characteristics. Treatment effect size heterogeneity across subgroups was tested by including the corresponding multiplicative interaction term into the binary logistic regression model. A significant interaction ($P<0.05$) term indicates that the estimated heterogeneity between treatments differs between different subgroups. We also conducted sensitivity analysis to assess the robustness of the main results in patients who received reperfusion therapy (EVT or IVT alone) and by excluding patients receiving rescue EVT, respectively. Two-tailed $P<0.05$ was considered statistically significant. Statistical analyses were performed using SPSS version 25.0 (IBM Co., Armonk, NY). Figures were drawn using GraphPad Prism 8 (GraphPad Software Inc., San Diego, CA).

RESULTS

Patient Characteristics

According to the inclusion and exclusion criteria, we identified 657 patients with minor AIS with anterior circulation LVO within 24 hours after onset. We further excluded 85 patients: (1) 28 patients without prestroke functional independence; and (2) 57 patients lost to follow-up at 90 days. The remaining 572 patients constituted the study population. The flow chart is shown in Figure 1.

A total of 449 patients were treated with SMT alone, and 123 patients were treated with SMT plus EVT. The median age was 68, and 183 (32.0%) were women, median NIHSS score at baseline was 3, and median onset-to-door time was 166 minutes. About 92.5% (529) of patients kept NIHSS score ≤5 before treatment, and 43 (7.5%) patients aggravated to NIHSS score >5 before treatment. Among the entire cohort, 331 (57.9%) patients achieved excellent functional outcomes, 415 (72.6%) patients achieved good functional outcomes, 19 (3.3%) patients had sICH, and 35 (6.1%) patients died within 90 days. Baseline characteristics of patients with and without 90-day mRS measurement are shown (Table S1).

There were 58 of 123 (47.2%) patients receiving perfusion imaging in the EVT group and 150 of 449 (33.4%) patients receiving perfusion imaging in the SMT group. Patients in the EVT group were more likely to receive perfusion imaging at baseline than the SMT group (P=0.006). Moreover, there were 58 of 208 (27.9%) patients treated with SMT plus EVT in patients with perfusion imaging and 65 of 364 (17.6%) patients treated with SMT plus EVT in patients without perfusion imaging (Figure S1 and Table S2). In the EVT group, the proportion of excellent functional outcome of patients with minor disabling AIS and minor nondisabling AIS was 49.2% and 36.8% (P=0.199), respectively. In the SMT group, the proportion of excellent functional outcome of patients with minor disabling AIS and minor nondisabling AIS was 36.5% and 42.6% (P=0.201), respectively.

Baseline Characteristics

Table 1 summarizes baseline characteristics in the 2 treatment groups. Compared with the SMT group, patients in the EVT group had higher NIHSS score on admission (median [interquartile range], 3 [2–5] versus 3 [1–4]; P=0.032), lower proportion of prior antiplatelet usage (18

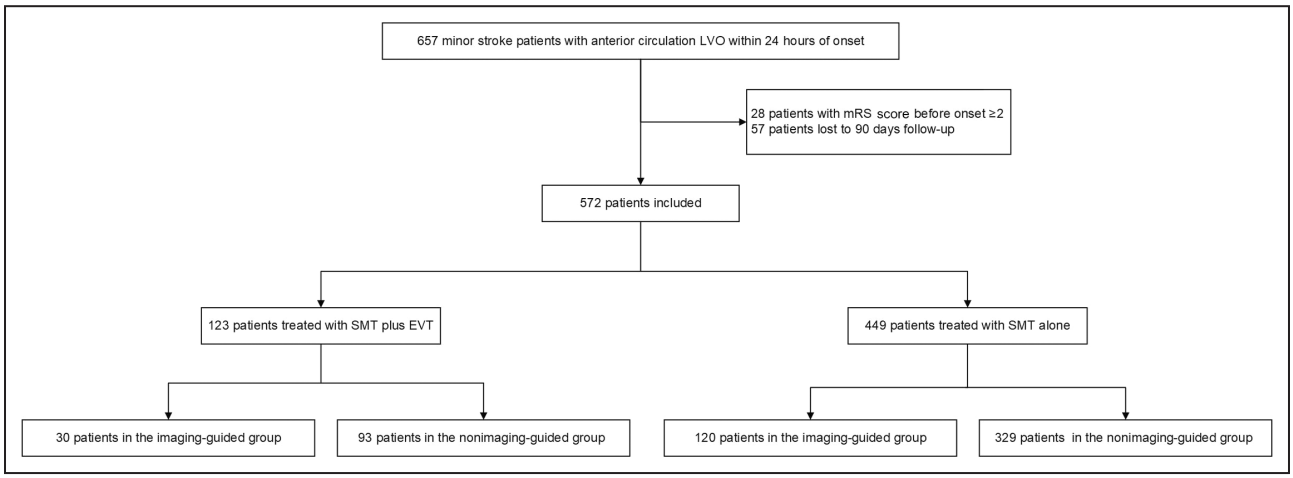

Figure 1. Flow chart of patient selection.
EVT indicates endovascular treatment; LVO, large vessel occlusion; mRS, modified Rankin scale; and SMT, standard medical treatment.

Table 1. Characteristics of Patients With Endovascular Treatment Versus Standard Medical Treatment in Minor Strokes With Large Vessel Occlusion

Characteristic	Unmatched			Propensity score matching		
	EVT (N=123)	SMT (N=449)	*P* Value	EVT (N=117)	SMT (N=117)	Standardized difference*
Age, y, median (IQR)	69 (60–76)	68 (59–77)	0.771	69 (60–76)	68 (58–79)	0.094
Female sex	41 (33.3)	142 (31.6)	0.744	41 (35.0)	32 (27.4)	0.161
Medical history						
Current smoking	40 (32.5)	155 (34.5)	0.748	39 (33.3)	43 (36.8)	0.072
Hypertension	75 (61.0)	299 (66.6)	0.285	71 (60.7)	81 (69.2)	0.174
Diabetes	21 (17.1)	78 (17.4)	1.000	21 (17.9)	20 (17.1)	0.022
Hyperlipidemia	10 (8.1)	40 (8.9)	0.859	10 (8.5)	6 (5.1)	0.122
Coronary heart disease	11 (8.9)	26 (5.8)	0.216	11 (9.4)	7 (6.0)	0.117
Atrial fibrillation	25 (20.3)	61 (13.6)	0.086	19 (16.2)	20 (17.1)	0.023
Previous stroke/transient ischemic attack	19 (15.4)	77 (17.1)	0.785	19 (16.2)	14 (12.0)	0.115
Prior antiplatelet usage	18 (14.6)	108 (24.1)	0.027	18 (15.4)	17 (14.5)	0.024
Prior anticoagulant usage	5 (4.1)	7 (1.6)	0.145	3 (2.6)	3 (2.6)	0.001
Baseline measurements						
Baseline National Institutes of Health Stroke Scale score, median (IQR)	3 (2–5)	3 (1–4)	0.032	3 (2–5)	3 (2–5)	0.060
Minor nondisabling acute ischemic stroke	68 (56.7)	274 (61.0)	0.402	64 (56.1)	72 (61.5)	0.108
Onset to door, median (IQR), min	165 (60–360)	166 (80–435)	0.155	165 (61–343)	180 (86–521)	0.375
Onset to groin puncture, median (IQR), min	372 (219–549)	NA	NA	375 (220–554)	NA	NA
Onset to needle, median (IQR), min	167 (101–234)	171 (114–232)	0.809	167 (101–234)	172 (107–245)	0.003
Systolic blood pressure, mean (SD), mm Hg	149 ± 23	152 ± 21	0.255	150 ± 22	153 ± 21	0.144
Diastolic blood pressure, mean (SD), mm Hg	85 ± 16	84 ± 13	0.959	85 ± 15	85 ± 13	0.007
Intravenous thrombolysis	67 (54.5)	289 (64.4)	0.047	67 (57.3)	66 (56.4)	0.017
Occlusion sites			0.851			0.225
Internal carotid artery	34 (27.6)	110 (24.5)		33 (28.2)	24 (20.5)	
Middle cerebral artery, first segment	59 (48.0)	213 (47.4)		57 (48.7)	55 (47.0)	
Middle cerebral artery, second segment	20 (16.3)	83 (18.5)		17 (14.5)	23 (19.7)	
Anterior cerebral artery	10 (8.1)	43 (9.6)		10 (8.5)	15 (12.8)	
Stroke cause			0.024			0.271
Large artery atherosclerosis	78 (63.4)	292 (65.0)		77 (65.8)	70 (59.8)	
Cardioembolic etiology	30 (24.4)	67 (14.9)		25 (21.4)	20 (17.1)	
Other etiology	2 (1.6)	6 (1.3)		2 (1.7)	2 (1.7)	
Undetermined etiology	13 (10.6)	84 (18.7)		13 (11.1)	25 (21.4)	
Recanalization	114/122 (93.4)	250/422 (59.2)	<0.001	108 (93.1)	63 (56.8)	1.428

Categorical variables are expressed as numbers (%) and continuous variables as median (IQR) or mean (SD). EVT indicates endovascular treatment; IQR, interquartile range; NA, not available; and SMT, standard medical treatment.

*The difference between the groups divided by the pooled SD; a value >0.1 is interpreted as a meaningful difference.

of 123 patients [14.6%] versus 108 of 449 patients [24.1%]; *P*=0.027), and lower rate of IVT (67 of 123 patients [54.5%] versus 289 of 449 patients [64.4%]; *P*=0.047).

Association Between EVT and Outcomes

Crude rates of excellent functional outcome (mRS score 0–1), good functional outcome (mRS score 0–2), sICH, and mortality in each treatment group are presented in Table 2. Details about the 90-day mRS score for the 2 treatment groups are presented in Figure S2. No significant difference was found in excellent functional outcome between the EVT and SMT group (52.8% versus 59.2%; unadjusted odds ratio [OR], 0.771 [95% CI, 0.516–1.151]; adjusted OR, 0.793 [95% CI, 0.515–1.219]; *P*=0.209). Similarly, there was no difference between groups concerning the good functional outcome (adjusted OR, 0.798 [95% CI, 0.513–1.243], *P*=0.319). EVT

Table 2. Multivariable Analysis for Primary and Secondary Outcomes and Safety Outcomes

	Unmatched				Propensity score matching			
	EVT	SMT	Adjusted OR (95% CI)*	*P* value	EVT	SMT	Adjusted OR (95% CI)†	*P* value
mRS at 90 d, median (IQR)‡	1 (0–3)	1 (0–3)	1.201 (0.835–1.726)	0.324	1 (0–3)	1 (0–3)	1.186 (0.725–1.941)	0.496
Primary outcome								
mRS 0–1	65 (52.8)	266 (59.2)	0.793 (0.515–1.219)	0.290	61 (52.1)	71 (60.7)	0.733 (0.416–1.292)	0.282
Secondary outcome								
mRS 0–2	84 (68.3)	331 (73.7)	0.798 (0.513–1.243)	0.319	79 (67.5)	86 (73.5)	0.722 (0.385–1.353)	0.309
Safety outcomes								
24-h symptomatic intracerebral hemorrhage	10 (8.1)	9 (2.0)	3.760 (1.373–10.294)	0.010	9 (7.7)	2 (1.7)	4.267 (0.833–21.860)	0.082
Mortality at 90 d	11 (8.9)	24 (5.3)	1.863 (0.864–4.015)	0.112	10 (8.5)	5 (4.3)	2.345 (0.700–7.855)	0.167

Categorical variables are expressed as numbers (%) and continuous variables as median (IQR). EVT indicates endovascular treatment; IQR, interquartile range; mRS, modified Rankin Scale; OR, odds ratio; and SMT, standard medical treatment.

*Adjusted by baseline characteristics with a *P* value <0.1 in univariate analysis.

†Adjusted by baseline characteristics with a standardized difference >0.1 in univariate analysis after propensity score matching analysis.

‡Shift analysis by ordinal regression for OR.

was not significantly associated with mortality (adjusted OR, 1.863 [95% CI, 0.864–4.015]; *P*=0.112). The rate of sICH was higher in the EVT group than in the SMT group (10 of 123 patients [8.1%] versus 9 of 449 patients [2.0%]; *P*=0.002), with an adjusted OR of 3.760 (95% CI, 1.373–10.294; *P*=0.010).

Association Between EVT and Outcomes When Guided by Perfusion Imaging

Baseline characteristics of the nonimaging-guided group and the imaging-guided group are presented in Table S3. Crude rates of clinical outcomes are available in Table 3.

Efficacy Outcomes

In the imaging-guided group, multivariable logistic regression analysis showed that EVT was associated with higher odds of excellent functional outcome (60.0% versus 50.8%, unadjusted OR, 1.451 [95% CI, 0.643–3.272]; adjusted OR, 2.849 [95% CI, 1.006–8.067]; *P*=0.049; Table 3), after adjusting for age, baseline NIHSS score, previous stroke, coronary heart disease, diabetes, hypertension, IVT, and vessel occlusion sites.

Safety Outcomes

EVT was associated with higher odds of mortality in the nonimaging-guided group (11.8% versus 5.5%,

Table 3. Crude Rates of Each Outcome in 2 Treatment Groups According to Selection Guided by Perfusion Imaging

	EVT (N=123)	SMT (N=449)	*P* value*	Adjusted OR (95% CI)†	*P* value‡
mRS 0–1					
Imaging-guided group (n=150)	18/30 (60.0)	61/120 (50.8)	0.418	2.849 (1.006–8.067)	0.049
Nonimaging-guided group (n=422)	47/93 (50.5)	205/329 (62.3)	0.028	0.582 (0.356–0.949)	0.030
mRS 0–2					
Imaging-guided group	22 (73.3)	88 (73.3)	1.000	2.399 (0.705–8.169)	0.162
Nonimaging-guided group	62 (66.7)	243 (73.9)	0.190	0.635 (0.374–1.076)	0.091
24-h symptomatic intracerebral hemorrhage					
Imaging-guided group	0 (0)	0 (0)	NA	NA	NA
Nonimaging-guided group	10 (10.8)	9 (2.7)	0.003	4.343 (1.550–12.169)	0.005
Mortality at 90 d					
Imaging-guided group	0 (0)	6 (5.0)	0.600	NA	NA
Nonimaging-guided group	11 (11.8)	18 (5.5)	0.060	2.736 (1.161–6.447)	0.021

Categorical variables are expressed as numbers (%).

**P* values obtained by univariate analysis.

†Adjusted by baseline characteristics with a *P* value <0.1 in univariate analysis.

‡*P* values obtained by multivariable analysis.

EVT indicates endovascular treatment; mRS, modified Rankin Scale; NA, not available; OR, odds ratio; and SMT, standard medical treatment.

adjusted OR, 2.736 [95% CI, 1.161–6.447]; *P*=0.021) but not in the imaging-guided group (no patients receiving EVT in this group died). Regarding sICH, EVT was associated with higher odds of sICH in the nonimaging-guided group (10.8% versus 2.7%, adjusted OR, 4.343 [95% CI, 1.550–12.169]; *P* <0.001) but not in patients whose therapy selection was guided by perfusion imaging (no patients in this group had sICH; Table 3).

Propensity Score Matching Analysis

We matched 117 pairs of patients who received EVT and SMT. The distributions of patient characteristics between 2 groups in the matched sample were similar (available in Table 1). No significant difference was found in excellent functional outcome between the EVT and SMT group after propensity score matching (52.1% versus 60.7%; adjusted OR, 0.733 [95% CI, 0.416–1.292]; *P*=0.282, Table 2). There was no difference in the proportion of 90-day good functional outcome in the EVT group and the SMT group (79 of 117 patients [67.5%] versus 86 of 117 patients [73.5%]; *P*=0.309), either. Mortality at 90 days occurred in 10 of 117 patients (8.5%) in the EVT group and 5 of 117 patients (4.3%) in the SMT group (*P*=0.167). The rate of sICH was 7.7% (9 of 117 patients) in the EVT group and 1.7% in the SMT group (2 of 117 patients; *P*=0.082; Table 2). Successful recanalization was achieved in 108 (93.1%) patients in the EVT group.

Subgroup Analysis

When analysis was stratified according to predefined subgroups, some significant heterogeneity in the treatment effect size was found (Figure 2). EVT was associated with lower odds of excellent functional outcome in patients with baseline NIHSS score ≤3 (adjusted OR, 0.523 [95% CI, 0.291–0.940]; *P*=0.030) and atrial fibrillation (adjusted OR, 0.297 [95% CI, 0.090–0.977]; *P*=0.046).

Sensitivity Analysis

Sensitivity analyses were conducted in patients who received reperfusion therapy and by excluding patients receiving rescue EVT. Only the rate of sICH was significantly higher in the EVT group than in the IVT alone group (adjusted OR, 3.513 [95% CI, 1.212–10.182]; *P*=0.021) (Tables S4 through S7).

DISCUSSION

The present nationwide cohort study found that EVT did not lead to better functional outcomes at 90 days after stroke onset and was associated with higher rates of sICH in patients with minor AIS with anterior circulation LVO when compared with SMT alone. However, selection guided by perfusion imaging significantly enhanced the benefit of EVT, namely EVT being related with better functional outcomes but not with an increase in the rate of sICH.

The absence of benefit of EVT is consistent with the findings of most previous studies.[7,10–13,21–23] An observational multicenter study reported EVT was effective to recanalize the occluded vessel but increased the risk of serious bleeding significantly without improving the functional outcome, suggesting that EVT was not justified routinely in minor strokes.[7] Another study demonstrated a shift toward a lower NIHSS score in patients with an LVO stroke presenting with mild symptoms who underwent primary thrombectomy as compared with best medical therapy alone.[8] However, both studies have small sample sizes, thus limiting their statistical power. The lack of improved clinical outcomes in the EVT group in our study may be attributed to several reasons. First, patients with minor AIS may experience intrinsic ischemic preconditioning owing to their good collateral circulation status,[13] which could limit the advantages of EVT. Furthermore, performing EVT might result in bleeding or reperfusion injury. Overall, current findings suggest that EVT should not be regularly considered in patients with unselected minor AIS with LVO.

Current guidelines recommend using perfusion imaging to guide the administration of EVT in the extended time window,[4] although it remains controversial in patients with minor AIS. Haussen et al used CTP to determine the ischemic core and perfusion defect for mild strokes, and their findings were in favor of EVT.[8] In contrast, another study of 47 mildly symptomatic patients with AIS owing to LVO who presented a target mismatch >15 mL and mismatch ratio >1.8 on perfusion imaging found no significant difference of NIHSS score shift from admission to discharge between medical management and EVT group.[12] Both studies were underpowered by the small sample size and monocentric design. Based on a relatively large multicenter analysis, we show that EVT as compared with SMT alone is associated with higher rates of excellent functional outcome in patients guided by perfusion imaging. Several possible factors may explain this. First, a salvageable ischemic penumbra may still be detected after selection by perfusion imaging in patients with minor AIS. Second, recanalization of the occluded vessel after EVT could rescue the ischemic brain tissue, although it may progress to infarct in patients within the SMT group. These findings, therefore, indicate that selection guided by perfusion imaging is an important modifier of the impact of EVT on functional outcomes in patients with minor AIS.

The rate of sICH at 24 hours was 8.1% in the EVT group of the present study, which was comparable with other studies (1.18%–11.8%).[7,10,13,24] The association between EVT and high sICH rates observed here

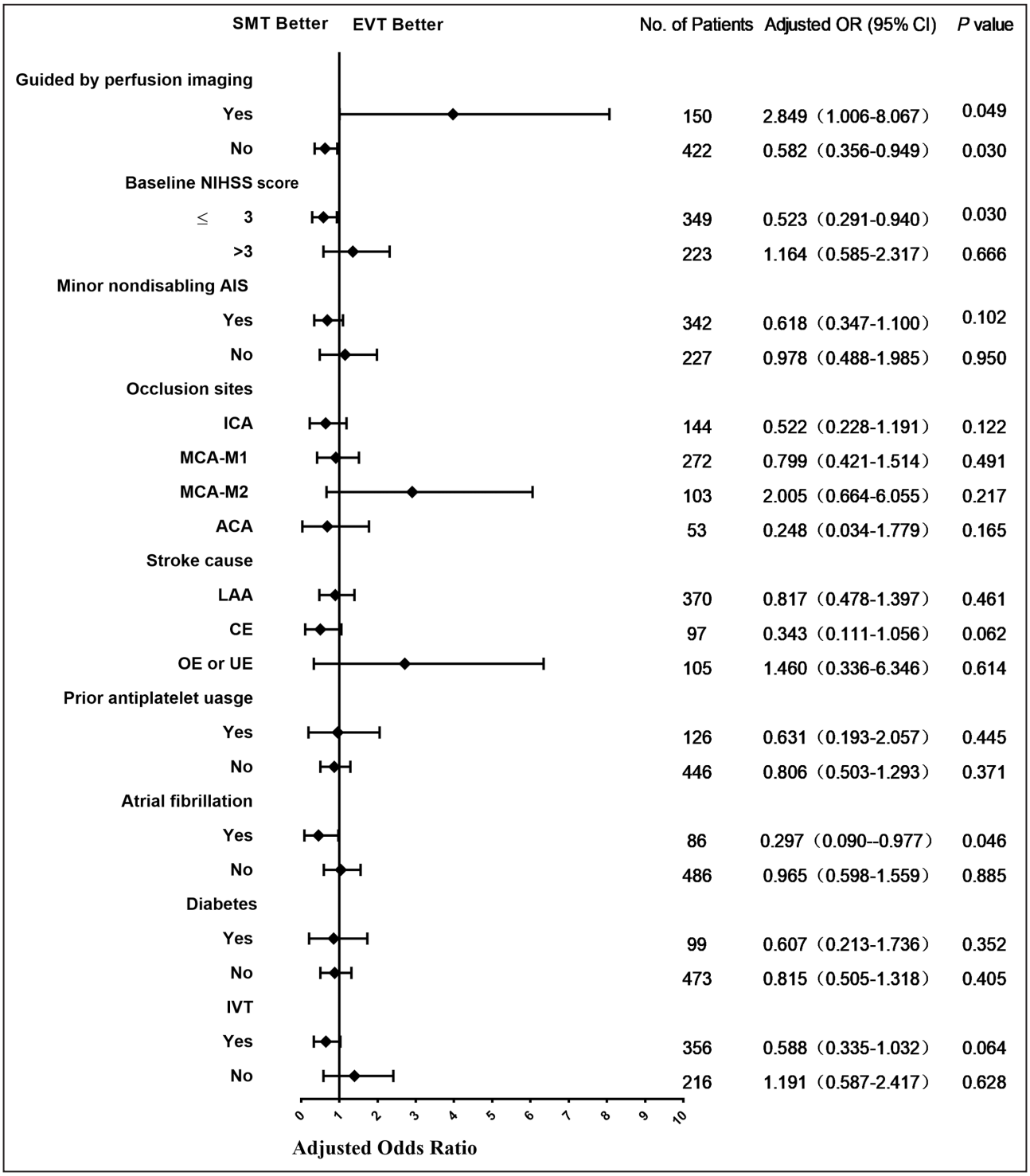

Figure 2. Forest plots for primary outcome in unmatched patients with different baseline characteristics.
This forest plot summarizes the odds ratio obtained for comparison of endovascular treatment and standard medical treatment on primary outcome (mRS score 0–1) across all prespecified subgroups. The odds ratio was calculated by using binary logistic regression taking the following variables into account: age, baseline NIHSS score, onset to door time, hypertension, diabetes, coronary heart disease, previous stroke/transient ischemic attack, IVT, and location of occlusion. ACA indicates anterior cerebral artery; AIS acute ischemic stroke; CE, cardioembolic etiology; EVT, endovascular treatment; ICA, internal carotid artery; IVT, intravenous thrombolysis; LAA, large artery atherosclerosis; MCA-M1, first segment of the middle cerebral artery; MCA-M2, second segment of middle cerebral artery; mRS, modified Rankin scale; NIHSS, National Institutes of Health Stroke Scale; OE, other etiology; OR, odds ratio; SMT, standard medical treatment; and UE, undetermined etiology.

could be explained by the complications of EVT procedure, such as endothelial cell injury, vessel rupture, and potential reperfusion injury. Another possible explanation is the higher proportion of atrial fibrillation and the higher score of baseline NIHSS in the EVT group, which are both extensively reported risk factors for sICH.[25,26]

Currently, the evidence for the effectiveness of EVT in minor AIS with LVO is sparse and ambiguous, and randomized clinical trials are just in preparation or underway (ENDO-LOW [Endovascular Therapy for Low NIHSS Ischemic Strokes], NCT 04167527, and MOSTE [Minor Stroke Therapy Evaluation], NCT 03796468). In practice, patients may hesitate to make the decision whether to receive EVT because of mild or quickly resolved symptoms and high costs. Our results demonstrated the benefit of EVT in patients with minor AIS when guided by perfusion imaging, providing a potential subgroup of patients with LVO and mild symptoms who could benefit from EVT. Additionally, our results may shed light on the importance of perfusion imaging in treatment triage for patients with minor AIS with LVO, pointing out one possible direction for future randomized clinical trials.

The nonrandomized design is the fundamental limitation. The potential risk of selection bias existed although we use the method of propensity score matching to balance the differences between the 2 treatment groups. Second, the large number of patients who received SMT alone compared with EVT may suggest the existence of a lack of equipoise among participating centers regarding the decision-making process of EVT in patients with stroke with mild symptoms. Third, the subgroup analysis may not be sufficiently powered. Larger sample size study and randomized trials are needed to confirm this finding. Fourth, the analyses of mRS score at 90 days may be subject to potential bias because of the loss to follow-up, although this influence was minimal in our study because of comparable baseline characteristics among patients with and without the 90-day mRS measurements. Last, the mRS may not be sensitive enough to assess the functional prognosis of patients with minor AIS,[13] and we have not been able to detect a significant difference in our primary outcome. The outcome measure of individual daily living such as Barthel Index would be better to compare clinical outcomes of these patients in future studies.

CONCLUSIONS

Our study does not support the routine use of endovascular therapy in unselected patients with minor AIS with anterior circulation LVO. However, our results do suggest that endovascular therapy could be beneficial for patients when guided by perfusion imaging. Randomized trials are needed to confirm these findings.

ARTICLE INFORMATION

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Disclosures

The authors declare that they have no competing interests.

Supplemental Material

Tables S1–S7
Figures S1–S2

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SUPPLEMENTAL MATERIAL

Table S1. Baseline Characteristics of Patients with Endovascular Treatment (EVT) versus standard medical treatment (SMT) in patients with and without mRS score at 90 days

Characteristic	With mRS at 90 days (N=572)	Without mRS at 90 days (N=57)	*P* Value
Age, median (IQR), y	69 (59-79)	68 (60-75)	0.102
Female	66 (31.7)	117 (32.1)	1.000
Current smoking	84 (40.7)	111 (30.5)	0.017
Hypertension	139 (66.8)	235 (64.6)	0.648
Diabetes mellitus	41 (19.7)	58 (15.9)	0.253
Hyperlipidemia	34 (16.3)	16 (4.4)	＜0.001
Coronary heart disease	14 (6.7)	23 (6.3)	0.861
Atrial fibrillation	38 (18.3)	48 (13.2)	0.114
Previous stroke/TIA	44 (21.2)	52 (14.3)	0.037
Prior antiplatelet usage	72 (34.6)	54 (14.8)	＜0.001
Prior anticoagulant usage	5 (2.4)	7 (1.9)	0.765
Baseline NIHSS score, median (IQR)	3 (2-4)	3 (1-4)	0.585
Minor non-disabling AIS	115 (55.8)	227 (62.5)	0.130
Systolic blood pressure, mean (SD), mmHg	152 ± 22	151 ± 21	0.701
Diastolic blood pressure,	85 ± 14	84 ± 14	0.219

mean (SD), mmHg

TIA = transient ischemic attack; NIHSS = National Institutes of Health Stroke Scale;

AIS=acute ischemic stroke.

Table S2. Characteristics of Patients with Endovascular Treatment (EVT) versus standard medical treatment (SMT) in patients with perfusion imaging

Characteristic	EVT (N=58)	SMT (N=150)	*P* Value
Age, median (IQR), y	69 (59-78)	69 (59-79)	0.938
Female	23 (39.7)	43 (28.7)	0.137
Current smoking	21 (36.2)	63 (42.0)	0.529
Hypertension	34 (58.6)	105 (70.0)	0.140
Diabetes mellitus	10 (17.2)	31 (20.7)	0.699
Hyperlipidemia	8 (13.8)	26 (17.3)	0.677
Coronary heart disease	6 (10.3)	8 (5.3)	0.221
Atrial fibrillation	10 (17.2)	28 (18.7)	1.000
Previous stroke/TIA	11 (19.0)	33 (22.0)	0.708
Prior antiplatelet usage	13 (22.4)	59 (39.3)	0.023
Prior anticoagulant usage	2 (3.4)	3 (2.0)	0.620
Baseline NIHSS score, median (IQR)	3 (2-4)	3 (2-4)	0.057
Minor non-disabling AIS	31 (55.4)	84 (56.0)	1.000
Onset to door, median (IQR), min	205 (88-416)	192 (100-395)	0.978
Onset to groin puncture, median (IQR), min	384 (249-551)	NA	NA
Onset to needle, median (IQR), min	218 (138-312)	206 (142-295)	0.814
Systolic blood pressure, mean (SD),	151 ± 24	152 ± 21	0.708

mmHg			
Diastolic blood pressure, mean (SD), mmHg	85 ± 16	85 ± 14	0.977
IVT	29 (50.0)	112 (74.7)	0.001
Occlusion sites			0.839
ICA	10 (17.2)	32 (21.3)	
M1	34 (58.6)	78 (52.0)	
M2	9 (15.5)	28 (18.7)	
ACA	5 (8.6)	12 (8.0)	
Stroke cause			0.099
LAA	33 (56.9)	73 (48.7)	
CE	16 (27.6)	32 (21.3)	
OE	2 (3.4)	4 (2.7)	
UE	7 (12.1)	41 (27.3)	
Recanalization	55/57 (96.5)	74/140 (52.9)	0.001
Ischemic core volume, median (IQR), ml	25.87 (11.25-34.83)	7.6 (2.18=18.25)	0.004
Penumbra volume, median (IQR), ml	48.50 (27.25-83.53)	17.2 (6.1-49.0)	0.008
Mismatch ratio, median (IQR), ml	2.4 (1.5-3.9)	3.1 (1.9-4.7)	0.333

EVT = endovascular treatment; SMT = standard medical treatment; TIA = transient ischemic attack; NIHSS = National Institutes of Health Stroke Scale; AIS=acute ischemic stroke; IVT = intravenous thrombolysis; ICA = internal carotid artery; M1 = first segment of middle cerebral artery; M2 = second segment of middle cerebral

artery; ACA = anterior cerebral artery; LAA = large artery atherosclerosis; CE = cardioembolic etiology; OE = other etiology; UE = undetermined etiology; NA = not available.

Table S3. Baseline Characteristics of Non-imaging-guided Group and Imaging-guided Group

Characteristic	Non-imaging-guided Group (N=422)	Imaging-guided Group (N=150)	*P* Value
Age, median (IQR), y	69 (60-76)	68 (59-77)	0.771
Female	41 (33.3)	142 (31.6)	0.744
Medical history			
Current smoking	143 (33.9)	52 (34.7)	0.920
Hypertension	273 (64.7)	101 (67.3)	0.618
Diabetes mellitus	68 (16.1)	31 (20.7)	0.211
Hyperlipidemia	41 (9.7)	9 (6.0)	0.182
Coronary heart disease	27 (6.4)	10 (6.7)	0.850
Atrial fibrillation	74 (17.5)	12 (8.0)	0.005
Previous stroke/TIA	67 (15.9)	29 (19.3)	0.373

Prior antiplatelet usage	85 (20.1)	41 (27.3)	0.085
Prior anticoagulant usage	9 (2.1)	3 (2.0)	1.000
Baseline measurements			
Baseline NIHSS score, median (IQR)	3 (2-5)	3 (1-4)	0.756
Minor non-disabling AIS	255 (60.4)	87 (59.2)	0.845
Onset to door, median (IQR), min	118 (60-189)	760 (539-1372)	< 0.001
Onset to groin puncture, median (IQR), min	302 (202-395)	805 (548-1141)	< 0.001
Onset to needle, median (IQR), min	167 (107-225)	565 (437-873)	< 0.001
Systolic blood pressure, mean (SD), mm Hg	150 ± 21	153 ± 22	0.137
Diastolic blood pressure, mean (SD), mm Hg	84 ± 14	86 ± 13	0.072
IVT	338 (80.1)	18 (12.0)	< 0.001
EVT	93 (22.0)	30 (20.0)	0.645
Ischemic core volume, median (IQR), ml	NA	12.87 (2.68-21.00)	NA

Penumbra volume, median (IQR), ml	NA	49.00 (21.50-97.00)	NA
Mismatch ratio, median (IQR)	2.8 (1.9-4.7)	3.0 (1.3-3.9)	0.457
Occlusion sites			0.597
ICA	111 (26.3)	33 (22.0)	
M1	196 (46.4)	76 (50.7)	
M2	78 (18.5)	25 (16.7)	
ACA	37 (8.8)	16 (10.7)	
Stroke cause			0.008
LAA	268 (63.5)	102 (68.0)	
CE	83 (19.7)	14 (9.3)	
OE	7 (1.7)	1 (0.7)	
UE	64 (15.2)	33 (22.0)	

Categorical variables are expressed as numbers (%) and continuous variables as median (interquartile range, IQR) or mean (standard deviation, SD).

TIA = transient ischemic attack; NIHSS = National Institutes of Health Stroke Scale; AIS= acute ischemic stroke; IVT = intravenous thrombolysis; EVT = endovascular treatment; ICA = internal carotid artery; M1 = first segment of middle cerebral artery; M2 = second segment of middle cerebral artery; ACA = anterior cerebral artery; LAA = large artery atherosclerosis; CE = cardioembolic etiology; OE = other etiology; UE = undetermined etiology.

Table S4. Characteristics of EVT versus IVT alone Groups

Characteristic	EVT (N=123)	IVT alone (N=289)	*P* Value
Age, median (IQR), y	69 (60-76)	68 (58-77)	0.928
Female	41 (33.3)	91 (31.5)	0.730
Medical history			
Current smoking	40 (32.5)	106 (36.7)	0.433
Hypertension	75 (61.0)	188 (65.1)	0.435
Diabetes mellitus	21 (17.1)	49 (17.0)	1.000
Hyperlipidemia	10 (8.1)	37 (12.8)	0.235
Coronary heart disease	11 (8.9)	15 (5.2)	0.183
Atrial fibrillation	25 (20.3)	46 (15.9)	0.318
Previous stroke/TIA	19 (15.4)	43 (14.9)	0.881

Prior antiplatelet usage	18 (14.6)	74 (25.6)	0.014
Prior anticoagulant usage	5 (4.1)	4 (1.4)	0.134
Baseline measurements			
Baseline NIHSS score, median (IQR)	3 (2-5)	3 (2-4)	0.338
Minor non-disabling AIS	68 (56.7)	164 (56.7)	1.000
Onset to door, median (IQR), min	165 (60-360)	117 (60-179)	0.002
Onset to groin puncture, median (IQR), min	372 (219-549)	NA	NA
Onset to needle, median (IQR), min	42 (31-63)	50 (40-66)	0.010
Systolic blood pressure, mean (SD), mm Hg	149 ± 23	151 ± 21	0.388
Diastolic blood pressure, mean (SD), mm Hg	85 ± 16	84 ± 14	0.980
IVT	67 (54.5)	289 (100)	< 0.001
Occlusion sites			0.949
ICA	34 (27.6)	76 (26.3)	

M1	59 (48.0)	134 (46.4)	
M2	20 (16.3)	54 (18.7)	
ACA	10 (8.1)	25 (8.7)	
Stroke cause			0.154
LAA	78 (63.4)	182 (63.0)	
CE	30 (24.4)	50 (17.3)	
OE	2 (1.6)	6 (2.1)	
UE	13 (10.6)	51 (17.6)	
Recanalization	114 (93.4)	197 (70.6)	< 0.001

Categorical variables are expressed as numbers (%) and continuous variables as median (interquartile range, IQR) or mean (standard deviation, SD).

EVT = endovascular treatment; AIS=acute ischemic stroke; IVT = intravenous thrombolysis; TIA = transient ischemic attack; NIHSS = National Institutes of Health Stroke Scale; ICA = internal carotid artery; M1 = first segment of middle cerebral artery; M2 = second segment of middle

cerebral artery; ACA = anterior cerebral artery; LAA = large artery atherosclerosis; CE = cardioembolic etiology; OE = other etiology; UE = undetermined etiology; NA = not available.

Table S5. Primary and Secondary Outcomes and Safety Outcomes of EVT versus IVT alone Groups

	EVT (N=123)	IVT alone (N=289)	*P* Value*	Adjusted OR (95%CI)†	*P* Value‡
Primary outcome					
mRS 0-1	65 (52.8)	182 (63.0)	0.062	0.600 (0.345-1.046)	0.072
Secondary outcome					
mRS 0-2	84 (68.3)	212 (73.4)	0.338	0.648 (0.360-1.166)	0.148
Safety outcomes					
24h-sICH	10 (8.1)	8 (2.8)	0.031	3.513 (1.212-10.182)	0.021
Mortality at 90 days	11 (8.9)	13 (4.5)	0.105	2.115 (0.885-5.052)	0.092

Categorical variables are expressed as numbers (%).

*P values obtained by univariate analysis.

†Adjusted by baseline characteristics with a P value < 0.1 in univariate analysis.

‡P values obtained by multivariable analysis.

EVT = endovascular treatment; IVT = intravenous thrombolysis; mRS = modified Rankin Scale; sICH = symptomatic intracerebral hemorrhage;

OR = odds ratio; CI = confidence interval.

Table S6. Characteristics of EVT versus SMT Groups by Excluding Patients Receiving Rescue EVT

Characteristic	EVT (N=80)	SMT (N=449)	*P* Value
Age, median (IQR), y	69 (59-78)	68 (59-77)	0.845
Female	30 (37.5)	142 (31.6)	0.303
Medical history			
Current smoking	30 (37.5)	155 (34.5)	0.613
Hypertension	50 (62.5)	299 (66.6)	0.522
Diabetes mellitus	12 (15.0)	78 (17.4)	0.747
Hyperlipidemia	8 (10.0)	40 (8.9)	0.678
Coronary heart disease	6 (7.5)	26 (5.8)	0.609
Atrial fibrillation	15 (18.8)	61 (13.6)	0.228
Previous stroke/TIA	14 (17.5)	77 (17.1)	1.000

Prior antiplatelet usage	14 (17.5)	108 (24.1)	0.249
Prior anticoagulant usage	1 (1.3)	7 (1.6)	1.000
Baseline measurements			
Baseline NIHSS score, median (IQR)	4 (2-5)	3 (1-4)	0.002
Minor non-disabling AIS	42 (54.5)	274 (61.0)	0.314
Onset to door, median (IQR), min	210 (91-432)	166 (80-435)	0.306
Onset to groin puncture, median (IQR), min	387 (246-548)	NA	NA
Door to needle, median (IQR), min	44 (30-64)	50 (40-66)	0.108
Systolic blood pressure, mean (SD), mm Hg	150 ± 21	152 ± 21	0.365
Diastolic blood pressure, mean (SD), mm Hg	85 ± 15	84 ± 13	0.945
IVT	37 (46.3)	289 (64.4)	0.003
Occlusion sites			0.824
ICA	16 (20.0)	110 (24.5)	

M1	42 (52.5)	213 (47.4)	
M2	15 (18.8)	83 (18.5)	
ACA	7 (8.8)	43 (9.6)	
Stroke cause			0.113
LAA	53 (66.3)	292 (65.0)	
CE	18 (22.5)	67 (14.9)	
OE	1 (1.3)	6 (1.3)	
UE	8 (10.0)	84 (18.7)	
Recanalization	74 (93.7)	250 (59.2)	< 0.001

Categorical variables are expressed as numbers (%) and continuous variables as median (interquartile range, IQR) or mean (standard deviation, SD).

EVT = endovascular treatment; SMT = standard medical treatment; TIA = transient ischemic attack; NIHSS = National Institutes of Health Stroke Scale; AIS=acute ischemic stroke; IVT = intravenous thrombolysis; ICA = internal carotid artery; M1 = first segment of middle cerebral artery;

M2 = second segment of middle cerebral artery; ACA = anterior cerebral artery; LAA = large artery atherosclerosis; CE = cardioembolic etiology; OE = other etiology; UE = undetermined etiology; NA = not available.

Table S7. Primary and Secondary Outcomes and Safety Outcomes by Excluding Patients Receiving Rescue EVT

	EVT (N=80)	SMT (N=449)	*P* Value*	Adjusted OR (95%CI)†	*P* Value‡
Primary outcome					
mRS 0-1	50 (62.5)	266 (59.2)	0.622	1.307 (0.767-2.228)	0.325
Secondary outcome					
mRS 0-2	62 (77.5)	331 (73.7)	0.579	1.327 (0.723-2.435)	0.361
Safety outcomes					
24h-sICH	2 (2.5)	9 (2.0)	0.676	1.231 (0.233-6.509)	0.807
Mortality at 90 days	2 (2.5)	24 (5.3)	0.403	0.536 (0.121-2.367)	0.411

Categorical variables are expressed as numbers (%).

*P values obtained by univariate analysis.

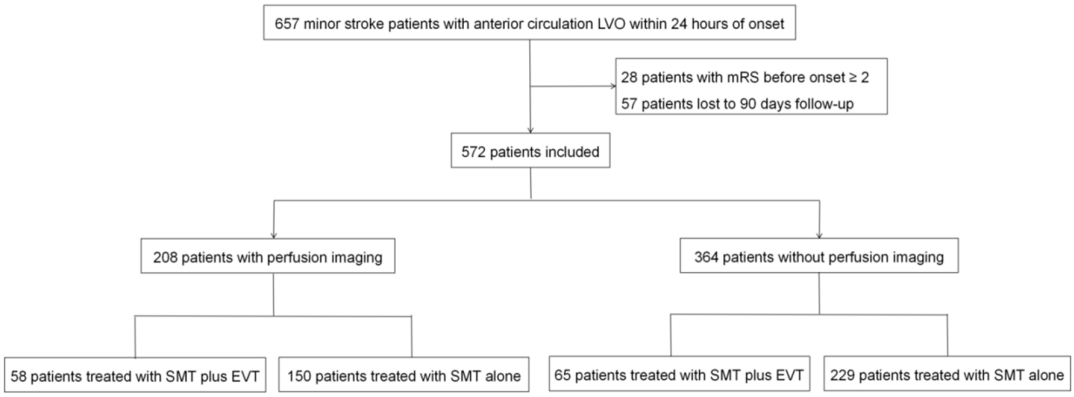
†Adjusted by baseline characteristics with a P value < 0.1 in univariate analysis.

‡P values obtained by multivariable analysis.

EVT = endovascular treatment; SMT = standard medical treatment; mRS = modified Rankin Scale; sICH = symptomatic intracerebral hemorrhage;

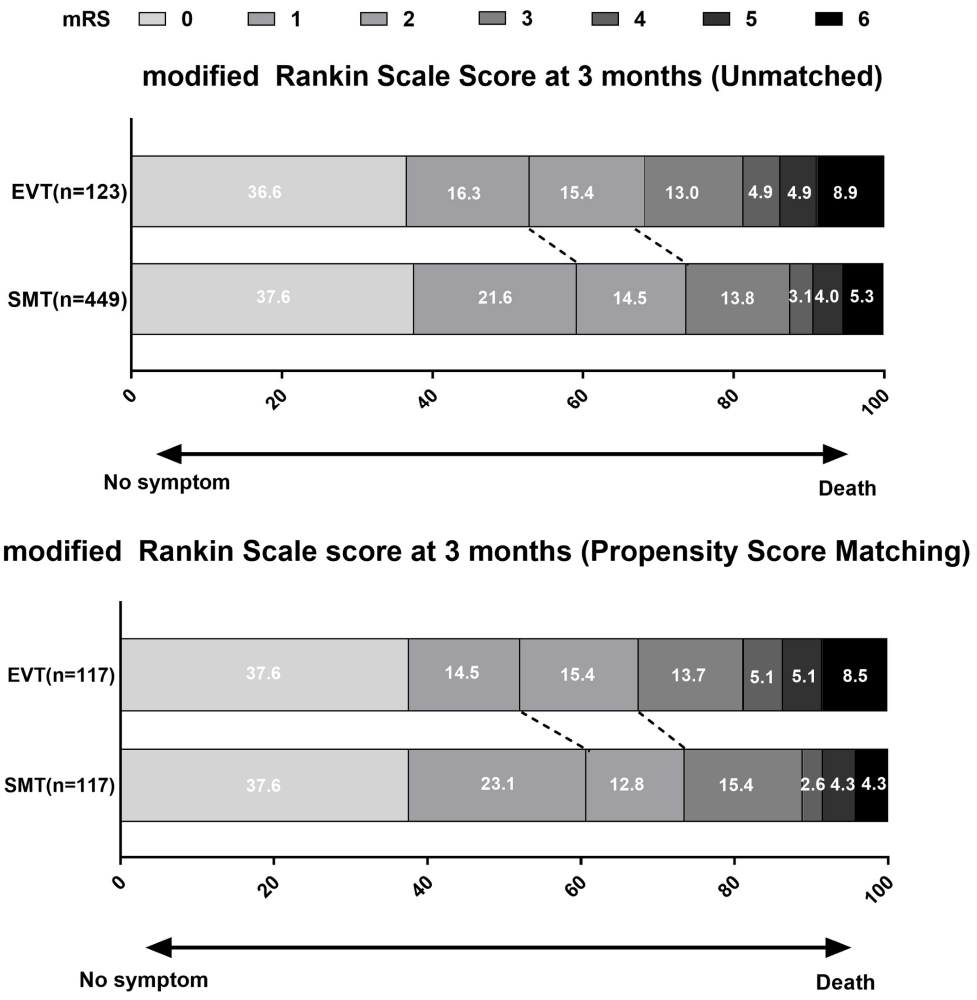
OR = odds ratio; CI = confidence interval

Figure S1. Flow chart of patient selection for patients with and without perfusion imaging at baseline



LVO= large vessel occlusion; EVT = endovascular treatment; SMT = standard medical treatment

Figure S2. Distribution of the Modified Rankin Scale Score at 90 Days in All Patients and the Propensity Score Matching Data Set



EVT = endovascular treatment; SMT = standard medical treatment