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ORIGINAL ARTICLE

IV thrombolysis plus thrombectomy versus IV thrombolysis alone for minor stroke with anterior circulation large vessel occlusion from the IRETAS and Italian SITS-ISTR cohorts

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Abstract

Introduction The aim of this study was to compare the outcomes of patients treated with intravenous thrombolysis (IVT) <4.5 h after symptom onset plus mechanical thrombectomy (MT) <6 h with those treated with IVT alone <4.5 h for minor stroke (NIHSS ≤5) with large vessel occlusion (LVO) in the anterior circulation.

Patients and methods Patients enrolled in the Italian Registry of Endovascular Treatment in Acute Stroke (IRETAS) and in the Italian centers included in the SITS-ISTR were analyzed.

Results Among the patients with complete data on 24-h ICH type, 236 received IVT plus MT and 382 received IVT alone. IVT plus MT was significantly associated with unfavorable shift on 24-h ICH types (from no ICH to PH-2) (OR, 2.130; 95% CI, 1.173–3.868; p=0.013) and higher rate of PH (OR, 4.363; 95% CI, 1.579–12.055; p=0.005), sICH per ECASS II definition (OR, 5.527; 95% CI, 1.378–22.167; p=0.016), and sICH per NINDS definition (OR, 3.805; 95% CI, 1.310–11.046; p=0.014). Among the patients with complete data on 3-month mRS score, 226 received IVT plus MT and 262 received IVT alone. No significant difference was reported between IVT plus MT and IVT alone on mRS score 0–1 (72.1% versus 69.1%), mRS score 0–2 (79.6% versus 79%), and death (6.2% versus 6.1%).

Conclusions Compared with IVT alone, IVT plus MT was associated with unfavorable shift on 24-h ICH types and higher rate of 24-h PH and sICH in patients with minor stroke and LVO in the anterior circulation. However, no difference was reported between the groups on 3-month functional outcome measures.

Keywords Minor stroke · Thrombolysis · Thrombectomy · Large vessel occlusion

Introduction

Evidence-based recommendations regarding the optimal management of patients with anterior circulation large vessel occlusion (LVO) and mild neurological deficits (minor

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stroke with National Institutes of health Stroke Scale (NIHSS) score ≤5) are lacking, as those patients were excluded from prospective trials or their number was markedly underrepresented [1–3].

In the pre-thrombectomy era, early neurological deterioration was seen in 30% of patients who were treated with intravenous thrombolysis (IVT) for minor stroke due to terminal internal carotid artery (ICA) or tandem occlusions [4]. Despite long-term functional outcome following early neurological deterioration improved with rescue thrombectomy, it remained poor overall in patients receiving IVT for minor stroke with LVO [5]. No significant difference in safety and efficacy outcomes after acute reperfusion treatment was found in disabling versus nondisabling mild acute ischemic stroke due to endovascular treatment (EVT)-targetable vessel occlusion [6].

Two previous studies, one French and the other German, showed that IVT plus mechanical thrombectomy (MT) within 6 h after symptom onset in patients with minor stroke and LVO did not result in better functional outcomes at 3 months but was associated with symptomatic intracerebral hemorrhage (sICH) at 24 h compared with IVT alone [7, 8].

Two ongoing trials—ENDOLOW (NCT04167527) and IN EXTREMIS-MOSTE (NCT03796468)—are comparing EVT associated with the best medical treatment (BMT) to BMT in patients with minor stroke with LVO in anterior circulation.

The aim of the present study was to compare the outcomes of patients with minor stroke and LVO in the anterior circulation treated with IVT within 4.5 h after symptom onset plus mechanical thrombectomy (MT) within 6 h after symptom onset with those treated with IVT alone within 4.5 h after symptom onset.

Methods

Study design, participants, and procedures

We conducted a study on prospectively collected data of 16031 patients registered in the Italian Registry of Endovascular Treatment in Acute Stroke (IRETAS, an ongoing, multicenter, observational Internet-based registry) [9] between January 2011 and December 2020 for treatment with IVT plus MT and 112499 patients registered in the Italian centers included in the Safe Implementation of Thrombolysis-International Stroke Registry (SITS-ISTR, an ongoing, multicenter, observational Internet-based registry) [10, 11] between May 2001 and December 2020 for treatment with IVT alone. Centers that have treated both patients with IVT plus MT and patients with IVT alone are reported in Supplemental Table 1.

Inclusion and exclusion criteria

We included patients with minor stroke (baseline NIHSS score ≤5) receiving IVT alone within 4.5 h after symptom onset and patients receiving IVT <4.5 h after symptom onset plus MT <6 h after symptom onset, with complete data on site occlusion in the anterior circulation. We excluded patients with concomitant occlusions in the anterior and posterior circulation or concomitant occlusions in the left and right side. We included patients with complete data on ICH type at 24 h for analyses using intra-cranial bleeding measures as outcomes and patients with complete data on modified Rankin scale (mRS) score at 3 months for analyses using functional outcome measures as outcomes.

Since data are extracted from national registries, the choice of treatment (IVT alone or IVT plus MT) was at the discretion of the neurologist and neuroradiologist according to national [12] and international guidelines [13]

Data collection

We collected data on age, sex, hypertension, diabetes mellitus, hyperlipidemia, previous stroke or transient ischemic attack, atrial fibrillation, prior use of antiplatelets, prior use of oral anticoagulants with INR <1.7, pre-stroke mRS score, NIHSS score at baseline and at 24 h, occlusion site on CT or MR angiography before IVT (isolated intra-cranial ICA occlusion, isolated M1- or M1-M2-segment middle cerebral artery (MCA) occlusion, isolated M2-segment MCA occlusion, isolated A1-segment ACA occlusion, T-type carotid occlusion (combination of terminal segment ICA occlusion with ipsilateral A1-segment ACA occlusion and ipsilateral M1-segment MCA occlusion), tandem occlusion (combination of extra-cranial ICA occlusion with intra-cranial artery occlusion in the ipsilateral anterior circulation), onset-to-needle time, onset-to-groin time and recanalization according to thrombolysis in cerebral infarction (TICI) scale for IRETAS cohort, types of intracerebral hemorrhage (ICH) at 24 h, and mRS score at 3 months.

Outcomes

Intra-cranial bleeding measures at 24 h were the (a) type of ICH according to the European Cooperative Acute Stroke Study (ECASS) II classification [14] (hemorrhagic infarction type 1 (HI-1) defined as small petechiae along the margins of the infarct; hemorrhagic infarction type 2 (HI-2) defined as more confluent petechiae within the infarcted area, but without space-occupying effect; parenchymal hemorrhage type 1 (PH-1) defined as a clot not exceeding 30% of the infarcted area with some mild space-occupying

effect); parenchymal hemorrhage type 2 (PH-2) defined as dense blood clot exceeding 30% of the infarct volume with significant space-occupying effect); (b) parenchymal hemorrhage (PH-1 or PH-2); (c) symptomatic ICH (sICH) according to the Safe Implementation of Thrombolysis in Stroke-Monitoring Study (SITS-MOST) definition (PH-2 combined with a neurological deterioration of 4 points or more on the NIHSS from baseline not attributable to general anesthesia, or leading to death); (d) sICH according to the European Cooperative Acute Stroke Study (ECASS) II definition (any ICH combined with a neurological deterioration of 4 points or more on the NIHSS from baseline not attributable to general anesthesia, or leading to death); and (e) sICH according to the National Institute of Neurological Disorders and Stroke (NINDS) definition (any ICH combined with a neurological deterioration of 1 point or more on the NIHSS from baseline not attributable to general anesthesia, or leading to death).

Functional outcome measures at 3 months were as follows: (a) mRS score, (b) excellent outcome (mRS score ≤1), (c) favorable outcome (mRS score ≤2), and (d) mortality at 3 months.

Statistical analysis

We performed statistical analyses using SPSS 22.0 statistical package and STATA-16 software. Normally distributed continuous variables were presented as means and standard deviation (SD) and compared using Student's *t*-tests. Not-normally distributed continuous variables were presented as median and IQR and compared using Mann-Whitney *U*-test. Categorical variables were expressed as frequency and percentage and compared using χ^2 test. Proportions were calculated for categorical variables, dividing the number of events by the total number excluding missing/unknown cases.

Descriptive analysis was used to identify differences between the treatments (IVT plus MT versus IVT alone) in characteristics of patients included in the IRETAS and SITS-ISTR cohorts with complete data on 24-h ICH type and 3-month mRS score.

Ordinal regression was used to estimate the association of IVT plus MT (versus IVT alone) with unfavorable distribution shift of 24-h ICH types (from no ICH to PH-2) and 3-month mRS (from 0 to 6) by calculating the crude odds ratio (OR) with two-sided 95% confidence intervals (CI). Binary regression was used to estimate the association of IVT plus MT (versus IVT alone) with PH and sICH at 24 h, excellent and favorable outcome, and mortality at 3 months by calculating the ORs with two-sided 95% CI.

Binary regression was used to estimate the effect of IVT plus MT (versus IVT alone) on PH and sICH at 24 h, excellent and favorable outcome, at 3 months across occlusion sites; heterogeneity of IVT plus MT (versus IVT alone) effect by occlusion site subgroups was tested using a multiplicative interaction term. Analyses using intra-cranial bleedings as outcome measures were adjusted for group differences in baseline characteristics of patients with complete data on ICH type at 24 h, while analyses using functional outcomes as outcome measures were adjusted for group differences in baseline characteristics of patients with complete data on mRS score at 3 months (probability value <0.05).

Results

We identified 241 patients registered in the IRETAS cohort by 36 centers who received IVT plus MT and 441 patients registered in the SITS-ISTR cohort by 103 centers who received IVT alone. Characteristics per treatment of the patients included in the IRETAS and SITS-ISTR cohorts are reported in Table 1. Atrial fibrillation, previous ischemic stroke/TIA, and prior use of antiplatelet therapy were significantly more frequent in the SITS-ISTR group, whereas pre-stroke mRS score 0–1 was significantly more frequent in the IRETAS group. The groups were significantly different in distribution of baseline NIHSS score and occlusion site. The rate of TICI 2b/3 was reported in 83.2% of the patients treated with IVT plus MT. Distribution of 24-h ICH types was different between the groups, and the rate of 24-h PH was significantly higher in the IRETAS group. No difference was reported between the groups on 3-month functional outcome measures.

Among the patients with complete data on 24-h ICH type, 236 received IVT plus MT and 382 received IVT alone. Characteristics per treatment of the cohorts are reported in Supplemental Table 2. Atrial fibrillation, previous ischemic stroke/TIA, and prior use of antiplatelet therapy were significantly more frequent in the SITS-ISTR group, whereas pre-stroke mRS score 0–1 was significantly more frequent in the IRETAS group. The groups were significantly different in distribution of baseline NIHSS score and occlusion site. After adjustment for group differences in baseline characteristics, IVT plus MT was significantly associated with unfavorable shift on 24-h ICH types (from no ICH to PH-2) in ordinal regression (OR, 2.130; 95% CI, 1.173–3.868; p=0.013) (Table 2). IVT plus MT group was significantly associated with higher rate of 24-h PH (6.8% versus 2.1%; OR, 4.363; 95% CI, 1.579–12.055; p=0.005), higher rate of 24-h sICH according to ECASS II definition (4.3% versus 1.9%; OR, 5.527; 95% CI, 1.378–22.167; p=0.016), and higher rate of 24-h sICH according to NINDS definition (5.5% versus 3%; OR, 3.805; 95% CI, 1.310–11.046; p=0.014) in binary regression. No significant difference was reported between IVT plus MT and IVT alone on 24-h sICH according to SITS-MOST definition (2.1% versus 0.5%).

Table 1 Characteristics per treatment of patients included in the IRETAS and Italian SITS-ISTR cohorts

	IVT plus MT (*n*=241)	**IVT alone** (*n*=441)	***p* value**
Demographics			
Age (years)	69.5 (14)	68.8 (14.1)	0.554
Male sex	235 (53.3)	117 (48.5)	0.262
Medical history			
Hypertension	132 (54.8)	266 (60.5) [440]	0.167
Diabetes mellitus	25 (10.4)	68 (15.5) [440]	0.080
Atrial fibrillation	41 (17)	106 (24.1) [440]	0.032
Previous ischemic stroke/TIA	10 (4.1)	72 (16.4) [440]	<0.001
Hyperlipidemia	56 (23.2)	131 (29.8) [440]	0.073
Antiplatelet therapy	53 (22)	136 (30.8)	0.016
Oral anticoagulant therapy	9 (3.8)	10 (2.3)	0.329
Baseline data			
Pre-stroke mRS score 0–1	212 (95.9)	387 (89.2) [434]	0.003
NIHSS score			0.007
0	10 (4.1)	59 (13.4)	
1	11 (4.6)	17 (3.9)	
2	33 (13.7)	47 (10.7)	
3	52 (21.6)	78 (17.7)	
4	60 (24.9)	113 (25.6)	
5	75 (31.1)	127 (28.8)	
Occlusion site			<0.001
Isolated intra-cranial ICA	4 (1.7)	35 (7.9)	
Isolated M1-segment MCA	110 (45.6)	156 (36.4)	
Isolated M2-segment MCA	88 (36.5)	209 (47.4)	
Isolated A1-segment ACA	1 (0.4)	10 (2.3)	
T-type carotid	9 (3.7)	14 (3.2)	
Tandem	29 (12)	17 (3.9)	
Onset-to-needle time (minutes)	155 (124–207)	165 (130–205)	0.347
Onset-to-groin time (minutes)	218 (153–283)	-	NA
TICI 2b/3	193 (83.2) [232]	-	NA
24-h intra-cranial bleeding measures			
ICH	[236]	[382]	0.009
No	205 (86.9)	352 [92.1]	
HI-1	8 (3.4)	15 (3.9)	
HI-2	7 (3)	7 (1.8)	
PH-1	11 (4.7)	2 (0.5)	
PH-2	5 (2.1)	6 (1.6)	
PH	16 (6.8) [236]	8 (2.1) [382]	0.005
sICH			
SITS-MOST definition	5 (2.1) [236]	2 (0.5) [379]	0.113
ECASS II definition	10 (4.3) [234]	7 (1.9) [368]	0.127
NINDS definition	13 (5.6) [234]	11 (3) [368]	0.136
3-month functional outcome measures	[226]	[262]	
mRS score			0.953
0	124 (54.9)	136 (51.9)	
1	39 (17.3)	45 (17.2)	
2	17 (7.5)	26 (9.9)	
3	14 (6.2)	17 (6.5)	
4	12 (5.3)	17 (6.5)	
5	6 (2.7)	5 (1.9)	
6	14 (6.2)	16 (6.1)	

Table 1 (continued)

	IVT plus MT (*n*=241)	**IVT alone** (*n*=441)	***p* value**
mRS score ≤1	163 (72.1)	181 (69.1)	0.487
mRS score ≤2	180 (79.6)	207 (79)	0.911
Death	14 (6.2)	16 (6.1)	1.000

Continuous variables are presented as mean and standard deviation (SD) or median and interquartile range (IQR). Categorical variables are expressed as frequency and percentage. Proportions were calculated for categorical variables, dividing the number of events by the total number excluding missing/unknown cases. Numbers within square brackets indicate number of events. Statistical significance was established at two-tailed 0.05 level (p <0.05)

IRETAS Italian Registry of Endovascular Treatment in Acute Stroke, *SITS-ISTR* Safe Implementation of Thrombolysis in Stroke-International Stroke Thrombolysis Registry, *IVT* intravenous thrombolysis, *MT* mechanical thrombectomy, *TIA* transient ischemic attack, *mRS* modified Rankin scale, *NIHSS* National Institutes of health Stroke Scale, *ICA* internal carotid artery, *MCA* middle cerebral artery, *ACA* anterior cerebral artery, *TICI* thrombolysis in cerebral infarction, *ICH* intracerebral hemorrhage, *HI* hemorrhagic infarction, *PH* parenchymal hemorrhage, *sICH* symptomatic intracerebral hemorrhage, *SITS-MOST* Safe Implementation of Thrombolysis in Stroke-Monitoring Study, *ECASS* European Cooperative Acute Stroke Study, *NINDS* National Institute of Neurological Disorders and Stroke

Table 2 Ordinal and binary regression: IVT plus MT versus IVT alone on 24-h intra-cranial bleeding measures

	IVT plus MT (*n*=236)	**IVT alone** (*n*=382)	**Adjusted OR (95 CI)**	***p* value**
ICH			2.130 (1.173–3.868)	0.013
No	205 (86.9)	353 (92.1)		
HI-1	8 (3.4)	15 (3.)		
HI-2	7 (3)	7 (1.8)		
PH-1	11 (4.7)	2 (0.5)		
PH-2	5 (2.1)	6 (1.6)		
PH	16 (6.8)	8 (2.1)	4.363 (1.579–12.055)	0.005
sICH				
SITS-MOST definition	5 (2.1)	2 (0.5) [3]	9.543 (0.948–96.057)	0.056
ECASS II definition	10 (4.3) [2]	7 (1.9) [14]	5.527 (1.378–22.167)	0.016
NINDS definition	13 (5.6) [2]	11 (3) [14]	3.805 (1.310–11.046)	0.014

Categorical variables are expressed as frequency and percentage. Proportions were calculated for categorical variables, dividing the number of events by the total number excluding missing/unknown cases. Numbers within square brackets indicate number of events. Adjustment for atrial fibrillation, previous ischemic stroke/TIA, antiplatelet therapy, pre-stroke mRS score 0–1, NIHSS score (5 points as reference), and site occlusion (tandem occlusion as reference). Statistical significance was established at two-tailed 0.05 level (p <0.05)

IVT intravenous thrombolysis, *MT* mechanical thrombectomy, *ICH* intracerebral hemorrhage, *HI* hemorrhagic infarction, *PH* parenchymal hemorrhage, *sICH* symptomatic intracerebral hemorrhage, *SITS-MOST* Safe Implementation of Thrombolysis in Stroke-Monitoring Study, *ECASS* European Cooperative Acute Stroke Study, *NINDS* National Institute of Neurological Disorders and Stroke

Among the patients with complete data on 3-month mRS score, 226 received IVT plus MT and 262 received IVT alone. Characteristics per treatment of the cohorts are reported in Supplemental Table 3. Diabetes mellitus, atrial fibrillation, previous ischemic stroke/TIA, dyslipidemia, and prior use of antiplatelet therapy were significantly more frequent in the SITS-ISTR group, whereas pre-stroke mRS score 0–1 was significantly more frequent in the IRETAS group. The groups were significantly different in distribution of baseline NIHSS score and occlusion site. After adjustment for group differences in baseline characteristics, no significant difference was reported between IVT plus MT and IVT alone groups on 3-month mRS score shift in ordinal regression (from 0 to 6) and on rates of mRS 0–1 (72.1% versus 69.1%), mRS 0–2 (79.6% versus 79%), and death (6.2% versus 6.1%) at 3 months in binary regression (Table 3).

There was no evidence of significant heterogeneity of effects of IVT plus MT (versus IVT alone) across different occlusion sites on 24-h PH and sICH (Supplemental Table 4). Significantly worse effect of IVT plus MT was found in patients with M1-segment MCA occlusion on 24-h PH (OR, 8.953; 95% CI, 1.375–58.284) and sICH according to ECASS II definition (OR, 8.924; 95% CI, 1.016–78.383).

Table 3 Ordinal and binary regression: IVT plus MT versus IVT alone on 3-month functional outcome measures

	IVT plus MT (*n*=226)	**IVT alone** (*n*=262)	**Adjusted OR (95 CI)**	***p* value**
mRS score			1.172 (0.796–1.725)	0.421
0	124 (54.9)	136 (51.9)		
1	39 (17.3)	45 (17.2)		
2	17 (7.5)	26 (9.9)		
3	14 (6.2)	17 (6.5)		
4	12 (5.3)	17 (6.5)		
5	6 (2.7)	5 (1.9)		
6	14 (6.2)	16 (6.1)		
mRS score ≤1	163 (72.1)	181 (69.1)	0.867 (0.547–1.376)	0.546
mRS score ≤2	180 (79.6)	207 (79)	0.753 (0.434–1.245)	0.253
Death	14 (6.2)	16 (6.1)	2.407 (0.906–6.393)	0.178

Categorical variables are expressed as frequency and percentage. Adjustment for diabetes mellitus, atrial fibrillation, previous ischemic stroke/TIA, dyslipidemia, antiplatelet therapy, pre-stroke mRS score 0–1, NIHSS score (5 points as reference), and site occlusion (tandem occlusion as reference). Statistical significance was established at two-tailed 0.05 level (p <0.05)

IVT intravenous thrombolysis, *MT* mechanical thrombectomy, *mRS* modified Rankin scale

The direction of ORs unfavored IVT plus MT in patients with isolated M1- and M2-segment MCA occlusion on sICH according to NINDS definition. However, no significant effect was found.

There was evidence of significant heterogeneity of effects of IVT plus MT (versus IVT alone) across different occlusion sites on 3-month mRS score ≤1 (p value for interaction = 0.024) (Supplemental Table 5). The direction of ORs unfavored IVT plus MT across different strata, except OR in patients with isolated M1-segment MCA occlusion. Significantly worse effect of IVT plus MT was found in patients with tandem occlusion (OR, 0.064; 95% CI, 0.005–0.887). There was no evidence of significant heterogeneity of effects of IVT plus MT (versus IVT alone) across different occlusion sites on 3-month mRS score ≤2. The direction of ORs unfavored IVT plus MT across different strata, except OR in patients with isolated M1-segment MCA occlusion. However, no significant effect was found.

Discussion

Our study shows that IVT plus MT was significantly associated with unfavorable shift on 24-h ICH type (from no ICH to PH-2) and higher rate of 24-h PH (6.8% versus 2.1%) and 24-h sICH according to ECASS II (4.3% versus 1.9%) and NINDS (5.6% versus 3%) definitions, compared with IVT alone group, in patients with minor stroke and anterior circulation LVO. However, no significant difference was reported between IVT plus MT and IVT alone on mRS score 0–1 (72.1% versus 69.1%), mRS score 0–2 (79.6% versus 79%), and death (6.2% versus 6.1%) at 3 months. Similar to the previous data from patients receiving MT for moderate/severe stroke with LVO [1], the successful recanalization was achieved in 83% of patients treated with IVT plus MT. Compared with the previous data from patients receiving MT for moderate/severe stroke with LVO [1], our study shows that the rates of PH and sICH remained low in patients with minor stroke and LVO, while favorable functional outcome at 3 months was better. Since higher baseline NIHSS score is a strong predictor of ICH and unfavorable outcomes, the results of our study could be explained by the specific setting including patients with mild neurological deficits.

Our study shows that IVT plus MT was associated with higher ORs of 24-h PH and sICH according to the ECASS II definition but also with higher ORs of 3-month mRS score ≤1 and mRS score ≤2 in patients with isolated M1-segment MCA occlusion, whereas the effect of IVT plus MT on mRS score ≤1 was worse in patients with tandem occlusion. It is known from RCTs that the benefit of MT over best medical therapy is greatest in stroke patients with M1-segment MCA and intra-cranial ICA occlusions [1], while it remains uncertain in tandem and distal occlusions. However, it is also known that any ICH at 24-h CT scan is often found in patients with successful recanalization after MT and some patients experience unfavorable outcomes in the form of PH and/or sICH following reperfusion treatments despite vessel recanalization [15].

Our data are in line with two previous studies including patients with minor stroke and LVO who were eligible to IVT and MT according to classic time window [7, 8]. A multicentric retrospective observational study collected the data from 45 French stroke centers and matched 214 patients receiving IVT plus MT and 384 patients receiving IVT alone [7]. Compared with IVT alone, IVT plus MT was not associated

with higher ORs of 3-month mRS score ≤1 (0.96; 95% CI, 0.75–1.24) and mRS score ≤2 (0.77; 95% CI, 0.57–1.04) but was associated with higher ORs of any ICH (2.42; 95% CI, 1.75–3.37) and sICH (3.01; 95% CI, 1.77–5.11). Similar to our study, occlusion site significantly modified the effect of IVT plus MT. IVT plus MT was associated with higher ORs of mRS score ≤1 in proximal M1-segment MCA occlusion (3.26; 95% CI, 1.67–6.35) and in distal M1-segment MCA occlusion (1.69; 95% CI, 1.01–2.82) but with higher ORs of any ICH in distal M1-segment MCA occlusion (2.33; 95% CI, 1.18–4.60). Compared to our study, differences between IVT plus MT and IVT alone were more pronounced in patients with M2-segment MCA. In these patients, IVT plus MT was associated with lower OR of mRS score ≤1 (0.53; 95% CI, 0.38–0.75) but also with higher ORs of any ICH (3.47; 95% CI, 2.21–5.45) and sICH (4.40; 95% CI, 2.20–8.83; $p<0.0001$). Despite the large cohort, the number of tandem occlusions was small, precluding comparisons in this subgroup. A recent study has matched 272 patients included in the German Stroke Registry-Endovascular Treatment (GSR-ET) from 25 sites in Germany who received IVT alone plus MT and 272 patients included in the SITS-ISTR who received IVT alone for minor stroke and LVO, despite about 20% of the included patients had a stroke with LVO in the posterior circulation [8]. In particular, the rate of sICH was significantly higher in patients treated with IVT plus MT than those treated with IVT alone (4.4% vs. 1.0%), but there was no significant difference in mRS score 0–2 (82.9% versus 77.0%) and mortality (7.9% vs. 5.9%) at 3 months. The effects of IVT plus MT and IVT alone were not assessed by occlusion site.

A recent retrospective study includes Chinese patients with minor stroke and LVO within 4.5 h from symptom onset; direct MT met the prespecified statistical threshold for noninferiority for the 3-month functional outcomes, compared with bridging therapy [16]. However, in the lack of solid evidence for superiority of IVT plus MT over IVT alone in patients with minor stroke and LVO, we believe that a comparison between IVT plus MT and direct MT within the classic time window for treatment is not currently feasible. Instead, similar to extending time window for treatment IVT and MT using advanced imaging in patients with moderate/severe stroke with LVO according to new guidelines [13, 17], a comparison between IVT alone and IVT plus MT beyond the classic time window for treatment could currently be feasible in patients with minor stroke and LVO. Recently, a nationwide cohort study including patients with minor stroke with LVO within 24 h from symptom onset found that standard medical treatment (including IVT in more than half of the cases) plus MT did not lead to better functional outcomes at 3 months and was associated with higher rate of sICH when compared with standard medical treatment (including IVT in nearly two-thirds of cases). 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 [18].

Currently, the evidence for the effectiveness of EVT in minor stroke with LVO is sparse and remains ambiguous. As the current national [12] and international guidelines [13] of revascularization treatments for minor stroke with LVO recommend to include patients with minor stroke and LVO in RCTs, the results of the two ongoing trials—ENDOLOW (NCT04167527) and IN EXTREMIS-MOSTE (NCT03796468)—enrolling also minor strokes with tandem occlusion within 8 and 24 h after symptom onset, respectively, are awaited.

We are aware that our study has some limitations. First, the present study did not randomize patients by treatment, but it is based on a retrospective analysis of prospectively collected data. Second, the number of missing data for outcome measures might have influenced the final outcome. Third, reasons for the treatment choices were not recorded; it is likely that these choices were influenced by center-specific standards regarding the treatment of minor stroke patients with LVO and unmeasurable factors related to individual physician's decision, which might have influenced our key findings. Finally, data on collateral circulation are not available.

Notwithstanding these limitations, our study confirms data from French and German centers in a large Italian cohort of minor stroke patients with LVO from prospective multicenter registries, reflecting real-life practice.

Conclusions

Our study shows that in patients with minor stroke and LVO in the anterior circulation, IVT <4.5 h after symptom onset plus MT <6 h after symptom onset was significantly associated with unfavorable shift on 24-h ICH types and higher rate of PH and sICH at 24 h as compared with IVT alone within 4.5 h after symptom onset. However, no difference was reported between the groups on 3-month functional outcome measures.

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Declarations

Ethical approval The present study was in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

Informed consent Informed consent to use anonymized and aggregated data for participation in the studies including stroke patients treated

with acute revascularization treatments was obtained in all patients of each center.

Conflict of interest MC: consultancy or advisory board fees or speaker's honoraria from Boehringer Ingelheim, Pfizer/Bristol Meyer Squibb, and Daiichi Sankyo. MS: consultancy fees from Proctorship for Medtronic. AS: consultancy fees from Stryker. MB: consultation fees from Stryker, Penumbra. AZ: speaker fees and consulting fees from Boehringer Ingelheim, Medtronic, Cerenovus, and advisory board from Daiichi Sankyo and Boehringer Ingelheim and Stryker. ADV: consultancy fees from Boehringer Ingelheim and Daiichi Sankyo. All other authors report no conflicts of interest.

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