Original research

Outcome of patients with dissecting versus atherosclerotic tandem occlusion acute ischemic stroke

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ABSTRACT

Background The different pathophysiological mechanisms leading to tandem occlusion (TO), namely arterial dissection or atherosclerosis, may have an impact on the outcome of patients with acute ischemic stroke (AIS) undergoing endovascular thrombectomy (EVT).

Methods Consecutive AIS patients with occlusion of the cervical internal carotid artery and concomitant intracranial large vessel occlusion who received EVT between 2011 and 2023 as part of the Italian Registry of Endovascular Treatment in Acute Stroke (IRETAS) were deemed eligible. We compared clinical and radiological outcomes of patients with dissecting TO versus atherosclerotic TO by the propensity score matching approach.

Results Overall, 2148 patients (mean age 69.3±12.8 years; males 64.5%) qualified for the analysis. Of these, 236 (10.9%) had dissecting TO, and 1912 (89.1%) atherosclerotic TO. As expected, patients with dissecting TO stroke were younger and had a lower burden of major cardiovascular risk factors. In the matched cohort, we observed no difference between the two groups in either 90-day functional independence (OR 1.33; 95% CI 0.94 to 1.83; p=0.115) or in any of the secondary endpoints, except for a reduced risk of parenchymal hematoma type 2 (OR 0.37; 95% CI 0.14 to 0.98; p=0.046) in the group of patients with dissecting TO stroke, which, however, did not affect patient outcome.

Conclusions The outcome of patients undergoing EVT because of dissecting TO stroke does not differ from that of patients with atherosclerotic TO stroke. The etiology of the underlying vascular lesion should not be regarded as a contraindication to EVT procedures in these cases.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ The best treatment approach in cases of acute ischemic stroke due to tandem occlusion (TO), defined as simultaneous occlusion of an intracranial artery and ipsilateral occlusion or high-grade stenosis of a cervical artery, is uncertain, and it may vary according to the pathophysiological mechanism underlying the vessel lesion.

WHAT THIS STUDY ADDS

⇒ This large multicenter study from Italy compares two groups of patients with TO stroke defined by the most common of such mechanisms, atherosclerotic TO versus dissecting TO, and shows that the specific etiology of tandem lesion is not associated with a difference in either short-term functional outcomes or other clinical or radiological endpoints.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Our findings suggest that the etiology of the underlying vascular lesion should not be regarded as a contraindication to endovascular thrombectomy procedures in patients with TO acute ischemic stroke.

BACKGROUND

Tandem lesions, defined as simultaneous occlusion of an intracranial artery and ipsilateral occlusion or high-grade stenosis of a cervical artery, account for up to 20% of acute ischemic stroke (AIS) cases due to large vessel occlusion (LVO).[1] Despite the established benefits of endovascular thrombectomy (EVT) for AIS, the evidence from randomized controlled trials (RCTs) demonstrating the efficacy of EVT in tandem lesions stroke is less convincing, both because they included patients with tandem lesions in limited numbers and because they were not specifically designed to evaluate the safety and efficacy of EVT in these cases.[1 2] This leaves substantial uncertainty regarding the best treatment approach in these cases, so that, in clinical practice, neurointerventionalists have to make decisions based on evidence from observational studies, meta-analyses of subgroups from RCTs, and expert opinion.[2–4] Further complicating the issue is the fact that tandem lesions can be the result of different pathophysiological mechanisms, with theoretical implications for the management of the extracranial vessel occlusion and impact on patient outcomes. The most common of such mechanisms is rupture of an extracranial atherosclerotic plaque with superimposed thrombosis leading to local occlusion and subsequent distal occlusion via artery-to-artery embolization (atherosclerotic tandem lesions; 60–70% of cases). Alternatively, a dissection in the cervical portion of the artery may cause local occlusion with later propagation of thromboemboli to the intracranial circulation (dissecting tandem lesions; 20–30% of cases). Other mechanisms, including embolization from a chronic total occlusion ("stump embolization") or a remote embolus (from the heart, aorta, or the venous circulation), which may lodge in a cervical vessel and partially decompose with further embolization to the intracranial circulation, are uncommon.[1] To date, studies investigating whether the effect of EVT in AIS due to tandem lesions varies according to lesion etiology have been limited and have yielded inconsistent results.[5–8] To fill this gap, we compared clinical and radiological outcomes of patients with atherosclerotic tandem lesions with those of patients with dissecting tandem lesions, selected from a large cohort of Italian patients undergoing EVT for AIS.

METHODS

We followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines[9] (online supplemental material).

Study design and population

The Italian Registry of Endovascular Treatment in Acute Stroke (IRETAS) collects clinical and instrumental data on EVT for AIS. It includes all consecutive patients undergoing these procedures according to current guidelines, with voluntary participation from 55 Italian academic and hospital institutions. Organizational details and the objectives of this prospective, multicenter, national registry are described elsewhere.[10] The IRETAS was approved by the Italian Ministry of Health in 2006. The use of anonymized data for retrospective analyses does not require additional approvals.

Patients admitted at the participating centers between January 2011 and December 2023 were identified. Inclusion criteria were as follows: (1) age 18 years or older with no limitations on pre-stroke functional status; (2) time from symptom onset or last-time known well (LKW) ≤24 hours; (3) AIS with LVO of anterior circulation including terminal internal carotid artery (ICA), segments M1/M2 of the middle cerebral artery or segment A1 of the anterior cerebral artery and concomitant occlusion of cervical ICA (*anterior TO, a-TO*); and (4) treatment with any EVT modality for clot removal, with or without prior intravenous thrombolysis administration.

The etiology of the cervical arterial lesion was defined according to its morphology on digital subtraction angiography (occluded ICA with no contrast filling at the level of the carotid bulb with sign of atherosclerotic disease (calcifications) for atherosclerosis and suprabulbar flame-shaped lesion for dissection). A double lumen contour with a narrow eccentric true lumen (string sign), periluminal hematoma, and/or widening of the artery (pseudoaneurysm) on CT angiography provided support to the diagnosis of cervical artery dissection (CeAD).[11] Endovascular and medical therapeutic interventions were administered to all patients in accordance with published guidelines or, in cases where there was no clear evidence in favor of a treatment, at the discretion of the physician in charge of the patient. The neurointerventional approach of extracranial vessels was based on the operator's preference and included stenting with/without angioplasty or EVT without stenting/angioplasty. If a stent was deployed in the ICA, the type of antiplatelet therapy was administered according to the local protocol of each center.

Study variables

Demographic and clinical variables were collected and defined as reported previously[12] (see also online supplemental methods).

Outcome measures

The primary efficacy outcome was good functional outcome, defined as a modified Rankin Scale (mRS) score of 0 to 2 at the 90-day follow-up visit. Secondary outcomes were: (1) 90-day overall shift in the distribution of mRS; (2) successful recanalization, defined as modified Thrombolysis in Cerebral Infarction (TICI)[13] score 2b-3; (3) excellent recanalization, defined as TICI score 3; (4) distal embolization, defined as emboli to new territory and emboli to distal territory; and (5) early neurological improvement (ENI), defined as a difference between baseline and discharge National Institutes of Health Stroke Scale (NIHSS) score of ≥4 points.[14]

Secondary safety outcomes were: (1) symptomatic intracerebral hemorrhage, defined according to the European Collaborative Acute Stroke Study (ECASS) III criteria as any cerebral hemorrhage accompanied by clinical deterioration, with an increase of ≥4 points on the NIHSS or death[15]; (2) parenchymal hematoma type 2 (PH-2); (3) petechiae within the infarcted area

(hemorrhagic infarction (HI) 1 and 2) according to the ECASS II classification of hemorrhagic infarction[16]; (4) in-hospital mortality; and (5) 90-day mortality.

Statistical analysis

Descriptive statistics were used to summarize the study cohort overall and by exposure group (dissecting TO vs atherosclerotic TO). Continuous variables were summarized as mean (SD) or median (IQR) according to distribution, and categorical variables as counts (percentages). Between-group differences were explored with t-tests/Mann–Whitney U tests and χ^2/Fisher's exact tests as appropriate, to characterize baseline imbalances. Univariable logistic regression was performed to estimate the unadjusted association between the exposure group and primary and secondary outcomes. As expected, the two groups defined by the etiology of extracranial arterial lesion (dissecting TO and atherosclerotic TO) differed significantly in their baseline characteristics. Therefore, a propensity score matching (PSM) approach was adopted to reduce potential confounding and allow a more reliable assessment of the association with the outcome.[17] The propensity score was estimated through logistic regression including a predefined set of covariates, selected based on prior literature, as they were known to be associated both with the exposure (etiology of extracranial arterial lesion) and the outcome. Variables showing highly unbalanced distributions (<10% in one category) were excluded to avoid unstable estimates. The appropriate matching strategy was identified as summarized in the Supplement (see online supplemental methods). In addition to dichotomous analyses, an ordinal shift analysis was performed to evaluate differences across the entire distribution of mRS scores. The analysis was conducted in the PSM cohort using a proportional odds cumulative logit mixed model, including a random intercept for each matched set (subclass) to account for within-set correlation. Matching weights derived from the propensity score model were incorporated as case weights.

Adjusted models included age, emergent stenting, and pre-event mRS as covariates. Analyses were conducted using available data only; no imputation of missing data was performed. Results are reported as ORs with 95% CIs. A two-sided p value<0.05 (two-tailed) was considered statistically significant. Analyses were conducted in R 4.4.2 (RStudio, Posit, Boston, MA, USA).[18]

RESULTS

Of the 26 799 patients with AIS who underwent EVT included in the IRETAS database during the study period, 2776 (10.4%) had a TO and were considered for participation. Of these, 628 (22.6%) were excluded because they did not undergo any intracranial treatment (n=97; 3.5%), had unknown or other TO etiology (n=41; 1.5%), posterior circulation TO (p-TO, n=333; 12.0%), or were lost to follow-up (n=157; 5.6%), leaving 2148 patients (mean age 69.3±12.8 years; males 64.5%; n=2107 (93.4%) since 2015) eligible for inclusion in the present study. Among them, 236 (10.9%) had a dissecting TO and 1912 (89.1%) an atherosclerotic TO (figure 1).

Baseline demographic, clinical, and radiological characteristics of the study group according to the etiology of TO are summarized in table 1. As expected, patients in the CeAD group were younger (mean age 55.1±10.7 vs 71.1±11.8 years), had a lower burden of cardiovascular risk factors (41.9% vs 7.7%, no major cardiovascular risk factors) and vascular comorbidities, and were less likely to be taking medication for the prevention of thrombotic events (7.6% vs 34.6%) at the time of the index event compared with patients in the atherosclerotic group. Similarly, they had a lower degree of pre-event functional impairment (pre-event mRS 0, 95.3% vs 77.2%) and less severe stroke (median NIHSS score 16 (IQR 9) vs 17 (IQR 8)) at the time of hospital admission. Regarding the time metrics for interventional procedures, despite the shorter time interval between symptom onset and the start of EVT in the dissecting TO group (226 (IQR 145) vs 250 (IQR 173) minutes), the time to achieve successful reperfusion from groin puncture tended to be longer compared with that in the atherosclerotic group (95 (IQR 69) vs 85 (IQR 60) minutes).

Matching procedures

For the PSM analysis, among the evaluated strategies, caliper matching with a 1:3 ratio, caliper width of 0.20, and no replacement provided the best balance between covariate balance and statistical power. This approach achieved the lowest standardized mean difference (SMD=0.024), indicating excellent covariate balance, and the highest composite score (0.825) across all tested methods. The matched cohort included 713 patients (224 dissecting TO and 489 atherosclerotic TO; online supplemental table S1; figures S1 and S2).

Primary endpoint

Although in the unmatched cohort stroke patients with dissecting TO showed a higher rate of functional independence at 90 days compared with those with atherosclerotic TO (62.7% vs 42.2%; OR 2.31; 95% CI 1.75 to 3.06; p≤0.001), in the matched cohort we observed no significant difference in the primary outcome between the two groups (OR 1.33; 95% CI 0.94 to 1.83; p=0.115; table 2). Similarly, ordinal shift analysis using a proportional odds mixed model showed a significant favorable shift of the entire mRS distribution in the group with dissecting TO stroke compared with the group with atherosclerotic TO stroke (OR 1.34; 95% CI 1.01 to 1.78; p=0.046), but such an association was not confirmed after adjustment for age, emergent stenting, and pre-event mRS (adjusted OR (aOR) 1.30; 95% CI 0.97 to 1.75; p=0.075; Figure 2).

In multivariable analysis within the matched cohort, emergent stenting was independently associated with a higher likelihood of functional independence at 90 days (OR 2.73; 95% CI 1.86 to 4.01; p≤0.001). Conversely, diabetes mellitus (OR 0.48; 95% CI 0.24 to 0.95; p=0.035) and longer LKW-to-recanalization time (>6 hours; OR 0.46; 95% CI 0.32 to 0.67; p≤0.001) were associated with reduced odds of favorable outcome.

Interaction analysis

In the analysis of 90-day functional independence, no significant interactions were found across subgroups defined by the prespecified key variables LKW-to-recanalization time (<6 hours vs ≥6 hours), emergent carotid stenting, or diabetes (online supplemental figure S3).

Secondary endpoints

In the unmatched cohort, no significant differences were observed between dissecting TO strokes and atherosclerotic TO strokes in terms of successful (TICI 2b-3; 74.2% vs 73.7%; OR 1.11; 95% CI 0.81 to 1.54; p=0.539) or excellent (TICI 3; 48.3% vs 46.9%; OR 1.10; 95% CI 0.84 to 1.45; p=0.497) intracranial recanalization. Dissecting TO was associated with a lower risk of symptomatic intracranial hemorrhage (5.9% vs 9.9%; OR 0.57; 95% CI 0.31 to 0.96; p=0.048), parenchymal hematoma type 2 (2.5% vs 6.7%; OR 0.36; 95% CI 0.14 to 0.75; p=0.015), in-hospital mortality (4.2% vs 11.3%; OR

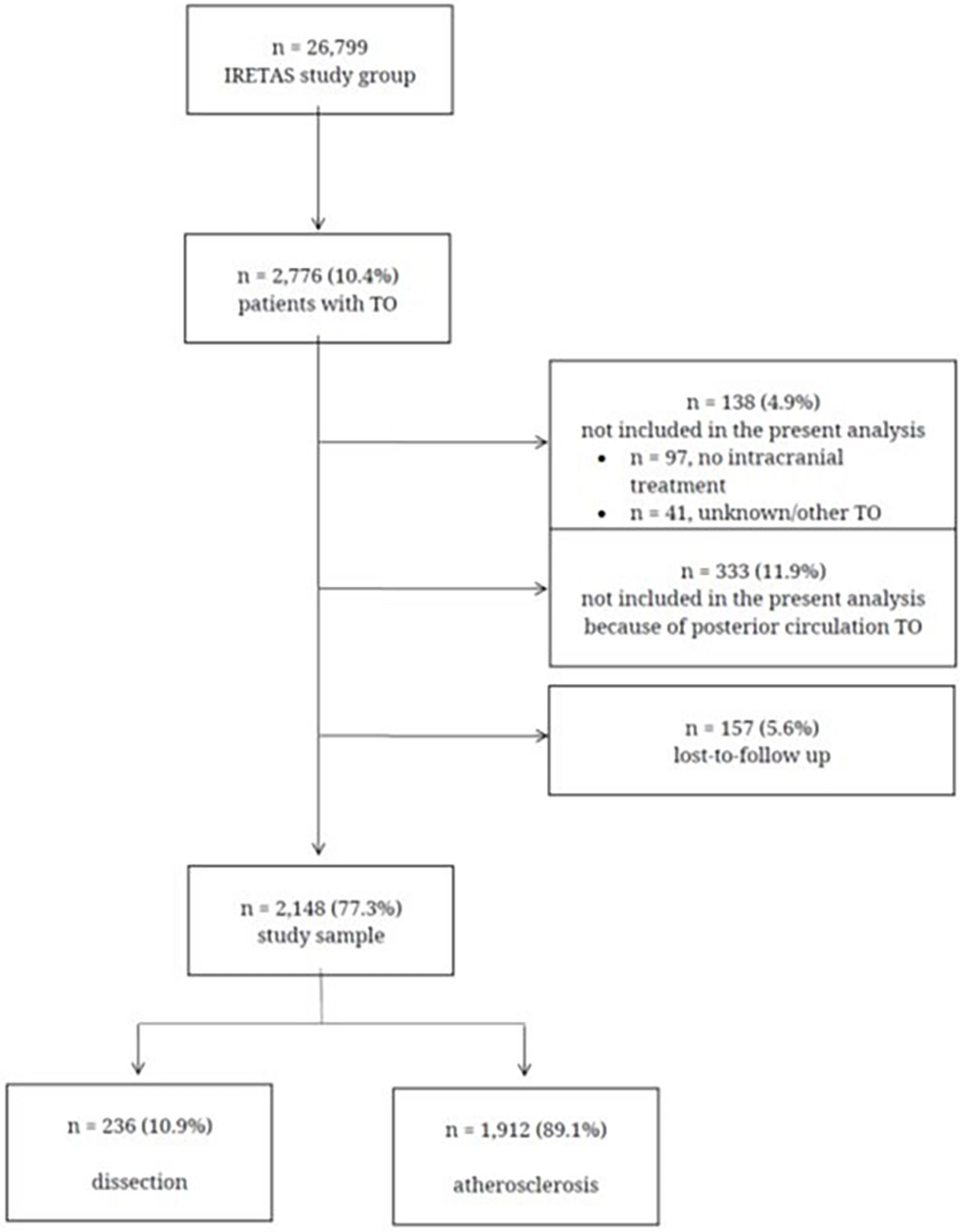

Figure 1 Participants' enrollment and eligibility criteria flowchart. IRETAS, Italian Registry of Endovascular Treatment in Acute Stroke; TO, tandem occlusion

0.36; 95% CI 0.18 to 0.66; p=0.002), and 90-day mortality (8.1% vs 22.1%; OR 0.31; 95% CI 0.19 to 0.49; p≤0.001). No differences were observed for petechial hemorrhage (15.3% vs 16.0%; OR 0.94; 95% CI 0.64 to 1.35; p=0.744), early neurological improvement (44.1% vs 41.4%; OR 1.38; 95% CI 0.99 to 1.66; p=0.063), or distal embolism (11.4% vs 10.1%; OR 1.14; 95% CI 0.73 to 1.73; p=0.537). After PSM, no difference was observed between the two groups for any of the secondary outcome measures, except for a reduced risk of parenchymal hematoma type 2 (OR 0.37; 95% CI 0.14 to 0.98; p=0.046) among dissecting TO strokes compared with atherosclerotic TO strokes (table 2).

DISCUSSION

Adding to the controversy over optimal management strategies for patients with TO stroke is the theoretical possibility that this is not a homogeneous category but, rather, several features could be identified that contribute to influencing patient outcome, thus leading to individualized treatment approaches. The etiology of the underlying vascular lesion is one of these features. Actually, it cannot be ruled out a priori that the outcome of patients with dissecting TO stroke differs from that of patients with atherosclerotic TO stroke because of the peculiar biology of these two clinical entities. The results of our study, conversely, do not reveal any differences in the clinical and radiological outcomes of the

Table 1 Demographic, clinical, and radiological characteristics of the cohort according to the etiology of the arterial lesion

Parameter	Dissecting TO (n=236)	Atherosclerotic TO (n=1912)	P value
Age (years), mean±SD	55.1±10.7	71.1±11.8	≤0.001
Sex, n (%)			
Male	189 (80.1)	1197 (62.6)	≤0.001
Vascular risk factors, n (%)			
Hypertension	74 (31.4)	1222 (63.9)	≤0.001
Dyslipidemia	30 (12.7)	527 (27.6)	≤0.001
Diabetes	11 (4.7)	332 (17.4)	≤0.001
Smoking	39 (16.5)	517 (27.0)	≤0.001
No major cardiovascular risk factors	99 (41.9)	148 (7.7)	≤0.001
Comorbidities, n (%)			
Atrial fibrillation	11 (4.7)	339 (17.7)	≤0.001
Coronary artery disease	4 (1.7)	176 (9.2)	≤0.001
Heart failure	2 (0.8)	93 (4.9)	0.002
History of brain ischemia	6 (2.5)	95 (5.0)	0.104
Pre-event mRS score			
0	223 (95.3)	1436 (77.2)	≤0.001
1	6 (2.6)	233 (12.5)	
2	4 (1.7)	108 (5.8)	
3	1 (0.4)	53 (2.9)	
4	0 (0.0)	15 (0.8)	
5	0 (0.0)	14 (0.8)	
Prior therapy, n (%)			
Antiplatelets	16 (6.8)	550 (28.8)	≤0.001
Oral anticoagulants	2 (0.8)	111 (5.8)	≤0.001
Statins	12 (5.1)	352 (18.4)	≤0.001
Admission NIHSS score, median (IQR)	16(10-19)	17(12-20)	0.002
ASPECTS, median (IQR)	9(8-10)	9(8-10)	0.501
Intracranial occlusion location, n (%)			
ICA	42 (17.8)	349 (18.3)	0.314
MCA-M1	164 (69.5)	1384 (72.4)	
MCA-M2	30 (12.7)	175 (9.2)	
A1	0 (0.0)	4 (0.2)	
Emergent stenting, n (%)	130 (55.1)	1062 (55.5)	0.893
Sedation type, n (%)			
No sedation/anesthesia	16 (9.3)	272 (18.0)	0.007
Conscious sedation (CS)	60 (34.9)	467 (31.0)	
General anesthesia (GA)	86 (50.0)	725 (48.1)	
Switch from CS to GA	10 (5.8)	43 (2.9)	
Number of passes, median (IQR)	3 (2–4)	3 (2–4)	0.333
Intravenous thrombolysis, n (%)	131 (57.7)	876 (47.1)	0.003
Intraprocedural heparin, n (%)	6 (2.5)	117 (6.1)	0.025
Intraprocedural antiplatelets, n (%)	39 (16.5)	264 (13.8)	0.258
IA-tPA, n (%)	6 (2.5)	57 (3.0)	0.840
Time metrics (min), median (IQR)			
LKW to puncture	226 (170–315)	250 (180–353)	0.006
LKW to recanalization	339 (260–418)	345 (268–450)	0.432
Puncture to recanalization	95 (60–129)	85 (58–118)	0.004
Procedural complications, n (%)			
Subarachnoid hemorrhage	12 (5.1)	86 (4.5)	0.684
Pseudoaneurysm	1 (0.4)	12 (0.6)	1.000
Other complications	12 (5.1)	80 (4.2)	0.496
mRS score 0–2 at discharge, n (%)	70 (40.7)	444 (29.9)	0.004

A1, segment A1 of the anterior cerebral artery; ASPECTS, Alberta Stroke Program Early CT Score; IA-tPA, intra-arterial tissue plasminogen activator; ICA, internal carotid artery; LKW, last-time known well; MCA, middle cerebral artery; mRS, modified Rankin scale; NIHSS, National Institute of Health Stroke Scale; TO, tandem occlusion.

two groups, except for a lower tendency to bleeding within the infarcted area among patients with dissection.

Our main findings are entirely consistent with those derived from the Thrombectomy in Tandem Lesions (TITAN) collaborative network by Gory and co-workers,[5] from the Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands (MR CLEAN) registry by Compagne and co-workers,[6] and from the more recent retrospective multicenter cohort registry by Galecio-Castillo and co-workers,[8] who observed that patients with TO stroke undergoing EVT have similar 3-month outcomes regardless of the etiology of the underlying vascular lesion and are, indirectly, reinforced by the results of the recent multicenter observational CERES-TANDEM study,[19] which showed no impact of atherosclerosis or dissection etiology on the effect of emergent carotid stenting in patients with tandem lesion stroke. Conversely, they are in apparent disagreement with those derived from the multicenter, retrospective study conducted by Da Ros and co-workers[7] who detected 90-day clinical independence after EVT more often among patients with dissecting TO stroke than among those with atherosclerotic TO stroke.

As regards secondary endpoints, our findings are also broadly in line with those of the other comparative studies and further emphasize the assumption that in patients with TO AIS receiving EVT procedures, the etiology of the underlying vascular lesion does not have an impact on any of the patients' outcomes. The only notable exception in this regard is the observation by Galecio-Castillo and co-workers[8] that ICA dissection as a cause of TO stroke is associated with higher rates of distal embolism and lower rates of successful recanalization than atherosclerotic lesions when undergoing EVT procedures, a finding which, if confirmed, could have implications for the choice of the most appropriate therapeutic approach in these cases, suggesting the opportunity to implement strategies aimed at reducing the rate of distal embolization.

The reasons for the discrepancies in the results arising from the comparative studies published to date, including our own, are far from obvious. Notwithstanding, differences in baseline characteristics of the patient cohorts as well as in several methodological aspects are noteworthy and should be considered when trying to explain their seemingly different conclusions. First, the assessment of the burden of major cardiovascular risk factors reveals a risk profile that varies substantially between the cohorts. From this point of view, the subgroup of patients with dissection in the study by Galecio-Castillo and co-workers[8] exhibits baseline features much more similar to those of patients with a degenerative vascular disease than to those of patients with

Table 2 Primary and secondary outcomes according to the etiology of the arterial lesion

Outcome	Dissecting TO (n=236)	Atherosclerotic TO (n=1912)	Unmatched comparison OR (95% CI)	Unmatched comparison P value	Dissecting TO (n=224)	Atherosclerotic TO (n=489)	Matched analysis OR (95% CI)	Matched analysis P value
Primary outcome								
mRS score 0–2 at 90 days, n (%)	148 (62.7)	806 (42.2)	2.31 (1.75 to 3.06)	<0.001	138 (61.6)	260 (53.2)	1.33 (0.94 to 1.83)	0.115
Secondary outcomes								
Successful intracranial recanalization (TICI 2b-3), n (%)	175 (74.2)	1409 (73.7)	1.11 (0.81 to 1.54)	0.539	166 (74.1)	355 (72.6)	1.31 (0.89 to 1.93)	0.177
Excellent intracranial recanalization (TICI 3), n (%)	114 (48.3)	896 (46.9)	1.1 (0.84 to 1.45)	0.497	108 (48.0)	222 (45.4)	1.23 (0.88 to 1.71)	0.234
Symptomatic ICH, n (%)	14 (5.9)	189 (9.9)	0.57 (0.31 to 0.96)	0.048	13 (5.8)	32 (6.5)	0.94 (0.47 to 1.88)	0.862
Parenchymal hematoma type 2, n (%)	9 (2.5)	129 (6.7)	0.36 (0.14 to 0.75)	0.015	5 (2.2)	28 (5.7)	0.37 (0.14 to 0.98)	0.046
Petechial hemorrhage, n (%)	36 (15.3)	306 (16.0)	0.94 (0.64 to 1.35)	0.744	35 (15.6)	66 (13.5)	1.26 (0.79 to 2.01)	0.336
ENI, n (%)	104 (44.1)	791 (41.4)	1.38 (0.99 to 1.96)	0.063	99 (44.2)	219 (44.8)	0.96 (0.63 to 1.44)	0.831
Distal embolism	27 (11.4)	194 (10.1)	1.14 (0.73 to 1.73)	0.537	25 (11.2)	49 (10%)	1.11 (0.65 to 1.89)	0.710
In-hospital mortality, n (%)	10 (4.2)	216 (11.3)	0.36 (0.18 to 0.66)	0.002	10 (4.5)	35 (7.2)	0.66 (0.31 to 1.41)	0.285
90-day mortality, n (%)	19 (8.1)	422 (22.1)	0.31 (0.19 to 0.49)	≤0.001	19 (8.5)	64 (13.1)	0.73 (0.42 to 1.27)	0.269

ENI, early neurological improvement; ICH, intracerebral hemorrhage; mRS, modified Rankin Scale; TICI, Thrombolysis in Cerebral Infarction; TO, tandem occlusion.

a non-atherosclerotic vasculopathy.[20–22] Second, there is heterogeneity among the studies in the definition of tandem lesion, for which standardization would be advisable. Thresholds for ICA stenosis vary from ≥70% in the study by Galecio-Castillo and co-workers[8] to ≥90% in the study by Da Ros and co-workers as well as in that of Gory and co-workers,[5 7] or to complete occlusion in the study by Compagne and co-workers[6] and in ours, a discrepancy which, along with other factors, might potentially influence the outcome of patients with TO stroke.[23] Given the primary aim of our study, we deemed that limiting the analysis to the category for which the definition of tandem lesion is less ambiguous, namely "ICA occlusion," would ensure readily interpretable results. Conversely, we are aware that this precludes the possibility of making a direct comparison of our findings with those of the studies that employed different thresholds for ICA stenosis. Third, although the observational and retrospective design represents the main drawback of all the comparative studies, only in the analysis by Galecio-Castillo and co-workers and in ours was an attempt made to reduce the obvious imbalance between the two groups of patients by the application of PSM, a robust method of adjustment for confounders that minimizes their effects. This is a strength of such analyses over others based on traditional, less adequate methods of multivariate adjustment but, at the same time, renders the results of the studies not fully comparable. Another point of strength of our analysis is that although retrospective and not derived from a population-based study, it is derived from a prospective, country-wide registry of patients with AIS undergoing EVT at the main stroke referral centers in Italy. This not only facilitated the inclusion of a large number of subjects, which ensures statistically stable results, but also allows generalization of our findings to a real-life population. Notwithstanding, we acknowledge some notable limitations. Although PSM was used to mitigate the imbalance between the two groups of patients being compared, decision-making as to individual treatment was ultimately at the discretion of the treating practitioner at each center, leading to a wide array of treatment options that are challenging to adjust for accurately. For instance, unmeasured factors, including vascular anatomy, collateral status, or other clinical variables, may have influenced patient outcomes and have led to inherent bias. In

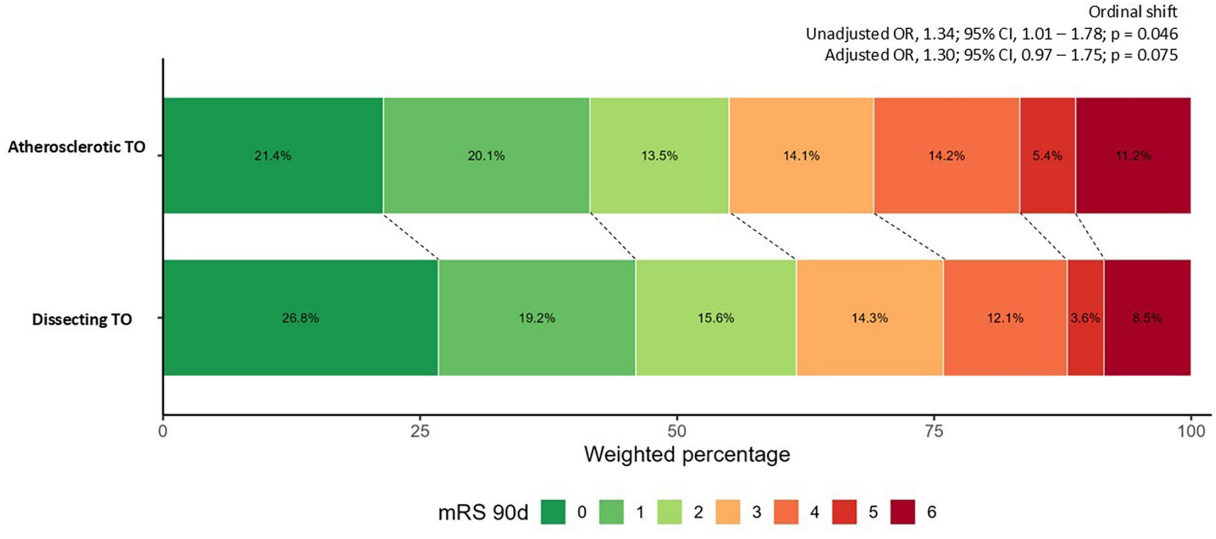

Figure 2 Distribution of 90-day modified Rankin Scale (mRS) scores in patients with tandem occlusion (TO) stroke secondary to cervical carotid artery dissection or carotid atherosclerosis.

addition, radiological image analyses of angiograms were not centralized nor blinded to TO etiology, potentially introducing interobserver variability and interpretive bias, just as the lack of central adjudication for the primary and some secondary outcomes introduces a potential risk of measurement bias. Even though these potential drawbacks cannot be disregarded, we still acknowledge the inherent challenges of implementing such adjudications in a large multicenter study. Finally, our results should be interpreted carefully considering the evolution of techniques and devices as well as of treatment protocols over the years, which could lead to some heterogeneity in patient outcomes in such a long-term study as ours. Notwithstanding this, since more than 93% of the study population was treated after 2015, following the widespread adoption of modern EVT techniques and contemporary standards of care, it is highly unlikely that this had a significant impact on our results.

CONCLUSIONS

In the largest retrospective cohort study of patients with TO AIS undergoing EVT who were compared based on the etiology of the vascular lesion, we have provided novel evidence that the specific etiology of tandem lesion is not associated with differences in either short-term functional outcomes or other clinical or radiological endpoints. A small but significant increase in hemorrhagic transformation of the infarcted lesion associated with atherosclerotic TO was observed; however, this did not appear to affect patient outcome. Our findings suggest that the etiology of the underlying vascular lesion should not be regarded as a theoretical contraindication to EVT procedures in patients with TO AIS.

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