RESEARCH ARTICLE

Emergent Carotid Stenting for Acute Anterior Circulation Ischemic Stroke With Tandem Lesions

The Multicenter CERES-TANDEM Study

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Abstract

Background and Objectives

The management of anterior circulation tandem lesion stroke remains controversial, given its under-representation in randomized thrombectomy trials and uncertainty regarding optimal extracranial carotid intervention. We aimed to determine whether emergent carotid stenting (eCAS) during endovascular thrombectomy (EVT) for anterior circulation tandem lesions improves 90-day functional outcomes compared with a no-stenting strategy.

Methods

We conducted an international multicenter longitudinal retrospective cohort study (CERES-TANDEM, NCT06965036) of consecutive adults treated at 49 comprehensive stroke centers in Europe, North America, and Singapore for anterior circulation acute ischemic stroke due to tandem lesions from January 1, 2018, to December 31, 2024. Exclusion criteria were primary hemorrhagic stroke, absence of intracranial occlusion, presentation >24 hours from symptom onset, and age younger than 18 years. We compared 90-day modified Rankin Scale (mRS) scores between participants receiving eCAS and those receiving no stenting during EVT. The primary estimand was mRS shift, analyzed by stabilized inverse probability of treatment weighting (IPTW)–weighted ordinal regression. Additional estimands were direct-effect estimand adjusting for successful recanalization (defined as Thrombolysis in Cerebral Infarction grade 2b or higher) and symptomatic intracranial hemorrhage (sICH) (estimand 2) and stratum estimand restricting to never-crossers (estimand 3).

Results

Of 4,053 patients (mean age 70 years, 65.5% female), 2,522 underwent eCAS and 1,531 received no stenting. After IPTW, eCAS was associated with an improved 90-day functional outcome (common odds ratio (OR) 1.31; 95% CI 1.17–1.47;$p < 0.001$) and higher odds of mRS score 0–1 (OR 1.27; 95% CI 1.08–1.50; $p = 0.005$) and mRS score 0–2 (OR 1.30; 95% CI 1.13–1.51; $p < 0.001$), without a significant increase in sICH (OR 1.21; 95% CI 0.93–1.56; $p = 0.15$). Findings were consistent in direct-effect (common OR 1.17; 95% CI 1.04–1.31; $p = 0.008$) and stratum (common OR 1.37; 95% CI 1.21–1.55; $p < 0.001$) estimands. There was no interaction for intracranial occlusion site, IV thrombolysis, sedation technique, EVT approach, or access site. Sensitivity analysis including recanalization in IPTW-weighted estimand 1 framework confirmed the association of eCAS with improved 90-day functional outcomes (common OR 1.14, 95% CI1.02–1.27, $p = 0.008$).

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Glossary

cOR = common odds ratio; **eCAS** = emergent carotid stenting; **END** = early neurologic deterioration; **EVT** = endovascular thrombectomy; **IPTW** = inverse probability of treatment weighting; **IVT** = IV thrombolysis; **mRS** = modified Rankin Scale; **NIHSS** = NIH Stroke Scale; **OR** = odds ratio; **OTG** = onset to groin; **sICH** = symptomatic intracranial hemorrhage; **TICI** = Thrombolysis in Cerebral Infarction.

Discussion

In this large real-world cohort, eCAS during EVT for anterior circulation tandem lesions was associated with superior 90-day functional recovery without increased hemorrhagic risk. These findings support consideration of eCAS in clinical practice and warrant confirmation in randomized trials.

Trial Registration Information

Registered in clinicaltrials.gov, NCT06965036.

Classification of Evidence

This study provides Class II evidence that in patients with stroke due to anterior circulation tandem lesions, eCAS during EVT improves 90-day functional outcomes compared with EVT alone.

Introduction

Tandem lesion stroke, defined as concurrent extracranial carotid high-grade stenosis or occlusion and intracranial vessel occlusion, remains a distinct and underinvestigated subset of acute ischemic strokes. Several landmark randomized controlled trials have established endovascular thrombectomy (EVT) as the standard treatment for large vessel occlusions.[1,2] However, these studies included few participants with tandem lesions, limiting the generalizability of their findings.[2-4] In the Highly Effective Reperfusion Evaluated in Multiple Endovascular Stroke (HERMES) meta-analysis, only 122 of 1,287 patients had tandem lesion stroke, leading to a critical gap in current guidelines.[5] In a pooled analysis of the Iproving Reperfusion Strategies in Acute Ischaemic Stroke (IRIS) bridging IV thrombolysis to thrombectomy trials, 340 of 2,267 patients had tandem lesion stroke, with most of the trials lacking anatomical data on the tandem occlusions,[4] precluding the ability to detect clinically important effects on functional and safety outcomes.[6] Optimal management strategies—particularly concerning emergent stenting of the extracranial carotid artery—thus remain highly controversial.[3,6,7]

Although observational studies suggest potential benefits of emergent carotid stenting (eCAS), they also highlight risks such as hemorrhagic transformation and clinical deterioration, underscoring the need for large-scale data.[7] Identification of features that could stratify the potential benefit of eCAS in patients with anterior circulation tandem lesions could guide more individualized treatment strategies.

We conducted a multicenter study to determine whether eCAS during EVT for anterior circulation tandem lesions improves 90-day functional outcomes compared with a no-stenting strategy.

Methods

Study Design and Participants

The CERES-TANDEM (CollaborativE Research on Emergent Stenting in TANDEM lesion stroke) study was an investigator-initiated longitudinal retrospective study, pooling data from 49 comprehensive high-volume stroke centers in Europe (41 sites), North America (7 sites), and Singapore (1 site). A steering committee designed and supervised the study, supported by an independent monitoring committee.

We included consecutive patients with imaging-confirmed tandem lesion acute ischemic stroke between January 1, 2018, and December 31, 2024, undergoing EVT for clot removal. Tandem lesion was defined as the simultaneous occurrence of a cervical carotid occlusion or high-grade stenosis (>75%), demonstrated by either CT or MR-based imaging in the hyperacute setting, which caused the acute ischemic stroke. The presence of carotid tandem lesions was defined by each site's investigators. We excluded patients who had no intracranial arterial occlusion, those with primary hemorrhagic stroke or with hemorrhagic infarction at the time of first imaging, and those presenting more than 24 hours after symptom onset/last seen well. Only adults (>18 years at the time of stroke) were included, with no limitations in baseline functional status, stroke severity (NIH Stroke Scale [NIHSS] score 1 or higher), baseline ASPECTS, or tandem occlusion etiology, aiming to reproduce real-world care. The study report follows the Strengthening the Reporting of Observational Studies in Epidemiology guideline.[8]

Data Collection and Definitions

We collected demographic data, vascular risk factors, baseline functional status, treatment-related data, time metrics, recanalization status achieved, and the outcomes of interest (eTable 1, eFigure 1). All data regarding vascular imaging and the endovascular procedure were collected, including type of imaging; ASPECTS; perfusion-imaging volumes of cerebral blood flow–based core; Tmax-based penumbra; anterograde/retrograde approach; eCAS; stent placement and type; and antithrombotic regimen in the hyperacute, acute, and post-acute stages. We defined (1) large vessel occlusion (intracranial) as an occlusion of the internal carotid artery or middle cerebral artery M1 segment and medium vessel occlusion (intracranial) as any occlusion in the M2-M4 and A1-A4 segments; (2) high-intensity antithrombotic treatment as any treatment administered in the hyperacute stage (within 24 hours) with triple or dual antiplatelets, any use of IV glycoprotein IIb/IIIa inhibitors, or any combination of anticoagulation plus antiplatelet treatment, while low-intensity antithrombotic treatment was limited to single antiplatelet treatment. A predefined data frame and dictionary were shared with all participating centers. After data entry was completed, individual records entered by each site were reviewed by a team of neurologists and interventional neuroradiologists (M.R., V.T., F.D.). Case and center-specific queries were sent as needed to confirm data accuracy and validity, and data were consolidated through algorithm-generated queries for critical variables. Follow-up calls or meetings with sites were conducted as needed.

Study Outcomes

The primary outcome was the 90-day modified Rankin Scale (mRS) score shift, analyzed using an ordinal scale ranging from 0 to 6. Secondary outcomes were 90-day excellent outcome (mRS score 0–1) and good functional outcome (mRS score 0–2 or unchanged compared with the prestroke mRS score). Additional outcomes included (1) symptomatic intracranial hemorrhage (sICH) according to European Cooperative Acute Stroke Study (ECASS) III criteria[9]; (2) successful recanalization, defined as a Thrombolysis in Cerebral Infarction (TICI) scale score of 2b or higher at the intracranial site[10]; (3) early neurologic deterioration (END), defined as worsening of 4 points or more in the NIHSS score compared with the pre-EVT NIHSS score within 48 hours of EVT.

Outcomes were abstracted from available records and internal registries and were reviewed by site investigators. Before data set finalization, outcomes were consolidated through queries for re-adjudication in cases of missing variables. All outcome definitions were shared with sites and included in the data entry case report forms.

Statistical Analysis

Assuming a common odds ratio (cOR) of 1.2 for our primary outcome from our previous meta-analysis[3] and a 3% risk of dropouts/missing data, we planned to include 1,100 participants in no-stenting and eCAS groups to achieve 80% power to detect a meaningful difference at the 0.05 level.

Medians with interquartile ranges (IQRs) and means with SDs together with percentages were used to present the distribution of ordinal, continuous, and categorical variables. Baseline characteristics across groups were compared using the Pearson $\chi 2$ test for categorical variables and t test or the Kruskal-Wallis test, as appropriate, for continuous and ordinal variables. All analyses were conducted in accordance with the estimand framework (International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use, ICH; E9(R1)).[11,12] The estimand is represented here by the difference in outcomes between eCAS and no-stenting groups. The estimand is based on a scientific question of interest and can be applied to all study objectives.[11,12] We prespecified a total-effect estimand using treatment-policy strategy, a controlled direct-effect estimand adjusting for post-treatment recanalization and bleeding, and a defined-stratum estimand restricting the population to never-crossers. The primary outcome was compared between the eCAS and no-stenting strategies in patients with tandem lesion stroke.

The primary estimand (treatment-policy centered) aimed at identifying the effect of eCAS on mRS score, regardless of other interventional outcomes (total effect). The population included all participants, with the eCAS group represented by those undergoing eCAS and the no-stenting group including all those receiving any conservative treatment, regardless of any later crossover from the latter to the former intervention. A stabilized inverse probability of treatment weighting (IPTW) approach was used to adjust for baseline confounding between eCAS and no-stenting groups. The propensity score for receiving eCAS was estimated by logistic regression including a predefined set of variables (IPTW model) expected to potentially influence the indication: demographics and vascular risk factors (age, sex, hypertension, dyslipidemia, diabetes, smoking, atrial fibrillation, previous stroke or TIA, prestroke mRS score, previous stroke or TIA, previous antithrombotic therapy), index stroke–related data (witnessed stroke onset, imaging modality, ASPECTS, NIHSS score on admission, large or medium vessel occlusion, occlusion side), and treatment-related data (access route, type of anesthesia (general vs sedation), IV thrombolysis (IVT), onset-to-groin [OTG] time). Stabilized weights were applied in a weighted ordinal regression for the primary outcome to estimate the total effect (weighted ordinal regression; estimand 1). Results were reported as cOR with 95% CIs for shift toward a lower mRS score in the eCAS vs no-stenting group. The proportional odds assumption was assessed for violation. A sensitivity analysis included recanalization status in IPTW variables (reverse temporal approach).

We specified interaction analysis for access route, approach, large/medium vessel occlusion, type of sedation, IVT, and periprocedural antithrombotic treatment intensity in the context of estimand 1. For each group, we fitted a cumulative

proportional regression model, incorporating patient-level IPTW and adjusting for age, sex, prestroke mRS score, NIHSS score at admission, ASPECTS, atrial fibrillation, and OTG time. From each model, we extracted the interaction coefficient (β) and its standard error and reported the ratio of odds ratios (ROR = $e^{\hat{\beta}}$), 95% CI, and 2-sided Wald p values ($p_{interaction}$) for effect modification in a forest plot.

For estimand 1, we prespecified a sensitivity analysis to account for the potential impact of successful intracranial recanalization on eCAS indication (reverse temporal association; sensitivity analysis on estimand 1). We re-estimated IPTW including successful recanalization in the predefined set of covariates, to adjust for its potential influence on eCAS decision. Additional sensitivity analyses included center, region (Europe, Asia), and calendar year as covariates in the IPTW. We also calculated the E-value for the primary outcome in estimand 1 framework to estimate potential confounder effect.

A second estimand aimed at identifying the effect of eCAS on mRS not mediated by successful reperfusion or sICH (direct effect, estimand 2). In the full cohort, we included successful recanalization (TICI score 2b-3) and sICH as factors in the IPTW-weighted ordinal regression, reporting the adjusted cORs for eCAS (estimand 2).

A third stratum estimand restricted the no-stenting group to participants who did not receive any treatment on the extracranial segment (excluding cases undergoing eCAS or any angioplasty procedure at the cervical occlusion site at the time of EVT or within 24 hours from EVT) (estimand 3). We repeated the IPTW and IPTW-weighted ordinal regression for the primary, secondary, and additional outcomes, replicating the propensity model and weighting covariates of the primary estimand.

This study adhered to a superiority framework, with all results reporting two-sided tests that compared the effects of eCAS with those in the no-stenting group. Effect estimates are provided with 95% CIs, and all p values are 2-sided with values less than 0.05 considered statistically significant. The proportional odds assumption was assessed for the primary outcome. The steering committee ensured the necessary completion of all critical data at local sites. Missing data were handled with multiple imputation if <3% missing were found for each covariate, or cases were excluded. All analyses were conducted with R v. 4.3.3. The protocol was deposited (clinicaltrials.gov/NCT06965036), and the statistical plan was attached to the study protocol at registration sites.

Role of the Funding Source

This research-led independent study received no funding.

Standard Protocol Approvals, Registrations, and Participant Consents

The protocol was approved by the institutional review boards of the central proposing institutions (Vall d'Hebron Research Institute, Spain, VHIR#PR/AG73/2024, and Bufalini Hospital, Cesena, Italy, CEROM#0001–765/2024) and participating sites according to their local regulations, with informed consent obtained from the participants/legal representatives, or waived by the local review board.

Data Availability

Aggregate data can be shared on reasonable request to the lead author.

Results

Overall, the CERES-TANDEM study included 4,584 participants, of whom 4,053 had anterior circulation stroke due to tandem lesions and were included in the planned analysis (Figure 1). Among 4,053 patients (median age 70 years [IQR 60–78]; 65% women), 2,522 underwent eCAS and 1,531 received no stenting. Overall, the etiology of the cervical carotid lesion was atherosclerosis in 88% of patients and dissection in 12%.

Compared with the no-stenting group, patients receiving eCAS were younger (median age 69 vs 72 years, $p < 0.001$), were more frequently female (70.3% vs 57.6%, $p < 0.001$), more frequently had a good functional status at baseline (mRS score 0–2 95.3% vs 92.4%, $p < 0.001$), had higher prevalence of smoking and lower prevalence of atrial fibrillation, had a lower NIHSS score at admission (15 vs 16 points, $p < 0.001$), had a higher prevalence of intracranial large vessel than medium vessel occlusion together with extracranial cervical carotid occlusion (20.1% vs 17.2%, $p = 0.027$), and more frequently underwent advanced imaging despite similar ASPECTS, perfusion core, and penumbra features at baseline (Table 1). Patients with eCAS had longer onset-to-recanalization time for the intracranial occlusion (absolute difference between medians, 18 minutes) and more frequently received high-intensity antithrombotic treatment (33.1% vs 15.7%, $p < 0.001$; Table 1).

Patients in the eCAS group had lower median mRS score at 90 days compared with the no-stenting group (median mRS score 3, IQR 1–4, vs 4, IQR 2–5, $p < 0.001$; Table 2). Excellent and good functional outcomes were significantly more prevalent in the eCAS group compared with the no-stenting group (mRS score 0–1, 29.1% vs 20.2%, $p = 0.005$; mRS score 0–2 or unchanged from baseline, 47.1% vs 34.9%, $p < 0.001$; Table 2). The eCAS group had numerically higher rates of sICH (11.1% vs 9.3%, $p = 0.15$), and significantly higher rates of successful reperfusion (90.9% vs 75.9%, $p < 0.001$) and lower occurrence of END (18.5% vs 21.8%, $p = 0.025$; Table 2).

In the primary estimand analysis, after balancing covariates by stabilized IPTW (eTable 1, eFigure 1), the weighted ordinal regression analysis highlighted a consistent benefit of eCAS vs no stenting on functional outcome (cOR = 1.31, 95% CI

1.17–1.46, p value < 0.001; Figure 2; Table 2). Overall, eCAS was associated with a 31% increase in the odds of a 1-point shift toward lower disability on the mRS, corresponding to an E-value of 1.95. Regarding secondary outcomes, eCAS was associated with a 27% increase in excellent outcome (OR 1.27, 95% CI 1.08–1.50, p value = 0.005) and good functional outcome (OR 1.30, 95% CI 1.13–1.51, p value < 0.001) compared with the no-stenting strategy. Rates of sICH did not significantly differ after balancing covariates using stabilized IPTW while a positive effect on recanalization (OR 3.09, 95% CI 2.53–3.77, p value < 0.001) and a preventive effect for END (OR 0.82, 95% CI 0.69–0.98, p value = 0.025) were observed with eCAS (Table 2). The sensitivity analysis, re-estimating IPTW including successful recanalization in the set of covariates, confirmed the association of eCAS with improved 90-day functional outcome (cOR 1.14, 95% CI 1.02–1.27, p = 0.008; eFigure 2). The estimate was similar when including center, region, or calendar year in the IPTW (eTable 2).

The interaction analysis, incorporating patient-level inverse probability weights and adjusting for predefined covariates, revealed that the effect of eCAS was not modified by access route (ratio of ORs 0.79, 95% CI 0.42–1.47, $p_{interaction}$ = 0.456), retrograde approach (ratio of ORs 0.96, 95% CI 0.74–1.24, $p_{interaction}$ = 0.729), presence of medium vs large vessel occlusion (ratio of ORs 1.31, 95% CI 0.99–1.73, $p_{interaction}$ = 0.062), type of sedation (ratio of ORs = 0.86, 95% CI 0.68–1.09, $p_{interaction}$ = 0.207), IVT (ratio of ORs 1.12, 95% CI 0.90–1.41, $p_{interaction}$ = 0.315), or periprocedural antithrombotic treatment intensity (ratio of ORs 1.28, 95% CI 0.97–1.70, $p_{interaction}$ = 0.078; Figure 3). There was no impact of atherosclerosis or dissection etiology on the effect (ratio of ORs = 1.25, 95% CI 0.95–1.65, $p_{interaction}$ = 0.193).

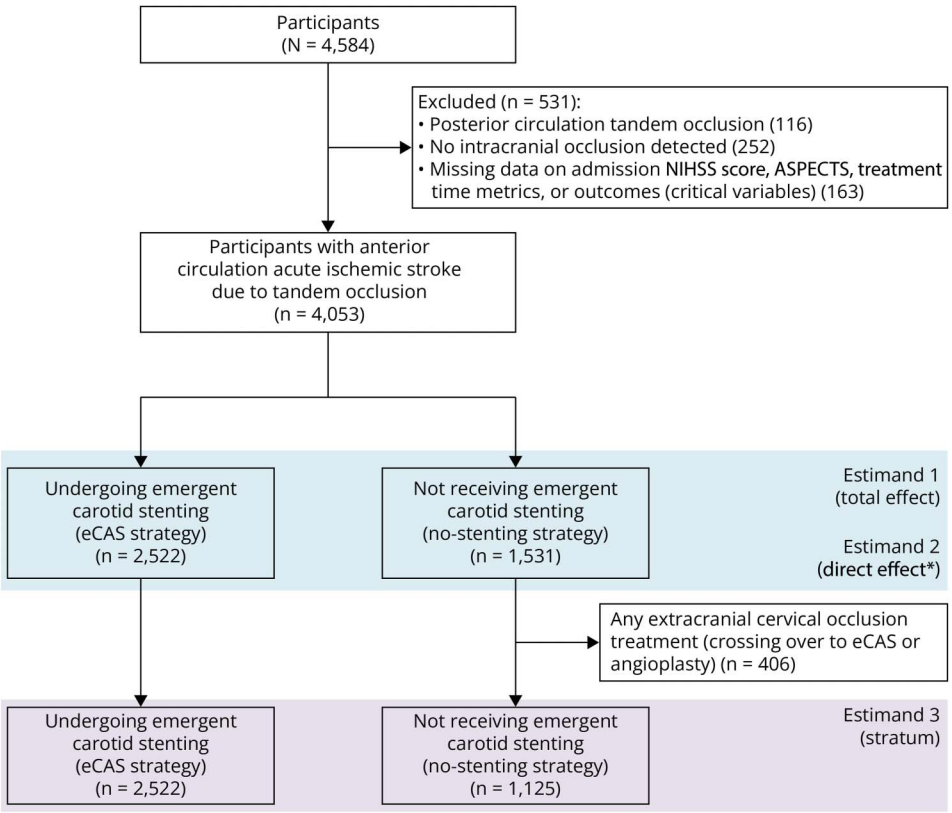
The secondary estimand approach confirmed the association of eCAS with higher odds of lower mRS score at 90 days (acOR 1.17, 95% CI 1.04–1.31, p value = 0.008, Table 2), independently from sICH or successful recanalization.

When restricting the analysis to participants not crossing over to eCAS within the first 24 hours (estimand 3; eTable 3), eCAS was associated with higher odds of a 1-point shift toward better functional status according to the mRS score at 90 days (cOR 1.36, 95% CI 1.20–1.54, p < 0.001, Table 2, eFigure 3).

Discussion

In this large, international, multicenter CERES-TANDEM cohort of 4,053 patients with acute anterior circulation tandem

Figure 1 Study Population



*Estimand 2 (direct effect) includes successful recanalization and symptomatic intracranial hemorrhage in the regression analysis for the primary outcome.

Table 1 Baseline Characteristics of the Cohort

	No-stenting (n = 1,531)	Emergent carotid stenting (n = 2,522)	*p* Value
Age, median (IQR)	72 (61–81)	69 (60–77)	<0.001
Female	882 (57.6)	1773 (70.3)	<0.001
Hypertension	1,040 (67.9)	1,673 (66.3)	0.312
Dyslipidemia	621 (40.6)	1,103 (43.7)	0.051
Diabetes	329 (21.5)	582 (23.1)	0.256
Smoking	498 (32.5)	927 (36.8)	0.007
Atrial fibrillation	381 (24.9)	241 (9.6)	<0.001
Previous stroke or TIA	161 (10.5)	239 (9.5)	0.307
Baseline modified Rankin Scale 0–2	1,414 (92.4)	2,403 (95.3)	<0.001
Previous antithrombotic use			<0.001
None	1,285 (83.9)	2,270 (90.0)	
SAPT	238 (15.5)	228 (9.0)	
DAPT	0 (0.0)	11 (0.4)	
VKA	1 (0.1)	0 (0.0)	
DOAC	3 (0.2)	3 (0.1)	
DOAC + APT	4 (0.3)	10 (0.4)	
NIHSS score at admission, median (IQR)	16 (11–20)	15 (9–19)	<0.001
Witnessed onset	932 (60.9)	1,497 (59.4)	0.356
ASPECTS	8.00 (7.00–10.00)	8.00 (7.00–10.00)	0.471
Brain imaging at admission			<0.001
NCCT	758 (49.5)	781 (31.0)	
CT perfusion	592 (38.7)	1,354 (53.7)	
MRI	181 (11.8)	387 (15.3)	
Perfusion imaging CBF core (mL)	8.00 (0.00–28.00)	8.00 (0.00–32.00)	0.817
Tmax 6 s (mL)	117.5 (80.0–172.0)	128.0 (76.3–210.8)	0.136
Tmax10 s (mL)	43.0 (12.0–99.5)	44.0 (15.0–85.0)	0.557
IVT	728 (47.6)	1,155 (45.8)	0.292
Onset-to-needle (OTN) time for IVT (minutes)	122.00 (94.00–180.00)	120.00 (82.00–180.00)	0.063
Onset-to-groin (OTG) time (minutes)	265.00 (183.00–395.75)	260.00 (184.00–418.00)	0.857
Occlusion side (left)	826 (54.0)	1,359 (53.9)	0.993
Extracranial lesion etiology			
Atherosclerosis	1,337 (87.3)	2,234 (88.6)	0.253
Dissection	194 (12.7)	288 (11.4)	
Intracranial artery occlusion			
LVO	264 (17.2)	507 (20.1)	0.027
MeVO	1,267 (82.8)	2015 (79.9)	

Continued

Table 1 Baseline Characteristics of the Cohort *(continued)*

	No-stenting (n = 1,531)	Emergent carotid stenting (n = 2,522)	*p* Value
Multiple intracranial occlusion sites		31 (2.0)	0.320
Intracranial occlusion site			
ICA terminus	397 (25.9)	521 (20.7)	<0.001
M1	852 (55.6)	1,463 (58.0)	
M2	232 (14.4)	469 (18.6)	
M3–M4	35 (2.3)	46 (1.8)	
A1–A2	11 (0.7)	19 (0.8)	
A3–A4	3 (0.2)	0 (0.0)	
Sedation type			
General anesthesia	583 (38.1)	965 (38.3)	0.934
Sedation	948 (61.9)	1,557 (61.7)	
Access route			
Femoral	1,516 (99.0)	2,364 (93.7)	<0.001
Radial	14 (0.9)	158 (6.3)	
Number of passes (median IQR)	2.00 (1.00–3.00)	2.00 (1.00–3.00)	<0.001
Onset to recanalization[a] (OTRec, minutes)	312.00 (212.75–444.25)	330.00 (235.25–514.00)	<0.001
Antithrombotic treatment intensity[b]			
High	241 (15.7)	834 (33.1)	<0.001
Low	1,290 (84.3)	1,688 (66.9)	

Abbreviations: APT = antiplatelet treatment; ASPECTS = Alberta Stroke Program Early Computerized Tomography Score; CBF = cerebral blood flow; CT = computerized tomography; DAPT = dual antiplatelet treatment; DOACs = direct oral anticoagulants; LVO = intracranial large vessel occlusion, including internal carotid artery and M1 and A1 segments; MeVO = intracranial medium vessel occlusion, including M2, M3, M4, A2, A3, and A4 segments; NCCT = noncontrast computerized tomography; NIHSS = NIH Stroke Scale; SAPT = single antiplatelet treatment; VKA = vitamin K antagonist.
[a] Recanalization of the intracranial occlusion.
[b] Classified as high-intensity antithrombotic treatment in case of DAPT, IV/intra-arterial glycoprotein IIb/IIIa inhibitor, antiplatelet plus anticoagulant combination, and triple antiplatelet treatment; classified as low-intensity antithrombotic treatment in cases of single antiplatelet use.

lesion treated with EVT, eCAS was associated with a significant shift toward better 90-day functional outcome (cOR for a 1-point improvement in mRS, 1.31) and higher rates of excellent outcome, without a significant increase in sICH.

Our findings complement individual-patient meta-analytic data from the HERMES and IRIS collaboration, in which conclusions regarding acute carotid stenting were limited by the low sample size, trial inclusion criteria, and lack of data on occlusion patterns.[2,4,6] The HERMES meta-analysis pooled 5 randomized controlled trials including 122 tandem lesion cases but lacked comparison on stenting and included mainly participants with mRS score 0–1 at baseline, patients largely presenting within 12 hours, and those with no large infarct.[2] The IRIS analysis pooled data from 6 randomized trials including 113 participants with tandem lesions undergoing eCAS but was limited to patients with good prestroke functional outcome and eligibility as per original trial criteria, and by the nonrandomized nature of the decision for or against eCAS.[4,6] CERES-TANDEM provides real-world, contemporary insight in over 4,000 cases, thereby enhancing statistical power to detect clinically meaningful differences. The findings from CERES-TANDEM show the overall benefit of eCAS compared with a no-stenting strategy regarding functional outcome. Our results are in line with the potential benefit highlighted by the IRIS meta-analysis, with the lower treatment effect in our study potentially attributable to restricting the intervention to eCAS only, in contrast to IRIS where the intervention group also included patients treated with percutaneous angioplasty alone.[4]

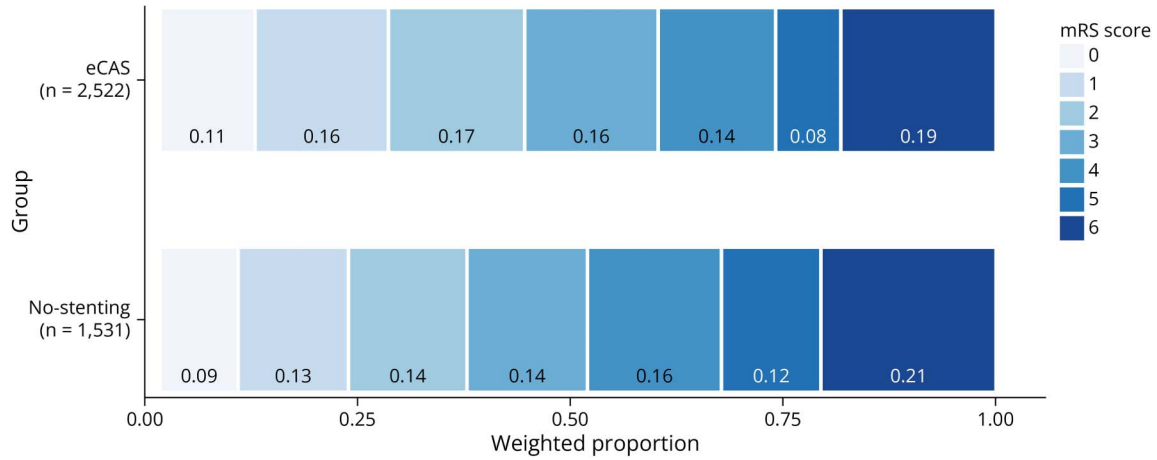
Given the inherent subjectivity in selecting patients for stenting, driven by clinical, imaging, and procedural considerations, we sought to mitigate confounding by applying IPTW alongside an estimand-based framework. For the primary estimand, we conducted a temporal sensitivity analysis

Table 2 Outcomes Based on Predefined Estimands

			Estimand 1 (treatment-policy, total effect)		Estimand 2 (direct effect)		Estimand 3 (stratum)	
	eCAS	No-stenting	cOR (95% CI)	*p* Value	cOR (95% CI)	*p* Value	cOR (95% CI)	*p* Value
Primary outcome								
mRS score ordinal shift (median, IQR)	3 (1–4)	4 (2–5)	1.31 (1.17–1.47)	<0.001	1.17 (1.04–1.31)	0.008	1.37 (1.21–1.55)	<0.001
sICH[a]			—	—	0.16 (0.13–0.20)	<0.001	—	—
Successful recanalization[a]			—	—	3.00 (2.55–3.53)	<0.001	—	—
Secondary outcomes[b]								
mRS score 0–1 (excellent outcome) (n, %)	733 (29.1)	309 (20.2)	1.27 (1.08–1.50)	0.005	—	—	1.28 (1.03–1.60)	0.027
mRS score 0–2 or unchanged (n, %)	1,188 (47.1)	535 (34.9)	1.30 (1.13–1.51)	<0.001	—	—	1.42 (1.19–1.71)	<0.001
Additional outcomes[b]								
sICH (n, %)	280 (11.1)	143 (9.3)	1.21 (0.93–1.56)	0.153	—	—	1.48 (1.12–1.95)	0.006
Successful recanalization (n, %)	2,292 (90.9)	1,162 (75.9)	3.09 (2.53–3.77)	<0.001	—	—	3.61 (2.90–4.49)	<0.001
Early neurologic deterioration (n, %)	467 (18.5)	333 (21.8)	0.82 (0.69–0.98)	0.025	—	—	0.87 (0.71–1.06)	0.17

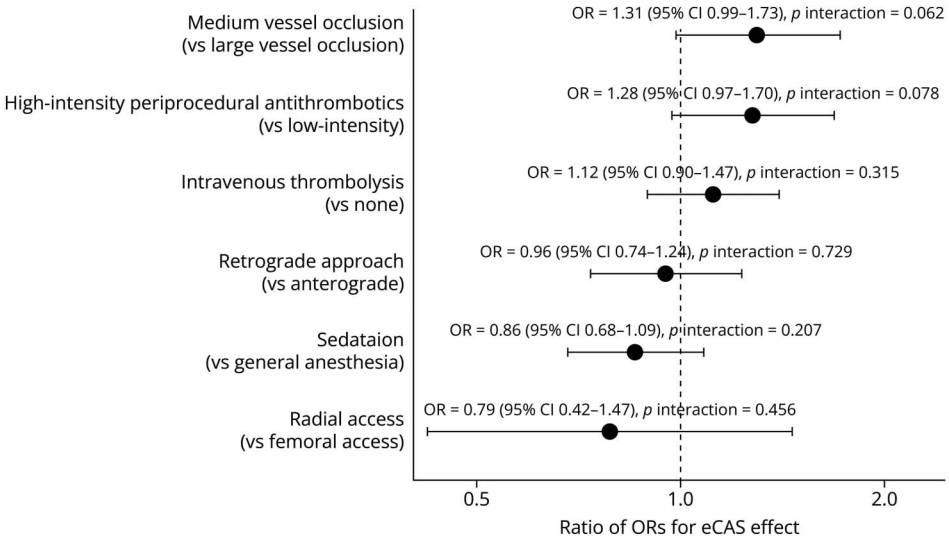
Estimand 1: whole population considered.
Estimand 2: population as in estimand 1; overall treatment effect adjusted for successful recanalization and sICH in logistic regression.
Estimand 3: principal-stratum population restricted to those never crossing between no-stenting and eCAS groups, excluding from the former all cases undergoing any angioplasty procedure at the cervical site within the first 24 hours.
Stabilized inverse probability of treatment weighting (IPTW) was implemented in all estimands to adjust for potential confounding in the indication for eCAS: demographics and vascular risk factors (age, sex, hypertension, dyslipidemia, diabetes, smoking, atrial fibrillation, previous stroke or TIA, prestroke mRS score, previous stroke or TIA, previous antithrombotic therapy), index stroke–related data (witnessed stroke onset, imaging modality, ASPECTS, NIHSS score on admission, LVO, occlusion side), and treatment-related data (radial/femoral access, anesthesia type (general vs sedation), IV thrombolysis (IVT), onset-to-groin (OTG) time).
[a] Logistic regression covariates in estimand 2 approach (direct effect of eCAS).
[b] Odds ratio (OR) and 95% CI.

Figure 2 Modified Rankin Scale Scores at Day 90



Scores on the modified Rankin Scale range from 0 to 6, with higher scores indicating more severe disability. Results from the IPTW-weighted ordinal logistic regression score are reported, with bars representing weighted proportions of patients at each scale score for each group (estimand 1, primary outcome). n: number of patients in each group; IPTW = inverse probability of treatment weighting.

Figure 3 Interaction Analysis of Emergent Carotid Stenting vs No Stenting for a 1-Point Improvement in the mRS Score in Patients With Tandem Lesions



The within-variable interaction terms are presented as corresponding ratios of ORs and $p_{interaction}$ values. Results were calculated based on the primary estimand and were adjusted for age, sex, prestroke mRS score, baseline NIHSS score, endovascular procedure time metrics, and atrial fibrillation. mRS = modified Rankin scale; NIHSS = NIH Stroke Scale; OR = odds ratio.

by incorporating successful recanalization into the IPTW model, therefore assuming a reverse temporal relationship between recanalization and decision to eCAS. For the second estimand, we adjusted for key baseline covariates using logistic regression. Across all analytic approaches, eCAS consistently demonstrated superior outcomes for functional status at 3 months compared with the no-stenting strategy, with moderate to strong robustness also confirmed by the E-value.

Observational meta-analyses of eCAS vs no-stenting strategies have suggested improved functional outcomes (pooled OR 1.52, 95% CI 1.19–1.95) at the cost of higher hemorrhagic risk.[3] Such results were potentially influenced by the intensity of antithrombotic treatment necessary to maintain stent patency, with a marginal benefit of high-intensity treatment over low-intensity antithrombotics.[7] In our cohort, the effect of eCAS was achieved without a significant excess of sICH, potentially reflecting advances in patient selection, device technology, and periprocedural management beyond the limits imposed by previous randomized controlled trials. To this extent, only a marginal trend toward higher effect with medium vessel occlusion and high-intensity antithrombotic treatment emerged, which may encourage clinicians to consider appropriate management with antithrombotics to ensure the successful deployment of the stent during eCAS.

In the context of acute ischemic tandem lesions, our findings suggest that IVT does not seem to influence the benefit of eCAS on functional outcome, therefore suggesting the administration of IVT independently of the potential decision to perform eCAS afterward. Such findings integrate the current literature and support the general safety of IVT in the context of tandem lesions, emerging from observational studies.[13] Moreover, the effect of eCAS seems to be consistent and independent of access route, intracranial large or medium vessel occlusion, concomitant IVT, and sedation modality.

Our study has limitations. CERES-TANDEM remains observational, and unmeasured confounding remains. Although our estimand-based approach, particularly for the second estimand, may have reduced the confounding by indication by including recanalization status in the weighting procedure, confounding by indication may still remain, because eCAS was not pursued in those without full recanalization. Results should, therefore, be interpreted with caution, given the nonrandomized nature of the indication. Second, our population seems to align with previous observational studies,[14,15] although it differs from the population included in randomized controlled trials,[2] suggesting that the implementation of thrombectomy in the real world may enlarge the original boundaries. Third, detailed subgroup analyses were limited by heterogeneity in practice, and despite a longitudinal effort to ensure completeness of data, selection and reporting bias may be present. This particularly applies to antithrombotic strategies because, although the APT-eCAS collaborative meta-analysis found no clear safety signal for high-intensity antithrombotics,[7] randomized trials are needed to define optimal periprocedural medical therapy. Fourth, our analysis did not take into account late carotid revascularization treatment, with patients undergoing percutaneous angioplasty and those receiving stenting or carotid endarterectomy >48 hours after stroke categorized in the no-stenting group in primary estimand and were a priori excluded in remaining estimand. Given the potential selection of patients with lower rates of worsening, not leading to stenting after conservative treatment, our results should be interpreted with caution because of the potential underestimation of the benefit of eCAS over no-stenting. A further limitation arises from the local

adjudication of images, with potential intrinsic bias. The inclusion of more fragile patients, as well as those not referred for EVT, may further inform on the role of eCAS. Finally, the decision to eCAS, IVT, antithrombotics, and treatment operations relied on clinicians managing the patient. Such limitations, however, do not differ from those in randomized controlled trial data pooled in IRIS and HERMES meta-analysis, where stenting and antithrombotics were given according to clinical decision and in a nonblinded fashion for treatment allocation.[4]

Our results support a paradigm in which eCAS during thrombectomy for tandem occlusions could be considered, given its association with improved functional recovery and reperfusion success without prohibitive hemorrhagic risk. Future randomized trials—such as the ongoing PICASSO (NCT05611242),[16] Thrombectomy in Tandem Lesion (TITAN) (NCT03978988), Endovascular Acute Stroke Intervention-Tandem Occlusion (EASI-TOC) (NCT039789884), and Carotid Artery Stenting During Endovascular Treatment for Acute Stroke (CASES) (NCT06511089) trials—will be critical to corroborate these observational findings, clarify the ideal stenting strategy (e.g., lesion order and device choice), and establish the safest and most effective antithrombotic regimens in this high-risk population.

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