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Abstract

Background and objectives: Management of carotid lesions during endovascular therapy (EVT) in patients with acute ischemic stroke (AIS) due to tandem lesions remains controversial, and long-term prognosis data are scarce. We evaluated 90-days and 1-year follow-up outcomes of emergent carotid artery stenting (eCAS) versus non-eCAS in these patients.

Methods: Data from a prospective mandatory population-based registry of Code Stroke in Catalonia (Spain) between 2017 and 2023 were analyzed. Patients with large vessel occlusion and ipsilateral $\geq 50\%$ atheromatous cervical internal carotid artery (ICA) stenosis undergoing EVT were identified. eCAS and non-eCAS groups were compared. The primary outcome was the shift in the modified Rankin Scale (mRS) score at 90-days and 1-year of follow-up, adjusted using Inverse Probability of Treatment Weighting. Stratified analyses in predefined key subgroups according to sex, age, degree of ICA stenosis, ASPECTS, baseline NIHSS and previous intravenous thrombolysis were performed. Secondary outcomes included successful recanalization (modified Thrombolysis In Cerebral Infarction [mTICI] $\geq 2b$), 90-day favorable functional outcome (mRS 0-2), hemorrhagic transformation (HT) and 90-day mortality.

Results: Among 578 patients included (mean age 70.2 years-old, 140 [24.2%] women), 344 patients (59.5%) underwent eCAS. eCAS was associated with a better functional outcome at 90 days (cOR for a 1-point less on the mRS score 1.47, 95% CI 1.20-1.82, $p < 0.001$) and 1 year of follow up (cOR of 1.47, 95% CI 1.16-1.85), $p = 0.001$), and with higher successful recanalization rates (OR 4.28, 95% CI 2.61-7.0, $p < 0.001$), without increasing HT risk or mortality. The benefit of eCAS was consistent in both moderate (50-69%) and severe ($\geq 70\%$) ICA stenosis subgroups. Among eCAS group, patients under dual antiplatelet therapy at 24 hours showed higher rates of favorable functional outcome (54.6% vs. 22.9%, $p < 0.001$). Potential treatment effect differences were observed for women and older patients.

Discussion: In this population-based study of patients with AIS due to tandem lesions, eCAS was associated with a better mid and long-term functional outcome without safety concerns, even in moderate ICA stenosis. Limitations include the observational design and possible

unmeasured confounders. Further studies are needed to explore the mechanisms underlying the differential effects of eCAS in women and older patients.

Classification of Evidence: This study provides Class II evidence that in patients with acute ischemic stroke and tandem lesions undergoing endovascular therapy, emergent carotid artery stenting is associated with favorable functional outcome at 90 days compared to endovascular therapy alone.

Introduction

Acute ischemic stroke (AIS) due to tandem lesions (TL) involving the extracranial Internal Carotid Artery (ICA) represent up to 20% of all AIS undergoing endovascular therapy (EVT)¹. TL are associated with lower recanalization rates, higher mortality and poorer functional prognosis². Although EVT benefits are well established for the intracranial occlusion in these patients¹, there is no consensus among stroke neurologists and neurointerventionalists regarding the best treatment of the ICA lesion^{3,4}, with two mutually exclusive approaches: revascularization via emergent carotid artery stenting (eCAS) during EVT, or conservative management and deferred decision-making regarding carotid revascularization. While eCAS during EVT enables immediate carotid revascularization and stabilization of the ruptured carotid plaque, it may increase the procedure duration⁵ and may be technically difficult in some patients. eCAS also requires early antithrombotic therapy to prevent acute stent occlusion⁶, potentially increasing the risk of hemorrhagic transformation (HT)^{7,8}. Conversely, deferring revascularization might increase the risk of early stroke recurrence and may negatively affect hemodynamics in the affected hemisphere.

Some observational studies⁹⁻¹¹ and a recent meta-analysis¹² suggest that, compared to a conservative strategy, eCAS may be associated with higher recanalization rates and a better functional prognosis at 90 days of follow-up with no significantly increased risk of HT. eCAS seems to be safe even when intravenous thrombolysis (IVT) has been priorly administered¹²⁻¹⁴. However, data on long-term benefit of eCAS are scarce and there is heterogeneity among studies in the definition of TL (thresholds for ICA stenosis may vary from 50%, 70%, 90% or

complete occlusion), in the outcome measurement, stroke etiologies included, and methods used to control for confounders.

In addition, most studies were conducted in highly specialized EVT-capable centers, which may reduce their external validity. Therefore, pending the publication of ongoing randomized trials^{15–19}, there is a need to confirm the potential benefit of eCAS in large population-based studies, with standardized follow-up and broad definition of TL. Moreover, information on treatment effect differences in key subgroups is scarce.

This study addresses the following research questions: 1) Does eCAS improve functional outcomes and remain safe in patients with AIS due to atherosclerotic TL? 2) Is the benefit of eCAS sustained at 1-year follow-up? 3) Is eCAS effective and safe across clinically relevant patient subgroups?

Methods

Study design and population

The Stenting Extracranial Carotid artery stenosis dURING endovascular treatment in patients with acute Ischemic Stroke (SECURIS) study was an observational study based on the Code Stroke Registry of Catalonia (CICAT), a region of Spain with a population near 8 million inhabitants. Study design, data collection, and reporting adhered to the STROBE statement guidelines²⁰. CICAT is a prospective, population-based, mandatory registry including data from all consecutive Code Stroke patients in Catalonia. For this study, patients who underwent EVT for AIS in any of the ten comprehensive stroke centers (CSC) that perform EVT in Catalonia between January 2017 and March 2023 were identified. Inclusion criteria were as follows: 1) age ≥ 18 years old; 2) previous modified Rankin Scale (mRS) score 0–3; 3) time from symptom onset or last time seen well (LTSW) ≤ 24 hours; 4) AIS with large vessel occlusion (LVO) of anterior circulation including terminal ICA (TICA), segments M1/M2 of the middle cerebral artery (MCA) or segment A1 of the anterior cerebral artery (ACA); 5) concomitant atheromatous stenosis of cervical ICA $\geq 50\%$; and 6) treatment with any EVT modality, with or without prior IVT administration.

Patients with lack of critical follow-up data (mRS score at 90 days and follow-up computed tomography (CT) within the first 36 hours after treatment) were excluded. Patients with non-atheromatous etiology of ICA stenosis (e. g., dissection) were also excluded, except for those with an indeterminate etiology due to the coexistence of atrial fibrillation and atheromatous ICA stenosis.

Standard Protocol Approvals, Registrations, and Patient Consents

The study protocol was approved by the Ethics Committee of Hospital de la Santa Creu i Sant Pau (IIBSP-SEC-2023-136) and the CICAT scientific committee. The need for written informed consent was waived due to the retrospective nature of the study.

Study variables

Collected directly from the CICAT registry were data as follows: demographic data (age, sex); relevant previous medical history (prior mRS score, hypertension, dyslipidemia, diabetes, ischemic heart disease, antithrombotic treatment, peripheral arteriopathy, previous stroke, smoking); index event characteristics and metrics (baseline National Institute of Health Stroke Scale (NIHSS) score, Alberta Stroke Program Early CT Score (ASPECTS), occlusion site, vital signs, time from onset to hospital arrival, door-to-needle and door-to-groin puncture times); treatment data (IVT, number of passes, EVT-associated complications (arterial perforation, artery dissection or distal embolism), general anesthesia use, final modified Thrombolysis In Cerebral Infarction [mTICI]²¹ score) and presence of HT in the first follow-up CT at 24-36 hours.

Additional data not included in the registry but collected from electronic health records were furnished anonymized by the staff of the 10 CSC: stroke etiology according to TOAST criteria²², degree of ICA stenosis (according to North American Symptomatic Carotid Endarterectomy Trial (NASCET) criteria²³ in the last angiographical series previous to stent decision), HT classification on the follow-up CT if not provided in the CICAT registry and antithrombotic regimen at 24 hours after EVT. The degree of ICA stenosis was determined by investigators of each center based on angiography reports or, when not specified, through a review of source imaging. Investigators were all stroke neurologists not blinded to the eCAS

status. Decisions regarding eCAS, prior IVT, antithrombotic regimen, and initiation time were at the discretion of each practitioner. Since during the study period tenecteplase was not an approved indication for AIS according to the Spanish Agency for Medicines and Medical Devices (AEMPS), it was not used in routine clinical practice. Accordingly, we assume that most of the patients received alteplase.

Study outcomes

The primary outcome was the shift on the mRS score at two time points: 90 days and 1 year of follow-up. At 90-days of follow-up, mRS score was assessed centrally through a structured telephone interview conducted by certified central evaluators who were blinded to the clinical information. The 1-year mRS score was assessed by the treating neurologist, not blinded to eCAS status, during routine follow-up, either in person or by telephone.

Pre-planned stratified analysis in key subgroups for the primary outcome included: sex, degree of ICA stenosis prior to stenting decision (50-69% and $\geq 70\%$), stroke severity according to baseline NIHSS score (mild: ≤ 10 points, moderate-severe: 11-20 points, very severe: >20 points), ASPECTS (0-5 points, 6-8 points, 9-10 points), age (<80 years-old and ≥ 80 years-old) and prior IVT.

Secondary efficacy outcomes were favorable functional outcome at 90 days and 1 year of follow-up defined by a mRS score 0-2 or 3 if the previous mRS was 3; and successful recanalization after EVT defined by final mTICI $\geq 2b$. Secondary safety outcomes were mortality at 90 days of follow-up and the presence of relevant hemorrhagic transformation (HT), defined as the presence of either symptomatic intracerebral hemorrhage (SICH) or any parenchymal hemorrhage (PH) defined according to the European Cooperative Acute Stroke Study-II (ECASS-II) criteria²⁴ in the 24-36 hours follow-up CT scan^{25,26}.

Statistical analysis

Categorical variables were reported using counts (n) and percentages (%), and quantitative variables were reported as means and standard deviations (SD) or medians and interquartile range (IQR) if non-normally distributed according to the Shapiro-Wilk test.

Univariable analyses using the χ^2 test for categorical variables and the Student-t test for continuous variables (or Wilcoxon Rank Sum test when a non-parametric test was required) were performed to compare differences between the eCAS and non-eCAS groups.

To explore the relationship between eCAS and the primary outcome, ordinal logistic regression was used to perform a shift analysis. mRS score was assessed using the full-scale range (from 0 to 6). An Inverse Probability of Treatment Weighting (IPTW) approach using a propensity score for adjusting for possible confounders influencing the decision regarding stent placement was applied. The propensity score was computed using a multivariable logistic regression model, accounting for the following pre-specified variables, selected for their potential association with both the individual decision to perform eCAS and the primary outcome: previous mRS score, age, atrial fibrillation, baseline NIHSS, ASPECTS, time from LTSW to groin puncture, previous IVT and the number of passes. This analysis was repeated in the two time points.

For the graphical depiction of treatment effect in key subgroups as previously described, a forest plot was constructed and p for interaction was calculated.

Regarding secondary outcomes, favorable functional outcome at 90 days was assessed by dichotomizing the mRS score (as previously described), performing a multivariable logistic regression analysis also adjusted for the IPTW. Number needed to treat (NNT) for achieving a favorable functional outcome was calculated. Successful recanalization, mortality at 90 days of follow-up and relevant HT rates were compared between the eCAS and non-eCAS groups. A multivariable logistic regression analysis adjusted for the pre-specified variables (number of passes, previous IVT, time from LTSW to groin puncture, age, ASPECTS and baseline NIHSS score) was performed.

Additional exploratory analyses were performed in the eCAS group to assess the relationship between antithrombotic regimen at 24 hours from EVT and favorable functional outcome. Predictors of relevant HT in the eCAS group were also assessed.

Analyses were conducted using available data only; no imputation of missing data was performed. A two-tailed p-value <0.05 was considered significant. All statistical analyses were performed using Stata version 17.0 (StataCorp, College Station, TX).

Data availability

Anonymized data not published within this article will be made available by request from any qualified investigator.

Results

Study population

Of the 6096 EVT performed in Catalonia during the study period, 5656 of them involved anterior circulation, and 937 were initially identified as TL on the first angiographical series. After excluding non-atherothrombotic etiologies and those patients who did not meet inclusion criteria, a total of 578 patients were finally included (Figure 1). Differences between patients included in the analysis and those excluded due to missing follow-up data are detailed in eTable1.

Patient demographic, clinical and radiological characteristics are summarized in Table 1. Mean age was 70.2 years-old (SD=10.8), and 140 patients (24.2%) were women. eCAS was performed in 344 patients (59.5%). Women were less represented in the eCAS group compared to the non-eCAS group (21.2% vs. 28.6%, $p=0.041$). eCAS and non-eCAS groups were similar in key prognostic variables such as age, previous mRS, systolic blood pressure (SBP), glycemia, baseline NIHSS score, ASPECTS, and LTSW-to-groin puncture time. Compared with the non-eCAS group, patients in the eCAS group had higher rates of atrial fibrillation (9.9% vs. 4.7%, $p=0.022$), received less frequently IVT (36.1% vs. 47.9%, $p=0.005$), underwent a smaller number of passes (1 vs. 2, $p<0.001$) and had higher rates of general anesthesia during the procedure (25.6% vs. 14.5%; $p<0.001$). Procedure duration and rates of arterial perforation, dissection and distal embolism during EVT were similar between both groups.

Primary outcome

The median mRS score at 90 days for all of the patients was 3 (IQR 2-5), being significantly lower in the eCAS group compared with the non-eCAS group (3 [1-5] vs. 3 [2-5]; $p = 0.016$). When applying IPTW, the distribution of propensity scores was well balanced between treatment groups, as evidenced by substantial overlap in the density plots (eFigure 1). After

adjusting for the IPTW, eCAS was independently associated with better functional outcomes (cOR for a 1-point less in the mRS of 1.47, 95% CI 1.20 -1.82; $p<0.001$). Information of mRS score at 1 year of follow-up was available for 501 patients. The benefit of eCAS persisted at 1 year of follow-up (cOR of 1.47, 95% CI 1.16 – 1.85, $p = 0.001$) (Figure 2).

A graphical depiction of treatment effect in key subgroups is shown in Figure 3. No significant heterogeneity in the treatment effect of eCAS was observed, as assessed in the interaction analysis. However, potential differences on treatment effect were observed for women, older patients and lower ASPECTS. Since the degree of ICA stenosis and sex were not initially included in the IPTW (unlike the other variables used to define the strata), further stratified analyses were performed in these subgroups after adjusting for the IPTW. After adjustment, eCAS was associated also with better functional prognosis in moderate (50-69%) ICA stenosis at 90 days (cOR 3.70, 95% CI 1.49-9.09, $p = 0.04$) and at 1 year of follow-up (cOR 4.17, 95% CI 1.41-12.5, $p=0.01$). Contrariwise, after adjustment, a lack of benefit of eCAS persisted in women (eFigure 2).

Secondary outcomes

At 90 days of follow up, a favorable functional outcome was observed in 244 patients (42.2%): 45.9% in the eCAS group vs. 36.8% in the non-eCAS group, representing a risk ratio for a better functional outcome of 1.25, 95% CI 1.02-1.53; $p=0.028$. In the adjusted multivariable logistic regression analysis, eCAS was independently associated with a higher probability of a 90-day favorable functional outcome (OR 1.43, 95% CI 1.12-1.82; $p=0.004$). The NNT to achieve a favorable outcome was 11. Likewise, at 1 year of follow-up eCAS persisted independently associated with a higher probability of a favorable functional outcome (OR 1.35, 95% CI 1.04-1.76; $p=0.023$).

Final mTICI was available for 575 patients of the 578 included patients. Successful recanalization was observed in 483 patients (84%), 315 (91.7%) in the eCAS group vs. 170 (73.0%) in the non-eCAS group ($p<0.001$). This association remained significant after adjusting for the pre-specified variables (OR 4.28, 95% CI 2.61-7.01; $p<0.001$). Furthermore, this association remained significant when the analysis was repeated only in patients who had

received ≥ 1 passes, in order to rule out unsuccessful treatments due to lack of access to the intracranial occlusion.

Relevant HT was observed in 87 patients (15.1%), of whom 51 cases (8.9%) met the criteria for sICH. According to the ECASS-II classification, HT subtypes were distributed as follows: 36 patients had PH1, 36 had PH2, 5 had HI1, 7 had HI2, and 3 had remote PH. A slight but non-significant trend towards a greater risk of relevant HT was observed in the eCAS group compared to the non-eCAS group (58 (16.9%) vs 29 (12.5%), $p=0.142$).

At 90 days of follow-up, 121 patients had died (20.9%), 20.6% in the eCAS group and 21.4% in the non-eCAS group ($p=0.833$). Mortality rates at 1 year of follow-up were 24% in the eCAS group and 29.9% in the non-eCAS group ($p=0.200$).

Specific eCAS group analyses

The follow-up CT showed relevant HT in 58 (16.9%) of the 344 patients who underwent eCAS. In a multivariable logistic regression analysis, only higher baseline NIHSS scores, greater number of passes and arterial perforation during EVT independently predicted a relevant HT after eCAS (Table 2).

In the eCAS group ($n=344$), specific antithrombotic regimen at 24 hours post-EVT was available for 339 patients. Among them, 227(67.0%) received dual antiplatelet therapy (DAPT), 64 (18.9%) single antiplatelet therapy (SAPT), 2 (0.6%) anticoagulation therapy only, 5 (1.5%) both anticoagulation and antiplatelet therapy, and 41 (12.1%) any antithrombotic agent. Lower ASPECTS ($p<0.001$) and higher NIHSS scores ($p=0.012$) were the only variables independently associated with DAPT delivery at 24 hours post-EVT. Neither atrial fibrillation nor prior IVT were associated with DAPT delivery at 24 hours post-EVT. Patients receiving anticoagulation therapy at 24 hours post-EVT were excluded from further analyses given their small representation within the study cohort ($n=7$). Of the remaining patients, those under DAPT at 24 hours post-EVT showed a higher proportion of favorable functional outcome at 90 days of follow-up (54.6% vs. 22.9%, $p<0.001$), a lower rate of relevant HT (5.1% vs. 13.8% $p=0.045$) and lower mortality (12.3% Vs 37.1% $p<0.001$) compared to patients receiving other regimens.

In adjusted multivariable regression analyses, these associations remained statistically significant.

Overall, this study provides Class II evidence that in patients with AIS and TL undergoing EVT, eCAS is associated with favorable functional outcome at 90 days compared to EVT alone.

Discussion

In this population-based study, eCAS during EVT was associated with a better functional outcome in patients with AIS secondary to TL, with no increased risk of relevant HT. This benefit remained significant at 1 year of follow-up. Our findings support previously reported data on the potential benefit of eCAS in these patients⁹⁻¹² and add valuable information on the safety and effectiveness at long-term follow-up and in key subgroups.

Notably, after adjustment, the cOR of a favorable shift in the mRS score at 90 days in our study was 1.47, closely aligned with the cOR of 1.46 reported in 2023 by Farooqui M. et al⁹. This observation might be explained by the fact that both studies had similar inclusion/exclusion criteria, as well as similar adjustment, and increases the evidence of the potential size effect of eCAS in these patients. However, our study goes further in providing additional data, as it was conducted in a real-life scenario over an extended inclusion period and included all AIS admitted to the ten CSC that currently perform EVT in Catalonia, thereby reducing the risk of hospital selection bias and enhancing the external validity of our results.

Long-term follow-up data of patients with TL treated with eCAS are scarce. One recent observational study found eCAS as an independent predictor of favorable functional outcome at 1 year of follow-up, despite its small sample size and unicenter design²⁷. Our study reinforces this finding and provides more robust evidence supporting the potential long-term benefit of eCAS. Moreover, we observed that the magnitude of this benefit, the cOR, remained consistent at both 90 days and 1 year of follow-up, further strengthening its clinical relevance.

We observed some differences in baseline characteristics between patients who underwent eCAS and those who did not. First, a significantly higher rate of atrial fibrillation was observed

in the eCAS group. This may be partly related to a higher prevalence of ischemic heart disease and hypertension, both established risks factors for atrial fibrillation²⁸. However, given the limited number of cases, a chance finding cannot be excluded. Still, as atrial fibrillation was included in the IPTW, we are confident potential confounding was controlled. Second, women were underrepresented in the eCAS group. This disparity may be partly attributed to the perception among treating physicians of a higher procedural risk in women, influenced by their historical underrepresentation in carotid revascularization trials and the higher rates of periprocedural complications reported in this population²⁹. Regarding the potential benefit of eCAS in key subgroups, no significant modification of the treatment effect was observed across subgroups, although some findings warrant further consideration.

First, a potential benefit was observed not only in patients with severe ($\geq 70\%$) ICA stenosis, but also in patients with moderate (50-69%) ICA stenosis, although they represented only 15.9% of the study population. This finding is important because the definition of TL is highly heterogenous between studies. It ranges from the strict 90% threshold used in the TITAN registry¹¹ to the ambiguous “extracranial internal carotid occlusive or stenotic lesion” definition used in the STRATIS registry¹⁰, suggesting an underrepresentation of patients with moderate stenosis in these registries. Our results not only reinforce the idea that eCAS should not be dismissed outright in patients with moderate (50%-69%) ICA stenosis, but also highlights the need for a more standardized definition of TL.

After adjustment, we observed a lack of benefit of eCAS in women with TL, although this observation might be unpowered due to the relatively small sample size of women included. Data on sex-specific influences during the acute phase of TL are scarce. Prior trials suggested a reduced benefit of elective carotid endarterectomy in women³⁰, as well as higher rates of restenosis or occlusion following elective CAS³¹. Several factors may contribute to these findings, including older age and greater comorbidity at stroke onset, smaller arterial diameters, and more stable plaque composition, which may reduce the potential benefit of eCAS³². Since these studies were not conducted in the setting of AIS, these observations can only be inferred to our population cautiously. Nevertheless, these sex-based differences highlight the need for

304 tailored therapeutic approaches and further research to understand underlying sex-specific
305 factors influencing treatment outcomes.

306 As previously reported^{12-14,33}, our results showed that IVT did not impact on the potential
307 benefit of eCAS, and should not be avoided in patients who may be potential candidates to
308 eCAS if there are not contraindications.

309 In patients with lower ASPECTS, the benefit of eCAS did not reach statistical significance.
310 Recent randomized trials³⁴⁻³⁶ demonstrated the efficacy and safety of EVT in patients with large
311 ischemic core despite poorer functional outcomes than non-large core patients. Although
312 patients with TL are underrepresented or even excluded from these trials, observational data
313 suggest that patients with TL and a large core may benefit from EVT similarly to non-TL
314 patients³⁷. Moreover, eCAS might provide a slight additional benefit compared to non-eCAS³⁸.
315 However, these findings should be interpreted with caution due to the high risk of bias and the
316 small number of eCAS patients included. Our study was probably unpowered to demonstrate a
317 significant benefit of eCAS in patients with ASPECTS 6-8, and those with ASPECTS 0-5 were
318 highly underrepresented (n=20), making it difficult to draw meaningful conclusions.

319 Elderly patients did not benefit significantly from eCAS, consistent with previous reports³⁹.
320 Notably, in the context of elective carotid revascularization outside the acute phase, elderly
321 patients who underwent CAS experienced poorer outcomes than those who underwent carotid
322 endarterectomy, largely attributed to an increased risk of periprocedural stroke⁴⁰. The
323 underlying mechanisms of this finding may involve not only their higher comorbidity burden
324 but also anatomical factors (increased vascular tortuosity and calcifications) and a distinct
325 plaque composition that increases their vulnerability to rupture during stenting⁴¹.

326 In addition to better functional outcome, patients who underwent eCAS showed a 4-time fold
327 increased probability of successful recanalization after EVT, which is also a well-established
328 predictor of favorable functional outcome in patients with TL⁴². However, this association may
329 partly reflect a reverse causality: clinicians may have been more inclined to perform eCAS in
330 cases where successful recanalization had already been achieved. Inversely, poorer
331 recanalization rates in the non-eCAS group may be explained by failed attempts of intracranial

recanalization or the impossibility of crossing the extracranial stenosis to perform intracranial thrombectomy. Information on the EVT approach strategy for the eCAS group (anterograde vs. retrograde) was not available, so this limitation cannot be totally addressed. To partially address potential bias due to the latter scenario, we repeated the analysis in those patients who underwent at least one pass (thus the intracranial occlusion was reached), and the association remained consistent. Nevertheless, the lack of registration of failed intracranial thrombectomies, stenting attempts and EVT approach could have introduced bias into the results.

Several reasons may explain the better outcomes observed in the eCAS group, including improved cerebral hemodynamics of the affected hemisphere, which may lead to smaller infarctions or a reduced risk of early stroke recurrences, among others. Previous randomized trials^{43–45} have demonstrated the efficacy of non-emergent symptomatic carotid revascularization in reducing ipsilateral ischemic recurrences, although specific data on recurrence risk following eCAS is lacking.

Regarding antithrombotic therapy following eCAS, we observed better effectiveness and safety outcomes in patients receiving DAPT at 24 hours from EVT. This observation may partly be explained by the fact that these patients had more favorable baseline characteristics, which likely influenced physicians' decisions based on an assumed better prognosis or a decreased perceived risk of bleeding. Furthermore, lower rates of HT in early follow-up CT may have also influenced DAPT initiation based on current guidelines, which recommend DAPT as the optimal approach for elective CAS⁴⁶. While reverse causality cannot be excluded, previous studies have also identified early DAPT initiation as an independent predictor of good outcome in patients with AIS due to TL treated with eCAS⁴⁷. Thus, despite potential confounding, our findings suggest that DAPT seems to be safe, even when prior IVT has been administered.

Finally, we aimed to assess independent predictors of HT in patients receiving eCAS. The only variables that remained associated with relevant HT after the multivariable regression analysis were higher NIHSS score, higher number of passes and arterial rupture during EVT. Interestingly, neither previous IVT nor prior anticoagulation therapy were among them,

supporting previous evidence that suggests that IVT should not be withheld in AIS patients with TL who are likely to require eCAS^{13,14}.

The main strength of our study is that it is based on a mandatory, population-based registry that consecutively includes all patients with AIS undergoing EVT in a region of 8 million inhabitants, which not only allowed the inclusion of a large number of patients, but also enhances the external validity of the results and its generalization to a real-life population. Furthermore, the primary outcome (mRS at 90 days of follow-up) was assessed blindly and centrally, thereby limiting observer bias. In addition, using the IPTW as the statistical adjustment method to control for confounders significantly reduced the risk of selection bias in a procedure (eCAS) that is potentially highly influenced by practitioner experience and even CSC internal protocols.

We acknowledge some limitations of this study. First, we cannot rule out selection bias due to the exclusion of patients with missing follow-up data. As shown in eTable 1, while baseline characteristics were generally similar, excluded patients underwent a higher number of passes and had lower rates of successful recanalization, suggesting more complications during EVT that may have influenced outcomes and the eCAS decision. Second, although it is based on a prospective registry, some data were collected retrospectively by the participating centers, which may have led to inherent bias. Specially, despite its close concordance with 90-day mRS score, 1-year mRS score was not centrally assessed. Also, radiological image analyses of angiographies and follow-up CT was not centralized nor blinded to eCAS status, potentially introducing inter-observer variability and interpretive bias. Information on the follow-up image modality used (CT or magnetic resonance imaging [MRI]) was not available, which might have influenced the classification of HT. Nevertheless, MRI is exceptionally uncommon as follow-up imaging in our clinical setting due to its higher cost and limited availability. CT is the standard practice, therefore, the risk of bias introduced by this limitation is considered minimal. Third, although the IPTW was employed to mitigate selection bias, decision-making as to stent placement and antithrombotic regimen were ultimately at the discretion of the treating practitioner at each center, leading to a wide array of treatment combinations that are

challenging to adjust for accurately. For instance, unmeasured factors, including vascular anatomy, collateral status, or other clinical considerations, may have influenced the decision to perform eCAS. Finally, the absence of data on stroke recurrence during follow-up results in a significant limitation. This limits our ability to assess the potential safety concern of an increased rate of peri-procedural strokes in the eCAS group, as well as the possible efficacy benefit of a reduced incidence of recurrent strokes during follow-up in this group.

Conclusions

In patients with AIS due to TL, eCAS performed during EVT was found to be safe and associated with a better functional outcome, even in a long-term follow-up. DAPT may be safe and associated with a better functional outcome than other antithrombotic regimens. The benefit of eCAS seems consistent not only in patients with severe ($\geq 70\%$) ICA stenosis, but also in moderate (50-69%) stenosis, and further research is needed to assess potential sex-related or age-related differences on the benefit of emergent carotid revascularization.

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Figure legends

Figure 1. Participant flowchart. Abbreviations: EVT, endovascular therapy; ICA, internal carotid artery.

Figure 2. Modified Rankin Scale score distributions at 90 days of follow-up (A) and 1 year of follow-up (B) for eCAS and non-eCAS groups. Abbreviations: eCAS, emergent carotid artery stenting; mRS, modified Rankin scale.

Figure 3. Stratified analyses of treatment effect of eCAS in key subgroups at 90 days of follow-up (A) and 1 year of follow-up (B). Abbreviations: ASPECTS, Alberta Stroke Program Early Tomography Score; CI, confidence interval, eCAS, emergent carotid artery stenting; ICA, internal carotid artery; mRS, modified Rankin scale; NIHSS, National Institute of Health Stroke Scale; OR, odds ratio.

Supplemental Figure 1. Density plot comparing the distribution of eCAS/non eCAS before and after IPTW, demonstrating improved covariate balance.

Supplemental Figure 2. Adjusted ordinal regression analysis stratified by sex and stenosis degree prior to stenting decision. Abbreviations: aOR, adjusted Odds Ratio; CI, confidence interval; eCAS, emergent carotid artery stenting; ICA, internal carotid artery; mRS, modified Rankin scale.

Tables

Table 1. Patients clinical and radiological characteristics

	Total (n=578)	eCAS (n=344)	Non-eCAS (n=234)	p
Demographics				
Age, mean (SD)	70.2 (10.8)	70.5 (10.2)	69.8 (11.7)	0.438
Sex (female), n (%)	140 (24.2)	73 (21.2)	67 (28.6)	0.041
Previous medical history				
Previous mRS, mdn (IQR)	0 (0-1)	0 (0-1)	0 (0-1)	0.117
Current smoking, n (%)	206 (35.5)	131 (38.2)	74 (31.6)	0.106
Hypertension, n (%)	367 (63.6)	228 (66.5)	139 (59.4)	0.083
Diabetes, n (%)	143 (24.8)	92 (26.8)	51 (21.8)	0.170
Dyslipidemia	283 (49.1)	181 (52.8)	102 (43.6)	0.030
Ischemic heart disease, n (%)	81 (14.0)	59 (17.2)	22 (9.4)	0.008
Atrial fibrillation, n (%)	45 (7.8)	34 (9.9)	11 (4.7)	0.022
Previous ischemic stroke, n (%)	63 (10.9)	40 (11.7)	23 (9.8)	0.488
Previous antiplatelet therapy, n (%)	173 (29.9)	116 (33.7)	57 (24.4)	0.016
Previous anticoagulant therapy, n (%)	46 (8.0)	30 (8.7)	16 (6.8)	0.412
Previous statin therapy, n (%)	222 (38.4)	145 (42.2)	77 (32.9)	0.025
Stroke severity and acute phase variables				
Baseline NIHSS score, mdn (IQR)	16 (11-20)	16 (11-20)	17 (11-20)	0.945
SBP (mmHg), mdn (IQR)	150 (135-169)	153 (135-170)	150 (134-167)	0.156
Glycemia (mg/dL), mdn (IQR)	125 (107-155)	125 (106-155)	124 (108-155)	0.682
ASPECTS, mdn (IQR)	9 (8-10)	9 (8-10)	9 (8-10)	0.434
LTSW-groin puncture (hours), mdn (IQR)	4.3 (2.7-9.3)	4.5 (2.7-9.3)	4.1 (2.6-9.3)	0.705
IVT, n (%)	236 (40.8)	124 (36.1)	112 (47.9)	0.005
Endovascular treatment				
Number of passes, mdn (IQR)	1 (1-3)	1 (1-2)	2 (1-3)	<0.001
mTICI $\geq$ 2b, n (%)	483 (84.0)	313 (91.5)	170 (73.0)	<0.001
General anesthesia, n (%)	122 (21.1)	88 (25.6)	34 (14.5)	0.001
Arterial perforation*, n (%)	13 (2.7)	7 (2.4)	6 (3.1)	0.646
Artery dissection*, n (%)	28 (5.8)	20 (6.9)	8 (4.2)	0.207
Distal embolism*, n (%)	29 (6.0)	20 (6.9)	9 (4.7)	0.307
Groin puncture-recanalization (minutes), mdn (IQR)	62 (40-95)	65 (43-95)	59 (38-95)	0.123
TOAST classification				
Atherothrombotic, n (%)	525 (90.8)	317 (92.2)	208 (88.9)	0.182
Undetermined (two/more causes), n (%)	53 (9.2)	27 (7.9)	26 (11.1)	0.182

Legend: Abbreviations: ASPECTS, Alberta Stroke Program Early CT Score; CI, confidence interval; eCAS, emergent carotid artery stenting; IQR, interquartile range; IVT, intravenous thrombolysis; LTSW, last time seen well; mdn, median; mRS, modified Rankin Scale; mTICI: modified Thrombolysis In Cerebral Infarction; NIHSS, National Institute of Health Stroke Scale; OR, odds ratio; QRS, interquartile range; SBP, systolic blood pressure; SD, standard deviation.

*Information available for 480 patients

Table 2. Analysis of predictors of relevant hemorrhagic transformation in the eCAS group

Bivariable analysis	HT (n=58)	No HT (n=286)	p value
Age, mean (SD)	69.8 (9.7)	70.6 (10.3)	0.570
Sex (female), n (%)	12 (20.7%)	61 (21.3%)	0.914
Previous anticoagulation, n (%) ^a	5 (8.8%)	19 (6.8%)	0.590
Previous atrial fibrillation, n (%)	9 (15.5%)	25 (8.7%)	0.115
Glycemia, mdn (IQR) ^b	137 (117-178)	121 (105-151)	0.005
ASPECTS, mdn (IQR)	8 (7-10)	9 (8-10)	0.001
Baseline NIHSS, mdn (IQR)	19 (15-22)	16 (11-20)	<0.001
Prior IVT, n (%)	22 (37.9%)	102 (35.7%)	0.743
LTSW-groin puncture (hours), mdn (IQR)	4.8 (2.8-9.4)	4.4 (2.6-9.3)	0.391
Number of passes, mdn (IQR)	2 (1-3)	1 (1-2)	0.052
Arterial perforation, n (%) ^c	4 (7.8%)	3 (1.3%)	0.020
Successful recanalization, n (%) ^d	51 (87.9%)	362 (92.3%)	0.282
Multivariable logistic regression analysis	OR	95% CI	p value
Baseline NIHSS	1.08	1.02-1.15	0.009
Number of passes	1.35	1.09-1.68	0.007
Arterial perforation	9.18	1.76-47.93	0.009

Legend: Abbreviations: ASPECTS, Alberta Stroke Program Early Computed Tomography Score; CI, confidence interval; HT, hemorrhagic transformation; IVT, intravenous thrombolysis; LTSW, last time seen well; NIHSS, National Institute of Health Stroke Scale; OR, odds ratio; QRS, interquartile range; SD, standard deviation.

^aAvailable for 338 patients.

^bAvailable for 331 patients.

^cAvailable for 288 patients.

^dAvailable for 342 patients.