

ORIGINAL CONTRIBUTION

Acute Carotid Stenting for Tandem Lesions in Patients Randomized to Endovascular Treatment With or Without Thrombolysis: Results From the IRIS Individual Participant Data Meta-Analysis

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BACKGROUND: Equipoise persists whether patients with stroke with carotid tandem lesions undergoing endovascular treatment (EVT) should undergo acute carotid stenting, and whether intravenous thrombolysis (IVT) before EVT should influence this decision. We assessed functional and safety outcomes of acute carotid stenting in patients with carotid tandem lesions randomized to IVT plus EVT or EVT alone.

METHODS: Individual participant data meta-analysis of 6 randomized clinical trials conducted in Asia, Europe, and Oceania between 2017 and 2021 investigating IVT plus EVT versus EVT alone in patients with carotid tandem lesions presenting directly to EVT-capable centers. The primary outcome was the 90-day modified Rankin Scale score, assessed with mixed-effect ordinal regression models. Safety outcomes were any intracranial hemorrhage and symptomatic intracranial hemorrhage. A secondary analysis used inverse probability of treatment weighting. Treatment effect heterogeneity between IVT plus EVT and EVT alone was assessed in a 2-step meta-analysis.

RESULTS: Overall, 340 of 2267 (15%) patients had carotid tandem lesions with 113 of 329 (34%) undergoing acute carotid stenting. Stenting was associated with better 90-day functional outcomes (adjusted common odds ratio, 1.60 [95% CI, 1.03–2.47]), confirmed in inverse probability of treatment weighting analysis (adjusted common odds ratio, 1.66 [95% CI, 1.08–2.54]). Patients undergoing stenting had no statistically significant higher rates of any intracranial hemorrhage (44% versus 35%; adjusted odds ratio, 1.30 [95% CI, 0.79–2.15]) and symptomatic intracranial hemorrhage (6.3% versus 3.7%; adjusted odds ratio, 2.09 [95% CI, 0.78–5.59]). No heterogeneity in treatment effect was observed in patients randomized to IVT plus EVT (adjusted common odds ratio, 2.07 [95% CI, 1.06–4.07]) or EVT alone (1.21 [95% CI, 0.59–2.50]; $P_{\text{interaction}}=0.81$).

CONCLUSIONS: In this international individual participant data meta-analysis of patients with carotid tandem lesions randomized to EVT alone or IVT followed by EVT, acute carotid stenting during EVT was associated with better functional outcomes, and this association was not modified by prior treatment with IVT.

GRAPHIC ABSTRACT: A graphic abstract is available for this article.

Key Words: intracranial hemorrhages ■ meta-analysis ■ stroke ■ thrombolytic therapy ■ treatment effect heterogeneity

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Nonstandard Abbreviations and Acronyms

EVT	endovascular treatment
ICH	intracranial hemorrhage
IPD-MA	individual participant data meta-analysis
IPTW	inverse probability of treatment weighting
IVT	intravenous thrombolysis
mRS	modified Rankin Scale

Approximately 15% to 20% of all patients undergoing endovascular treatment (EVT) for acute large-vessel occlusion stroke have carotid tandem lesions.^{1,2} In accordance with clinical guidelines, these patients should receive usual stroke care with both intravenous thrombolysis (IVT) and EVT, if eligible.^{3,4} Whether the carotid tandem lesion itself should be treated during EVT or at a later time remains unclear. Currently, guidelines report a lack of high-quality evidence to provide recommendations regarding the treatment of tandem lesions in patients undergoing EVT. Despite the lack of evidence, timely treatment of the carotid tandem during the EVT procedure may be required, with acute carotid stenting during EVT emerging as a promising strategy despite significant practice variation among centers and interventionists.⁵⁻¹⁰

Treatment of carotid tandem lesions during EVT with stent deployment can reduce the risk of early stroke recurrence and prevent the need for a second intervention. However, acute stenting of the carotid tandem lesion will require the use of additional antithrombotic medications to prevent stent stenosis, potentially increasing the risk of intracranial hemorrhage (ICH), especially in combination with prior IVT.^{1,2,11} Furthermore, hyperperfusion syndrome after restoration of carotid flow can further increase the risk of hemorrhagic transformations,¹² and the additional manipulation required has been associated with higher rates of distal embolization during the procedure.¹⁰

Whether prior use of IVT should influence the decision to acutely treat the underlying tandem lesion remains uncertain. Despite nonrandomized evidence suggesting that acute stenting is safe even among patients who received IVT before EVT,¹¹ a recent survey of physicians treating acute ischemic stroke revealed that approximately one-third of the respondents would prefer to skip IVT before EVT for patients with a carotid tandem lesion, possibly as a consequence of concerns with hemorrhagic complications in patients who may require carotid artery stenting and immediate dual antiplatelet therapy to prevent stent stenosis.¹³

This study investigated the association between acute stenting of carotid tandem lesions during EVT and functional and safety outcomes in participants with large-vessel acute ischemic stroke presenting directly at

EVT-capable centers who were randomized to IVT plus EVT or EVT alone.

METHODS

Data Sharing Statement

Access to data is available on reasonable request and approval from the IRIS Collaboration Committee. Data sharing can only occur within a secure cloud-based virtual environment. Requests regarding data access should be made to Y.R.B. (Amsterdam UMC, Amsterdam, the Netherlands, y.b.roos@amsterdamumc.nl).

Study Population

The IRIS collaboration conducted an individual participant data meta-analysis (IPD-MA) of randomized clinical trials that investigated the noninferiority of EVT alone versus IVT plus EVT in patients with large-vessel anterior circulation stroke presenting directly to centers capable of performing EVT. Six randomized clinical trials were identified, and their leading investigators agreed to share individual participant data for the IPD-MA. All patients were treated with EVT using a second-generation device and were randomly allocated to receive IVT before EVT or EVT alone. In this study, we included all patients from the IRIS IPD-MA with anterior circulation stroke and carotid tandem lesion. Details on the search strategy, systematic review, and risk of bias assessment are available in the *Supplemental Methods* and *Figures S1 through S3*. Further details on study protocol and data pooling for the IRIS IPD-MA have been previously published.¹⁴ Results of this analysis are reported in adherence to the PRISMA-IPD guidelines for individual participant data meta-analyses. Informed consent was obtained from either the patients or their relatives in each included clinical trial. Ethics approval was obtained from the ethics committee of each leading clinical trial center. Further details are provided in the IRIS IPD-MA study protocol and publications of the included trials.¹⁴

Imaging Assessment

The presence of carotid tandem lesion was defined by each study's independent imaging core laboratory as the presence of stenotic or occlusive disease in the ipsilateral extracranial carotid artery on either computed tomography or magnetic resonance angiography (computed tomography angiography or magnetic resonance angiography) and digital subtraction angiography with specific definitions varying between trials (*Table S1*). Patient-level data regarding the cause of the tandem lesion (atherosclerosis versus dissection) and the degree of stenosis were not available for some of the trials; therefore, no distinctions were made for the purpose of this study. For some trials, the presence of a carotid tandem lesion was assessed in more than 1 imaging modality; these cases were considered carotid tandem lesion cases if at least 1 imaging assessment by the core laboratory described the presence of a carotid tandem lesion. All available clinical and core laboratory individual participant data were collected and pooled for this analysis. Attempts to retrieve additional information were made but sharing of imaging data and centralized rescaling were not possible for the purpose of this study.

Intervention

Acute stenting of the underlying tandem lesion was allowed in the study protocols of all 6 trials at the discretion of the treating physicians, either before or after treatment of the intracranial occlusion. For this study, we considered the placement of acute stenting (with or without angioplasty, before or after the primary thrombectomy) as the intervention of interest, with the control group including all patients with a carotid tandem lesion that did not receive acute stenting (including patients receiving angioplasty alone, deferred treatment of the carotid tandem lesion at a later time with stenting, angioplasty or endarterectomy, or best medical treatment).

For patients randomized to IVT plus EVT the thrombolytic drug used was alteplase at a dose of 0.9 mg/kg for all trials except for patients included in the SKIP trial, which followed a dose of 0.6 mg/kg in accordance with local Japanese guidelines, and for patients in the DIRECT-SAFE trial, which allowed the use of intravenous tenecteplase at a dose of 0.25 mg/kg ($n=25$).

Outcomes

The primary outcome was functional improvement, defined as a 1-point improvement in the 7-level ordinal 90-day modified Rankin Scale (mRS) score (mRS score, 0: no symptoms, 6: death). Secondary outcomes were the rates of functional independence (mRS score 0–2 versus mRS score 3–6), excellent functional outcome (mRS score 0–1 versus mRS score 2–6), severe disability or death (mRS score 5–6 versus mRS score 0–4), National Institutes of Health Stroke Scale score assessed at 5 to 7 days (or at the time of discharge if earlier), rates of ICH of any type, rates of symptomatic ICH (defined as evidence of intracranial hemorrhage and increase of ≥ 4 points on the National Institutes of Health Stroke Scale), and total procedure duration (minutes).

Statistical Analysis

For the primary analysis, we assessed the effect of acute stenting using mixed-effect ordinal regression models (cumulative link mixed-effect models) for the primary outcome. For secondary outcomes, generalized mixed-effect logistic and linear models were used for binary and continuous outcomes, respectively. All models included random intercepts and slope for the effect of treatment (acute stenting) across the included studies. All analyses were adjusted for age, sex, baseline National Institutes of Health Stroke Scale score, onset-to-randomization time, prestroke mRS score, occlusion location, history of atrial fibrillation (previous or de novo diagnoses), and randomization allocation (IVT plus EVT or EVT alone). Results are reported as adjusted common odds ratios (ordinal outcomes), adjusted odds ratios (binary outcomes), and beta coefficients (continuous outcomes) with corresponding 95% CIs. Continuous outcomes were logarithmically transformed ($\log[\text{var}+1]$) and estimates are reported back-transformed as percentages ($[\exp\{B\}-1]\times 100$). All P values are 2-tailed, and significance was defined at the 0.05 level.

As acute carotid stenting during the EVT procedure was based on the treating interventionist's decision and not on randomization, bias by indication could result in spurious associations if the decision to acutely treat a tandem lesion was

influenced by the clinical profile and by the overall success of the EVT procedure. To mitigate this risk, we conducted a secondary analysis using inverse probability of treatment weighting (IPTW). First, we calculated the propensity scores for each patient based on the predicted probability of receiving acute stenting. To derive the propensity scores, we used logistic regression models with stratified intercepts per study. The variables included in the model were based on clinical rationale and not on P value examination. The predicted probabilities (propensity score) of each patient being assigned to acute stenting were used to compute the IPTW, defined as $1/\text{propensity score}$ for patients receiving treatment and $1/(1-\text{propensity score})$ for patients not receiving treatment. This approach produces patient-level weights that are inversely related to the probability of each patient receiving the treatment they received. The IPTW were then stabilized by multiplying the weight with the crude probability of exposure to the received treatment as follows: proportion of exposed[overall]/propensity score[patient] for the exposed group and $(1-\text{proportion of exposed[overall]})/\text{propensity score[patient]}$ for the unexposed group. The final IPTW were trimmed at the first and 99th percentiles to prevent extreme weights from inflating the variances and CIs of the estimates. The stabilized IPTW were used to produce estimates of marginal common odds ratios using weighted regression models within each included trial. In practice, this analysis used the IPTW from each patient to create pseudopopulations on which the baseline characteristics are equally distributed across both treatment arms in each of the included trials separately. Weighted proportional odds models were used for ordinal outcomes, weighted linear regression models for continuous outcomes, and weighted logistic regression models for binary outcomes for each individual study data set. Robust variance estimates were used in all linear models. To ensure a balance in baseline characteristics between the treatment arms, we inspected standardized differences before and after weighting to ensure balanced characteristics in patients exposed and unexposed. These results can be interpreted as a marginal (populational) effect for pseudopopulations that balances the prespecified covariates.

Given the small number of observations in some of the included trials, we conducted a sensitivity analysis of the primary and IPTW analyses, excluding trials with <10 participants undergoing acute carotid stenting.

To assess whether the effect of acute stenting during EVT was modified by prior treatment with IVT we tested for the presence of treatment-covariate interaction between acute stenting and randomization allocation. To prevent the risk of ecological bias, we followed 2-step mixed-effects meta-analysis.¹⁵ First, we fitted ordinal cumulative link models within each individual trial, including terms for acute stenting, randomization to IVT, and their multiplicative interaction, as well as the adjustment covariates used for the primary analysis. The within-trial estimates and variances were then pooled using mixed-effects meta-analytical methods to provide an overall summary of the effect modification based on within-trial information only. A similar analysis is reported for the secondary outcomes. Effect modification is reported as P value for interaction. Conditional estimates for the effect of acute stenting in patients treated with IVT+EVT and EVT alone are reported but should be considered exploratory in the absence of significant P values for interaction.

For all analyses, missing data were treated with multiple imputations by chained equations. All regression results are based on pooled estimates from the imputed data in accordance with Rubin's rules. The descriptive results were based on complete data only. All analyses were conducted using R version 4.2.0.

RESULTS

The IRIS IPD-MA pooled participant-level data from 2334 individuals included in 6 clinical trials randomizing patients to IVT plus EVT or EVT alone between 2017 and 2021. Both Asian and Western populations are well represented with trial conducted in China (DEVT and DIRECT-MT), Japan (SKIP), Australia, New Zealand, Southeast Asia (DIRECT-SAFE), and Europe (MR CLEAN-No IV and SWIFT DIRECT). In total, the IRIS IPD involved >190 EVT-capable stroke centers in 15 countries. Patients with posterior circulation stroke ($n=21$) and those with missing information on the presence of carotid tandem lesions ($n=46$) were excluded from this analysis. Of the remaining 2267 patients, 340 (15%) had a carotid tandem lesion. Data regarding acute stenting were available for 329 (97%) patients, with 113 (34%) of these patients treated with acute carotid stenting during the EVT procedure (Figure S1). Information regarding the timing of stenting placement (before or after intracranial thrombectomy) was not available for 5 of the 6 included trials. Percutaneous angioplasty was performed in 72 of 99 (33%) patients in the acute carotid stenting arm. Within the control arm, 27 of 166 (16%) patients received percutaneous angioplasty (without carotid stenting) during EVT. No information regarding the subsequent treatment (endarterectomy, EVT, or best medical treatment) were available for either group. The proportion of patients with carotid tandem lesions who underwent acute stenting varied significantly among the included trials ($P<0.001$), ranging from 23% in DIRECT-SAFE to 62% in DIRECT-MT (Table S2).

Patients who received acute stenting were more likely to be male (82% versus 66%) and to have large artery atherosclerosis as the stroke cause (81% versus 55%) and to have lower rates of atrial fibrillation (7% versus 21%). Other baseline differences are described in Table 1. Absolute standardized differences before and after IPTW are reported in Figure 1 and Table S3.

In the primary analysis, patients with tandem lesions undergoing acute stenting had significantly better 90-day mRS score distribution (Figure 2) with higher odds of better functional outcome (adjusted common odds ratio, 1.60 [95% CI, 1.03–2.47]; $P=0.04$) and higher rates of excellent functional outcome (adjusted odds ratio, 1.91 [95% CI, 1.05–3.46]; $P=0.03$). The rates of functional independence and severe disability or death were also in favor of acute carotid stenting but were not statistically significant (Table 2). Patients undergoing acute

stenting had higher rates of ICH (44% versus 35%; adjusted odds ratio 1.30 [95% CI, 0.79–2.15]; $P=0.30$) and symptomatic ICH (6.3% versus 3.7%; adjusted odds ratio, 2.09 [95% CI, 0.78–5.59]; $P=0.14$), but these differences were not statistically significant (Table 2).

The IPTW adjusted analysis revealed similar results to the primary analysis for the primary outcome (adjusted common odds ratio, 1.66 [95% CI, 1.08–2.54]; $P=0.02$) and for the secondary outcomes (Table 2).

A sensitivity analysis excluding trials with less than 10 cases undergoing acute stenting (effectively excluding the DEVT and SKIP trials) remained consistent with the primary results (Table S4).

As expected, GP2B3A antagonists were more frequently used during the procedure in patients who received carotid stenting (33% versus 5.1%), with other procedural details being similar between the groups (Table 3). Complications during the procedure were reported in 20 of 96 (21%) patients receiving carotid stenting and 24 of 155 (15%) patients in the EVT without carotid stenting group. Distal embolization to a different arterial territory at the end of the EVT procedure was observed in 7 of 106 (6.6%) patients who received carotid stenting during EVT and 6 of 184 (3.3%) patients who did not receive carotid stenting. Recurrent stroke in the follow-up period was reported in 1 of 68 (1.5%) patients in the carotid stenting with EVT group and in 3 of 113 (2.7%) patients in the EVT without carotid stenting group (Table 3).

Of the included 329 patients, 156 (47%) were randomized to IVT and EVT, and 173 (53%) to EVT alone (Table 1; Table S5). Acute stenting during EVT was performed in 52 of 156 (33%) patients in the IVT + EVT arm and 61 of 173 (35%) in the EVT alone arm, with no major differences in baseline characteristics between patients receiving acute stenting with or without prior IVT (Table S5). Procedural details stratified by randomization arm are reported in Table S6. For the primary outcome, the association between acute carotid stenting and better functional outcomes was not modified by randomization to IVT plus EVT (adjusted common odds ratio, 2.07 [95% CI, 1.06–4.07]) or EVT alone (1.21 [95% CI, 0.59–2.50], $P_{\text{interaction}}=0.81$; Figure 3). Furthermore, no evidence of treatment effect heterogeneity was observed for the secondary and safety outcomes (Table S7).

DISCUSSION

In this international IPD-MA of patients with large-vessel occlusion stroke presenting directly to centers capable of performing EVT, carotid tandem lesions were detected in 15% of the patients, with lower rates in trials conducted in Asia and higher rates in trials conducted in Europe, a finding consistent with previous epidemiological data.¹⁶ Among our study population, one-third of patients with

Table 1. Baseline Characteristics

Characteristic	Acute carotid stenting, N=113	No acute carotid stenting, N=216	P value
Treatment allocation			0.71
IVT plus EVT	52 (46%)	104 (48%)	
EVT alone	61 (54%)	112 (52%)	
Age, y	67 (60–74)	69 (60–76)	0.33
Sex			0.008
Female	20 (18%)	74 (34%)	
Male	93 (82%)	142 (66%)	
Medical history			
Hypertension	57/111 (51%)	119/ 214 (56%)	0.44
Diabetes	17/ 102 (17%)	34/ 180 (19%)	0.64
Ischemic stroke	11/ 111 (9.9%)	25/ 215 (12%)	0.63
Atrial fibrillation	8/ 113 (7.1%)	45/ 215 (21%)	0.002
Antiplatelet use	21/ 101 (21%)	47/ 176 (27%)	0.84
Anticoagulant use (VKA or DOAC)	3/ 101 (3.0%)	4/ 176 (2.3%)	0.72
Stroke cause (TOAST)			0.008
Cardioembolic	2 (1.8%)	37 (17%)	
Large artery atherosclerosis	92 (81%)	119 (55%)	
Undetermined	19 (17%)	60 (28%)	
Prestroke mRS score			0.66
0	97 (86%)	174 (81%)	
1	11 (9.7%)	29 (13%)	
2	4 (3.5%)	11 (5.1%)	
3+	1 (0.9%)	2 (0.9%)	
Baseline NIHSS score	15.0 (11.0–18.0)	16.0 (12.0–20.0)	0.05
Baseline ASPECTS score	8.00 (8.00–10.00)	9.00 (8.00–10.00)	0.70
Occlusion location (CTA/MRA)			0.15
ICA	55/ 112 (49%)	121/ 215 (56%)	
M1+	57/ 112 (51%)	94/ 215 (44%)	
Occlusion location (first DSA)			<0.0001
ICA	56 (50%)	123/ 207 (59%)	
M1	47 (42%)	70/ 207 (34%)	
M2	7 (6.2%)	14/ 207 (6.8%)	
Other	3/113 (2.7%)	34/207 (16%)	
Onset to randomization time, min	138 (104–198)	123 (85–184)	0.22
Glucose, mmol/dL	6.66 (5.73–7.88); (n=102)	6.84 (5.90–7.80); (n=178)	0.42
Systolic blood pressure, mm Hg	153 (135–171); (n=101)	149 (133–170); (n=182)	0.46
Diastolic blood pressure, mm Hg	83 (76–93); (n=101)	81 (72–92); (n=182)	0.51

Data are shown as n (%) and median (IQR). ASPECTS indicates Alberta Stroke Program Early Computed Tomography Score; CTA, computed tomography angiography; DOAC, direct oral anticoagulant; DSA, digital subtraction angiography; EVT, endovascular treatment; IQR, interquartile range; IVT, intravenous thrombolysis; MRA, magnetic resonance angiography; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; and VKA, vitamin K antagonist.

carotid tandem lesions underwent carotid stenting during the EVT procedure. Acute carotid stenting appears to be feasible and is associated with better functional outcomes in this population. Importantly, the association between acute stenting and better functional outcomes did not differ between patients randomized to treatment with IVT plus EVT or EVT alone.

There is clinical plausibility to favor acute stenting over deferred treatment in patients with carotid tandem lesions and acute ischemic stroke. First, acute treatment at the time of intervention may reduce the chances of stroke recurrence due to embolization from an unstable plaque and early reocclusion in the time interval between stroke treatment and deferred carotid lesion

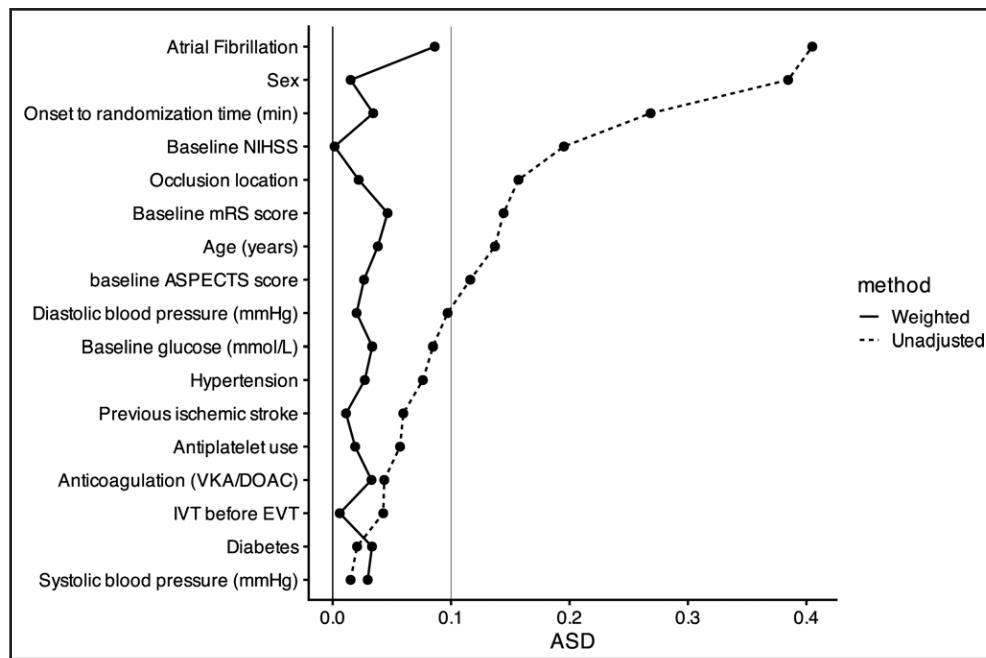


Figure 1. Absolute standardized differences in baseline characteristics between patients with carotid tandem lesion receiving acute stenting during endovascular treatment vs no acute stenting during endovascular treatment before and after inverse probability of treatment weighting.

ASD indicates absolute standardized difference; ASPECTS, Alberta Stroke Program Early Computed Tomography Score; DOAC, direct oral anticoagulant; EVT, endovascular treatment; IVT, Intravenous thrombolysis; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; and VKA, vitamin K antagonist.

treatment (usually within 2 weeks). Nonetheless, the rate of stroke recurrence in our study population was low in both treatment arms. Second, acute treatment of the tandem lesion during the same procedure will avoid exposing the patient to a second intervention at a later time, possibly reducing the rates of complications and simplifying treatment and rehabilitation plans. Third, it has been suggested that resolution of the stenotic or occlusive carotid lesion during the EVT procedure could

improve reperfusion status and consequently lead to better functional outcomes.^{5–7,11,17–21} Our results support previous observational evidence of a benefit of acute stenting during EVT. However, these results should be interpreted carefully, given their observational nature. As the treatment decision for carotid stenting was not based on randomization, it is possible that interventionists felt more comfortable treating a tandem lesion in patients for which a successful recanalization and more

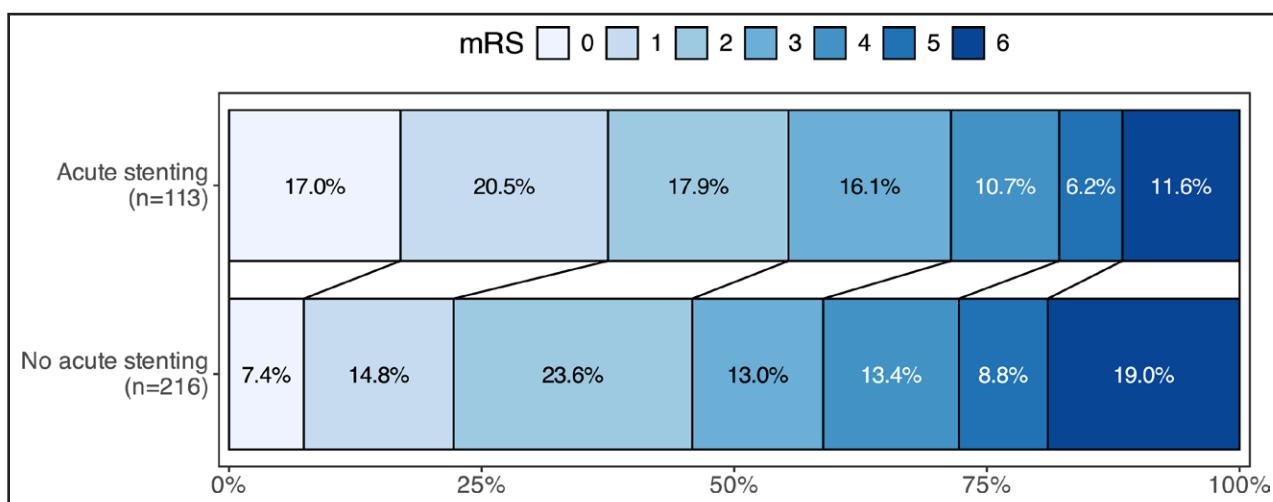


Figure 2. Distribution of modified Rankin Scale (mRS) score at 90 days for patients with carotid tandem lesions treated with and without acute carotid stenting during endovascular treatment.

Data on 90-day mRS scores were not available for 1 patient in the acute stenting arm.

Table 2. Primary and Secondary Outcome Results

	Acute carotid stenting, N=113	No acute carotid stenting, N=216	Effect estimate [95% CI]	P value	IPTW adjusted effect estimate [95% CI]	P value
Primary outcome						
mRS score (ordinal)*	2.00 (1.00–4.00)	3.00 (2.00 to 5.00)	1.60 [1.03 to 2.47]	0.04	1.66 [1.08 to 2.54]	0.02
Secondary outcomes						
mRS score 0–1*	42 (38%)	48 (22%)	1.91 [1.05 to 3.46]	0.034	1.89 [1.10 to 3.25]	0.02
mRS score 0–2*	62 (55%)	99 (46%)	1.28 [0.75 to 2.20]	0.36	1.38 [0.86 to 2.22]	0.19
mRS score 5–6*	20 (18%)	60 (28%)	0.72 [0.38 to 1.35]	0.30	0.77 [0.35 to 1.72]	0.53
NIHSS score (5–7 d)†	5 (1 to 12)	5 (1 to 14)	-0.06 [-0.32 to 0.19]	0.63	-0.03 [-0.38 to 0.31]	0.84
Any ICH‡	49 (44%)	72 (35%)	1.30 [0.79 to 2.15]	0.30	1.46 [0.89 to 2.40]	0.14
sICH§	7 (6.3%)	8 (3.7%)	2.09 [0.78 to 5.59]	0.14	1.91 [0.48 to 7.63]	0.36
Procedure duration, min	75 (55 to 109)	59 (37 to 95)	0.25 [0.10 to 0.40]	0.002	0.27 [0.13 to 0.41]	<0.001

Data are shown as median (IQR) and n (%); EVT indicates endovascular treatment; ICH, Intracranial hemorrhage; IPTW, inverse probability of treatment weighting; IQR, interquartile range; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; and sICH, symptomatic intracranial hemorrhage.

*Data on 90-day mRS score were missing for 1 patient in the carotid stenting during EVT group.

†Assessed at 5 to 7 d or at discharge time if earlier. Data on NIHSS score were missing for 1 patient in the carotid stenting group and 9 patients in the no carotid stenting group.

‡Data on any ICH was missing for 1 patient in the carotid stenting group and 9 patients in the no carotid stenting group.

§Data on sICH were missing for 1 patient in the carotid stenting group and 1 patient in the no carotid stenting group.

||Data on procedure duration were missing for 4 patients in the carotid stenting group and 4 patients in the no carotid stenting group.

favorable reperfusion was achieved, which are therefore more likely to have better functional outcomes. Although this possibility should not be overlooked, our data do not suggest that patients with successful (expanded Treatment in Cerebral Infarction 2B-3) and excellent (expanded Treatment in Cerebral Infarction 2C-3) reperfusion were more likely to undergo carotid stenting during EVT (Table 3).

Although carotid stenting during EVT is a promising strategy with potential benefits, stenting during EVT has also been associated with a higher risk of ICH attributed to the additional antithrombotic medications required to prevent stent occlusion.^{22–26} The potential increased risk of ICH in patients receiving acute stenting during EVT raises important questions about the role of IVT before EVT. It is plausible to assume that for patients receiving acute stenting and additional antithrombotic medications, prior IVT administration could further increase the risk of bleeding, with a recent survey showing that one-third of stroke physicians avoid IVT before EVT for patients with the presence of a carotid tandem lesion that can directly undergo EVT.^{2,13,27} Despite these concerns, a large observational meta-analysis of patients with carotid tandem lesion who underwent acute stenting suggested better outcomes and no increase in ICH with IVT before EVT versus EVT alone. Although encouraging, the results of this study should be interpreted cautiously as the IVT group had significantly shorter onset to treatment times potentially introducing indication bias in favor of IVT.¹¹ In fact, a subsequent analysis of the IRIS IPD-MA including patients with carotid tandem lesion who were randomized to IVT plus EVT or EVT alone has shown the addition of IVT was not associated with better (or worse) functional outcomes when compared with

EVT alone.²⁸ In our study, patients receiving acute carotid stenting had higher numeric rates of hemorrhagic complications, although this association was not statistically significant. Moreover, there was no evidence in our data that the risk of ICH was higher among patients receiving prior IVT. Our data also suggests higher rates of distal embolization among patients receiving acute stenting, but overall, the number of events is small and not statistically significant.¹⁰ Importantly, despite the potentially higher rates of ICH and distal embolization, acute carotid stenting remained associated with better functional outcomes at 90 days in our population.

Equipoise regarding the ideal timing for treatment of carotid tandem lesions persists as illustrated by the lack of strong recommendations in guidelines and by the wide variability in rate of acute stenting across different trials and countries included in our analysis (Table S2). The observational nature of our study precludes definitive conclusions regarding the efficacy and safety of acute stenting during EVT. Several randomized clinical trials are currently enrolling patients with the first results expected soon, including TITAN (URL: <https://www.clinicaltrials.gov>; Unique identifier: NCT03978988), EASI TOC (URL: <https://www.clinicaltrials.gov>; Unique identifier: NCT03978984), START URL: <https://www.clinicaltrials.gov>; Unique identifier: (NCT05902000), PICASSO (URL: <https://www.clinicaltrials.gov>; Unique identifier: NCT05611242), and CASES (URL: <https://www.clinicaltrials.gov>; Unique identifier: NCT06511089). The results of these trials are likely to provide more conclusive evidence regarding the optimal treatment strategy for patients with stroke with carotid tandem lesions. Although randomized evidence remains unavailable, our study provides supporting evidence that

Table 3. Procedural Details

	Acute stenting, N=113	No acute stent- ing, N=216	
Early recanalization	5/ 111 (4.5%)	0/ 208 (0%)	0.88
General anesthesia	33/ 102 (32%)	43/ 181 (24%)	0.38
Intracranial stenosis	4/ 78 (5.1%)	9/ 142 (6.3%)	0.95
Balloon-guided catheter	34/ 103 (33%)	90/ 174 (52%)	0.36
Extracranial ICA angioplasty	72/99 (33%)	27/166 (16%)	0.71
First-line device			0.77
Aspiration	9/ 111 (8.1%)	19/ 205 (9.3%)	
Other	3/ 111 (2.7%)	9/ 205 (4.4%)	
Stent retriever	96/ 111 (86%)	177/ 205 (86%)	
None	3/ 111 (2.7%)	0/ 205 (0%)	
IA thrombolytic	1/ 107 (0.9%)	5/ 198 (2.5%)	0.38
GPIIb/IIIa antagonist	37 (33%)	11/ 216 (5.1%)	<0.0001
No. of passes	2.00 (2.00, 3.00)	2.00 (2.00, 3.00)	0.87
eTICI score			
2B-3	96/ 111 (86%)	173/ 204 (85%)	0.52
2C-3	54/ 111 (49%)	102/ 204 (50%)	0.82
Complications			
Embolization to new territory	7/ 106 (6.6%)	6/ 184 (3.3%)	0.31
Perforation	2/ 103 (1.9%)	3/ 182 (1.6%)	0.86
Dissection	0/ 102 (0%)	4/ 182 (2.2%)	0.99
New stroke	1/ 68 (1.5%)	3/ 113 (2.6%)	0.61
Rescue IVT	1/ 78 (1.3%)	5/ 137 (3.6%)	0.63

Data are shown as median (IQR) and n (%). eTICI indicates expanded Treatment in Cerebral Infarction; IA, intra-arterial; IQR, interquartile range; and IVT, intravenous thrombolysis.

acute stenting is an acceptable strategy in patients with tandem lesions of atherosclerotic cause. Furthermore, our study provides randomized evidence suggesting that prior treatment with IVT should not determine the decision to acutely treat carotid tandem lesions with stent placement during EVT.

Limitations

Our study had several limitations. First, our tandem lesion population was heterogeneously defined across the included trials, and no detailed information about tandem lesion cause was available. Both dissection and atherosclerosis cases were included in this analysis, which may have introduced bias, as different tandem lesion causes may warrant different treatment strategies, with conservative treatment being favored in patients with dissection. Second, no information is available on the follow-up treatment strategy for tandem lesions in the group not undergoing carotid stenting during EVT. The control arm is likely heterogeneous, including patients who received percutaneous angioplasty without stenting, endarterectomy, and patients for whom no further invasive

treatment was deemed necessary after the EVT procedure, for example, due to severe disability. Differences in treatment strategies in the control group could have influenced outcomes. Furthermore, information regarding carotid patency and postprocedural treatments in the acute stenting group are also unavailable. Third, the 2 studies with smaller sample sizes (DEVT and SKIP) had few cases of patients undergoing acute stenting. A sensitivity analysis excluding the DEVT and SKIP trials yielded results similar to our primary analysis. Fourth, it is not possible to determine whether the decision to perform acute stenting was made before or after the treatment of the acute intracranial occlusion. This likely varied between centers and treating interventionists. It is possible that interventionists felt more comfortable performing acute stenting in patients for whom the EVT procedure was successful (good reperfusion) and without complications, therefore introducing bias by indication. However, our data showed no differences in the final expanded Treatment in Cerebral Infarction scores, number of passes, or complication rates between the groups, suggesting that procedural success was not a determining factor in the decision to acutely stent the carotid tandem lesion. In fact, our data showed that acute stenting was more frequently performed in patients with stroke of large artery atherosclerosis cause, suggesting that interventionists may have been more inclined to acutely stent patients in whom the tandem lesion was considered highly suspicious or for whom no other causes of stroke were evident. Fifth, our study population includes only patients presenting directly to centers capable of performing EVT who were randomized to EVT alone or IVT (almost all with alteplase) plus EVT. Therefore, generalization to transfer patients or patients treated with other thrombolytic agents (tenecteplase) is limited. Finally, regarding acute carotid stenting as an intervention, the data presented in this study are of an observational nature (randomization was performed only for the decision to provide IVT before EVT versus EVT alone). While IPTW adjusted analysis provides an estimation of the treatment effect for balanced pseudopopulations, it can only account for differences in measured confounders. Because assuming the absence of unmeasured confounders is unrealistic, no causal claims regarding the clinical benefit of acute stenting should be established based on our results.

Conclusions

In this international IPD-MA of patients with stroke with carotid tandem lesions randomized to EVT alone or IVT followed by EVT, acute carotid stenting during EVT was associated with better functional outcomes, and this association was not modified by prior treatment with IVT. Our results suggest that acute stenting during EVT appears safe and is potentially beneficial, and prior

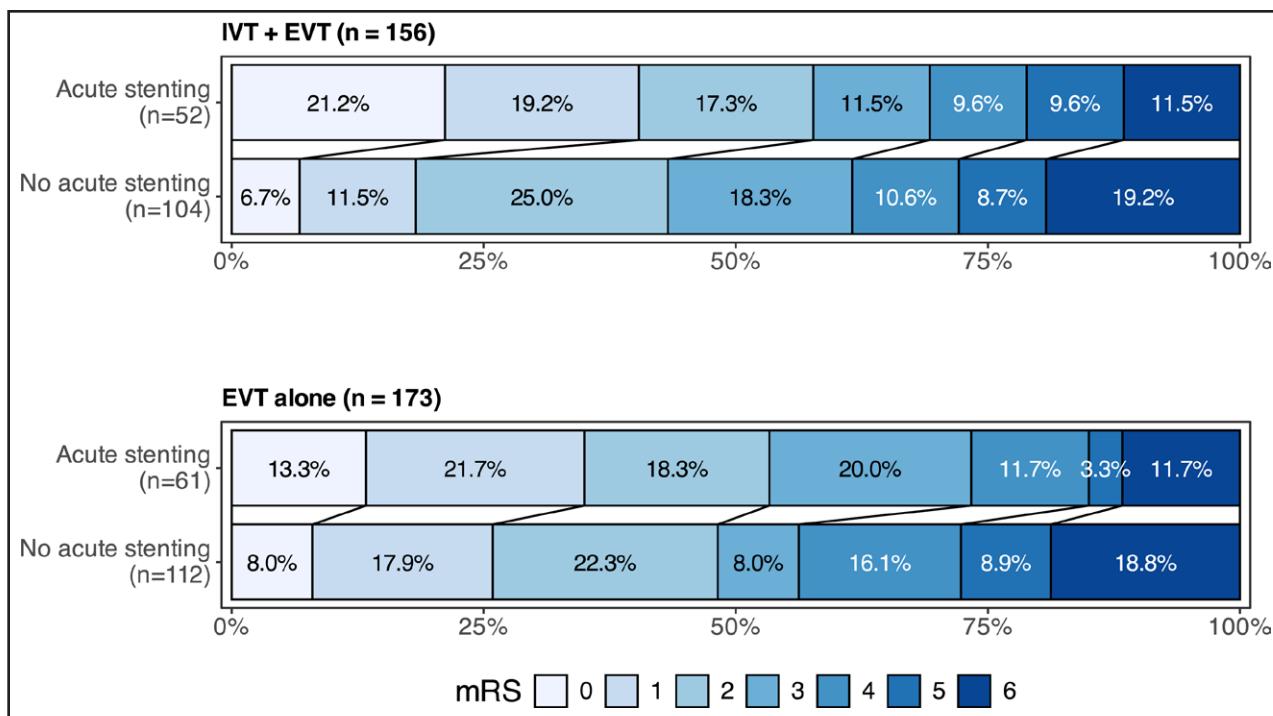


Figure 3. Distribution of modified Rankin Scale (mRS) score at 90 days for patients with carotid tandem lesions treated with and without acute carotid stenting during endovascular treatment (EVT) and stratified by treatment randomization to intravenous thrombolysis (IVT) plus EVT or EVT alone.

Data on the 90-day mRS score was not available for 1 patient in the acute stenting arm.

treatment with IVT should not inform the acute stenting decision. Ongoing randomized clinical trials are expected to provide conclusive evidence on the efficacy and safety of acute carotid stenting.

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Author Contributions

The IRIS collaboration was conceptualized by Drs Majoie, Roos, Kimura, Suzuki, ZM, Mitchel, Yan, Zhang, Yang, Liu, QY, RN, Treurniet, Kappelhof, WJ, Gralla, and Fischer. Data collection and study organization were directly coordinated by Drs Cavalcante, Kappelhof, Treurniet, and Kaesmacher. Drs Cavalcante, Treurniet, Kappelhof, Kaesmacher, and Lingsma designed the study plan. Drs Cavalcante, Treurniet, Kappelhof, and Kaesmacher prepared the first draft of the manuscript with feedback from all authors. Data pooling and statistical analysis were conducted by Dr Cavalcante with inputs from Treurniet, Kappelhof, and Lingsma, and Drs Nieboer. Drs Cavalcante, Treurniet, and Kappelhof had direct access to and verified the data reported in this manuscript. All authors participated in patient enrollment, data collection, curation of pooled data, and critical review of the manuscript. All authors approved the final version of the manuscript and are responsible for the decision to submit the results for publication.

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Supplemental Material

IRIS Collaborators List

Supplemental Methods—Systematic Search Strategy

Tables S1–S7

Figures S1–S3

PRIMA-IPD MA Checklist

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