Endovascular Stroke Treatment of Acute Tandem Occlusion: A Single-Center Experience

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ABSTRACT

Purpose: To evaluate outcomes and prognostic factors in patients with acute ischemic stroke caused by tandem internal carotid artery/middle cerebral artery occlusion undergoing endovascular treatment.

Materials and Methods: Characteristics of consecutive patients with tandem occlusion (TO) were extracted from a prospective registry. Collateral vessel quality on pretreatment computed tomographic (CT) angiography was evaluated on a 4-point grading scale, and patients were dichotomized as having poor or good collateral flow. Outcome measures included successful reperfusion according to Thrombolysis In Cerebral Infarction score, good outcome at 3 months defined as a modified Rankin scale score $\leq$ 2, symptomatic intracranial hemorrhage (ICH; sICH), and mortality.

Results: A total of 72 patients with TO (mean age, 65.6 y $\pm$ 12.8) were treated. Intravenous thrombolysis was performed in 54.1% of patients, and a carotid stent was inserted in 48.6%. Successful reperfusion was achieved in 64% of patients, and a good outcome was achieved in 32%. sICH occurred in 12.5% of patients, and the overall mortality rate was 32%. Univariate analysis demonstrated that good outcome was associated with good collateral flow ($P = .0001$), successful reperfusion ($P = .001$), and lower rate of any ICH ($P = .02$) and sICH ($P = .04$). On multivariate analysis, good collateral flow (odds ratio [OR], 0.18; 95% confidence interval [CI], 0.04–0.75; $P = .01$) and age (OR, 1.08; 95% CI, 1.01–1.15; $P = .01$) were the only predictors of good outcome. The use of more than one device for thrombectomy was the only predictor of sICH (OR, 10.74; 95% CI, 1.37–84.13; $P = .02$).

Conclusions: Endovascular treatment for TO resulted in good outcomes. Collateral flow and age were independent predictors of good clinical outcomes at 3 months.

ABBREVIATIONS

ASPECTS = Alberta Stroke Program early computed tomography score, CI = confidence interval, ICA = internal carotid artery, ICH = intracranial hemorrhage, mRS = modified Rankin scale, NIHSS = National Institutes of Health Stroke Scale, OR = odds ratio, sICH = symptomatic intracranial hemorrhage, TICI = Thrombolysis In Cerebral Infarction, TO = tandem occlusion

Treatment of tandem internal carotid artery (ICA)/intracranial artery occlusion remains technically challenging. Despite evidence from recent endovascular stroke trials (1–5) that patients with tandem occlusion (TO) benefit from endovascular therapy, a standardized guideline for emergent management of TO has not been

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established. Some of the major randomized trials excluded patients with suspected TO (5), and, despite clinical experience and case series (6,7) of combined angioplasty or stent placement in the ICA with intracranial thrombectomy, the optimal approach to treatment remains uncertain. Given the low recanalization rate and generally poor outcomes reported after intravenous thrombolysis (IVT) in patients with TO (8), more data on contemporary endovascular reperfusion strategies in this subpopulation are needed. The aim of the present study was to report the outcomes and prognostic factors in a large cohort of patients with anterior circulation acute ischemic stroke as a result of TO treated with endovascular therapy.

MATERIALS AND METHODS

Patients

Informed consent to treatment was obtained from all patients or their relatives, and the study was approved by and conducted in accordance with the guidelines of our institutional review board. Consecutive patients with anterior circulation acute ischemic stroke were identified from our prospective endovascular stroke registry (started in August 2009). Patients were selected based on following criteria: (*i*) computed tomographic (CT) angiography documentation of TO (ie, extracranial ICA plus terminal ICA, M1, M2, or A1 segments or a combination of them; intracranial ICA plus M1, M2, or A1 segments or a combination of them) and confirmed as having extracranial ICA occlusion by microcatheter injection at angiography; (*ii*) onset to groin puncture within 5 hours from symptom onset; (*iii*) National Institute of Health Stroke Scale (NIHSS) score $\geq$ 10; (*iv*) modified Rankin scale (mRS) score $\leq$ 2 before stroke; and (*v*) available 3-month mRS score.

Treatment

Based on current guidelines, IVT was administered (alteplase 0.9 mg/kg; 10% of the dose as a bolus and the remaining infused over 60 min) within 4.5 hours after symptom onset and continued during the endovascular procedure (9,10). After retrograde common femoral access was obtained by using a 10-cm, 6-F introducer sheath (Radifocus Introducer II, Terumo, Tokyo, Japan; n = 23) or, more recently, 80-cm Neuron MAX 088 system (Penumbra, Alameda, California; n = 49), angiography of the ipsilateral common carotid artery was performed to evaluate the extent and likely cause of thrombosis (atherosclerosis, dissection, cardiac embolism). In case of an unstable or near-occlusive atherosclerotic plaque or dissection in the ICA, a stent was placed (Wallstent; Boston Scientific, Marlborough, Massachusetts) without the use of any embolic protection device. Angioplasty was performed after stent placement with a 4.5–5.5-mm balloon catheter (Falcon Grande; Medtronic, Minneapolis, Minnesota) with the use of an embolic protection device in case of a suboptimal angiographic result (ie, residual lumen stenosis > 30%). In patients with stroke of defined cardioembolic origin, (ie, atrial fibrillation or recent myocardial infarction), stent placement was replaced by primary angioplasty to reduce hemorrhagic complications resulting from combined anticoagulant (for secondary stroke prevention) and antiplatelet therapy (for in-stent thrombosis prevention).

Intracranial thrombectomy was performed by using a coaxial system composed of a 6-F guiding catheter (Neuron 070; Penumbra; or Envoy DA; Codman & Shurtleff, Raynham, Massachusetts) or a 6-F, 80-cm sheath (Neuron MAX 88; Penumbra) advanced into the intrapetrous portion of the ICA to increase system stability and an intermediate aspiration catheter (5MAX ACE 64; Penumbra) connected to a dedicated aspiration pump during mechanical thrombectomy, with its distal tip in contact with the thrombus. The choice of device was at the discretion of the neurointerventionalist and consisted of the Penumbra aspiration system (Penumbra; n = 22), stent retriever systems such as Solitaire AB (ev3, Plymouth, Minnesota; n = 4), Revive SE (Codman & Shurtleff; n = 17), or Trevo Retriever (Stryker Neurovascular, Mountain View, California; n = 2), and, more recently, new aspiration devices such as the MAX ACE aspiration system (Penumbra; n = 27) with A Direct Aspiration First Pass Technique (ADAPT) technique (11–15). In case of unsuccessful thromboaspiration, a microcatheter (Rebar 18 [ev3], Prowler Select Plus [Codman & Shurtleff], or Trevo Pro 18 [Stryker Neurovascular]) was advanced over a 0.014-inch microwire (Transend soft tip; Boston Scientific) through the occluded vessel, and a stent retriever was deployed with its distal tip beyond the thrombus. The retrieval of the coaxial system through the carotid stent was performed after the stent retriever was gently withdrawn into the inner lumen of the intermediate catheter under synchronous continuous aspiration, thereby preventing the mesh of the stent retriever and the ICA stent from entangling each other. Postprocedural angiography was then performed to evaluate the result of intracranial thrombus retrieval based on the Thrombolysis In Cerebral Infarction (TICI) score. The choice of general anesthesia or conscious sedation was individualized based on clinical severity, presence of agitation, aspiration risk, or seizures.

Intraprocedural administration of intravenous heparin (range, 1,000–7,000 IU) and/or antiplatelet therapy (lysine acetylsalicylate) was at the discretion of the neurointerventionalist, regardless of previous IVT. Administration of clopidogrel 75 mg and/or aspirin 100 mg within 24 hours after the endovascular procedure was decided by neurointerventionalists and stroke neurologists based on previous IVT, clinical severity, baseline Alberta Stroke Program early CT score (ASPECTS) (16),

and risk of hemorrhagic complications, regardless of stent placement.

Follow-up

Brain CT was performed 24 hours after the procedure to evaluate for intracranial hemorrhage (ICH) and infarct size (per ASPECTS). Hemorrhagic complications and their severity were defined according to the European Cooperative Acute Stroke Study criteria (no hemorrhage, hemorrhagic infarction 1, hemorrhagic infarction 2, parenchymal hematoma 1, or parenchymal hematoma 2) (17). Symptomatic ICH (sICH) was defined as a hemorrhage associated with an increase in NIHSS score of at least 4 points (18). All patients with stent placement and without ICH started single or dual antiplatelet therapy 24 hours after IVT. For patients treated with stent placement who had minor or major ICH, the timing of antiplatelet therapy was discussed based on baseline ASPECTS, follow-up ASPECTS (with CT or magnetic resonance imaging), severity of hemorrhagic complications, and previous IVT. Clopidogrel (75 mg) and/or aspirin (100 mg) were administered orally or via nasogastric tube in case of persisting dysphagia. No heparin was administered after treatment. A CT angiogram of extra- and intracranial vessels was performed within 48 hours after endovascular therapy to evaluate vessel patency. In case of stent placement, follow-up ultrasound or CT angiography was performed at least twice during the first year after the procedure to exclude recurrent stenosis.

Prognostic Variables

Baseline characteristics included in the analysis were age, sex, NIHSS score, intracranial occlusion site, history of hypertension, diabetes, smoking, atrial fibrillation, ASPECTS, and collateral circulation quality on pretreatment CT angiography. Collateral vessels were defined on a scale from 0 to 3 derived from the Prolyse in Acute Cerebral Thromboembolism II trial (19): a score of 0 indicates no collateral vessels, a score of 1 indicates collateral vessels to the periphery of ischemia, a score of 2 indicates collateral vessels filling 50%–100% of ischemic area, and a score of 3 indicates collateral vessels filling 100% of ischemic area. The collateral vessel score was then dichotomized into poor (score of 0/1) and good (score of 2/3) collateral circulation.

Procedural prognostic variables used for analysis were carotid stent placement, IVT, intraprocedural intravenous heparin and/or antiplatelet therapy, antiplatelet therapy soon after endovascular procedure, device employed (stent retriever vs thromboaspiration device), symptom onset to groin puncture time, symptom onset to reperfusion time, groin puncture to reperfusion time, number of device attempts, use of more than one device type (ie, rescue device), and type of anesthesia (general vs conscious sedation).

Outcome Measures

Safety and efficacy measures were good functional outcome (mRS score 0–2 at 3 mo), mortality, patency of ICA stent at 3-month follow-up imaging, posttreatment angiographic results assessed by TICI score (with successful reperfusion defined as TICI $\geq$ 2b) (20), 24-hour follow-up ASPECTS, and presence of ICH or sICH.

Statistical Analysis

Statistical analysis was performed by using Stata software (version 13; StataCorp, College Station, Texas). Descriptive statistics consisted of mean $\pm$ standard deviation or median with interquartile range for parameters with Gaussian distributions (after confirmation with histograms and the Kolmogorov–Smirnov test) or frequencies and percentages as appropriate. Comparison of continuous variables was performed by Student t test or Mann–Whitney U test. Comparison of categoric variables was performed with a Fisher exact test. Variables with a univariate P value $<$ .05 were further tested for the prediction of good outcome (ie, mRS score $\leq$ 2) and symptomatic ICH in different multivariate logistic regression analyses. A P value $<$ .05 was considered statistically significant for all analyses.

RESULTS

Of 215 patients treated with thrombectomy between August 2009 and January 2016, 143 did not fulfill selection criteria, leaving 72 patients with TO suitable for analysis. **Table 1** summarizes demographic, radiologic, and clinical characteristics at baseline. Mean age was 65.6 years $\pm$ 12.8, mean NIHSS score was 19 $\pm$ 2.9, and mean ASPECTS was 6.9 $\pm$ 2.28. Procedural data are provided in **Table 2**. Stent placement was performed in 48.6% of patients. IVT was administered to 54.1% of patients (39 of 72) before endovascular therapy; during the procedure, 19 of 39 patients treated with IVT and endovascular therapy received intravenous heparin at a median dose of 5,000 IU, and the same dose was used for 21 of 33 patients treated with endovascular therapy alone. Intravenous antiplatelet therapy (ie, lysine acetylsalicylate at a median dose of 500 mg) was used in 22.8% of patients treated with stent placement. Of 35 patients treated with stent placement, 34.2% received dual and 54.2% single antiplatelet therapy; 11.4% were not treated with antiplatelet therapy within the first 24 hours after the endovascular procedure (data not reported in the table). The only procedural complication was a middle cerebral artery perforation with fatal subarachnoid hemorrhage. Successful reperfusion was obtained in 63.9% of patients. Only one patient had stent reocclusion (asymptomatic) at 48-hour follow-up imaging, and it persisted at 3 months despite dual antiplatelet therapy. sICH occurred in 12.5% of cases. Good functional outcome at 3 months

Table 1. Demographics, Risk Factors, and Radiologic Variables at Baseline (N = 72)

Variable	Value
Age (y)	65.6 ± 12.8
Male sex	44 (61.1)
Mean NIHSS score	19 ± 2.9
Hypertension	53 (73.6)
Diabetes	12 (16.6)
Atrial fibrillation	22 (30.5)
Current smoking	3 (4.1)
ASPECTS	6.9 ± 2.28
Extracranial ICA occlusion	66 (91.6)
Intracranial ICA occlusion	6 (8.3)
Site of intracranial occlusion*	
M1	45 (62.5)
M2	8 (11.1)
t-ICA	3 (4.1)
t-ICA + M1	16 (22.2)
Collateral adequacy (%)	
Good	31 (43)
Poor	41 (57)

Note–Values presented as mean ± standard deviation where applicable. Values in parentheses are percentages.
ASPECTS = Alberta Stroke Program early computed tomography score; M1 = proximal portion of middle cerebral artery; M2 = midportion of middle cerebral artery; NIHSS = National Institutes of Health Stroke Scale; SD = standard deviation; t-ICA = terminal intracranial internal carotid artery.

Table 2. Procedural Data (N = 72)

Parameter	Value
Stent placement	35 (48.6)
IVT	39 (54.1)
Antiplatelet therapy	8/35 (22.8)
Intravenous heparin	40 (55.5)
Type of anesthesia	
General	54 (75)
Conscious sedation	18 (25)
Device for thrombectomy	
Stentriever	24 (33.3)
Thromboaspiration	26 (36.1)
Combined	21 (29.1)
Median onset groin puncture time (min)	225
Median onset reperfusion time (min)	305
Median groin reperfusion time (min)	81
Median device attempts	3

Note–Values in parentheses are percentages.
IVT = intravenous thrombolysis.

was achieved in 31.9% of patients, and the mortality rate was 31.9% (Table 3).

Univariate analysis for predictors of good functional outcome revealed a significant association with age (P = .004), baseline and follow-up ASPECTS (P = .0005 and P < .0001, respectively), presence of good leptomeningeal collateral vessels (P = .0001), lower number of device passes (P = .007), successful reperfusion (P = .001), and lower rate of any ICH (P = .02) and sICH (P = .04). No significant associations were found .with traditional vascular risk factors, IVT, stent placement, baseline NIHSS score, and use of procedural intravenous heparin (Table 4). We further analyzed potential risk factors for sICH and found that the most robust were baseline ASPECTS (P = .006), collateral flow (P = .008), the use of an additional device for thrombectomy (P = .003), and groin puncture to reperfusion time (P = .008; Table 5). On multivariate analysis, the presence of good collateral flow (OR, 0.19; 95% CI, 0.04–0.9; P = .03) and age (OR, 1.08; 95% CI, 1.01–1.15; P = .01) were the only factors significantly associated with good functional outcome. The use of more than one device for thrombectomy was the only factor associated with sICH (OR, 10.74; 95% CI, 1.37–84.13; P = .02).

Table 3. Safety and Efficacy Outcomes (N = 72)

Outcome	Incidence
3-mo stent patency	34/35 (97.1)
Successful reperfusion	46 (63.9)
24-h follow-up ASPECTS	2.63 ± 2.39
Any ICH	34 (47.2)
Subarachnoid hemorrhage	1/34 (2.9)
Hemorrhagic infarction 1	2/34 (5.8)
Hemorrhagic infarction 2	3/34 (8.8)
Parenchymal hemorrhage 1	13/34 (38.2)
Parenchymal hemorrhage 2	14/34 (41.1)
Symptomatic ICH	9 (12.5)
3-mo mRS score ≤ 2	23 (31.9)
3-mo mRS score ≤ 3	30 (41.6)
Mortality	23 (31.9)

Note–Values presented as mean ± standard deviation where applicable. Values in parentheses are percentages.
ASPECTS = Alberta Stroke Program early computed tomography score; ICH = intracranial hemorrhage; mRS = modified Rankin scale.

DISCUSSION

Treatment of patients with TO is complicated by a high risk of intracranial bleeding following stent placement and mandatory antiplatelet therapy. This risk may increase in patients pretreated with IVT (21). Moreover, carotid stenosis/occlusion is associated with a high rate of stroke recurrence (22). Therefore, TO is an extremely challenging condition that requires technical skills and careful consideration of the best treatment approach and postprocedural antithrombotic management.

Recent TO series (21,23,24) have shown relevant differences, with a broad range, in the rates of successful reperfusion (62.5%–100%), good clinical outcome (29%–63%), mortality (8%–39%), and sICH (0%–21%). The

Table 4. Univariate Analysis of Good vs Poor 3-Month Outcome

Variable	Good Outcome (n = 23)	Poor Outcome (n = 49)	*P* Value
Age (y)	59.43 ± 11.72	68.57 ± 12.41	.004
Right hemisphere	13 (56.5)	24 (49)	.6
Single intracranial occlusion	17 (74)	28 (57)	.2
IVT	14 (61)	25 (51)	.4
General anesthesia	20 (87)	34 (69.3)	.1
Stent placement	14 (61)	21 (43)	.2
Stent patency	14 (100)	20 (95)	1.00
Baseline ASPECTS	8.22 ± 1.81	6.34 ± 2.15	.0005
Thromboaspiration device	15 (65)	32 (65.3)	1.00
Rescue device	6 (26)	17 (34.7)	.5
Median onset groin puncture time (min)	227.50	225	.66
Median onset reperfusion time (min)	311.5	305	.63
Median groin puncture reperfusion time (min)	80.5	81	.12
Successful reperfusion	21 (91.3)	25 (51)	.001
Device passages	2.30 ± 1.58	3.57 ± 1.91	.007
Good collateral flow	18 (78)	13 (26.5)	.0001
Onset NIHSS score	18.17 ± 3	19.47 ± 2.82	.07
ICH	6 (26)	28 (57)	.02
Symptomatic ICH	0	9 (18.3)	.04
Procedural intravenous heparin	11 (48)	29 (59)	.4
Follow-up ASPECTS	4.35 ± 2.38	1.84 ± 1.91	< .0001

Note–Values presented as mean ± standard deviation where applicable. Values in parentheses are percentages.
ASPECTS = Alberta Stroke Program early computed tomography score; ICH = intracranial hemorrhage; IVT = intravenous thrombolysis; NIHSS = National Institutes of Health Stroke Scale.

Table 5. Univariate Analysis of Risk Factors for sICH

Variable	sICH (n = 9)	No sICH (n = 63)	*P* Value
Age (y)	68 ± 12	65.27 ± 13	.53
Procedural intravenous heparin	7 (77)	35 (55.5)	.28
IVT	4 (44)	33 (52)	.73
Procedural intravenous antiplatelet therapy	3 (33)	5 (8%)	.05
Baseline ASPECTS	5.1 ± 1.7	7.2 ± 2.1	.006
Good collateral flow	0	31 (49)	.008
Onset NIHSS score	19.6 ± 2.6	18.9 ± 2.9	.5
Stent placement	4 (44)	31 (49)	1.00
Thromboaspiration device (%)	6 (66.5)	41 (65)	1.00
Rescue device	7 (77)	16 (25.5)	.003
Successful reperfusion	4 (44)	42 (66.5)	.2
Onset to reperfusion time (min)	275 ± 69.7	318.7 ± 97	.13
Groin puncture to reperfusion time (min)	129.66 ± 78.22	85.47 ± 40.12	.008
Device passages	4.4 ± 2.7	2.9 ± 1.7	.03
General anesthesia	6 (66.5)	48 (76)	.68

Note–Values presented as mean ± standard deviation where applicable. Values in parentheses are percentages.
ASPECTS = Alberta Stroke Program early computed tomography score; IVT = intravenous thrombolysis; NIHSS = National Institutes of Health Stroke Scale; sICH = symptomatic intracranial hemorrhage.

present study is one of the larger series of patients with acute ischemic stroke secondary to TO undergoing endovascular therapy with or without stent placement. Our results show a rate of successful reperfusion rate of 64%, a good clinical outcome rate of 32%, a mortality rate of 32%, and an incidence of sICH of 12.5%, consistent with previous studies.

Compared with the largest published series by Malik et al (N = 77) (23) and Behme et al (N = 170) (24), the present study population is characterized by a higher

baseline NIHSS score and lower baseline ASPECTS. These differences in baseline characteristics could explain the relatively low rate of good outcome found in the present study. However, almost one third of our patients were completely independent (ie, mRS score $\leq$ 2), and more than 40% were independent in walking and personal activities of daily living with some dependence for domestic activities (ie, mRS score $\leq$ 3) at 3 months. In contrast, a previous study (8) found a good outcome at 3 months after IVT alone in only 18.2% of patients with TO. A pooled analysis of randomized trials (1) identified treatment benefit based on ordinal mRS score analysis in the 122 of 1,287 patients included who had TO (OR, 2.95; 95% CI, 1.38–6.32). There was no statistical heterogeneity in treatment effect between TO cases and others. However, the difference in mRS score of 0–2 for patients with TO did not reach significance in its own right (45.9% vs 27.8%; OR, 1.81; 95% CI, 0.96–3.40) (1). Overall, the available data indicate that patients with TO, despite their severe clinical presentation and higher risk of poor outcome, do benefit from endovascular therapy (with or without stent placement). As shown in **Table 4**, patients with good outcome nevertheless had a mean posttreatment ASPECTS of 4.35, indicating large infarct size, whereas those with poor outcome had a significantly lower score.

In the present study, 54.2% of patients with TO were treated with single and 34.2% with dual antiplatelet therapy after the procedure, whereas 11.4% did not receive any antiplatelet agent based on the infarct size. We did not use glycoprotein IIb/IIIa inhibitors in patients treated with stent placement because they have been reported to increase the risk of ICH, with no evidence of any reduction in death or disability (25). In addition, vessel patency at follow-up imaging was demonstrated in all patients except one, despite this patient receiving dual antiplatelet therapy. It must be highlighted that no patient in the present study who had a stent inserted and received single or no antiplatelet therapy in the 24 hours after the endovascular procedure showed the development of in-stent thrombosis.

Our results showed that sICH was not related to previous IVT or antiplatelet therapy after the procedure, whereas only a weak association was found with intraprocedural administration of lysine acetylsalicylate. Therefore, our policy of balancing infarct volume and antithrombotic strategy (ie, use of single or no antiplatelet therapy at all in more than 80% of patients) appeared safe in our cohort.

The only independent predictor of sICH in our experience was the use of an additional device for thrombectomy. Although a greater number of device passes was associated with sICH on univariate analysis, it did not remain significant on multivariate analysis and therefore did not explain the association between the use of an additional device and sICH. The additional device used in case of failure after the first attempt was a stent retriever in all cases. Existing data have found relatively low rates of ICH in patients treated with stent retrievers (1,26,27). However, there are limited safety data in this specific patient group.

We found that good collateral circulation and age were independent predictors of good outcome in patients with TO, consistent with the broader range of patients with stroke (28,29). In a recent study (28), we found that the evaluation of collateral flow in patients with acute ischemic stroke by using CT angiography and conventional angiography was reliable. Interestingly, the 58 of 135 patients with TO in that study had significantly worse collateral flow, which may contribute to poor outcomes in this group.

The main limitation of the present study is the heterogeneity of treatment in this observational cohort. This heterogeneity resulted from the need to individualize treatment based on onset NIHSS score, ASPECTS, and previous IVT. However, we believe it important to guide endovascular therapy strategy based on the most probable etiology, ie, avoiding stent placement in patients with atrial fibrillation or myocardial infarction and therefore reducing the risk of bleeding complications associated with concomitant antiplatelet and anticoagulant therapy. Nonetheless, the prospective enrollment at a single center adopted in our study may have allowed greater standardization of the treatment algorithm. Another limitation is the lack of a control group, which reduces the ability to draw conclusions about treatment benefit.

In conclusion, endovascular therapy for acute ischemic stroke secondary to TO can achieve good outcomes with an acceptable safety profile. The presence of good collateral vessels, age, and the use of an additional device for thrombectomy should be considered as crucial variables when planning future studies on this issue.

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